Adherence to Stroke Quality Indicators in Colorado: Monitoring Temporal Trends by Sharing a Common Dataset

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Background: Quality improvement initiatives in stroke care tend to be organized on a hospital-by-hospital basis. The ability to monitor statewide trends in stroke is hampered by a shortage of adequate statewide clinical data, due in part to the lack of a common database. We report here on the adherence to hospital-based quality indicators for stroke, as seen broadly in Colorado over a period of 13 quarters (Q2-2006 through Q2-2009). Methods: The Colorado Stroke Alliance is a grassroots collaboration of 36 hospitals, representing approximately 90% of the strokes occurring in Colorado. Our database now includes more than 10,000 stroke events. In concert with the Colorado Department of Public Health and Environment (CDPHE), we have prospectively monitored clinical measures of stroke care since 2006, using the American Stroke Association’s Get With The Guidelines® patient management tool (GWTG-Stroke). Here, we report the temporal change in our hospitals’ average overall adherence to 7 standard quality indicators. We calculate the linear regression of average adherence rates by quarter, and we indicate the statistical significance for these regressions by ANOVA P values. We also compare adherence data for the first 6 quarters with those of the most recent 7 quarters, using the Chi Square test for significance. Results: For five of the seven indicators, linear regression showed statistically significant improvement. For the two indicators without significant improvement (anticoagulation for atrial fibrillation and anti-thrombotic at discharge), the initial adherence rates were already above 90%. For all indicators except anticoagulation for atrial fibrillation, the most recent 7 quarters were significantly better than the first 6 quarters. The greatest absolute improvement (~12%) was noted for giving IV t-PA within one hour of arrival, for patients presenting within 2 hours of symptom onset. Conclusions: GWTG-Stroke data have typically been used for individual hospital quality improvement, but by sharing data important trends in statewide patterns of care may be identified. In Colorado, we have seen significant, positive changes in the adherence to stroke quality indicators over the past 13 quarters. A common, shared dataset of this sort may be useful to inform the planning of state systems of stroke care, and to monitor changes in the care that is rendered.

Table. Temporal Trends in Adherence

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Linear Regression, by Quarter</th>
<th>Averages, by Epoch (%, #)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slope</td>
<td>R²</td>
</tr>
<tr>
<td>Anticoag. If</td>
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<td>-0.055</td>
</tr>
<tr>
<td>Antithrombotic at DC</td>
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<td>0.078</td>
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<td>Antithrombotic in 48 hr</td>
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<td>DVT Prophylaxis</td>
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<td>IV rt-PA in 1h</td>
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<td>0.442</td>
</tr>
<tr>
<td>Medication if LDL &gt;100</td>
<td>0.012</td>
<td>0.753</td>
</tr>
<tr>
<td>Smoking Cessation</td>
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</table>

*S Statistically significant, positive-slope linear regression. P <0.01 (Chi Square)

Reducing Falls in the Stroke Population of an Acute Care Hospital: A Performance Improvement Approach

Deborah Stuart, Julie Raigh-Riiberg-Bancer, Christy Jennings, Joe Tidwell, Debbie Coggins, Aubrey Reed, Donna Rose; UT Med Ctr, Knoxville, TN

Background and Issues: Falls among stroke patients during hospitalization are a major concern. The National average is 2.23 versus 7 South Neuro/Stroke Unit was 2.91. Risk factors include, being in a strange environment, altered mental status, altered nutrition, and confusion, muscle weakness, including balance and gait issues. The Neuro/Stroke Unit at the University of Tennessee Medical Center in Knoxville, Tennessee, launched a performance improvement (PI) team to address the falls rate among stroke patients. The PI team used methods to reduce falls through evidence based practice. Methods: The team elected to use a 90 day, Plan, Do, Study Act model (P.D.S.A.). A “Near Miss” form was created to keep a daily log of at risk patients who attempted to get out of bed without assistance. This log was monitored in two week increments during the three P.D.S.A. cycle and evaluation. Strategies used to develop performance improvement plan included review of the most recent literature and brainstorming. The team determined that a valid more realistic approach was to alter the traditional unit routines rather than altering a characteristic of the population. The three P.D.S.A. cycles were: 1. Reschedule routine vital sign monitoring to allow more flexibility for staff to be available during high risk periods. 2. Coordinated patient assessment rounds prior to high risk periods. 3. Reference cards for float personnel including stroke risk factors, warning signs and patient care standards. Results: A baseline measurement of “near misses” was evaluated for the period prior to the first P.D.S.A. cycle. The baseline count was 139 “near misses”. At the end of the three P.D.S.A. cycles the “near miss” count was 10. In addition, the average monthly fall rate for 2008 was 2.91 and for the 90 day P.D.S.A. cycle the average monthly rate was 1.67. Conclusions: The result of this project indicates that when staff restructures daily nursing care and restructures to accommodate special needs of the stroke patient, fall rates and “near misses” can be dramatically reduced. The nursing team is more aware of the process of fall risk assessment, prevention and outcomes. This first hand knowledge has allowed the staff to focus more on developing a comprehensive plan of care which includes thorough education, more frequent, timely assessments, and ultimately, a safer environment.

Redesigning Stroke Education Using a Health Literacy Approach

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Background and Purpose: The Stroke & Cerebrovascular Center envisioned a stroke patient education guide that could be customized to address individual patient needs while meeting health literacy challenges within an 11 hospital health system. Although many people read and comprehend at a 6th to 8th grade level, most currently available consumer education materials are written at a high-school or greater level. Methods: A multidisciplinary group identified learning needs and assigned topics to be written at a 6th grade reading level. Group members researched existing materials, including resources from the ASA and NSA. All documents were subjected to a computerized readability assessment (SMOG- Simple Measure of Gobbledygook) to determine the grade readability level. Trade and generic names of medications were excluded from the SMOGging process. The writing topics were edited to improve their SMOG score. Results: Conclusions: Currently available stroke patient education materials are written for a 7th grade to college reading level. It was surprising to find the verbiage required to achieve the reading level recommended by national health literacy groups. Despite aggressive editing, some terms and concepts could not be sufficiently simplified to achieve the target reading level while preserving the desired message. Healthcare providers overestimate their ability to communicate in terms patients and families can understand.

Increasing Registered Nurse IV rt-PA Administration Competency

Karen Yarbrough, Tina Randall, Brigid Blaber; UMMC, Baltimore, MD

Background: As a result of reviewing acute stroke management in an academic primary stroke center it was evident there were inconsistencies how nursing staff would respond to an inpatient stroke code. It was apparent we needed to increase the number of RNs who were capable of administering IV rt-PA. A consistent protocol was needed to ensure each inpatient stroke code was attended to by an IV rt-PA competent nurse. The purpose of this performance improvement project was to develop an effective IV rt-PA registered nurse competency program. Methods: A Neurology-ED performance improvement committee met to identify barriers for in house rapid IV rt-PA administration. Barriers identified were: a lack of ICU beds; and the majority of IV rt-PA was administered by ED RN staff causing a lack of experience with IV rt-PA administration by Neuroscience RNs. The following interventions were implemented to increase RN IV rt-PA competency: IV rt-PA Competency Skills Checklist was developed; 4 hour IV rt-PA workshop was developed with the following curriculum: acute ischemic stroke
Effectiveness of a Statewide Stroke Coordinator Network: The Maryland Stroke Center Consortium

Karen L. Yarbrough, UMMC, Baltimore, MD; Maryland Stroke Cntr Consortium

Background and Purpose: In 2006, the Maryland Institute for Emergency Medical Services Systems implemented a Primary Stroke Center (PSC) designation. Several Maryland hospitals had achieved Joint Commission PSC certification. Maryland stroke coordinators found it challenging to interpret and maintain PSC requirements. As a result, a stroke coordinator network was developed in 2007, the Maryland Stroke Center Consortium (MSCC). The mission of the MSCC is to provide a collaborative forum to develop strategies to improve stroke systems of care. The MSCC is an independent organization but has an affiliate relationship with the American Heart Association and The Maryland Stroke Alliance. The purpose of this performance improvement (PI) project is to measure effectiveness of the MSCC. Methods: To measure MSCC effectiveness, we compared outcome data for 2008 and 2009, including: 1) number of acute stroke admissions to Maryland PSCs, 2) last known well to ED arrival time, 3) performance measure compliance, 4) participation in statewide research and PI projects. Data was obtained from the Get With The Guidelines: Stroke database which includes 33 Maryland PSCs. Results: Total admissions to Maryland PSCs remained unchanged for both years. Median last known well to ED arrival times were essentially the same for both years (145; 152 minutes). Four performance measures did not meet benchmarking goals for 2008 and compliance increased in 2009. These include: 1) IV-rt-PA 2 hours increased from 55% to 75%, 2) stroke education for patients and families, increased from 40% to 73%, 3) dysphagia screen increased from 75% to 80%, and 4) percentage of IS or TIA patients with LDL < 100 who are discharged on cholesterol lowering drugs increased from 79% to 85%. The MSCC has been able to impact patients and providers; three research studies have been endorsed by the MSCC and > 85% Maryland PSCs have committed to participate. Conclusions: The MSCC needs to develop effective public awareness campaigns, as total admissions to PSCs and time to reach ED remain unchanged for both years. The MSCC is an effective forum to provide evidence-based practice for stroke survivors in the community.

The Sleep-stroke Connection

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Background: During obstructive sleep apnea (OSA), the blood supply to the brain is reduced and blood pressure is raised. These changes place the patient at increased risk for ischemic stroke. The mortality rate for patients with stroke and OSA is higher than for those patients with stroke and no OSA. Recent studies show increased mortality, morbidity, and unfavorable clinical outcomes, including poor rehabilitation potential, in stroke patients with OSA. Recommendations from these studies include systematic screening for OSA. As a nationally recognized leader in acute stroke management, our institution treats approximately 600 TIA and ischemic strokes yearly. It was a priority of our institution to implement a plan to meet this recommendation to optimize patient care and reduce risk for recurrent strokes. Method: In collaboration with the Sleep Laboratory, the Saint Luke’s Brain and Stroke Institute implemented an OSA screening protocol for TIA and ischemic stroke patients. The order for Apnea Link screening is a part of the approved admission orders for TIA and ischemic stroke patients. Technicians from the Sleep Laboratory implement the screening test and forward the results to advance practice nurses (APNs) in the Stroke Institute. The APNs discuss the results with the patients, families, and attending physicians. The APN institutes an order for a formal out-patient sleep study for those patients with abnormal results. The Sleep Laboratory follows by scheduling the study with the patient. Results: Over the past ten months, 206 patients received the screening. From the 206 screened patients, 86 patients had normal screens, 23 completed formal studies, 13 are currently scheduled for formal studies, 72 patients refused further studies, and 23 are being followed to schedule a study. Conclusion: Collaborative work by the Pulmonary Service, Sleep Laboratory, and the Stroke Institute resulted in a systematic method to screen the TIA and ischemic stroke patient populations for OSA. The implementation of evidenced based practice at our Stroke Institute resulted in a process that should decrease the incidence of recurrent stroke. Further tactics are needed to increase the number of patients who follow through with the formal sleep study. APNs impact stroke outcomes and contribute to the success of our Stroke Institute.

Can CT Perfusion More Accurately Predict Vasospasm in Subarachnoid Hemorrhage?

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Objective: Patients suffering from aneurysmal subarachnoid hemorrhage (SAH) may experience arterial vasospasm (VS) leading to strokes and worsening outcome. Commonly, Transcranial Doppler ultrasound (TCD) is used to monitor for VS and to indicate angiography. We were interested in study how CT perfusion (CTP) could add to monitor patients for VS. Background: Commonly serial clinical examinations and noninvasive TCD are used to monitor SAH patients for VS even though angiography is still regarded as the gold standard for detecting VP. However, TCD can be misleading patients whose VS occurs in the more distal arterial system of practice that undetectable, relying on unregulated and unconfirmed this diagnostic uncertainty. Methods: CT perfusion (CTP) parameter included cerebral blood flow (CBF) and volume (CBV) as well as the mean transition time (MTT) contrasts requires perfusing the brain. In a blinded fashion, the CTP findings were compared to both TCD and angiography results. Of 100 SAH patients, 92 had both TCD and CTP performed, whereas 47 had CTP/TCD angiography. VP was diagnosed in 24 patients of possible vs VS and only 17 actually vs VS and only 17 actually had the gold standard we found among the patients with VS CFP had a higher sensitivity (i.e., detecting any abnormality; 100% vs 80%) and specificity (i.e., actual presence of VS; 83% vs 33%). Among those who have had no clinical symptoms of VS, the CTP and TCD comparison with angiography identified a sensitivity of 80% for both CTP and TCD, whereas the specificity was 70% and 50%, respectively. Conclusions: The diagnosis of both symptomatic and asymptomatic VS in patients with SAH can be improved using CT perfusion which is a noninvasive and often readily available method. This improvement is likely the result of better detection of distal VS, which can not be easily identified on TCD. Therefore, CTP is routinely performed at our center to diagnose or exclude both symptomatic and asymptomatic vasospasm in patients with SAH.

Interprofessional Stroke Orientation for Community Stroke Rehabilitation Teams

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Background and purpose: The Southwestern Ontario Stroke Strategy and its partners identified a gap in rehabilitation services for stroke survivors after they leave hospital. An innovative proposal to provide integrated, individualized services in a variety of settings was submitted and accepted by the South West Local Health Integration Network providing just under $2 million to develop three new interprofessional Community Stroke Rehabilitation Teams (CSRT). The CSRT are each comprised of an Occupational Therapist, Recreation Therapist, two Rehabilitation Therapists, Registered Nurse, Physiotherapist, Social Worker, and a Speech Language Pathologist. Through their interdisciplinary composition, these teams are a rich resource of knowledge and skills for comprehensive care of the stroke survivor and caregiver. There are few community stroke orientation programs available with an interprofessional focus. This presentation will describe the program we developed. Methods: An interprofessional planning committee selected several areas to guide the development of the orientation: 1) Core stroke knowledge and skills, 2) Working together (interprofessional collaboration [IPC]), 3) Assessment of the community stroke survivor and caregiver, 4) Communication, 5) Working in the community, 6) Caring for the stroke survivor and caregiver. This led to a 10-day orientation addressing the “need-to-know” knowledge and skills, with an emphasis on team building. IPC exercises included role-playing, case studies, and graduated case studies targeted at team member’s response to stroke survivor scenarios. Results: Daily evaluations using a standardized tool indicated the orientation was useful and prepared participants for IPC practice in the community. Participant comments: “I received great information and am beginning to understand the inner workings of this team”. “Team guidelines helped me to recognize the characteristics and strengths of my colleagues”. Situations that challenged participants included role expectations and overlapping professional scope of practice, the mix of regulated and unregulated health care providers, and how to provide efficient and effective care in a large geographical region. Conclusions: Imbedding a culture of IPC within the design of the orientation solidified IPC as a practice expectation and not just a surface concept. The focus on vision and IPC allowed for the development of interprofessional understanding and trust among team members. Through an IPC orientation, the ED and Neuroscience nursing division adopted a policy that each unit will alternate monthly sending a nurse to an interpatient stroke code. We will continue to audit each interpatient stroke code to determine there were no delays in providing acute stroke therapies.

Can CT Perfusion More Accurately Predict Vasospasm in Subarachnoid Hemorrhage?
Using Stroke as an Educational Platform to Expand Neurologic Expertise in Non-neuroscience Nurses Across a Healthcare System

Margaret Stecker, Jobyna D Schuppenuhauer, University Hospis Case Med Ctr, Cleveland, OH; Mary Beth Rauzi, University Hospis Richmed Med Ctr, Richmond Heights, OH; Christine Garrett, University Hospis Bedford Med Ctr, Bedford, OH; Natalie Ruch, Linda Smith, Erin Supan, Leigh Ann McCartney, Cathy Silia; University Hospis Case Med Ctr, Cleveland, OH

Background and Purpose: The University Hospitals Neurological Institute (UHNI) Neuroscience Nursing Practice Center (NNPC) was approached by nursing leaders within the healthcare system to develop a standardized neurological nursing assessment that would target non-neuroscience nurses. As hospitals develop subspecialties, nurses become increasing unprepared and subpar for caring for patients with unfamiliar diagnoses; however, 7-15% of all strokes occur in hospitalized patients, most of whom are post-surgical or post-procedural. The NIH Stroke Scale is used in many stroke units, but as a primary measure of ischemic stroke severity, is limited in its capacity to assess subtle deficits or assess patients with other neurologic emergencies. Method: Nursing leaders at the UHNI Neurosciences leadership and nurse education were endorsed by this resource as critical to the success of these relationships, gaining early spoke facility oversight. It is understood that the nursing leads at the hub and spokes are the primary coordinators of all Telestroke activities.

Results: Learning needs varied considerably across the health system hospitals. Learning objectives were developed to incorporate these needs. A point presentation was generated to teach a basic neurological assessment with a focus on stroke; this included the NIHSS. A Neuro-Education Ambassador Program was offered to nurses managing the health system and participants were identified from the hospitals to attend a regional Train the Trainer retreat. These retreats include an interactive demonstration of how to complete the NIHSS as an added assessment tool. The participants are provided the core presentation along with speaker notes and these Neuro-Education Ambassadors then disseminate the standardized neurological nursing assessment to their system hospitals.

Conclusions: The standardized neurological nursing assessment and the Neuro-Education Ambassador Program were enthusiastically supported by health system nurse leaders. A pre and post test was developed to measure the effectiveness of this program in improving stroke awareness and increasing confidence in the performance of a neurological assessment among non-neuroscience nurses. Future goals of the UHNI-NNPC are to use this infrastructure to develop standardized nursing documentation in an electronic medical record within the healthcare system.

Variations showing p < 0.05 were determined from baseline to follow-up. Variables showing p < 0.01 were significant from all visits to follow-up. Published abstracts and Pags were embargoed for release until date and time of presentation, conference or until embargoed time was reached. Failure to honor embargo policies will result in the abstract being withdrawn and barred from presentation. 2010 International Stroke Conference Poster Presentations e257

Developing a Statewide Strategy to Improve Primary Stroke Center Compliance for Stroke Education

Karen Yarbrugh, UMMC, Baltimore, MD; Rhonda Chatmon, American Heart Association, Baltimore, MD; Maryland Stroke Ctr Consortium

Background: The Joint Commission for Accreditation of Healthcare Organizations (The Joint) has identified performance measure indicators for obtaining Primary Stroke Center (PSC) certification. One performance indicator is to calculate the percentage of stroke and TIA patients who were given educational written materials addressing all of the following: personal risk factors for stroke, signs and symptoms of stroke and activation of EMS, needs for follow up and medications. The Maryland Stroke Center Consortium identified a barrier to achieving >85% statewide compliance with this measure which included; lack of funding to provide written materials. The goal of this performance improvement project was to obtain funding to develop a stroke discharge toolkit meeting PSC requirements and available to all Maryland PSCs. Methods: The MSCC reviewed stroke education performance measure outcome data for 2008 and 2009 from the Get With The Guidelines: Stroke program improvement database. In 2008: only 40.2% of all stroke and TIA patients admitted to a Maryland PSC received written stroke educational materials. Increased compliance occurred in 2009 with 70% of all patients admitted to Maryland PSCs receiving written stroke education material. Overall this reflected an opportunity to improve compliance with the stroke education performance measure in the state of Maryland. A stroke education workgroup of the MSCC partnered with the Maryland Stroke Alliance and American Heart Association and developed a stroke discharge toolkit meeting all PSC requirements. The Maryland Department of Health and Hygiene was identified as a funding source to print the stroke discharge toolkit. Results: Funding was obtained from the Maryland Department of Health and Mental Hygiene to print copies of the stroke discharge toolkit for accessibility to all Maryland PSCs. The stroke discharge toolkit will be available in PDF format on The Stroke Alliance website. Conclusions: Primary Stroke Centers have a stroke discharge toolkit a pilot study of 50 patients measuring patient and family stroke knowledge pre and post implementation of the discharge toolkit will be performed. In addition, measurement of patient and caregiver satisfaction will be obtained. This stroke discharge kit reflects educational requirements of the JC400 and will assist in the standardization for stroke discharge education in the state of Maryland.

Safety & Efficacy of Thrombolysis in Ischemic Stroke Patients Aged 80 Years or Older: Comparison With Less Than 80 Years

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Background: Stroke is a leading cause of death and disability in the elderly. The number of elderly patients with acute ischemic stroke within 12 hours from first abnormal time (FAT), were selected based on our monthly analysis of data we discovered an area for improvement. We were falling below acceptable percentages in this area. Study: We tracked a few months of data and looked at other things we had tried to improve the compliance that had, essentially, failed. ACT: We created a web alert through WEB VS targeting the physicians caring for the patient. This proved to improve the quality of care we deliver to out stroke patients. Conclusion: We have gone from a low compliance of about 15% to about 70% of all patients receive stroke education material. The stroke nurses were responsible for sending a web alert if the patient had not had a lipid panel drawn or if the patient’s LDL is above 100. We decided to try the web alert method for a few months, monitor the progress, then reanalyze our data to determine if the change was improving. We selected this project as it is a simple way to improve the quality of care we deliver to our patients. We noticed we had two different populations of patients; those who were still very young and the younger than 80 years. We believe the older group was more likely to have high cholesterol levels (100+). The adjusted OR of thromboysis in patients aged 80 years or older versus younger than 80 years ranged between 5-10 and < 80 years and the heterogeneity of these ORs between two age groups were examined. Patients showing p < 0.25 between patients with and without thrombolysis were selected for...
adjustments. Results: A total of 1195 patients met our eligibility criteria. Two-hundred seventy-one patients (22.6%) received thrombolyis (intravenous thrombolysis, 94; intraarterial, 80; and combined, 97). Among 219 patients ≥80 years (18.3%), 46 received thrombolysis; and among 980 < 80 years (61.7%), 225 (23%) did. Thrombolysis morbidity did not differ by age group. With respect to NIH, the adjusted OR was 2.57 (95% confidence interval, 1.20 to 2.67) in those ≤80 years, and 4.52 (1.67 to 12.25) in those <80 years. There was no heterogeneity of ORs between 2 age groups (P = 0.86). Adjustments were done for initial NIH stroke scale, blood pressure, diabetes, prior antipatelet use, prior anticoagulant use, FAT to arrival, and stroke subtype (TOAST classification). For assessing efficacy, we further excluded 52 patients because mRS was not available. With respect to favorable mRS, the adjusted OR was 1.61 (1.58 to 4.49) in those <80 years, and 1.71 (1.05 to 2.78) in those ≥80 years. There was also no heterogeneity of ORs (P = 0.91). Adjustments were done for initial NIH stroke scale, prestroke mRS, blood pressure, fasting blood glucose, diabetes, atrial fibrillation, FAT to arrival, and stroke subtype. Conclusion: This study shows that thrombolysis may be safe and effective in ischimic stroke patients ≥80 years compared to those <80 years. Thrombolysis should be considered as a therapeutic option even in the elderly stroke patients.

Introduction: Several studies have suggested that MRI has the potential to be the first decision-making indication for thrombolytic therapy in hyper-acute ischemic stroke. Diffusion-weighted MRI (DWI) is superior to CT in terms of evaluating deep white matter, but it is unclear whether deep white matter lesions on DWI (DWI-W) has different impact on patients clinical recovery after intravenous tissue plasminogen activator thrombolyis (iv-PA). Hypothesis: DWI findings can predict clinical recovery after iv-PA in patients with hyperacute stroke. Methods: Eighty-three consecutive patients with hyperacute anterior circulation ischemic stroke were enrolled. All patients underwent MRI within 3 hours and received iv-PA. A relationship between Alberta Stroke Programme Early CT Score (ASPECTS) on DWI (DWI-ASPECTS), DWI-W, early dramatic improvement (a ≥ 10-point reduction in the total NIHSS score or a total NIHSS score of 0-2 after 24 hours), early improvement (a > 4-point reduction in the total NIHSS score after 24 hours), worsening (a < 4-point increase in the total NIHSS score after 24 hours) were assessed. Results: The median (range) of the baseline DWI ASPECTS value was 9 (5-10) and DWI-W was found in 36 (43%) patients. Patients with early dramatic improvement had shorter time from onset to iv-PA (116.1 ± 54.9 vs 133.2 ± 33.1 min, P = 0.0281), higher grade of DWI-ASPECTS (9.2 ± 0.9 vs 8.4 ± 1.6, P = 0.0157). DWI-W were less frequently seen in patients with than without early dramatic improvement (26% vs 54%, P = 0.0215). Multivariate logistic regression analysis demonstrated that absence of DWI-W (OR 1.60, 95% CI 1.08-2.31, P = 0.0279), higher ASPECTS (OR 1.56, 95% CI 1.06-2.46, P = 0.0346) and shorter time from onset to iv-PA (OR 0.98, 95% CI 0.97-0.99, P = 0.0429) were independent predictors of early dramatic improvement, respectively. Conclusion: DWI-ASPECTS and DWI-W lesion appear to be useful tools for predicting early dramatic improvement.

Introduction: The malignant profile was defined by the DEFUSE group as an MRI pattern associated with symptomatic intracranial hemorrhage (siCH) and poor clinical outcome following early reperfusion. We assessed the outcomes of patients with the Malignant profile, based on the presence or absence of reperfusion, in the combined DEFUSE-EPITHET database. Methods: In the DEFUSE and EPITHET studies a baseline MRI was obtained prior to treatment with IV PA or placebo in the 3-6 hour time window. In order to standardize PWI processing, baseline PWI scans from both studies (N = 174) were reprocessed using an automated software program (RAPID). Baseline DWI volumes and reperfusion status determined in the original studies were used for this analysis. The Malignant profile was defined as originally proposed in DEFUSE as a baseline DWI lesion >100mL and/or a PWI lesion of >100mL using Tmax delay ≥8 seconds. Mismatch was defined as a PWI lesion that was 10 mL or more and >120% of the DWI lesion. Poor outcome was defined as a modified Rankin score of 5 or 6 at 90 days and/or death. Odds ratios for achieving poor outcome in association with reperfusion were assessed for patients with the Malignant profile and compared with all other patients with a PWI/DWI mismatch (Target Mismatch profile). Results: 121 patients were included in this analysis; 26 Malignant profile, 84 Target Mismatch, 11 No mismatch. Of the Malignant profile patients who repurfsed, 83% (5/6) had poor outcome compared to 50% (10/20) of Malignant patients who did not repurfsed (OR 5.0, P = 0.019). There was a significant reduction in the odds of poor outcome in Target Mismatch patients who experienced reperfusion (OR 0.16, P = 0.013). Of the OR for poor outcome based on reperfusion status differed significantly between patients with the Malignant profile and Target Mismatch profile (P = 0.01). Conclusion: As originally defined, the Malignant Profile appears to identify patients who do not benefit and may be harmed from early reperfusion. Reperfusion of large volumes of severely ischimic tissue may result in brain hemorrhage or extensive edema. In contrast, reperfusion is associated with a significantly reduced rate of poor outcome among patients with the Target Mismatch profile. Identification of optimal imaging thresholds for defining the Malignant profile is important because excluding these patients from reperfusion therapies may improve outcomes.

Introduction: The PENUMBRA Pivotal Stroke Trial showed that despite high rates of recanalization with the PENUMBRA system in patients with acute ischemic stroke (IS), dispositionally poor functional outcomes were documented at three months following treatment. The study design did not require a control arm and the safety and outcomes of PENUMBRA were descriptively compared to historic controls from other trials of acute recanalization therapies. We aimed to analyze recanalization rates, symptomatic intracranial hemorrhage (siCH), mortality and favorable functional outcome rates between patients enrolled in PENUMBRA and patients treated with iv-PA who were enrolled in the control arm of two randomized trials (CLOTBUST and TUCSON). Subjects & Methods: Control patients (treated with intravenous thrombolysis and intermittent ultrasound surveillance of vessel patency) with NIHSS ≥12 and non-protocol MALIGNANT profiles were compared in terms of age, baseline NIHSS-score, recanalization, siCH, 3-month mortality and favorable functional outcome at three months. siCH was defined using PENUMBRA Trial definition as imaging evidence of ICH with chronic worsening (NIHSS >3) within 24 hours from stroke onset. Persisting occlusion, partial and complete recanalization were defined on the basis of baseline mismatch scores predicted by PWI-DWI mismatch score compared to TMI data from PENUMBRA. Favorable functional outcome was defined as a modified Rankin Scale (mRS) score of 0-2. Results: Baseline stroke severity was similar between patients enrolled in PENUMBRA (mean NIHSS-score 17.6 ± 5.2 points, n = 123) and historic controls (NIHSS 16.3 ± 5.3 points, n = 168; P = 0.101). The control group was older compared to PENUMBRA trial (88 ± 15 years vs 63.5 ± 13.5years; P = 0.01). Time to treatment initiation was on average 2 hours later (2.3 ± 0.6 hrs vs 4.3 ± 1.5 hrs; P = 0.001) in PENUMBRA. The rate of any recanalization after treatment with PENUMBRA was higher than following intravenous thrombolysis [82% (54%TIMI 2 and 27% TIMI 3) vs 39% (partial 25% complete recanalization); P < 0.001]. The rate of siCH tended to be higher with PENUMBRA (11.2% vs 4.4%; P = 0.182 by Fishers exact test). Mortality at three months was higher with PENUMBRA (32.8% vs 14.1%; P = 0.006) and favorable functional outcome rate that was higher in historic controls (39.1% vs 25.0%; P = 0.038). Conclusions: Recanalization in patients treated with PENUMBRA system via systemic thrombolysis achieved better functional outcomes likely due to earlier treatment initiation. These data support the fact that currently no evidence exists that within 3 hours from symptom onset primary intra-arterial recanalization could be any better than systemic IVPA.
90 minutes of symptom onset demonstrated the greatest benefit. The time frame for maximum benefit among ischemic stroke patients treated with intra-arterial thrombolysis is controversial.

Methods: From January 2005 to June 2009, consecutive patients with acute ischemic stroke who underwent emergent endovascular intervention were included. Patients were stratified into quartiles based on the time interval between symptom onset and microatherectomy placement at the site of occlusion. Patient characteristics and outcomes were compared between quartiles including age, admission National Institutes of Health Stroke Scale score (NIHSS), discharge NIHSS, discharge modified Rankin scale (mRS), and in-hospital mortality. Results: A total 101 patients (54 women; mean age: ± standard deviation 68.6 ± 13.8years) with a baseline NIHSS 15.5 were included in the analysis. Discharge NIHSS, NIHSS improvement rate, discharge mRS and mortality results are presented in the table below according to quartiles of time interval between symptom onset and initiation of treatment.

<table>
<thead>
<tr>
<th>Time interval between symptom onset and treatment (minutes)</th>
<th>Number of patients</th>
<th>Age (mean ± SD)</th>
<th>NIHSS at baseline (mean ± SD)</th>
<th>NIHSS improvement (points)</th>
<th>Mortality</th>
<th>NIHSS 0-2</th>
<th>Discharge mRS</th>
<th>Discharge mRS 0-2</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>116-212</td>
<td>24</td>
<td>65.7 ± 12.3</td>
<td>17.2 ± 6.4</td>
<td>13.2 ± 4.5</td>
<td>0.09</td>
<td>16 (66.7%)</td>
<td>9 (37.0%)</td>
<td>3 (12.5%)</td>
<td></td>
</tr>
<tr>
<td>213-288</td>
<td>26</td>
<td>63.3 ± 13.9</td>
<td>14.8 ± 5.3</td>
<td>8.9 ± 13.4</td>
<td>0.01</td>
<td>19 (73.1%)</td>
<td>15 (57.7%)</td>
<td>4 (15.4%)</td>
<td></td>
</tr>
<tr>
<td>292-368</td>
<td>25</td>
<td>70.3 ± 13.4</td>
<td>14.9 ± 10.6</td>
<td>10 ± 12.4</td>
<td>0.003</td>
<td>15 (60.0%)</td>
<td>7 (28.0%)</td>
<td>4 (16.0%)</td>
<td></td>
</tr>
<tr>
<td>370-1100</td>
<td>26</td>
<td>69.4 ± 18.3</td>
<td>14.7 ± 7.1</td>
<td>18 ± 4.1</td>
<td>0.12</td>
<td>13 (50.0%)</td>
<td>6 (23.1%)</td>
<td>3 (11.6%)</td>
<td>0.305</td>
</tr>
</tbody>
</table>

There were no significant differences in clinical outcomes within the first three quartiles. Those patients treated after 368 minutes from stroke onset, had significantly lower rate of discharge mRS 0-2 (p < 0.01), lower rate of NIHSS improvement ≥ 4 points or return to zero (p < 0.049), and higher discharge NIHSS (p < 0.005) when compared with the other quartiles.

Conclusion: In our analysis, there was a prominent reduction in clinical benefit among patients treated with endovascular treatment after 6 hours compared with those treated at earlier time intervals between symptom onset and treatment mandating careful assessment of the “late thrombolyis” concept.

P18

Bridging IV-IA Rescue Increases Recanalization and Likelihood of Good Outcome in Non-Responder IV-PA Treated Patients: A Case-Control Study

Martí Rubiera, Marc Ribo, Jorge Pagola, Francisco Romero, Olga Maisterra, David Rodríguez-Luna, José Álvarez-Sabin, Carlos Molina; Hosp Vall d’Hebron, Barcelona, Spain

In the last few years, there has been a great development of intraarterial (IA) reperfusion therapies for the treatment of acute ischemic stroke. However, there’s still debate about the safety and efficacy of the “bridging therapy”: the IA reperfusion rescue for non-responders intravenous (IV) PA treated patients. Our aim was to compare recanalization rates, early clinical course and long-term outcome in IV and bridging IV-NA rescue thrombolysis using a case-control approach.

Patients & Methods: We studied consecutive stroke patients with a proximal acute intracranial occlusion who received IA reperfusion procedures (IA PA / mechanical thrombus disruption / thrombectomy) after unsuccessful IV thrombolysis (IV-NA group). Unsuccessful IV thrombolysis was defined as lack of clinical improvement and arterial mechanical thrombus disruption / thrombectomy) after unsuccessful IV thrombolysis (IV-IA group). Unsuccessful IV thrombolysis was defined as lack of clinical improvement and arterial mechanical thrombus disruption / thrombectomy) after unsuccessful IV thrombolysis (IV-IA group). Unsuccessful IV thrombolysis was defined as lack of clinical improvement and arterial mechanical thrombus disruption / thrombectomy) after unsuccessful IV thrombolysis (IV-IA group). Unsuccessful IV thrombolysis was defined as lack of clinical improvement and arterial mechanical thrombus disruption / thrombectomy) after unsuccessful IV thrombolysis (IV-IA group).

Stroke characteristics and outcomes

<table>
<thead>
<tr>
<th>IVT &lt; 3 hrs + IAT</th>
<th>(n = 123)</th>
<th>IVT3-4.5 hrs + IAT</th>
<th>(n = 18)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admit blood glucose (mg/dl)</td>
<td>137.0 ± 50.1</td>
<td>134.3 ± 59.8</td>
<td>0.827</td>
<td></td>
</tr>
<tr>
<td>Baseline NIHSS median</td>
<td>18 (2–39)</td>
<td>18 (6–31)</td>
<td>0.629</td>
<td></td>
</tr>
<tr>
<td>Onset to IAT (min)</td>
<td>124.2 ± 31.9</td>
<td>210.4 ± 35.5</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Onset to IAT (min)</td>
<td>323.9 ± 273.4</td>
<td>425.9 ± 268.3</td>
<td>0.141</td>
<td></td>
</tr>
<tr>
<td>Mechanical embolus retrieval</td>
<td>34 (27.6%)</td>
<td>5 (27.8%)</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Final mTICI ≥ 2b</td>
<td>74 (60.2%)</td>
<td>8 (44.4%)</td>
<td>0.306</td>
<td></td>
</tr>
<tr>
<td>Discharge mRS 0-3</td>
<td>48 (39.0%)</td>
<td>1 (5.6%)</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>Symptomatic ICH</td>
<td>10 (8.1%)</td>
<td>1 (5.6%)</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>15 (12.2%)</td>
<td>5 (27.8%)</td>
<td>0.138</td>
<td></td>
</tr>
</tbody>
</table>

Background: The ECASS-3 study concluded that IV t-PA (IVT) was safe and effective when administered between 3 and 4.5 hrs from symptom onset. Several prior studies report low recanalization rates after IVT for large artery occlusions; many such patients are treated with intra-arterial therapy (IAT). We assessed bridging IVT beyond 3 hrs from symptom onset in patients who then receive IAT. Methods: We identified patients from our stroke registry who received IVT (0.9 mg/kg I-PA) and IAT for acute anterior circulation stroke from 1998 to 2008. We excluded patients who received GP IIb/IIIa inhibitors. Demographics, baseline NIHSS, recanalization rates (mTICI score ≥ 2b), mortality, symptomatic ICH (sICH), and discharge mRS were collected. No mismatch imaging criteria were used for selection. We compared patients who received IVT within 3 hours of symptom onset (IVT < 3 hrs) versus those who received ‘off label’ IVT between 3 to 4.5 hrs (IVT3-4.5). Results: 141 patients received IVT/IAT with 123 receiving IVT within 3 hrs and 18 between 3 to 4.5 hrs from onset. Both groups had similar age, gender distribution, stroke risk factors, admission blood glucose, baseline NIHSS and rates of mechanical embolus retrieval. Patients in the IVT 4.5 group had lower rates of recanalization and higher mortality, but these differences were not statistically significant. Patients in the IVT < 3 group had significantly better outcomes (mRS 0-3) despite equal rates of sICH. On multivariate regression analysis, controlling for stroke risk factors, time to IAT, baseline NIHSS and recanalization, IVT bridging within 3 hours remained an independent predictor of good outcome (OR 5.6, 95% CI 1.34, 7.683). Conclusions: Bridging IVT within 3 hrs of symptom onset compared with 3 to 4.5 hrs leads to better outcome. Very few IVT3-4.5 patients achieved a good outcome and mortality was high. This analysis is limited by a small sample number. Future prospective studies are needed to validate these results. Better methods are also needed to identify patients who may benefit from Bridging IVT3-4.5hrs.

2010 International Stroke Conference Poster Presentations

P20

Temporary Endovascular Bypass in Acute Stroke: Experience After 50 Patients

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Introduction: In addition to well-established therapeutic strategies such as local intra-arterial fibrinolysis (LIF) and mechanical thrombectomy (MT), the use of stents is receiving increasing attention as a potentially useful tool in the setting of acute thromboembolic stroke. The obvious benefit of immediate reperfusion after stenting may possibly be outweighed by an increase in the rate of hemorrhage with double antiplatelet medication, however. Thus, usage of a temporary endovascular bypass followed by stent retrieval appears desirable. Patients and Methods: Between 03/2008 and 05/2009 a total of 53 target lesions in 50 Patients experiencing thromboembolic stroke have been treated by endovascular means involving the application of a fully retrievable self expandable nitinol stent (Solitaire, ev3) in one center. The Stent, previously approved for aneurysm bridging, recently received CE-mark for stroke treatment. The Solitaire was used in conjunction with rTPA in 24/50 and after failed attempts of MTE with approved devices (MERCI, Penumbra, and phenox) in 21/50. In 29/50, the Solitaire was used as at first line including simultaneous placement of a Penumbra aspiration/distal access catheter, in 21/50 patients it was the only device. In 32/50 patients the stent had to be placed more than once with a max of 5 redeployments. The stent was used at least for partial retrieval of the clot in 34/53 and was permanently implanted in 6 cases. There were 4 adverse events, none of which were related to the use of the stent (microwire perforation or access vessel
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dissection). Results: In 39/53 lesions immediate distal recanalization (TICI 2a or better) was seen after stent deployment. The final rates of recanalization were 75.5% for TICI 2b and 3 results and 86.6% for all TICI 2/3. The average angio-to-recuperpation time (ART) was 48.7min with the Solitaire opposed to 68min in patients treated without the stent (p = 0.021) during the same time period. Its first line was reduced ART but did not improve outcomes (p = 0.1187). Due to the nature of a case series, mRS at 90-day follow could not be obtained in enough patients to prove any clinical benefit attributable to the technique in comparison to our own database of 150 endovascular stroke treatments. The only patients that exhibited significant immediate NIHSS improvement (>4 points) were those with mca-occlusion (p = 0.019). Conclusion: This temporary endovascular bypass technique with a retrievable stent is a versatile asset to the armamentarium of endovascular stroke treatment. It allows for immediate flow restoration thus potentially enhancing the effect of iv- and ia lytics without the necessity of long term antithrombosis. From our series of 50 patients we conclude that the angiographic results are at least equal to any of the approved MTE devices with a high rate of TICI 2b/3 recanlization and that ART can be drastically reduced with this technique.

**P21**

Combined Cardiac Catheterization and Therapeutic Hypothermia Following Cardiac Arrest Is Feasible and Safe
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Introduction: Mild therapeutic hypothermia (MTH) has been associated with potential adverse events, including cardiac dysrhythmias, coagulopathy and infection. Many cardiac arrest patients undergo cardiac catheterization with percutaneous coronary intervention (PCI); however the safety and feasibility of this combined therapy remains unclear. Hypothesis: We assessed the safety and feasibility of combined MTH and cardiac catheterization for the treatment of cardiac arrest.

Methods: Single-center cohort study of 90 patients treated with MTH within a six-hour window following cardiac arrest and restoration of spontaneous circulation who remained unresponsive on admission. Thirty-six subjects (40%) underwent cardiac catheterization; of these, 20 underwent PCI. Those undergoing PCI were compared to the 70 patients who underwent MTH without PCI. The primary endpoint was the rate of dysrhythmias, asymptomatic or serious. Secondary end points were good neurologic outcome at discharge, the rate of adverse events (dysrhythmia, coagulopathy, hypothermia and infection) and mortality. Results: PCI that took place before the patients were completely rewarmed were included. Patients who underwent PCI plus MTH suffered more adverse events, but this did not reach statistical significance (55% vs. 31%, p = 0.054) in comparison with the patients who received only MTH. No significant difference was found in the rates of cardiac dysrhythmias (30% vs. 19%, p = 0.269), infection (5% vs. 5.7%, p = 0.90), coagulopathy (1% vs. 4%, p = 0.90) or hypothermia (5% vs. 7%, p = 0.08). The PCI plus MTH group achieved similar neurological outcomes: modified Rankin Scale ≤3 (30% vs. 22%, p = 0.42) and survival (40% vs. 30%, p = 0.40). PCI did not affect the speed of inducing MTH (time to target temperature 4hrs vs. 5hrs; p = 0.29).

Conclusions: Cardiac catheterization with or without PCI is feasible and safe when combined with MTH, and is not associated with increased cardiac or neurological risk.

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**P22**

Failure of Mechanical Clot Retrieval to Affect Poor Outcome Associated With Large Thrombus Burden
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Dallas, TX; Rohan Arora, Drexel Univ, Philadelphia, PA; P. Roc Chen, Nusrat Harun, Sean I Savitz; Univ of Texas - Houston, Houston, TX

Background and Purpose: Previous studies have found that large intra-arterial (IA) thrombi (e.g. grade 4) are associated with longer procedure duration and poor clinical outcomes in patients that undergo endovascular therapy for acute ischemic stroke ). However, no studies have yet determined whether mechanical clot retrieval improves procedure time, recanalization rates and clinical outcome compared to previous medical and/or mechanical techniques.

Methods: A retrospective review of our IA treatment stroke database included procedure time, recanalization, symptomatic intracranial hemorrhage (sICH), poor outcome (discharge modified Rankin Score &gt;4) and mortality. Only patients with modified Thrombolysis in Myocardial Infarction thrombus grades of 4 were included (large thrombus, &gt;2 vessel diameters) → /− Merci retriever deployment. Cases that employed the Penumbra aspiration device were excluded.

Results: Data were collected on 100 patients with grade 4 thrombi (29 Merci, 71 non-Merci). Both groups had similar baseline NIHSS scores, age, vascular risk factors and location of arterial occlusion. Neopten patients showed no benefit (e96% vs. 52%, p = 0.122) and had longer (median, range) procedure durations (140, 35-300 minutes vs. 110, 37-415, p = 0.021) compared to non-Merci. There were no differences in rates of sICH (5.9% vs. 2.2%, p = 0.626) or mortality (38% vs. 25%, p = 0.269), between Merci and non-Merci cases. Multivariate analysis adjusted for age, baseline NIHSS and artery of involvement showed that use of the Merci device was independently associated with poor outcome (OR=5.43; 95% CI, 1.08-27.4; p = 0.041).

Conclusion: In this retrospective study, we find that newer thrombectomy devices do not affect poor outcomes from grade 4 thrombosis. In fact, the use of the MERCI device seemed to actually worsen outcomes in these patients compared to other endovascular approaches. More research is needed to develop effective endovascular treatments and devices to improve outcome in these unfortunate patients.

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**P23**

Bringing Forward Reperfusion With Oxygenated Blood Perfusion Beyond Arterial Occlusion During Endovascular Procedures in Acute Ischemic Stroke Patients
Marc Ribo, Carlos Molina, Marta Rubiera, Jorge Pagola, David Rodríguez-Luna, Pilar Meier, Alan Flores, José Alvarez-Sabín; Hosp Vall dHebron, Barcelona, Spain

Background: The high rates of arterial recanalization achieved with endovascular procedures are not always accompanied by the expected clinical improvement. The fact that most of these procedures are time consuming implies a delayed reperfusion of the penumbral tissue despite the capacity of earlier microcatheter access to the ischemic tissue beyond the clot. We aimed to explore the safety and feasibility of microcatheter driven oxygenated blood perfusion (MOB) beyond the occluding clot. Methods: We studied consecutive acute stroke patients undergoing endovascular procedures. Timing of all procedural steps was recorded. We then explored the safety and feasibility of repeated injections of oxygenated blood directly obtained from the femoral artery at the moment. After post-occlusion patency was angiographically confirmed, oxygenated blood was manually injected through the microcatheter beyond the occlusion every time the clot was crossed. Pre and post perfusion flow was continuously monitored with TCD.

Results: We studied 42 consecutive patients undergoing urgent endovascular procedures (mean age 69 ± 12; median NIHSS 19 (18-21) of them 25 patients (60%) received iv tPA prior to endovascular procedure. The occluded arteries were: MCA (n=21), ICA (n=13), basilar artery (n=6) and PCA (n=2). The recorded time frames were: symptomatic to arterial puncture: 206±120 minutes, arterial puncture to clot: 28:22 minutes. The occluding clot was successfully crossed with the microcatheter with distal branches patency confirmation in 33 patients (78%). Recanalization could be achieved in 30 cases (71.4%) in a mean time from symptoms onset of 326±108 minutes. The mean time from first clot-crossing to recanalization/endpoint of procedure was 113±79 minutes. Repeated manual injections of MOB were performed in 10 patients. Patients with/without MOB presented similar baseline characteristics. Median number of MOB injections was 3 (8-24) and the mean injected blood volume was 28±12 ml. During MOB a non-pulsatile flow appeared in previously non visible distal branches. Median number of MOB injections was 3 (IR:2-4) and the mean injected blood volume was 28±12 ml. During MOB a non-pulsatile flow appeared in previously non visible distal branches. Median number of MOB injections was 3 (IR:2-4) and the mean injected blood volume was 28±12 ml. During MOB a non-pulsatile flow appeared in previously non visible distal branches. Median number of MOB injections was 3 (IR:2-4) and the mean injected blood volume was 28±12 ml. During MOB a non-pulsatile flow appeared in previously non visible distal branches. Median number of MOB injections was 3 (IR:2-4) and the mean injected blood volume was 28±12 ml. During MOB a non-pulsatile flow appeared in previously non visible distal branches. Median number of MOB injections was 3 (IR:2-4) and the mean injected blood volume was 28±12 ml. During MOB a non-pulsatile flow appeared in previously non visible distal branches. Median number of MOB injections was 3 (IR:2-4) and the mean injected blood volume was 28±12 ml. During MOB a non-pulsatile flow appeared in previously non visible distal branches. Median number of MOB injections was 3 (IR:2-4) and the mean injected blood volume was 28±12 ml. During MOB a non-pulsatile flow appeared in previously non visible distal branches. Median number of MOB injections was 3 (IR:2-4) and the mean injected blood volume was 28±12 ml. During MOB a non-pulsatile flow appeared in previously non visible distal branches. Median number of MOB injections was 3 (IR:2-4) and the mean injected blood volume was 28±12 ml. During MOB a non-pulsatile flow appeared in previously non visible distal branches. Median number of MOB injections was 3 (IR:2-4) and the mean injected blood volume was 28±12 ml. During MOB a non-pulsatile flow appeared in previously non visible distal branches. Median number of MOB injections was 3 (IR:2-4) and the mean injected blood volume was 28±12 ml. During MOB a non-pulsatile flow appeared in previously non visible distal branches. Median number of MOB injections was 3 (IR:2-4) and the mean injected blood volume was 28±12 ml. During MOB a non-pulsatile flow appeared in previously non visible distal branches.

Conclusions: Microcatheter driven autologous oxygenated blood perfusion beyond the occluding clot seems a safe procedure feasible in more than ¾ of acute stroke patients undergoing endovascular procedures. MOB may intermittently advance reperfusion up to 2 hours until final recanalization is achieved.
Validation of Transcranial Doppler Criteria for Possible Rescue Interventional Therapy: A Multiple Center Prospective Study

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Background: We previously derived Transcranial Doppler (TCD) criteria for angiographic lesion that required interventional therapy (affected MCA mean flow velocity/affected MCA MFV <0.6). Objective: To validate our criteria in prospective cohort study of acute stroke patients enrolled from multiple stroke centers. Methods: Patients presented with acute stroke and ultrasound TCD was performed. Low-dose alteplase administration was started before and in a blind fashion to vascular gold standard test (e.g.,Digital subtraction angiography (DSA), MR angiography (MRA) or CT angiography (CTA)). Mean flow velocity (MFV) of proximal MCA (>65 mm depth) at occlusions site was measured with corresponding MFV of contralateral MCA. If affected MCA MFV < unaffected MCA MFV (aMCA MFV/aMCA MFV) ratio was < 0.6, proximal occlusion was suspected. Result: Seventy five patients underwent emergency TCD and vascular imaging for an acute/subacute stroke assessment. Mean age: 62 ± 14, Male: 81 %. Baseline NIHSS 16 (Inter Quartile (IQ) range: 8-20), Median time to TCD was 5.5 hours (0-2.10), Median time to global standard vascular imaging was 8 hours. Out of 59 (92 %) had aMCA MFV/aMCA MFV ratio < 0.6. Where as only one patient (1.6 %) had ratio > 0.6 and did not have proximal arterial occlusion that require reactivation. Conclusion: This was a cohort study of an acute stroke patient toward neurological improvement in group A + C than in group B. Brain death occurred in 0.6 % patients. Symptomatic hemorrhage did not arise in any patients that group A + C. The agreement between our previously proposed TCD with aMCA/aMCA ratio < 0.6 and gold standard vascular imaging was very good (Kappa: 0.6, P<0.001) Conclusion: Our emergency TCD criteria for rescue therapy is valid. TCD can be used as screening tool for proximal intracranial occlusion that may require interventional approach.

Valuation of Doppler Criteria for Predicting sICH in Patients With Acute Proximal Occlusions: Data From Randomized Trials

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Background: We previously derived Transcranial Doppler (TCD) criteria for angiographic lesion that required interventional therapy (affected MCA mean flow velocity/affected MCA MFV <0.6). Objective: To validate our criteria in prospective cohort study of acute stroke patients enrolled from multiple stroke centers. Methods: Patients presented with acute stroke and ultrasound TCD was performed. Low-dose alteplase administration was started before and in a blind fashion to vascular gold standard test (e.g.,Digital subtraction angiography (DSA), MR angiography (MRA) or CT angiography (CTA)). Mean flow velocity (MFV) of proximal MCA (>65 mm depth) at occlusions site was measured with corresponding MFV of contralateral MCA. If affected MCA MFV < unaffected MCA MFV (aMCA MFV/aMCA MFV) ratio was < 0.6, proximal occlusion was suspected. Result: Seventy five patients underwent emergency TCD and vascular imaging for an acute/subacute stroke assessment. Mean age: 62 ± 14, Male: 81 %. Baseline NIHSS 16 (Inter Quartile (IQ) range: 8-20), Median time to TCD was 5.5 hours (0-2.10), Median time to global standard vascular imaging was 8 hours. Out of 59 (92 %) had aMCA MFV/aMCA MFV ratio < 0.6. Where as only one patient (1.6 %) had ratio > 0.6 and did not have proximal arterial occlusion that require reactivation. Conclusion: This was a cohort study of an acute stroke patient toward neurological improvement in group A + C than in group B. Brain death occurred in 0.6 % patients. Symptomatic hemorrhage did not arise in any patients that group A + C. The agreement between our previously proposed TCD with aMCA/aMCA ratio < 0.6 and gold standard vascular imaging was very good (Kappa: 0.6, P<0.001) Conclusion: Our emergency TCD criteria for rescue therapy is valid. TCD can be used as screening tool for proximal intracranial occlusion that may require interventional approach.

Cilostazol Inhibits Early Neurological Deterioration in Patients With Acute Ischemic Stroke

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Introduction: Although aspirin is widely recommended as a treatment for acute ischemic stroke, the effect of aspirin on stroke outcome is modest. Furthermore, early neurological deterioration occasionally arises in patients with acute ischemic stroke despite antithrombotic treatment. Cilostazol, a phosphodiesterase 3 inhibitor and antiplatelet agent, is approved in Japan for secondary prevention in stroke patients during the chronic phase. Cilostazol improves cerebral blood flow not only by inhibiting platelet activation but also by increasing vasodilatation, and therefore might exert favorable effects on patients with acute ischemic stroke. Patients and Methods: We randomized study compared the effects of oral aspirin (300 mg daily) alone (group A) or cilostazol (200 mg daily) (group A+C) for 14 days administered within 48 hours of stroke onset to patients admitted to our hospital with non-cardioembolic stroke. Patients with dysphoria or disorders in consciousness that preceded oral drug administration and prior treatment with any antithrombotic drugs were excluded. We assessed neurological symptoms using the NIH stroke scale (NIHSS) before and after 14 days of drug administration. Acute ischemic stroke was confirmed in all patients by brain MRI including diffusion weighted imaging. No other antithrombotic drugs were administered during the observation period unless neurological deterioration (NIHSS > 2) occurred. Results: Sixty-eight patients were enrolled in the study. One patient each was withdrawn from group A due to erupption and gastrointestinal bleeding, and one with eruption and two with palpitation were withdrawn from group A+C. Symptomatic hemorrhage did not arise in any patients in group A or group A+C. Symptomatic hemorrhage was frequently during the observation period in group A than group A+C (28% vs. 6%; p = 0.043).Fishers exact probability test). Among the patients without neurological deterioration during the observation period, 14 days, the mean value of the change in the NIHSS also tended to be greater toward neurological improvement in group A + C than in group A (1.86 0.15 vs. 1.30 0.12; p = 0.089.Students t-test). Conclusion: Patients treated with aspirin plus cilostazol during the acute phase of stroke had less neurological deterioration and more rapid neurological improvement than those treated with aspirin alone. Cilostazol might inhibit early neurological deterioration and promote neurological improvement in patients with acute ischemic stroke.

C-reactive Protein and Its Pharmacologic Reduction as Predictor of Outcome in the Early Treatment With Aspirin and Extended-release Dipyridamole versus Low Dose Aspirin Alone for TIA/Ischemic Stroke Within 24 Hour of Symptom-onset (EARLY-Trial)

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Introduction: Acute ischemic stroke triggers an inflammatory response that is associated with an increase of C-reactive protein (CRP). We compared the effect of early initiation of ASA and ER-DP versus early 100mg ASA in patients presenting with TIA or ischemic stroke within 24 hours following symptom onset. HYPOTHESIS: We did not hypothesize that increase in inflammatory markers correlate with outcome and that treatment with ASA + ER-DP will reduce inflammation in reduced hostile response compared to ASA alone. We did investigate patients after ischemic stroke in 46 certified German stroke units. Patients were randomized either to open label ASA + ER-DP or 100mg ASA alone within 24 hours following TIA or ischemic stroke. After 7 days of initial treatment, all patients were treated for up to 90 days with open label ASA+ER-DP. Primary endpoint was the centralized, blinded assessment of mRS at 90 days by a standardized telephone interview. Blood samples for inflammatory markers were taken on admission and day 7 for hsCRP, MCP-1 and MMP-9 measurements (log-transformed for analysis). Results: A multiple logistic regression model was applied to investigate the impact of early treatment, stroke severity at baseline (NIHSS), weight, systolic blood pressure, diabetes, previous stroke, baseline hsCRP and change at day 7. A total of 425 patients with TIA/stroke were analyzed in this model. Baseline hsCRP levels >5mg/L were identified as independent predictor of poor outcome (OR 4.0; 95% CI 2.0-8.0, adjusted for other factors in the model). Also increases of hsCRP within the first 7 days were detrimental for the outcome (adjusted OR 0.7; CI 0.5-0.8). Patients with severe strokes (NIHSS > 5) treated with ASA + ER-DP only showed a moderate increase in hsCRP compared to patients treated with ASA in which hsCRP was more than doubled (p<0.01), which correlated with improved outcome at 90 days in patients treated with ASA + ER-DP. Furthermore MMP-9 levels showed a non-significant trend downward in patients treated with ASA + ER-DP particularly in patients 70 years, while it was increased in the ASA treated group (p = 0.065). Conclusions: In the EARLY trial baseline as well as hsCRP plasma level at day 7 were identified as independent predictors of poor outcome at 3 months following TIA/stroke. In patients with severe strokes the changes in hsCRP plasma level were found significantly different between treatments. Pharmacological intervention with ASA + ER-DP showed reduced elevation of hsCRP in severe strokes when compared to initial ASA treatment. Similarly MMP-9 increased in elderly patients treated with ASA, which was discussed as indicator for higher risk of bleeding, while treatment with ASA + ER-DP did not show increase of hsCRP. Further studies and case-control studies indicate that ASA + ER-DP provides a wider range of protection than inhibition of platelets (Clinical Trials.gov number: NCT00562588).
Inflammatory Markers Changed Over Time After Acute Ischemic Stroke and Were Likely to Correlate With Stroke Severity and Outcome

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Background: Many soluble molecules involved in inflammation has been indicated to be risk markers for atherosclerosis, some of which can even predict stroke severity and outcome, but results were conflicting. Purpose: Our study was designed to investigate the time course of selected inflammatory markers, high sensitive C-reactive protein (hs-CRP) and interleukin-6 (IL-6), after acute ischemic stroke (<6h after symptom onset) and to seek its potential clinical implications. Methods: 47 patients with ischemic stroke and 40 age and sex matched healthy controls were prospectively enrolled in this study. Blood samples were withdrawn at serial time points (3 or 6h, 12h, 24h, 48h, 3d and 7d) after symptom onset for stroke patients and only once at admission for control group. hs-CRP and IL-6 were tested by commercially available assays. Clinical severity and outcome (at 3 months after symptom onset) were assessed by NIHSS score and modified Rankin Scale. Results: hs-CRP and IL-6 level at each time point in stroke patients was significantly higher than those in healthy controls (all \(p<0.001\) for hs-CRP and all \(p<0.001\) for IL-6). Both elevated from 3h after symptom onset, then peak at 3 days, and started to fall down again at 7 days, but still higher than healthy controls. hs-CRP and IL-6 levels in Diabetes and smoker patients were significantly higher compared to those without Diabetes, but they were not significantly different between hypertension versus normal blood pressure patients, as well as between patients with hyperlipopemia versus those who without. Patients with more severe clinical symptom (NIHSS \(\geq 8\)) and patients who developed early neurological deterioration (END) and those who had worse clinical outcome showed higher hs-CRP and IL-6 time course compared to those who did not. Conclusion: hs-CRP and IL-6 elevated very early (3-6h) after acute ischemic stroke, peak at 3 days, and were likely to correlate with stroke severity, END and clinical outcome. Patients with Diabetes were more likely to develop more significant inflammatory reactions after stroke.

Effect of Combined Aspirin and Extended-release Dipyridamole versus Clopidogrel on Functional Outcome and Recurrence in Patients With Acute Ischemic Stroke: A PRoFESS Subgroup Analysis

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Introduction: Chronic antiplatelet therapy is effective at reducing recurrence after ischemic stroke. However, the relative safety and efficacy of combined aspirin-dipyridamole vs. clopidogrel in patients with acute ischemic stroke, remains uncertain. Methods: The factorial PRoFESS secondary prevention trial assessed antiplatelet and BP lowering strategies in 20,332 patients; 1,360 were randomised within 72 hours of ischemic stroke to combined aspirin (25 mg twice/day) and extended-release dipyridamole (200 mg twice/day, n = 672) or clopidogrel (75 mg/day, n = 688). For this subgroup analysis, the primary outcome was functional outcome at 30 days; secondary outcomes included recurrence and death at up to 90 days. Analyses were adjusted for baseline prognostic variables and BP treatment assignment. Results: Patients were representative of the whole trial (age 67 years, NIHSS 3, small artery occlusion 59% and baseline variables were similar between treatment groups. The mean time from stroke to recruitment was 58 hours. By 90 days, treatment was no longer being taken in 121 (18%) patients randomised to Asp/ER-DP and 86 (12.5%) assigned to clopidogrel (\(p = 0.006\)). Combined death or dependency (shift analysis of modified Rankin Scale at day 30), odds ratio, OR (95% confidence interval), 0.79 (0.79-0.75) did not differ between the treatment groups. Non-significant trends to reduced recurrence (OR 0.56, 95% CI 0.26-1.18) and vascular events (OR 0.71, 95% CI 0.36-1.37) were present with Asp/ER-DP. Rates of death, major bleeding and serious adverse events did not differ between the treatment groups. Conclusion: Treatment with combined aspirin and extended-release dipyridamole versus clopidogrel in 1,360 patients with acute mild ischemic stroke did not differ in effects on functional outcome, recurrence, death, bleeding, or serious adverse events. Administration of both treatments was practical and well tolerated.

Two Years Experience From Finnish Telestroke Pilot Project 2007–2009

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Background: Two years experience from the Finnish Telestroke pilot project between the Department of Neurology, Helsinki University Central Hospital (HUCH), the Hub, and five hospitals, the Spokes. The project was sponsored by The State Provincial Office of Southern Finland and the participating hospitals, which were the Central Hospital of Lapland, Rovaniemi (in Northern Finland), Länsi-Pohja Central Hospital, Kemi (in North-West Finland), South Karelia Central Hospital, Lappeenranta, Kymenlaakso Central Hospital, Kotka, and the Regional Hospital of Kuusansoki (in South-East Finland). All the participating hospitals have a stroke unit. Thrombolysis treatment and the follow-up of the patients were carried out at the treating hospital. Methods: The teleconsultations were started before the participating hospitals in May 2007 after about one year preparation period. During the preparation period the tasks of the participating hospitals were trained. Lectures including simulation training were given by the faculty of HUCH and local staff. During the two-way interactive audio-visual consultation the decision whether or not to give thrombolysis was based on: 1) the consultant going through a check-up list of indications and contraindications for thrombolysis together with the treating physician; 2) clinical assessment of NIHSS by the treating physician under guidance of the consultant; 3) evaluation of the head CT scan by the consultant together with the treating physician; 4) decision by the consultant and the treating physician under guidance of the consultant; 5) evaluation of the head CT scan by the consultant going through a check-up list of indications and contraindications for thrombolysis. The time from stroke to thrombolysis in 59 patients (range 3-26, mean 130 min, consult delay 13 min) was adjusted for baseline prognosis variables in 108 consecutive patients. Complete follow-up data were collected in 226 (21/43) of the patients with complete follow-up data had a favorable outcome (mRS 0-2). Interpretation A special feature of the Finnish Telestroke is the high proportion of consultations leading to thrombolytic treatment. It may be due to thorough education before and during the pilot project. Another feature worth to mention is that the consultant provided teleconsultation while on duty at our neurological emergency room and thus extra costs for the manpower were negligible.

High Sensitive C-Reactive Protein and Interleukin-6 but Interleukin-18 Levels Correlated With Cerebral Artery Stenosis

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Purpose: inflammatory reaction plays a very important role in the process of atherosclerosis and stroke, and is likely to be correlated with atherosclerotic artery stenosis. But its pathophysiological mechanism is still uncertain. Our study was designed to investigate the relationship between circulating inflammatory biomarkers, high sensitive C-reactive protein (hs-CRP), interleukin-6 (IL-6) and interleukin-18 (IL-18) and intra- or extracranial artery stenosis in acute ischemic stroke patients (<7 days after symptom onset). Methods: Fast blood samples were withdrawn on the second morning after admission in 427 acute ischemic stroke patients. Magnetic resonance angiography and carotid Doppler ultrasound were respectively for intra- and extracranial arteries assessment. The concentrations of these biomarkers were measured by commercially available immunoassays. Results: IL-6 levels in patients with intra- or extracranial artery stenosis were significantly higher than those without (4.2\(\pm\)2.3 vs 3.4\(\pm\)1.6 ng/ml, p < 0.04), while Hs-CRP and IL-6 did not differ between the two groups (p = 0.16 and p = 0.76, respectively). This was also true for intracranial artery stenosis cases (4.3\(\pm\)2.9 vs 3.8\(\pm\)1.5 ng/ml, p = 0.43, p = 0.58 for Hs-CRP and IL-6, respectively). Hs-CRP (p = 0.03) and IL-6 (p = 0.004) levels positively correlated with the severity of extracranial artery stenosis. Patients with the highest quartile of Hs-CRP and IL-6 level had the highest risk for severe (\(\geq 70\%\)) extracranial artery stenosis versus the first quartile (OR, 7.5; 95% CI, 2.8-21.2; p < 0.001 for Hs-CRP and OR, 4.7; 95% CI, 1.9-11.6; \(p < 0.001\) for IL-6). IL-18 showed no relationship with the severity of extracranial artery stenosis (p = 0.93). Conclusions Plasma Hs-CRP levels associated with extracranial artery stenosis, and IL-6 levels associated with both intra- and extracranial artery stenosis, which may implicate that inflammatory reaction plays a more important role in the pathophysiology of extra- than intracranial artery stenosis. Although IL-18 has been indicated in the pathophysiology of coronary atherosclerotic heart disease, it showed no relationship with cerebral atherosclerosis. Further strictly designed studies concerning both acute and convalescent phase of stroke are needed.

Telestroke in Northern Alberta, Canada: A Two Year Experience With Small Remote Hospitals

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Background: In acute ischemic stroke, thrombolysis offers hope for improving recovery and this is best achieved in the settings of a comprehensive stroke program. Small remote regional hospitals usually do not have such expertise making appropriate treatments in such situations difficult. The availability of two-way real time audio and visual telemedicine allows for consultations that makes treatment in distant hospitals feasible. Where such two-way video link is not available, telephone (teleconsultation) may offer an alternate means of treating such
Choline Precursors in Acute and Subacute Ischemic and Hemorrhagic Stroke: An Updated Meta-analysis of Randomized Controlled Trials

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Background: Damage to cell membrane integrity is an important event leading to cell death in ischemic and hemorrhagic stroke. Choline precursors are exogenous agents that are converted to choline in the body and promote the maintenance, repair, and de novo formation of cell membrane phospholipids. Several studies of citicoline in stroke have been conducted. Most of these studies performed to date were underpowered to detect a modest, but clinically, benefit. Methods: We performed a systematic search of four published randomized controlled trials of choline precursors in ischemic and hemorrhagic stroke. The primary analytic endpoint was death or dependency in choline precursors and control groups, respectively, at the end of trials. Odds ratio (OR) with 95% confidence interval (CI) was used as a measure of the association between choline precursors and outcomes of stroke. We pooled data across trials using the fixed-effects model. Results: The systematic search identified 10 trials with abstractable data. All trials tested citicoline (CDP-choline). Among the 2279 patients enrolled across all trials, choline precursors were associated with a reduction in death or dependency (OR 0.65, 95% CI 0.54-0.77; p < 0.0001; NNT-9.5) at the end of trials based on fixed-effects model. The reduction was consistent in ischemic (OR 0.71, 0.59-0.86; p = 0.0004) and hemorrhagic (OR 0.56, 0.32-0.97; p = 0.04) stroke (figure). No dose effect was evident, with both higher (1000-2000mg daily) (OR 0.64, 0.52-0.78; p = 0.0001) and lower (500-750mg daily) (OR 0.66, 0.49-0.90; p = 0.004) doses of citicoline showing reduced death or dependency (OR 0.65, 95% CI 0.54-0.77; p = 0.0001). Among those who arrived after 2 hours, treatment in patients with ischemic stroke who arrived the hospital within 48 hours. We only included patients with acute ischemic lesion on subsequent diffusion MRI. Univariate and multivariate regression analyses were performed to evaluate factors influencing prehospital delay. Results: Among 500 patients (mean 65.3% ± 12.1 years, 61.6% men), the median time interval from symptom onset to arrival was 473.5 (interquartile range [IQR] 170-1312.5) minutes. The number of patients who arrived within 3 hours was 132 (26.4%) and within 6 hours was 512 (43%). Univariate analysis showed that early arrival was significantly associated with the following factors: atrial fibrillation, coronary heart disease, National Institutes of Health Stroke Scale (NIHSS), consultation by Emergency Medical Services (EMS), history of diabetes mellitus or hyperlipidemia and who visited primary physician after stroke were inversely correlated with early arrival. When patients were divided into two groups by arrival time (within 3 hours and after 3 hours), previous stroke history and knowledge about stroke was an indicator for their health, awareness of stroke symptoms, however, patients who had diabetes mellitus or hyperlipidemia and who visited primary physician after stroke were inversely correlated with early arrival. When patients were divided into two groups by arrival time (within 3 hours and after 3 hours), and awareness of stroke were also significantly associated with early arrival. On multivariate analysis, NIHSS score (OR: 0.912; 0.861-0.966), transportation by EMS (OR: 0.543; 0.526-0.930), awareness of stroke symptoms (OR: 0.278; 0.170-0.454) were associated early arrival. Conclusion: The time interval from stroke onset to arrival at hospital was decreased when the patients knew about their symptoms as a stroke and use of EMS. To increase the rate of intravenous rt-PA therapy and ameliorate patient symptoms, intensive general public education would be an important factor.

Social Determinants of Emergent Neurological Evaluation in the Acute Stroke/TIA Patient

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Background: The ASA has recommended that stroke patients receive an evaluation and decision for treatment within 1 hour of arrival at the hospital, yet research shows that many patients are still not managed in a timely fashion. A timely evaluation is especially crucial for patients who have arrived in time for consideration of ICP. Aim The objective of this study was to examine factors associated with delay in neurological evaluation. Methods: In the multi-ethnic community based Stroke Warning Information and Faster Treatment Study (SWIFT), we prospectively identified, and randomized ischemic stroke and TIA patients (able to sign consent) to determine efficacy of a culturally tailored stroke preparedness strategy. Data collected at baseline includes acute stroke parameters, stroke knowledge, severity, social resources and vascular risk. Factors associated with receiving treatment within 1 hour of hospital arrival were assessed through chi-square and multivariate logistic regression and were stratified to account for differential impact of these factors by those who arrived under and over two hours. Results: We enrolled 818 patients: 50% Hispanic; 55% women. Only 43% of those arriving within 2 hours were seen by a neurologist within 1 hour. In this group of patients, neurological evaluation under 1 hour was associated with living with someone else (OR = 6.2, 95%CI = (1.5, 25.9), preliminary diagnosis of an ischemic stroke (OR = 3.8, 95% CI = (1.5, 8.9), and white race (OR = 7.0, 95% CI = (2.0, 23.9) for white vs. Hispanic race). For those who arrived after 2 hours, treatment in under 1 hour was associated with arrival by EMS (OR = 3.6, 95% CI = (1.5, 8.8). Gender and age were controlled for in this both models but did not achieve significance. Discussion: Our study indicates that when patients do make it to the hospital on time, fewer than half may be seen by the neurologist in time for the administration of therapy. For those who have arrived early enough to be seen in time, failure of stroke vs. TIA may play a part in the speed with which the patient is seen in the emergency room.

Evaluation of TIA Patients in an Outpatient Clinic Using ABCD2 Score Results in Low Stroke Rate

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Background: The AHA scientific statement on evaluation of TIA supports the urgent evaluation of TIA patients with suspected ischemic stroke. Our study aimed to investigate factors associated with prehospital delays after acute ischemic stroke in Korea. Methods: A prospective, multicenter study was conducted in 14 hospitals in Korea from March 2009 to July 2009. We interviewed 500 consecutive patients with acute ischemic stroke who arrived the hospital within 48 hours. We only included patients with acute ischemic lesion on subsequent diffusion MRI. Univariate and multivariate regression analyses were performed to evaluate factors influencing prehospital delay. Results: Among 500 patients (mean 65.3 ± 12.1 years, 61.6% men), the median time interval from symptom onset to arrival was 473.5 (interquartile range [IQR] 170-1312.5) minutes. The number of patients who arrived within 3 hours was 132 (26.4%) and within 6 hours was 512 (43%). Univariate analysis showed that early arrival was significantly associated with the following factors: atrial fibrillation, coronary heart disease, National Institutes of Health Stroke Scale (NIHSS), consultation by Emergency Medical Services (EMS), history of diabetes mellitus or hyperlipidemia and who visited primary physician after stroke were inversely correlated with early arrival. When patients were divided into two groups by arrival time (within 3 hours and after 3 hours), and awareness of stroke were also significantly associated with early arrival. On multivariate analysis, NIHSS score (OR: 0.912; 0.861-0.966), transportation by EMS (OR: 0.543; 0.526-0.930), awareness of stroke symptoms (OR: 0.278; 0.170-0.454) were associated early arrival. Conclusion: The time interval from stroke onset to arrival at hospital was decreased when the patients knew about their symptoms as a stroke and use of EMS. To increase the rate of intravenous rt-PA therapy and ameliorate patient symptoms, intensive general public education would be an important factor.
Background: MMD is a rare but important cause of intracranial hemorrhage (ICH) in young adults. ICH is the presenting symptom in approximately 50% of BAVM patients, yet ICH risk factors are poorly understood. We performed a genome-wide association study (GWAS) to investigate association of single-nucleotide polymorphisms (SNPs) with ICH presentation in BAVM patients. Methods: A total of 234 self-reported Caucasian BAVM samples from UCSF were genotyped on the Affymetrix Genome-Wide Human SNP Array 6.0. Quality control assessment removed SNPs and samples with low genotyping call rates (allelic frequency >0.05) and 670,097 SNPs were tested for allelic association in PLINK v1.06. Genomic inflation factor based on the median chi-square statistic was calculated to assess potential population structure. Logistic regression analysis of SNPs, assuming an additive genetic model, was performed to adjust for the effects of age and sex. Results: The genomic inflation factor was 1.02, indicating no significant inflation of P-values due to population structure. Allelic tests of association were performed on 5 SNPs associated with ICH presentation at p < 1x10^-5 on chromosome 2, 6, 9, and 20, and 20, although none reached genome-wide level of significance (p*). Minor alleles of each SNP were present at a higher frequency in ruptured vs. unruptured BAVMs, all with odds ratios >2.5. Results were similar after age and sex adjustment. All 5 SNPs were located in intergenic regions, with 2 SNPs on 20q23.13 showing the strongest signal (p* = 3x10^-10). Conclusions: Several SNPs showed suggestive evidence of association with ICH presentation in BAVM patients. An additional 153 Caucasian samples are currently being genotyped and will be added to the GWAS analysis. Top hits will then be replicated in 350 samples of other race-ethnic groups and in other independent BAVM cohorts. These results may lead to identification of novel genes associated with BAVM hemorrhage.

Gender Differences in Clinical Presentation and Treatment Outcomes in Moyamoya Disease

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Background and Purpose: Moyamoya disease (MMD) is a rare cerebrovascular disease known to occur more frequently in females. We studied the largest single-center experience with MMD in North America to determine whether there are gender differences in clinical presentation and treatment outcomes after vasorecvascularization surgery for MMD. Methods: A consecutive series of 33 MMD patients undergoing revascularization procedures by a single neurosurgeon during a 17 year period (1991–2008) was analyzed. Patients that had not yet reached a minimum of 6 months post-operative follow-up were excluded from this analysis. The remaining 264 MMD patients undergoing a total of 452 revascularization procedures were followed for an average of 4.8 years (0.5–16.8 years) after surgery. Gender differences in symptoms at initial presentation and long-term outcomes after surgical revascularization were analyzed in logistic regression and survival analyses. Results: Overall, 191 females and 73 males (ratio 2.6:1) undergoing a total of 452 revascularization procedures (84.7% direct MCA bypass) were included in this analysis. Females were more likely to present with transient ischemic attacks (TIA) at initial presentation (OR: 2.01; P = 0.012). No association was observed between gender and initial presentation with ischemic stroke, hemorrhagic stroke, or seizures.

Both males and females experienced significant improvement on modified Rankin Scale (mRS) following surgical revascularization (<0.0001). Adverse post-operative events (i.e., ischemic stroke, hemorrhage, or death) after surgery occurred in 15 patients (5.7%), including hemorrhage (N = 7) and ischemic stroke (N = 8) after treatment. In Kaplan-Meier survival analysis, 5-year cumulative risk of adverse post-operative events was 8.3% in females versus 2.7% in males (Figure 1; log rank P = 0.13). In multivariate Cox proportional hazards analysis, there was a trend for female gender to be associated with adverse post-operative events (HR: 2.61, P = 0.21). Conclusions: Female MMD patients are at 2-fold higher risk of developing TIA as a presenting symptom than males, and females may be at higher risk for adverse post-operative events. The role of gender-specific influences in the pathophysiology of MMD merits further study.

Cerebrovascular Dysplasia in Endoglin and Alk1 Haploinsufficient Mice After VEGF Stimulation: Evidence for a “Response-to-Injury” Hypothesis for Hereditary Hemorrhagic Telangiectasia

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Background and Purpose: In hereditary hemorrhagic telangiectasia (HHT) patients with haploinsufficiency of endoglin (ENG; HHT1) or activin receptor-like kinase 1 (ALK1; HHT2), the brain arteriovenous malformation (AVM) phenotype is incompletely penetrant. We tested the hypothesis that the response to a microenvironmental stimulus triggers an abnormal vascular morphological response (dysplasia) and compared effects in the two genotypes. Methods: We injected 2 x 10^5 genome copies of AAV-VEGF or AAV-LacZ control, adeno-associated viral vectors (AAV) expressing vascular endothelial growth factor (VEGF) or LacZ, into the striatum (n = 8) or cortex (n = 3) of Eng+/−, Eng/Eng+/− (cortex injection only) and wild-type (WT) mice, aged three months. The capillary density and morphology were analyzed at six weeks. Capillary density (number of capillaries per 100x objective field) and dysplasia index (number of capillaries > 15 µm per 200 capillaries) were analyzed. Results: VEGF overexpression caused a similar increase in capillary density in the striatum and cortex, regardless of genetic Background (p = 0.05), except that in the cortex, Alk1−/− mice had a 33% higher (p < 0.05) capillary density than other genotypes. Capillary densities in AAV-VEGF and AAV-LacZ-injected striatum were: 237.3 ± 30.0 objective fields and 174.24 ± 24 (Eng+−), 248 ± 37 and 173.32 ± 32 (Alk1−/−). 248 ± 33 and 179 ± 28 (WT) (p < 0.05, AAV-VEGF versus AAV-LacZ). In the cortex, capillary densities were 33% higher in Alk1−/− mice (342 ± 76) than Eng/Eng+/− (258 ± 56) and Eng+/− (259 ± 46) mice (p < 0.05). Few dysplastic capillaries were observed in WT or haploinsufficient mice injected with AAV-LacZ. However, injection of AAV-VEGF resulted in cerebrovascular dysplasia in haploinsufficient mice. Eng+/− (stratum: 3.0 ± 0.1; cortex: 2.3 ± 1.2; >Eng/Alk1−/− (cortex: 1.5 ± 1.1) > Alk1−/− (stratum: 0.7 ± 0.5; cortex: 1.2 ± 0.8). Conclusions: Both angiogenic stimulation and genetic alteration are necessary for the development of dysplasia, the degree of which simulates the relative penetrance of brain AVM in HHT1 (HHT1−/−) HHT2 patients. These observations are consistent with the hypothesis that AVM in HHT patients is associated with a very high degree of patient satisfaction and a substantial reduction in the number of outpatient TIA admissions.
Methods: We ligated both common carotid arteries in adult female New Zealand White rabbits, and studied early cellular and molecular changes at the rabbit BT in response to increased flow in the posterior circulation. Results: Within 2 days and 5 days of hemodynamic alteration, internal elastic lamina (IEL) was degraded in the periperal region that experienced high wall shear stress (WSS) and high positive WSS gradient (WSSG)}, albeit with a continuous intact overlying endothelial layer indicated by PECAM-1 staining. The prominent IEL loss was associated with localized apoptosis and elevated expression of matrix metalloproteinase (MMP)-2 and -9. A small number of inflammatory cells were scattered through the adventitia of the bifurcation, but without any spatial correlation with EL loss and MMP elevation.

Conclusions: Our results suggest that the high WSS/high positive WSSG hemodynamic condition triggers degenerative changes manifested by apoptosis and increased expression of MMPs in non-inflammatory cells already present in the media and intima. This destructive response to a specific hemodynamic stimulus may explain how hemodynamics contribute to aneurysm initiation at bifurcation apices and other locations where IAs preferentially occur.

Anticipate Aneurysm Rupture: Flow Following Hemodynamic Insult

Continued Progressive Aneurysm Development Despite Normalization of Flow Following Hemodynamic Insult

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Background: Hemodynamic insult has been speculated to be a key factor in intracranial aneurysm formation, however it is unclear if sustained insult is necessary or if progressive injury occurs after normalization of a hemodynamic insult. We hypothesized that despite the normalization of wall shear stress (WSS) by adaptive outward vascular remodeling, aneurysmal degradation would continue beyond the known 28-day-period of elevated WSS. Method: Rabbits underwent bilateral common carotid artery ligation or sham operations. A subgroups received multiple angiography to track WSS over 12 weeks. Basilar terminus (BT) was harvested at 5 days, 3, 12, and 27 weeks post-operation. A semi-quantitative aneurysm development score (ADS) was defined on histology as normalized luminal length of vessel wall exhibiting internal elastic lamina (IEL) loss, media thinning and bulging, multiplied by the media thinning percentage. This score and its component variables were evaluated over the above-specified timepoints and compared with the WSS time course. Results: Ligated rabbits (n=17) demonstrated localized degenerative, aneurysmal changes at the BT. All 5-day rabbits had prominent IEL loss. Media thinning and bulging significantly progressed, leading to a large aneurysmal sac with collagenous wall at 27 weeks. While WSS returned to pre-ligation baselines within 5 weeks, the ADS significantly increased over the entire study duration. Conclusion: Hemodynamic insult alone can trigger destructive vascular remodeling, which is identifiable as early as 5 days post-insult and continues towards aneurysm formation well past the period of elevated WSS. Normalization of increased flow insult does not stop the degenerative process leading to intracranial aneurysm formation.

Energy Loss and Wall Shear Divergence: New Hemodynamic Parameters to Anticipate Aneurysm Rupture

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Purpose: We introduced new hemodynamic parameters, Energy loss (EL) and wall shear divergence (WSD) to anticipate rupture of incidental cerebral aneurysms. Methods: EL is considered the lost power which transferred into other types of energy when flow passed through the aneurysm. WSD is a new Wall shear stress parameter which considered opening force of the possible rupture point. Four incidentally found Internal Carotid -Posterior Communicating artery (IC-pcom) aneurysms ruptured during their conservative observation (ruptured-IA). Twenty stable unruptured-aneurysms (stable-IA) with the same location and similar size were examined with EL and WSD. Results: The flow inside the ruptured-IA appeared more complex, and they crashed strongly into aneurysm surfaces. On the contrary, the flow inside of the stable-IAs passed smoothly through the aneurysm. The EL in ruptured-IA was 5.3 times higher than that of stable-IAs. In ruptured-IAs, the flow diverted opposite direction and created tension force on the rupture point of the aneurysm (WSD point). This finding was negative in the stable-IAs. Conclusion: The results indicate that the EL and WSD may be an important parameter to estimate aneurysm growth and rupture.
increased mortality compared to those with completely obliterated aneurysms. Incompletely occluded aneurysms experienced higher rates of post-treatment SAH and had risk factors for poor clinical (final mRS >3) or poor angiographic outcome (aneurysm not completely occluded). Results: After multivariate analysis, risk factors for a poor clinical outcome included baseline mRS =2 (OR 0.23 [95% CI: 0.38, 0.66] p <0.01), aneurysm size ≥ 25 mm (OR 3.32 [95% CI: 1.51, 7.28] p <0.01) and posterior circulation location (OR 0.16 [95% CI: 0.07, 0.43] p <0.01). Risk factors for incomplete angiographic obliteration included fusiform morphology (OR 2.42 [95% CI: 0.10, 0.68] p <0.01) posterior circulation location (OR 0.33 [95% CI: 0.13, 0.83] p <0.02), and endovascular treatment (OR 0.14 [95% CI: 0.06, 0.32] p <0.01). Patients with incompletely occluded aneurysms experienced higher rates of post-treatment SAH and had increased mortality compared to those with completely obliterated aneurysms. Conclusions: Our results suggest that patients with poor baseline functional status, those with giant aneurysms, and those located in the posterior circulation had a significantly higher proportion of poor outcomes at final follow-up. Fusiform morphology, posterior circulation location, and endovascular treatment were risk factors for incompletely obliterated aneurysms at follow-up angiography.
Predictors of Acute Clinical Deterioration in Stroke Patients Receiving Intravenous Low-dose rt-PA: A Multicenter Observational Study

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Background and Purpose: The goal of this study was to determine clinical factors which contribute to acute neurological deterioration of stroke patients receiving intravenous (IV) low-dose recombinant tissue plasminogen activator (rt-PA) therapy. Methods: A retrospective, multicenter, observational study was conducted to evaluate the efficacy of IV rt-PA therapy using 0.6 mg/kg alteplase in clinical practice in 10 major stroke centers in Japan (Stroke Acute Management with Urgent Risk-factor Assessment and Improvement [SAMURAI] Study group). A total of 566 consecutive stroke patients (355 men, 72±12 years old) treated with IV rt-PA from October 2005 through July 2008 whose 24-hour National Institutes of Health Stroke Scale (NIHSS) score was available were studied. Acute deterioration was defined as 4 point or more increase in NIHSS score at 24 hour from the baseline NIHSS score. Results: Acute deterioration was present in 56 patients (9.9%, 38 men, 72±12 years old). Median baseline NIHSS score was 11 (IQR 7-16) in the patients with acute deterioration, and 13 (IQR 7-19) in those without (p=0.047). The patients with acute deterioration more commonly had diabetes mellitus (p<0.01), hypertension (p=0.035), internal carotid artery (ICA) occlusion (p<0.001), and prior use of oral hypoglycemic agents (p=0.028) and statin (p=0.022) than the patients without deterioration. After multivariate analysis, acute deterioration was independently related to baseline NIHSS score (OR 0.92, 95% CI 0.87-0.97 per 1-point increase, p=0.003), systolic blood pressure (1.19, 1.01-1.41 per 10-mmHg increase, p=0.040), diabetes mellitus (2.44, 1.18-4.92, p=0.014), ICA occlusion (6.96, 3.34-18.41, p<0.001). In the patients with acute deterioration, any intracranial hemorrhage (ICH, 42.9% vs. 17.5%, p=0.001) and symptomatic ICH (19.6% vs. 2.2%, p=0.001) occurred within the initial 36 hours, as well as mortality at 3 months (25.0% vs. 4.3%, p<0.001) were more common, and independent activity of daily living, corresponding to modified Rankin Scale (mRS) ≤2, at 3 months was less common (8.7% vs. 58.5%, p<0.001) than those without deterioration. Conclusions: Lower baseline NIHSS score, higher systolic blood pressure, diabetes mellitus, ICA occlusion were independent predictors of acute clinical deterioration in ischemic stroke patients receiving low-dose IV rt-PA therapy.

The Association of Matrix Metalloproteinase 2 and 9 With Different Atherosclerotic Morphology of Carotid Plaques

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Background: Unstable carotid atherosclerotic plaques are characterized by rupture of their cap, leading to thromboembolism and stroke. Matrix metalloproteinases (MMPs) have been implicated in the progression of atherosclerosis as well as in promoting the plaque rupture. The aim of this study was to correlate the expression of MMP-2 and MMP-9 with carotid plaque instability. Methods: Eighty atherosclerotic plaques were collected from 74 patients undergoing carotid endarterectomy. Clinical information was obtained from each patient, and macroscopic and microscopic morphology of plaque was examined. Immunohistochemical expression of MMP-2 and MMP-9 was graded by semi-quantitative scales. Results: Matrix metalloproteinases expression was strongly correlated with the expression of MMP-2 (P<0.001) and MMP-9 (P<0.001). There were significant correlations of increased MMP-2 expression with cap rupture (P<0.002), intraplaque hemorrhage (P=0.039), and thin fibrous cap (P=0.002) and increased MMP-9 expression with cap rupture (P<0.001) and large lipid core (P=0.013). Conclusions: Our results suggest that MMP-2 and MMP-9 are strongly correlated with instability of human carotid plaque, and differently associated with morphological structures of atherosclerosis.
Reduced Estimated Glomerular Filtration Rate is Associated With Stroke Outcome After Intravenous Low-dose rt-PA: The Stroke Acute Management With Urgent Risk-factor Assessment and Improvement (SAMURAI) Study

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Background: The goal of this study was to determine whether renal dysfunction affects the outcome of stroke patients treated with intravenous (IV) low-dose recombinant tissue plasminogen activator (rt-PA). Method: A retrospective, multicenter, observational study (the Stroke Acute Management With Urgent Risk-factor Assessment and Improvement [SAMURAI] Study) was conducted to identify effects of underlying risk factors on rt-PA therapy using 0.6 mg/kg/70 kg in 10 major stroke centers in Japan. A total of 554 consecutive stroke patients (556 men, 71 ± 12 years) with a premorbid modified Rankin Scale (mRS) < 2: received IV rt-PA from October 2005 through July 2008 were studied. Renal dysfunction was defined as reduced estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m². Results: Renal dysfunction was present in 173 patients (31.2%). Patients with renal dysfunction were older (p < 0.001) and more commonly had hypertension (p < 0.001), atrial fibrillation (p < 0.002), prior ischemic heart disease (p = 0.004) and prior use of antithrombotic agents (p < 0.001) than patients without renal dysfunction. In renal dysfunction patients, any intracranial hemorrhage (ICH; 28.3% vs 17.1%, p = 0.003) and symptomatic ICH (8.1% vs 2.4%, p = 0.004) were more frequent within 36 hours, as well as mortality at 3 month (12.7% vs 3.9%, p = 0.001) were more common, and chronic independence at 3 month corresponding to mRS ≤ 2 was less common (44.5% vs 54.1%, p = 0.044) than patients without renal dysfunction. After multivariate adjustment, renal dysfunction was independently associated with any ICH (OR 1.82, 95%CI 1.16-2.86, p = 0.004), symptomatic ICH (OR 2.93, 95% CI 1.10-8.13, p = 0.033), and chronic mortality (OR 2.93, 95% CI 1.33 - 6.62, p = 0.008), but was not related to chronic independence (OR 0.78, 95% CI 0.51 - 1.20, p = 0.255). Conclusions: Reduced eGFR was an independent predictor of ICH within 36 hours and mortality at 3 months in ischemic stroke patients receiving low-dose IV rt-PA therapy.

Background/Conclusions: Reduced eGFR was associated with ICH within 36 hours and mortality at 3 months in ischemic stroke patients receiving low-dose IV rt-PA therapy.

A National Study Comparing Carotid Artery Stent Placement With Carotid Endarterectomy in Octogenarians and Non-octogenarian Population

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Background/Objective: Recently, higher rates of poor outcomes have been reported with endovascular treatment of carotid artery stent placement (CAS) among patients aged ≥80 years (octogenarians). With the increasing octogenarian population and greater utilization, there is a need for identifying differential outcomes between CAS and carotid endarterectomy (CEA) in patient subsets defined by age in general practice. Methods: We analyzed the data from the Nationwide Inpatient Sample (NIS) which is representative of all admissions in the United States from 2004-2008. We assessed incidence and outcomes of post procedure complications including carotid infarction or hemorrhage, cardiac complications, postoperative respiratory insufficiency and post procedure hematomata between the two procedures. In-hospital mortality, discharge status, length of stay, and hospital charges were compared in multivariable model, adjusted for patients age, hospital characteristics and presence of medical comorbidities in patients aged ≥80 years (group I) and those aged < 80 years (group II). The co-morbidities adjusted for in the model included: congestive heart failure, coronary artery disease, diabetes mellitus, hypertension, peripheral vascular disease, and renal failure. Results: Of the total 405,919 estimated patients, who received treatment for carotid artery disease during the study period, 91% underwent CEA and the remaining 9% underwent CAS. A majority of patients (approximately 92% in each group) were presumed to have cerebral ischemic symptoms. Of the total 405,919 procedures, 20% were performed among patients aged ≥80 years (group I). CAS was more often performed in hospitals with a higher setting (p < 0.001) in both group I and II, post operative neurological complications were rarer in patients undergoing CAS (p = 0.004) whereas post operative respiratory failure was higher in patients undergoing CEA (p < 0.001); however complication rates were not significantly different for treatments in group I. There was no statistically significant difference in the discharge outcomes, disability or in-hospital mortality between CAS and CEA in either group after adjusting for potential confounders. In both groups, patients who underwent CEA had approximately 50% relatively higher hospital charges (<0.0001) despite a minimally shorter length of stay (1.2 days versus 1.3 days, p < 0.0001). Conclusions: CEA remains the predominant procedure for treating carotid artery disease in United States regardless of patients age. Although the multivariate adjusted analysis did not demonstrate any difference in outcomes between the CAS and CEA in patients aged ≥80 years as well as patients < 80 years, prominently higher hospital charges may limit widespread acceptance of CAS in United States.

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Staged Carotid Balloon Angioplasty and Stent Placement

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Introduction: Carotid stenting occasionally results in hyperperfusion syndrome, and rarely causes fatal intracerebral hemorrhage (ICH). The purpose of this study was to find efficacy and safety of staged carotid balloon angioplasty and stent placement. Patients & Techniques: Since May 2005, we performed balloon angioplasty and stent placement in separate sessions in cases of impaired cerebral perfusion due to extremely severe stenosis of the carotid artery. One to two weeks after angioplasty with a 3-mm or 4-mm diameter balloon catheter, stent placement was performed with distal protection. A consecutive 23 cases were reviewed in terms of clinical and radiologic outcome and procedure-related complications. Results: 21 male and 2 female patients underwent the staged procedures. Median age of the patients was 71 years (range, 50 to 83). The length between balloon angioplasty and stent placement was 7 days (range, 7 to 18). Balloon angioplasty was performed with 3-mm balloon catheter in 20 cases, 3.5-mm in 1 and 4-mm in 2. No patient experienced procedure-related hyperperfusion syndrome or ICH. There was no thromboembolic event during the period between balloon angioplasty and stent placement. Excellent clinical outcome could be achieved in all the cases except one who suffered from delayed stent thrombosis. Conclusion: Staged balloon angioplasty and stent placement seems to be a safe and effective procedure in cases of impaired cerebral perfusion that are at risk of procedure-related hyperperfusion syndrome or ICH.
deficits due to intracranial hemorrhage. It is essential to predict HPS because of its high morbidity or mortality. 2D perfusion color mapping enables to clarify cerebral perfusion status using only digital subtraction angiography (DSA) and its workstations. We report the 2D perfusion color mapping can predict HPS. Materials and Methods: 860 patients who had performed CAS have registered. All of the patients were analyzed with SPECT before and after CAS, including acetazolamide study. Transcranial doppler (TCD) have been performed before, during, and after CAS if possible. HPS was defined neurological deficits and intracranial or subarachnoid hemorrhage with CT or MRI. DSA was performed with Allura Xper FD20/10 (Philips). Perfusion 2D color mapping was analyzed with 8ml/sec contrast medium infusion from common carotid artery for 1 second. Maximum enhancement, start to peak, average wash-in rate, average travel time were revealed. The data were compared with SPECT and TCD. Results: 4/860 cases have presented HPS. All of the patients manifested misery perfusion (Powers stage 2) before CAS with SPECT. Mean middle cerebral artery flow velocity markedly increased after CAS with SPECT. 2D perfusion color mapping showed remarkable hyperperfusion state after CAS, especially maximum enhancement and average wash-in rate. Discussion: 2D perfusion color mapping images have a lot of potential for evaluating cerebral hemodynamics with great ease compared with SPECT or TCD. It enables to analyze cerebral blood flow status immediately during CAS. It might be useful for intracranial percutaneous transluminal angioplasty/stenting, and symptomatic vasospasm following subarachnoid hemorrhage for studying cerebral hemodynamics. It could be also available for some diseases functional changes occur prior to structural. Conclusion: 2D perfusion color mapping requires only one more inflation. It needs no more devices and one-click analysis within less than 1 minute. It is very useful modality during CAS for analyzing cerebral perfusion status.

Impact of Open-cell vs. Closed-cell Stent Design in the Outcome of Carotid Stenting

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Purpose: The type of the stent cell design has been considered responsible for modifying the morbimortality rate after carotid artery stenting (CAS) although other series did not support the superiority of a specific carotid stent cell design. We investigated the impact of open-versus closed-cell stent design after CAS on 30-days neurological complications. Materials & Methods: Seven hundred and seventy-nine patients with ICA stenosis ≥ 70% (21% asymptomatic) were treated with CAS in the last 11 years and followed prospectively. Of them, 350 with close-cell stent and 429 with open-cell stent. In both groups, mean age, sex, clinical presentation, vascular risk factors, indication for PTA, degree of carotid stenosis, contralateral carotid occlusion, angiographic characteristics of the stenosis, number of dilatations, and final angiographic result showed no differences. Distal protection during CAS was more frequently used in patients with open-cell stenting (97.0% vs. 62.5%). Hypotension, bradycardia, and asystole were more frequent in the close-cell stent group without reaching statistical significance. Thirty-day morbimortality (TIA, minor stroke, stroke, and death) were registered. Results: Mortality was 1.5% in the close-cell stent group and 0.7% in the open-cell stent group (p=NS). Major stroke, 0.9% vs. 0.2%, minor stroke, 0.3% and 1.0%, and TIA, 3.6% and 3.2%, respectively. Major morbimortality (minor stroke included) were 2.7% and 1.9% respectively (p=NS). A second PTA as a consequence of severe restenosis was similar in both groups (5.4 vs 2.1% respectively). Conclusion: Our data do not support the superiority of a specific carotid stent cell design with respect to 30-days morbimortality.

Superficial Temporal Artery- Middle Cerebral Artery (STA-MCA) Bypass in Patients With Severe Steno-occlusive Disease of Intracranial Internal Carotid and Middle Cerebral Artery


Background: The International Cooperative Study of Extracranial / Intracranial arterial anastomosis (EC/IC Bypass) study in patients with symptomatic carotid artery disease failed to demonstrate a reduction in the risk of subsequent ischemic stroke. Subsequent reports found that superficial temporal artery-middle cerebral artery (STA-MCA) bypass surgery improved the cerebral oxygen extraction fraction and possibly useful in patients with impaired cerebral hemodynamic and vasorelative reserve (VR). We evaluated cerebral hemodynamics and VR in patients with symptomatic carotid artery disease (ICAD) or severe ICAD with carotid steno-occlusive disease (CSO), both with steno-occlusive disease to select patients who could benefit from STA-MCA bypass surgery. Methods: Diagnostic transcranial doppler (TCD) and vasomotor reactivity (VMR) testing with voluntary breath-holding, according to a standard scanning protocol, were performed in patients with severe ICA or MCA disease. Intraoperative data derived using previously published criteria, blunted flow in the distal arterial segments and breath-holding index (BHI) ≤ 0.69. Artery-to-artery embolization was excluded by TCD monitoring for spontaneous emboli. Patients with inadequate BHI were further evaluated with acetazolamide-challenged HMPAO-SPECT perfusion. (HMPAO-SPECT demonstrated metabolic perfusion deficit (vasodilatory failure) in 22/14 of them underwent STA-MCA bypass surgery. There were no periprocedural complications and during subsequent follow up (mean: 8 months; range: 3 to 12 months) none of the patients developed any new cerebral ischemic event. Early morning headache and lethargy noted in 8 patients resolved completely. TCD and acetazolamide-challenged HMPAO-SPECT repeated at 5±2 months revealed significant improvement in cerebral metabolic perfusion as well as VR. 6 out of the 8 patients with inadequate VR and on medical therapy developed new cerebral ischemic events during follow up. Conclusion: Patients with symptomatic severe intracranial steno-occlusive disease and severe stenosis in the STA-MCA, multivessel vasodilatory reserve carry a high risk of cerebral ischemic events. Assessment of cerebral hemodynamics and vasorelative reserve with TCD and quantification of metabolic hypoperfusion and vasodilatory failure by acetazolamide-challenged HMPAO-SPECT may be used to select patients who would benefit from STA-MCA bypass surgery.

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Early Carotid Angioplasty and Stenting for Secondary Stroke Prevention

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Purpose: The benefit of endarterectomy has been proven to be dependent of the timing of surgery in relation to the presenting TIA or stroke event. We investigated the safety of performing CAS early after those events, comparing the 30 days morbidity and mortality rates with respect to delayed procedures in otherwise stable patients. Material & Methods: Seven hundred and ninety-one patients with symptomatic ICA stenosis ≥ 70% were treated with PTA in the last 18 years and followed prospectively. 111 of them (14%) within the first 2 weeks after the clinical event (44% TIA and 56% stroke with total recovery or mild clinical symptoms). When comparing patients in the early group with those operated later, mean age, sex, clinical presentation, vascular risk factors, indication for PTA, degree of carotid stenosis, contralateral carotid occlusion, angiographic characteristics of the stenosis, number of dilitation, and final angiographic result showed no differences. Distal protection during CAS was more frequently used in the early group (85% vs. 78% and 90% vs. 61% respectively) reflecting that the decision to intervene early cases was taken in 2006. Hypotension and bradycardia, were less frequent in the early group without reaching statistical significance. Thirty-day morbimortality (TIA, minor stroke, stroke, and death) were registered. Results: TIA was more frequent (7% vs. 4%) but without significance (p=0.1) in the early group. However, death or stroke were similar (0.9% in the early group vs. 1.9%) as it was the combination of minor stroke, permanent stroke, death or any cause (2.7% vs. 2.3%). Conclusion: As with endarterectomy, delaying CAS after an index ischemic event may drive to a quickly decline of the treatment benefit in the secondary prevention of stroke or death. Our results in patients treated in the first 2 weeks show no differences with those obtained in stable patients, favoring an immediate intervention to avoid the high immediate and short-term risk of stroke.

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Opium Addiction Plays a Significant Role in Developing Intracerebral Hemorrhage Among Young Patients

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Introduction: Amphetamines, Cocaine and Cannabis abuse were defined as major risk factors developing hemorrhagic strokes especially among Young adult. However the relation between Primary Intracerebral Hemorrhage (PICH) and opium addiction has rarely been investigated before. Hypothesis Based on the large proportion of admitted PICH cases among Iranian opium addicted patients, we hypothesized that opium addiction plays a role as a risk factor for developing PICH among young population. Method: A case-control study was performed in Ahzara tertiary care hospital, Isfahan, Iran (2006-2009). A total of 172 patients with PICH and 812 matched control cases from other wards of hospital without cerebrovascular event histories were included. Risk factors of PICH including age, sex, cigarette smoking and history of PICH with/without ICH (I-Chronic ICH and I-Diabetic ICH) and significant depression were evaluated. The odd ratios for risk factors were calculated for 2 groups of patients, those at the age of 15-45 and those above 45. Results: Fourteen (3female, 11male) patients (mean age 37.92: ± 8.31)
and 280 people (125 male, 155 female) in control group (mean age 34.17±7.00) at the age of 15-45 were included (P=0.05) as well as 158 (61 female, 97 male) patients (mean age 66.24±10.79) and 532 people (213 female, 319 male) in control group (mean age 64.41±10.80) older than 45 (P=0.05). Using logistic regression modeling, the values of odd ratio were found to be 9.56 (95% confidence interval (CI) 2.45-37.29, P=0.001) for opium addiction and 5.44 (95% CI 1.22-23.70, P=0.013) for HTN among younger group, while P values for smoking, HD and DM were not significant. Contrariwise in patients older than 45 the values of odd ratio were 10.57 (95%CI 6.59-16.95, P=0.000) for HTN, 2.12 (95% CI 1.22-3.70, P=0.007) for HD and 1.94 (95% CI 1.21-3.13, P=0.008) for DM while P values for opioid addiction and smoking were insignificant. Conclusion: A positive correlation is observed between opium addiction and development of PICH in young patients but not in older adults. Some previous studies have shown that opioid addiction causes endothelial dysfunction and thus, PICH can be seen in a group of young adults who have been susceptible to developing the condition during early stages of opium addiction. Therefore, opium addiction can be an important independent risk factor for PICH in young patients.

Vitamin D Deficiency and Acute Ischemic Stroke: Correlation Between Vitamin D Levels and Stroke Severity

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Background: Multiple studies show that vitamin D deficiency plays a role in increasing the risk of cardiovascular disease. Reduced vitamin D was also identified in the majority of patients with acute stroke in one study, which suggests that vitamin D deficiency might be a risk factor for stroke. Objectives: The objective of our study was to investigate whether vitamin D deficiency at the time of acute stroke presentation was a risk factor for stroke and can predict the stroke severity. Methods: This was a prospective study to measure the level of serum 25-hydroxy vitamin D upon admission in acute ischemic stroke patients within 24 hours of symptom onset. Patients were categorized into 3 groups for Vitamin D levels (sufficient: >30ng/ml; insufficient: 20-30ng/ml; and deficient: <20ng/ml). The severity of the acute stroke was measured using the NIH Stroke Scale (NIHSS) and the type of stroke was defined according to the TOAST criteria. The Pearson correlation was used to determine the correlation between vitamin D level and NIHSS. The Student t-test was performed for differences in means of NIHSS for each vitamin D level group. Results: 38 patients (21 males and 17 females) were recruited between February 2009 and August 2009 who presented to our institution within 24 hours of their acute ischemic stroke. The NIHSS stroke scales ranged between 1 to 26, 25-hydroxy Vitamin D ranged between 6.3 to 48.6ng/ml. 20 of 36 patients were vitamin D insufficient or deficient. This study showed a significant correlation between vitamin D and the severity of the acute ischemic stroke (Pearson Correlation: -0.427, p<0.001). The mean NIHSS for Vitamin D deficiency, insufficiency, and sufficiency were 9, 5.5, and 4.1 respectively. Discussion: Several studies showed the vitamin D may be a risk factor for acute ischemic stroke. These results support prior evidence that vitamin D may be a risk factor for ischemic stroke. This study shows that vitamin D levels were inversely correlated with stroke severity.

Transcranial Doppler Ultrasound for Detecting Intracranial Stenosis in Elderly People: Results From the Ultrasound Screening in Adults for Intracranial Disease (USAID) Study

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Introduction: Transcranial Doppler ultrasound (TCD) is an easily available non-invasive test that can be used to identify intracranial stenosis for screening in epidemiological studies. However, the success rate of adequate screening by TCD depends upon the availability of adequate bone windows. We performed this population-based study to determine the success rate of adequate screening by TCD in elderly US population. Methods: We used a national database to identify non-Hispanic white and African-American subjects aged 65-84 years, from a well-defined geographic area. Subjects were randomly selected from this database and invited for participation in this study. Brief clinical history and physical examination followed by TCD study was performed using transcranial and transforaminal windows in all study participants. Results: A total of 99 subjects participated in the study; mean age (± standard deviation) was 72 ± 7 years; 42 men and 17 were African-American. All insonation windows were present in 62 subjects. In another 9 subjects bilateral transcranial windows were present but transforaminal windows were absent. Presence of insonation windows according to subject characteristics is shown in Table. Transcranial bone windows were more likely to be absent in women compared with men (40% versus 12%, p < 0.05) and African-American compared with whites (53% versus 23%, p < 0.05). There was no association between presence of various cardiovascular risk factors and the presence of insonation windows. Conclusion: Either transcranial or transforaminal bone windows can be inadequate for successful TCD study in about 39% of elderly population particularly in women and African-Americans. These findings have implications for patient and technique selection in large population based cohort studies.
Smoking is Associated With TIAs at a Younger Age

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Background: Smoking is a major modifiable stroke risk factor. However there is limited literature comparing current smokers and ex-smokers to non-smokers. We sought to study the profile of ischemic strokes and transient ischemic attacks (TIAs) in current smokers, ex-smokers and to compare with non-smokers. Methods: This is a retrospective study of acute ischemic stroke and TIA patients who presented to the Foothills Medical Center, Calgary from April 2002 to May 2007. All patients underwent CT head and a CT angiogram of the head and neck at presentation. The demographic, clinical, risk factor, mechanism of stroke, treatment, and follow up details were retrieved from chart review. The patients were divided into 3 categories depending on their smoking habits: current smokers, ex-smokers - patients who had quit smoking <3 months and non-smokers. Results: The total number of ischemic stroke and TIA patients was 1047. Among them, 790 (75.4%) patients had stroke and 257 (24.6%) had TIA. 233 (22.3%) were current smokers, 131 (12.5%) were ex-smokers and 683 (65.2%) were non-smokers. The mean age of stroke presentation amongst smokers, ex smokers and non smokers was 65.5±1.44, 68.0±15.4 and 67.6±14.4 years (p<0.19). The mean age of TIA presentation amongst smokers, ex smokers and non smokers was 56.7±12.3, 72.2±9.5 and 69.1±13.5 years respectively (p=0.001). Vascular risk factors were significantly more common in ex smokers compared to current cigarette smokers and non smokers [hypertension (p=0.001) and dyslipidemia (p=0.003)]. Significant neck vessel disease was seen in 6.6% of smokers, 16% of ex-smokers and 10.8% of non-smokers (p=0.15). CTA of the intracranial vessels revealed significant atherosclerotic >50% stenosis in 5.6% of smokers, 1.5% of ex-smokers and 3.7% of non-smokers (p=0.18). The large artery atherosclerotic TOAST classification was determined the etiology of stroke in a similar proportion in all groups ex-smokers (25.0%), smokers (26.1%) and nonsmokers (20.2%). There were no significant differences in 3 month outcome between the groups. Conclusion: Current smokers present with TIAs much earlier in life than ex-smokers and non smokers. This may reflect cessation in later years but does raise concerns that smoking may make even modest plaque vulnerable to injury and thrombus formation causing TIA at an early age.

High Prevalence of Carotid and Intracranial Atherosclerosis in Hispanic General Population: An Autopsy Study in Mexico City

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Background & Objectives: Few autopsy studies on cerebral atherosclerosis have been performed in Hispanic populations. The aim of this study was to determine the prevalence and determinants of carotid and intracranial atherosclerosis in the Mexican general population. Methods: We measured atherosclerotic lesions in the carotid arteries, basal intracranial arteries, left descending coronary artery, right coronary artery, abdominal aorta, and renal arteries in persons 1 to 91 years of age who died as a result of external causes in Mexico City and were autopsied in the central forensic laboratory within 48 hours after death. Atherosclerosis was described according to the AHA grading system as follows: Types I-III (early atherosclerotic lesions) and types IV-V (advance plaques lesions): there were not type VI lesions (complicated plaques). Also, plaques were classified as nonstenotic plaques and stenosis ≥50%. This report describes the results of carotid and intracranial lesions. Results: We studied 104 men and 77 women; median age was 34 years (IQR 20–60). Atherosclerosis was documented in 163 persons (90%): carotid 86.5%, intracranial 49%; both territories 57%. Table describes atherosclerosis severity according with age groups and arterial territory. Atherosclerosis was associated with diabetes and hypertension, and mainly with the presence of two or more risk factors (P<0.001). However, atherosclerosis was observed in 60% (carotid) and 40% (intracranial) of persons without traditional risk factors. More than 90% of studied subjects had concomitant coronary atherosclerosis. Conclusions: There was a high prevalence of cerebral atherosclerosis in the Mexican general population including a high proportion of persons without known vascular risk factors.

Table: Presence of insonation windows according to patients’ characteristics

<table>
<thead>
<tr>
<th>Subjects (n=99)</th>
<th>Transtemporal window present (n=71)</th>
<th>Transforaminal window present (n=87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65–74 years</td>
<td>76</td>
<td>53 (70%)</td>
</tr>
<tr>
<td>75–84 years</td>
<td>23</td>
<td>18 (78%)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>42</td>
<td>37 (88%)</td>
</tr>
<tr>
<td>Women</td>
<td>57</td>
<td>34 (60%)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>82</td>
<td>63 (77%)</td>
</tr>
<tr>
<td>African-American</td>
<td>17</td>
<td>9 (47%)</td>
</tr>
<tr>
<td>History of diabetes mellitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13</td>
<td>9 (69%)</td>
</tr>
<tr>
<td>No</td>
<td>86</td>
<td>62 (72%)</td>
</tr>
<tr>
<td>History of hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>55</td>
<td>37 (67%)</td>
</tr>
<tr>
<td>No</td>
<td>44</td>
<td>34 (77%)</td>
</tr>
<tr>
<td>History of hyperlipidemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>50</td>
<td>34 (68%)</td>
</tr>
<tr>
<td>No</td>
<td>49</td>
<td>37 (76%)</td>
</tr>
<tr>
<td>History of cigarette smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>15</td>
<td>10 (67%)</td>
</tr>
<tr>
<td>Past</td>
<td>47</td>
<td>39 (83%)</td>
</tr>
<tr>
<td>Never</td>
<td>37</td>
<td>22 (59%)</td>
</tr>
<tr>
<td>*p-value &lt;0.05 using chi-square test.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This research has received full or partial funding support from the American Heart Association, National Center.

Differences in Risk Factors Between Intracranial and Extracranial Atherosclerosis in a Predominantly White American Population

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Background: Intracranial atherosclerosis is implicated as the mechanism of ischemic stroke in 8% to 10% of Caucasian patients. Little is known about the difference in risk profile between patients with extracranial (ECA) and intracranial atherosclerosis (ICA) in a Caucasian population. We sought to identify clinical factors associated with the different patterns of cerebral atherosclerosis. Methods: Data from a prospective cohort study at two university based hospitals where computed tomography angiography (CTA) was systematically performed in the acute phase of ischemic stroke were analyzed. Patients with ECA and ICA, defined as ≥50% stenosis of a cerebral large artery on CTA, were included for analysis. We compared the prevalence and the number of risk factors between patients with ECA and ICA. A multivariate regression model was used to identify independent predictors for ECA and ICA. Results: A total of 742 patients underwent CTA/CTA over a 4-year period. The mean age of the population was 68.1±15 years, 384 subjects (52%) were males and 624 (84%) were Caucasian. One hundred thirty four patients (34%) were classified as ECA, 143 subjects (37%) were classified as ICA and 111 (29%) as both ECA and ICA. Patients classified as ICA and ECA/ICAHATH patients also had a higher prevalence of hypertension (69% and 79% vs. 58%, p<0.001), diabetes (20% and 25% vs. 14%, p<0.03), coronary artery disease (22% and 40% vs. 17%, p<0.001) and peripheral vascular disease (3.5% and 8.2% vs. 2.2%, p=0.03) when compared with patients classified as ECA. In a multivariate regression model, the only independent predictors for site of atherosclerosis were smoking for ECA (OR 1.9, 95% CI 1.1-3.9) and age for ICAHATH (OR 1.02, 95% CI 1.005 - 1.04). Conclusion: There is a significant disparity in the vascular risk profile factors of Caucasian ECAHATH and ICAHATH patients. This suggests that vascular bed-specific atherosclerosis may be related to susceptibility to individual factors, as well as the total burden of risk factors. Identification of ICAHATH-prone individuals may be useful in identifying a population who would benefit from intracranial vascular imaging, and potentially more aggressive stroke prevention strategies.
Serum Apolipoprotein is Associated With Thrombotic Stroke Subtype

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Background: Traditional lipid parameters such as low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), total cholesterol and triglycerides have been well known as major targets for treatment in stroke patients. Recently, the impacts of apolipoprotein on vascular events such as coronary artery disease have been highlighted. However, sparse data are available for the patients with ischemic stroke. Objectives: We tried to assess the impact of apolipoprotein including apolipoprotein-Al (Apo-AI), apolipoprotein B (Apo-B), apolipoprotein CIII (Apo-CIII) and apolipoprotein E (Apo-E) on ischemic stroke. Especially, we focused on the differences of apolipoprotein between thrombotic stroke and non-thrombotic stroke. Methods: From a prospectively collected stroke registry (KOSUR), acute ischemic stroke patients were enrolled in this study. The patients who had been taking statins were excluded. The patients were classified into thrombotic group (definite large artery atherosclerosis, cardioembolism, small vessel occlusion cases) and non-thrombotic stroke group according to the TOAST classification. Apo-AI, Apo-B, Apo-CIII and Apo-E were measured at admission. To prove the possible association between apolipoprotein and thrombotic-stroke subtype, multivariate logistic regression tests were performed using quartiles of apolipoprotein as covariate. Results: Finally, 402 patients (female 36.5%, mean age 66.7 ± 12.03 years old) were included. The patients were composed of 259 thrombotic strokes (159 patients for large artery atherosclerosis, 142 small vessel occlusion) and 101 cardioembolic-stroke. Hypertension, diabetes, smoking, and gender were associated with thrombotic-stroke subtype. Among the apolipoproteins, only Apo-B was significantly associated with thrombotic stroke (independent t-test, p = 0.009, thrombotic-stroke mean of 85.55 ± 29.25, and Apo-B stroke group 78.92 ± 23.47). On the multivariate logistic regression analyses to predict thrombotic stroke (covariates included hypertension, diabetes, smoking status, and gender), increasing quartile of Apo-B was proved as independent predictor of thrombotic-stroke stroke. Conclusion: Elevated level of Apo-B was associated with thrombotic stroke subtype. The association between Apo-B and thrombotic-stroke subtype was mediated by LDL-cholesterol. Further investigation about the role of apolipoprotein on pathophysiology of ischemic stroke is needed.

Elevated Fasting Triglyceride in Small Vessel Occlusive Stroke

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Background & objective: It is widely supposed that elevated LDL is associated with large artery atherosclerotic stroke (LAA). However, the association of dyslipidemia and small vessel occlusive stroke (SVO) has not been well defined. This study was to investigate the abnormalities of lipid profile in SVO with comparison to other stroke subtype, especially LAA. Methods: From September 2004 to August 2005, we prospectively registered baseline characteristics for all consecutive acute ischemic stroke patients admitted 7 days from onset in 4 university hospitals located in Seoul metropolitan region of South Korea. From this registry, we analyzed data for fasting lipid profiles and ischemic stroke subtypes. T-test and ANCOVA were performed to compare the lipid profiles between SVO and other subtype. Results: Of 1254 patients (age, 66.3 ± 12.1 years; male, 56.1%; median initial NIHSS score, 4), 373 (27.6%) had SVO, 480 (35.5%) had LAA and 199 (14.7%) had SVD and other subtype. Median BMI was 28.0 ± 7.4 (SD 6.0), 33.1% were lean, 34.1% overweight, 29.5% obese, and 3.3% morbidly obese. Breakdown of stroke subtype: 21.8% large vessel disease (LVD), 34.6% small vessel disease (SVD), 19.5% cardioembolism (CE), and 24.1% unknown/other. After adjusting for confounders, compared to unknown/other stroke subtype, odds of SVO and LVD were greater in obese than in lean persons (OR 1.55, p = 0.0% and OR 2.48, p = 0.0%). Presence of CE did not significantly differ between obese vs. lean persons (OR = 1.64, p = 0.29). When assessed as a continuous variable, after adjusting for confounders, each 1 kg/m² increase in BMI was associated with a 6% increase in odds of LVD (p = 0.0). Conclusions: Obese ischemic stroke patients of lower socioeconomic means are significantly more likely than their lean counterparts to experience recent cerebral ischemia due to cerebrovascular atherosclerosis, even after adjusting for major confounders. Intensified efforts at curbing obesity may reduce atherosclerotic strokes in such underserved populations.

Frequency of Abnormal Glucose Metabolism Among Ischemic Stroke and TIA Patients in the South Based on Oral Glucose Tolerance Testing

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Background: Previous studies suggest that abnormal glucose metabolism is common among ischemic stroke patients with a lower prevalence of diabetes. The purpose of this study was to determine the frequency of abnormal glucose metabolism in our ischemic stroke population by performing an oral glucose tolerance test in patients who had at least one risk factor for diabetes. Methods: All ischemic stroke or TIA patients who were evaluated at Emory University Hospital or The Emory Clinic from July 2008 through June 2009 with no history of diabetes or swallowing problems and one risk factor for diabetes were eligible for this retrospective analysis. Risk factors for diabetes included hemoglobin A1c ≥5.8, BMI ≥25.0, family history of diabetes, or a history and clinical exam suggestive of a peripheral neuropathy. Patients underwent blood glucose measurements after overnight fasting and two hours after a 75 gm glucose load. Diabetes, impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) were defined according to the American Diabetes Association criteria. Results: Overall, 55 patients met the study criteria. The mean age of the group was 63.2 ± 14.8, 45% were female, 42% were African American, and mean BMI was 28.9 ± 5.4. Median time from stroke onset to glucose measurements was 19 days (range, 1–330). Abnormal glucose metabolism was detected in 34 (62%) patients, including 14 patients with newly diagnosed diabetes, 15 patients with IGT and 5 patients with IFG. Of the 14 patients diagnosed with diabetes, 11 were diagnosed based on 2-hr glucose levels but not by fasting glucose. 1 was diagnosed by fasting glucose but not by 2-hr glucose level and 2 were diagnosed by both fasting glucose and 2-hr glucose levels (p = 0.006). Fasting blood glucose levels classified 10 (18%) patients as normal though glucose tolerance testing revealed that 7 of these patients had IGT and 3 had diabetes. Conclusions: Oral glucose tolerance testing is a method of prevalence of prediabetes and abnormal glucose metabolism in our ischemic stroke and TIA patients. The use of fasting blood glucose alone to screen ischemic stroke or TIA patients at risk for diabetes may underestimate the frequency of abnormal glucose metabolism.

Unmarried Working Men and Unhappily Married At Age 40-65 Carry Excess Risk of 34-year Stroke Mortality

UriGoldbourt; Tel AvivUniv, Tel Aviv, Israel

Sparse data exist to permit examination of the association between marital status and satisfaction and the risk of stroke. Among 10,059 male civil servants and municipal employees (mean age 49.2 years) who participated in the Israeli Ischemic Heart Disease study in 1963, 88% were working form Europe, North Africa and the Near-East. 82.3% were married once, 12.8% were married twice or more, 235 (2.3%) never married, and 257 men (2.6%) were divorced, separated or widowed. Two years later, subjects (N=9343 responders) were queried whether they considered their marriage successful (43%, quite successful (45%), not so successful (4%) and unsuccessful (N=236, 3.3%). Mortality was ascertained by matching with the national death registry using the national ID and verifying names. Underlying cause of death through 1997 was determined from ICD-8, ICD-9 and ICD-10 coding with a re-ascertainment and editing process at the central Bureau of Statistics. Among the unmarried men 343(8.7%) men died as compared to 64.9% among married counterparts. Corresponding unadjusted stroke rates were 8.4 and 7.1 per 1000 respectively. Using age using age at death of stroke as the time variable in a Cox proportional hazards model and adjusting for Socio-economic status (SES) index, body mass index, blood pressure, smoking habits, family size, and baseline prevalence of diabetes and CHD, the hazard ratio of subsequent fatal stroke for unmarried men in layers 1 was 1.64 (95% CI 1.26, p = 0.04) and 1.04 (CI 0.24, p = 0.03), CI 1.30-2.09). In addition, among married men, adjusted estimated hazards of fatal stroke 1965-1997 were 1.18 (95% CI 0.98-1.41), 1.09 (2.97-1.49) and 1.48 (1.11-2.43) for the quite- not-quite- and marriage than their lean counterparts to experience recent cerebral ischemia due to cerebrovascular atherosclerosis, even after adjusting for major confounders. Intensified efforts at curbing obesity may reduce atherosclerotic strokes in such underserved populations.
unsuccessful marriage relative to "very successful". In conclusion, married men were at a lower risk of long-term stroke, excluding those reporting utter dissatisfaction with their married life.

Factors Predicting the Presence of Acute Ischemic Lesions on Diffusion Weighted in the Stanford TIA Study (Two Aces) - P74

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Background: In 2002 a new definition of TIA was proposed: "a brief episode of neurological dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction". The AHA has recently endorsed this definition of TIA but excluded the phrase "with clinical symptoms typically lasting less than 1 hour" because "the 1-hour time point does not accurately distinguish between patients with or without acute cerebral infarction". We investigated the incidence of acute DWI lesions, as well as associated clinical features, among patients with transient cerebral ischemia with symptom duration < 1 hour compared with longer lasting symptoms. Methods: Consecutive patients with a clinical diagnosis of TIA who underwent MRI from March 2007 to May 2009 were included. We investigated the relation between DWI lesion occurrence and vascular risk factors, history of atrial fibrillation, ABCD2 items and the presence of symptomatic ICA stenosis (>50%) using binary logistic regression. Results: One hundred seventy three cases met the inclusion criteria; the median ABCD2 score was 4 (IQR 3-5). Median time to MRI was 48 hours (IQR 23-92). Each 4 hour case lasted symptoms for < 1 hour and in 89 symptoms lasted 1 hour. The prevalence of positive DWI lesions was the same (15%) in both groups. The median ABCD2 score was lower among patients with symptoms < 1 hour (3; IQR 2-4) compared to those with longer lasting symptoms (4; IQR 3-5) p < 0.0001. The prevalence of atrial fibrillation; ICA stenosis; stroke risk factors and median delay to obtaining MRI were not different. After adjustment for stroke risk factors, clinical score, stroke mechanism and MRI delay, 2 factors were associated with the occurrence of an acute DWI lesions among patients with symptoms lasting less than 1 hour: unilateral weakness, odds ratio 7.7 (95% CI: 1.5-39), p = 0.014 and atrial fibrillation, OR: 8.8 (95% CI: 1.8-44.0), p = 0.008. These same two factors were also associated with DWI lesions among patients with symptom duration > 1 hour: unilateral weakness, OR: 11.8 (95% CI: 2.5-63.0), p = 0.008 and atrial fibrillation: OR: 8.8 (95% CI: 1.8-44.0), p = 0.008. Conclusion: In our cohort of patients with transient ischemic attack, the rate of DWI positive lesions was no different in patients with brief (<1 hour) vs. longer duration symptoms. These data support exclusion of the 1-hour time window in the new AHA definition of TIA. Clinical features appear to be more important than symptom duration in predicting DWI lesions, unilateral weakness and atrial fibrillation were strongly associated with acute DWI lesions independent of time.

Using MRI as the Witness: Multimodal MRI-based Determination of Acute Onset - P75


Background: In approximately 25% of ischemic stroke patients, the exact onset is unknown, and the time last known well (LKW) places them beyond the treatment window. Recent studies suggest that discrepancies between acute FLAIR and DWI can identify patients with onset > 3 hours with high specificity but low sensitivity. We hypothesized that multimodal imaging can improve the sensitivity of identifying stroke onset of < 3 hours. Methods: We retrospectively analyzed datasets collected from 2005-2009 in stroke patients receiving MRI with within 12 hours of LKW (n = 323) and identified those potentially tPA-eligible. Patients were excluded if any of the following were true: symptoms discovered > 30 min after LKW, imaging was post-thrombolysis, presented with > 100 cc DWI lesion before < 3 hours, or admission NIHSS score < 4 or >25. Patients were classified as FLAIR negative (-), or with subtle (+), or profound (+++) abnormality. Lesions were outlined on acute DWI and superimposed on the other imaging modalities. A decision tree was created using recursive partitioning with k-fold cross-validation, (k = 10). Input factors were age, sex, NIHSS score and imaging (DWI volume, absolute apparent diffusion coefficient (ADC), relative FLAIR and relative b-value). Results: 116 patients’ images were analyzed (102 with FLAIR). Mean ± SD age was 68 ± 16, 58 (50%) males, and median NIHSS score 10 (IQR 6-16). Images were grouped into <3 h (n = 25), 3-6 h (n = 58), and 6-12 h (n = 33) windows. Stroke subtypes were cardioembolic (41%), large vessel (21%), small vessel (6%), undetermined (27%) or other determined cause (8%). Frequency of abnormal FLAIR imaging (see figure) increased with increasing time (p < 0.03). Absence of FLAIR (-) identified stroke onset <3 h with 62% specificity (95% CI: 79-94%) and 42% sensitivity (21-66%). The decision tree first branched on DWI volume, then absolute ADC, age, b-value intensity, FLAIR intensity, and then sex. Decision tree analysis achieved the same specificity but 64% sensitivity (63-96%). Conclusion: Multimodal imaging can improve the ability of MRI to “witness the onset of stroke” better than qualitative FLAIR assessments alone when human witnesses do not exist. Since our decision model uses parameters that can be quickly and objectively measured, this technique may be feasible for acute stroke decision-making.

Apparent Diffusion Coefficient Correlates With Tmax in Acute Ischemic Stroke - P76

Archana Purushotham, Maarten G Lansberg, Michael Mlynash, Jean-Marc Olivot, Roland Bammer, Stephanie M Kemp, Gregory W Albers; Stanford Univ, Palo Alto, CA

Background: Tmax is one of the MR perfusion measures used to estimate the penumbra in acute stroke. Tmax maps with a threshold of > 6 seconds can reasonably estimate the size...
of the final infarct in patients who do not have early recanalization. However, an elevated Tmax reflects delayed arrival of blood to brain tissue, and does not provide a direct assessment of cerebral blood flow (CBF). The apparent diffusion coefficient (ADC), derived from diffusion-weighted images, is a marker of ischemic damage to tissue. We sought to determine if there is a relationship between the ADC and Tmax both within the diffusion lesion and in the perfusion-diffusion mismatch region in acute stroke. Methods: As part of the DEFUSE study, 74 stroke patients were treated with IV tPA 3 to 6 hours after symptom onset. They underwent MRI scans immediately before, 3 to 6 hours after, and 30 days post-treatment. Subjects (n = 33) with technically adequate quality scans at all study timepoints and a baseline perfusion volume > 10 mL were included for this analysis. Voxel-based analysis of predicted infarct in red vs. penumbra in green, and the region of final infarct (drawn blinded to patient outcome), demonstrated a relationship between ADC and Tmax values in acute ischemic lesions. Since the ADC reflects the severity of ischemic injury and has been shown to correlate with CBF, this supports the physiological relevance of Tmax, and suggests that it may be a valid surrogate measure for CBF.

A Multiparametric Predictive CT Model of Penumbra vs. Core Infarction for Acute Ischemic Stroke

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Background: Objective imaging methods to identify the best candidates for acute stroke recanalization therapies are urgently needed. Prior CT approaches to visually distinguish penumbra from core employing mismatch have shown poor interrater reliability. Methods: An analysis of imaging and clinical data was performed on 32 patients meeting the following inclusion criteria: acute anterior circulation MCA or ICA occlusion, successful recanalization with thrombolytics or mechanical therapy (TIMI 2 or 3), treatment within 8 hours of onset, pre-treatment perfusion CT, and post-treatment imaging for final infarct > 24 hours from onset. Subjects were randomly divided into derivation (n = 21) and validation (n = 11) cohorts. Pretreatment perfusion CT parameters were analyzed by logistic regression to identify variables independently predicting final tissue outcome (infarct or salvage) on a voxel-by-voxel basis. Results: A total of 1,237,938 voxels were included in model development and validation. The model volume has two branches with a median equal to 34% (male) and 51% (female) respectively. The model substantially outperformed single parameter and visual inspection models. Conclusions: A multiparametric CT model incorporating information from multiple perfusion maps was developed that distinguishes salvageable tissue from tissue destined for infarct despite early repufusion using a voxel-based analysis. This model achieved an overall accuracy of 79%, a value comparable to similar MR models. This model offers a more reliable approach than visual mismatch for assessing the penumbra with multimodal CT.

Conversion of Ischemic but Viable Tissue Into Infarction is Different Between Men and Women

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Background: The relationship between gender and ischemic stroke outcome in humans is not well understood and highly variable across the published studies. Evidence from experimental stroke models suggests that female rodents develop smaller infarcts as compared to age-matched male rodents. We hypothesize that sex is a marker for tissue susceptibility to ischemia and thus play role in determining tissue outcome in human stroke. Methods: We studied 141 consecutive patients (53 women and 88 men) with acute ischemic stroke and DWI/MTT mismatch > 25% of the DWI lesion volume. All patients had a baseline MRI obtained within 12 hours of symptom onset and a follow-up MRI on day 4 or later. The amount of lesion growth was calculated as percentage of initial DWI/MTT mismatch that was infarcted on the follow-up MRI [percentage mismatch lost or PML = (Final volume - DWI volume) / (MTT volume - DWI volume) × 100%]. Statistical analysis explored relationships with gender and other known predictors of infarct growth including age, admission mean arterial pressure, admission blood glucose, admission NIHSS score, etiologic stroke subtype, time from symptom onset to MRI, IV thrombolytic therapy, and baseline DWI and MTT lesion volumes with the goal of learning how these factors related to the PML. Results: There was no difference in PML between men and women (median and IQ range; 19%, 2-46% and 11%, 3-55% respectively, p = 0.72). There was, however, an interaction between sex and age; median PML was 7% (0-12%) in women and 18% (1-35%) in men when only patients younger than the population median (71 years) were considered (p = 0.06). The PML was not different between men and women ≥71 years old (25% in both women and men). The linear regression model revealed that gender (p = 0.03) and the interaction term between age and gender (p = 0.02) were independent predictors of PML. In patients ≥70 years old, the women to men ratio of PML estimated from the regression model was 0.42 (95% CI, 0.15-0.90). Conclusion: There is a sex difference in tissue outcome after ischemic stroke. The magnitude of sex-outcome relationship is influenced by age; women ≥70 years old are subject to approximately 2.5 times less infarct growth as compared to their male counterparts. The interaction between age and sex could explain the apparent discrepancy in human studies dealing with sex differences in stroke outcome.

Leptomeningeal Collateral Perfusion in Acute MCA Occlusion Reveals Inherent Vulnerability to Failure: Quantifying the Hemodynamics of FLAIR Vascular Hyperintensity

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Background: Slow filling of the MCA downstream from an occlusion or tight stenosis causes FLAIR vascular hyperintensity (FVH) on MRI. This noninvasive finding may provide clues to the relationship between the ADC and Tmax both within the diffusion lesion and in the perfusion-diffusion mismatch region in acute stroke. Methods: As part of the DEFUSE study, 74 stroke patients were treated with IV tPA 3 to 6 hours after symptom onset. They underwent MRI scans immediately before, 3 to 6 hours after, and 30 days post-treatment. Subjects (n = 33) with technically adequate quality scans at all study timepoints and a baseline perfusion lesion volume > 10 mL were included for this analysis. Voxel-based analysis of predicted infarct in red vs. penumbra in green, and the region of final infarct (drawn blinded to patient outcome), demonstrated a relationship between ADC and Tmax values in acute ischemic lesions. Since the ADC reflects the severity of ischemic injury and has been shown to correlate with CBF, this supports the physiological relevance of Tmax, and suggests that it may be a valid surrogate measure for CBF.
adequacy of collateral perfusion with implications for clinical outcome and likelihood of revascularization. We quantified the intravascular hemodynamic parameters associated with FVH in leptomeningeal collateral flow distal to acute MCA occlusion, providing novel insight on collateral failure. Methods: FLAIR and perfusion MRI were acquired in 50 consecutive cases of acute stroke due to isolated proximal MCA (M1) occlusion verified by conventional angiography. Angiographic collaterals were graded with the ASITN/SIR scale. FVH was noted in proximal and distal MCA segments. Cerebral blood volume (CBV) and mean transit time (MTT) were calculated in these locations. Results: 10 men and 40 women (mean age 66.3 ± 17.6 years) were included in our analyses. Median NIHSS was 17.5 points (IQR 8.75). Collateral grade was distributed across the entire scale. Proximal FVH (pFVH) immediately distal to the M1 occlusion was noted in 45/50 (90%). Distal FVH (dFVH) at the periphery of the MCA territory was noted in 27/50 (54%). 10% had neither pFVH nor dFVH, 36% pFVH without dFVH, and 54% both pFVH and dFVH. CBV varied considerably between distal and proximal sites across cases. Distal MTT near collateral inflow routes ranged from 0.00-14.26 sec (mean 2.11) and proximal MTT at the distal and proximal end of the occlusion ranged from 0.00-16.76 sec (mean 4.21). FVH correlated with MTT delays of approximately 1 sec or greater (p < 0.01). Conclusions: Retrograde arterial delivery of collateral flow beyond an MCA occlusion is associated with prominent slowing evident as FVH and often exceeding MTT thresholds for penumbral tissue. Progressive slowing from distal to proximal segments compounded by CBV decelerations may predispose to collateral failure.

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Ultra-early Recanalization and Re-occlusion in Patients With Acute Ischemic Stroke: A Multimodal Serial Angiographic Study

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Objective: To determine the rate of ultra-early recanalization and re-occlusion in patients with acute ischemic stroke, effect of intravenous recombinant tissue plasminogen activator (rt-PA), and overall effect on clinical outcomes among patients with ischemic stroke. Spontaneous recanalization and re-occlusion occurring within hours after symptom onset have been reported in anecdotal cases. Methods: We compared the findings between computed tomographic (CT) angiography and subsequent catheter angiography (within 2 hours) to determine the status of occlusion in a series of patients with ischemic stroke evaluated within 6 hours of symptom onset. We subsequently evaluated the effect of ultra-early recanalization and re-occlusion on clinical outcomes and symptomatic intracranial hemorrhage (ICH). Results: A total of 48 patients (mean age ± standard deviation [SD] 66 ± 14 years; 22 were men) were analyzed. The median time interval (range) between CT angiography and symptom onset was 165 (22-967) minutes. The median time interval (range) between CT angiography and catheter angiography was 271 (37-968) minutes. Ultra-early recanalization was observed in 6 (12.5%) patients and was more frequent in patients treated with intravenous rt-PA than those not treated in the interim period between CT angiogram and catheter angiogram (24% versus 4%, p = 0.07). All the patients who experienced ultra-early recanalization had neurological improvement by 24 hours as compared with only 19 (45%) patients without ultra-early recanalization. None of the patients with ultra-early recanalization suffered symptomatic ICH. Ultra-early re-occlusion was observed in 4 (8%) of 48 patients. Conclusions: We found that ultra-early recanalization or re-occlusion occurs in approximately 20% of the patients within 6 hours of initial evaluation. The findings support the dynamic nature of arterial occlusion in acute ischemic stroke.

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Diffusion Tensor Imaging in Acute Stroke: Seeing is Believing

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Background: Diffusion-weighted imaging (DWI) is one of the most sensitive and ubiquitous diagnostic tools for acute ischemic stroke. Diffusion tensor imaging (DTI) may improve the sensitivity of DWI in acute stroke lesion depiction. Based on this premise, we have conducted a retrospective study investigating the comparative yield of each modality in acute stroke. Methods: We queried the University of Utah Hospital quality-control stroke database to obtain a list of consecutive patients who prompted a “brain attack” by presenting to the ED or within the hospital with sudden onset of acute stroke-like symptoms from January 21, 2009 - June 20, 2009. The charts of these patients were reviewed and only those whom had undergone MRI with both DWI and DTI sequences were included. Studies were performed on a 1.5 Tesla. A positive scan was defined as high signal on DWI or DTI with low signal on the corresponding ADC (apparent diffusion coefficient) map. Positive or negative results were recorded (as determined by two board-certified neuroradiologists), along with the clinical diagnosis (stroke, TIA, or non-stroke, as determined by the stroke team) and the period of time from the onset of symptoms to imaging (classified as 0-3 hrs, >3-6 hrs, >6-12 hrs, >12-24 hrs, >24 hrs).

Results: The initial query yielded 135 patients with acute stroke-like symptoms, of whom 58 had MRIs performed that included both DWI and DTI sequences. In 23 patients, both DWI and DTI sequences were negative; all 23 had non-stroke diagnoses, including TIA. Timing of imaging in these patients was 0-3 hrs in 22%, >3-6 hrs in 26%, >6-12 hrs in 22%, >12-24 hrs in 26%, and >24 hrs in 4%. In the remaining 35 patients, imaging was positive on both
DWI and DTI sequences; all had ischemic stroke as their clinical diagnosis. Timing of imaging in these patients was 0-3 hrs in 3%, >3-6 hrs in 6%, >6-12 hrs in 37%, >12-24 hrs in 23%, and >24 hrs in 31%. In the patients with positive DTI and DWI, 19 (54%) had lesions much more conspicuous on DTI than DWI and 6 (17%) had additional ischemia identified on DTI that was not seen on DWI. Two scans had more detectable signal abnormality and greater lesion number. In 39% of the 23 DTI scans with lesions that were either more detectable or greater in number, the location of the lesions of interest was brainstorm or cerebellar. The difference between DWI and DTI may be due to differences in number of diffusion encoding directions, differences in b-value, or differences in signal to noise ratio. There was no association between timing of imaging and either increased intensity or detection of lesion number on DTI (Chi-square NS). Conclusion: When a patient has a clinical presentation that localizes to the posterior fossa, DTI may heighten the sensitivity for lesion detection over DWI. Furthermore, additional small areas of ischemia may be detectable, which could potentially help with diagnosis of stroke etiology.

Patients who had symptom resolution followed by recurrence of symptoms while in the hospital and brain infarction were labeled “TIA followed by stroke.” Patients who had symptom resolution without recurrence of symptoms yet DWI positive changes were labeled “clinical TIA with infarction.” We sought to compare symptoms, lesion location, patient demographics and stroke etiologies in the three groups of patients. Results: 83 patients met inclusion criteria: 20 had NIHSS = 0 infarcts; 17 had TIA followed by stroke, and 46 had clinical TIA with infarction. The most frequent symptoms experienced by patients with NIHSS = 0 infarct were headache, vertigo, nausea, ataxia, confusion, and blurred vision. The posterior circulation, and specifically, the cerebellum, was most commonly infarcted in this group. The distributions of stroke etiologies differed among groups. Most patients with NIHSS = 0 infarcts were discharged home. Discussion: While the NIHSS examination identifies many stroke symptoms, this tool will fail to identify some strokes involving the posterior circulation. Some of the unscoured symptoms were subtle, but others were potentially disabling. A missed infarction could be a missed opportunity to institute appropriate preventative measures.

The present study indicates that occlusion-site is the important determinant to predict the outcome of ischemic stroke patients.

**Fig. Possible mechanism of ‘Spear arrow’ formation**

**NIHSS = 0 Does NOT Equal the Absence of Stroke**

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**Background:** The NIH Stroke Scale examination is a useful tool for identifying stroke. Not all stroke symptoms and signs are captured as deficits on the NIHSS examination. **Purpose:** We sought to determine the symptoms commonly experienced and the stroke localization of patients with brain infarction and an NIHSS score of 0. **Methods:** We studied all patients who presented with acute neurological symptoms to our stroke center from 2004-2008 yet had an NIHSS score of 0 despite confirmation of brain infarction on MRI with diffusion weighted imaging (DWI). Patients who did not have symptom resolution with persistent NIHSS score of 0 were labeled “NIHSS = 0 infarcts.”

The present study indicates that occlusion-site is the important determinant to predict the outcome of ischemic stroke patients.

**Patient and Stroke Characteristics and Outcomes**

<table>
<thead>
<tr>
<th>Age, mean ± SD</th>
<th>NIHSS = 0 infarcts</th>
<th>TIA followed by stroke</th>
<th>Clinical TIA with infarction</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>54.1 ± 15.4</td>
<td>69.2 ± 13.0</td>
<td>63.2 ± 15.5</td>
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<td>0.070</td>
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<tr>
<td>Gender, % female</td>
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<td>41.2</td>
<td>54.3</td>
<td>0.304</td>
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<tr>
<td>Ethnicity, %</td>
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<td>White</td>
<td>Hispanic</td>
<td>Asian</td>
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<tr>
<td>35.0</td>
<td>58.8</td>
<td>50.0</td>
<td>15.0</td>
<td>0</td>
</tr>
<tr>
<td>White</td>
<td>50.0</td>
<td>41.2</td>
<td>8.7</td>
<td>0</td>
</tr>
<tr>
<td>Hispanic</td>
<td>15.0</td>
<td>0</td>
<td>8.7</td>
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<tr>
<td>Asian</td>
<td>0</td>
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<td></td>
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<tr>
<td>Symptoms, %</td>
<td>Headache</td>
<td>Vertigo</td>
<td>Nausea</td>
<td>Ataxia</td>
</tr>
<tr>
<td>45.0</td>
<td>23.5</td>
<td>30.0</td>
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<tr>
<td>Headache</td>
<td>45.0</td>
<td>23.5</td>
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<tr>
<td>Vertigo</td>
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<tr>
<td>Nausea</td>
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<tr>
<td>Ataxia</td>
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<td>Limb weakness</td>
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<tr>
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<td>Cerebellar involvement, %</td>
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<td>Limited to posterior circulation involvement, %</td>
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<td>Small vessel</td>
<td>Cryptogenic</td>
<td>Other</td>
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<tr>
<td>Large vessel</td>
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<td>41.2</td>
<td>17.6</td>
<td>5.9</td>
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<tr>
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<td>23.5</td>
<td>5.9</td>
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<td>Other</td>
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<td>Disposition, %</td>
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<td>Inpatient rehab</td>
<td>Skilled nursing</td>
<td>Other</td>
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<tr>
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<td>10.0</td>
<td>10.0</td>
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<td>5.0</td>
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<tr>
<td>Skilled nursing</td>
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<td>11.8</td>
<td>13.0</td>
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<tr>
<td>Other</td>
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<td>11.8</td>
<td>6.5</td>
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<td>mRS, median (range)</td>
<td>1 (0–5)</td>
<td>1 (0–6)</td>
<td>0 (0–6)</td>
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**The Curcumin-based Derivative CNB-001 Attenuates Ischemia-induced Cell Death in vitro and Reduces Embolism-induced Clinical Deficits in vivo in a Rabbit Stroke Model: Neuroprotection is Mediated via an Erk-ORP150 Pathway**

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**Background and Purpose:** Curcumin, which has been used for centuries in India as a food flavoring, preservative and medicinal herb has been shown to have significant neuroprotective properties. We synthesized a hybrid curcumin pyrazole derivative designated CNB-001, created by combining cyclohexyl bisphenol A, a molecule with known neurotrophic activity and curcumin. In the present study, we characterized the neuroprotective activities and mechanisms action of CNB-001 using both in vitro and in vivo stroke assays.

Methods: For in vitro analysis, we used the following HT22 cell assays: (1) an oxytosis assay induced by exogenous glutamic acid to inhibit cystine uptake and induce programmed cell death and (2) an ischemia

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assay using iodoacetic acid (IAA), an irreversible inhibitor of the glycolytic enzyme glyceraldehyde 3-phosphate dehydrogenase to deplete energy metabolism. For in vivo analysis, we used the rabbit small clot embolic stroke model (RSCEM, STROKE: 1958-1988, 2004), which is based upon the injection of blood clots into the cerebral vasculature to produce various behavioral endpoints, which were measured quantitatively as a P-value (effect size of stroke dose).

**Results:** We found that CNB001 protects HT-22 cells from glutamic acid-induced oxytosis with an EC_{50} of 700 mM and IAA-induced toxicity with an EC_{50} of 0.6 mM (90% cell viability) when CNB001 was added both during and at the end of a 2 hr exposure to 20 mM IAA. In addition, if CNB001 was added to the cultures after the 2 hr exposure to IAA, there was still significant protection by CNB001 when used at a concentration of 1 mM (approx 80% viability). Since CNB001 was neuroprotective in vitro, we determined if CNB001 could improve behavior using the RSCEM when CNB001 was administered following embolization. CNB001 (100 mg/kg) given 5 or 60 minutes following embolization significantly increased P0 values to 2.16 ± 0.46 mg (n = 21) and 2.80 ± 0.59 mg (n = 17), respectively, compared to a vehicle-treated control value of 0.84 ± 0.38 mg (n = 21). To elucidate the mechanism(s) of action of CNB001, we studied the effects of CNB001 on two different pathways. First, both in the cell culture model and in rabbit brains, Extracellular Signal-Regulated Kinase (ERK) activation was decreased following ischemia and CNB-001 prevented the decrease. CNB-001 also increases the level of the inducible endoplasmic reticulum chaperone oxygen-regulated protein 150 (ORP150) which is decreased in embolized rabbit brain.

**Conclusions:** Our study shows that we can use a series of specific in vitro assays to identify novel compounds that will have neuroprotective activity in a rigorous animal model of embolic stroke, a necessity in order to initiate a clinical trial. In addition, we identified 2 molecular pathways that are involved in CNB-001-induced neuroprotection, pathways that will allow us to further identify novel drug targets to treat stroke.

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**Neuroprotective Effect of Human Chorionic Gonadotropin in Transient Focal Cerebral Ischemia in Rats**

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**Introduction:** Different growth factors have been found to improve the long-term outcome in animal models when administered the first few days after stroke. Human chorionic gonadotropin (hCG), like other neurotrophic factors, promotes proliferation of endogenous neural stem cells. This study examined effects of hCG when administered 24 h after stroke.

**Methods:** Physiologically controlled male Long Evans rats (270-335g) received 90 min middle cerebral artery occlusion (MCAo) by poly-L-lysine-coated intraluminal suture. At 24 hr after stroke, animals were randomized into 4 treatment groups in a double-blinded manner: (Group 1) Saline, on days 1, 3, 5, 7, 9; (Group 2) hCG (440 IU/l/day, on days 1, 3, 5, 7, 9); (Group 3) hCG (440 IU/l/day, on days 1, 3, 5, 7, 8, and 9); and (Group 4) hCG (220 IU/l/day, on days 1, 2, 3, 4, 5, 7, 8, and 9). All treatments were given IM, n = 10 per group. The neurological status was evaluated during occlusion (at 60 min) and on day 1, 2, 3, 7, 14, 21 and 28 after MCAo; a grading scale of 0-12 was employed (0=normal score; 12=maximum deficit). Twenty-eight days after MCAo, brains were perfusion-fixed, and lesion volume and percent of normal tissue loss relative to unlesioned hemisphere were determined. **Results:** Physiological variables were stable and showed no significant differences between groups. Treatment with hCG (Groups 3 and 4) significantly improved the neurobehavioral deficit compared to the vehicle group on weeks 2 (3.0±0.8 and 4.6±0.5 vs. 6.8±0.1mm, respectively), 3 (2.0±0.8 and 4.5±0.5 vs. 6.0±0.6mm, respectively) and 4 (2.0±0.6 and 3.5±0.5 vs. 5.9±0.6mm, respectively) (p<0.001, vehicle vs. Group 3; p<0.01, vehicle vs. Group 4). Histologically, the vehicle group showed large hemorrhagic infarcts with pan-necrosis and cystic changes. By contrast, hCG-treated brains contained preserved normal and subcortical structures and a subacute infarct core. hCG (Groups 3 and 4) significantly reduced total lesion volumes compared to vehicle group (12.6±23.7 vs. 83.2±21mm^3^, respectively), increased residual (normal) tissue in the infarcted hemisphere (472±17 and 440±18 vs. 337±32mm^3^, respectively), reduced tissue loss in the contralateral hemisphere (82±13 and 70±16 vs. 144±22mm^3^, respectively) (p<0.05). Groups 2 and 3 (p<0.001, vehicle vs. Group 3; p=0.002 vehicle vs. Group 4). **Conclusion:** These results demonstrate that treatment with hCG, when administered at 24 hr after onset of MCAo, confers behavioral and histological improvement. Extensive human experience exists for hCG, suggesting high potential for translation into studies of acute human stroke.
Effect of Citicoline Treatment in Animal Models of Focal Cerebral Ischemia: A Systematic Review and Meta-analysis.

Dolors Giralt, Lidia García-Bonilla, Maite Mendioroz, Sophie Domínguez-Montanari, Anna Rosell, Joan Montaner; Neurovascular Risk Lab, Vall d’Hebron Hosp, Barcelona, Spain

Introduction: Citicoline (cytidine-5’-diphosphocholine or CDP-choline) is a precursor essential for the synthesis of phosphatidylcholine, one of the cell membrane components that is degraded during cerebral ischemia to free fatty acids and free radicals. Therefore, citicoline is a candidate neuroprotective drug for ischemic stroke. Any decision to proceed to clinical trial for such drugs should be based on an unbiased assessment of all available data. Here we use for the first time a systematic review and meta-analysis to assess the evidence for a protective effect of citicoline in animal models of focal cerebral ischemia. Methods: Forty two studies of citicoline treatment in animal models of cerebral ischemia were identified from PubMed and hand searching of abstracts of scientific meetings. A total of 18 studies were excluded from the analysis because these works were not based on a focal ischemic model of the middle cerebral artery occlusion; six studies were in Chinese and two in French. Fifteen studies were identified describing procedures involving 313 animals and reporting the effect of citicoline on infarct size (n=313) or functional outcome (n=104). The quality of the studies (range score 0-11) was analyzed based on the recommendations of good laboratory practice. Results: Overall, citicoline reduced infarct volume by 21% (95% confidence interval (CI), 20-22%; p<0.001) and the reduction was higher in transient ischemia (22%, 95% CI, 20-23%; p<0.001) than in permanent ischemia models (19%, 95% CI, 19-20%; p<0.001). A considerable improvement in neurological outcome was also observed (11%; 95% CI, 9-13%; p<0.001), although only three works reported such data. The quality of the studies (range score 6-11) was modest (4, interquartile range, 3-7). However, when stratifying the meta-analysis by quality score (0-4 range, low quality vs 5-11, high quality) studies with greater quality showed a greater effect of citicoline on infarct size reduction than in those with less quality (23%; 95% CI, 22-25%; p<0.001 vs 20%; 95% CI, 19-20%; p<0.001). Conclusion: Meta-analysis provides an effective technique for the aggregation of data from experimental stroke studies. We conclude that in animal models of focal cerebral ischemia, citicoline reduces the infarct volume and improves outcome, pointing citicoline as a candidate neuroprotective drug for human stroke.

Phosphodiesterase-4 Inhibitor Rolipram Increases Infarct Volume in a Rat Embolic Experimental Stroke Model

Fan Yang, Dong Xue, Mark Fisher; Univ CA Irvine, Irvine, CA

Genetic studies have implicated the phosphodiesterase-4 (PDE4) pathway, specifically PDE4D, in stroke pathogenesis. However, the precise relationship between PDE4 expression and stroke has remained uncertain. In order to define the relationship between PDE4 pathways and stroke pathogenesis, we studied the role of the PDE4 inhibitor rolipram in an experimental stroke model that approximates human stroke. We hypothesized that PDE4 regulates infarction in this model, which utilizes a single clot made one day prior to experimental stroke. Wistar rats were treated with rolipram (3mg/kg ip) one hour prior to onset of cerebral ischemia. We induced ischemia by injection of the clot to the origin of middle cerebral artery via the external carotid artery and internal carotid artery. There were no significant differences between groups for blood vessels of T1 and T2 diabetic pigs compared to the control animals (Figure). The mRNA expression was significantly higher intra- and extra-cranial vessels T1 and the T2 animals compared to corresponding controls (all p-values <0.02 for each vessel pair). Discussion: IL-6, IL-12, and MCP-1 are common mediators in the human inflammatory cascade implicated in atherosclerosis. Our immunohistochemical and mRNA expression data suggest that humanoid plaques seen in the diabetic/hyperlipemic pig mimics human cerebrovascular disease, with key mediators of inflammation being differentially expressed. With our validated model, we will elucidate the temporal and spatial sequence of expression of these and other inflammatory mediators. Ultimately, we expect this humanoid model of diet induced insulin resistance and type 2 diabetes to study pathogenesis and new therapeutic options for stroke and to facilitate the development of treatments for human cerebrovascular disease.

Inhibition of Cytosolic Phospholipase A2 Alpha Protects Against Focal Brain Ischemic Damage in Mice

Jian Zhang, Rung-Chi Li, Adam Sapirstein; Johns Hopkins Univ, Baltimore, MD

The cytosolic phospholipase A2c (cPLA2c) has been implicated in mediating ischemic stroke damage but its mechanism is unclear. It has been reported that cPLA2 enhances post-ischemic inflammatory damage following cerebral ischemia and reperfusion in experimental stroke models. Here, we tested the effect of arachidonoyl trifluoromethyl ketone (ATK), an inhibitor of cPLA2c, on stroke injury in mice. Male C57BL/6 mice, in each of 5 treatment groups, were subjected to 1 hour of transient MCA occlusion (MCAO) followed by 24 hours of reperfusion. Mice were treated with intraperitoneal injection of 10 mg/kg ATK, 10 mg/kg NS398 (a COX-2 inhibitor), or an equivalent volume of vehicle at times determined by the group designation (Table 1). Following reperfusion, neurological deficits were scored and the brain injury was measured using MTT staining. Treatment with the ATK 1 hour before MCAO, 1 hour after reperfusion and 6 hours later reduced hemispheric infarct size by 43% as compared to treatment with vehicle (P<0.05). Treatment with NS398 produced similar injury reduction (50%, P<0.05). PNS compared to ATK treatment. Similar results were also seen when the time of MCAO was reduced to 30 minutes. When mice were treated with only the first 2 ATK doses the reduction in injury compared to vehicle treatment was not significant. Similarly, a single pretreatment dose of ATK failed to significantly reduce the volume of stroke injury. The results suggest that inhibition of cPLA2c may reduce cerebral ischemia and reperfusion injury. In this model it is necessary to inhibit cPLA2c before ischemia and for an extended time following reperfusion in order to decrease injury.

Table 1.

<table>
<thead>
<tr>
<th>Time</th>
<th>Group</th>
<th>MCAO</th>
<th>Reperfusion</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Vehicle</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>NS398 3 doses</td>
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<td>X</td>
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<tr>
<td></td>
<td>ATK 3 doses</td>
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<td>X</td>
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<td></td>
<td>ATK 2 doses</td>
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<td>ATK 1 dose</td>
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MR Spectroscopy and Diffusion-Weighted MRI Can Accurately Measure Both Reduced and Increased Brain Temperature

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Aim: To assess whether Magnetic Resonance Spectroscopy (MRS), and Diffusion-Weighted imaging (DWI) can be used measure temperature change in a brain “phantom”. Methods: MRS and DWI sequences were performed in a clinical 1.5T MR scanner on a commercial phantom containing a number of brain metabolites at physiological concentrations at temperatures between 30º and 40ºC. The Proton Resonance Frequency (PRF) of water (temperature dependent) was compared to the PRF of NAA (temperature independent). This provided an internal correction for magnetic field inhomogeneity and other factors besides temperature that may influence the PRF of water. Acquired diffusion coefficient (ADC) values were calculated from DWI using the equation ADC = ln(Si/S0)/bi Results: The relationship between the water-NAA frequency shift and temperature in the phantom was T = 1–4.8011F + 285.77 (R2 = 0.96; p < 0.0001) with F in Hertz and T in degrees Celsius (ºC). ADC also correlated well with temperature, with the relationship T = -42.90X/S0 + 139.8722 (R2 = 0.99; p < 0.0001) with ADC in 10-3 mm2/sec and T in ºC. We were able to estimate temperature to within ±1.1ºC (95% Confidence Intervals) of the measured brain phantom temperature using this scanning method in vitro. Conclusion: Both MRS and ADC data can be used to detect temperature changes in vitro. Since the PRF measured using spectroscopy is independent of tissue type, this method shows the most promise for in-vivo use, and is now being extended to measure regional brain temperature in a Phase IIb, randomised clinical trial of hypertension for the treatment of acute ischaemic stroke.

Altered Multiscale Cerebral Blood Flow Regulation in Elderly With Stroke

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Introduction: Cerebral blood flow (CBF) is tightly regulated in the narrow range despite the changes of systemic blood pressure (BP) in order to meet the brain’s metabolic demands. The CBF regulation can be assessed non-invasively from the coupling between CBF velocity (BFV) and BP fluctuations. Previous studies of the CBF regulation have mainly focused on large time scales (>10 sec), and the BP-BFV coupling at smaller time scales is not well studied partly due to technical difficulties. The aim of this study was to determine the BFV-BP coupling at different time scales or frequencies, the newly designed multimodal pressure-flow (MMFP) method was used to quantify phase shifts between BP and BFV oscillations at time scales of 2.6-50 sec and 0.02-0.39 Hz. A mixed model with subjects as a random factor was applied to determine the effects of frequency and stroke on BFV-BP phase shifts. Possible effects of age, sex, BMI, mean BP and CO2 levels were considered in the model. Results: In the controls, the phases of BFV oscillations were advanced compared to the BP phases (i.e., positive BFV-BP phase shift) (Fig. 1B), indicating a faster recovery of BFV mediated by the compensatory cerebrovascular autoregulatory mechanisms. Both control and stroke groups had larger BP-BFV phase shifts at lower frequencies (<10 sec) (Fig. 1C). At all tested frequencies, stroke subjects had smaller BP-BFV phase shifts than controls (p < 0.0028) (Fig. 1C), suggesting a reduced CBF regulation. The effects of frequency and stroke were independent of age, sex, BMI, mean BP and CO2 levels. Conclusions: CBF regulation affects the BP-BFV coupling over a wide range of time scales or frequencies (0.02-0.39 Hz) that is beyond the traditionally assumed active region of cerebral autoregulation (<0.1 Hz). The multiscale CBF regulation is significantly reduced in the elderly patients with stroke over all tested time scales.

Quantifying the Impact of Pre-treatment MRI Inclusion Criteria on Type-I/Type-II Error in Experimental Stroke Modeling

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Background: Design of preclinical trials should match clinical trials, including pre-treatment MRI inclusion criteria. We investigated the impact of pre-treatment MRI inclusion criteria on Type-I/II errors using data from an ongoing preclinical trial. Methods: N = 75 spontaneously-hypertensive rats received 45 minutes of transient middle cerebral artery occlusion. Diffusion-weighted imaging and gradient-echo imaging were performed 30-minute post-occlusion for measurement of baseline lesion volume and application of pre-defined MRI inclusion/exclusion criteria. N = 64 animals met inclusion criteria. N = 11 were excluded for: lesion volume <50 mm3 (N = 8); intracerebral hemorrhage and lesion extension into the cerebellum (N = 3). Three hypothetical cases were investigated to assess Type-I/II errors. Case 1 assumed no treatment effect. Cases 2 and 3 assumed a treatment effect and a 33% reduction in lesion volume. For Case 1, N = 8 small strokes were assigned to the treatment group with N = 3 large strokes assigned to control. For Case 2, N = 3 large strokes were assigned to the treatment group with N = 8 small strokes assigned to control. For Case 3, N = 11 excluded strokes were randomly assigned. Excluded animals randomly replaced included animals for a total N = 64. Results: Lesion volume was 239 mm3 (41) with MRI inclusion criteria and 218 mm3 (105) without. For Case 1 with MRI inclusion, there was no difference in lesion volume for treatment vs. control (p = 0.07). However, Case 1 without MRI inclusion resulted in Type I error with a decrease in lesion volume for a treatment that has no effect [119 mm3 (124) vs. 291 (106), p < 0.01]. For Case 2 with MRI inclusion, there was a decrease in lesion volume for treatment vs. control [149 mm3 (39) vs. 254 mm3 (30), p < 0.01]. However, Case 2 without MRI inclusion resulted in Type II error with negative results for a treatment that has a true positive effect (p = 0.26). Case 3, with or without MRI inclusion, resulted in a decrease in lesion volume for the treatment group (p < 0.01), representing a true-positive result. Conclusions: In this study, we show how pre-treatment MRI inclusion criteria may reduce variability and the number of animals required to determine preclinical drug efficacy. Most importantly, pre-treatment MRI inclusion criteria reduce Type-I/II errors, thereby reducing study bias.


**Analysis of the Effect of the Number of Passes of the Merci Retriever During Mechanical Thrombectomy on Mortality and Outcomes**

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**Background:** Mechanical embolectomy using the Merci Retriever was approved for clot retrieval in 2004. Six passes of the device were allowed in the MERCI and MultiMerci Trials. The Saint Luke's Brain and Stroke Institute (SLBSI) has used the device in approximately 340 cases since 2004. Many cases have intra-operative complications requiring several passes of the device to achieve reperfusion. We sought to evaluate whether good outcomes and mortality were influenced by the number of passes of the device.

**Methods:** SLBSI enrolled 62 patients in theMerci Registry between June '07 and May '09. We analyzed these data dichotomized according to whether the case required 1-2 (n = 31) or >2 (n = 31) passes in regard to good outcomes (modified Rankin Score (mRS) of 0-2) mortality at 90 days adjusting for age and baseline National Institutes of Health Stroke Scale (NIHSS) score and length of the procedure. Although the length of the procedure was statistically longer when more passes were required, the length of the procedure did not significantly influence outcomes. IA- tPA was more frequently used adjunctively in the cases where there were >2 passes.

**Table 1** summarizes the results of the unadjusted model. Though there was a trend in the direction of better outcomes with fewer passes, the number of passes was not a statistically significant predictor of good outcomes in any of the models. The unadjusted risk of good outcome at 1.5 (1.0667) is not statistically significant. In the adjusted model, the number of passes was a significant predictor of mortality, but not after adjusting for age or baseline NIHSS score or the combination of age, baseline NIHSS score and length of the procedure. Although the length of the procedure was statistically longer when more passes were required, the length of the procedure did not significantly influence outcomes. IA-tPA was more frequently used adjunctively in the cases where there were >2 passes using chi-square or Fisher's exact test. NIHSS scores at 24 hours, site of vessel occlusion and use of intra-arterial (IA) tissue plasminogen activator (tPA) are also reported.

**Results:** Table 1 summarizes the results of the unadjusted model. Though there was a trend in the direction of better outcomes with fewer passes, the number of passes was not a statistically significant predictor of good outcomes in any of the models. The unadjusted risk of good outcome at 1.5 (1/0.667) is not statistically significant. In the unadjusted model, the number of passes was a significant predictor of mortality, but not after adjusting for age or baseline NIHSS score or the combination of age, baseline NIHSS score and length of the procedure. Although the length of the procedure was statistically longer when more passes were required, the length of the procedure did not significantly influence outcomes. IA-tPA was more frequently used adjunctively in the cases where there were >2 passes.

**Conclusions:** In our series neither number of passes with the Merci Retriever nor length of procedure influenced good outcomes or mortality rates though there was a trend toward better outcomes in cases requiring 1 or 2 passes. These results support the continued practice of using the Merci Retriever up to 6 passes in appropriate cases.

**References:**

- Reza Jahan, Jeff Saver, David Liebeskind, UCLA Med Cntr, Los Angeles, CA; Paul Kim, Gene Sung, U. of Southern California Keck Sch of Medicine, Los Angeles, CA; Merci/Multi Merci investigators

**Background:** Intracranial hemorrhage is a feared complication of recanalization procedures of acute cerebral ischemia. Recently, major trials and registries of intravenous fibrinolysis have employed more clinically informed definitions for symptomatic intracranial hemorrhage (SICH) that correlate the presence of substantial amounts of blood with definite neurologic deterioration. The rate of SICH in mechanical thrombectomy has not previously been characterized with this approach.

**Methods:** We analyzed the datasets of the MERCI and Multi-MERCI multicenter clinical trials of mechanical thrombectomy. For this analysis, symptomatic intracranial hemorrhage (SICH) was defined as in the SITS-MOST registry (SM-SICH) as the combination of radiologic parenchymal hematoma occupying 30% or more of the infarct bed and the occurrence of neurologic deterioration defined as worsening by 4 points or more on the NIH Stroke Scale (NIHSS). To determine radiologic hemorrhage, all 24 hour post-treatment brain images obtained in the trial were reviewed and concordance reached by a vascular neurologist and a neuroradiologist and rated according to a modification of the ECASS Trial method (HT1, HT2, PH1, PH2). Demographic and clinical variables from the clinical trial datasets were analyzed. **Results:** Among the 305 patients enrolled in the trials, mean age was 67.6 and mean entry NIHSS 20. The average time from last known well to start of the endovascular procedure was 4.4 hours. Site of occlusion was the intracranial internal carotid artery in 32%, the M1 middle cerebral artery in 49%, and isolated M2 occlusion in 9% and the posterior circulation in 9%. 47% of cases had NIHSS 6 or greater at NIHSS 64% of cases were treated with alteplase. The rate of SM-SICH was 2.0%, SM-SICH was noted in 1.9% thrombectomy only, 3.2% IV lysis plus thrombectomy, 2.1% thrombectomy plus IA lytic or mechanical adjunctive and 0% IV lysis plus thrombectomy plus IA lytic or mechanical adjunctive. SM-SICH was most common among patients who were treated with alteplase (4.5%); TPA/M1 3.9% 4.6% TPA/M2 3.4% 0.0% increasing the odds of SM-SICH by 9.5 (95% CI 1.1-82.5, p = 0.04). Patients with SM-SICH tended to have lower rates of good 90 day outcome (mRS 0-2, 0% vs 33%, p = 0.20) and higher 90 day mortality (67% vs 37%, OR 3.4, 95% CI 0.6-18.5, p = 0.29). Conclusion: The rate of SITS-MOST hemorrhages in patients undergoing mechanical thrombectomy with the Merci Retriever is low, occurring in 2.0%. Failure to achieve recanalization increases the likelihood of symptomatic hemorrhage and SM-SICH is associated with lower rates of functional recovery and higher mortality. These observations may be used to provide additional information to patients and practitioners on the risks and benefits of endovascular clot retrieval.

**Stent-assisted Percutaneous Transluminal Angioplasty (SAPTA) for Acute Stroke Thrombolyis of Large Artery Occlusion Utilizing Self-expanding Intracranial Stents: A Single Center Series of 31 Consecutive Patients**

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**Background:** Tissue-plasminogen activator (tPA) has been shown relatively ineffective in the treatment of ischemic stroke with large vessel occlusion, prompting use of alternative therapies. Various endovascular techniques have been attempted with variable success. Intracranial SAPTA is a proposed means of recanalization initially performed with balloonexpandable stents. Data using self-expanding intracranial stents is lacking. This has caused us to critically review our experience using self-expanding intracranial stents in emergent endovascular thrombolysis of acute ischemic stroke. **Methods:** A prospective database all patients undergoing SAPTA for acute stroke from 6/06 to 6/09 served as the basis for the study. Data including time of stroke onset, time to SAPTA, recanalization, admission NIHSS, lesion location/ severity, TICI perfusion pre and post-procedure, time to recanalization, means of recanalization, discharge NIHSS/ mRS, and 3 mos NIHSS/mRS were recorded. The data was statistically analyzed and compared to historical controls. **Results:** 31 consecutive patients, 55% male, underwent SAPTA for acute stroke utilizing 40 stents. Mean patient age: 59(32-83). Mean presenting NIHSS: 142(26-2). 9 received I-PA with no immediate improvement. All patients demonstrated perfusion abnormality and large vessel occlusion by non-invasive imaging. Mean time to DSA was 541 min. All lesions demonstrated pre-procedure TICI 0-1 flow. Lesion location: 3 rt carotid T, 4 rt carotid T, 8 T M1, 6 n M1, 1 LT M1, 4 tandem Lt ICA/MCA, 1 intracranial Lt ICA, 3 basilar, and 1 pt P2. Mechanical devices were used in 42% of cases. 23 patients received IV tirofiban. 9 patients received I-PA. 33% of patients underwent pre-stent angioplasty. 17% required post-dilatation. Technical outcome: 100% achieved TICI 2a – 3 recanalization post SAPTA; mean time to recanalization: 752 minutes. 1 intra-operative hemorrhage occurred following stent deployment requiring ICA sacrifice. 1 stent occluded on PDA#1 causing infarct progression. Clinical outcome: At discharge, 32% of patients had a mRS of 0-2, 45% 3-4, and 23% 5-6. At 3 month follow up, 52% of patients had a mRS of 0-2, 24% 3-4, and 24% 5-6. Patients alive at 3 mos t/0s were 83% (95% CI 26.3) and 10% had a 3 mos in death in mean NIHSS 4. Symptomatic hemorrhage occurred, all at 3 mos in 3 additional patients due to stent occluded secondary to infarct progression. **Conclusion:** Our single center experience suggests SAPTA is an effective means of recanalization in acute stroke. The clinical outcome data is promising given the stroke severity and likelihood of response to conventional therapy. The moderately high rate of hemorrhagic conversion was likely secondary to the need for worse clinical presentation. Rts are necessary to determine true efficacy and safety of this treatment modality.

**Frequency, Predictors, and Consequences of Symptomatic Intracranial Hemorrhage in MERCI/Multi-MERCi Trials**

Reza Jahan, Jeff Saver, David Liebeskind, UCLA Med Cntr, Los Angeles, CA; Paul Kim, Gene Sung, U. of Southern California Keck Sch of Medicine, Los Angeles, CA; Merci/Multi Merci investigators

**Background:** Intracranial hemorrhage is a feared complication of recanalization procedures of acute cerebral ischemia. Recently, major trials and registries of intravenous fibrinolysis have employed more clinically informed definitions for symptomatic intracranial hemorrhage (SICH) that correlate the presence of substantial amounts of blood with definite neurologic deterioration. The rate of SICH in mechanical thrombectomy has not previously been characterized with this approach.

**Methods:** We analyzed the datasets of the MERCI and Multi-MERCI multicenter clinical trials of mechanical thrombectomy. For this analysis, symptomatic intracranial hemorrhage (SICH) was defined as in the SITS-MOST registry (SM-SICH) as the combination of radiologic parenchymal hematoma occupying 30% or more of the infarct bed and the occurrence of neurologic deterioration defined as worsening by 4 points or more on the NIH Stroke Scale (NIHSS). To determine radiologic hemorrhage, all 24 hour post-treatment brain images obtained in the trial were reviewed and concordance reached by a vascular neurologist and a neuroradiologist and rated according to a modification of the ECASS Trial method (HT1, HT2, PH1, PH2). Demographic and clinical variables from the clinical
12 vs. 62 ± 13, p = 0.003) and had higher NIHSS scores (18.3 ± 6.4 vs. 16.6 ± 5.9, p = 0.049) than those without. PH were commonly occurred in futile recanalization group (44% vs. 2%, p < 0.001). Multivariate logistic regression analysis revealed that the independent predictors of futile recanalization were age ≥ 1.037 (95% CI 1.011-1.07) and PH 34.410 (95% CI 7.80-151.80).

Conclusion: Despite recanalization, about half of patients suffered futile recanalization after IAT. Hemorrhagic transformation was most important predictor of futile recanalization. A strategy both reducing hemorrhagic transformation and facilitating recanalization is needed in IAT.

P102
The Carotidien Trans Sodium Crocetinate Improves Clinical Rating Scores When Administered to Rabbits Following Multiple Infarct Ischemic Strokes: A Combination Therapy Study With Tissue Plasminogen Activator
Paul A Lachapla, UCSD Neurosciences, La Jolla, CA

Background and Purpose: An interesting molecule designated as trans-sodium crocetinate (TSC), is a carotidien related to naturally produced crocetin that can be purified from Saffron. TSC is a pure trans-tomer that has the ability to act as a free radical scavenger, especially on hydroperoxide generation. However, the primary mechanism of action is hypothesized to be related to its ability to enhance oxygen diffusion between erythrocytes and tissues, in essence, creating an oxygen gradient in favor of tissue over blood. Because TSC is a multifunctional compound, it may be beneficial to treat stroke. The effects of TSC alone or in combination with a thrombolytic were evaluated on clinical ratings in a randomized, blinded study using a rabbit small clot embolic stroke model (RSCSM). Methods: All surgical and embolism procedures are as described previously (STROKE 35:1985-1988, 2004). Rabbits were embozied by injecting small blood clots into the brain vasculature via an indwelling carotid catheter. TSC or saline were administered IV bolus to achieve embolization. Behavior was measured 24 hours following embolization in order to calculate the effective stroke dose (P50) that produces neurologic deficits in 50% of the rabbits. A treatment is considered beneficial if it significantly increases the P50 compared to control. In this study, we determined the effects of TSC alone and in combination with the FDA-approved thrombolytic, tissue plasminogen activator (tPA). For thrombolytic studies, tPA (3.3mg/kg) was given IV, 1 or 3 hours post-embolization, with 20% as a bolus injection over one minute, followed by the remaining 80% infused over 30 min. Results: TSC (0.25 mg/kg) given 5 or 60 minutes following embolization significantly (p = 0.05) increased P50values by 104 and 181%, but not when given 3 hours post-embolization (e.g. increase of <0.05%). IR (3.3 mg/kg) produced a significant increase in P50when given 1, but not 3 hours following embolization. In combination studies, when TSC was administered 1 hour and tPA was given either 1 or 3 hours following embolization, the group P50values were increased by 281% and 140%, respectively. In addition, TSC plus tPA administered 3 hours following embolization significantly (p < 0.05) increased the group P50value by 90%. Conclusions: TSC may be useful for the treatment of AIS either alone or when administered before or concomitant with tPA to improve clinical rating scores with a therapeutic window for TSC therapy up to 3 hours in rabbits. In conclusion, we have demonstrated considerable efficacy for TSC in the rabbit embolic stroke model. Our studies suggest that TSC may either be used as a monotherapy or in combination with current FDA-approved thrombolytic therapy to improve clinical outcome in acute ischemic stroke patients.

P103
Minocycline to Improve Neurologic Outcome (MINOS) Early Phase Clinical Trial
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Background: Minocycline is a promising neuroprotective agent that is effective in multiple pre-clinical stroke models, including those using tissue plasminogen activator (tPA) for clot lysis. Minocycline has multiple mechanisms of action including inhibition of PARP-1 and MMP-9. The Minocycline to Improve Neurologic Outcome Study (MINOS) is an early phase II/III trial of intravenous (IV) minocycline in acute ischemic stroke. Methods: In an open label dose escalation design, minocycline is administered IV within 6 hours of the onset of symptoms at prespecified dose tiers of 3, 4, 5, 6, or 10 mg/kg and repeated every 12 hours for a total of 6 doses. The modified continual reassessment method is used to choose the next dose. Patients can be treated with tPA. Minocycline levels for pharmacokinetic analysis and MMP-9 levels are measured at various time points. Subjects are followed for 90 days with modified Rankin Scales (mRSs) done at 30 and 90 days. The trial remains ahead of its recruitment schedule and has enrolled 49 of our 60 patients. We anticipate finishing enrollment in October or November 2009. Of the 49 patients enrolled in the study, the majority received the highest dose of 10 mg/kg. Most of the 49 patients are Caucasian, 57% percent are male and 65% received tPA. The mean baseline NIHSS was 8.3 (5.7–12.1) and the mean onset to infusion time was 399.5 minutes (52–699). The mean infusion (SD = 48.8, range 197 to 371). The mean infusion time for the first minocycline dose was 66.8 minutes (SD = 12.7, range 54 to 118). Minocycline IV infusion has been well tolerated. Only 1 dose limiting toxicity has occurred thus far at the 10 mg/kg dose. At 80 days 61% had favorable outcome defined by mRSs of 0.1 (23/38) and there was no significant difference between the dose tiers in the proportion of favorable outcome. There were no symptomatic ICH by SITS MOST criteria and 1/32 by NINDS criteria. Pharmacokinetic analysis revealed a half life of about 24 hours. The effect on MMP-9 levels will be presented. Conclusions: 1) Minocycline is safe and well tolerated up to doses of 10 mg/kg IV alone and in combination with tPA. 2) The half life of minocycline is long, about 24 hours, allowing 24 hour dosing. 3) Minocycline may be an ideal agent to use in combination with tPA and should be tested in a phase III trial in acute ischemic stroke.
Mechanical Thrombectomy Significantly Improves Functional Outcome in a Stroke Cohort With Middle Cerebral Artery (MCA) Occlusion

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Introduction: The extent to which mechanical thrombectomy affects patient functional outcome in acute stroke remains controversial in part due to the absence of an appropriate control group in their studies. The purpose of this study was to assess the effects of the recently approved Penumbra System on patient functional outcome using the patients from the PROACT II study as historical controls. PROACT II assessed the effects of intra-arterial (IA) pro-urokinase in a stroke cohort with occlusion of the MCA. Methods: This study was a retrospective review of 89 consecutive patients with large vessel occlusion in the MCA and who were treated with the Penumbra System at 7 international centers. All patients reviewed had presentation within 8 hours of symptom onset with an occlusion (TIMI 0 or 1) of a treatable MCA. The primary endpoint was good functional outcome as defined by a modified Rankin Score (mRS) score of ≤2 at 90 day post-procedure. Results from the PROACT II trial were used as the historical control. Results:

<table>
<thead>
<tr>
<th>PROACT II PLACEBO</th>
<th>PENUMBA MCA GROUP (N=89)</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)(years)</td>
<td>64</td>
<td>66</td>
</tr>
<tr>
<td>Female</td>
<td>39%</td>
<td>50.6%</td>
</tr>
<tr>
<td>Baseline NIHSS (median)(range)</td>
<td>17 (4-28)</td>
<td>15 (5-25)</td>
</tr>
<tr>
<td>TIMI 2-3</td>
<td>18%</td>
<td>87.6%</td>
</tr>
<tr>
<td>Symptomatic ICH</td>
<td>2%</td>
<td>5.6%</td>
</tr>
<tr>
<td>mRS 2 at 90 Days</td>
<td>25%</td>
<td>51.4%</td>
</tr>
<tr>
<td>Death at 90 Days</td>
<td>27%</td>
<td>14.6%</td>
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=JAMA 1999;282-2003-2011 + P value is for testing against PROACT II placebo using a 2-tailed Fisher’s Exact Test.

Conclusion: These results suggest that when compared with the appropriate population, the Penumbra System is effective in the revascularization of large vessel occlusion in the MCA leading to good functional outcome. This was associated with a higher rate of symptomatic ICH over the PROACT II placebo patients but similar to those seen in IA thrombolytic therapies.

P015 Endovascular Therapy for Acute Ischemic Stroke Due to Large Vessel Infracastral Occlusion: A Ten Year Single Center Experience

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Background: As endovascular therapy for acute ischemic stroke (AIS) have evolved over time, we sought to report outcomes and hemorrhagic complications in a single-center series of patients treated with a multitude of approaches over the last 10 years. Methods: Retrospective review of a prospectively collected database of acute stroke interventions from 1999 to 2009 was performed. Demographic, radiologic, and outcome data were analyzed. Successful recanalization was defined as TIMI grade 2 or 3. Functional outcome, mortality at 3 months, and symptomatic intracerebral hemorrhage (sICH), defined as any intraparenchymal hematoma (IPH) within 48 hours of the procedure, were assessed. Favorable outcome was defined as modified Rankin Score ≤2. Results: A total of 446 patients were analyzed. Median age was 69 (55.5% female). Median NIHSS was 17 (95% confidence interval: 14-20). Successfull recanalization occurred in 300 patients (72%). Complete recanalization (TIMI 3) occurred in 91 patients (21.9%). Occlusion sites were: M1 (46.5%), M2 (14.1%), ICA terminus (23.6%), tandem intra/extracranial carotid occlusion (17.5%), vertebralbasilar (14.5%). Median time from symptom onset to procedure start was 4.8 hours. Median procedure duration: 109 minutes. Favorable outcomes were seen in 38% of patients. Mortality at 3 months: 35%. Rate of sICH: 8.8%. Treatment modalities included: intra-arterial thrombolitics alone (22.4%) or in combination with mechanical thrombectomy (57.3%), MERCI clot retrieval (49.1%), Penumbra (4.0%), intra/extracranial stenting (29.7%), intra/extracranial angioplasty (33.4%), manual aspiration (6.5%). GpIIbIIIa inhibitors were administered in 36.3% of patients. In univariate analysis, factors found to be significantly associated with favorable outcomes were: age, history of hypertension and/or diabetes, admission serum glucose, admission NIHSS, presence of ICA terminus occlusion, procedure -preprocedure ASPECTS score, intubated state during the procedure, and successful recanalization. In multivariate analysis, age (OR 0.88, 95% CI 0.85-0.92, P <0.0001), admission NIHSS (OR 0.88, 95% CI 0.81-0.96, P <0.007 ), pre-procedure ASPECTS score (OR 0.177, 95% CI 1.23-2.56, P =0.002), successful recanalization (OR 9.14, 95% CI 2.35-35.6, P <0.001), and time to treatment (OR 0.995, CI 0.996-0.999, P =0.011) remained significant predictors of favorable outcome. Conclusions: Our single center experience indicates that endovascular therapy for AIS patients has similar rates of favorable outcomes and safety profile compared to those reported in multi-center studies employing more homogeneous treatment modalities. Our findings may provide pilot data for planning of future randomized trials involving multiple recanalization methods.
Incidence, Predictors, and Outcomes of Intracranial Vessel Perforation During Endovascular Therapy for Acute Ischemic Stroke

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Background and Purpose: Incidence and prognosis of vessel perforation during endovascular therapy for acute ischemic stroke (AIS) have been poorly described. We sought to review our experience with this complication at our institution over a ten-year period. Methods: Retrospective review of a prospectively acquired database of AIS patients with large vessel intracranial occlusions receiving endovascular therapy at the University of Pittsburgh Medical Center during the time period 1999 to 2009. Univariate and multivariate logistic regression analyses were performed investigating the association between perforation and the following variables: age, gender, admission blood pressure, admission glucose, admission NIMSS, occlusion location (vertebrobasilar, M1, M2, ICA terminus, tandem, intra- and extracranial occlusion), procedure duration, time to recanalization, thrombolytic regimen, and patient outcome. Results: Of 448 consecutive patients that were included in the study, 18 (4.0%) experienced intra-procedural perforation. In patients with perforation, inhospital mortality was 16/18 (88.8%) versus 121/414 (29%) in non-perforated patients (P<0.001). Rate of favorable outcome was 0% in perforated patients versus 37.6% in non-perforated patients (P<0.001). In univariate and multivariate analyses, history of hypertension (OR 1.016, 95% CI 0.04-0.67, P<0.012), procedure duration (OR 1.003, 95% CI 1.0006-1.007, P<0.02), and successful recanalization (TIMI 2 or 3) (OR 0.13, 95% CI 0.03-0.50, P=0.003) were significantly associated with perforation. Conclusions: Our findings indicate that vessel perforations during endovascular therapy for AIS, while of relatively low incidence, are catastrophic events with extremely high mortality rates. Factors found to be significantly associated with the incidence of this complication are absence of history hypertension, long procedure duration, and absence of vessel recanalization. Our findings do not support the notion that pharmacological thrombolysis decreases the incidence of vessel perforation.

Impact of Fetal-variant Willisian Circle on Cerebral Blood Flow Volume

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Background: The anatomical variations of the circle of Willis may be a risk for ischemic cerebral infarction. Ultrasound-derived volumetric flow analysis can assess the relative flow of brain circulation. The aim of this study was to investigate anterior and posterior flow using ultrasound-derived application of CBF volume measurements at the bedside. The fetal-variant circle of Willis appears to be an important determinant in anterior and posterior CBF volume distribution of the brain circulation.

Mean Wall Share Stress as Function of Age in Major Cerebral Arteries: Measurement With Quantitative Magnetic Resonance Angiography in 301 Healthy Adults

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Introduction: Wall shear stress (WSS), the frictional drag along arterial walls, has been the established hemodynamic force involved in the development of atherosclerosis. Regions of low and oscillating WSS associate with atherosclerotic lesions. The purpose of this study was to investigate the level of mean WSS (MWSS) in major cerebral arteries by age groups. Methods: MWSS was estimated by the following Poiseuille relation: WSS = 32μQ/d^2. Where Q is the mean volumetric flow rate (ml/min), D is the vessel lumen diameter (cm) and μ is the blood viscosity (poise). Q and D were measured from the NOVA software (VarSol, Inc., Chicago, IL). MWSS values in 17 cerebral arteries including common carotid artery (CCA), internal carotid artery (ICA), vertebral artery (VA), basilar artery, middle cerebral artery, anterior cerebral artery (ACA A1 and A2), posterior cerebral artery and posterior communicating artery (PCOM) were measured on a 3T MRI imager (Excte; GE Healthcare, Milwaukee, W) and obtained in 301 subjects between May 2004 and March 2009 (age: 18-84 with mean of 47, 157 M and 144 F). Subjects were divided into 7 age groups: 18-27 years old (17 M, 19 F), 28-37 (35 M, 21 F), 38-47 (26 M, 36 F), 48-57 (34 M, 32 F), 58-67 (32 M, 19 F), 68-77 (20 M, 13 F) and 78-4 F). Independent variables including age and systolic blood pressure (SBP) were assessed in a multiple regression model to predict MWSS, flow diameter and values. The unpaired Student’s t-test was used to examine if MWSS differences in age groups were statistically significant (p<0.05). Statistical analyses were performed using MedCalc for Windows, version 10.4.5.0 (MedCalc Software, Mariakerke, Belgium). Results: MWSS decreased with age in all vessels except the PCOMs, LACA and LACA2. MWSS for CCAs and VAs was similar, varying from 8.2-2.4 to 4.4-1.2 dynes/cm². MWSS for ICAs ranged from 12.6-5.3 to 7.2-1.7 dynes/cm². All other intracranial arteries MWSS except PCOMs were similar, varying from 22.5-5.8 to 11.4-4.3 dynes/cm². A significant drop in MWSS occurred between age groups 48-57 and 58-67 (<0.05 for 12 vessels), which accounted for 37-62% of total decline throughout the 7 decades. Flow decreased with age except the PCOMs. Furthermore, SBP increased with age. Conclusions: MWSS decline with age may be due to a decrease in flow. The marked drop in MWSS between the 48-57 and 58-67 age groups corresponded with an increase in diameter and SBP but no significant drop in flow.

Vascular Protection in Diabetic Stroke: Role of Matrix Metalloprotease-dependent Vascular Remodeling

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We have previously shown that temporary focal ischemia by middle cerebral artery occlusion (MCAO) causes greater hemodynamic derangement (HR) in diabetic-goto-Kikuzaki (GK) rats, a model that presents with increased cerebrovascular MMP activity and tortuosity. Purpose: The goals of this study were to test the hypotheses that 1) diabetes-induced cerebrovascular
remodeling is MMP-dependant, and 2) prevention of vascular remodeling by glycemic control or MMP inhibition reduces HT in diabetes after focal ischemia. Methods: Male Wistar control and diabetic GK rats were treated with vehicle, metformin (300 mg/kg/day) or minocycline (5 mg/kg/day) from the onset of diabetes in GK rats (6 weeks) till they reached the weight for MCAO (11 weeks, 270-300 g). A cohort was then sacrificed after injection of the resin PUA4 to visualize brain vascular vessels and vascular tortuosity/curvature. Diameter, number of collaterals between MCA and ACA and number of anastomoses within the MCA tree were measured as indices of remodeling. In a second cohort, MMP activity was evaluated by zymography of isolated MCAs. A third cohort was subjected to 3h MCAO/21h reperfusion and infarct size and HT were evaluated as indices of neurovascular injury. Minocycline treatment was given for 6 days prior to MCAO to provide vasoprotective resistance to MMPs play an important role during ischemic injury. Results: All remodeling markers including MMP-9 activity were increased in diabetes and treatment with both metformin and minocycline prevented these changes (Table). There was no change in infarct size by metformin or minocycline yet both incidence and severity of HT were significantly reduced with both treatments. Conclusions: These results provide evidence diabetes-mediated stimulation of MMP-9 activity promotes cerebral remodeling and augmented remodeling contributes to increased HT in diabetes. Both metformin and minocycline offer vascular protection which have important clinical implications for patients with diabetes who are at a 4- to 6-fold higher risk for stroke. *p<0.05 vs GK vehicle, n=7-14/group.

### Table

<table>
<thead>
<tr>
<th>Control</th>
<th>Diabetes</th>
<th>Diabetes + metformin</th>
<th>Diabetes + minocycline</th>
<th>Control + minocycline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tortuosity index</td>
<td>1.2 ± 0.01*</td>
<td>2.0 ± 0.1</td>
<td>1.2 ± 0.01</td>
<td>1.1 ± 0.01*</td>
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<td>Lumen diameter</td>
<td>0.03 ± 0.001</td>
<td>0.09 ± 0.003</td>
<td>0.03 ± 0.004*</td>
<td>0.02 ± 0.002*</td>
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<tr>
<td># of collaterals</td>
<td>71 ± 6</td>
<td>154 ± 18</td>
<td>96 ± 8</td>
<td>50 ± 3</td>
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<tr>
<td># of anastomoses</td>
<td>71 ± 9</td>
<td>276 ± 33</td>
<td>122 ± 13</td>
<td>68 ± 7</td>
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<tr>
<td>MMP-9 activity (% standard)</td>
<td>60 ± 3%</td>
<td>460 ± 150</td>
<td>175 ± 64</td>
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<tr>
<td>Infarct size (%)</td>
<td>30 ± 4.3%</td>
<td>9.8 ± 1.8</td>
<td>9.5 ± 2.3</td>
<td>5.1 ± 0.9</td>
</tr>
<tr>
<td>HT (ug/g)</td>
<td>4.2 ± 0.7*</td>
<td>22.5 ± 8.8</td>
<td>8.9 ± 1.9</td>
<td>3.1 ± 1.2*</td>
</tr>
</tbody>
</table>

This research has received full or partial funding support from the American Heart Association, Greater Southeast Affiliate (Alabama, Florida, Georgia, Louisiana, Mississippi, Puerto Rico & Tennessee).

### Abstracts and presentations are embargoed for release at date and time of presentation or time of AHA/ASA news event. Information may not be released before then. Failure to honor embargo policies will result in the abstract being withdrawn and barred from presentation.
PPARγ Protects Against Vascular Dysfunction With Aging

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Diverse forms of vascular dysfunction occur with aging including carotid artery disease, a major risk factor for stroke. Peroxisome proliferator activated receptor-γ (PPARγ) is a ligand-activated transcription factor that may protect the vasculature. The role of PPARγ in blood vessels during aging is unknown. We used heterozygous knockin mice expressing the P40SL dominant negative mutation in PPARγ (L/+ ) to examine the hypothesis that PPARγ protects against age-induced vascular dysfunction. Responses of carotid arteries from young (8-9 mo) and old (24 mo) L/+ mice and wild-type littermates were examined in vitro. In arteries from wild-type mice, acetylcholine (Ach, an endothelium-dependent agonist) produced relaxation that was not altered in old mice. In contrast, responses to Ach in arteries from L/+ mice was markedly impaired with age. For example, relaxation of the carotid artery to 10 μM Ach was 85±1% and 52±4% in old wild-type versus old L/+ mice, respectively (P<0.05). Impaired responses to Ach in old L/+ mice were not improved by apocynin or PuMA, inhibitors of NADPH oxidase and poly (ADP-ribose) polymerase (PARP), respectively, but were restored to normal by tempol, a scavenger of superoxide. Relaxation of the carotid artery to nitroprusside was similar in all groups. These findings provide the first evidence that age-related endothelial dysfunction occurred earlier and to a greater extent following interference with normal PPARγ function. The mechanism that accounts for this change may involve superoxide but not NADPH oxidase. Our findings suggest a novel role for PPARγ in age-induced oxidative stress and vascular dysfunction.

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Mast Cell Regulated Perivascular Gelatinase Activity in Experimental Ischemic Stroke

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Background and Purpose: Ischemic blood-brain barrier (BBB) damage causes hazardous expansive brain edema and hemorrhages. BBB is formed by the microvascular basal membrane (BM) and adjacent glial cells siding cerebral capillaries and postcapillary venules. Recent evidence suggests that perivascularly positioned immunocompetent granulomatous mast cells (MCs) compromise the integrity of BBB following sudden ischemia. We studied whether MCs regulate the enzymatic gelatinase activity produced by matrix metalloproteinases (MMMPs) –2 and –9 known to degrade the main constituents of BM following ischemia. Methods: Genotypically altered rats (Wt/Wt) born with no MCs (n=8) and their wild-type (WT) littermates (n=7) subjected to 60-min middle cerebral artery occlusion (MCAO) followed by 3-h reperfusion. Rats were also treated with an inhibitor of MC degranulation (sodium cromoglycate), 20.4/11005 3.7 (WT) (P<2.2 2.6 (Ws/Ws) compared with 20.3±1.7 (WT) (P=0.016) and 9.6/11005 1.5 (cromoglycate), 20.4/11006 3.7 (WT) (P<0.001). Importantly, MC-deficiency and pharmacological MC stabilisation reduced counts of gelatinase-positive microvessels: 8.6:–2.6 (Ws/Ws) compared with 20.3±1.7 (WT) (P=0.016) and 9.6/11005 1.5 (cromoglycate), 20.4/11006 3.7 (WT) (P<0.001). Gelatinase activity localized in microvessels but also in neuronal somas within the infarcted area. Conclusions: The results demonstrate that MCs are involved in the regulation of microvascular gelatinase activity in early ischemia-reperfusion injury in the rat brain. These observations further support the involvement of MCs in disrupting the integrity of BBB and suggest novel lines of research in stroke. Regulation of MCs may furnish an important means of treating acute stroke.

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Microglial Toll-like Receptor-4 and Ischemic Preconditioning

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Background: Ischemic preconditioning (IPC) is a robust neuroprotective phenomenon in which a brief period of cerebral ischemia confers tolerance to subsequent ischemic challenge. Inflammatory responses in brain are critical in the pathophysiology of stroke and IPC. Both microglia and Toll-like receptors (TLRs) are central in these responses. However, the role of microglial TLR4 in IPC is unknown. We hypothesise that microglial TLR4 signaling is required for both optimal IPC-mediated neuroprotection and IPC-mediated attenuation of inflammatory responses seen following stroke. Methods: We performed middle cerebral artery occlusion (MCAO) on TLR4/- and wild-type (WT) mice using established paradigms for stroke and IPC. We first assessed infarct volume and neurobehavioral outcome. We then used ex vivo flow cytometry to characterize the inflammatory infiltrate in ischemic cortex following stroke alone or IPC followed by stroke. We also carried out in vitro experiments on cultured primary microglia from TLR4/- and WT mice to characterize the role of TLR4 in modulating the microglial response to hypoxia/hypoglycemia (ischemia). We used qRT-PCR and microarray oligonucleotide hybridisation Methods to analyze both our ex vivo and in vitro data. IPC induced 35% and 4% reductions in infarct volume in WT and TLR4/- mice, respectively. Myeloid cellular content and phenotype in ipsilateral cortex was markedly influenced by both IPC and genotype. In vitro ischemia induced characteristic profiles of genomic changes that were markedly disparate in microglia derived from TLR4/- and WT mice. Hypoxia inducible factor-1 (HIF–1) gene targets such as vascular endothelial growth factor (VEGF) and monocyte chemotactic protein-1 (MCP-1) were differentially regulated by IPC and genotype in both ex vivo sorted- and in vitro derived-microglia. Conclusions: These findings provide insights into the influence of both IPC and TL4 signaling on the pathophysiologic state of microglia in the ischemic penumbra. These results may help identify molecular targets for therapeutic intervention in stroke.

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The Therapeutic Effect of Netrin-1 Overexpression via AAV Gene Transfer

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Backgrounds: In addition to their role in axon guidance during CNS development, netrins have been implicated in angiogenesis. Netrin-1 in particular was found to be proangiogenic in some studies, while also acting anti-angiogenic in others. More importantly, Netrin-1 also acts as an anti-apoptotic factor in developing floor plate and Netrin-1 administration attenuates ischemia-induced apoptosis. The aim of this study is to determine whether overexpression of Netrin-1 via adenovirus-associated viral (AAV) gene transfer confers neuroprotection. Methods: Stroke was induced unilaterally by the intraluminal filament (MCAO) method under isoflurane/N2O/NE anesthesia. 1x1015 genome copies of AAV-Netrin-1 (replication-incompetent vector encoding chicken Netrin-1) or AAV-LacZ were injected medial and posterior to ischemic lesion in the rat ipsilateral sensori-motor cortex at 3 days following dMCAO. Transgene expression was analyzed by RT-PCR (primer sets specific for chicken netrin1: 5’-gcggcgctgcag-3’ and 5’-ctcagcgcggctc-3’) immunohistochemical staining and western blot analyses using antibody to chicken Netrin-1. Double immunofluorescence staining with cell type specific markers was performed to determine the cell type specific expression of the endogenous and transduced Netrin1 at various time points following vector injection or dMCAO. Infarct volume was determined at 3 weeks following gene transfer. Results: Our data indicate that endogenous Netrin-1 was induced in the neurons in the peri-infarct regions during the first week after MCAO. There was no Netrin-1 immunoreactivity found in the endothelial cells either in the sham or MCAO animals at any given time point examined in this study. Following AAV-N1 gene transfer, transduced Netrin-1 immunoreactivity was also found mainly in the neurons in the peri-infarct regions. The expression of transduced Netrin-1 began at 1 day and plateaued about 3 weeks following vector injection. Although rats received Netrin-1 gene therapy in general had a smaller infarct volume compared to those received AAV-LacZ, the difference was not significant (AAV-LacZ: 8.5 ± 0.8x103 mm3; AAV-Netrin-1: 6.7 ± 0.7x103 mm3, P = 0.005). Conclusions: Both ischemia-induced endogenous and transduced Netrin-1 were found in the neurons of the peri-infarct regions. However, overexpression of Netrin-1 via AAV gene transfer at 3 days following MCAO did not significantly reduce the infarct size. Ongoing investigation will further determine the optimal therapeutic window for AAV-Netrin-1 gene therapy and its effect on angiogenesis, vascular permeability, CST axonal remodeling and gait function recovery following experimental stroke. This research has received full or partial funding support from the American Heart Association, National Center.
Deletion of Mitochondrial Uncoupling Protein 2 Increased Brain Damage After Transient Focal Ischemia by Suppression of Anti-oxidant Genes and Enhancement of Inflammatory Chemokinase

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Background and Purpose: Mitochondrial uncoupling proteins (UCPs) are inner mitochondrial membrane proteins that dissipate the mitochondrial proton gradient by transporting H+ across the inner membrane, thereby stabilizing the inner mitochondrial membrane potential and reducing the formation of ROS (Mehta & Li 2009). Previous studies have provided conflicting evidence as to whether UCP2 is protective or destructive after ischemic brain stroke. The objectives of this study are to clarify the effects of UCP2 on ischemic brain damage and to explore whether deletion of UCP2 gene alters expression profile of other genes after transient cerebral ischemia. Methods: Middle cerebral artery occlusion (MCAO) of 1 hr duration was induced in UCP2 knock out (UCP2KO) and wild type mice. Animals were sacrificed 24 hr after reperfusion. The infarct size was depicted using the TTC staining. The integrity of the circle of Willis of UCP2KO and wild type mice was examined by carbon black injection. Transection levels of 84 genes in the cortical ischemic penumbra area were detected using a Mouse Stress Toxicity POR array (Super Array). The results were normalized against housekeeping genes Hprt1 and p-actin. Protein levels of inflammatory chemokines were determined using western blot. Results: The results showed that deletion of UCP2 gene significantly increased infarct size and there was no obvious vascular abnormalities observed. The Super Array study demonstrated that knocking out UCP2 gene significantly suppressed DNA repair gene gcl1, antioxidative gene GSTM1 and neuroprotective gene GMD2. Several inflammatory proteins were increased in the UCP2KO animals after MCAO including CTACK, CXCL16, Eotaxin-2, fractalkine, and BLC. Conclusion: Knocking out of UCP2 gene exacerbates neuronal death after cerebral ischemia and repression and deletion of UCP2 gene suppressed inflammatory response and cell survival and enhanced inflammatory chemokines. References: Mehta S & Li PA 2009 J Cereb blood flow Metab29:1069-78

The Extracellular Calcium-Sensing Receptor (CaSR) Promotes Ischemia-induced Injury in Hippocampal Neurons

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Intracellular calcium overload is well established as a mechanism of neuron death following ischemia. Overactivity of glutamate receptors/channels and the loss of inhibitory signaling through gamma-aminobutyric acid (GABA) may contribute to the cell injury. The extracellular calcium-sensing receptor (CaSR), which is a member of family C G-protein-coupled receptor, was originally found in parathyroid glands where it senses minute changes in extracellular [Ca2+] and couples to multiple intracellular signaling responses and secretory function. Activation of CaSR by extracellular Ca2+ releases intracellular Ca2+ stores and influx through channels in many cell systems. The CaSR is strongly expressed in the brain. To test the hypothesis that changes in the expression and activity of neuronal CaSRs are involved in promoting injury in the ischemic cascade, we generated flox allele CaSR/KO and wild type WT mice using a line of mice that conditionally generate CaSR deletion during brain development. We further used a line of mice with a transgenic CamKIIa-Cre mouse line. Global cerebral ischemia was induced by occlusion (10 min) of both common carotid arteries, followed by 3-day reperfusion in 3-month-old male mice. Brain sections from K0 and wild-type (WT) mice were prepared for immunohistochemistry for CaSR expression and TUNEL staining. In uninjured WT mice, CaSR expression was localized to the CA1, CA3, and dentate gyrus (DG) of the hippocampal formation. CaSR expression in these regions was absent in the KO mice, confirmed by immunohistochemistry. The targeted CaSR KO mice were phenotypically normal in terms of size, general behavior, and brain anatomy. In WT mice, ischemia profoundly increased CaSR expression in the CA1, CA3 and DG when compared to sham controls. TUNEL-positive neurons were also increased in the hippocampus of injured mice. In contrast, the number of TUNEL-positive neurons was significantly (p<0.05) decreased in CA1 (by ~25%), CA3 (by ~70%), and DG (by ~85%) of ischemic wild type CaSR+ mice compared to WT mice. It has been previously demonstrated that type B GABA receptor 1 (GABA-B-R1) can heterodimerize with the CaSR and suppress its protein expression and that the expression of GABA-B-R1 is significantly decreased in the brain subregions of ischemic injury, raising the question whether the decreased GABA-B-R1 expression is directly associated with the increased CaSR levels in neurons under ischemic condition. To address this, we performed in vitro knockout of GABA-B-R1 in cultured hippocampal neurons. We found that the expression of the CaSR was indeed increased in neurons lacking the GABA-B-R1 expression. Our data reveal an important role for the CaSR in potentiating ischemic neuronal death, and this regulation may be mediated by other members of family C GPCR.
Cost-effectiveness of Telestroke for Ischemic Stroke: A Literature-based Decision-analytic Model

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Background and Purpose: Stroke is a time-critical illness with potential for devastating effects on individuals and substantial societal costs. Due to the short time window and limited availability of stroke specialists, only 2-4% of ischemic stroke patients receive intravenous tissue plasminogen activator (TPA), the only FDA approved treatment for ischemic stroke. Telestroke, two-way, audiovisual technology that links stroke specialists to remote emergency department physicians and their stroke patients, has emerged as an efficacious method of delivering stroke specialist care to hospitals without such expertise on site. In this research, we investigate the cost-effectiveness of this technology compared to ‘usual care’ (remote emergency departments without telestroke consultation) using a literature-based decision-analytic model.

Methods: A decision-analytic model was developed for both 90-day and lifetime horizons. Model inputs were taken from published literature where available and supplemented with Western states' telestroke experiences when necessary. Costs were gathered using a societal perspective and converted to 2008 U.S. dollars. Outcomes were measured in incremental cost per quality adjusted life-year (ICER) gained. In the lifetime horizon model, both costs and QALYs were discounted at 3% annually. Both one-way sensitivity analyses and Monte Carlo simulations were performed. Results: In the base case analysis, compared to ‘usual care’, we found that telestroke results in an incremental cost-effectiveness ratio (ICER) of $305,321/QALY in the 90-day horizon and $3,925/QALY in the lifetime horizon. Sensitivity analyses demonstrated that the most influential model variables were the probabilities of achieving various modified Rankin Scores based on receipt of TPA. For the 90-day and lifetime horizons, 2.2% and 96.7% of 1,000 Monte Carlo simulations yielded ICERs less than $50,000/QALY, a ratio commonly considered acceptable in the US. Conclusion: The results confirm our intuition that telestroke costs are up front but benefits of improved stroke care are life-long. When a lifetime perspective is taken, telestroke appears cost-effective compared to ‘usual care’. However, limitations of this model include an entry point of ischemic stroke (vs. stroke-like symptoms) and lack of robust literature on several critical elements (for example, the percentage of patients transported with and without TPA). A prospective trial of telestroke cost-effectiveness is necessary to address these shortcomings.

EMS Treatment and Transport of Stroke Patients Post IV IFA: Baseline Adherence to Recommended Processes of Care for “Drip and Ship” Patients

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Background: The AHA guidelines for care of acute ischemic stroke and IFA patients were updated in 2007, and include guidelines for post IFA care by EMS personnel. Baseline analysis of EMS adherence to these processes is necessary to establish a baseline for future comparisons.

Table. Patient and EMS Characteristics and Outcomes

<table>
<thead>
<tr>
<th>Pt Characteristics</th>
<th>Overall (n=100)</th>
<th>MA Stroke Center (n=50)</th>
<th>MS Stroke Center (n=50)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median[IIQ]</td>
<td>73.5 [73,5,85.0]</td>
<td>80 [62.0,86.6]</td>
<td>69.5 [56,38,83.0]</td>
<td>0.07</td>
</tr>
<tr>
<td>Gender (M)</td>
<td>49.0</td>
<td>42.0</td>
<td>56.0</td>
<td>0.16</td>
</tr>
<tr>
<td>Race (white)</td>
<td>88.0</td>
<td>96.0</td>
<td>80.0</td>
<td>0.01</td>
</tr>
<tr>
<td>Ambulatory status at baseline (n=92)</td>
<td>95.7</td>
<td>97.7</td>
<td>93.9</td>
<td>0.37</td>
</tr>
<tr>
<td>NIHSS at admission, median[IIQ]</td>
<td>10 [6,17]</td>
<td>13 [6,28,18.0]</td>
<td>6 [5,12]</td>
<td>0.01</td>
</tr>
</tbody>
</table>

—Past Medical History—

Dyslipidemia | 35.0 | 28.0 | 42.0 | 0.14 |
Stroke/Tia | 21.0 | 18.0 | 24.0 | 0.46 |
Diabetes | 19.0 | 12.0 | 26.0 | 0.07 |
HTN | 68.7 | 70.0 | 67.4 | 0.78 |
AFib | 19.0 | 34.0 | 4.0 | <0.001 |
Smoking | 19.0 | 8.0 | 30.0 | 0.01 |
CAD/MI | 25.0 | 28.0 | 22.0 | 0.49 |

EMS Factors

Time b/w call and EMS arrival at OSH | 17 [10,30] | 27 [18,39] | 10 [9,17] | 0.01 |
Time b/w EMS arrival and Departure from OSH | 24 [18,34] | 23 [28,40] | 18 [15,24] | 0.005 |
Time b/w EMS departure from OSH and arrival at Hub | 23 [16,45] | 29 [16,62] | 22 [16,29] | 0.23 |
Time b/w IFA bolus and Departure from OSH | 33 [18,62] | 52 [41,80] | 18 [13,5,28] | <0.001 |
Type of Vehicle (Air) (n=79) | 44.3 | 42.2 | 47.1 | 0.67 |
Distance from hub | 42.0 | 30.0 | 54.0 | 0.02 |
Transfer from same state (n=93) | 81.7 | 94.0 | 67.4 | 0.001 |
ALS or EMT-P provider in EMS vehicle | 72.0 | 80.0 | 64.0 | 0.08 |
EMS time spent <15 min in remote ED | 7.0 | 2.0 | 12.0 | 0.05 |

EMS Documentation

Any Documentation by EMS in MR | 62.0 | 60.0 | 64.0 | 0.68 |
—Among those with EMS data—

1-pre-arrival hospital notification | 36.0 | 52.0 | 20.0 | 0.001 |
3-2 stroke scale by EMS | 8.0 | 16.0 | 0.0 | 0.00 |
3-02 sat monitored during transport | 47.0 | 50.0 | 44.0 | 0.55 |
4-02 sat maintained >92% | 44.0 | 52.0 | 38.0 | 0.11 |
5-EMG monitored during EMS transport | 54.0 | 50.0 | 58.0 | 0.42 |
6-BP recorded at 15 min s/p IFA for 1st hr or 30 min during transfer | 35.0 | 48.0 | 22.0 | 0.01 |

Composite Score median[IIQ] | 2 [0,4] | 4 [0,5] | 1 [0,4] | 0.07 |
Safety Outcomes

Symptomatic ICH in 36 hrs | 7.0 | 6.0 | 8.0 | 0.70 |
Death | 18.0 | 20.0 | 16.0 | 0.60 |
adherence to these recommended practices by EMS personnel is unknown. Given the increasing use of the “drip and ship” approach, it is even more important to understand how EMS care is provided. We assessed adherence to these recommendations among a group of drip and ship IPA patients transported to two large metropolitan tertiary care stroke centers located in the greater Boston and Los Angeles metropolitan areas. Methods: We reviewed IRB approval to retrospectively review 100 consecutive drip and ship IPA cases from Jan-Dec 07. Presence of EMS documentation in the hospital record was measured. We assessed adherence to 6 measures selected for their relevance to EMS care: hospital pre-arrival notification; pre-hospital stroke screening performed, O2 saturation monitored and use of supplemental O2 for <92%, continuous ECG monitoring, CT and frequent BP monitoring. Factors significant in univariate analysis (p<0.01) were included in a multivariate ordinal regression model to determine their relationship to a one point improvement in adherence to a composite score in which all 6 measures contributed equally (STATA 9.0). Results: EMS interfacility documentation was missing in 38% of cases and the overall median composite score was 2(0,4). Patients with EMS documentation had lower median NIHSS (8 vs. 14; p<0.04), less hypertension (62% vs. 81%; p<0.04) and more often transported by air (50% vs. 18%; p<0.02) compared to those without EMS data. There were significant differences in univariate analysis with respect to patient and EMS characteristics but these differences were not significant at the two centers but did emerge when analyzed combined (Table). Univariate predictors of a 1 pt increase in the EMS composite score were the presence of a non-BLS (ALS or EMT-P) provider (OR 26.38, 95%CI 7.17-97.08; p<0.0001), EMS time of a non-BLS (ALS or EMT-P) provider (OR 27.37, 95%CI 7.3-103.3; p<0.001). Conclusion: EMS interfacility care was poorly documented, and when documented was highly variable, as were EMS response times. The best predictor of baseline adherence was an advanced level of EMS training. The use of standardized statewide protocols for post IPA EMS care may increase compliance, especially among BLS providers. Further research is needed to understand differences in EMS care patterns and improve adherence.

Impact of Primary Stroke Center on Delivery of Thrombolytic Therapy in Nations One of the Largest Integrated HMO Systems of Health Care

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Background/Purpose: To increase the proportion of ischemic stroke patients treated with thrombolytic therapy, the Brain Attack Coalition and AHA/ASA recommend establishment of primary stroke centers. However, the empiric impact of PSCS on delivery of lytic therapy has not been extensively documented, especially in hospital systems with complete before and after data ascertainment and in integrated HMO systems of health care. We evaluated IPA patients with ischemic stroke from a large integrated HMO system before and after the establishment of primary stroke centers. Methods: We collected data on all patients admitted with ischemic stroke during the 2 years before and 2 years after implementation of a primary stroke center using a comprehensive stroke registry (MedScape). Results: In the pre-PSC, from March 2003 to April 2007, 3 of 909 (0.33%) ischemic stroke patients were treated with intravenous IPA. Also, 7 of these patients received endovascular recanalization therapy. The odds ratio for receiving IV TPA was increased in the intervention period by 12.72 (95% CI 3.47-40.0, p<0.0001). During the intervention period, median time from onset to start of TPA was 134 minutes and median door to needle time was 71.1 minutes. The mean age of treated patients was 74.1% were female. Median NIHSS was 11.0 at the time of symptomatic hemorrhage was 1(34) 2.9%. Among treated patients, 52.9% (18/34) achieved a very favorable outcome at 3 months (mRS 0-1) (6.9% vs. 7.8%; RR 0.91; 95%CI 0.78-1.07). Among stroke patients with Pneumonia; those that received higher intensity of stroke care (OCI 2-3) had lower mortality compared to those receiving less intensive care (OCI 0-1) (30.5% vs. 60.3%; HR 0.50 (95%CI 0.41-0.61). A similar pattern was observed when we looked specifically at stroke unit admission: 30 day mortality was lower among pneumonia patients admitted to a stroke unit (35% vs. 41.0%; HR 0.86 (95%CI 0.69-1.06). Conclusion: The prevalence of pneumonia (71%) among ischemic stroke patients admitted to Regional stroke centers in Ontario is lower than reported in other observational studies and metaanalysis. This might be a non-significant factor of incident risk for stroke in the elderly population. Further research is needed to examine outcomes in high and low volume thrombolysis centers.

Does Organized Inpatient Care Decrease the Incident Risk of Stroke-associated Pneumonia?

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Introduction: Organized care has shown to decreased morbidity and mortality after stroke. Pneumonia is one of the most common complications after stroke affecting ~10-40% of patients. Limited information is available on the risk of pneumonia in patients receiving elevating levels of organized care. Hypothesis: Higher level of access to organized in-patient stroke care is associated with decreased incident risk of stroke-associated pneumonia (SAP) and decreased mortality among patients with pneumonia. Methods: We selected for their relevance to EMS care may increase compliance, especially among BLS providers. Further research is needed to understand differences in EMS care patterns and improve adherence.

Healthcare Engineering Methods Can Improve Inpatient Stroke Care Quality

Linda Williams, VS HSR&D Ctr on Implementing Evidence-based Practice, Indianapolis, IN; Heather Woodward-Hagg, Roubeth HA Med Ctr, Indianapolis, IN; Dawn Bravata, Virginia Daggett, Laurea Piue, Teresa Damush; VS HSR&D Ctr on Implementing Evidence-based Practice, Indianapolis, IN

Background/Objectives: Inpatient stroke care quality can be assessed by measurement of key process indicators. How quality improvement programs can be most effectively structured to improve stroke care is not well described. The objectives of this pilot project were to: 1) develop and implement a stroke quality improvement program based on System Redesign/Lean Six Sigma principles; and 2) to evaluate its impact on inpatient stroke care quality. Methods: Working with Department of Veterans Affairs clinicians and managers, we identified stroke champions and teams at all seven Veterans Integrated Service Network 11 facilities. Using a collaborative model we developed a training program for stroke teams that included in-person and web-based sessions covering System Redesign and Lean improvement Methods. Sites selected two Joint Commission stroke quality indicators on which to focus: dysphagia screening before oral intake and discharge on cholesterol lowering medication. Teams attended a 2-day intensive at which time they created a System Redesign map, including stroke indicator data collection and stroke team of care maps for each site. We developed a standardized electronic stroke order set, and developed site-specific initial Plan-Do-Study-Act (PDSA) cycles for the two indicators. Teams participated in monthly group and site-specific calls with system redesign facilitators for six months to help address site-specific barriers to improvements. Facilitators monitored the types of improvement strategies used, number of PDSA cycles completed, and team participation in calls. Data on the two indicators from 2007 were compared to six months post-intervention data (June-November 2007 and June-November 2008). Results: A total of 52 charts from high volume and low volume stroke sites had effectively implemented the electronic stroke order set. Health IT interventions (e.g. electronic orders/reminders) and provider training were the most commonly
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Standardized Discharge Orders After Stroke: Results of the Quality Improvement in Stroke Prevention (QUISP) Trial

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Background: Proven strategies to reduce risk of stroke recurrence are under-utilized. We sought to evaluate the impact of standardized discharge stroke orders on treatment practices in a cluster-randomized trial. Methods: The Quality Improvement in Stroke Prevention (QUISP) trial randomized 12 hospitals to continue usual care or to receive assistance in the development and implementation of standardized stroke discharge orders. All patients with ischemic stroke were identified during a 12-month period prior to implementation and for 12 months afterwards, and were followed for 6 months after discharge. The primary outcome was optimal treatment at 6 months, defined as taking a statin, having blood pressure <140/90 mmHg, and receiving anticoagulation if atrial fibrillation was diagnosed. The primary analysis treated the hospital as the unit of analysis, comparing optimal treatment rates–adjusted for race, age, dementia, atrial fibrillation, and history of bleeding–between intervention and non-intervention hospitals using a paired t test. Findings: With patients as the unit of analysis (N = 3361), rates of optimal treatment increased from 37% to 45% in the intervention hospitals (p = 0.001) and did not change in the non-intervention hospitals (39% to 40%; p = 0.46). However, in the primary analysis with hospital as the unit of analysis, the odds of optimal treatment were not significantly increased at intervention compared to non-intervention hospitals (OR 1.40, 95% CI 0.70-2.75, p = 0.27). The figure demonstrates the OR for changes in rates of optimal treatment post- vs. pre-intervention at intervention and non-intervention hospitals. Interpretation: Implementation of standardized discharge orders after stroke was associated with increased rates of optimal secondary prevention but the improvement was not significant in the primary analysis with hospital as the unit of analysis.

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Developing Benchmarks for Acute Stroke Care in Ontario: Using the Registry of the Canadian Stroke Network

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Background: Performance benchmarks for acute stroke care are limited and have not been generated in Canada. The province of Ontario has 11 specialized regional stroke center hospitals (RSC) that participate in an acute stroke registry to collect stroke care process indicators. There is a need to find measures that address adherence to key Canadian Best Practice recommendations. Purpose: To develop benchmarks for 9 acute stroke quality indicators to establish Canadian benchmarks for acute stroke care. Methods: Hospital rates of performance and benchmarks were calculated for nine acute stroke quality of care indicators for patients admitted between April 1, 2006 and Dec 31, 2007 (N = 8,109) at 11 specialized stroke hospitals in the province of Ontario, Canada. The Achievable Benchmark of Care (ABCTM) methodology was used and each benchmark represents the average performance for the top 25% of the hospitals. Results: Using the ABC calculation, four out of nine benchmarks were ≥ 90%, and two-things were ≥ 85%. Most benchmarks were set by only 2 – 3 hospitals and the range of adherence across the 11 hospitals varied from over 50% to as low as 7%. Neuroimaging within 24 hours of stroke symptom onset had the highest benchmark (99%) and the narrowest range of adherence across the 11 hospitals (82-99%). Stroke unit care benchmark was 84% but demonstrated the widest range of adherence across the 11 hospitals (47-98%). The lowest adherence was for use of thrombolysis. Conclusions: The ABC method for setting high performance benchmarks may aid in the transition from performance measurement to performance improvement. High performing hospitals could share practices with others that make their impressive performance achievable.
characteristics known to be associated with adverse cardiovascular prognosis. Increase, reduction, or reversal of the normal, 10-20mmHg nocturnal dip in night-time blood pressure is associated with an increase in future risk of cardiovascular events with relative risk values reported as high as 6.8 in some groups. In older subjects (>70 years), low diastolic BP and 24 hour pulse pressures (mean systolic blood pressure in excess of 105 mmHg) have been recently reported as being associated with significantly increase mortality in older hypertensives. We reviewed ambulatory blood pressure results on 200 consecutive patients with Stroke or TIA attending a secondary prevention clinic for cerebrovascular disease to determine the prevalence of adverse blood pressure characteristics. Methods: Ambulatory blood pressure monitoring (ABPM) readings were performed using British Hypertension Society certified devices in 200 consecutive patients enrolled between May 2006 and December 2007. Morning and evening measurements were taken at 30 minute intervals during daytime and hourly from 23:00 to 07:00 hours. Where an individual had undergone a number of assessments, readings from an individual's first presented to the clinic were excluded. Mean systolic and diastolic readings of the 200 patients were, respectively, 136 ± 0.8 and 85 ± 0.2 mmHg (mean ±SEM). 118 (59%) were female. 59 (20%) patients were hypertensive as defined by a BP ≥ 140/90 mmHg and 77 (33.5%) if defined as ≥135/85 mmHg. One hundred subjects (50%) experienced nocturnal systolic dips of <10% on monitoring, of these 39 were ‘reverse dippers’ who raised their BP at night. 30 subjects (15%) were extreme dippers who dropped their nocturnal systolic BP by >20 mmHg. Of 96 patients who were 70 years or older, 23 (24%) had a 24 hour pulse pressure >70 mmHg all of whom had an abnormal nocturnal dip. Of the 123 normotensive (24hour BP<135/85mmHg) subjects 58% had adverse blood pressure characteristics, 48 (39%) being non-dippers or reverse dippers and 23 (19%) extreme dippers. Conclusion: Blood pressure characteristics other than hypertension associated with increased cardiovascular risk are also common in patients with stroke and TIA. The majority of ‘normotensive’ stroke patients still demonstrate adverse characteristics. This finding would serve to reinforce the American Heart Association guideline that control of blood pressure in subjects with cerebrovascular disease should be individualised.

Background: Although there is consistent evidence supporting the effectiveness of antplatelet agents and hypertension control for secondary stroke prevention, there is less available information about adherence to these therapies. Our purpose was to examine adherence to antplatelet and antihypertensive medications after stroke and to identify factors associated with adherence. Methods: We utilized data from the Secondary Prevention of Small Subcortical Strokes (SPS3) trial, a multicenter international trial testing aspirin versus aspirin plus clopidogrel as well as two blood pressure lowering regimens for secondary prevention of cerebrovascular events. Adherence to the antplatelet agents is measured by pill counts and to the antihypertensive medications by self-report. Adherence scores dichotomized as good (<80%) or inadequate (<80%). Adherence was examined and compared among aspirin, clopidogrel/placebo, and the antihypertensive medications at years 1, 2, and 3. Multivariable logistic regression was utilized to identify demographic and clinical factors predictive of adherence at years 1, 2, and 3. Results: Patients active on both study arms at the annual visits were included in the analyses (526 at year 1, 471 at year 2, and 323 at year 3). Adherence rates were significantly correlated between antplatelet and antihypertensive medications. Using a composite variable which combined adherence to the antplatelet and the antihypertensive medications, 84% were adherent at year 1, 85% at year 2, and 87% at year 3. We assessed: age, sex, marital status, employment status, total number of medications, self-rating of health (excellent to poor), functional status, and baseline cognitive function and measures of adherence, only producing 5 significant associations (OR 2.24; 95% CI 1.28, 3.93), at least one missed visit during the previous year (OR 0.43; 95% CI 0.23, 0.80), and annual self-rating of health (OR 0.63; 95% CI 0.47, 0.84) were independently associated with adherence. At years 2 and 3, only self-rating of health was associated with adherence, with a decrement in rating associated with a decrease in adherence (Year 2: OR 0.57; 95% CI 0.31, 0.99; Year 3: OR 0.37; 95% CI 0.19, 0.72). Conclusion: Although adherence is often reported to decline over time, in this clinical trial adherence remained stable in the initial 3 years after stroke. This most likely reflects the high level of involvement with the trial clinics. Self-rating of health was a consistent and significant predictor of adherence in the first 3 years after stroke. These findings suggest that those patients with lower self-rating of health may be more likely to be engaging in adherence to medications and require additional focused interventions to improve adherence.

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Does Excision of the Left Atrial Appendage During Minimally Invasive Surgical Ablation for Atrial Fibrillation Remove the Need for Long Term Anticoagulation: The Potential Role of Left Atrial Size

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Background: Minimally invasive surgical ablation (MIS), with isolation of the pulmonary veins, ablation of the left atrial autonomic ganglionic plexi and excision of the left atrial appendage (LAA) is becoming an established treatment for atrial fibrillation (AF). Excision of the LAA is included to reduce the potential for future embolic events and has been used by many to justify discontinuation of oral anticoagulant therapy 3-6 months after surgery. Objectives: This is a retrospective study to assess the incidence of thrombo-embolic complications after MIS for AF with current anticoagulation practice. Methods: MIS for AF was performed on 44 pts. AF was paroxysmal in 10, persistent in 10 and long standing persistent in 24 pts. Mean left atrial transseptal diam (LATS) was 4cm (range 3.7 – 6.6cm). Excluding 2 pts with mitral valve disease, the mean CHADS2 score for stroke risk was 1.0 (range 0-4). Pts were followed for 30 – 12 months. Anticoagulation was discontinued (but not until ≥ 6 months after surgery) in 20 of 42 pts at their request. Results: No patient who remained on anticoagulant medication had a thrombo-embolic event. Stroke occurred within 3 months of discontinuing anticoagulation in 2 pts. Both pts had hypertension as their only CHADS risk factor. Neither had had symptomatic AF after the 2 month blanking period post surgery and both had had a 24 hour holter with no AF recorded prior to discontinuation of anticoagulant. Both were in sinus rhythm at the 1 month post surgery and had no recurrence of symptoms. Both pts may have provided a substrate for thrombus formation, even after removal of the LAA. No thrombus was identified on transeosophagal echocardiography performed shortly after the surgery, but...
neither was another cause of stroke identified. Conclusions: 1. In the setting of a significantly dilated left atrium, a CHADS2 score <2 may not indicate a low risk for discontinuing oral anticoagulation after MIS. 2. Excision of the LAA, particularly when performed on a beating heart, where a small remnant is inevitable, may not be sufficient to reliably prevent stroke in pts with dilated atri, in whom relatively static blood, as evidenced by spontaneous echo contrast, is often observed.

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Efficacy of Homocysteine Lowering Therapy With Folic Acid in Stroke Prevention: A Meta-analysis of Randomized Controlled Trials

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Background: Although lower serum homocysteine concentration is associated with a reduced risk of stroke in epidemiologic studies, randomized controlled trials have yielded mixed findings regarding the effect of therapeutic homocysteine lowering on stroke prevention. We performed a meta-analysis of randomized controlled trials to assess the efficacy of folic acid supplementation in the prevention of stroke. Methods: Salient trials were identified by formal literature search. Relative RR (95% confidence interval (CI)) was used as a measure of the association between folic acid supplementation and risk of stroke, pooling data across trials using a fixed-effects model. Findings: The search identified 13 randomized controlled trials of folic acid therapy to reduce homocysteine, enrolling 39,005 participants, in which stroke was reported as an outcome measure across all trials. folic acid supplementation was associated with a trend toward mild benefit that did not reach statistical significance in reducing the risk of stroke (RR 0.93, 95% CI 0.85-1.03; p=0.16). In the subgroup of 6 trials (19,768 participants) that used combination therapy of folic acid plus vitamins B6 and B12, a benefit was observed (RR 0.85, 95% CI 0.71-0.97; p=0.02). Also a potential gender effect was noted, with folic acid supplementation treatment showing benefit in the 9 trials (27,428 patients) which disproportionately enrolled male patients (men/women >2, RR 0.88, 95% CI 0.78-0.98; p=0.03). Conclusion: Folic acid supplementation did not demonstrate a major effect in averting stroke. However, potential mild benefits, especially when folate is combined with B vitamins and in male patients, merit further investigation.

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Antiplatelet vs. Anticoagulant Therapy Recommended as Best Medical Care in the Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPPECT Trial)

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Background/Objective: There are only sparse randomized trial data to guide the choice of optimal therapy for secondary prevention in young patients with cryptogenic stroke and PFO. Randomized trials are lacking, comparing medical therapy to PFO closure. In the RESPPECT trial, a recommendation for best medical therapy (monotherapy or combination of aspirin/ clopidogrel/dipyridamole categorized as antiplatelet (AP) vs. warfarin anticoagulant (AC)) is made by a study physician prior to randomization, based on all clinical and diagnostic data available at that time. Our objective was to identify baseline factors associated with choice of best medical therapy. Methods/Results: A complete dataset was available for 561 patients, randomized between 8/2/2003 and 6/30/09; 42% were female, mean age was 45.5 years, mean NIHSS at study entry was 1 and median days from stroke to randomization was 77. The association of recommended best medical therapy with age, gender, 11 past medical/co-morbid factors, initial NIHSS, stroke territory, presence of an atrial septal aneurysm, days from stroke to randomization and randomization date was assessed with standard bivariante and multivariate analyses. AP was recommended for 399/561 (71%) of subjects and AC for 29% of subjects. MCA infarcts (49% of AP subjects vs. 59% of AC subjects), presence of an atrial septal aneurysm (32% AP vs. 43% AC) and earlier randomization date were associated with AC recommendations in bivariate analyses (all P < 0.05). After controlling for age and gender, MCA infarcts (OR = 1.1, 95% CI 1.0-1.2), and earlier randomized patients (for each successive year OR = 0.84, 0.72-0.97) were independently associated with increased AC recommendation. Conclusions: Despite a lack of evidence from randomized trials, RESPECT study physicians are non-randomly assigning patients to AP vs. AC. Increased use of AC was observed in patients where the case for embolic etiology may have been more compelling (MCA infarct) or the perceived risk of recurrence may have been higher (atrial septal aneurysm). Decreasing frequency of recommendations for AC over time may be due to negative trials of anticoagulation for secondary stroke prevention published since the RESPECT trial began.

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Stroke Symptoms and Risk Factor Awareness Amongst High School Children in Pakistan

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Background: The burden of stroke is increasing in developing countries like Pakistan. Enhancing public knowledge of stroke symptoms and risk factors will be an important component of future treatment and prevention strategies. Objective: We sought to determine awareness of stroke symptoms and risk factors in the Pakistani high school student population in Lahore, a large city in Pakistan. Design: We conducted a survey of high school students in Sargoda, Pakistan to determine their knowledge about stroke symptoms and risk factors using a questionnaire administered by school teachers. We randomly selected 15 high schools in Sargoda district and interviewed 20 students from each school. Nine of the 15 schools were government run and 6 were private schools. Students were between 14 - 22 years of age, male (151) and female (149). One hundred and eighty were from government run schools and 120 from private schools. Results: Eighty nine percent of the students had heard about stroke disease and 46% had knowledge of at least one stroke risk factor. This awareness was higher in females (60%) compared to males (31%) and in 10th grade compared to 9th grade students. Twenty three percent of the students said that they would call an ambulance for acute stroke. Thirty percent knew that stroke patients get benefit from aspirin. Thirty three percent reported that a stroke event may have been more compelling (MCA infarct) or the perceived risk of recurrence may have been higher (atrial septal aneurysm). Decreasing frequency of recommendations for AC over time may be due to negative trials of anticoagulation for secondary stroke prevention published since the RESPECT trial began.

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Long Term Clinical Outcomes in Stroke Patients Using Clopidogrel and Proton Pump Inhibitors

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Background and Purpose: Clopidogrel is a commonly used antiplatelet agent for secondary prevention of stroke. Recent studies have focused on a pharmacological interaction between Proton Pump Inhibitors (PPIs) and Clopidogrel that leads to a significant increase in the rate of myocardial infarction (MI) and cardiovascular outcomes in the immediate post-coronary intervention period. The presence and significance of this interaction in the stroke population is unknown. Objective: To investigate the effects of combined Clopidogrel and Proton Pump Inhibitor (PPI) therapy on risk of recurrent stroke, myocardial infarction (MI,) and death in a cohort of geriatric patients following first ischemic stroke. Methods: This was a retrospective review of de-identified, prospectively collected, electronic medical data held in a multispeciality group practice. Data was collected in a cohort of 280 geriatric patients (mean age 76.4 years at the time of first stroke,) under the supervision of a stroke neurologist. Results: Prior to the index stroke, 83/280 (30%) of patients were on a PPI versus 145/280 (52%) subsequent to the stroke. There were 35 recurrent strokes, 4 MIs, and 43 deaths over a mean follow-up period of 3.75 years. Combined use of a PPI + Clopidogrel post-stroke was not associated with an increased risk of recurrent stroke or MI. However, the combination was associated with an increased risk of death (unadjusted odds ratio 2.48, z = 2.70, 95% CI 1.28 to 4.81, p < 0.007; adjusted OR 2.93, z = 2.61, 95% CI 1.36 to 6.21 p < 0.005) Other independent predictors of death included older age, female sex, and history of atrial fibrillation. Conclusion: Geriatric patients are at a high risk of vascular events. Clopidogrel is, therefore, used often for vascular event intervention and prevention. Prescription and over-the-counter usage of PPI medications in this population is also high. Our data suggests that the hypothesis, which is that the combination of PPI medications and Clopidogrel may increase risk of death in elderly stroke patients, warrants further exploration.

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Assessing Perceived Stress Provides Targets for Stroke Prevention
Mariam D Kashani, Ami H Eliaison, Jacqueline A Hoffman, Marina N Vernalis; Walter Reed Army Med Ctr, Washington, DC

Background: Stroke prevention traditionally targets cholesterol and blood pressure control. While these measures are valuable, this limited focus may overlook other variables that increase risk for stroke. Objective: We sought to examine a broader approach to stroke prevention by assessing individual intervention program (IPP) by identifying multiple behavioral factors associated with stroke risk. Our integrative program targets cardiovascular (CV) risk reduction through behavior interventions to improve nutrition, exercise, sleep and stress. Methods: Subjects entering the IPP completed questionnaires including the Perceived Stress Scale (PSS), EwNorth Sleepiness Scale (ESS), Fatigue Scale, Pittsburgh Sleep Quality Index (PSQI) and Berlin Questionnaire for Sleep Apnea. Data collection also included anthropometrics and a CV-relevant lab panel. Differences between subjects with high stress (PSS≥23) and those with low stress (PSS≤23) were analyzed by t-test. Results: Of 351 completing IPP enrollment, 45% scored above a moderate level of stress (PSS>14). Subjects with moderate to high stress (PSS≥14) showed higher BMI (31.3±5.9 vs 29.0±5.9, p=0.001), increased Waist Circumference (101.5±7.4 cm vs 98.2±13.8, p=0.04), glucose (98.1±28.2 mg/dl vs 92.8±14.6, p=0.03) and Lp-PLA2 (strongly associated with stroke risk, 220.6±10.4 ng/ml vs 195.6±6.7, p=0.02). High-stress subjects also demonstrated greater daytime sleepiness (ESS=10.4±5.1 vs 7.8±4.8, p<0.001), greater fatigue (5.4±2.2 vs 3.4±2.4, p=0.001), lower sleep quality (PSQI 8.5±4.4 vs 5.9±4.0, p<0.001) and shorter sleep duration (19 min less/24 hr, p=0.04) with a higher risk for sleep apnea (65% at high risk vs 41%, p<0.003) than their low-stress counterparts. Conclusion: Assessing stress levels in patients can provide targets for intervention in stroke prevention. High stress is associated with numerous behavioral, biochemical and anthropometric factors that increase stroke risk. Comprehensive stroke risk prevention could benefit from an integrative approach that includes lifestyle behavioral assessment to identify as well as to reduce stroke risk and improve quality of life indicators.

Impact of Menopausal Status and Ethnicity on Stroke Risk Factors
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Background: Epidemiologic studies have identified risk factors (RF) for stroke in women. The majority of women who experience a stroke have at least one modifiable RF. An increased prevalence of stroke has recently been reported in middle-aged women possibly related to the under-recognition of modifiable RF that occur around menopause. In addition to menopausal status, certain ethnic groups have an increased risk for developing specific RF. Hypothesis: Menopausal status and ethnicity will increase the prevalence of modifiable stroke risk factors. Methods: A total of 2259 women were evaluated for the presence of modifiable vascular RF during a comprehensive stroke/cardiovascular evaluation. The women were categorized by ethnicity and menopausal status. Dyslipidemia, HTN and the Metabolic Syndrome (MS) were diagnosed according to JNC 8 guidelines, NCEP ATP III criteria. Results: The majority of the women (80%) in the sample were post-menopausal (n=1384), 57% (n=774) Caucasian, 25% (n=339) African American (AA) and 14% (n=195) Hispanic. Thirty percent of the women (n=888) were pre-menopausal: 34% (n=238) Caucasian, 22% (n=153) AA and 38% (n=263) Hispanic. The remaining nine percent (n=207) were peri-menopausal: 45% (n=90) Caucasian, 27% (n=51) AA and 23% (n=46) Hispanic. Statistical significant increases of HTN and dyslipidemia (p<0.05) were observed in all ethnic groups with the transition through menopause. There were specific ethnic variations in stroke RF as well as the timing of their onset. AA and Hispanics also had significant increases in the incidence of the MS, elevated triglycerides and diabetes (all p<0.05). In AA women, the significant increase of these RF occurred between pre and peri-menopause. In Hispanic women, a significant increase in dyslipidemia occurred between pre and peri-menopause, while the MS increased between peri and post-menopause. Caucasian women had significant increases in the MS and dyslipidemia between peri and post-menopausal stages. Stroke risk scores were consistently higher in AA women across all menopausal stages. Three percent (n=77) women experienced premature menopause; 30% Caucasian, 30% Hispanic, 39% AA. Modifiable RF in this group were high: 45% HTN, 45% MS, 42% dyslipidemia, 92% overweight. Conclusion: The data supports our hypothesis that menopausal status and ethnicity influence the incidence of modifiable stroke risk factors. As evidenced by the women with premature menopause having a high incidence of stroke risk, the age of menopause onset is not significant. Ideally, healthcare providers should evaluate for stroke risk when women are pre-menopausal and closely monitor them as they progress through menopause. IPP RF identification and patient education can empower women to take control and reduce their risk for stroke.

Stroke Follow-up: What is Stopping Patients From Returning to Clinic?
Susan E Alderman, Mary J Hess, Loren F Shen, Sean I Savitz, James C Grotta, Deborah L East; Univ of Texas Houston Med Sch, Houston, TX

Background: A stroke patient’s post-hospital visit with a stroke specialist is part of standard clinical practice and includes assessment of neurological impairment, recovery status, medications and preventive practices. Little is known about how many patients follow up in the stroke clinic, affiliated with the admitting hospital, why they do not return, or if failure to return is associated with functional outcomes. Objective: To determine the proportion of ischemic stroke patients, hospitalized on our inpatient stroke service, who completed a follow up visit in our stroke clinic and to identify factors associated with failure to return for follow-up care. Method: Retrospective cohort study evaluating adult ischemic stroke patients admitted to a Comprehensive Stroke center from 11/1/08 to 3/31/09. Study time frame was chosen to allow data collection while avoiding a period of post-hurricane community disruption. Factors were evaluated using Fisher’s exact test, Wilcoxon signed-rank test, Chi-square analysis of Maximum Likelihood Estimates (MLE), and Odds Ratio. Results: Are reported for 225 patients, eighty-four percent (190) of which did not return to clinic for follow-up, despite hand written instructions given by nurses at time of discharge. Twenty-six percent of those not returning for follow-up were transferred from our in-hospital stroke service to another service prior to discharge. There was no significant difference between patients returning or not returning for follow-up in terms of demographics, length of stay, travel distance from home, insurance status, arrival NIHSS, t-PA or other therapies, social support system, or research participation. Patients were more likely to follow-up if they were discharged to a home address rather than to either a control group or an experimental group (CI, 3.09-27.04, p>0.0001), if they arrived at the hospital by car (OR 3.3; 95% CI, 0.61-18.57, p<0.003), if their 90 day modified Rankin Score (mRS) was <1 (OR 3.13; 95%CI, 1.34-7.31, p=0.008) or if their discharge mRS was <1 (OR 2.28; 95% CI, 1.03-5.05, p=0.043). Conclusions: A low percentage of stroke patients admitted to our hospital during the study period returned for follow-up. Factors most closely associated with clinic follow-up indicated that patients with adequate physical mobility and accessible transportation enabled them to return to clinic. We expected to find that travel distance, insurance and social support status would be associated with failure to follow up in clinic. These factors may be masked or overcome by superior outcomes, leading to greater independence, for the recovering stroke patient. A prospective study is needed to better identify barriers to follow-up and to identify improved nursing interventions which assist the patient along the continuum of care.

The Effect of Augmented Visual Feedback on Motor Learning of Reaching Movements in Novel Dynamic Environments in Chronic Stroke Survivors
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Background and Purpose: Sensorimotor abnormalities after stroke make stroke control of limb and environmental dynamics difficult to achieve. However, augmented visual feedback during learning of novel dynamics may make such tasks easier to learn. The purpose of this ongoing AHA funded study (#0820136Z) is to test if augmented visual feedback can improve motor learning of a reaching task in chronic stroke survivors. Methods: A randomized controlled design was used to assign chronic stroke subjects to either a control group or an experimental group. Subjects performed reaching movements while holding the handle of a 2-joint Inmotion2 robotic system (Interactive Motion Tech Inc., MA) on 3 days spread over a week. On the first two days, subjects in the control group received true feedback of their movement while subjects in the experimental group received augmented feedback of their movement (position control with a visual force field with a 30 cm vertical displacement from the straight line to the target was magnified two-fold). On the third day, subjects in both groups were tested for improvement in normal reaching (without any force field) and
A Systems Approach to Stroke Care: The University Hospitals Cleveland Experience

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Background and Purpose: In 1993, University Hospitals Case Medical Center began its expansion from a single tertiary academic medical center to its current 11 hospital health system. In 2006, the University Hospitals Neurological Institute (UHNI) was formed with the vision of integration to deliver the highest quality care throughout the health system. Methods: The UHNI established a multidisciplinary Stroke & Cerebrovascular Center led by a Medical Director (MD) with support from an Operations Manager (OM) who coordinated the stroke system program. A UHNI Stroke System Initiative was launched with support from the hospital leadership. Clinical and administrative representatives from each hospital met to identify their specific needs and opportunities. The Stroke Center MD and OM worked with the Neuroscience Nursing Practice Center to develop Stroke Clinical Practice Guidelines (CPG), educational modules, patient assessment and documentation tools. The Stroke Center OM traveled to each hospital to facilitate development of Stroke Quality Improvement Committees (SQIC) and to facilitate Joint Commission Stroke Certification. The SQICs developed action plans and reported progress to UHNI hospital and system leadership. Results: Each participating hospital appointed a Stroke Program MD and Coordinator to lead their SQIC. The Stroke CPG, educational modules, and documentation tools were implemented throughout the health system. Compliance with standardized stroke measures such as Get With the Guidelines and the use of the CPG are monitored monthly and reported to the SQIC and the UHNI Stroke System Coordination staff. System plans are updated at quarterly meetings and annual department meetings. At each hospital, the Stroke program MD is the department chair. The effects of the CPG are monitored monthly and reported to the SQIC and the UHNI Stroke System Coordination staff. System plans are updated at quarterly meetings and annual department meetings.

Baseline Results of an Acute Ischemic Stroke Registry Including Acute Multimodal Imaging (ASTRAL)

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Introduction: Stroke registries are valuable tools to obtain information about stroke epidemiology and management. The Acute Stroke Registry and Analysis of Lausanne (ASTRAL) prospectively collects epidemiological, clinical, laboratory and multimodal brain imaging data of acute ischemic stroke patients in the Centre Hospitalier Universitaire Vaudois (CHUV). Here, we provide design and Methods used to create ASTRAL and present baseline data (2003-2008) of our patients. Methods: All consecutive patients admitted in CHUV from 01/01/2003 until 31/12/2008 with acute ischemic stroke arriving within 24 hours were included in ASTRAL. Patients arriving beyond 24 hours, with transient ischemic attack, intracerebral hemorrhage, subarachnoidal hemorrhage or cerebral sinus venous thrombosis were excluded. Recurrent ischemic strokes were registered as new events. Results: Between 2003-2008, 1742 events of 1653 patients were registered in ASTRAL. There was a preponderance of males, even in the elderly and in the augmented feedback group. Conclusions: Preliminary data from this AHA funded study suggests that augmented visual feedback has the potential to cause greater learning of dynamic motor tasks in stroke subjects than training with true feedback. This learning also has the potential to cause larger improvements in normal reaching movements. The implications of these findings are very important for stroke rehabilitation.

Rapid Assessment for the Prevention of Ischemic Disease (RAPID) Care Discharge Clinic: Advanced Practice Model for Secondary Stroke Prevention

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Background: Stroke recurrence within 30 days after TIA or stroke is estimated to be 5-15%. The percentage of stroke prevention knowledge retained during the acute stroke hospitalization remains unclear. After evaluation of our discharge process we identified an opportunity to improve our method for providing the TIA and stroke patient with a comprehensive secondary stroke prevention plan. We wanted to develop a continuum of care for the patient once discharged from the hospital. The purpose of this performance improvement project was to determine the effectiveness of developing a secondary stroke prevention discharge clinic using a Neuroscience ACNP. Methods: The stroke and neurocritical division of an academic primary stroke center developed a Rapid Care Discharge Clinic using an acute care nurse practitioner (ACNP). The Rapid Care ACNP is credentialed and has a practice agreement with a vascular neurology practice. Stroke and neurocritical staff from the primary care and hospital transferred their knowledge to the ACNP. The ACNP collects patient information from the patient and their family and completes the ACNP visit, which includes: refilling of medications, counseling on smoking cessation, weight loss, blood pressure, lipid and diabetes control, cardiac evaluation, and a TIA/stroke prevention plan. The team wishes to improve our method for providing the TIA and stroke patient with a comprehensive secondary stroke prevention plan. We wanted to develop a continuum of care for the patient once discharged from the hospital. The purpose of this performance improvement project was to determine the effectiveness of developing a secondary stroke prevention discharge clinic using a Neuroscience ACNP. Results: The stroke and neurocritical division of an academic primary stroke center developed a Rapid Care Discharge Clinic using an acute care nurse practitioner (ACNP). The Rapid Care ACNP is credentialed and has a practice agreement with a vascular neurology practice. Stroke and neurocritical staff from the primary care and hospital transferred their knowledge to the ACNP. The ACNP collects patient information from the patient and their family and completes the ACNP visit, which includes: refilling of medications, counseling on smoking cessation, weight loss, blood pressure, lipid and diabetes control, cardiac evaluation, and a TIA/stroke prevention plan.
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diagnostic tests from the hospital stay. Practice guidelines determine when a patient needs to be seen by the on call vascular neurologist. The ACP consultation and diagnostic test results are faxed to the PMD within 48-72 hours. Effectiveness for RAPID Care was defined as the TIA and stroke patient had a secondary stroke prevention consultation within 7 days of acute hospitalization. Results: Over 75 TIA and mild stroke patients have been evaluated in RAPID Care within one week of their acute hospitalization. All RAPID Care patients were evaluated by a vascular neurologist within 30 days of TIA or stroke. No patient was lost to follow up. Conclusion: RAPID Care allows continuum of care for secondary stroke prevention for TIA and stroke patients within one week of hospital discharge using an ACPN model of care. Future plans include measuring physician and patient/family satisfaction for RAPID Care.

Collaborative Nurse Physician Practice: Implementing Clinical Practice Guidelines From Neuro ICU Throughout the Continuum

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Background and Purpose: With all the new guidelines on stroke care released in 2009 from the American Heart Association/American Stroke Association (AHA/ASA), the Stroke team at Inova Fairfax Hospital believed it was paramount to create an adhoc team to craft evidence based, patient safe, user friendly stroke documentation tools. The team consisted of an intensivist, critical care nurses, stroke nurses, pharmacy, rehab, lab and radiology. Focus of documentation incorporated best practices from the SPARKL trail with statins, New Guidelines for Hemorrhagic stroke, prescriptive measures for ICP and a focus on patient education with risk factors. Methods: Qualitative and Quantitative methodology was utilized. Members of the team were given the option to read evidenced based practice articles disseminated at our quality meeting, attend presentations on the new guidelines in journal club, attend stroke grand rounds, participate in webinars provided by Get with the Guidelines. Education was recorded by the program manager as part of the joint commission standards for staff education. Results: Increase in orderset and pathway use expanded from 40% to 75% in a four month period. Safety handoffs and communication improved among the team as displayed in 100% chart audits of performance measures. On July 22, 2009 the hospital was re-certified as a Primary Stroke Center with no requirements for Improvement identified. Conclusion: The commitment from all stakeholders' developers of the tool was essential to the success of implementing the evidence based guidelines. Having various opportunities for education of the new evidence assisted in handwriting best practices and compliance for rendering safe, quality, efficient care for stroke patients.

An Anti Coagulation Clinic May Identify Minor Hemorrhage Otherwise Undetected

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Background: Nurse run anticoagulation clinics are not a new concept. In efforts to increase patient satisfaction and adherence to management recommendations, our Primary Stroke Center has been operating a nurse run clinic for the past ten years. Literature supports improved patient satisfaction and indirectly patient outcomes with person to person interactions. Methods: A nurse run clinic for anticoagulation related to anticoagulation use. Many institutions have organized nurse managed clinics in efforts to achieve this goal. Objectives/Purpose: Examine characteristics of patients in a nurse run anticoagulation clinic to identify complications and possible benefits of such a clinic. Method: Community Institutional Review Board approval was obtained. All patients in the anticoagulation database from 2007-2009 were reviewed; those receiving skilled nursing care were excluded. A survey was administered per phone by two research students. Survey items included age, gender, length of time on anticoagulation, indication for treatment, bleeding events, hospitalization, and fall rates. Results: Among all clinic patients, 44/50 (88%) felt nurses listened to concerns, 48/50 (96%) were confident in the care provided by such a clinic, 25/50 (50%) were treated for posterior circulation infarcts or failure of other therapies. Minor bleeding events occurred in 8/50 (16%) including epistaxis, bleeding gums, or bleeding after clipping nails; 1 (2%) experienced internal bleeding following a fall. Fourty four of fifty (88%) felt nurses listened to concerns, 49/50 (98%) were confident in the nurses, and 49/50 (98%) received clear instructions. However, only 38/50 (76%) felt they were provided clear instructions regarding meds/test results/complications. Conclusion: A nurse managed clinic is beneficial in detecting minor hemorrhage events. Close monitoring may provide better care. Although patients feel confident in the care provided by such a clinic there is indication improvements can be made with regard to education regarding the specifics of management.

Integrating Automated Prompts Into Standard Physical Assessments to Reduce Aspiration Risk From Dysphagia in Stroke Patients

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Introduction: Stroke patient’s are at a 56% percent risk of developing dysphagia, a swallowing disorder which can lead to aspiration pneumonia. Dysphagia may occur because of pharyngeal muscle weakness or paralysis because of poor awareness / sensation of food in mouth or throat. Pneumonia is one of the leading complications of stroke and a significant cause of death after a stroke. Most post-stroke pneumonia cases result from aspiration. Our hospital sought to establish a methodology for reducing the incidence of dysphagia in stroke patients with the aim of performing dysphagia screens in >65% of stroke patients. Methods: A dysphagia screen for use in the hospital was created. Nurses screened all stroke and TIA patients prior to any oral intake including medications to decrease the risk of aspiration. Protocols required that any patient exhibiting problems with swallowing remain NPO until a formal evaluation by speech therapy was completed. Initially, this precautionary step was often forgotten by nurses. To counter this problem, a dysphagia screen query was integrated into the hospital’s existing computer documentation system. Nurses were prompted with the question “Is this a possible stroke or TIA patient?” as a reminder during the physical assessment. Results: Data collection began in October 2006. The results of random sampling of 30 stroke patients were entered on a monthly basis. Compliance rates increased from a baseline of 16.7% to 63.6% in January 2007, before declining to 36.7% in August 2007. At this point the dysphagia screen reminder was added to the emergency room nursing assessment in the computer. By May 2008 the compliance rate reached 82.4%. At this time, a dedicated Nurse Practitioner was hired as the Stroke Program Clinical Coordinator to further monitor compliance and integrate the dysphagia screen into the Inpatient Assessment. As a result compliance rates of >85% have been maintained. Conclusion: Our efforts to improve the percentage of stroke patients screened for dysphagia in our facility has improved significantly with the integration of the dysphagia screen into the existing computer documentation system. As a part of the physical assessment, the nurse is required to address whether the patient is a possible stroke or not and then proceeds to fill out the screen. This is indeed an improvement. This method not only reminds nurses of the importance of the dysphagia screen, but also forces them to address the issue at that moment. Automating prompts into standard physical assessments can serve as a useful way to increase the completion of dysphagia screens and reduce dysphagia rates in stroke patients.

Acute Stroke Program With Multidisciplinary Approach

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Objectives: The 2006 Louisiana Health Report Card states that strokes are the third leading cause of death for men and women in all ethnic groups. The survivors of this devastating disease are often left with severe permanent disabilities changing their lives forever. The F.A.S.T. (face, arms, speech, time) Alert program has been implemented to improve patient outcomes by providing state-of-the-art treatment options within a designated time frame. F.A.S.T. Alert utilizes a multidisciplinary team to ensure rapid and efficient responses to patients with new onset stroke symptoms. Methods: The F.A.S.T. Alert Assessment Tool is used to document door-to-treatment times throughout the continuum of care for stroke patients. Emergency Response staff in the field notifies the Emergency Department (ED) of a possible acute stroke prior to arrival. The patient is assessed using the F.A.S.T. Alert assessment tool and if positive stroke symptoms are present, a F.A.S.T. Alert code is activated. This is accomplished by calling the operator, who makes the overhead announcement hospital-wide. This announcement activates the multidisciplinary team in order to provide rapid response times from each department. The radiology department prepares for a stat CT (Computerized Tomography) scan of the brain to be done within 15 minutes of arrival to the ED and results interpreted within 25 minutes. Concurrently, labs are drawn within 10 minutes of arrival and results obtained in 45 minutes. Once CT results are obtained, the neurologist is called to consult. Based on the current data, having a F.A.S.T. Alert program has allowed for vast improvement in treatment of acute stroke patients. F.A.S.T. Alert Assessment Tool is used to document door-to-treatment times throughout the continuum of care for stroke patients. Over 75 TIA and mild stroke patients have been evaluated in RAPID Care allowing continuum of care for secondary stroke prevention for TIA and stroke patients within one week of their acute hospitalization. All RAPID Care patients were evaluated by a vascular neurologist within 30 days of TIA or stroke. No patient was lost to follow up. Conclusion: By implementation of the F.A.S.T. Alert Program, patients have more treatment options, thus yielding better patient outcomes. Based on the current data, having a multidisciplinary approach has allowed for faster treatment times.
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**DEFUSE and EPITHET: Two Different Studies With One Consistent Message**

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**Background:** The DEFUSE (n=74) and EPITHET (n=101) studies have in common that a baseline MRI was obtained prior to treatment (IPAI in DEFUSE, IPAI or placebo in EPITHET) in the 3-6 hour time-window. There were however important methodological differences between the studies. A standardized reanalysis of pooled data was undertaken to determine the effect of these differences on baseline characteristics and study outcomes. **Methods:** To standardize the studies 1) the DWI and PWI source images were reprocessed and segmented using automated image processing software (RAPID), 2) patients were categorized according to their baseline MRI profile as either Target Mismatch (PWITmax/CBV MR ratio > 1.8 and an absolute mismatch >15 mL), Malignant (DWI or PWITmax/CBV MR lesion > 100 mL), or No Mismatch. 3) favorable clinical response was defined as NIHSS score of 0-1 or a ≥8 points improvement on the NIHSS at day 90. **Results:** Prior to standardization there was no difference in the proportion of Target Mismatch patients between EPITHET and DEFUSE (54% vs 49%, p=0.8), but the EPITHET study had more patients with the Malignant profile than DEFUSE (35% vs 9%, p<0.01) and fewer patients that had No Mismatch (11% vs 42%, p<0.01). These differences in baseline MRI profiles between EPITHET and DEFUSE were largely eliminated by standardized processing of PWI and DWI images with RAPID software (Target Mismatch 49% vs 48%, Malignant 15% vs 8%; No Mismatch 36% vs 25%; p=NS for all comparisons) Reperfusion was strongly associated with a favorable clinical response in mismatch patients (figure). This relationship was not affected by the standardization procedures (poled odds ratio of 8.6 based on original data and 6.6 based on standardized data). **Conclusion:** Standardization of image analyses procedures in acute stroke is important as non-standardized techniques introduce significant variability in DWI and PWI imaging characteristics. Despite methodological differences, the DEFUSE and EPITHET studies show a consistent and robust association between reperfusion and favorable clinical response in Target Mismatch patients regardless of standardization. These data support an RCT of IPAI in the 3-6 hour time-window for Target Mismatch patients identified using RAPID.

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**Clinical Diffusion Mismatch and MRA Diffusion Mismatch Are Specific but Not Sensitive to Identify Perfusion Diffusion Mismatch**

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**Background:** The perfusion-diffusion mismatch (PDM) is used in clinical trials and practice as a marker of the ischemic penumbra to select patients who might benefit from thrombolytic treatment. The clinical-diffusion (CDM) and MRA-diffusion (MDM) mismatch models have been proposed as simpler alternatives, because they do not require acquisition or quantitative processing of perfusion-weighted imaging (PWI). **Purpose:** Taking PDM measurements from an imaging core lab as the gold standard, we determined the sensitivity, specificity, and accuracy of qualitative PDM judgment, CDM and one MDM model from the literature, and one novel MDM model in a thrombolytic eligible sample. **Methods:** Retrospective analysis was performed of 90 hemispheric stroke cases which presented within 3 hours after symptom onset, received IPAI and had good quality pretreatment multimodal MRI including diffusion-weighted imaging (DWI), PWI, and MRA. The CDM was defined as NIHSS > 8 and DWI volume < 25mL. We defined the MDM as abnormal MRA correlating with index stroke and DWI volume < 25mL. We also evaluated the DEFUSE MDM criteria (MDM-D), which is defined as DWI < 25mL and MRA scale of 3 as well as DWI < 15mL and MRA scale of 2. Comparison was also made using more stringent PDM criteria (volume of mismatch region 50mL or 70mL) **Results:** The reviewers qualitative assessment of PDM was 82% sensitive and 100% specific compared to quantitative measurement of PDM. The MDM-D model was 47% sensitive, 90% specific with an accuracy of 57% compared to PDM. The MDM-D model did not differ from the MDM model. The CDM model had a sensitivity of 31%, a specificity of 72% and 38% accuracy, which was not significant (X2, p=0.82). MRA abnormality revealed sensitivity of 83% and specificity of 65% and an accuracy of 80% for predicting PDM. The results from each model are presented in the Table. With more stringent PDM definitions, the accuracy of the MDM and CDM increases, and the accuracy of the MRA and qualitative model decreases. **Conclusion:** Qualitative review of PDM rapidly and most accurately predicts ischemic penumbra as defined by the quantitative PDM. For models that do not use PWI, MDM models are most sensitive and MRA abnormality alone is most specific. The CDM is insensitive to PDM. Abnormal MRA alone accurately predicts ischemic penumbra but does not exclude patients who might not benefit from thrombolytic therapy. MDM models are specific but insensitive, excluding patients who might be the target of thrombolytic therapy. Table: Sensitivity, Specificity and Accuracy of mismatch models and qualitative review of multimodal imaging in predicting ischemic penumbra.

**Table.**

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<th>Model</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
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<td>MDM-D</td>
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<td>90%</td>
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<td>MDM</td>
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<td>90%</td>
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<td>72%</td>
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<td>Qualitative PDM reading</td>
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**Diffusion-perfusion Mismatch Selection for Clinical Trials: Visual Determination Reliably Estimates Quantitative Mismatch Criteria**

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**Introduction:** In patients with ischemic stroke, tissue at risk can be approximated using MRI mismatch (a difference between mean transit time (MTT) and diffusion-weighted (DWI) lesion volume). The routine use of quantitative methods to measure mismatch is not yet practical in the acute setting, and clinicians often rely on a qualitative evaluation. The accuracy of this qualitative read is unknown. The purposes of this study are 1) to compare quantitative assessments and quantitative measurements of mismatch and 2) to evaluate the inter-rater reliability of these assessments.**Methods:** We included MRI scans from 70 treatment eligible patients. Patients were included if they had evaluable DWI and PWI images within 3 hours from onset prior to intravenous tPA treatment and acute ischemic stroke on DWI with a lesion >10ml. An expert reader measured lesion volumes using an established semi-automated quantitative method. We defined quantitative mismatch a priori, as a difference >50ml between the MTT and DWI volumes. Greater than two weeks later, the same reader evaluated all patients for qualitative mismatch (a visually apparent difference between MTT and DWI lesions). To evaluate the inter-rater reliability of the qualitative reads, five readers of various levels of experience in stroke MRI interpretation independently assessed a subgroup of 25 patients.**Results:** There was a significant association between qualitative and quantitative evaluations of mismatch (n=70, 6–66, p<0.001). The quantitative >50ml threshold showed high sensitivity (0.88), specificity (0.71), accuracy (0.81) and positive predictive value (0.82) for discriminating mismatch by visual inspection. Visual inspection identified 81% of patients with quantitative mismatch >50ml. Agreement between the five readers for qualitative mismatch was significant (n=25, 6 range=0.5-1). Using the quantitative >50ml threshold, the five readers agreed with the quantitative reads in 72-88% of the cases. Discrepant cases (n=13) had an average mismatch of 50ml, suggesting that 50ml is a good discriminator of mismatch by qualitative judgment (Table).**Conclusion:** We found that the qualitative identification of mismatch agreed well with a quantitative mismatch threshold of >50ml and that readers reliably identified patients with mismatch using visual inspection. Our results suggest that a qualitative determination of mismatch in thrombolytic eligible patients may be sufficient for patient selection in clinical trials using mismatch as an inclusion criterion.

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<tr>
<th>Table: DWI, MTT, and MTT-DWI (Mismatch) Statistics</th>
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</thead>
<tbody>
<tr>
<td><strong>DWI Average (SD) [ml]</strong></td>
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<tr>
<td><strong>Quantitative Measurement</strong></td>
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<tr>
<td>No Mismatch (n=28)</td>
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<tr>
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<td><strong>Qualitative Assessment</strong></td>
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<tr>
<td>Mismatch (n=45)</td>
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<tr>
<td><strong>Discrepant Cases Between Methods</strong> (n=13)</td>
</tr>
<tr>
<td>False Negatives &amp; False Positives</td>
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**Neuroimaging of Cerebral Ischemia in Clinical Practice From 2002 to 2009:**

**Expanding Windows, Modalities, and Therapeutic Strategies**

David S Liebeskind, Liliana R Gomez, Qiang Hao, James W Seyer; UCLA, Los Angeles, CA

**Background:** From triage to therapy, neuroimaging modalities have been rapidly adopted in the community leading to a transformation in the management of acute stroke and transient ischemic attack (TIA) patients. Such changes in the use of imaging have not been previously chronicled. We conducted a longitudinal observational study on the use of imaging in acute stroke and TIA between 2002 and 2009 with a survey instrument.**Methods:** A web-based survey of neurologists was conducted almost 7 years after initial results were obtained from the same population in 2002. Elements of the two survey instruments contained identical questions regarding imaging of acute cerebral ischemia and the management of such cases.**Results:** 610 complete survey responses were recorded in 2009, compared with 716 in 2002. Both surveys similarly represented a broad range of neurologists, in various systems of care across the United States and more than 41 countries. Imaging of TIA has become more akin to acute stroke (83% in 2009 vs. 89% in 2002, p<0.03). Outpatient DWI continues to grow (84% vs. 78%, p<0.006) and telestroke has rapidly evolved. Telestroke access has increased in the office and at home, with access at both locations doubling (41% vs. 16%) during this period. The vast majority of respondents endorsed an image-based window (83% vs. 83%, p=NS). Use of specific early imaging findings including presence of arterial occlusion, parenchymal changes, and mismatch has also grown dramatically (all p<0.001). CT angiography (84% vs. 63%, p<0.001) and CT perfusion (45% vs. 28%, p<0.001) have rapidly expanded, whereas emergent MRI remained did not proliferate (51% vs. 53%, p=NS). Use of other angiographic modalities including TCD (39% vs. 45%, p=0.024) and MR angiography (80% vs. 84%, p=0.05) has been offset by growth of multimodal CT. Benchmark times for acute image acquisition (77% vs. 57%, p<0.001) and interpretation (76% vs. 68%, p=0.001)
have greatly accelerated. Interestingly, knowledge of costs for such studies (64% vs. 77%, p<0.001) and the impact of such costs in clinical decisions to order studies (46% vs. 51%, p=0.075) have both decreased. Fewer respondents view intra-arterial thrombolyis as investigational and more devices abound (both p<0.001). Conclusions: From 2002 to 2009, imaging of stroke and TIA has expanded to provide greater access to more therapeutic strategies with the use of a broader range of modalities.

Optimal Perfusion Thresholds for Prediction of Tissue Destined for Infarction in the Combined EPITHET and DEFUSE Dataset

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Background: The optimal perfusion weighted MRI (PWI) marker of significant hypoperfusion remains controversial. Recently, the time to peak of the residue function (Tmax) parameter has proven to be a useful biomarker, most notably by providing perfusion estimates that are highly correlated with both clinical outcome and infarct growth attenuation. However, uncertainty exists regarding the optimal Tmax threshold and predictive performance compared to alternative perfusion parameters, such as mean transit time (MTT). We addressed these questions using the combined EPITHET (n=101) and DEFUSE (n=74) database. Methods: Perfusion maps were generated using automated image processing software (RAPID). To assess penumbra thresholds that predict tissue infarction in the absence of reperfusion, we analyzed acute Tmax and MTT maps from patients with: less than 50% tissue reperfusion, less than 20 ml absolute reperfusion, a final lesion volume of at least 10 ml. Patients with Parenchymal Hematomas (ECASS PH 1-2) were excluded. FLAIR or T2 scans from Day 30 (DEFUSE) and Day 90 (EPITHET) were registered to the acute PWI maps allowing for measurement of perfusion values in infarcted and salvaged tissue (Figure). An ROC analysis was used to summarize the maps by their area under the curve values (AUCs) reflecting the predictive value of each map. AUCs were then compared between MTT and Tmax maps and the optimal cut points were determined using Youden’s index. Results: Twelve patients fulfilled the inclusion criteria outlined above. Tmax maps yielded significantly higher AUC values than MTT maps with a median (IQR) AUC of 0.78 (0.70-0.83) vs. 0.67 (0.60-0.75), p=0.016. This difference between MTT and Tmax maps was visually apparent. The median optimal threshold for Tmax was 5 s (4-6) providing a sensitivity and specificity for infarction of 76% (67-79) and 78% (73-82) respectively. For MTT the optimal threshold was 9.0 s (7.0-10.0) with sensitivity and specificity of 58% (47-75) and 75% (70-79). Conclusion: Tmax was a better predictor than MTT of tissue destined for infarction in patients who did not have reperfusion. Defining PWI lesions based on a Tmax threshold between 4 and 6 seconds appears optimal for early identification of critically hypoperfused tissue in stroke patients imaged 3-6 hours after symptom onset.

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2010 International Stroke Conference Poster Presentations

P165

Pre-treatment DWI is Superior to CT-ASPECTS in Detecting Excellent to Fairly Good Outcome After Intravenous rt-PA Therapy

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Background: ASPECTS is a quantitative topographic score to evaluate the extent of early ischemic change (EIC) in the middle cerebral arterial territory on CT as well as on diffusion-weighted MRI (DWI). DWI can more clearly delineate the extent of EIC within 3 hours after stroke onset as compared with CT. There were a few data regarding the comparison of ASPECTS between DWI and CT and rt-PA therapy in same patients so far. This study aimed at elucidating the relationship between DWI-ASPECTS and CT-ASPECTS before rt-PA therapy and their associations with clinical outcome. Methods: A retrospective observational study was conducted to clarify the practical conditions of IV rt-PA therapy using 0.6 mg/kg alteplase in 10 major stroke centers in Japan. Studied were a total of 381 consecutive patients with anterior circulation ischemic stroke (249 men, 72±11 years) who were treated with intravenous rt-PA from October 2005 through April 2008, underwent both DWI with CT and rt-PA therapy. Excluded were patients with fairly severe to severe disability, corresponding to a modified Rankin Scale (mRS) 4 or 5 before symptom onset. The MRI study was performed immediately after the CT study. An ASPECTS (10 for no EIC and 0 for the largest EIC) was assessed on the initial DWI and CT studies. Chronic functional outcome was assessed with mRS at 3 months after stroke onset. Results: Of 381 patients, 230 (60.4%) had excellent to fairly good outcome (mRS 0-3) at 3 months. The pre-treatment DWI-ASPECTS (median 8, IQR 6-9) was lower than the pre-treatment CT-ASPECTS (8, 10) (P<0.001). DWI-ASPECTS was positively related with CT-ASPECTS (r=0.565, P<0.001). The optimal cutoff score of DWI-ASPECTS to predict the patients with mRS 0-3 at 3 months was 7±3 with a sensitivity of 86% and specificity of 45%, and the area under the receiver-operating characteristic (ROC) curve was 0.681. On the other hand, the optimal cutoff score of CT-ASPECTS was >9 with a sensitivity of 76% and specificity of 48%, and the area under the ROC curve was 0.635. Conclusion: DWI-ASPECTS had a positive relationship with CT-ASPECTS. Compared with the former score, a lower cutoff than the latter, DWI-ASPECTS may be useful to predict excellent to fairly good outcome (mRS 0-3) at 3 months with higher sensitivity as compared with CT-ASPECTS.

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The Extent of White Matter Disease on Acute Magnetic Resonance Imaging Is an Independent Predictor of Outcome in Ischemic Stroke

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Background: After years of conflicting data regarding the prognostic value of white matter disease (WMD) in acute ischemic stroke (AIS), recent studies reported an association between severe WMD and poor outcomes. This association has not been studied in a patient cohort who had Magnetic Resonance Imaging (MRI) in the hyperacute phase. Purpose: To determine the association between the severity of MRI white matter hyperintensities (WMH) and prognosis in acute ischemic stroke patients who had multimodal MRI within the first 12 hours in view of endovascular intervention. Methods: Over 2 years, 145 consecutive patients with AIS who had multimodal MRI within the first 12 hours and National Institute of Health Stroke Scale Score (NIHSS) performed within the preceding hour were identified. The outcome measure was modified Rankin Scale (mRS) at 3 months dichotomized to good (0-1) and unfavorable outcome (2-6). Quantitative analysis of infarct volume on Diffusion Weighted Imaging (DWI) and WMH volume on Fluid Attenuated Inversion Recovery (FLAIR) sequences were performed using validated computer-assisted techniques. These lesion volumes were further adjusted for head size using intracranial area measurements. Multivariate logistic regression was used to assess the association between WMH volume and dichotomous clinical outcomes while adjusting for demographics and other clinical and laboratory prognostic markers. Results: The study population (44% female) had mean age 65 ±15, mean NIHSS 9.2 ±8, median WMH volume 2.9 ml (Interquartile Range: 0.8-26), the n and median DWI volume 7.1 ml (IQR: 29). The time from stroke onset to performance of MRI was 6 hours (IQR: 2.8) and 72% had anterior circulation infarcts. Eighteen percent of this cohort received intravenous thrombolytic treatment. At 3 months, 37% had good outcome. In bivariate analyses, higher volumes of WMH correlated with unfavorable outcomes on follow up (p<0.001). After adjustment for age, gender, infarct volume, admission NIHSS, admission blood glucose, presence of old infarction, atrial fibrillation, and performance of thrombolyis, WMH volume remained as an independent predictor of outcome on follow up (p<0.001). The direction and significance of this association is
remained unchanged when mRS was dichotomized into independent (0-2) vs dependent/death (3-6) categories and used as the outcome measure in a second multivariate logistic regression analysis. The other variables that were independently associated with unfavorable outcomes were higher infarct volumes on DWI, higher NIHSS and female gender. Conclusions: The independent association between WHIM on acute MRI and long-term outcomes among A3 patients evaluated for endovascular recanalization treatments provides an important early prognostic tool and its use might be considered as a stratification variable for subjects enrolled in future acute phase trials.

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Post-Infarct Visual Cortical Plasticity Assessment Using the Immediate-Early Gene Arc

Steven R Zeiler, Johns Hopkins, Baltimore, MD; Richard J O'Brien, Johns Hopkins Bayview Med Ctr, Baltimore, MD; Paul F Worely, Johns Hopkins Univ, Baltimore, MD

Observations in stroke patients and primes indicate that cortical plasticity plays a crucial role in affecting recovery. In order to better define, and eventually manipulate post-stroke cortical plasticity with the goal of encouraging recovery, we designed a model of post-stroke cortical plasticity in the mouse visual cortex. We hypothesized that we could, using a functional technique based on immediate-early gene Arc induction, monitor the representation of eye input in the visual cortex in control mice and in mice with focal strokes. Previously, our group and others have shown that monocular stimulation selectively induces Arc transcription and translation in the ipsilateral binocular zone of the visual cortex; the spatial extent of this activation is increased with monocular enucleation indicating that Arc expression marks visual cortex plasticity. Using a photocaging system, we created focal infarcts which ablate the binocular zone expressing Arc after monocular stimulation. After a seven day recovery period, ipsilateral monocular stimulation induced Arc expression in a more medial area formally mapped as the monocular zone indicating new neuronal responsiveness. To address whether this new area of induction was a direct effect of the stroke and therefore independent of visual stimulation, we stimulated neither eye after creation of a binocular zone infarct. In these animals, there was no Arc induction over baseline, indicating that visual cortex Arc expression after a binocular zone infarct is visually mediated and not secondary to peri-ischemic edema or inflammatory mediators. Therefore, visual cortical Arc induction after a focal binocular zone infarct marks plastic neurons driven by visual stimulation. This finding is important as it allows us to ask two important questions. First, what makes these neurons receptive to plastic changes? Second, how can we modify the quantity and/or quality of this plasticity to affect a more robust recovery? Studies in the mouse visual cortex allow a combination of environmental and genetic interventions to address these questions. Overall, this newly designed model system will be an important tool for elucidating the mechanisms of and interventions in post-stroke cortical plasticity.

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Niacin Treatment of Stroke Increases Neuronal Migration and Axonal Regeneration in Rats

Xu Cui, Michael Chopp, Alex Zacharek, Cynthia Roberts, Jieli Chen; Henry Ford Health System, Detroit, MI

Background & Objective: Cholesterol is known to be an essential modulator of physicochemical state and functional activity in physiological membranes, and plays an essential role in the regulation of synaptic function and cell plasticity. Synaptic plasticity is related to behavioral change and functional recovery after stroke and brain injury. Niacin (nicotinic acid) is the most effective medication in current clinical use for increasing high-density lipoprotein cholesterol (HDL-C). We tested the hypothesis that Niacin treatment of stroke increases HDL-C level, promotes dendrite outgrowth in the ischemic brain. Methods: Male Wistar rats were subjected to 2h of middle cerebral arterial occlusion (MCAO) and treated with or without Niaspan (extended-release Niacin, 40 mg/kg) daily for 14 days started 24h after MCAO. Immunostaining and Western blot assays were performed. Doublecortin (Dcx) and Neurofilament light chain (marker of neuronal migration marker) and Nogo receptor expression, and Syntrophophynsin and Bielschowsky silver (axon markers) were measured in the ischemic brain. To further investigate the basis of Niacin-induced neurite outgrowth, in vitro primary cortical neuron (PCN) culture was performed. Western blot, real time PCR and siRNA knockdown of Tia2 gene expression in cultured PCN were employed. Results: Niaspan treatment of stroke rats significantly increased serum HDL-C, promoted dendrite outgrowth in the ischemic brain. In addition, Niacin treatment also significantly increased Nogo receptor expression in the ischemic brain compared to MCAO control animals (p<0.05). Western blot assay showed that Niaspan treatment of stroke significantly increased Angiopoietin-1 and Tia2 expression in the ischemic brain. Mechanisms underlying the Niacin-induced synaptic plasticity and axonal regeneration were investigated using an in vitro models. We found that Niaspan treatment of stroke rats significantly increased serum HDL-C, promoted neuronal migration and dendrite outgrowth. The Tia1/Tie2 pathways appear to mediate Niacin-induced dendrite outgrowth.

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Cerebral Blood Volume on CT Perfusion as a Parameter for Induced Hyper tension Therapy in Atherosclerotic Ischemic Stroke

Ji Man Hong, Jin Soo Lee, Sung Yeon Sohn, Dong Hoon Shin, Kyoon Huh; Ajou Univ Med Ctr, Suwon, Korea, Republic of

Background: Recent studies have proposed that induced hypertension therapy (IHT) in patients with acute ischemic stroke and its progression was beneficial. Hemodynamic components might contribute to the effect; however, the associated factors are not clear. This study aimed to clarify the important parameters of CT perfusion used in this study compared the contralateral area, the respective increase systolic blood pressure by 30 mmHg or more than initial blood pressure. The parameters of CT perfusion used in this study compared the contralateral area, the respective increase systolic blood pressure by 30 mmHg or more than initial blood pressure. The parameters of CT perfusion used in this study compared the contralateral area, the respective increase systolic blood pressure by 30 mmHg or more than initial blood pressure. The parameters of CT perfusion used in this study compared the contralateral area, the respective increase systolic blood pressure by 30 mmHg or more than initial blood pressure. The parameters of CT perfusion used in this study compared the contralateral area, the respective increase systolic blood pressure by 30 mmHg or more than initial blood pressure.

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ASPECT Score and Clinical Outcomes in Patients With Unknown Onset and Wake-up Strokes

Branko N Huisa, Rema Raman, Brett C Meyer, Karin Ernstrom, Gilda M Tafreshi, Andrew B Stermer, Thomas M Hemmen; UCSF Stroke Ctr, San Francisco, CA

Background: One quarter of ischemic strokes occur during sleep. They are commonly excluded from thrombolytic therapy and clinical trials due to a unknown time of stroke onset. In many patients, the stroke may occur shortly before awakening. It has been suggested that early ischemic changes in CT do not differ in acute stroke patients with known onset and patients who recently woke with stroke. Patients with minimal ischemic changes on CT after awakening with stroke may be amenable to thrombolytic therapy. Methods: We used the ASPECTS to evaluate CT scans of wake up and known onset stroke patients. A prospectively collected acute stroke database was used and included patients from January 2005 to June 2009. We classified the wake-up strokes, “AWOKE” group, as all ischemic stroke patients that were “last seen normal” more than 3 hours ago, who arrived between 04:00 to 10:00 hours and who had a head CT within 15 hours from last seen normal. We classified the controls, “DOCUMENTED” group, by randomly selecting patients who had a head CT up to 4 hours from stroke onset. Five different stroke neurologists performed ASPECTS on all initial head CT, blinded to patient group and time of onset. Possible confounders were assessed. Data was analyzed using Wilcoxon rank and Fisher Exact test, as appropriate. Results: We identified 37 ischemic stroke patients in the AWOKE group. Twenty-eight AWOKE and 68 DOCUMENTED patients had suitable imaging for the ASPECTS. Of these, 14 AWOKE and 38 DOCUMENTED patients had available day mRS scores. Baseline demographics and risk factors were similar in both groups, including age, gender, diabetes, hypertension, baseline NIHSS and baseline mRS. There was a significant difference in the initial ASPECTS as a continuous variable between the AWOKE (9.0±1.9) and DOCUMENTED (9.8±0.7) group (p = 0.0019) but no significant difference was found on a dichotomized analysis; ASPECTS (8-10) AWOKE (89.3%) DOCUMENTED (95.6%) p = 0.35. There was a trend toward better 90 day mRS (0-1) in the AWOKE group (78.6%) vs the DOCUMENTED group (47.4%) p = 0.061. Conclusion: Initial ASPECTS were similar between patients with wake-up strokes and those with known acute onset within 4 hours of symptoms. This may suggest that a subset of wake-up stroke patients could be suitable for thrombolytic therapies. Further studies are needed to prove the safety and efficacy of such approach.

Support: SP09TRIAS - SP50NS044448

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Post-Infarct Cortical Plasticity Assessment Using the Immediate-Early Gene Arc

Steven R Zeiler, Johns Hopkins, Baltimore, MD; Richard J O'Brien, Johns Hopkins Bayview Med Ctr, Baltimore, MD; Paul F Worely, Johns Hopkins Univ, Baltimore, MD

Observations in stroke patients and primes indicate that cortical plasticity plays a crucial role in affecting recovery. In order to better define, and eventually manipulate post-stroke cortical plasticity with the goal of encouraging recovery, we designed a model of post-stroke cortical plasticity in the mouse visual cortex. We hypothesized that we could, using a functional technique based on immediate-early gene Arc induction, monitor the representation of eye input in the visual cortex in control mice and in mice with focal strokes. Previously, our group and others have shown that monocular stimulation selectively induces Arc transcription and translation in the ipsilateral binocular zone of the visual cortex; the spatial extent of this activation is increased with monocular enucleation indicating that Arc expression marks visual cortex plasticity. Using a photocaging system, we created focal infarcts which ablate the binocular zone expressing Arc after monocular stimulation. After a seven day recovery period, ipsilateral monocular stimulation induced Arc expression in a more medial area formally mapped as the monocular zone indicating new neuronal responsiveness. To address whether this new area of induction was a direct effect of the stroke and therefore independent of visual stimulation, we stimulated neither eye after creation of a binocular zone infarct. In these animals, there was no Arc induction over baseline, indicating that visual cortex Arc expression after a binocular zone infarct is visually mediated and not secondary to peri-ischemic edema or inflammatory mediators. Therefore, visual cortical Arc induction after a focal binocular zone infarct marks plastic neurons driven by visual stimulation. This finding is important as it allows us to ask two important questions. First, what makes these neurons receptive to plastic changes? Second, how can we modify the quantity and/or quality of this plasticity to affect a more robust recovery? Studies in the mouse visual cortex allow a combination of environmental and genetic interventions to address these questions. Overall, this newly designed model system will be an important tool for elucidating the mechanisms of and interventions in post-stroke cortical plasticity.

Support: SP09TRIAS - SP50NS044448
**P171** Vermicelli Pasta Handling as a Measure of Forepaw Dexterity in Rats With Focal Ischemic Stroke

Miranda Brenneman, Roger Strong, Qingran Li, Gena Mathew, Xiaopei Xi, Sean I Savitz; Univ Texas Med Sch Houston, Houston, TX

**Background:** A novel measure of dexterous forepaw function has recently been described that is quantitative, easy to administer, and sensitive to the effects of damage to sensory and motor systems in the CNS of rats. We investigated whether this new test would show lasting deficits following acute ischemic stroke caused by reversible common carotid artery/middle cerebral artery occlusion (CCA/MCAo), a model of selective cortical infarction. **Methods:** In this study, 10 Long Evans rats at 3 months of age underwent CCA/MCAo occlusion for 2 hrs. The nine surviving animals were given 7cm lengths of vermicelli and the number of forepaw adjustments were counted as the rats manipulated the pasta by repeatedly adjusting the forepaws. Testing was done on animals that had fasted during the prior 12 hours. In addition, we quantified a series of abnormal movements indicative of impaired forepaw use including: 1) paws together when the pasta was still long; 2) guide and grasp limb switch; 3) failure to contact the pasta; 4) dropping the pasta; 5) paws apart when pasta was short; 6) pulling pasta with mouth; 7) hunched posture; 8) iron grip; 9) guiding paw around the grasp paw; 10) angling with head tilt. Testing was administered pre-operatively and once a week for 4 weeks after stroke. **Results:** Compared to pre-stroke testing, the number of adjustments made with the impaired limb decreased over time. Repeated measures found a significant impairment (p<0.05) on testing at weeks 2-4. Compared with pre-stroke testing, the number of atypical behaviors increased significantly after stroke (p<0.05 for weeks 1-3 by repeated measures testing). **Conclusions:** There was a persistent and sustained decrease in the number of adjustments made with the impaired limb and an increase in abnormal behaviors following stroke. These data suggest that, after cortical stroke in the rat, forepaw dexterity (digit use) is severely impaired and compensatory maneuvers are utilized in order to manipulate the pasta. The reduction in paw function over time may also be complicated by such behavioral issues as motivation. This test may be relevant to hand usage in stroke patients and is a novel test for translational research involving dexterous forelimb function.

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**P172** Atorvastatin Major Metabolite Orthohydroxyatorvastatin Protects From Excitotoxic Cell Death and Reduces the Association of NMDA Receptors to Lipid Rafts

Veronica Guirao Salguero, Núria DeGregorio Rocabado, Jovita Ponce, Antonio Dávalos, Teresa Gasull; Fundació Institut dinvestigació en Ciències de la Salut Germans Trias i Pujol, Badalona, Spain

Excess brain extracellular glutamate in cerebral ischemia leads to excitotoxic neuronal damage through overactivation of the N-methyl-D-aspartate (NMDA) subtype of glutamate receptors, and several statins have been reported to allow cortical neurons to become resistant to this excitotoxic damage. It is well known that atorvastatin (ATV), one of the most prescribed statins, hydroxilates in the liver to produce mainly orthohydroxyatorvastatin (o-HATV), a compound whose levels in serum might double the level of its parent compound. The metabolite o-HATV, unlike other ATV derived molecules, has been reported to have a specific effect inhibiting membrane cholesterol crystalline domain formation. We hypothesize that o-HATV prevents NMDA-induced neuronal cell death and reduces the presence of NMDA receptors in the cholesterol-rich membrane structures called lipid rafts. Primary neuronal cultures were pre-treated with ATV or o-HATV for 3 days. At 11 days in vitro 100 μM NMDA was added to the medium containing pretreatments and cell death was determined. Lipid raft domains were isolated, and the NMDA receptor present in these lipid rafts was quantified by Western blot. We found that sustained treatment with o-HATV protected neurons from NMDA-induced cell death with and EC50 with 95% confidence intervals of 11 (3.4-37) nM. Maximal protection obtained after treatment with ATV or o-HATV was 88% and 85%, respectively. Concentrations of ATV or o-HATV inducing maximum neuroprotection reduced by 36% and 38%, respectively, the association of NMDAR1 to lipid rafts. (Figure 1) In conclusion, we now report that o-HATV prevents NMDA-induced neuronal cell death and reduces the NMDA receptors in lipid raft domains. Since o-HATV concentrations found in serum of patients on statins are relevant for neuroprotection, o-HATV might greatly contribute to the beneficial effect reported in the stroke outcome of the stroke patients pretreated with statins.

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**P173** Language Changes Co-occur With fMRI and Motor Changes Following Motor Therapy for Chronic Hemiparesis

Stephen Page, Univ of Cincinnati, Cincinnati, OH; Stacy Hamish, Univ of Florida, Gainesville, FL; Marcus Meinzer, Univ of Florida, Gainesville, FL; Jonathan Trinastic, Univ of Florida, Gainesville, FL; Kari Dunning; Univ of Cincinnati, Cincinnati, OH

**Introduction:** It is known that the neural substrates of language and motor systems operate on similar principles. Additionally, subcortical structures such as basal ganglia and thalamus may play an important role in the functional recovery of the motor and language systems. Better understanding of the neural mechanisms underlying functional recovery in stroke may lead to more efficient therapy delivery, by incorporating integration of therapies if generalization between modalities is possible. The objective of this case series was to determine whether language function changes co-occur with movement changes after participating in an affected arm training program. **Hypothesis:** It was hypothesized that subjects would exhibit changes on the Western Aphasia Battery Quotient (WAB) that would co-occur with changes in affected arm function and with cortical changes, assessed by functional magnetic resonance imaging (fMRI). **Method:** The upper extremity portion of the Fog-Meyer Test (FM), Action Research Arm Test (ARAT), WAB, fMRI were each administered to 5 subjects exhibiting chronic, stable, hemiparesis and chronic aphasia. Two to 4 weeks prior to therapy, a neuropsychosis was surgically implanted epidurally using fMRI-guided neuronavigation, then engaged in task specific training for the affected arm occurring 3 to 4 hours/week for up to 6 weeks. The FM, ARAT, and AMAT were again administered one week after the intervention phase was completed. **Results:** All subjects exhibited increases on the FM, ARAT and WAB, indicating increased motor and language abilities after motor therapy for upper extremity hemiparesis. The three subjects who improved the greatest on the FM also showed the greatest WAB improvement. Task-related activity changes between the pre and post fMRI scans revealed distinct patterns associated with high improvers in language and motor tests, characterized by either more strongly right lateralized activity or increased overall activity while performing a finger tapping task. Subjects exhibiting smaller changes on the outcome measures showed variable patterns of activation, such as bilateral widespread increases or decreases in activity associated with slight behavioral improvements. Subjects exhibited subsequent aphasia improvement to varying degrees despite no participation in speech and language therapy. Increased right lateralization of BOLD activity and/or decreased overall BOLD activity during a motor task occurred for individuals with greatest improvement on motor and language tests, possibly indicating better neural specialization or neural efficiency. **Conclusions:** Data confirm that interventions focused on motor rehabilitation can sometimes cause language changes. To our knowledge, these are the first data confirming this long held clinical tenet.

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**P174** Increase in Cerebral Perfusion After Intra-arterial or Intravenous Injection of Mononuclear Cells in a Rat Model of Ischemic Stroke

Malikajunaraao Kasam, Vivek Misra, Sushil Sharma, Miranda Brenneman, Xiopei Xi, James C Grotta, Sean I Savitz; Univ of Texas, Houston, Houston, TX

**Background:** Stem cells represent a new therapeutic approach under investigation for acute ischemic stroke. In contrast to IV administration, an intra-arterial (IA) delivery of cells has the advantage of selective targeting to the ischemic brain. However, this approach may lead to embolization. To address this concern, we investigated the effects of intra-carotid injections of bone marrow cells on cerebral perfusion in a rodent model of ischemic stroke. **Methods:** Retired breeder Long Evans rats underwent middle cerebral artery occlusion for 3 hrs. Autologous bone marrow mononuclear cells were prepared at 24 hrs after stroke and re-infused 2 hrs later through the collateral internal carotid artery (n=3) or femoral vein (n=3). A separate group of animals received an intra-carotid injection of saline at 24 hrs after stroke (n=3). All animals underwent imaging with MRI on a 7T scanner before and 20 min after stroke. In IA group, the mean difference in cerebral blood volume (CBV) increased from 0.86 ± 0.05 before to 1.22 ± 0.07 (p < 0.001) after injection. In IV group, the mean difference in CBV increased from 0.87 ± 0.05 before to 1.19 ± 0.06 (p < 0.001) after injection. **Conclusions:** IA delivery of stem cells resulted in sustained increases in cerebral perfusion compared to IV delivery.
injection. Multimodal imaging consisted of diffusion weighted imaging (DWI), perfusion weighted imaging (PWI), and T2 weighted imaging. Perfusion-weighted images were acquired using dynamic susceptibility contrast echo-planar imaging. **Results:** The mean time to peak (TTP) in the infarct region of IA cell-treated animals decreased from 25.4ms to 23.6ms while in the contralaterally transplanted group an average decrease of TTP decreased from 21.4ms to 21.1ms. IV administration of cells led to a decrease on TTP from 16.3ms to 14.5ms in the infarct region and a decrease on TTP from 13.4ms to 12.6ms in the contralateral cortical. In IA-saline treated animals, TTP increased from 22.2ms to 29.16ms in the infarct region and from 22.0ms to 23.2ms in the contralateral cortical. These results were also observed using other perfusion parameters. By using an area of restricted diffusion indicative of ischemic injury in the rest of the brain. **Conclusion:** IA or IV delivery of mononuclear cells in aged rats at 24 hours after stroke increases perfusion within the ischemic lesion. The mechanisms underlying the changes after perfusion are being investigated. This study supports the safety of intravascular injections of mononuclear cells as a potential new therapy for ischemic stroke.

**Table 1. Table Percent Differences in Perfusion using Time To Peak (TTP) maps from the PWI of the Ischemic Lesion or Contralateral Cortex before and after injection with IA or IV bone marrow cells or IA saline. Negative percent indicates an increase in cerebral perfusion**

<table>
<thead>
<tr>
<th>Delivery</th>
<th>Infarct</th>
<th>Contralateral Cortex</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA Cells</td>
<td>-7.40%</td>
<td>-2.10%</td>
</tr>
<tr>
<td>IV Cells</td>
<td>-11.3%</td>
<td>-13.5%</td>
</tr>
<tr>
<td>IA Saline</td>
<td>+30.2%</td>
<td>+5.2%</td>
</tr>
</tbody>
</table>

**P175**

Intraarterial Transplantation Results in Superior Delivery of Neural Stem Cells to the Ischemic Brain in Contrast to Intravenous Infusion


Stem cell transplantation represents a promising experimental therapeutic avenue for stroke. Furthermore, emerging minimally invasive intravascular transplantation techniques have begun to bridge the gap between the laboratory and clinic. Intravenous (IV) infusion is an attractive candidate based on ease of administration and clinical precedent. However, recent studies have reported poor cell delivery to the brain and cell entrapment in peripheral organs. Intraarterial (IA) delivery may overcome limitations of IV by utilizing a more direct route to the central nervous system. For both intravascular techniques, in depth assessment of biodistribution must be conducted before stem cell based therapies can come to fruition. Here we utilize a multi-modality imaging approach to explore the biodistribution of transplanted neural stem cells (NSCs) in a mouse model of hypoxic-ischemic (HI). Mouse NSCs were transduced with a bioluminescence imaging (BLI) reporter gene harboring a monomeric RFP and firefly luciferase. HI was induced in adult mice and NSCs were transplanted IA or IV at 24 hours after stroke. In vivo BLI was used to track transplanted cells and regions of interest (ROIs) were used to quantify photon flux. Immediately after transplant, BLI revealed significantly higher luciferase activity in the head region of IA groups (p < 0.001) whereas IV transplanted groups showed marked increased luciferase activity in the torso of the mice (p < 0.014). One week following transplant, luciferase signal disappeared in the torso of both groups but remained significantly higher in the brain of IA transplanted mice (p = 0.025). At one and two weeks, animals were sacrificed and whole organ homogenates were further analyzed for luciferase activity. Ex vivo analysis, at one week revealed that 50% of the animals had 69% of total signal coming from brain versus 27% in the IV transplanted animals (p < 0.0001). At two weeks, signal from the brain homogenates were significantly higher than the rest of the organs in the IA transplanted animals (p < 0.001) but not in IV transplanted animals. These data suggest that intraarterial transplantation results in superior delivery of NSCs to the ischemic mouse brain in comparison to intravenous infusion.

**P176**

The Impact of Stroke on Posturo-respiratory Coupling During Quiet Standing in Older Adults

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Background: Exaggerated postural sway during quiet standing has been linked to fall risk in people with chronic stroke. Spontaneous respiration perturbs the body position and significantly contributes to the magnitude and speed of anteroposterior sway. Therefore, an inability to dissipate respiratory perturbations, as evidenced by increased “posturo-respiratory coupling,” may indicate an elevated fall risk. We hypothesized that individuals with chronic interactions would exhibit increased posturo-respiratory coupling during quiet standing. **Methods:** We studied 25 stroke subjects > 6 months after the first large vessel hemispheric infarct affecting < 1/3 of the middle cerebral artery territory (aged 51-79 years, height 1.68 ± 0.10 cm, body mass 76 ± 14 kg) and 35 age- and sex-matched controls (aged 50-80 years, height 1.67 ± 0.11 cm, body mass 71 ± 13 kg). Subjects stood on a force platform with eyes-open and eyes-closed for 3-minutes each. Postural sway (i.e., center-of-pressure) and anterioposterior respiratory flow volume were simultaneously recorded. Summary statistics were used to calculate the magnitude of postural sway, the dominant respiratory oscillations and the corresponding oscillations of anteroposterior postural sway were extracted from each signal using an Empirical Mode Decomposition algorithm. Instantaneous phase shifts at each point along the two extracted oscillatory signals were calculated using the Hilbert transform. These phase shifts were then used to quantify the degree of posturo-respiratory coupling with an entropy-based synchronization analysis. **Results:** Stroke participants were 7.8 ± 5.0 years post-acute event and had good outcomes as evidenced by the scores on the modified NIH Stroke Scale scores 2.4 ± 0.6. Compared to controls, the stroke group demonstrated increased magnitude and speed of postural sway, particularly when standing with eyes-closed (p < 0.01). Groups exhibited similar degrees of posturo-respiratory coupling when standing with eyes open. The degree of posturo-respiratory coupling increased across both groups when subjects stood with eyes closed compared to controls (p < 0.001); however, an exaggerated increase was observed in the stroke group (p < 0.05) as compared to controls (17%) (p < 0.03). Conclusion: Increased posturo-respiratory coupling when standing with eyes-closed suggests an active role of visual feedback in the dissipation of bodily perturbations induced by respiration. In patients with chronic MCA stroke, pronounced increases in posturo-respiratory coupling during eyes-closed standing indicate greater dependence on visual feedback to dissipate these perturbations. Future studies are needed to determine whether impairment of mechanisms compensating body sway manifest in low-light environment and contribute to falls.

**P177**

Shh and Tgf-β Signaling Pathways Activated by BMSCs Increase IPA Activity After Stroke in Mice

Hongxi Xin, Li Hong Shen, Yi Li, Zheng Gang Zhang, Michael Chopp; Henry Ford Hosp, Detroit, MI

Endogenous tissue plasminogen activator (tPA) and its inhibitor, plasminogen activator inhibitor 1 (PAI-1), play a major role in the development of the CNS and regulate neurite remodeling after damage. BMSCs increase neurite outgrowth and concomitantly increase IPA activity in the ischemic brain. To probe the signaling pathways that underlie BMSC mediated activation of IPA, we investigated the sonic hedgehog (Shh) and transforming growth factor beta (TGF-β) signaling pathways in astrocytes. Immunofluorescence double staining revealed significantly increased Shh expression and decreased the TGF-β1 signal expression in astrocytes in mice subjected to middle cerebral artery occlusion (MCAo) and treated with BMSCs (1x10⁶ cells at 24 hours post stroke), compared to MCAo controls (n = 6/group) (by 103% ± 22% and 43% ± 12%, respectively). In vitro oxygen and glucose deprivation (OGD) and co-culture of astrocytes and BMSCs were then employed to model the in vivo condition and to investigate the relationship between Shh and Tgf-β signaling pathways and IPA activity. Similar to in vivo data, both RT-PCR and Western blot showed co-cultured astrocytes with BMSCs significantly increased Shh level (by 51% ± 12%) but decreased TGF-β1 expression under OGD conditions compared to astrocytes alone (by 36% ± 5%). ELISA analysis also revealed that BMSCs reduced expression of TGF-β1 in OGD astrocytes from 239.24 ± 13.68 pg/mL to 173.18 ± 35.03 pg/mL (P < 0.05). ELISA analysis also revealed that BMSCs significantly increased Shh expression (by 17%) (p < 0.001) but decreased TGF-β1 expression (by 51% ± 12%) as compared to MCAo controls (n = 6/group). The NgR served as a common receptor for several potent inhibitors of neurite regeneration may contribute to functional recovery after stroke.

**P178**

Combination Treatment With Niaspan and Simvastatin of Experimental Stroke, Induces Axonal Regeneration and Improves Functional Outcome

Amjad Shehatah, Jieli Chen, Xu Cui, Cynthia Roberts, Mei Li, Michael Chopp; Henry Ford Hosp, Detroit, MI

**Introduction:** Several clinical trials have demonstrated the efficacy and safety of combined Niaspan and Simvastatin with clinical improvement in multiple lipid parameters and inhibition of atherosclerosis. Previous studies have shown that Statin or Niaspan mono-therapy of stroke animals induces angiogenesis and improves functional outcome. Whether combination treatment with Niaspan and Statin of stroke regulates functional outcome has not been investigated. In this study we examined the effect of Niaspan and Simvastatin combination treatment on experimental stroke of rats. **Methods:** Adult male rats (n = 8/group) were subjected to middle cerebral artery occlusion (MCAo) and treated with or without combination treatment (Niaspan 40mg/kg and Simvastatin 1mg/kg) starting 24 hours after MCAo and daily for 14 days. A battery of neurological functional tests was performed. Axonal damage and regeneration were evaluated by Amyloid Precursor Protein (APP), Biechowsky silver, Nogo66 Receptor (NgR) immunoactivity in ipsilateral ischemic brain. Immunoreactive microglia (Iba-1) were also measured in the ischemic brain. **Results:** Combination treatment with Niaspan and Simvastatin significantly improved functional outcome after stroke (p < 0.05) as well as significantly increased axonal area, increased axonal area was measured by decreased APP and increased Biechowsky silver expression in the ischemic brain compared to non-treatment MCAo control (p < 0.05). Combination treatment with Niaspan and Simvastatin of stroke significantly decreased Iba-1 immunoreactive microglia in the ischemic brain (p < 0.05). These data serves as a common rationale for several potent inhibitors of neurite outgrowth. Combination treatment with Niaspan and Simvastatin of stroke significantly decreased NgR expression (p < 0.05). **Conclusions:** These data suggest that treatment of experimental stroke with combination of Niaspan and Simvastatin significantly improves functional outcome, reduces axonal damage, increases axonal density and decreases Iba-1 immunoreactive microglia. Decreased expression of the NgR leading to axonal regenration may contribute to functional recovery after stroke.
Characterizing Brain Reorganization After Stroke Utilizing fMRI
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Background: Stroke occurs when blood supply to some part of the brain is compromised. Patients who have strokes show different levels of reorganization resulting in the ability to compensate for cognitive, perceptual, and sensorimotor deficits. In a previous study, Prabhakaran et al. (2007) examined the neural substrates underlying word generation in chronic stroke (at least 6 months post-stroke) patients. While normal subjects displayed activations in the left-lateralized fronto-temporo-parietal network, stroke patients showed decreased activation in the affected cortical regions and increased activation in the homologous regions of the normal hemisphere suggesting reorganization of structure-function relationships. The objective of this on-going study is to characterize the reorganized areas activated during cognitive performance using functional imaging (fMRI) to assess functional mapping changes after stroke. Patients with stroke patients were compared with controls using fMRI. The objective was to identify patients and normal subjects. Methods: Structural and functional images were collected from 5 patients (2F, 3M, ages 43-73) in the acute stage (≤ 5 days from stroke onset), 1 patient (M, 47 yrs) in the sub-acute stage (≤ 30 days from stroke onset), and 1 patient (M, 49 yrs) in the acute and sub-acute stages of strokes as well as TIA and normal controls (5F, 7M, ages 24-77) while they performed verbal fluency task in the scanner. In this task subjects are asked to generate words beginning with a letter that is presented to them auditorily. Outside the scanner, patients first practice the task during which they generate words beginning with the same letters that are presented in the scanner, and their answers are recorded as a behavioral measure. In the scanner, patients are asked to name words aloud, but subvocally. Results: In the acute stage, stroke patients showed decreased activity in the area of the infarcted region, but overall show left-lateralized activation in fronto-temporal areas and other areas of the language network seen in normal and TIA controls. In the subacute stage, stroke patients showed increased activity in the right hemisphere regions involving contralateral homologous areas of the language network. Conclusions: Language recovery in stroke patients may require involvement of contralateral homologous brain regions of the language network to compensate for the affected brain regions due to the stroke. Future work will focus on characterizing adaptive and maladaptive networks during stroke recovery.

The Temporal Evolution of the Count of Endothelial Progenitor Cells After Ischemic Stroke
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Background: Endothelial Progenitor Cells (EPCs) have been associated with the prognosis of patients with ischemic stroke. However, there is insufficient information about the temporal evolution of the blood counts of these cells in patients with acute, subacute and chronic ischemic stroke. Methods: We studied prospectively patients with acute ischemic stroke. We excluded patients with previous stroke or heart disease, because these conditions have a transient ischemic attack (TIA) in the acute phase and patients with stroke onset more than 48 hours before inclusion in the study. Blood samples were obtained from venipuncture at three time-points: baseline (within 48 hours from the onset of stroke), 7 days and 3 months after the onset of stroke. We measured the percentage of EPCs by flow cytometry within 30 minutes after collecting the blood sample. We considered that a cell was an EPC when it was labeled for the following 3 markers: CD34, AC133 and KDR. Results: We studied 59 patients with a mean age of 67.6 ± 12.1 years, and 69.5 of them were men. EPCs counts (± SD) were: Baseline (0.0036 ± 0.0071), day 7 (0.0168 ± 0.0154), 3 months (0.0064 ± 0.0236). There was a statistically significant increase in the EPCs count at day 7 (p = 0.001). Conclusion: In patients with ischemic stroke, the count of Endothelial Progenitor Cells shows a peak at day 7 after the onset of stroke.

Migraine and Thrombophilic Disorders in Ischemic Stroke

Background: There are studies suggesting a relationship between migraine, especially with aura (MA), and some genetic hypercoagulable states (HS). However, it is unknown if migraine is associated to a higher prevalence of HS in ischemic stroke patients. Our goal was to determine whether HS are more frequent in migraineurs in a cohort of ischemic stroke patients under 55 years old. Methods: Observational prospective study with inclusion of consecutive patients under 55 years of age with a first-ever brain infarction or transient ischemic attack admitted to a Stroke Unit. A systematic questionnaire on hospital admission addressed the antecedent of MA or migraine without aura (MO) according to the International Classification of Headache Disorders-II. The physician who collected the information about the headache was blinded to other clinical details. We investigated the presence of the following HS: antiphospholipid antibodies including anticardiolipin and lupus anticoagulant; antithrombin III, protein C or S deficiency; activated protein C resistance: factor Leiden (A506G mutation) and prothrombin G20210A mutation by an extensive battery of hematomal tests. Results: One hundred fifty-four patients (95 men; mean ± SD age, 44.12 ± 8.4 years) were included into the study. Forty-four had migraine, 15 MA. The frequency of HS was higher in migraine than in non-migraine group (36.4% vs. 14.5%, P = 0.003) and there were no differences between MA and MO. However, when we analyzed each HS separately only protein C or S deficiency and prothrombin G20210A mutation were significantly more frequent in migraineurs than in non-migraineurs (13.6% vs. 2.7%, P = 0.01; 11.4% vs. 2.7% respectively, P < 0.05). After analysis for age, sex, race and presence of paroxymal atrial fibrillation, migraine was associated with a 3.3-fold (96% CI, 1.49 to 7.55) increased risk of HS diagnosis. Conclusion: migraine is associated to a higher frequency of HS in young patients with ischemic stroke. Screening for prothrombotic conditions should be considered in young patients with migraine and brain ischemia.

Factor V Leiden and Ischemic Stroke Risk: The Baltimore-Washington Young Stroke Study
Ali H Gamedani, John W Cole, Yuching Cheng, Mary J Sparks, Jeffrey R OConnell, Marcella A Wozniak, Barney J Stern, Bradton D Mitchell, Steven J Kitter; Univ of Maryland Sch of Medicine, Baltimore, MD

Background and Purpose: The Factor V Leiden (FVL) mutation (rs6025) has been associated with venous thromboembolism in young adults and ischemic stroke (IS) in children, but its relation to ischemic stroke in young adults remains uncertain because prior studies have been based on small numbers of cases. To test a hypothesis that IS is an important risk factor for FVL and is in participants of the Baltimore Young Onset Stroke Study, specifically among oral contraceptive users, smokers, cryptogenic strokes, and strokes without other vascular risk factors. Methods: Through a population-based case-control study, we identified 385 women and 509 men aged 15–49 years with first-ever IS and 957 controls, frequency-matched for age, race, and gender. FVL genotype was determined using the illumina 50K CVD SNP chip. Historical risk factor information was obtained using a standardized questionnaire, and stroke subtype was determined through adjudication by two neurologists. Logistic regression was used to calculate odds ratios for the entire population as well as for subgroups stratified by individual risk factors, the presence or absence of any stroke risk factor (smoking, oral contraceptives, hypertension, diabetes, and myocardial infarction), and stroke subtype, adjusted for age, race, and gender. Results: The prevalence of FVL was not increased among IS overall (0.64%) or among the subgroup of cryptogenic stroke patients (3.85%) compared to controls (3.65%). The FVL mutation was associated with IS in those with hypertension (OR = 7.9, p = 0.0047), but not in any of the other subgroups (see Table). Conclusions: The lack of association between the FVL mutation and IS in the overall sample is discordant with conventional clinical wisdom and suggests that FVL may act more as a weak modifying stroke risk factor among patients predisposed to vascular disease rather than as a strong proximate cause of ischemic stroke.

Stratified Analysis of Factor V Leiden and Ischemic Stroke Risk
Ali Gamedani, John W Cole, Bradton D Mitchell, Steven J Kitter; Univ of Maryland Sch of Medicine, Baltimore, MD

The Factor V Leiden mutation (rs6025) has been consistently associated with venous thromboembolism and ischemic stroke in children, but not with ischemic stroke in the general adult population. However, studies of Factor V Leiden and ischemic stroke in young adults have yielded conflicting reports. To determine whether Factor V Leiden is associated with ischemic stroke in young adults, we performed a meta-analysis of case-control studies of ischemic stroke in adults < 50 years of age. Through a Medline search we identified eighteen studies published between 1996 and 2009 that met established diagnostic and methodological criteria. Factor V Leiden was present in 154 of 2,045 cases (7.3%) and 217 of 5,307 controls (4.1%), yielding an odds ratio of 2.00 (95% CI 1.59-2.51). However, substantial heterogeneity was noted between these studies (p = 0.005 for Q-test of heterogeneity). We hypothesized that this heterogeneity was due to differences in study design, specifically in terms of case selection criteria. To test this hypothesis, we performed a stratified meta-analysis of the data. Studies that imposed additional criteria that increased the likelihood of a prothrombotic genetic predisposition were placed in the category of “selected” ischemic stroke studies, whereas studies that recruited cases from consecutive neurology referrals or hospitalizations were categorized as “unselected” ischemic stroke studies. Among “selected” ischemic stroke
Hemostatic and Inflammatory Markers as Risk Factors for Hemorrhagic Stroke in the Women's Health Initiative

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Background: Few studies have investigated hemostatic and inflammatory factors as risk factors for hemorrhagic stroke, and the results have been inconsistent. Therefore we investigated the association between hemostatic and inflammatory factors and the risk of hemorrhagic stroke in a nested case-control study within the Women's Health Initiative (WHI) Hormone Trials. Methods: The WHI Hormone Trials enrolled 27,347 postmenopausal women aged 50 to 79 years. In the WHI substudy, we studied patients with a history of hypertension or a neurologist-reviewed cases of centrally-adjudicated hemorrhagic stroke (23 intracerebral, 13 subarachnoid, and 3 unspecified hemorrhages) and 37 controls matched on age, randomization date, hysterectomy status, and history of cardiovascular disease. Blood collected at baseline samples was analyzed for the following hemostatic and inflammatory biomarkers: E-selectin, P-selectin, interleukin-6, matrix metalloproteinase-9, leukocyte count, fibrin D-dimer, factor VIII, plasminogen activator inhibitor-1 antigen, prothrombin fragment 1.2, plasmin-antiplasmin complex, thrombin activatable fibrinogen inhibitor, von Willebrand factor, fibrinogen, and platelet count. Results: Associations between biomarkers and hemorrhagic stroke were assessed by conditional logistic regression analysis with and without adjustment for ethnicity, body mass index, blood pressure and cigarette smoking. Cases had higher baseline levels of systolic blood pressure (136 versus 127 mmHg; p = 0.017), diastolic blood pressure (80 versus 73 mmHg; p = 0.001) and E-selectin (52 versus 42 ng/ml; p = 0.005), but lower platelet count (226 versus 257 fold/ml; p = 0.041) controls. Odds ratios (95% CI) for hemorrhagic stroke per 1SD increment in E-selectin levels were 2.46 (2.02-3.00) and 2.26 (1.35-4.02) after adjustment. The corresponding odds ratios per 1SD increment in platelet count were 0.38 (0.31-0.99) and 0.44 (0.19-1.20), respectively. The other biomarkers were not significantly associated with hemorrhagic stroke. Conclusion: These findings suggest that, among postmenopausal women, higher E-selectin levels or lower platelet counts may be associated with increased risk of hemorrhagic stroke.

Hypertension in Pregnancy is Associated With an Increased Risk of Cerebrovascular Disease

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Introduction: Hypertension is one of the most common medical complications of pregnancy affecting 6-8% of gestations in the United States. Pregnancy can induce vascular changes leading to hypertension. However, little data is available on the role of hypertension in pregnancy as a risk factor for the development of cerebrovascular disease. The Hypertension Detection and Follow-up Program (HDFP), a national multicenter trial, was conducted from 1971-1983 involving 10,940 American hypertensive adults aged 30-69 years. This study is a retrospective analysis of the HDFP data set to test the hypothesis that hypertension in pregnancy is a cerebrovascular risk factor. Methods: In total, 5,030 women were initially evaluated in the study and 3,447 (68.4%) of these had a history of pregnancy. Of this sample, 1,064 women had a history of hypertension in pregnancy, 170 of which were lost to follow-up at five years leaving a study sample of 894 women. They were compared to 2,743 women with history of pregnancy without hypertension after excluding 540 women lost to follow-up. Results: The (mean ± SD) age of patients with a history of hypertension in pregnancy was 46.5 ± 9.5 years compared to 51.5 ± 9.5 years in the control group. The (mean ± SD) blood pressures at the time of study entry were 163 ± 23 / 107 ± 13 mm Hg in those with a history of pregnancy and 163 ± 22 / 105 ± 9 mm Hg in the control group. Patients with a history of hypertension in pregnancy had a higher five year incidence of stroke and intracranial bleeding (odds ratio 2.37; 95% confidence interval 1.04 - 5.43; p = 0.05). Multivariable analysis matching for HDFP study cohort allocation, age, race, body mass index, diabetes mellitus, hypercholesterolemia, tobacco use, personal or family history of stroke, demonstrated that a history of hypertension in pregnancy was independently associated with an increased five year incidence of new stroke and intracranial bleeding (p < 0.05). Conclusion: Our study suggests that women with cerebrovascular events are more likely to have had a history of hypertension in pregnancy. Screening for a history of hypertension in pregnancy may be useful for profiling and ultimately treating women with hypertension in the community at higher risk for developing cerebrovascular disease.

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Vascular Cell Adhesion Molecule-1 (VCAM-1) Levels in Patients at Risk for Stroke: The Impact of Gender and Risk Factor Load

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Background and Objective: VCAM-1, a cellular adhesion molecule that facilitates attachment and transendothelial migration of leukocytes into atherosclerotic plaque, has been associated with increased risk of stroke and heart disease. We aimed to determine whether gender and clinical risk factors were associated with VCAM-1 levels in middle-aged patients free of cardiovascular events. Methods: The Sex Age and Variation in Vascular Functionality (SAVY) study was designed to measure sex differences in subclinical vascular disease and biomarkers in men and women aged 45 to 64 with at least one vascular risk factor (hypertension, dyslipidemia, type 2 diabetes, or smoking), but no cerebrovascular events. Fasting VCAM-1 levels were measured on serum from the first 65 (44 women, 21 men) subjects enrolled (R&D Systems; intra-assay coefficient of variation 3.6%). The correlations between VCAM-1 and age, gender, BMI, individual and total number of risk factors were analyzed with Pearson correlation coefficients (r). A multivariable linear regression model was developed using univariately significant factors. Results: Mean age was similar for men (55.0 yrs ± 5.1) and women (57.5 yrs ± 6.7; p = 0.11). Mean VCAM-1 levels were also higher in men (697.2 ± 176.3 ng/ml) than women (582.3 ± 138.2 ng/ml; p = 0.01). VCAM-1 levels were positively associated with BMI (r = 0.304, p = 0.01), number of risk factors (r = 0.452, p < 0.001), history of hypertension (665 ± 153 mg/dl vs. 570 ± 151 mg/dl; p = 0.02), and history of diabetes (733 ± 162 mg/dl vs. 599 ± 147 mg/dl; p = 0.023), but no correlation was found with age (r = -0.051, p = 0.7) or history of dyslipidemia (634 ± 140 mg/dl vs. 596 ± 225 mg/dl; p = 0.16). In the multivariable model (adjusted R² = 0.24, p < 0.001), only increasing number of risk factors (partial R² = 0.21, p = 0.0001) was independently associated with VCAM-1 levels, and there was a trend for male gender (partial R² = 0.04, p = 0.09). Conclusion: In similarly aged men and women, risk for stroke, men had higher mean VCAM-1 levels than women, however, total number of risk factors was independently associated with VCAM-1 levels. Hypertension and diabetes, which were both associated with VCAM-1, were accounted for by using the total number of risk factors. The SAWY enrollment is ongoing, and therefore analyses of VCAM-1 and vascular risk profiles will explore the differences in stroke risk during middle age.

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Stroke-associated Pneumonia (SAP): Risk Factors for Its Development and Affect on Stroke Outcome

Olga Finlayson, St. Michaels Hosp, Toronto, Canada; Moira Kapral, Univ of Toronto, Toronto, Canada; Ruth Hall, Erola Assianni, Institute for Clinical Evaluative Sciences, Toronto, Canada; Daniel Selchen, Gustavo Saposnik, St. Michaels Hosp, Toronto, Canada; On behalf of the Investigators of the Registry of the Canadian Stroke Network (RCSN), for the Stroke Outcome Ranch Canada (SORCan) working group

Introduction: Pneumonia is the common medical complication after stroke. Although several risk factors have been identified, limited information is available on the role of preexisting comorbidities (i.e., cancer, dementia, pre-stroke status) in the development of SAP. Moreover, the impact of SAP in the long-term clinical outcome is less clear. The aim of this study was to determine whether the population characteristics of SAP patients are associated with stroke outcome. Hypothesis: Several comorbid conditions increase the risk of SAP. SAP worsens stroke outcome. Methods: Retrospective cohort study of consecutive ischemic stroke patients admitted to participating institutions in the Registry of the Canadian Stroke Network (RCSN) between July 2003 and March 2007. Pneumonia was confirmed radiographically and occurred within the first 30 days of the hospital admission. Risk factors for developing SAP examined included: age, sex, stroke severity as measured by the Canadian Neurological Scale score (CNS), Charlson index, ischemic stroke subtype, hypertension, atrial fibrillation, coronary artery disease (CAD), dysphagia, COPD, cancer, dementia, preadmission independency. Outcome measures included 7-, 30-, and 365-day stroke mortality, institutionalization, and length of stay and modified Rankin score on discharge. Results: Overall, 8,251 patients were included in the study. SAP was observed in 587 patients (7.1%). Age over 80 years old, male gender, more severe stroke (CNS < 4), dysphagia, history of COPD, coronary artery disease and preadmission independency were statistically significantly associated with higher risk of SAP. Charlson index, cancer, hypertension, and atrial fibrillation were not associated with SAP. Overall, SAP increased death or dependency. Risk adjusted mortality at 30-day was 19.9% (CI 18.2-21.6%) in SAP and 13.3% (CI 12.6-14.0%) in non-SAP patients. Similar findings were observed for death at 7-, 30-, and 365-day. SAP was associated with a long-term care facility (16.4 vs. 9.1%, p < 0.001) and to be dependent on discharge (mRS>3) (85.5% vs. 60.8%, p < 0.01). Median length of stay was 19 (IQR 8-37) days in SAP group vs. 8 (IQR 5-16) days in non-SAP group. Conclusion: SAP is not a rare event following ischemic stroke (7.1%) and is associated with prolonged hospitalization, higher mortality and disability. More work should be done in order to identify the risk factors associated with developing SAP, age over 80 years old, male gender, severe stroke (CNS<4), being dependent on others for care prior to admission, dysphagia, COPD, and CAD.
Stroke-associated Pneumonia (SAP): Do Academic and Community Hospitals Have Similar Incident Risk and Outcomes?

Olga Finlayson, St. Michaels Hosp, Toronto, Canada; Moira Kapral, Univ of Toronto, Toronto, Canada; Ruth Hall, Eolina Asllani, Institute for Clinical Evaluative Sciences, Toronto, Canada; Daniel Selchen, Gustavo Sapovski, St. Michaels Hosp, Toronto, Canada; on behalf of the Investigators of the Registry of the Canadian Stroke Network (RCSN), for the Stroke Outcome Research Canada (SORCan) working group

Introduction: Organized and multidisciplinary stroke care reduces death and disability. However, access to organized and multidisciplinary stroke care varies across institutions. Limited information is available on the prevalence of pneumonia (a common medical complication after stroke), and mortality, between teaching/academic and non-academic centers.

Hypothesis: Non-academic centers have higher risk-adjusted pneumonia and mortality after an ischemic stroke than academic institutions.

Methods: A retrospective cohort study of ischemic stroke patients admitted to 162 acute care facilities in Ontario (N = 3199) participating in the 2002/2003 and 2004/2005 Registry of the Canadian Stroke Network - Ontario Stroke Audit database (RCSN-OSA). The OSA is a 20% random sample of stroke patients admitted to acute care facilities in Ontario. The OSA abstracts the clinical experience from the medical charts to evaluate the characteristics, management and outcomes of stroke patients admitted to acute care hospitals in Ontario. Each institution contributes a minimum of 10 charts with over-sampling at small volume institutions. SAP was defined radiologically within the first 30 days of the hospital admission for stroke.

Mortality and SAP rates were adjusted by age, sex, stroke severity and Charlson index.

Primary Outcome measures: Risk-adjusted SAP. Secondary outcomes included 7-, 30-, and 365-day risk-adjusted mortality. Results: The two OSA (FY0203 and 0405) resulted in 3199 stroke patients; 82% were admitted to community hospitals and 18% to academic hospitals. There was no difference in the SAP rate between community vs. academic hospitals (6.5% (CI 5.6-7.5%) vs. 6.6% (CI 6.6-10.7%)) respectively. There was no difference in the 7-, 30- and 365-day risk-adjusted stroke mortality between community and academic hospitals (7.0% (CI 6.0-7.9%) vs 7.5% (CI 5.5-9.5%) and in 15.5% (CI 14.2-16.8%) vs. 15.6% (CI 12.9-18.4%), respectively). Similar findings were observed for 1-year stroke mortality. Conclusion: In this provincial chart abstraction study, we found no significant difference in risk-adjusted SAP and stroke mortality rates between community and academic hospitals.

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HIV-Infection and Cerebrovascular Disease in the Era of Antiretroviral Therapy: Frequency and Diagnostic Correlates From a Large Nationwide Hospital Database

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Objective/Methods: Stroke is an increasingly recognized issue in patients with HIV-infection (HIV+). Several mechanisms have been proposed that include infectious, inflammatory, and atherosclerotic pathways, the latter being suggested to be related to CVD. Prospective and longitudinal studies are warranted to determine the incidence of CVD and factors, including ART, that contribute to increasing cerebrovascular risk in order to develop preventive treatment strategies.

Table 1. HIV-related US Hospital Admissions: Patient Characteristics

<table>
<thead>
<tr>
<th>Disease Groups</th>
<th>1998 Odds Ratio (CI)</th>
<th>2004 Odds Ratio (CI)</th>
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<tr>
<td>a) Viral Infections</td>
<td>1.40 (1.23–1.60)</td>
<td>1.67 (1.53–1.82)</td>
</tr>
<tr>
<td>b) Malignant Neoplasm:</td>
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</tr>
<tr>
<td>Lympathic-Hematopoetic</td>
<td>c) 1.68 (1.51–1.88)</td>
<td>c) 1.43 (1.32–1.55)</td>
</tr>
<tr>
<td>c) Blood, building organs</td>
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<td></td>
</tr>
<tr>
<td>d) Endocrine</td>
<td>e) 1.26 (1.08–1.46)</td>
<td>e) 1.15 (1.04–1.26)</td>
</tr>
<tr>
<td>e) Nutritional</td>
<td>f) 1.45 (1.18–1.79)</td>
<td>f) 1.28 (1.11–1.49)</td>
</tr>
<tr>
<td>f) Other Metabolic/Immunity</td>
<td>g) 1.42 (1.25–1.61)</td>
<td>g) 1.15 (1.06–1.24)</td>
</tr>
<tr>
<td>g) Psychoses</td>
<td>h) 1.24 (1.08–1.43)</td>
<td>h) NS</td>
</tr>
<tr>
<td>h) Tobacco Use</td>
<td>i) 0.19 (0.12–0.17)</td>
<td>i) 0.32 (0.29–0.35)</td>
</tr>
<tr>
<td>i) Other CNS Disorders</td>
<td>j) 2.20 (1.64–2.95)</td>
<td>j) NS</td>
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<tr>
<td>j) Peripheral NS</td>
<td>k) 0.51 (0.46–0.57)</td>
<td>k) 0.51 (0.47–0.55)</td>
</tr>
<tr>
<td>k) Hypertensive Diseases</td>
<td>l) 0.68 (0.55–0.84)</td>
<td>l) 1.40 (1.20–1.63)</td>
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<tr>
<td>l) Ischemic Heart Disease</td>
<td>m) 3.03 (1.98–4.64)</td>
<td>m) NS</td>
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<tr>
<td>m) Pulmonary Circulation</td>
<td>n) 1.46 (1.31–1.54)</td>
<td>n) NS</td>
</tr>
<tr>
<td>n) Other Heart Disease</td>
<td>o) 0.78 (0.63–0.97)</td>
<td>o) NS</td>
</tr>
<tr>
<td>o) Arterioli/Capillaries</td>
<td>p) 2.06 (1.33–3.20)</td>
<td>p) NS</td>
</tr>
<tr>
<td>p) Other Upper Respiratory</td>
<td>q) 0.14 (0.68–2.25)</td>
<td>q) 1.46 (1.32–1.62)</td>
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<tr>
<td>q) Pneumonia/Influenza*</td>
<td>r) 1.92 (1.60–2.29)</td>
<td>r) 1.35 (1.22–1.50)</td>
</tr>
<tr>
<td>r) COPD</td>
<td>s) 1.65 (1.36–2.00)</td>
<td>s) 1.83 (1.61–2.08)</td>
</tr>
<tr>
<td>s) Nephritis/Nephrotic Syndrome</td>
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</tr>
</tbody>
</table>

*Selection of diagnoses. CVD (cerebrovascular disease); NS (not significant).

Unusually High Prevalence of Patent Foramen Ovale in Patients With Incompetent Varicose Veins

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The pathogenetic role of Patent Foramen Ovale (PFO) and its prognostic and therapeutic implications have not yet been clearly defined. In this study we are reporting some of the results from an open label multicenter safety study of the Varisolve® procedure for the treatment of varicose veins in patients with right-to-left (R-L) cardiac shunt. Males and females (78%), 29% white Caucasian, age mean 46.2 (18-69) with symptomatic varicose veins responded to an advertisement to recruit subjects for a study of endovenous microfoam ablation (EMA). Subjects veins were screened by duplex ultrasound and those with isolat-
ed great saphenous vein (GSV) incompetence were tested for right to left (R-L) vascular shunt using transcranial Doppler of the middle cerebral artery (MCA) to detect the presence of bubble emboli following an injection agitated saline/blood/air mixture as a contrast at rest and with Valsalva. Of 221 subjects tested 85 (38.5%) were positive at rest (95% CI 32.5, 45.2) and 114 (51.6%) were positive after the Valsalva manoeuvre (95% CI 45.4 - 58.5). The total number of patients positive for R-L shunt either at rest or after Valsalva was 130 (58.8 %) (95% CI 52.5-65.1). This is significantly higher than the reported 26% prevalence of PFO in the general population [95% CI 24.4, 30.1]. The prevalence of R-L shunt in patients with GSV incompetence appears to be greater than in the general population. A link between R-L shunt and varicose veins is new and whether etiological or functional may improve the understanding of both conditions. The findings have importance in the treatment of varicose veins with foam sclerotherapy and EMA.

Incidence of Cerebral Venous Thrombosis in United States

Methods: The Nationwide Inpatient Survey (NIS) database is a national hospital admission database that contains 20% of stratified sample of US community hospital admissions. We pooled the data from 2002 to 2006 and used the International Classification of Disease 9th Revision (ICD-9) codes 437.6, 325 and 671.5(cerebral thrombosis in pregnancy) to identify patients admitted with primary diagnosis of CVT. We also identified occurrence of hydrocephalus, primary hypercoagulability, and secondary hypercoagulability as associated conditions during hospitalization. Secondary ICD-9 codes were used to identify ischemic stroke, intracerebral hemorrhage or subarachnoid hemorrhage. Samples were weighted to provide national estimates of hospitalizations and incidence was calculated using 2004 population national estimates from the census data. Results: A total 6369 patients, (5% pediatric) were admitted with primary diagnosis of CVT during the study period. The overall annual incidence of CVT was 0.9 per million. Pregnancy related CVT comprised 25% of these admissions. Incidence of CVT was three times higher in women (1.3 per million population) compared with men (0.4 per million population). CVT was more common in young population with 73% of cases aged 20-49 years. Primary and secondary hypercoagulability was identified in 5% and 1% of cases, respectively. Only 1% of the patients had hydrocephalus. Only 4% of patients suffered ischemic stroke. Hemorrhagic stroke and subarachnoid hemorrhage were diagnosed in 4% and 2% of the case, respectively. Seventy six percent of patients were discharged home and 2% of patients died in the hospital. Conclusion: The present study is one of the first studies that provide the incidence of CVT in United States among men and women.

Influence of Education on Risk Factors and Outcome in Patients With Ischemic Stroke: A Mexican Multicentric Stroke Registry

Methods: Educational level was categorized as: illiterate (0), primary school (1), elementary and high school (2), college and/or graduate school (3). Student's t test was used to determine statistical significance.

Results: There were 1,246 IS (90.6%) and 130 TIA (9.4%). Pertaining data is shown in Table. Estimated OR between low education and poor outcome was 1.7 (95%CI, 1.3-2.3; P<0.001) and remained independent (OR 1.5 (95%CI 1.1-2.2; P<0.001) and remained independent after adjusting with other variables. Conclusions: Low educational level was related to poor outcome and higher frequency of medical complications during acute ischemic stroke, mainly related to major burden of risk factors.

Role of Paradoxical Embolism in Patients With Cryptogenic Embolism

Methods: We reviewed 117 patients with diagnosis of acute cryptogenic stroke. Vascular and cardiologic workups were performed and brain MRI scan including diffusion-weighted imaging (DWI) was performed in all patients. For detecting PFO with RLS, agitated saline transcranial Doppler
(as-TCD) was carried out in all patients. The correlation between the presence and degree (microembol <20 vs. >20) of RLS and the number and distribution of acute ischemic lesions on DWI were evaluated. The baseline patient characteristics, including Framingham stroke risk strategy were compared between patients with and without RLS. Results: Among 107 patients with cryptogenic stroke, 87 patients were classified as cryptogenic embolism. PFO with RLS was very prevalent in patients with cryptogenic embolism; it is observed in 70.1% (69 of 97). The distribution of DWI lesions (anterior vs. posterior circulation) and the size or numbers of lesions were not different between PFO with RLS and negative group (Figure). However, there was a trend that patients with larger degree of RLS showed small scattered infarcts involving multiple vascular territories. The clinical characteristics, including Framingham stroke risk strategy were not different between the groups. Conclusions: Although our data did not provide the cause-result relationship between PFO with RLS and cryptogenic embolic stroke, PFO with RLS was very frequently observed in those patients. Our results suggested that PFO with RLS should be evaluated in patients with cryptogenic stroke, especially when the patients showed small scattered infarcts involving multiple vascular territories. Further studies with a more patients with prospective design are needed to prove the cause-result relationships.

Clinical Features of Cryptogenic Brain Infarction: The Fukuoka Stroke Registry (FSR)

Sohei Yoshimura, Hiroshi Sugimori, Tetsuro Ago, Masahiro Kamouchi, Takanari Kitazono, Mitsuo Iida, Dept of Medicine and Clinical Science, Graduate Sch of Med Sciences, Kyushu Univ, Fukuoka, Japan

Objectives: In spite of extensive examinations, obvious causes of ischemic stroke can not be identified in a certain percentage of stroke patients. This type of stroke is called cryptogenic brain infarction (CI). The objective of this study is to elucidate background and clinical characteristics of CI. Methods: We used the Fukuoka Stroke Registry (FSR), a prospective multi-centered study for stroke in Japan, in which 969 consecutive patients with acute ischemic stroke were enrolled from June 2007 to August 2008. We compared Background, comorbidities, clinical findings, laboratory data, therapy, and prognosis between CI group (67 patients, male 42%, average 70.1 years old) and known-cause (of brain infarction) group (920 patients, male 58%, average 71.4 ± 11.9 years old). Results: CI group had higher frequency of female and history of malignancy than known-cause group (19.4% vs. 10.6%, p = 0.029). CI group had lower levels of blood pressure, red blood cell count, serum total protein and triglyceride. There were no significant differences in NIHSS score on admission and mRS at discharge between the two groups. Multiple logistic regression analysis revealed that age (OR 0.975, p = 0.030), history of malignancy (OR 2.251, p = 0.034), serum total protein (OR 4.19, 95%CI 1.04-16.86, p = 0.044) were significantly associated with CI. Conclusions: CI patients are younger and have history of malignancy more frequently than patients with known-cause of brain infarction. During examination of young stroke patients without obvious causes of ischemic stroke, presentation of malignancy should be evaluated.

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Higher LA Pressure May Not Be Likely to Open the Right-to-left Shunt in Acute Ischemic Stroke Patients With Atrial Fibrillation

Junyos Aoki, Yasuyuki Ichigi, Kensekku Shibazaki, Yuki Sakamoto, Kimiko Fukunaga, Nobuyuki Kaneko, Kenichiro Sakai, Kazuto Kobayashi, Kyotaka Shibata, Kako Shigeta, Kawasaki Med Sch, Kurashiki, Japan

Background and Purpose: The detection rate of right-to-left shunt (RLS) is low in patients with atrial fibrillation (AF) compared with those without AF. We suspected that some patients with AF had heart failure, and LA pressure was high. If LA pressure was high in such patients, it was not likely to open the RLS. The ratio of the early mitral inflow velocity to diastolic mitral annular velocity (E/E'), which is a parameter of trans-thoracic echocardiography (TTE), reflects the LA pressure. We hypothesize that LA pressure plays an important role in opening RLS in acute ischemic stroke patients with AF. Methods: Consecutive acute ischemic stroke patients with AF within 24 hours of onset were enrolled. After all patients were examined using transcranial Doppler, they were classified into two groups (RLS group; patients with RLS, and non-RLS group; patients without RLS). Standard TTE was performed to assess the LA diameter and left ventricular ejection fraction (EF). E/E' was measured using the pulse Doppler method and tissue Doppler imaging. Blood sample were taken to determine plasma brain natriuretic peptide (BNP) concentration. Univariate history of previous stroke events was abstracted in April 2003 to July 2009, 171 patients (age, 78 years [interquartile range], 70-83; men, 89 [52%]) were entered into the study. RLS was found in 15 (9%) of 171 patients. LA diameter was 4.2 (3.7-4.6) cm in RLS group and 4.3 (3.8-4.8) cm in non-RLS group (p = 0.351). The frequency of BNP of >100 pg/ml was slightly higher in RLS group than non-RLS group (53% vs. 23 [15%], p = 0.017). EF was significantly lower in RLS group than non-RLS group (42.0% [54.3-68.8] vs. 61.0 [56.0-65.0], p = 0.029). However, E/E' was significantly lower in RLS group compared with non-RLS group (8.0 [8.3-12.6] vs. 13.6 [10.2-18.1], p = 0.008). The optimal cut-off of E/E' to differentiate the RLS group from the non-RLS group was 11.0 (sensitivity, 72%, specificity, 64%). Multivariate regression analysis demonstrated that E/E' of <11.0 (OR 4.19, 95%CI 1.04-16.86, p = 0.044) was an independent factor associated with the presence of RLS in patients with AF. Conclusion: Higher E/E' may be associated with the negative detection of RLS in acute ischemic stroke patients with AF. Higher LA pressure may not be likely to open the RLS.

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Changes in Clinical Management With the Use of Transesophageal Echocardiography in Patients With a First Cerebrovascular Ischemic Event

Kate C Young, Curtis G Benesch; Univ of Rochester Med Ctr, Rochester, NY

Introduction: The goal was to develop a decision rule 1) to detect the presence of a high risk source of embolus and 2) to predict a change in pharmaceutical management following transesophageal echocardiography (TEE) in subjects who present with a first cerebral ischemic event. Methods: We conducted a retrospective chart review of patients ≥18 years of age who underwent TEE after a first ischemic event and were admitted to the Stroke Service at Strong Memorial Hospital from 2004-2007 (n=287). Logistic regression and the two-stage linear step-up procedure to control the false discovery rate at 0.05 were used to identify a subset of variables for the final models. Receiver-operator characteristic curves were used to generate the decision rules. Results and Discussion: In this cohort, TEE identified a high risk source of embolus in 14.3% of patients while an additional 61.3% of the cohort had a (potential or low risk) source of embolus. TEE findings resulted in a change in pharmaceutical or clinical management in 31.4% of patients. Increasing age and no history of diabetes mellitus were independently associated with a high risk source of embolus. TEE would be recommended for non-diabetic individuals who were ≥65 years old (85%). Over 90% of patients with the curve (AUC) for detecting a high risk source of embolus was 0.773. Regarding changes in management after TEE, those patients with a history of hypertension or current smokers were less likely to undergo changes in management based on TEE results. The AUC was uninformative at 0.56 for predicting a change in management and additional analyses were terminated. Further prospective validation of these decision rules is needed.

This research has received full or partial funding support from the American Heart Association, National Center.

Patent Foramen Ovale May Be A Cause of Retinal Ischemia

Takeshi Iwagawa, Kenichiro Sakai, Nobuyuki Kaneko, Junyos Aoki, Kazuto Kobayashi, Masao Watanahe, Noriko Matsumoto, Kensekku Shibazaki, Yasuyuki Ichigi, Kazumi Kimura, Kawasaki Med school, Kurashiki, Japan

Introduction: Retinal ischemia is mainly caused by embolism. Systemic evaluation is recommended to avoid cardiovascular event. Carotid atherosclerosis and cardiac embolism are considered as embolic origin, but unknown embolic source is present. Our aim is to determine what unknown source of retinal ischemia is. To answer this enquiry, we compared clinical characteristics including embolic source between the patients of retinal ischemia and brain infarction on acute stroke unit. Methods: We consecutively enrolled retinal ischemic patients and ischemic stroke patients who admitted on acute stroke unit from April 2004 to June 2009. All patients were done cranial CT and / or MRI including MRA immediately on admission. Carotid sonography, transcranial Doppler ultrasound, Holter 24 hour electrocardiogram, transthoracic and / or transesophageal echocardiography, conventional cerebral angiography and / or computed tomography angiography were performed. Clinical characteristics including embolic source were compared between retinal ischemic and ischemic stroke patients. Results: Thirty seven retinal ischemic patients (male 26 cases; amaurosis fugax in 21 cases) and 1692 ischemic stroke patients (male 1067 cases, and median NIHSS 4) were enrolled into this study. Patients characteristics were not statistically different in age (69 ± 12 vs. 72 ± 12 years-old; p = 0.183), hypertension (59% vs. 67%; p = 0.848), diabetes mellitus (35% vs. 31%; p = 0.699), hyperlipidemia (46% vs. 35%; p = 0.366) between two groups. Retinal ischemic patients more frequently had patent foramen ovale (57% vs. 23%; p < 0.001) and less frequently atrial fibrillation (3% vs. 21%; p = 0.016) than ischemic stroke patients. There were no statistical differences in complicated lesion of aortic arch, carotid disease (males 16%, p = 0.599) and emboli in 31.4% vs. 11% (p = 0.711) between two groups. Conclusion: Patent foramen ovale was the most frequent embolic source of retinal ischemia. Patent foramen ovale may be a cause of retinal ischemia.
Large Aortic Plaques May Be Associated With Hypercoagulability
Noriko Matsumoto, Kimiko Fukunaga, Yuki Sakamoto, Nobuyuki Kaneko, Kenichiro Sakai, Kazuto Kobayashi, Junya Aoki, Shinji Yamashita, Takeshi Iwasawa, Masao Watanabe, Kazumi Shiba, Yassuyuki Iguchi, Kazumi Kimura; Dept of Stroke Medicine, Okayama, Japan

Purpose: Atheromatous disease of aortic arch (10–40 mm in thickness) has been considered to be associated with ischemic stroke. It is reported that patients with atheromatous disease of aortic arch was associated with hypercoagulability. However the relationship between aortic plaques and hypercoagulability is unknown. The aim of the present study was to assess the relationship between aortic arch plaque and hypercoagulability. Methods: We prospectively examined consecutive acute ischemic stroke patients admitted to our hospital with in 7 days of onset, who underwent transesophageal echocardiography (TEE). We divided the patients into the three groups according to the size of aortic plaque; Group S (<2mm in thickness, Group M: 2–4 mm in thickness, Group L: >4 mm in thickness, respectively. We compared clinical characteristics and laboratory parameter, including thrombin-antithrombin complex (TAT) and D-dimers among the three groups. Results: 358 patients (male 233 (63.5%), age 72.0 (60.0–80.0) years) were enrolled into the present study. Group S (<2mm, M (2–4mm) and L (>4mm) had 51 patients (14.3%), 170 patients (46.7%) and 132 patients (37.0%), respectively. Of the 3 groups, the patients in Group L were the oldest (70.0 (47.3–65.0) vs. 71.5 (63.0–78.3) vs. 75.0 (69.0–81.0) years, p<0.0001), and male was most frequently observed in Group L among the three groups (61.5% vs. 58.0% vs. 75.2%, p<0.004). Hypertension (51.9% vs. 69.5% vs. 78.0%, p=0.002) and diabetes mellitus (13.5% vs. 20.1% vs. 33.3%, p=0.004) were most frequent in the Group L. CRP (0.05 (0.03–0.9) vs. 0.09 (0.04–0.52) vs. 0.14 (0.06–0.44) mg/dl, p<0.0001), fibrinogen (261.1 (191.8–330.0) vs. 294.0 (251.5–343.0) vs. 31.3 (29.0–354.0) mg/dl, p<0.0001) and HbA1c (5.4 (5.2–5.8)% vs. 5.7 (5.4–6.1)% vs. 5.9 (5.6–6.4)%), p=0.012 were highest, HDL-cholesterol (53.5 (43.5–66.0) vs. 51.0 (41.0–59.0) vs. 44.5 (37.5–54.0) mg/dl, p<0.0001) was lowest in the Group L TAT (4.0 (1.0–10.0) vs. 4.4 (2.5–10.1) vs. 6.0 (3.5–10.3) ng/ml, p=0.025) and D-dimers (0.5 (0.3–0.9) vs. 0.7 (0.5–1.4) vs. 1.0 (0.6–2.3) mg/ml, p<0.0001). (Figure) were significantly highest in Group L. WBC, hematocrit, total cholesterol were not different among three groups. Conclusions: In patients with acute ischemic stroke, large aortic plaque is associated with hypercoagulability.

Brain Natriuretic Peptide Should Be a Good Biochemical Marker for Predicting Cardioembolic Stroke
Kenjiro Sakai, Kenzuke Shiba, Yassuyuki Iguchi, Takeshi Iwamato, Noriko Matsumoto, Junya Aoki, Masanobu Watanabe, Shinji Yamashita, Kazumi Kimura, Department of Stroke Medicine, Kawasaki Medical Sch, Kurashiki, Japan

Background and Purpose: Brain natriuretic peptide (BNP) has been reported to be useful in the assessment of patients with congestive heart failure. Recently, we reported that a BNP level of more than 110 pg/ml could differentiate cardioembolic stroke from non-cardioembolic stroke. The aim of this study was to prospectively investigate whether the above-mentioned theory was correct. Method: Between January 2008 and December 2008, consecutive patients with acute ischemic stroke within 24 hours of onset were prospectively enrolled. We measured BNP using rapid assay (SHIONOSPOT®BNP) on admission. Patients was classified into two groups based on BNP levels; high BNP group; BNP level 140.0 pg/ml and low BNP group; BNP level less than 140.0 pg/ml. Results: We prospectively enrolled consecutive 221 pts. We compared clinical characteristics among the three groups. Acute Only(AO), Multiple Recent(MR) and Acute Only(PO) groups had 139 pts, 41 pts and 41 pts, respectively. Male was more frequent than female in AO group (13.5% vs. 11.0%, p=0.041), and we found significant difference of age (p=0.0001) and hypertension (51.1% vs. 69.5% vs. 78.0% respectively, p=0.002). Moreover, patients were divided into two groups according to TOAST stroke classification (58.6% for AO, 38.5% for MR and 3.0% for PO, respectively, p=0.0001). Hypertension (75.3% for AO, 70.4% for MR and 70.7% for PO, respectively) and hyperlipidemia (33.8% for AO, 31.7% for MR and 43.4% for PO, respectively, p=0.0001) were highest, HDL-cholesterol (53.5 (43.5–66.0) vs. 51.0 (41.0–59.0) vs. 44.5 (37.5–54.0) mg/dl, p<0.0001) was lowest in the Group L TAT (4.0 (1.0–10.0) vs. 4.4 (2.5–10.1) vs. 6.0 (3.5–10.3) ng/ml, p=0.025) and D-dimers (0.5 (0.3–0.9) vs. 0.7 (0.5–1.4) vs. 1.0 (0.6–2.3) mg/ml, p<0.0001) (Figure) were significantly highest in Group L. WBC, hematocrit, total cholesterol were not different among three groups. Conclusions: In patients with acute ischemic stroke, large aortic plaque is associated with hypercoagulability.

Brain natriuretic peptide (BNP) levels may serve as a valuable objective predictor for stroke and TIA. Multiple recent TIA's and strokes are reflected in N2R2B levels. Women appear to have higher N2R2B levels.

Amino Acid Uptake Predicts the Vascular Remodeling in Patients With Misery Perfusion in Chronic Carotid Artery Occlusion
Katsufumi Kajimoto; National Cardiovascular Cntr, Suita, Japan

Background: Tissue uptake of L-(-methyl)-11C-methionine (11C-methionine) has been used to monitor amino acid metabolism and protein synthesis. 11C-methionine has been used clinically for the diagnosis of brain and other tumors. Recently, several reports have suggested a relation between 11C-methionine uptake and angiogenesis, particularly in gliomas and acute myocardial infarction. Vascular remodeling and arteriogenic angiogenesis. This study aimed to determine whether amino acid uptake predicts the vascular remodeling in patients with chronic cerebrovascular artery occlusion.

Methods: We prospectively examined amino acid uptake in chronic occlusive cerebrovascular artery disease. We prospectively enrolled consecutive patients with chronic cerebrovascular artery disease (58 patients, age 72 (63–80) years). We measured 11C-methionine uptake using positron emission tomography (PET) and amino acid uptake was evaluated using 11C-methionine PET in all patients. We analyzed the images in 2D and 3D planes: the levels of the basal ganglia and the centromedial semiovale. Each image was examined by placing hemispheric ROIs in the bilateral MCA areas. The ratios of lesion-to-contralateral normal side of CBF, CMRO2, OEF, and 11C-methionine uptake were analyzed. The analysis was divided into 3 groups by OEF and CMRO2 ratio, based on the comparison with 6 normal controls: Group A (misery perfusion group) with 11C-methionine uptake greater than in the NS group. In women, NR2Ab levels were higher than in men. Male AO pts had only slight elevations vs NS (p=0.25), but male MR and PO pts had significant elevation vs NS (p<0.005 and p=0.06, respectively). In females both AO and MR groups had significant elevations (p=0.05 and p=0.01, respectively) vs the NS group. Using a multiple regression model and ANOVA, relative contributions of the risk factors and NR2Ab level to the CVA/TIA state were determined. In men, only 2 of 8 variables, NR2Ab level (p<0.01) and HTN (p<0.001), were significant predictors for CVA/TIA. In females, the model identified 4 significant variables: NR2Ab levels (p<0.01), DM (p<0.05), HTN (p<0.001), and AF (p<0.05). Conclusions: NR2B levels may serve as a valuable objective predictor for stroke and TIA. Multiple recent TIA's and strokes are reflected in N2R2B levels. Women appear to have higher N2R2B levels.
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**Accuracy of Serum NSE and S-100 Protein in Predicting Outcome After Cardiac Arrest**

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**Background:** Serum neuron-specific enolase (NSE) and serum astroglial S-100j protein (S-100) levels within the first 3 days after cardiac arrest have been proposed as predictors for outcome of comatose post-cardiac arrest survivors. However, the cutoff levels for a 0% false positive rate (FPR) vary in different studies and the effect of therapeutic hypothermia on these serum levels has not yet been studied well. **Methods:** Successfully resuscitated comatose post-cardiac arrest patients were prospectively enrolled. Serum samples were drawn at 24, 48, and 72 hours after the arrest and stored at −70°C for up to 21 months prior to analysis for NSE and S-100 levels. Hemolyzed samples were excluded from the analysis. Poor outcome was defined as death or vegetative state at 3 months. The peak serum NSE and S-100 levels for each patient were used to evaluate the power to predict poor outcome using ROC analysis. The same peak values were used to compare serum levels between patients who did and did not undergo hypothermia. Continuous variables were compared using the Mann-Whitney U test and proportions with the χ² test. **Results:** Fifty-five patients were prospectively enrolled: 58 ± 17 years old, 17 (31%) females, arrest duration 21 ± 110 minutes (11 known), 43 (78%) out-of-hospital cardiac arrests. Good outcome was achieved in 11 (31%) hypothermia and 5 (29%) normothermia patients (p = 0.74). There was no difference in serum NSE or S-100 levels between the two groups (median [IQR]: NSE: 33.3 µg/L [19-83.0] vs. 61.9 µg/L [24.2-142.8], p = 0.4); and S-100 (0.43 µg/L [0.27-1.19] vs. 0.61 µg/L [0.21-1.72], p = 0.96), respectively. Three out of 16 (19%) survivors had serum NSE levels (33.7, 67.7, 85.0) > 33 µg/L, the cutoff that has been previously proposed to predict poor outcome. Serum NSE and S-100 levels in good outcome patients were lower than in poor outcome patients: median (IQR) for NSE 20.0 µg/L (14.5-30.2) vs. 77.6 µg/L (26.7-161.7), p < 0.001; and for S-100 0.23 µg/L (0.19-0.39) vs. 0.69 µg/L (0.30-2.05), p < 0.001. The cut-off values resulting in 0% FPR in our cohort are shown in the table:

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<th>Specificity</th>
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<td>0.81</td>
<td>0.69 (95%CI)</td>
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</tbody>
</table>

**Conclusions:** In our cohort of successfully resuscitated comatose post-cardiac arrest patients, a serum NSE level > 93.4 µg/L and a serum S-100 level > 1.08 µg/L in the first 24-72h predicted poor outcome with 100% specificity. Serum S-100 levels predicted poor outcome with the same accuracy as serum NSE levels. We did not observe an effect of therapeutic hypothermia on peak serum NSE and S-100 levels in this dataset. This research has received full or partial funding support from the American Heart Association, National Center.

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**P204**

**Local Glucose Metabolism Before and After Motor Cortex Stimulation for Post-stroke Pain**

Masaki Ito; Dept of Neurosurgery, Hokkaido Univ, Sapporo, Japan

**Background and Purpose:** Local cerebral glucose metabolism was semi-quantitatively analyzed in this study, therefore, we assessed local cerebral glucose metabolism in patients with ischemic stroke for assessment of post-stroke pain and improve glucose metabolism in the ipsilateral thalamus. Post-stroke pain may be related to the reduction of presynaptic glucose usage in the thalamus. Motor cortex stimulation (MCS) is a promising strategy to relieve post-stroke pain. In the internal capsule, corona radiata, and medulla oblongata. Its underlying mechanisms are still unclear. **Methods:** Asymmetry of cerebral glucose metabolism was assessed in patients with ischemic stroke before surgery. Asymmetry of local cerebral glucose metabolism in the ipsilateral thalamus before and after MCS was assessed. **Results:** Three out of 16 (19%) survivors had serum NSE levels (33.7, 67.7, 85.0) > 33 µg/L, the cutoff that has been previously proposed to predict poor outcome. Serum NSE and S-100 levels in good outcome patients were lower than in poor outcome patients: median (IQR) for NSE 20.0 µg/L (14.5-30.2) vs. 77.6 µg/L (26.7-161.7), p < 0.001; and for S-100 0.23 µg/L (0.19-0.39) vs. 0.69 µg/L (0.30-2.05), p < 0.001. The cut-off values resulting in 0% FPR in our cohort are shown in the table:

<table>
<thead>
<tr>
<th>Serum</th>
<th>Cutoff value</th>
<th>AUC</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSE</td>
<td>93.4</td>
<td>0.93</td>
<td>0.45 (95%CI)</td>
<td>0.69 (95%CI)</td>
<td>0.03</td>
<td>0.93</td>
</tr>
<tr>
<td>S-100</td>
<td>1.08</td>
<td>0.81</td>
<td>0.69 (95%CI)</td>
<td>0.53 (95%CI)</td>
<td>0.03</td>
<td>0.93</td>
</tr>
</tbody>
</table>

**Conclusions:** In our cohort of successfully resuscitated comatose post-cardiac arrest patients, a serum NSE level > 93.4 µg/L and a serum S-100 level > 1.08 µg/L in the first 24-72h predicted poor outcome with 100% specificity. Serum S-100 levels predicted poor outcome with the same accuracy as serum NSE levels. We did not observe an effect of therapeutic hypothermia on peak serum NSE and S-100 levels in this dataset. This research has received full or partial funding support from the American Heart Association, National Center.

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**P205**

**Intravenous Tissue Plasminogen Activator (rt-PA) in Anticoagulated Patients With Acute Ischemic Stroke: Safety and Outcomes**

Nobil Barazangi, Kristin Schmid, Jackie Phan, Ann Bedenk, Jack Rose, David Tong; CPMC, San Francisco, CA

**Background:** Although anticoagulation is a common intravenous (IV) rt-PA exclusion criterion, the data supporting this exclusion are limited. Frequently such patients receive no treatment or intra-arterial (IA) therapy, even though IV treatment is time consuming and there are few data supporting this approach. We hypothesized that IV rt-PA would be safe and effective in anticoagulated patients. **Methods:** A retrospective analysis of all IV rt-PA treated patients on warfarin (INR > 1.7), therapeutic heparin or low molecular weight heparin (LMWH) was performed. Informed consent was obtained prior to treatment in all patients. Outcome was determined by initial and discharge National Institute of Health Stroke Scale (NIHSS) score. Safety was evaluated by symptomatic hemorrhage rate ≤ 36 hours after treatment. **Results:** Between 9/08 and 8/09, 44 patients received IV rt-PA. Eight patients fulfilled the inclusion criteria (18%). Mean age was 73 (range 35-92); half were female. Six patients were receiving warfarin for atrial fibrillation (AF, n=5) and mechanical heart valve replacement (n=1). The mean INR was 2.1 (range 1.8-2.4). Two patients were receiving heparin (n=1; PT/TT 136) or LMWH (n=1; dose: 1 mg/kg bid) for cardiac stent placement or bridging therapy for known left atrial thrombus and AF, respectively. Five patients received 0.45 mg/kg and three patients 0.9 mg/kg rt-PA. The average time to treatment from symptom onset was 218 minutes (range 60-390). The average door to treatment time was 98 minutes (range 55-125). Two patients also received IA rt-PA following IV rt-PA. The average NIHSS improved from 12 to 2. One patient died of an MI unrelated to the stroke. There were no symptomatic intracranial hemorrhages and 2 asymptomatic intracranial hemorrhages. Two patients developed minor systemic bleeding (small groin and neck hematomas). **Conclusion:** These data suggest that IV thrombolysis can be effective and safe in anticoagulated patients. Exclusion of patients from thrombolytic therapy on the basis of anticoagulation alone should be reassessed. Use of IV thrombolysis in these patients may enable a significantly greater number of patients to receive thrombolytic therapy, particularly at institutions where IA therapy is unavailable. The use for IA therapy in anticoagulated patients needs to be reconsidered, given the generally lower treatment required for IA therapy.

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**P206**

**Adherence of Emergency Department Blood Pressure Management in Intracerebral Hemorrhage to the AHA Guidelines: A Population-based Study**

Erin M Grise, Ope Adeoye, Christopher Lindsell, Kathleen Alwell, Charles J Moomaw, Brett M Kissela, Daniel Woo, Matthew L Flaherty, Simona Ferioli, Pooja Khatri, Joseph P Broderick, Dawn Kleindorfer; Univ of Cincinnati, Cincinnati, OH

**Objectives:** Elevated blood pressure (BP) is common in intracerebral hemorrhage (ICH) but controversy exists on how to treat BP in the acute setting. Hypertension is associated with neurologic decline and hemorrhage expansion. However, aggressive BP reduction is also associated with worse outcomes. Based on limited literature, the 1999 AHA guidelines recommended that systolic blood pressure (SBP) greater than 160 mmHg or diastolic blood pressure greater than 105 mmHg should be modestly lowered in acute ICH. We hypothesized that treatment of elevated BP in acute ICH patients in the emergency department (ED) often occurs below the recommended threshold for treatment and that relative hypertension is common after treatment. **Methods:** Stroke cases occurring in the Greater Cincinnati/Northern Kentucky region during 2005 were reviewed. Patients with acute ICH presenting to any of 16 local hospitals were identified by ICD-9 codes 430-436. Blood pressures were recorded at ED presentation, and before and after treatment with anti-hypertensives. Hypertension was defined as BP ≥ 180/105 mmHg, based on the 1999 AHA guidelines. Relative hypertension was defined as SBP < 100 mmHg, Mann-Whitney U-tests and Chi-square tests were used for comparisons. **Results:** There were 290 patients with ICH identified. Median age was 72 years, 45.2% were...
male and 21.4% were black. Median estimated NHSS was 11.0 (range 0 to 40). On ED arrival, 133 patients met AHA criteria for treatment with anti-hypertensives; 102 of these patients (76.7%) received anti-hypertensives. There were a total of 129 patients treated for hypertension, of which 18 (14.0%) did not meet criteria at the time of treatment. Males were treated more frequently than females (51.1% v 39.0%, p = 0.030) and all races were proportionally represented. Median systolic pressure was 231.0 (range 110.0 to 320.0) mmHg. Of the 133 patients, 89 were African American (67.1%), 11 were Asian American (8.3%), 20 were Hispanic American (15.1%), seven were Native American (5.3%), and four had no recorded racial data (3.0%). 30.6% of the patients had hypertension for at least 10 years, but 7.5% of the patients died within the first year after diagnosis. In addition, 18.0% of the patients had high blood pressure at the time of diagnosis, and 4.3% of the patients had high blood pressure at the time of diagnosis.

**Conclusion:** Our findings indicate that hypertension is a significant comorbidity in acute stroke patients. Further studies are needed to investigate the long-term outcomes of hypertension in acute stroke patients.
P211
Development and Validation of a Clinical Scale Distinguishing Hemorrhagic and Ischemic Stroke in the First Two Hours After Onset
Nurses Sanssion, Univ of Southern California, Los Angeles, CA; Sidney Starkman, Univ of California Los Angeles, Los Angeles, CA; Scott Hamilton, Stanford, CA; David A Liss, Beth Israel Deaconess Med Ctr, Boston, MA; Charles J Halperin, Univ of Southern California, Los Angeles, CA; Richard Gage, Univ of Southern California, Los Angeles, CA; Robert Mehta, Santa Clara Valley Med Ctr, Sunnyvale, CA; Frank Fratt, Torrance Memorial Med Ctr, Torrance, CA; Samuel Stratton, Jeffrey L Saver, Univ of California Los Angeles, Los Angeles, CA; FAST-MAG investigators and Nurses
Objective: To develop a clinical scale to differentiate intracerebral hemorrhage (ICH) and cerebral ischemia in the first 2 hours after onset. After standard clinical scales to distinguish ICH from cerebral ischemia were designed in the non-interventional era to be applied in the subacute period, 6-72 hours after onset. For a clinical scale to be useful in guiding ambulance treatment and routing of hyperacute patients, it must utilize clinical features and historical variables that were not present 6-72 hours after onset. Methods: Analysis of patients enrolled through April 2008 in the NIH FAST-MAG trial of prehospital neurological stroke therapy. Final diagnoses of acute cerebral ischemia, acute intracranial hemorrhage, and stroke mimic were rendered by a central adjudication panel after review of all clinical and imaging data available through 3 months of follow-up. Cases were randomly assigned to derivation (D) and validation datasets. The 24 demographic, clinical, and physiologic potential predictive factors available at the time of paramedic encounter were analyzed by backward stepdown linear/additive logistic regression and classification tree analysis. Results: Among the first 713 subjects enrolled, mean age was 70 ± 13 years, 42% were women, and mean time from last known well to paramedic contact was 39 ± 52 minutes. Final diagnoses were acute cerebral ischemia in 525 (72%), intracranial hemorrhage in 164 (22%), and other/incomplete in 41 (6%). On univariate analyses, predictors of ICH were younger age, Hispanic ethnicity, black race, higher SBP, higher DBP, greater neurologic deficit on the Los Angeles Stroke Triage Scale, and longer time from onset to contact. A logit model with binary predictors was constructed that scored every patient on a 22 point scale and predicted ICH with specificity 77.2%, sensitivity 72.4%, accuracy 73.9%, and c statistic 0.74. In the validation dataset, predictive scale showed specificity 77.2%, sensitivity 72.4%, accuracy 73.9%, and c statistic 0.81. In the validation dataset, a logit model with binary predictors was constructed that scored every patient on a 22 point scale and predicted ICH with specificity 77.2%, sensitivity 72.4%, accuracy 73.9%, and c statistic 0.81. In the validation dataset, predictive scale showed specificity 77.2%, sensitivity 72.4%, accuracy 73.9%, and c statistic 0.81. Conclusion: A simple scale scoring patients on demographic, clinical, and blood pressure variables available to paramedics in the first two hours after stroke onset can distinguish intracranial hemorrhage from acute cerebral ischemia with moderate accuracy. This scale may be used to optimize routing of most appropriate stroke critical care centers and patient selection for prehospital and Emergency Department treatment trials. Support: NIH-NINDS U01 NS 44364

P212
How Accurate is a Stroke Alert System?
Timothy J Ingall, Maria I Aguilar, Bart M Demaerschalk, David W Dodick, Terri E Kiernan, Byron R Spencer, Bentley J Bobrow. Mayo Clinic Arizona, Phoenix, AZ
Background: Many Stroke Centers have a Stroke Alert (SA) system to notify their Stroke Teams if either EMS or ED personnel identify a patient with the recent onset of possible stroke symptoms. The Stroke Team responds promptly to SA activation to determine patient eligibility for acute stroke interventions. However, initial stroke diagnosis is imperfect and is associated with both under- and over-triage. Insufficient SA activation can disrupt Stroke Team patient care so we studied SA activation in the ED at Mayo Clinic Hospital, Phoenix, AZ (MCH) to determine how other predictors of SA criteria were associated with the many SA activations that did not result in a diagnosis of stroke. Methods: Over 11 months, information from the MCH ED was collected on every SA activation who determined whether the patient met 6 of 8 emergency criteria in the ED. Many SA criteria were used for initial diagnosis of stroke. Results: During 2006 and 2007, 257 consecutive ED SA activations, of which 172 originated from EMS providers and 65 from ED staff. Among these 237 SAs, 49 (21%) did not meet SA criteria [EMS 34 (20%); ED 15 (23%)]. SAs were determined to have been activated inappropriately due to resolution of FAST symptoms prior to SA activation in 7 patients (14%), more than 12 hours of FAST symptoms in 10 patients (20%), and non-FAST symptoms in 32 patients (66%). Stroke was the final diagnosis in 59% of all SAs, 69% of SAs meeting SA criteria, and 24% of SAs not meeting SA criteria. Discussion: 1. Diseases other than stroke can cause acute neurological symptoms so it is understandable that that a high % of SAs do not have stroke as a final diagnosis. However, the overall figure of 59% of all SA patients having stroke as the final diagnosis is comparable with previously published data. 2. SAs are disruptive for Stroke Team personnel who attend immediately to possible acute stroke patients. We found that approximately 20% of SAs were activated inappropriately with two-thirds of incorrect SAs being due to absence of FAST symptoms. An education program is planned for EMS and ED staff based on both better determination of the time of symptom onset, and identification of FAST symptoms. Conclusion: A SA system is associated with both over- and under-triage and requires ongoing education and quality improvement.

P213
Factors Associated With Neurological Outcomes Following Intracranial Angioplasty and/or Stent Placement: A Multicentric Study
Adnan I Qureshi, Nauman Tariq, Amee E Hassan, Gabriela Vazquez, Halitman H Muisse, MF Suri, Alexandros L Georgiadis, Ramachandra P Tummala, Robert A Taylor; Zeenat Qureshi Stroke Nach Ctr, Univ of Minnesota, Minneapolis, MN
Background: Transient or permanent neurological deficits can occur in the periprocedural period following intracranial angioplasty and/or stent placement. The patients at risk and time

P214
Presence of Cerebral Edema Predicts Poor Outcome in Patients With Cerebral Venous Thrombosis
Chris Fanale, Kathryn Leonard, Kristin Saltolito, Christy Casper, David Bar-Or; Swedish Med Ctr, Denver, CO
Background: Standard treatment of cerebral venous thrombosis (CVT) is systemic anticoag- ulation. Currently, there are no US guidelines for additional treatment with mechanical thrombectomy (MT). At our stroke center approximately half of the patients with CVT receive MT in addition to systemic anticoagulation. The purpose of this analysis is to describe clinical presentation of CVT, predictors of treatment with MT, and predictors of poor inpatient outcome. Methods: Data were collected for patients diagnosed with CVT from January 2006- June 2008. The following variables were examined: age, gender, history of migraines, transfer status, pregnancy, smoking status, etiology, presenting signs/symptoms, seizure, cerebral edema, intracranial hemorrhage (ICH), and sinus involvement. These variables were compared by treatment with MT, and by poor vs. moderate vs. good/marked Rankin score (p > 0.05). A total of 54 patients were admitted and treated for CVT over the study period. Average age was 40 years, 72% were female, and 30% had a history of migraines. The average number of presenting signs/symptoms was 2.9. The most common were headache (85%), vomiting (33%) and nausea (31%). Over 83% of patients had more than one sinus involved. The most common sinuses were the right transverse sinus (57%) and the superior sagittal sinus (57%). More than half of patients (54%) had MT, most commonly with tenecteplase and balloon angioplasty (69%). After adjustment, independent predictors of receiving treatment with MT (p < 0.10) included visual disturbances (OR: 6.17, p < 0.03), a genetic etiology (OR: 6.76, p < 0.05), and edema (OR: 4.37, p < 0.07). A poor outcome was greater in patients: > 65 or patients with edema, ICH, aphasia, or motor weakness (p < 0.05). Interestingly, every patient without evidence of cerebral edema by CT or MRI fully recovered from CVT at the time of hospital discharge. Independent predictors of poor outcome were MT in patients with edema include age (OR: 10.0, p < 0.05) and MT (OR: 11.2, p < 0.05). Overall outcomes are as follows: 70% of patients were discharged home, 9% expired in hospital, and 18% were dependent at discharge. Conclusions: Treatment with MT was greater in patients with a positive genetic etiology, cerebral edema, and visual disturbances. Surprisingly, multiple vessel involvement, ICH, and the absence of transiently poor outcome are independent predictors of poor outcome, while the presence of edema did. In patients with edema, death or dependence was greater with mechanical thrombectomy and older age.

P215
Cerebral Blood Volume and Central Venous Pressure: Perfusion MRI Correlates in the Intensive Care of Stroke
David S Lissiekind, Qing Hao, Jeffrey L Saver, Paul M Vespa, Latisha K Ali, Doojin Kim, Jeffrey R Alger, Xiao Hu, UCLA, Los Angeles, CA; for the UCLA Stroke Investigators
Background: Cerebral blood volume (CBV) is a critical hemodynamic parameter in the management of stroke. Although CBV predominantly resides in the venous circulation of the brain, the effect of immediate changes in central venous pressure (CVP) on CBV has not been studied with noninvasive perfusion modalities. We explored the correlation between CVP measures and contemporaneous values of CBV in stroke cases managed in an ICU setting. Methods: We prospectively recruited and continuously monitored noninvasive and invasive data. MRI was conducted in a consecutive series of large vessel stroke cases in the ICU. CBV was calculated from perfusion MRI and categorized as ischemic core, irreversible penumbra, reversible penumbra, normal, hyperemic and vascular voxels. CBV values (averaged over 12 hours within MRI) were correlated with relative proportions of CBV categories, including relative changes in cases with serial perfusion imaging. Results: 16 cases (3 men, 13 women; mean age 65.3±17.0 years) were analyzed, including 6 cases with serial perfusion imaging and CVP data. CBV values timed with perfusion MRI ranged from 2-16 (mean 8.63 units). CBV categories included brain volumes of 2.3% ischemic core, 1.7% irreversible penumbra, 7.0% reversible penumbra, 61.0% normal, 22.3% hyperemic and 10.1% vascular voxels. Overall, CBV did not directly correlate with relative proportions of CBV categories from ischemic core to hyperemia.
In cases with serial measures, however, changes in CVP were mirrored by parallel changes in CBV. Increased CVP resulted in decreased proportion of ischemic core and penumbral voxels. In cases with serial measures, however, changes in CVP were mirrored by parallel changes in CBV. Increased CVP resulted in decreased proportion of ischemic core and penumbral voxels.

### Predictive values of Spot sign, LDL cholesterol, and the combination

<table>
<thead>
<tr>
<th>Spot sign</th>
<th>LDL cholesterol ≤ 90 mg/dL</th>
<th>Spot sign and/or LDL cholesterol ≥ 90 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>94.4%</td>
<td>90.9%</td>
</tr>
<tr>
<td>Specificity</td>
<td>33.3%</td>
<td>60%</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>88.9%</td>
<td>90%</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>51.5%</td>
<td>62.5%</td>
</tr>
</tbody>
</table>

### Conclusions:

Hypercapnia can induce intracranial blood flow "steal" from ischemic brain tissues, and early initiation of non-invasive ventilatory correction with bi-level positive airway pressure (BiPAP) may improve cerebral hemodynamics in acute ischemic stroke (AIS). We aimed to determine safety and tolerability of BiPAP initiated on hospital day 1 without polysomnography study. Subjects & Methods: Consecutive AIS patients with a proximal arterial occlusion and daytime sleepiness and/or positive history of obstructive sleep apnea (OSA) were treated with BiPAP during all sleep periods, or continuously in patients with reduced level of consciousness and sonorous respiratory effort. BiPAP was initiated and titrated to clinical effect using 40% FIO2 (or 21% in known COPD), achieving inspiratory SAP (IPAP) of 12 cm H2O and expiratory PAP (EPAP) of 4-6 cm H2O on average; initially, either the peak inspiratory or spontaneous respiratory movements were selected based on breathing pattern. In patients with home BiPAP prescriptions, settings were matched to those used at home. Prevalence of adverse events in this sample was recorded. Results: Among 317 consecutive patients (median NIHSS score 5, interquartile range 2-13), 147 patients (47%) had BiPAP (NIHSS 12, IQR 6-17). Baseline stroke severity was higher in BiPAP patients (p < 0.001 Mann-Whitney U-test). BiPAP was tolerated by 60 patients and refused by 4 patients (7%). In-hospital mortality was 3.9% (12/307) in patients not receiving BiPAP, and 11.6% (7/60) in BiPAP patients (p = 0.020). After adjusting for baseline stroke severity, BiPAP was associated with mortality in a multivariate logistic regression model (OR: 2.74; 95% CI: 0.90-8.24; p = 0.073). All cause adverse events on either continuous or intermittent BiPAP included: vomiting (n = 1), vomiting/aspiration pneumonia (n = 1), respiratory failure/intubation (n = 1), hypotension requiring pressors (n = 1), and facial skin breakdown (n = 1). Of these, 6% were classified as serious adverse events directly attributable to BiPAP treatment. Conclusions: In patients with persistent arterial occlusions complicated by excessive sleepiness or OSA, BiPAP can be safely initiated without formal polysomnography with reasonable tolerability and a relatively small risk of serious complications when using standardized titration. Methods: These data should be taken into account in the design of future clinical trials utilizing noninvasive ventilatory correction in AIS.

### Conclusions:

Early hematoma growth is an independent determinant of mortality and poor outcome after intracerebral hemorrhage (ICH). The presence of spot sign on CT angiography (CTA) has been recently reported as a promising marker for hematoma expansion. However, whether other factors may improve the predictive accuracy of spot sign on early ICH growth remains unknown. We aimed to determine potential factors associated with hematoma growth in patients with acute ICH. Methods: We prospectively studied all patients with acute primary spontaneous ICH presenting within 6 hours after symptom onset to our Stroke Unit from July 2007 to July 2009 that had a CTA done on admission. ICH volume was measured on baseline (6h) and follow-up (24h) images. Significant hematoma expansion was defined as >30% or >6 ml hematoma enlargement. The Chi-square test was used for evaluation of the spot sign on CTA findings, and Student’s t-test for comparison of the spot sign on CTA findings in the group of patients who died or survived and those who survived. Results: Among 371 consecutive patients (median NIHSS score 5, interquartile range 2-13), 41 patients (11%) had a CTA done on admission. ICH volume was measured on baseline (6h) and follow-up (24h) images. Significant hematoma expansion was defined as >30% or >6 ml hematoma enlargement. The Chi-square test was used for evaluation of the spot sign on CTA findings, and Student’s t-test for comparison of the spot sign on CTA findings in the group of patients who died or survived and those who survived.

### Background & Purpose:

Safety and Tolerance of Early Non-invasive Ventilatory Correction (NIVC) in Acute Ischemic Stroke

Yi Zhang, Georgia Tsipouli, Anne W Alexandrino, Limin Zhao, Mary Brothour, April Sisson, Luis Cava, Damon Patterson, Aaron Anderson, Andrei V Alexandrino; Comprehensive Stroke Ctr, Univ of Alabama Hosp, Birmingham, AL

### Methods:

Conclusions: The diagnostic yield of CTA in addition to MRI/MRA in spontaneous intracerebral hemorrhage (ICH) or intraventricular hemorrhage (IVH) varies. MRI/MRA and CT angiography (CTA) are commonly used to identify underlying causes non-invasively, yet data is lacking about their relative diagnostic utility. We aimed to evaluate the diagnostic yield of CTA in addition to gadolinium-enhanced MRI/MRA in a cohort of patients with spontaneous ICH or IVH. Methods: Consecutive patients with spontaneous ICH or IVH were prospectively enrolled. All patients received non-contrast brain CT, gadolinium-enhanced MRI/MRA, and laboratory testing upon admission. CTA was performed in a subset of patients at the discretion of the treating team. CTA findings were extracted from the neuroradiologists report, and MRI/MRA findings were determined by independent review of two radiologists who were blinded to the CTA results. The final ICH etiology was determined by the treating stroke neurologist after review of the complete medical record. CTA findings were compared to the MRI/MRA findings and final diagnoses to determine the diagnostic utility of CTA. Student’s t-Test was used to compare groups, and Pearson’s Chi-Square, Fishers Exact Test, or McNemars Test to compare independent or paired proportions. Results: Of 160 prospectively enrolled subjects, 63 (39%) underwent CTA. Baseline variables were similar in those with and without CTA, except that fewer patients with diabetes or renal failure underwent CTA (Table). A secondary cause of ICH was identified in 24/63 cases (38%). CTA detected the underlying cause in 13/24 cases (54%): 4 arteriovenous malformations (AVM), 3 vasculitis, 2 dual sinus thromboses (DST), 2 hemorrhagic infarcts, and 1 arteriovenous fistula. In addition to these 13 cases, MRI/MRA also found 1 additional AVM, 2 hemorrhagic infarcts, 1 DST, 2 neoplasms, 1 cavernous malformation, 1 cortical vein thrombosis, and 1 case of Cail-Fleming Syndrome. MRI/MRA detected the underlying cause in 22/24 cases (92%). One small AVM was diagnosed only by catheter angiography and another AVM only by pathology. When comparing the diagnostic yield of MRI/MRA with CTA, MRI/MRA was superior (P = 0.004). Conclusion: The diagnostic yields of CTA and gadolinium-enhanced MRI/MRA in our select group of ICH or IVH patients were different. MRI/MRA was superior to CTA at detecting secondary causes of ICH. In ICH patients with gadolinium-enhanced MRI/MRA, the added diagnostic utility of CTA is limited.

### Performance Variables

Baseline Variables

<table>
<thead>
<tr>
<th>No (n=97)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>59 ± 16</td>
</tr>
<tr>
<td>Male Gender (%)</td>
<td>48</td>
</tr>
<tr>
<td>History of Hypertension (%)</td>
<td>64</td>
</tr>
<tr>
<td>History of Alcohol Abuse (%)</td>
<td>20</td>
</tr>
<tr>
<td>History of Ilicit Drugs (%)</td>
<td>12</td>
</tr>
<tr>
<td>History of Diabetes (%)</td>
<td>8</td>
</tr>
<tr>
<td>History of Renal Failure (%)</td>
<td>5</td>
</tr>
<tr>
<td>History of Malignancy (%)</td>
<td>11</td>
</tr>
<tr>
<td>Family History of ICH (%)</td>
<td>3</td>
</tr>
<tr>
<td>History of Cerebral Aneurysm (%)</td>
<td>22</td>
</tr>
<tr>
<td>History of Prior Stroke (%)</td>
<td>8</td>
</tr>
<tr>
<td>Location of ICH (%)</td>
<td>46</td>
</tr>
<tr>
<td>ICH Volume (Mean ± SD)</td>
<td>25 ± 25</td>
</tr>
</tbody>
</table>

### Frequency and Predictive Value of the CT Angiography Spot Sign in Secondary ICH

Josser E Delgado Almazno, Massachusetts General Hosp / Mallinckrodt Institute of Radiology, Boston / Saint Louis, MA; Hillary R Kelly, H. Bart Brouwers, Albert J Yoo, Michael J Stone, Pamela W Schafer, Joshua N Goldstein, Jonathan Rosand, Michael H Levy, R. Gilberto González, Javier M Romero; Massachusetts General Hosp, Boston, MA

### Purpose:

The presence of active contrast extravasation at multi-detector CT angiography (MDCTA), the spot sign, is a potent predictor of hematoma expansion and mortality in patients with primary
intracerebral hemorrhage (ICH). This study aims to determine the frequency and predictive value of this MDCTA finding in patients with secondary ICH (i.e. due to a vascular abnormality). Materials and Methods: Two experienced readers, blinded to clinical data, retrospectively reviewed CT angiograms (CTA) performed on 164 consecutive patients presenting to our Emergency Department within 24 hours of symptom onset. Baseline and follow-up ICH volumes were calculated with computer-assisted volumetric analysis. Hematoma expansion was defined as an increase of >6% or >30% from the baseline ICH volume. Disagreements were resolved by consensus. Results: We identified at least 1 spot sign in 25 of 154 patients with secondary ICH (15.2%). Inter-reader agreement for the presence of spot signs was almost perfect (kappa 0.84, 95% confidence interval [CI] 0.7-0.98). A follow-up CT was available in only 54 patients (32.9%) because (1) immediately after the baseline CT 61 patients underwent hematoma evacuation (48.4%), 14 endovascular or aspiration (8.5%) and 5 expired (5%), and (2) 5 patients did not have a follow-up CT performed (3.7%). The presence of a spot sign increased the risk of in-hospital mortality (44.0%, OR 2.5 [95% CI 1.1-4.1], p-value 0.035) but not of hematoma expansion (16.7%, OR 1.7 [95% CI 0.2-17.8], p-value 0.5). Spot signs were most common in patients with arteriovenous fistulae (41.7%), anterior cerebral artery aneurysms (18.2%), and middle cerebral artery aneurysms (17.1%). Importantly, spot signs were more commonly seen in patients with ICH secondary to anterior cerebral and anterior communicating artery aneurysms (100%, Table 2). Prevalence: 11.1 26.8

**Table 1. Predictive Value of the Spot Sign in Secondary ICH**

<table>
<thead>
<tr>
<th>Hematoma Expansion% (95% CI)</th>
<th>In-Hospital Mortality (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity:</strong></td>
<td></td>
</tr>
<tr>
<td>16.7 (6.8–63.5)</td>
<td>25.0 (13.7–40.7)</td>
</tr>
<tr>
<td><strong>Specificity:</strong></td>
<td></td>
</tr>
<tr>
<td>89.6 (76.6–96.1)</td>
<td>88.3 (80.9–93.2)</td>
</tr>
<tr>
<td><strong>PPV:</strong></td>
<td></td>
</tr>
<tr>
<td>16.8 (8.8–63.5)</td>
<td>44.0 (25.0–64.7)</td>
</tr>
<tr>
<td><strong>NPV:</strong></td>
<td></td>
</tr>
<tr>
<td>89.6 (76.6–96.1)</td>
<td>76.3 (68.2–82.9)</td>
</tr>
<tr>
<td><strong>Positive LR:</strong></td>
<td></td>
</tr>
<tr>
<td>1.6 (1.0–2.5)</td>
<td>2.1 (1.1–4.4)</td>
</tr>
<tr>
<td><strong>Negative LR:</strong></td>
<td></td>
</tr>
<tr>
<td>0.9 (0.7–1.3)</td>
<td>0.9 (0.7–1.0)</td>
</tr>
<tr>
<td><strong>Accuracy:</strong></td>
<td></td>
</tr>
<tr>
<td>81.5</td>
<td>71.3</td>
</tr>
</tbody>
</table>

**Table 2. Frequency and Predictive Value of the Spot Sign by ICH Etiology**

<table>
<thead>
<tr>
<th>ICH Etiology:</th>
<th>Spot Sign Frequency, %</th>
<th>Spot Sign Expansions, %</th>
<th>PPV for Hematoma Expansion, %</th>
<th>PPV for In-Hospital Mortality, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arteriovenous malformations, n=60</td>
<td>13.3</td>
<td>0</td>
<td>37.5</td>
<td></td>
</tr>
<tr>
<td>MCA aneurysms, n=23</td>
<td>17.1</td>
<td>n/a</td>
<td>28.8</td>
<td></td>
</tr>
<tr>
<td>Anterior communicating artery aneurysms, n=23</td>
<td>13.0</td>
<td>0</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Arteriovenous fistulae, n=12</td>
<td>41.7</td>
<td>0</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>ACA aneurysms, n=11</td>
<td>18.2</td>
<td>50</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>DICA aneurysms, n=10</td>
<td>0</td>
<td>n/a</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>PICA aneurysms, n=3</td>
<td>0</td>
<td>n/a</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Posterior communicating artery aneurysms, n=2</td>
<td>0</td>
<td>n/a</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>PCA aneurysms, n=2</td>
<td>0</td>
<td>n/a</td>
<td>n/a</td>
<td></td>
</tr>
</tbody>
</table>

**Results:** For a subset of 54 patients with a follow-up NCCT. Defined as an increase of HT (75.2±6.9 ml vs. 53.6±8.0 ml, p=0.05, and 118.5 ± 10.6 ml vs. 89.5 ± 6.9 ml, p=0.05) respectively. Mean ICH core volume showed no significant difference between the two groups. Mean rCBF and rMTT voxel values within the infarct core (as defined by DWI) were significantly different (p=0.010 for rMTT and p=0.042 for rCBF) and treatment with mechanical thrombectomy (area under the curve 0.85, p=0.01). Large vessel occlusion also correlated with HT (p=0.010). Treatment with TPA, age, admission set volume, and treatment modalities were not significant predictors of HT. The only clinical parameters significantly different between the two groups were NIH stroke scale score (NIHSS, 10.9±7.1 vs. 16.4±4.2, p=0.01) and treatment with mechanical thrombectomy (p<0.001). On multivariate analysis, the only independent predictors of HT were admission NIHSS, mean infarct core rMTT value, and treatment with mechanical thrombectomy (area under the curve 0.85, p=0.01), Overall model sensitivity was 70%, specificity 88%, positive predictive value 47%, and negative predictive value (NPV) 89%, for HT. Conclusion: In a multivariate model for risk of HT in acute ischemic stroke, which included both baseline CTP and DWI imaging, the only independent imaging parameter (NIHSS) was the only independent imaging parameter (NIHSS) was significant predictors, however DWI lesion volumes were not.

**Table 3. Hematoma Expansion and Outcome in Primary Intracerebral Hemorrhage**

<table>
<thead>
<tr>
<th>ICH Etiology:</th>
<th>Hematoma Expansion% (95% CI)</th>
<th>In-Hospital Mortality (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16.7 (6.8–63.5)</td>
<td>25.0 (13.7–40.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Specificity:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>89.6 (76.6–96.1)</td>
<td>88.3 (80.9–93.2)</td>
<td></td>
</tr>
<tr>
<td><strong>PPV:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16.8 (8.8–63.5)</td>
<td>44.0 (25.0–64.7)</td>
<td></td>
</tr>
<tr>
<td><strong>NPV:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>89.6 (76.6–96.1)</td>
<td>76.3 (68.2–82.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Positive LR:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.6 (1.0–2.5)</td>
<td>2.1 (1.1–4.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Negative LR:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.9 (0.7–1.3)</td>
<td>0.9 (0.7–1.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Accuracy:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>81.5</td>
<td>71.3</td>
<td></td>
</tr>
</tbody>
</table>

**Background and Purpose:** Hematoma expansion is associated with morbidity and mortality in primary intracerebral hemorrhage (ICH). Recent prospective study showed that contrast extravasation on CT angiography (CTA) could predict hematoma expansion in primary ICH. Our study is to examine whether contrast extravasation on CTA can also predict poor clinical functional outcome of primary ICH. Materials and Methods: We prospectively and consecutively studied 65 primary ICH patients who were not deep comatose at presentation within 2 hours of symptom onset undergoing baseline noncontrast CT (NCCT) and CTA, as well as follow-up NCCT at 24-hour. CTA scans were reviewed by a neuroradiologist and a neurologist independent of each other to identify the presence of contrast extravasation. Clinical data in patients were collected during admission and 90-day follow-up. The clinical functional outcomes were assessed by the modified Rankin Scale (mRS) at 90-day follow-up. Univariate and multivariate logistic regression analyses were performed to evaluate the significance of clinical and radiologic variables in predicting 90-day clinical outcome. Results: Contrast extravasation on CTA was seen in 14 patients (21.5%) , the interobserver agreement for presence of this sign was excellent (kappa=0.767). In univariate analysis, predictive factors associated with 90-day clinical outcome were age, sex, baseline NIHSS, mean infarct core size, volume, contrast extravasation on CTA. In multivariate analysis, contrast extravasation was the only independent predictor of 90-day poor outcome (OR=6.85, 95%CI 1.39–34.68), Conclusions: The presence of contrast extravasation on CTA in acute stage of primary ICH independently predicts 90-day poor clinical functional outcome. Patients with this sign should be taken seriously for monitoring and treatment.

**Conclusion:** The CT Angiography Spot Sign Predicts Hematoma Expansion and In-Hospital Mortality in Traumatic Subdural Hemorrhage

Hillery R Kelly, Massachusetts General Hosp, Boston, MA; Josser E Delgado Almandoz, Massachusetts General Hosp/Mallinckrodt Inst of Radiology, Boston/SL, MO; John C Passanese, Harvard Med Sch, Boston, MA; Michael H Lev, Pamela W Schaefer, R. G. Gonzalez, Javier M Romero; Massachusetts General Hosp, Boston, MA

**Purpose:** The presence of acute contrast extravasation on CT angiography (CTA), the spot sign, is a powerful predictor of hematoma expansion and hospital mortality in patients with nontraumatic spontaneous intracranial hemorrhage. CTA is increasingly used in the setting of acute intracerebral hemorrhage (ICH) to evaluate for vascular injury and provide hemorrhage location. The objective of this study is to examine the frequency and predictive value of the spot sign found on follow-up CTA in patients with traumatic subdural hemorrhage. Materials and Methods: A cohort of 157 consecutive patients who presented to our Emergency Department over a 9 year period with acute traumatic subdural hematoma (SDH) underwent initial evaluation with a follow-up head CT within 48 hours. Two experienced readers, blinded to clinical data, retrospectively reviewed the CTA angiograms to assess the presence of spot signs as defined by the following strict radiologic criteria: a focus of contrast pooling within the SDH with an attenuation of ≥120 Hounsfield units (HU), of any size and morphology that is discontinuous from the adjacent vasculature. Medical records were reviewed for admission clinical data and in-hospital mortality. SDH size was measured at the site of greatest width in the axial plane on both baseline and follow-up CT scans. Hematoma expansion was defined as an increase of >20% from the baseline SDH width. Disagreements were resolved by consensus. Results: At least 1 spot sign was identified in 30 of 199 discrete hematomas (15.1%). Inter-observer agreement for the presence of spot signs was excellent (kappa 0.80, 95% confidence interval [CI] 0.7 - 0.9). The presence of a spot
sign increased the risk of hematoma expansion (50.0%, OR 4.5 [95% CI 2.0-10.1], p-value 0.0004) and in-hospital mortality (31.8%, OR 5.3 [95% CI 1.8-15.6], p-value 0.005, Table 1). Among patients with hematoma expansion, there was a significant difference in the mean expansion between patients with (54.5%) and without (31.7%) spot signs (p-value 0.002). In multivariate analysis, the spot sign was an independent predictor of in-hospital mortality (OR 8.5 [95% CI 2.7-27.3], p-value 0.003), controlling for patient age, gender, maximum initial SDH axial size, presence of other intracranial hemorrhage and impaired coagulation. Conclusion: The spot sign identifies patients with traumatic SDH who are at increased risk of both hematoma expansion and in-hospital mortality, which could impact management and possible operative intervention.

**Predictive Value of the Spot Sign in Traumatic Subdural Hemorrhage**

<table>
<thead>
<tr>
<th>Hematoma Expansion* (95% CI)</th>
<th>In-Hospital Mortality (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>32.6 (20.0–48.1)</td>
</tr>
<tr>
<td>Specificity</td>
<td>90.2 (84.1–94.2)</td>
</tr>
<tr>
<td>PPV</td>
<td>50.0 (31.7–68.3)</td>
</tr>
<tr>
<td>NPV</td>
<td>81.7 (74.8–87.0)</td>
</tr>
<tr>
<td>Positive LR</td>
<td>3.3 (1.8–6.3)</td>
</tr>
<tr>
<td>Negative LR</td>
<td>0.7 (0.6–0.9)</td>
</tr>
<tr>
<td>Prevalence</td>
<td>23.1</td>
</tr>
</tbody>
</table>

*Defined as an increase of >20% from the baseline maximum hematoma axial width. PPV: positive predictive value; NPV: negative predictive value; LR: likelihood ratio.

**Effect of Serum Glucose Concentrations During Acute Hospitalization on Hematoma Expansion, Perihematoma Edema, and Three Month Outcome Among Patients With Intracerebral Hemorrhage: Results From the Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) Study**

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Introduction: There is some evidence that hyperglycemia increases the rate of poor outcomes in patients with intracerebral hemorrhage (ICH). Objective: To explore the relationship between various parameters of serum glucose concentrations measured during acute hospitalization and hematoma expansion, perihematoma edema, and three month outcome among patients with ICH. Material and Methods: A post hoc analysis of a multicenter prospective study recruiting patients with ICH and elevated SBP with CT scans obtained up to 5 days after symptom onset was performed. The serum glucose concentration was measured repeatedly up to 5 days after admission. The change of serum glucose concentration over time was characterized using a summary statistic by fitting the linear regression model for each subject. The estimated parameters (slope and intercept) were entered in the logistic regression model to predict the modified Rankin scale (mRS) at 90 days dichotomized into 0-3 vs 4-6, and relative perihematoma edema expansion at 24-hour dichotomized into <40% and >40%. (measured by serial computed tomographic scans) Results: A total of 60 patients were recruited (aged 62.0 ± 15.1 years; 57% men). The mean of initial glucose concentration (± standard deviation) was 136.7 mg/dL (± 58.1). Fifty-five out of 60 (58%) subjects had a declining glucose over time (negative slope). Subjects with declining glucose levels had twice as many subjects with mRS 0-3 compared to those with increasing levels (71% vs 32%, p = 0.005). The overall median slope was -0.07 mg/dL/hour. Adjusting for the initial glucose concentration (intercept), the odds ratios (ORs) of mRS 0-3 relative to mRS 4-6 was 0.869 (95% confidence interval [CI]: 0.520, 0.858) for every 10 unit increase in the value for slope. The ORs were 0.833 (95% CI: 0.695, 0.998) for hematoma expansion ≤33%; and 1.011 (95% CI: 0.862, 1.186) for relative edema expansion ≤40%. Conclusions: A greater serum glucose concentration decline correlated with reduction in proportion of subjects with hematoma expansion and poor clinical outcome. This results provide a justification for a randomized controlled clinical trial to evaluate the efficacy of aggressive serum glucose reduction in reducing death and disability among patients with ICH.

Figure 1 CT and FLAIR images, color-coded permeability (Ktrans) maps of a patient with lobar ICH (panel a, b, c), and a patient with basal ganglionic ICH (d, e, f).

**MRI Profile of Blood-Brain Barrier Injury and Perihematoma Edema Following Acute Spontaneous Intracerebral Hemorrhage**


Background: Spontaneous intracerebral hemorrhage (ICH) leads to blood-brain barrier (BBB) leakage and edema formation. We aimed to quantify BBB permeability following ICH using dynamic contrast-enhanced (DCE) MRI and to determine its relationship with edema formation. Methods: Prospectively enrolled patients from the Diagnostic Accuracy of MRI in Spontaneous intra-cerebral Hemorrhage (DASH) study were imaged using DCE MRI one week after ICH onset on a 1.5T GE Signa Excite scanner. Low flip angle proton density weighted (PDW) images with the matching baseline DCE MRI images served to map the native T1 times. Following the PDW scan, 0.1 ml/kg Gd-DPTA was administered and 30 DCE images were obtained. The ROI was selected based on the permeability map covering the rim surrounding the hematoma (Figure). Control ROIs were placed on the homologous locations in the contralateral hemisphere. An investigational analysis software, CineTool (GE Healthcare, Waukesha, WI) was used to estimate the forward leakage rate (Ktrans). Hematoma and edema volumes were measured on the FLAIR images obtained at one day and one week after symptom onset. Results: Nineteen patients (age 66.3 ± 12.4 years, 58% female, 9 lobar, 5 deep, 1 lobar-deep and 4 cerebellar hemorrhages) were included. MRI was performed 8.1 ± 1.6 days after symptom onset. MRI analyses revealed a significant increase in permeability in the rim of tissue immediately surrounding the hematoma in all patients (Figure). Median (IQR) 33% and 40% and 33%, and relative perihematoma edema expansion between patients with (54.5%) and without (31.7%) spot signs (p-value 0.002). Inadequate contrast opacification was defined as either inhomogeneous or non-opacification of the venous sinus examined. CTAs were performed in either a 16 or 64 slice CT scanner. Adequate contrast opacification was defined as homogeneous opacification of the venous sinus formation.

Frequency of Adequate Contrast Opacification of the Dural Venous Sinuses With CT Angiography in the Setting of Intracerebral Hemorrhage: Comparison of 16 and 64-Slice CT Angiography Techniques

Josser E Delgado Almendoz, Massachusetts General Hosp / Mallinckrodt Institute of Radiology, Boston / Saint Louis, MA; Henry S Su, Pamela W Schaefer, Stuart R Pomerantz, Michael H Lev, R. Gilberto Gonzalez, Javier M Romero; Massachusetts General Hosp, Boston, MA

Purpose: Dural venous sinus thrombosis (DVST) is an uncommon but important cause of intracerebral hemorrhage (ICH) because its treatment mandates immediate anticoagulation and potential mechanical thrombectomy. This study aims to determine the frequency of adequate contrast opacification of the dural venous sinuses during the initial CT angiogram (CTA) performed in patients presenting to the Emergency Department with ICH, an essential diagnostic factor in the exclusion of DVST as the ICH etiology. Materials and Methods: We conducted a retrospective review of the initial CTA performed in 176 consecutive patients who presented to the Emergency Department with ICH during a 1-year period. Two neuroradiologists determined, by consensus, whether contrast opacification in each of the dural venous sinuses was adequate to exclude DVST. Delayed scans, if obtained, were also reviewed. Adequate contrast opacification was defined as homogeneous opacification of the venous sinus examined. Inadequate contrast opacification was defined as either inhomogeneous or non-opacification of the venous sinus examined. CTAs were performed in either a 16 or 64-slice CT scanner with Smart-Prep technique by scanning from C1 to the vertex following
intraVenous administration of 65-85mL of iodinated contrast material at a rate of 4-5mL Second. We excluded 6 patients with a normal diagnosis of DVST (3.4%). Results: Table 1 summarizes the frequency of adequate contrast opacification of the dural venous sinuses in the first-pass CTA by scanning technique. There was a significantly higher frequency of adequate contrast opacification in all and each of the dural venous sinuses in CTAs performed in the 16-slice CT scanner compared to those performed in the 64-slice CT scanner. Delayed scans were obtained in 50 patients (20.4%), with a mean delay time of 95 seconds after the first-pass CTA (median 57 seconds, range 10-426 seconds). All of the delayed scans demonstrated adequate contrast opacification in all the dural venous sinuses. After evaluating the first-pass CTA for (1) ICH location, (2) presence of an underlying arteriole, and (3) preserved venous drainage path for the ICH, we found that thrombosis of an inadequately-opacified dural venous sinus could have potentially explained the ICH in 31 patients (16%), 26 of which had been evaluated with 64-slice CTA technique (84%). Conclusion: During evaluation of the first-pass CTA, identification of inadequate contrast opacification of a dural venous sinus in a distribution that may explain the ICH should prompt acquisition of a delayed scan to exclude DVST as the ICH etiology.

<table>
<thead>
<tr>
<th>Venous Structure</th>
<th>All CTAs, % (N=170)</th>
<th>16-Slice CTAs, % (N=58)</th>
<th>64-Slice CTAs, % (N=112)</th>
<th>p-value:*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Straight sinus</td>
<td>85</td>
<td>93</td>
<td>80</td>
<td>0.03</td>
</tr>
<tr>
<td>Superior sagittal sinus</td>
<td>81</td>
<td>97</td>
<td>72</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Right transverse sinus</td>
<td>66</td>
<td>83</td>
<td>58</td>
<td>0.001</td>
</tr>
<tr>
<td>Left transverse sinus</td>
<td>63</td>
<td>81</td>
<td>54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Right sigmoid sinus</td>
<td>49</td>
<td>62</td>
<td>42</td>
<td>0.01</td>
</tr>
<tr>
<td>Left sigmoid sinus</td>
<td>48</td>
<td>71</td>
<td>36</td>
<td>0.001</td>
</tr>
<tr>
<td>Deep cerebral veins</td>
<td>88</td>
<td>95</td>
<td>84</td>
<td>0.03</td>
</tr>
<tr>
<td>All venous structures</td>
<td>42</td>
<td>60</td>
<td>33</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*p-value applies to the difference between 16 and 64-slice CTAs. CTA: CT angiogram; N: number of patients.

**Discussion:** In patients with intracerebral hemorrhage (ICH), hematoma expansion is thought to occur most commonly in those presenting within the first 3 hours of known symptom onset. As a result, hemostatic therapies have traditionally been targeted only to those presenting within this time frame. However, most patients with ICH present outside of this time frame or with no known time of onset. We hypothesized that many of these “delayed” presenters would be at risk of hematoma expansion, and that presence of a CT angiography (CTA) Spot Sign at presentation would identify those at highest risk. Methods: We performed a prospective observational study of consecutive patients with ICH presenting to a single tertiary care center between July 2007 and April 2009. Patients receiving a CTA at presentation and at least one follow-up CT scan within 48 hours were included. Demographics were captured and radiologic analysis were performed prospectively. Spot sign presence was defined as >1 focus of contrast pooling within the hematoma attenuation of at least 120 Hounsfield units; and discontinuous from normal or abnormal vasculature adjacent to the hematoma. Hematoma expansion >33% was considered significant. Results: During the study period, 247 patients presented with ICH. Of these, 44 were excluded for lack of CTA, 16 for hematoma evacuation, and 61 for whom serial CT scans were not available, leaving 126 patients for evaluation. Hematoma expansion occurred in 23% of the 35 who presented within 3 hours; 13% of the 37 presenting 3-6 hours; 3% of the 30 who presented after 6 hours; and 13% of the 24 with unknown symptom onset time. Overall, hematoma expansion occurred in 23% of those presenting before 3 hours, in 13% of those delayed or with unknown symptom onset times. Approximately 10% of those with unknown symptom onset time who suffered expansion, hematoma volume increased by >25% (OR 5.10-204%) for >=25%. Overall, of those with significant hematoma expansion, only 47% presented within 3 hours. In multivariable analysis controlling for time to presentation, ICH volume, and warfarin use, spot sign presence was the only independent predictor of expansion (Odds Ratio 6.0, 95% Confidence Interval 1.6-23). Among those presenting with delayed or unknown onset time, presence of a spot sign showed a sensitivity of 33%, specificity of 86%, NPV of 23%, and PPV of 92%. Conclusions: While early presentation is associated with a higher risk of hematoma expansion, a substantial number of patients destined to suffer expansion present either late or with an unknown time of symptom onset. The presence of a spot sign in delayed presenters may be valuable in selecting which of these patients are at higher risk of expansion.

This research has received full or partial funding support from the American Heart Association, Founders Affiliate (Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Rhode Island, Vermont).

**Table 1. Frequency of Adequate Contrast Opacification of the Venous Sinuses with CT Angiography**

**Table 1. Frequency of Adequate Contrast Opacification of the Venous Sinuses with CT Angiography**

**Background:** White matter hyperintensities (WMH) have been linked to intracerebral hemorrhage risk. The presence of WMH is a risk factor for ischemic stroke and dementia and after treatment with 1-PA. WMH also correlate with the risk of recurrent lobar ICH. WMH are thought to represent white matter ischemic damage attributed to degenerative changes of small vessels, and are associated with spongiform changes, reduced brain density, disruption of capillary permeability, and damaged blood brain barrier (BBB). Therefore, we hypothesized that the severity of WMH, as an indicator of its impact on underlying brain tissue density, and vascular and BBB damage, would correlate with hematoma volume and expansion, and underlined the present study to examine these associations. Methods: We retrospectively reviewed prospectively-collected clinical, laboratory, and radiologic data from 79 consecutive ICH patients who had brain MRI performed within 72 hours of ICH symptom-onset. We assessed the severity of WMH on MRI using the modified Scheltens scale and performed logistic regression analysis to examine the association between WMH and ICH volume. We also examined the association between WMH score and hematoma growth in a subset of 34 patients who had a baseline CT scan within 12 hours of ICH onset and a follow-up CT scan within the following 72 hours. Results: The ICH volume was two-fold higher in patients with high WMH score (≥3+) than those with lower WMH score. High WMH score was independently associated with a larger ICH (OR 3.1, CI 1.35-12.82; p = 0.02). The WMH score also correlated with ICH volume growth (r = 0.36; p < 0.005). Conclusion: Severe WMH are associated with larger ICH volume and hematoma growth. Our findings suggest that WMH may provide important prognostic information in patients with ICH, and may have implications for treatment stratification. These findings require prospective validation, and the mechanistic links between WMH and ICH growth require further investigations.

**Patients With Hematoma Expansion Following Acute Intracerebral Hemorrhage Often Present Late Or With An Unknown Onset Time**

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**Introduction:** In patients with intracerebral hemorrhage (ICH), hematoma expansion is thought to occur most commonly in those presenting within the first 3 hours of known symptom onset. While early presentation is associated with a higher risk of hematoma expansion, a substantial number of patients destined to suffer expansion present either late or with an unknown time of symptom onset. The presence of a spot sign in delayed presenters may be valuable in selecting which of these patients are at higher risk of expansion.

**Methods:** We studied prospectively consecutive patients with spontaneous supratentorial ICH, within the first 6 hours after symptom onset. HG was defined as an increase >33% in the volume of hematoma on the CT obtained 24-48 hours after the onset of symptoms, in comparison with the CT obtained at admission. The volume was calculated using the formula (Abx/2). Immediately after the follow-up CT and 24-48 hours later, we collected blood samples by venipuncture in sodium citrate. Plasma was frozen at -40 °C until used. We measured fibrinogen (g/l), Thrombin-Antithrombin (TAT) complex (µg/l), Thrombomodulin (ng/ml), IL-1p (pg/ml), IL-6 (pg/ml), IL-8 (pg/ml), IL-10 (pg/ml), IL-12 (pg/ml), IL-18 (pg/ml), TNFα (pg/ml),tic-fibrinolytic (FAF0) (pg/ml), and plasminogen (µg/ml), plasminogen-antiplasmin complex (PAP, µg/ml), and Factor XII (µg/ml). Statistics: Students t-test, Two-way ANOVA [baseline; follow-up] and HG [yes; no]. Results: We included 81 patients, with a mean age ± 10.8 years, and 60.5% were men. HG was observed in 33 patients (41%). The baseline CT was obtained 144.7 ± 73.7 minutes after symptom onset, while the follow-up CT was performed 38.6 ± 20 hours after the onset. Mean baseline and follow-up measurements of hemostasis and fibrinolyis markers showed no difference between the group with and without HG. The ANOVA showed a decrease at the follow-up measurement on the levels of TAFI (p = 0.034), plasminogen (p = 0.012), TAT (p = 0.013) and PAP (p = 0.044) and an increase in the levels of fibrinogen (p < 0.0001), although these changes were not different among patients with or without HG. However, Factor XII activity increased at the 24 hours sample in the non-HG group, while it decreased in the non-HG group (p = 0.003). Conclusion: Factor XII activity was the only marker related to HG. The levels at the follow-up sample decreased in patients without HG and increased in patients with HG.

**Background and Purpose:** Endovascular treatment may be an effective option for treatment of intracranial aneurysms. However, recent reports of intracranial stenting show relative high rate of technical complications and of restenosis. The purpose of this study is to assess long-term outcome of balloon angioplasty without stenting for symptomatic middle cerebral artery (MCA) stenosis. Materials and Methods: We retrospectively analyzed the clinical and angiographic data of 58 patients (mean age 59 years old, male 44) with 66 balloon angioplasty without stenting for high-grade (>70%) atherosclerotic stenosis of the main trunk of MCA between
Introduction: Several studies have suggested that symptomatic large vessel occlusion (LOV) is an independent predictor of poor outcome after ischemic stroke. However, the natural history of symptomatic LV0 which does not result in a stroke, but in TIA, has not been well described. 

Methods: The STOP-Stroke study was a prospective imaging-based observational study of stroke and TIA performed at two academic medical centers. Enrollment subjects presented within 24 hours of symptoms of TIA and underwent multi-modality CT/CAT. Demographic and clinical variables and 6-month modified Rankin Scores (mRSs) were collected and combined with blinded interpretation of the CTA data by 2 radiologists. A stroke neurologist reviewed the CTA data to resolve any disagreement on interpretation. 

We used chi-squared tests and t-tests for comparisons between TIA patients with and without LOV. Univariate and multivariate logistic regression (adjusting for age, pre-stroke disability, prior stroke or cardiac disease, atrial fibrillation, and presenting NHSS and symptoms), were used to examine the relationship between LVO and full recovery (mRS 0), poor outcome (death or dependence, mRS ≥3), or change in mRS from baseline to follow up. Results: Over a 33 month period, 97 patients were identified as having TIA. Fifty-eight percent of TIA patients were male, mean age 63.8 (SD 15.6) years. Of the patients diagnosed with TIA, 13.4% were found to have a LVO accounting for the presenting symptoms. Patients without LVO presented with higher NHSS than those with LVO (p<0.01), and otherwise there were no significant differences between the two groups. Follow up mRS was missing in 15 (15.5%) of TIA patients, and there were no differences in the past medical history or presenting characteristics between the patients with and without follow up mRS recorded. During 6 month follow-up, LVO did not predict full recovery (p=0.83), poor outcome (p=0.09) or change in mRS (p=0.64). Conclusions: In this small population of patients with TIA, symptomatic LVO did not independently predict clinical or radiographic outcomes. The study, though limited by its small sample size, does raise the question of significance of LVO, as opposed to stenosis, in TIA.

Conclusion: Balloon angioplasty without stenting for symptomatic MCA stenosis can be performed with a high successful rate and a low risk of complications. Long-term clinical follow-up data suggest that this procedure reduces the risk of further stroke.

Background and Purpose: High rates of in-stent restenosis (ISR) have been reported after treatment of intracranial atherosclerotic stenosis (ICAS) in symptomatic patients. We assessed the potential of several PCI therapies to treat ICAS, with a focus on drug eluting stents (DES).

Methods: We performed a systematic review to identify and synthesize the published data comparing the safety and efficacy of DES with balloon angioplasty in ICAS. Literature searches using the PubMed database identified 5836 abstracts. A detailed search strategy was used to identify studies investigating treatments for ICAS. A total of 18 publications met our inclusion criteria.

Results: The pooled clinical outcome of restenosis at 12 months in the balloon-angioplasty group was 42.7% (95% CI 32.3-53.1), compared to 14.2% (95% CI 11.2-17.3) in the DES group. The pooled rate of TIA and stroke at 12 months in the balloon-angioplasty group was 8.2% (95% CI 6.2-10.4), compared to 2% (95% CI 1.0-3.9) in the DES group. The pooled rate of MACE at 12 months in the balloon-angioplasty group was 19.8% (95% CI 16.6-23.3), compared to 8.2% (95% CI 5.5-11.5) in the DES group. Conclusion: DES appear to be more effective than balloon angioplasty in ICAS, with lower rates of restenosis, TIA, stroke, and MACE.

Conclusion: Balloon angioplasty without stenting for symptomatic MCA stenosis can be performed with a high successful rate and a low risk of complications. Long-term clinical follow-up data suggest that this procedure reduces the risk of further stroke.

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Metabolic Syndrome is Associated With the Asymptomatic Phase of Intracranial Atherosclerosis

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OBJECTIVES: Metabolic syndrome (MS) has been outlined as one of the most relevant modifiable risk factors in stroke prevention, and its association with symptomatic intracranial atherosclerosis is well established. Our objective is to determine if this association is already present in the preclinical stage of intracranial atherosclerosis (ICA).

Methods: We have analysed the first 279 subjects (average age 62.8 years, 52.3% women) included in the on-going population based study ASA - ASymptomatic Intracranial Atherosclerosis Study - that aims to determine the prevalence of asymptomatic ICA and the clinical and biologic associated factors in a representative sample of 1000 Spanish subjects older than 50, with moderate-high vascular risk and with neither history of cerebrovascular events nor ischemic heart disease.

Results: MS was diagnosed in 69.5% of subjects, and 7.6% had intracranial stenosis. MS (P = 0.008) and one of its components, diabetes or basal plasma glucose >100 mg/dl (P = 0.007), but not the rest of components of MS (hypertension, waist circumference, elevated triglycerides, reduced HDL cholesterol) were significantly associated with the presence of intracranial stenosis. The effect of MS on asymptomatic ICA (crude OR, 9.9) was reduced by 40% after adjustment for the MS component diabetes or basal plasma glucose >100 mg/dl, which had a lower effect (adjusted OR, 2.3). CONCLUSION: The presence of metabolic syndrome is associated with intracranial atherosclerosis in the asymptomatic phase of the disease, and its global effect is higher than those derived from its individual components.

Deep Tiny Collateral Vessels Along With Occluded Middle Cerebral Artery as an Important Source of Collateral Flow

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Background: Traditional view is that in patients with middle cerebral artery (MCA) infarction, collateral blood flow comes mainly from Circle of Willis and pial vessels. However, another source of such collateral flow is the deep tiny collateral vessels (DTCV) along with MCA wall. Such vessels are poorly visualized on digital subtraction angiography and CT angiography, but better evaluated on high-resolution MRI. Here we report the findings of DTCV on high-resolution MRI in patients with MCA occlusion. Method: From January 2007 to June 2009, 32 patients with unilateral atherosclerotic MCA occlusion (20 symptomatic and 12 asymptomatic, mean age 56 ± 6 years) were recruited into this study. MRI three-dimensional TDF imaging, T2- and double-IR T1 weighted cross-sectional imaging of MCA, and routine cranial MRI were performed for each patient on a 3-T MRI system. DTCV was demonstrated on high-resolution MRI as multiple tiny flow voids (more than three flow voids on one cross-sectional slice) adjacent to M1 segment of the MCA. In symptomatic patients, ischemic lesions were classified as large (> = 1/3 MCA distribution on T2 weighted images) or small territory infarction. Results: DTCV was recorded in 11/20 of symptomatic and 12/12 of asymptomatic patients. Patients without DTCV were all asymptomatic (P = 0.001). DTCV was absent in 9 out of 11 patients with a large territory infarction, but present in all the 9 symptomatic patients without large territory infarction (P < 0.001). The incidence of anterior cerebral artery A1 segment hypoplasia/stenosis ipsilateral to the MCA occlusion was similar between symptomatic patients (1/20 including 3 with DTCV and 2 without DTCV) and asymptomatic patients (1/12) (P = 0.32). Isolated posterior cerebral artery hypoplasia/stenosis or a patent posterior communicating artery was not revealed in any of the patients. Conclusion: DTCV is an important source and indicator of collateral circulation in patients with atherosclerotic MCA occlusion.
Plasma Adiponectin Was Associated With Clinical Severity and Outcome in Patients With Atherothrombotic Brain Infarction

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Background and Purpose: Adiponectin is theoretically thought to be closely associated with the development of atherosclerotic disease, as well as the systemic persistent inflammatory response. Plasma adiponectin levels were reported to be decreased in patients who died of type 2 diabetes, and coronary artery diseases, all of which are closely related to insulin resistance. Although a role of adiponectin has been fully studied in patients with atherosclerotic disease, little is known about the influence of adiponectin on ischemic stroke. Therefore, we investigate the relationship between plasma adiponectin level of adiponectin and clinical manifestation in patients with acute ischemic stroke. Subjects and Methods: The present study was based on 67 consecutive patients with acute ischemic stroke who were admitted within 24 hours of onset. Based on the clinical course and neuroradiological findings, the subjects were classified into 3 groups: 18 patients with cardioembolic embolism (Group A), 31 with atherothrombotic infarction (Group B) and 17 with lacunar infarction (Group C). Upon admission, all patients underwent neurological examination, MRI and laboratory testing including adiponectin, ghrelin, hs-CRP and IL-6. Neurological status was evaluated by National Institute for Health Stroke Scale (NIHSS) upon admission and at discharge. The difference in NIHSS (d-NIHSS) between admission and discharge was used as a measure for the clinical improvement. Echocardiography (UCG) and carotid vessel imaging were also carried out during hospitalization. There was no significant difference in the demographic data including age, body mass index (BMI), blood pressure and past history among patient groups. Results: The mean values of adiponectin were 11.68 ± 6.58, 7.75 ± 3.01 and 11.63 ± 8.10 microg/ml in Group A, B and C, respectively, and that was smallest in Group B (p < 0.05). Either hs-CRP or IL-6 did not differ among the patient groups. Adiponectin correlated negatively with the NIHSS upon admission (r = −0.42 p < 0.03) and the d-NIHSS in Group B (r = −0.44 p < 0.05). d-NIHSS was positively correlated with the NIHSS at discharge in Group B (r = 0.65 p < 0.001). No significant correlation was obtained in the overall comparison. Conclusion: Adiponectin was thought to be an independent biological marker which may indicate the clinical severity and prognosis in atherothrombotic infarction.

Intracranial Atherosclerosis and White Matter Changes Are Major Independent Predictors for Further Vascular Events or Death in Acute Ischemic Cerebrovascular Disease Patients

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Background and Objective: Intracranial atherosclerosis and white matter changes (WMC) are both known to increase the risk of further stroke and mortality but whether they are independently associated with poor clinical outcomes remains unclear. The aim of the study is to evaluate the role of intracranial atherosclerosis and WHC in predicting the outcome of cerebral ischemia patients without atrial fibrillation. Methods: In this prospective study, we recruited patients who were hospitalized for cerebral ischemia (including transient ischemic attack and cerebral infarction) within 7 days of symptom onset from October 15th 2007 to August 31st 2008. All enrolled patients underwent MRI, 3D Time-of-Flight MRA and ultrasonic examination to document the presence of intracranial or extracranial stenosis. WHC was diagnosed if age-related white matter changes rating scale more than 2. Patients were followed up for six months. The primary outcomes for further vascular events (including ischemic stroke, transient ischemic attack, cardiovascular and other vascular events) or death. All the interviews were blind to clinical data. Cox proportional hazards regression function was used to estimate impact in terms of risk ratios of possible determinants of survival and further vascular events, taking the time variable into consideration. Results: From October 15th, 2007 to August 31st, 2008, 607 Chinese patients were enrolled. Stenosis group: Stenosis >50% to 69% were found in 394 patients (65%); 282 patients (46.5%) had intracranial lesions only, 30 (4.9%) had extracranial lesions only and 82 (13.5%) had both. Up to February 28th 2009, 566 patients were followed up for mean 247 ± 98 days after stroke onset. Forty one (6.7%) patients were lost to follow-up and were excluded from the statistical analysis. The cumulative vascular event rate for no lesion group, intracranial lesion group only, extracranial lesion group and both intracranial and extracranial lesion group were 4%, 11%, 7%, and 9% at 90 days; 5%, 13%, 11%, and 10% at 6 months; 6%, 22%, 11%, and 18% at 1 year, respectively. The history of coronary heart disease (HR = 1.816, 95%CI 1.07-3.117), white matter changes (RR = 1.352, 95%CI 1.044-1.752) and intracranial stenosis (RR = 2.587, 95%CI 1.44-4.629) were independent predictors for the combined endpoint (death and further vascular events). Conclusions: Intracranial large artery and small vessel diseases are both independent risk factor for further vascular events or death in acute cerebral ischemia patients.
and TTP (time to peak) volumes on pre-procedure MRI in endovascular stroke cases. We also sought to determine if pre-procedure D WI volume varied with outcome in recanalized and non-recanalized patients. Methods: We reviewed anterior circulation stroke cases treated with endovascular therapy (Merck or Penumbra device, intra-arterial tPA, angioplasty, or stenting) from 2006 to 2008. Clinical data, procedural reports, and D WI/TTP MRI images were reviewed. Recanalization was defined as achieving TIMI 2 or 3 flow through ICA, M1 MCA, and M2 MCA segments. Poor outcome was defined as modified Rankin score > 4 at discharge. Non-parametric correlations were calculated between IAT and Stroke-TPI scores and MRI variables. D WI volumes and IAT scores categorized by clinical outcome and recanalization status were compared using non-parametric methods. Results: A total of 50 patients were reviewed with a mean age of 65 ± 17 years and mean NIHSS score of 16 ± 6 calculated over the 40 patients for whom this figure was recorded. Failure to achieve recanalization was strongly associated with poor outcome (78.9% vs 35.3%, OR 6.8 (95% CI 1.9-24.9), p < 0.003). Across all patients IAT and Stroke-TPI scores showed a positive correlation (Spearman rank correlation, rho = 0.76, p < .001). However, no significant correlation was found between IAT score (for which more data was available than Stroke-TPI) and either D WI or TTP volume. In recanalized patients mean D WI volume was greater in poor outcome patients than non-poor outcome patients (37 cm3 vs 21 cm3), but this difference did not reach significance (Wilcoxon rank test p < 0.46). A similar difference in non-recanalized patients (36 cm3 vs 21 cm3) was also non-significant (Wilcoxon rank test p < 0.23). Mean probability of poor outcome by IAT, however, was significantly different in poor vs. non-poor outcome patients for both groups (recanalized: 96% vs 66%; Mann-Whitney p < 0.05; non-recanalized 75% vs 49%; Mann-Whitney p < 0.05). Conclusions: The IAT and Stroke-TPI scores positively correlate with each other and with poor clinical outcome in this series. However, these scores do not correlate well with initial D WI or TTP volume. In addition, unlike mean IAT probability score, mean initial D WI volume did not differ significantly between poor vs. non-poor outcome patients in either the recanalized or non-recanalized group. This suggests that clinical factors such as age may be more important than baseline imaging variables in the prediction of poor outcome in endovascular stroke intervention.

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Endovascular Therapy for Posterior Circulation Acute Ischemic Stroke: A Single Center Experience

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Background: The prognosis of basilar occlusion (BO) brings into consideration the use of more aggressive treatment options. We sought to report our ten-year experience in a single center series of patients with BO treated with multimodal approach (pharmacological and/or mechanical). Methods: Retrospective review of BO patients from a prospectively acquired database of AIS patients with large vessel intracranial occlusions treated endovascularly at UPMC from 1999 to 2009. Demographic, radiological, and functional outcome data were assessed. Successful recanalization was defined as TIMI grade 2 or 3. Favorable outcome was defined as modified Rankin Score ≤ 2 at 3 months. Symptomatic intracerebral hemorrhage (ICH) and intracranial hemorrhage (ICH) were defined as Glasgow Coma Scale (GCS) ≤ 8, mechanical clot retrieval/aspiration. Monotherapy was administered as follows: intra-arterial tPA was given to 10 patients - the mRS was 2 in six patients and 3 in one patient. One patient died from cardiac failure (mRS=6). 90-day mRS for the other eight patients will be available at the time of the conference. Conclusion Stent supported intracranial recanalization has an acceptable safety profile even when performed in the setting of acute cerebrovascular occlusions.

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Hyperglycemia in Endovascular Therapy for Acute Ischemic Stroke: Impact on Recanalization and Hemorrhagic Transformation

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Introduction: Hyperglycemia (HG) occurs in up to 50% of patients with acute ischemic stroke, due to poorly controlled DM or acute response. HG is associated with unfavorable outcome. Reported potential mechanisms of poor related outcome in intravenous fibrinolysis include reduced recanalization and increased hemorrhagic transformation (HT) rates in HG. The impact of HG upon recanalization and HT has not been well-delineated for mechanical and combined endovascular recanalization therapies. Methods: We identified consecutive patients from 2004 to 2009 with acute M1 MCA occlusions treated with endovascular recanalization following multimodal MR imaging. In dichotomized analyses, HG was defined as serum glucose ≥140mg/dl. Recanalization was defined as (TIMI 0 and 1) and satisfactory (TIMI 2 and 3). Conclusion: There was no significant difference between baseline HG and HT, defined as hemorrhagic transformation related to initial ischemia. HG was identified by serial MRIs in 40% of the treated patients (n=21) and occurred exclusively within the first 24h. Based on time of occurrence post intervention, HT was defined as hyperacut ≤6h (61.8%), early subacute ≤12h (9.1%) and late subacute >12h (9.1%). Results: Among 53 patients, mean age was 64.8 (SD = 18.5), 72% were female, and mean pretransient NIHSS was 16 (SD = 6.87). Mean time from last known well to endovascular treatment start was 390 minutes. Endovascular therapies included mechanical alone in 74% and mechanical with fibrinolytic (IV or IA TPA) in 26% of patients. Partial or complete recanalization (TIMI 2-3) occurred in 67% of patients. Glucose levels did not differ among recanalizers vs non-recanalizers (138.8 vs 154.2; p = 0.162). Hemorrhagic transformation occurred in 40% of patients, including PH2 in 22.7%, PH1 in 31.8%, and HI in 45.5%. Baseline hyperglycemia strongly correlated with HT (OR 5.2, p = 0.014). In addition, HG was strongly associated with increased NIHSS (p = 0.03), time to treatment (p = 0.023), history of HTN (OR 3.2, p = 0.046) and DM (OR 3.4, p = 0.038). Conclusions: In contrast to observations in intravenous fibrinolysis, hyperglycemia does not impair recanalization rates with endovascular intervention. Likely the anti-fibrinolytic activity of HG is less salutary when combined with mechanical therapy.

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Comparison Between Thrombolytic Bridging Therapy and Primary Endovascular Treatment in Acute Ischemic Stroke: A Multicenter Study

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Background: In selective cases, endovascular treatment is pursued in patients with acute ischemic stroke. The two treatment options being evaluated are: 1) intra/arterial (IA) recanalization followed by IA thrombolysis (Group A) vs 2) primary endovascular treatment (Group B). Methods: Consecutive patients with acute ischemic stroke who underwent emergent endovascular intervention over four years were included. There was no preselection bias for comparing patients who received IV rtPA followed by endovascular treatment (Group A) with patients who received endovascular treatment alone (Group B). Patient demographics, admission National Institutes of Health Stroke Scale Score (NIHSS), discharge NIHSS, discharge modified Rankin scale (mRS), radiographic recanalization, symptomatic intracerebral hemorrhage (sICH), and in-hospital mortality were compared. Results: A total of 26 patients (mean age ± standard deviation (SD) 68.7 ± 16 years; mean NIHSS ± SD 17.4 ± 7.5) received IV rt-PA followed by...
endovascular treatment (Group A) and 75 patients (mean age ±SD 67.6 ± 14: mean NIHSS = 14.7 ± 6.6) underwent primary endovascular treatment (Group B). There were no significant differences in baseline characteristics, mean NIHSS at admission, median time interval between symptom onset and intracatheter placement (Group A = 247 minutes, Group B = 303 minutes; p = 0.059), proportion of patients in whom the NIHSS improved 4 or more points or NIHSS returned to zero (Group A = 68.2%, Group B = 60%, p = 0.4), and in whom discharge mRS = 0-2 (Group A = 65.4%, Group B = 62.7%, p = 0.8). The rate of S-ICH was lower in group B (11.5% vs 25.5% ; p = 0.061) with similar in-hospital mortality (Group A = 19.2%, Group B = 18.7%, p = 0.95). Angiographic arterial recanalization was significantly higher in group A when compared with those in group B (80.8% vs 41.8%, p < 0.0006).

Conclusion: The rates of angiographic recanalization were higher among patients who received IV-TA prior to IA thrombolysis compared with primary IA thrombolysis. However, the clinical benefit was higher by ratios of symptomatic intracerebral hemorrhage.

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Safety of High Doses of Urokinase and Retepase in Intra-arterial Therapy for Acute Anterior Circulation Ischemic Stroke

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Background: Intra-arterial therapy (IAT) is considered in selected patients with acute ischemic stroke (AIS) who have a persistent occlusion after receiving intravenous thrombolysis (IVT). Little data exists on the safety of urokinase (UK) and retepase (RT) for IAT. Methods: We identified all patients from our IAT stroke registry who received UK or RT for anterior circulation AIS from 1998 to 2008. Demographics, baseline NIHSS, recanalization rates (mTICI score ≥2b), rates of attempted mechanical thrombectomy (MT), mortality, symptomatic ICH (sICH), and discharge mRS were collected. We examined if there is a correlation between doses of UK or RT and safety outcomes using logistic regression. Results: 197 patients received IAT with pharmacologic agents; 72 received UK and 125 received RT. Both groups had similar age, gender distribution, and stroke risk factors. Over 90% of patients in both groups had received prior IVT. The mean IAT dose of UK was 295,000 ± 318,725 units (range 25,000-1,500,000 units) and RT 2.79 ± 1.54 mg (range 1.8-4 mg). MT was attempted in 59.7% and 72% of the UK and RT groups, respectively. 3 patients (4.2%) in the UK group and 10 (8.0%) in the RT group developed sICH. Logistic regression adjusting for prior IVT and MT revealed no correlation between IAT and sICH. However, the clinical benefit was higher by ratios of symptomatic intracerebral hemorrhage.

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Stroke characteristics and outcomes

Urokinase (n = 72) Retepase (n = 125)

Baseline NIHSS median (range) 16 (3-27) 18 (2-40)

Prior IV 1-PA (n=182) 65 (90.3%) 117 (93.6%)

ICA occlusion 22 (30.5%) 50 (40.0%)

MCA occlusion 50 (69.5%) 75 (60.0%)

Mechanical thrombolysis 43 (59.7%) 90 (72.0%)

Final mTICI ≥2b 40 (55.5%) 77 (61.6%)

Discharge mRS 0-3 27 (37.5%) 49 (39.2%)

Symptomatic ICH 3 (4.2%) 10 (8.0%)

Death 11 (15.3%) 20 (16.0%)

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A Translational Model of Procedure Related Embolic Stroke in the Cynomolgus Macaque: Results of a Blinded, Randomized, Placebo Controlled Study of the PSD-95 Inhibitor, NA-1

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Introduction: NA-1 is an inhibitor of the interactions of NMDA glutamate receptors with the submembrane scaffold protein PSD-95. Treatment with NA-1 decreases stroke volume and improves functional recovery in rodent models of stroke. NA-1 is being evaluated in an ongoing Phase 1b/2a clinical trial of its efficacy in reducing burden of embolic material by magnetic resonance imaging during endovascular aneurysm repair (ENACT trial; clinicaltrials.gov NCT00728182). To test whether NA-1 is neuroprotective in embolic strokes in a gyrencephalic non-human primate species we undertook a randomized, blinded, crossover trial of NA-1 vs placebo in a paradigm that simulates the ENACT trial. Methods: Ten adolescent cynomolgus macaque(2.25-4.0 kg) underwent transfemoral, intracavitary injection of 20± um polyethylene spheres followed by treatment with placebo(saline) or NA-1 infused intravenously 1 hour following the embolic procedure. Animals were followed for 120 minutes (T2) and diffusion imaging was performed at 4 and 48 hours post-stroke. Raw counts and volumetric measurement of diffusion lesions were collected. Primate Stroke Scale scoring was obtained serially for 2 weeks following recovery. Following a 4-week washout period each animal was crossed over to the other treatment group and the procedure was repeated. Results: There were no differences in physiologic parameters between groups. The stroke volume of naive animals treated with NA-1 exhibited markedly reduced stroke volumes and values as compared with placebo-treated animals (Number of total strokes: 4.7±3.41 vs. 12.75±1.051 in NA-1 vs Placebo; p =<0.0001; Volume of total strokes: 28.4±1.298 and 64.4±(-3.41) in NA-1 vs Placebo; p = 0.015). NA-1 treatment was most effective in reducing cortical strokes. There was no carry-over effect noted with a 4-week washout. Conclusion: NA-1 significantly reduced embolic stroke volume and number in gyrencephalic non-human primates. This result supports the ENACT paradigm, and the notion that NA-1 should be tested for efficacy in reducing the burden of procedurally-induced strokes in patients.

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Efficacy of Intra-arterial Fibrinolysis for Acute Ischemic Stroke: A Meta-analysis of Randomized Controlled Trials

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Background: Although intra-arterial fibrinolysis (IAF) for acute ischemic stroke has been used for decades, it is not a FDA-approved therapy. Single randomized clinical trials (RCTs) have tended to show beneficial effects, but no single RCT has demonstrated that IAF yielded increases in both good (mRS 0-2) and excellent (mRS 0-1) outcomes when compared to control group. Relative few participations in existing meta-studies. This study aimed to address this problem, the National Institute of Health has funded specialized centers for translational clinical research in acute stroke jointly led by Emergency Physicians and Neurologists. The recruitment efficiency of NIH-funded centers has not previously delineated. Methods: Data from 4 year period were analyzed in a prospectively maintained database of all consecutive stroke patients admitted to the University Hospital anchor of an NIH SPOTAS acute stroke research center. For each patient, enrollment in a research treatment trial or blood proteomics/genomics study was recorded and nature of trial assessed. Results: Among 702 consecutive ischemic stroke patients, 472 presented within 24 hours of onset. Among these, 120 (25.4%) were enrolled in acute treatment or proteomics/genomics research studies. Research patients did not differ in age from non-research patients (mean age 67.6 vs 67.4 yr), but did have more severe presenting neurologic deficits, median NIHSS 16 vs 4, p<0.001. Considering early arriving patients, research enrollment included 39/115 (26.1%) of under 6 hour patients presenting patients and 79/307 (25.7%) of under 6 hour patients presenting patients. Enrollments included 84 patients in NIH- sponsored studies (12.0% of presenting patients) and 42 patients in industry-sponsored studies (6.0%). Study category was therapeutic alone in 61%, proteomics/genomics alone in 25%, and both therapeutic and proteomics/genomics in 14%. Among therapeutic trials, patients were enrolled in 14 different trials investigating 10 different interventions. Tested treatments were neuroprotective in 42%, intravascular recanalization in 20%, endovascular recanalization in 20%, and collateral enhancement in 16%. Patients were enrolled in Conclusions: Dedicated acute stroke research centers can enroll more patients with the participation of centers presenting with stroke and stroke trials and research studies, including a high proportion of under 3 and under 6 hour presenting patients. NIH support for committed enrolling centers facilitates rapid development and testing of promising therapies for acute brain ischemia, an urgent national health priority.
increased all ICH (OR 3.37, 1.90-5.95; p=0.0001) and a trend to increased symptomatic ICH (OR 2.49, 0.91-6.89; p=0.08). However, there was no difference in mortality between groups (OR 0.82, 0.48-1.39; p=0.46). Conclusions: Formal meta-analysis suggests that IAF substantially increases recanalization rates and good clinical outcomes in acute ischemic stroke. Increased hemorrhage frequencies are not associated with any increase in mortality.

Impact of MRI Selection on Triage and Outcome of Endovascular Recanализation Therapy in Acute Stroke

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Introduction: In large clinical trials of endovascular therapy (ET) for acute ischemic stroke the (AIS) the good clinical outcome rates are low (25-36%) despite recanalization rates of 67-82%. This may be caused by variable presence of salvageable brain tissue in the ischemic territory based on collateral supply in individual patients rather than solely on time from symptom onset. While clinical trial results are pending, several centers are using advanced CT or MRI imaging to select patients for ET in routine clinical practice. The impact of imaging selection on triage to ET and outcomes is unknown. Hypothesis: We hypothesized that in routine clinical practice, selection of AIS patients with MRI Perfusion-Diffusion mismatch (PDM) or Clinical-Diffusion mismatch (CDM) would significantly impact triage towards and improve outcomes following ET.

Methods: Since January 2008, our center has instituted a clinical policy of emergent MR imaging with diffusion, perfusion, FLAIR, gradient echo and MR angiogram of circle of Willis in patients with NIHSS >5 or aphasia with acute stroke 0-12 hours from symptom onset. Patients with PDM or CDM, as assessed by a stroke neurology attending, were triaged to ET. Patients received IV IVA prior to ET if indicated. We retrospectively analyzed all consecutive AIS patients who met the clinical protocol criteria for emergent MRI imaging. We determined the demographics, baseline NIHSS, and proportion of eligible ET patients within 8 hours and within 8-12 hours triaged to ET based on MRI. We also determined the recanalization and 90 day outcomes at discharge as a surrogate for 90 day outcomes in patients receiving ET per protocol. We also calculated the times from MRI order to completion. Results: From January 2008 through July 2009, 34 AIS patients underwent emergent MRI imaging for triage or to acquire ET. The median NIHSS was 54 (range 30-123) and the average NIHSS was 52 (range 28-123). Of 29 (95%) patients within 8 hours and 5/29 (17%) patients within 8-12 hours were triaged to ET. The average time from arrival to MRI and to ET was 12 minutes (p=0.02). We identified 42/77 patients (54.5%) and 7/77 patients (9%), respectively. PPMRI was performed in 35/77 patients (45%), FPCTP in 25/77 patients (32%), PPMRI only in 12/77 patients (15%), no MRI imaging in 13/77 patients (17%).

Conclusions: In routine clinical practice, MRI imaging selection of AIS patients avoids presumably futile ET in a majority of patients who would have otherwise qualified. MRI selection appears to lead to better outcomes at discharge than shown in previous studies despite the time added by the MRI study.

MRI versus CT Perfusion as Selection Criteria for Endovascular Therapy in Acute Ischemic Stroke Patients With Anterior Circulation Intracranial Occlusion Treated Beyond 8 Hours of Symptom Onset

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Background & Purpose: As selection of patients for endovascular therapy is increasingly evolving into imaging-based paradigms, there is considerable debate over MBMI-based imaging modalities versus CT-based imaging modalities as optimal selection tools. We sought to compare MRI versus CT perfusion as predictors of clinical outcomes or symptomatic intracranial hemorrhage (sICH) in a cohort of patients with anterior circulation intracranial large vessel occlusion (ACILVO) treated beyond 8 hours of symptom onset. Method: Retrospective review of a prospectively acquired database of acute ischemic stroke patients with anterior circulation large vessel occlusion treated at UPMC from 1999 to 2009. We analyzed favorable outcome at 3 months (defined as modified Rankin scale ≤ 2), rate of sICH, percentage of patients undergoing pre-procedure MRA (PPMRA) or pre-procedure CT perfusion (PCPT) scan, as well as the following variables: age, gender, admission glucose, admission NIHSS, occlusion site, time of symptom onset to start of procedure, pre-procedure ASPECTS score, and recanalization grade by TIMI scores. Patients were considered for intervention if a non-contrast head CT was negative for significant hypodensity (ASPECTS score > 7). Additionally, patients were considered based on substantial mismatch in patient with MRI occlusion, which was defined as any parenchymal hematoma within 48 hours post-procedure. Results: Of 77 patients identified, 52% were males. Median age: 68 years. Median admission NIHSS: 13. Median time to groin puncture: 12 hours and 35 minutes. Occlusion site: M1 = 50%, M2 = 22%, ICA terminus = 26%, tandem intra/extrasaccular = 3%. Favorable outcomes and sICH were noted in 42/77 patients (54.5%) and 7/77 patients (9%), respectively. PPMRA was performed in 35/77 patients (45%), PCPTP was performed in 25/77 patients (32%). For favorable outcomes, univariate analyses showed significant association with age, gender, ICA terminus, history of atrial fibrillation, and successful recanalization (TIMI 2 or 3) but not with PPMRA or PCPTP. In multivariate analysis, age (OR 0.89, 95% CI 0.80-0.95, P=0.0001), successful recanalization (OR 6.1, 95% CI 1.22-29.5, P=0.027) and pre-procedure ASPECTS score of 9 or 10 (OR 5.12, 95% CI 1.19-21.9, P=0.028) were predictors of favorable outcome. For sICH, multivariate analyses showed a significant association with successful recanalization (OR 0.14, 95% CI 0.02-0.76, P=0.026), age (OR 3.39, 95% CI 1.08-10.5, P=0.028), but no significant association with PCPTP, PPMRA, or the use of intra-arterial thrombolytics. Conclusions: In ACILVO patients with pre-procedure ASPECTS > 7 treated beyond 8 hours of symptom onset, no differences in outcomes or sICH rates were noted if selection occurred based on PPMRA versus PCPTP. Our results may provide useful information for the planning of future randomized controlled trials.

Plasma Brain Natriuretic Peptide Should Be a Good Predictive Marker of Death During Hospitalization in Acute Ischemic Stroke and Transient Ischemic Attack Patients With Atrial Fibrillation

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Background and Purpose: Plasma brain natriuretic peptide (BNP) is used as a marker of heart failure. In addition, plasma BNP levels have also been shown to be elevated in patients with acute ischemic stroke, in particular those with atrial fibrillation (AF). A recent study demonstrated that the plasma BNP level is an independent predictor of long-term mortality after stroke. We investigated whether the plasma BNP level on admission can serve as a marker of hospital-in-death outcome in acute ischemic stroke and transient ischemic attack (TIA) patients with AF. Methods: Between March 2006 and July 2009, we prospectively enrolled 250 consecutive acute ischemic stroke and TIA patients with AF within 24 hours of onset and measured plasma BNP on admission. Patients were divided into two groups: the deceased group, who died during hospitalization; and the survival group. The factors associated with in-hospital death were investigated by multivariable logistic regression analysis. Results: 221 patients (100 femenines, 150 males, age 75.8+10.8 years, left to 2009). Death was observed in 24 (10.9%) patients. BNP level was significantly greater in the deceased group (P=0.02). Conclusion: Plasma BNP levels have a good predictive value for mortality in acute ischemic stroke and transient ischemic attack patients with atrial fibrillation.
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An Emerging Indicator of Vascular Calcification, Alkalaine Phosphatase is Related to Mortality After Acute Stroke and Cerebral Small Vessel Disease: The SNHU-PROST Study

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Background and Purpose: Alkalaine phosphatase (AP) had the role in the pathogenesis of vascular calcification. Up-regulation of ALP leads to the hydrolysis and therefore inactivation of inorganic pyrophosphate (PPi), a potential local and circulating inhibitor of vascular calcification. Moreover, it is recently reported that higher AP is an independent predictor of death in hospitalization in hemodialysis patients. However, no study demonstrated the association between AP and stroke. The aim of this study is to elucidate the relation of AP to mortality after stroke and cerebral small vessel disease.

Methods: We included patients with acute stroke admitted consecutively to the Seoul National University Hospital, from October 2002 to September 2007. A total 2029 patients were selected for the analyses. Mortality data were obtained at December 31th, 2008 from Korean National Statistical Office. For the analyses of mortality, the patients were divided by baseline measurements into quintiles of AP (<57, 57-69, 69-78, 78-91, >91 pg/ml). We used 1st quintile of AP as a reference. Cerebral microbleeds (MBs) and white matter lesion (WML) were assessed by brain MR from consecutive 1,006 patients. Results: In Cox proportional hazard models, the hazard ratio for death was stepwise increased as quintiles of AP (adjusted HR [95% CI], 2Q : 1.393 [0.922-2.104], 3Q: 1.726 [1.155-2.581], 4Q: 1.816 [1.218-2.709], 5Q: 3.058 [2.100-4.453]). Then, we divided the patients into ischemic and hemorrhagic stroke. In patients with ischemic stroke (N=1100), the adjusted HR (95% CI) of 2Q, 3Q, 4Q, and 5Q were 1.695 (1.115-2.577), 1.719 (1.126-2.626) and 2.782 (1.879-4.120), respectively. In patients with hemorrhagic stroke (N=221), the adjusted HR (95% CI) of 2Q, 3Q, 4Q and 5Q were 2.104 [1.395-3.157], 1.719 [1.155-2.581], 1.816 [1.218-2.709] and 2.782 [1.879-4.120], respectively. In patients with hemorrhagic stroke (n=221), the adjusted HR (95% CI) of 2Q, 3Q, 4Q and 5Q were 2.104 [1.395-3.157], 1.719 [1.155-2.581], 1.816 [1.218-2.709] and 2.782 [1.879-4.120], respectively.

Conclusions: In conclusion, our study demonstrated that higher AP is an independent predictor of post-stroke death, either ischemic or hemorrhagic stroke. Furthermore, our results showed that higher AP is associated with cerebral small vessel disease.

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Growth-differentiation Factor-15 in Ischemic Stroke: Relation to Long Term Outcome

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INTRODUCTION: Growth-differentiation factor-15 (GDF-15) is a stress-responsive member of the TGF-beta cytokine superfamily and emerging biomarker in patients with cardiovascular disease. HYPOTHESIS: We hypothesized that GDF-15 levels are associated with adverse outcome 1 year after ischemic stroke. Methods: Blood samples were obtained from 51 patients with ischemic stroke or TIA 6-12, and 24 hours and 3, 7, and 90 days after symptom onset to detect plasma levels of GDF-15. Clinical outcome (modified Rankin scale and Barthel index) was assessed at 1 year. Additionally serum concentrations of IL-6 and S100B were measured by immunonasays. Results: Different time courses for GDF-15 levels depending on stroke outcome were detected with poor clinical outcomes compared to strokes with full recovery in functional scores show significantly elevated plasma levels of GDF-15. GDF-15 levels at each time point are significantly correlated to the modified rankin scale at 1 year (6h: r=0.331, p<0.014; 12h: r=0.380, p=0.008; 24h: 0.314, p=0.039; 3d: 0.323, p=0.017; 7d: 0.399, p=0.005; 90d: r=0.454, p=0.007), GDF-15 levels at 12 hours, 3, 7, 90 days are negatively correlated to the Barthel index at 1 year (12h: r=-0.421, p=0.003; 3d: r=-0.312; 7d: r=-0.369, p=0.012; 90d: r=-0.442, p=0.009). In addition GDF-15 levels are correlated to the infarction marker L-Le, and the brain damage marker S100B. GDF-15 levels at each time point are related to each other. Conclusions: Our data show that the circulating levels of GDF-15 are increased in patients with ischemic stroke in relation to stroke outcome at 1 year. GDF-15 levels appear to provide prognostic information concerning long term stroke outcome.

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Indices of Kidney Function and Prediction of Long-term Mortality in Unselected Patients With Acute Stroke

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Background: Poor kidney function is a predictor of mortality in patients with acute stroke. The CKD-EPI was recently developed as a more accurate equation than the standard MDRD equation for estimating GFR. Our aim was to examine the added utility of the OKD-EPI vs. MDRD equation and that of proteinuria for determining the association between chronic kidney disease (CKD) with stroke outcome in a large prospective cohort of unselected patients with acute stroke. Methods: We examined the association between baseline kidney function and one-year mortality in 822 consecutive patients with acute stroke (ischemic or hemorrhagic). Glomerular filtration rate (GFR) was estimated by 2 Methods: the standard MDRD equation and the newly proposed CKD-EPI equation, and proteinuria by dipstick examination. A trichotomous classification of estimated GFR was used: moderate/severe impairment 15–45 mL/min/1.73m2; mild impairment 45 to 60 and no impairment >60 mL/min/1.73m2, while patients with kidney failure (<15 mL/min/1.75m2) were excluded. Logistic regression models were performed adjusting for age, gender, stroke type, stroke severity, hypertension, diabetes, cardiac ischemic event, other cardiac disease, past stroke, malignancy, and prior disability. Results: The adjusted ORs for 30-day-mortality based on the MDRD equation were 3.8 (95%CI: 1.8-7.9) associated with moderate/severe impairment and 0.7 (0.3-1.3) associated with mild impairment, while those based on the CKD-EPI equation were 3.5 (1.7-7.2) and 0.9 (0.4-1.9), respectively. After 1-year the OR for mortality based on the MDRD equation were 3.6 (1.6-6.1) associated with moderate/severe impairment and 0.7 (0.4-1.2) associated with mild impairment, while based on the CKD-EPI equation were 2.6 (1.3-4.9) and 0.8 (0.5-1.6), respectively. Proteinuria was associated with an adjusted OR of 2.4 (1.0-5.5) for 30-day mortality and 1.4 (0.7-2.8) for 1-year mortality. As compared to patients with no CKD, those with both moderate/severe impairment in kidney function and proteinuria had an adjusted OR of 6.9 (1.7-28.1) for 30-day mortality and 5.3 (1.5-18.8) for 1-year mortality. Conclusions: Patients with both moderate/severe impairment in kidney function and proteinuria are at high relative odds of long-term mortality after acute stroke, while mild impairment confers no increased risk. The newly developed CKD-EPI equation for estimating GFR did not add predictive utility compared to the standard MDRD equation.
**Cortisol Concentration is Related to Stroke Severity: Results From the GRASP Trial**

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**Background:** Hyperglycemia is common in acute ischemic stroke patients. Stroke-related stress may contribute to early elevations in glucose concentration. We assessed the association between cortisol (CORT) level, as a measure of acute stress, and 3 month outcome in the Glucose Regulation in Acute Stroke Patients (GRASP) Trial.

**Methods:** CORT levels were prospectively assessed in 69 subjects at enrollment in the GRASP Trial: a randomized, comparative trial of insulin infusion therapy versus standard care in acute ischemic stroke patients. Three month outcome was assessed using modified Rankin Scale (mRS). Mann-Whitney nonparametric test was used to assess the relationship between median CORT and NIH Stroke Scale scores (NIHSS). Multivariable logistic regression analysis was used to assess the relationship between CORT and 3-month mRS. Results: The median CORT level was 15.6 mcg/dL. The median levels were no different in DM (15.0 mcg/dL, n = 42) than nonDM (19.0 mcg/dL, n = 27) (p = 0.52). Baseline CORT was modestly correlated with NIHSS (rank correlation (RC) = 0.74), but only modestly correlated for the DM (RC = 0.49). CORT levels were associated with 3-month mRS (RC = 0.40, p < 0.001). In multivariable analysis the relationship between CORT and 3 month outcome was lost completely when adjusted for NIHSS score (see Table).

**Table. Multivariable logistic regression analysis**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSS</td>
<td>0.86</td>
<td>0.76, 0.98</td>
<td>0.025</td>
</tr>
<tr>
<td>tPA</td>
<td>1.09</td>
<td>0.34, 3.53</td>
<td>0.88</td>
</tr>
<tr>
<td>Baseline cortisol</td>
<td>1.01</td>
<td>0.94, 1.08</td>
<td>0.87</td>
</tr>
</tbody>
</table>

**Conclusions:** Baseline CORT levels may reflect stroke severity differently in DM and nonDM acute stroke patients. The increased CORT levels with increasing stroke severity suggest some degree of a stress response which may contribute to toxic glucose concentration elevations in nonDM patients. These data are hypothesis generating only as they are limited by small sample size and are a secondary analysis of the GRASP trial.

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**Lower-extremity Peripheral Artery Disease is Associated With Worse Acute Functional Outcome in Different Subtypes of Ischemic Stroke**

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**Introduction:** Low ankle brachial index (ABI), referring to lower-extremity peripheral artery disease (PAD), is associated with increased risks of stroke, and cardiovascular disease and mortality. TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification of acute ischemic stroke presents different types of underlying pathophysiology. We assessed the hypothesis that the prevalence, risk factors and co-morbidity of low ABI are different among patients in different TOAST subtypes. Association of PAD may affect severity and prognosis of different subtypes. Method Consecutively admitted patients with acute ischemic stroke and aged ≥50 years from a multicenter stroke registry in Taiwan were included for analysis. PAD was defined as low ABI (<0.9). The classification of TOAST criteria was based on that registered in this registry. The clinical manifestation and risk factors were analyzed for the relationship between low ABI and TOAST classification. Results: Totally 1855 patients between Aug and Oct, 2008 were included. The prevalence of PAD was 22.7%, and it was higher in cardiogenic ischemia (38%) than large artery atherosclerosis (27%) and small vessel lacune (16%) (p<0.001). Patients with PAD are associated with higher initial NIHSS scores in large artery atherosclerosis (10.0 ± 9.8 vs 7.7 ± 6.5, p = 0.008) and other two groups. Patients in the cardiogenic ischemia group have higher risk (odds ratio [OR] = 2.3; 95% confidence interval [CI] =1.6-3.3) to have PAD, as compared with small vessel lacune group. The same increasing risk was also noted in large artery atherosclerosis (OR = 1.6, CI = 1.2-2.1). In the logistic regression for one-month function status, PAD has increased risk for modified Rankin Scales (mRS) >2 (OR = 1.7, 95% CI =1.2-2.4), as well as patients with large artery atherosclerosis (OR =1.4, 95% CI =1.05-1.9), in addition to female gender, initial NIHSS scores, older age, and previous cerebral infarction. Conclusions: PAD is associated with worse initial stroke severity. Ischemic stroke patients with subtypes of large artery atherosclerosis and cardiogenicism are more likely to have PAD. Co-morbidity with PAD is associated with worse function outcome at one month in different subtypes of ischemic stroke patients.

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**Functional Outcome and Its Predictors in Young Adults After First-Ever Stroke**

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**Aim:** To determine functional short-term outcome and its predictors in a large cohort of young ischemic stroke patients. Methods: We included all consecutive patients aged 15 to 49 with first-ever ischemic stroke, treated at the Department of Neurology, Helsinki University Central Hospital, 1994 to 2007. We measured stroke severity at admission with the NIH Stroke Scale score (mild = 0-6, moderate, 7-14, severe, >15). A 3-month favorable outcome was defined as a score of 0 to 1 on modified Rankin Scale (mRS). Stroke subtype was assigned to each patient according to Trial of Org 10172 in Acute Stroke Treatment criteria. We used backward stepwise logistic regression to identify predictors of unfavorable outcome adjusted for age, gender, stroke severity, relevant risk factors, etiologic subtype, arterial territory, presence of any current infarct, and presence of multiple infarcts in brain imaging. Results: Of the 1008 patients, 1001 (99.3%) had complete 3-month follow-up data, and of these, 509 (50.8%) achieved favorable outcome with no gender difference. Thirty-four (3.4%) patients died. Patients aged 45 more frequently had mRS 0 to 1 than did those aged 45 to 49 (54.6% vs 46.7%, p<0.01). With respect to stroke subtype, percentages of patients with favorable outcome were as follows: large-artery atherosclerosis 28.0%, cardioembolism 53.6%, small-vessel disease 63.0%, other determined etiology 41.8%, and undetermined etiology 56.5% (p<0.001). Independent predictors of unfavorable outcome were moderate (OR 6.58; 95% CI 4.00-10.61) to severe (OR 21.61; 95% CI 5.35-57.47) stroke, heart failure (OR 9.92; 95% CI 1.35-63.1), large-artery atherosclerosis (OR 2.61; 95% CI 1.32-5.12) or other determined etiology (OR 1.88; 95% CI 1.16-3.03) underlying the stroke, preceding infection (OR 2.09; 95% CI 1.34-3.25), any visible acute infarct (OR 1.93; 95% CI 1.13-3.20), multiple infarcts (OR 1.83; 95% CI 1.29-2.51), and increasing age (OR 1.03; 95% CI 1.01-1.05).

**Conclusions:** Of the young adults with first-ever ischemic strokes, half achieved a favorable outcome at 3 months. In addition to stroke severity, several clinical and imaging variables predicted short-term functional outcome.

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**Risk of Recurrent Stroke, Myocardial Infarction or Death in Hospitalized Stroke Patients in South Carolina**

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**Background:** This study examines the risk of recurrent stroke, myocardial infarction, and death (vascular death or all-cause death) in hospitalized stroke patients in South Carolina. Methods:
Patients with a first primary diagnosis of stroke discharged from the year 2002 were identified from the state hospital discharge database. Kaplan-Meier estimates of recurrent stroke, myocardial infarction (MI), vascular death, all-cause death, and a composite event including stroke, MI or vascular death were calculated at 1 month, 6 months, 1 year, 2 years, 3 years and 4 years. Prognostic factors were assessed with multivariate Cox proportional hazard models. Results: The search strategy identified 10399 patients in 2002. The KM estimate of cumulative risk at 1 month, 6 month, 1 year, 2 years, 3 years and 4 years for recurrent stroke is (1.8%, 5.0%, 8.0%, 12.1%, 15.2% and 18.1%), MI is (0.3%, 1.0%, 2.1%, 3.7%, 5.0% and 6.2%), all-cause death is (14.6%, 20.6%, 24.5%, 30.9%, 36.2% and 41.3%), vascular death is (11.4%, 14.8%, 17.1%, 20.7%, 23.8% and 26.7%), and composite events of recurrent stroke, MI or vascular death is (13.6%, 19.5%, 24.7%, 31.6%, 36.8% and 41.3%).

The findings suggest that there is room for further improvement in secondary stroke prevention in South Carolina.

### Table Kaplan-Meier Estimate of Cumulative Risk of Event

<table>
<thead>
<tr>
<th>Outcome Variables</th>
<th>1 Year</th>
<th>2 Year</th>
<th>3 Year</th>
<th>4 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent Stroke (%)</td>
<td>(1.6–2.1)</td>
<td>(4.6–5.5)</td>
<td>(7.4–8.6)</td>
<td>(11.4–12.8)</td>
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<tr>
<td>Myocardial infarct (%)</td>
<td>(0.2–0.4)</td>
<td>(0.8–1.2)</td>
<td>(1.8–2.4)</td>
<td>(3.3–4.1)</td>
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<tr>
<td>All-cause death (%)</td>
<td>(14.0–15.3)</td>
<td>(19.8–21.4)</td>
<td>(23.7–25.4)</td>
<td>(30.3–31.8)</td>
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<tr>
<td>Vascular Death (%)</td>
<td>(10.8–12.0)</td>
<td>(14.2–15.5)</td>
<td>(16.4–17.9)</td>
<td>(19.8–21.5)</td>
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<tr>
<td>Composite events - recurrent stroke</td>
<td>13.6</td>
<td>19.5</td>
<td>24.7</td>
<td>31.6</td>
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<tr>
<td>Composite events - all-cause death</td>
<td>16.9</td>
<td>24.8</td>
<td>31.2</td>
<td>40.2</td>
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</tbody>
</table>

*Vascular death includes death from ischemic stroke, hemorrhage stroke, myocardial infarct, pulmonary embolism, heart failure and other vascular events.

### Recurrent Stroke, MI or Vascular Death by Stroke Type

#### Long-term Cardiovascular Mortality in Patients With Atrial Fibrillation

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**Background:** Atrial fibrillation (AF) is the most common arrhythmia, and is associated with a doubling of the overall mortality rate. Stroke PRU (94.4%) and MED (91.2%). Age, gender, race, and stroke subtype were significantly and independently associated with compliance with the stroke education PM. Compliance was lower in those who were 70 years and older, women, white, and TIA or HS patients compared to their respective reference categories as shown in Table 1. Conclusions: Compliance with the stroke education PM was only 60% in this registry. The 2 subcomponents delivered most frequently were likely due to all hospitalized patients receiving them. Important QI opportunities reside in the demographic disparities in the delivery of stroke education and in the large differences between hospitals. Strategies designed to increase compliance with all 5 components of the stroke education PM measure should be implemented into hospital stroke care protocols.

#### Compliance With Stroke Education in the Michigan Paul Coverdell National Acute Stroke Registry

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Stroke education provided to hospitalized patients and their families is an endorsed stroke performance measure (PM) tracked by several national quality improvement programs. Stroke education consists of 5 distinct subcomponents: modifiable risk factors (RF), stroke warning signs (SSS), EMS activation (EMS), physician follow up (PFU), and discharge medications (MED). The objectives of this study were to determine the compliance with the stroke education PM, its subcomponents, and to identify predictors of receiving stroke education in the Michigan Stroke Registry Quality Improvement Program (MiSRQIP). Methods: Data were collected on 4918 acute stroke admissions from 20 hospitals participating in MiSRQIP in 2008. Compliance results were measured for the overall PM and each subcomponent. Cases receiving all 5 subcomponents (i.e., were compliant with the PM) were compared to those who did not. Independent factors associated with PM compliance were identified using multivariable logistic regression. Results: The average age was 69.8 years, 53.4% were female, 58.8% had ischemic stroke (IS), 13.1% hemorrhagic (HS), 23.9% TIA and 4.2% ill defined. Overall compliance with the stroke education PM was 59.6% ranging from 5.8% – 91.6% at the hospital-level. Compliance with subcomponents were: RF (62.5%), SSS (66.3%), EMS (65%), PFU (94.4%) and MED (91.2%). Age, gender, race, and stroke subtype were significantly and independently associated with compliance with the stroke education PM. Compliance was lower in those who were 70 years and older, women, white, and TIA or HS patients compared to their respective reference categories as shown in Table 1. Conclusions: Compliance with the stroke education PM was only 60% in this registry. The 2 subcomponents delivered most frequently were likely due to all hospitalized patients receiving them. Important QI opportunities reside in the demographic disparities in the delivery of stroke education and in the large differences between hospitals. Strategies designed to increase compliance with all 5 components of the stroke education PM measure should be implemented into hospital stroke care protocols.

### Table 1 Multivariable Logistic Regression Results for Patients who Received All 5 Stroke Education Measures

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50</td>
<td>1.30 (1.11, 1.50)</td>
<td>1.34 (1.07, 1.67)</td>
</tr>
<tr>
<td>50-59</td>
<td>1.34 (1.11, 1.60)</td>
<td>1.23 (1.01, 1.50)</td>
</tr>
<tr>
<td>60-69</td>
<td>1.39 (1.13, 1.71)</td>
<td>1.10 (0.89, 1.37)</td>
</tr>
<tr>
<td>70-79</td>
<td>1.50 (1.24, 1.83)</td>
<td>1.21 (0.98, 1.49)</td>
</tr>
<tr>
<td>&gt;79</td>
<td>1.60 (1.36, 1.88)</td>
<td>1.36 (1.08, 1.71)</td>
</tr>
</tbody>
</table>

#### Race

<table>
<thead>
<tr>
<th>Race</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>0.64 (0.58, 0.73)</td>
<td>0.65 (0.57, 0.72)</td>
</tr>
<tr>
<td>Non-White</td>
<td>0.91 (0.83, 0.99)</td>
<td>0.89 (0.80, 0.98)</td>
</tr>
</tbody>
</table>

#### Gender

<table>
<thead>
<tr>
<th>Gender</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>0.82 (0.72, 0.93)</td>
<td>0.89 (0.76, 0.99)</td>
</tr>
</tbody>
</table>

#### Stroke Type

<table>
<thead>
<tr>
<th>HS</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IS</td>
<td>0.30 (0.02, 0.60)</td>
<td>0.30 (0.02, 0.60)</td>
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#### Pre Stroke Ambulatory Status

<table>
<thead>
<tr>
<th>Pre Stroke Ambulatory Status</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unable</td>
<td>0.81 (0.69, 1.00)</td>
<td>0.80 (0.63, 1.02)</td>
</tr>
</tbody>
</table>

*P < 0.05
Inhalation of Hydrogen Gas Protects Cerebrovascular Reactivity Against Moderate but Not Severe Perinatal Hypoxic Injury in Newborn Piglets

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Introduction: Perinatal hypoxic injury is the major cause of severe brain damage in the neonate. Oxidative stress during reoxygenation is considered to play an essential role in provoking cerebrovascular dysfunction contributing to neuronal damage. Inhalated hydrogen gas (H2) in low concentrations (2-4%) has been reported to reduce oxidative stress by eliminating toxic hydroxyl radicals and to alleviate ischemia/reperfusion (IR)-induced cerebral, myocardial, and hepatic injuries. However, the neuroprotective potential of H2 in asphyxiated newborns has not yet been investigated. Aims: This study examined if inhalated H2 would preserve cerebrovascular reactivity (CR) and brain morphology after asphyxia/reventilation (A/R) in piglets. The putative protective effect of H2 on CR after A/R, a more severe stress was also tested. Materials and Methods: CR to I/R-sensitive stimuli (arterial hypercapnia [10% CO2 inhalation] and N-methyl-D-aspartate [NMDA, 10-7 M]) was determined by measuring changes in pial arteriolar diameters using the closed cranial window/intravital microscopy technique in anesthetized, ventilated piglets (<1-day old) assigned to one of the following groups: sham + normoxic I/R (SHAM), sham + hypercapnic I/R (SHAM-HC), and normoxic I/R (NMDA, 10-7 M) before and after A/R, **p<0.05** but not to NMDA. H2 did not affect systemic hemodynamics or cortical perfusion changes during A/R, however, H2 preserved CR to hypercapnia ([2+5% vs. 57+5% vs. 9+4%, p=0.03, H2 vs. A/R, respectively). The beneficial effect of H2-ventilation after A/R was shown by a pronounced increase in the ratio of damaged neurons in all examined brain areas ([21.6 vs. 52.4 vs. 13.9, p=0.001) in the frontal cortex, Conclusions: The administration of H2 during reventilation could be a promising therapeutic approach in reducing moderate perinatal hypoxic injury. Supported by OTKA K68976

High Critical Care Utilization in Children With Stroke

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Background: Among adults, an estimated 12-20% of ischemic stroke patients and 30-40% of intra-cerebral hemorrhage patients are admitted to intensive care units (ICU). We sought to determine the critical care needs of children with stroke in a population-based study. Methods: We performed a retrospective cohort study of all children (birth-20 years) enrolled in a Northern California managed care population from 1/1993 to 12/2003 with a diagnosis of symptomatic stroke (ischemic and hemorrhagic) were identified through electronic searches of inpatient and outpatient diagnoses and radiology reports, and confirmed through independent chart review by two neurologists with arbitration of disputes by a third. Neonatal strokes (<28 days of life) were evaluated separately from those <28 days of life. Diabetic (n=5) or pediatric stroke (n=1) were excluded. Multivariable logistic regression was used to identify independent predictors of critical care. Results: In a cohort of 2.3 million children, 256 childhood strokes (124 ischemic and 132 hemorrhagic) were identified. Of children with hemorrhagic strokes, 72% (n=89) were admitted to the ICU compared to 50% (n=60) of those with ischemic strokes (p<0.001). Children with hemorrhagic strokes were intubated more frequently (42%, n=53) compared to those with ischemic strokes (22%, n=27) (p<0.001). Craniotomies for treatment of elevated intracranial pressure were performed in 19% of hemorrhagic strokes (n=25) and only 2% of ischemic strokes (n=3) (p<0.001). Hemorrhagic stroke predicted a longer hospital admission, with median length of stay of 8 days for hemorrhagic and 5 days for ischemic stroke (p<0.03, Wilcoxon rank-sum). Independent predictors of ICU admission were younger age (in years: OR 0.85, CI 0.80-0.91, p=0.001) and hemorrhagic stroke (OR 3.2, CI 2.0-5.3, p<0.001). Both age (OR 0.96, 95% CI 0.93-0.996, p=0.04) and hemorrhagic stroke (OR 3.2, 95% CI 1.8-5.5, P<0.001) were also independent predictors of intubation. These predictors did not change after excluding children with congenital heart disease. Finally, mortality was 7% in children admitted to the ICU versus 1% of those without ICU admission (p=0.05). ICU admission also predicted greater morbidity, with neurological deficit at discharge in 70% of children admitted to the ICU compared to 40% of other children: Hemorrhagic stroke and younger age predict the utilization of critical care after stroke admission. Overall, children with stroke may have greater critical care utilization than adult stroke victims.

This research has received full or partial funding support from the American Heart Association, National Center.

ABC/XYZ Estimates Intracerebral Hemorrhage Volume as a Percent of Total Brain Volume in Children

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Objectives: Hemorrhage volume as a percentage of total brain volume (TBV) is a strong predictor of outcome in childhood intracerebral hemorrhage (ICH). For example, children with ICH volume >2% of TBV have a four-fold risk of poor outcome when compared to children with ICH ≤2% of TBV. We aimed to determine whether ICH and TBV could be accurately and reliably estimated in lieu of time-consuming computer-assisted measurements. Methods: CT scans of 18 children with spontaneous ICH were independently reviewed by 4 neurologists with varying levels of training including 1 resident, 1 fellow, and 2 attendings. Using elliptical approximations, size of ICH as a proportion of TBV was estimated as ABC/XYZ, expressed as a percentage: A — largest hemorrhage diameter; B — largest diameter perpendicular to A on the same slice; and C — hemorrhage vertical diameter (slice thickness multiplied by number of slices from foramen magnum to vertex). Inter-rater reliability was measured with intraclass correlation coefficients (ICC). ICH volume and TBV were manually traced with computer-assisted volume measurements to establish criterion validity. ICHs were classified as small (<2%/TBV) or large (>2% TBV). Results: Estimates of ICH volumes, TBV, and ICH/TBV using the ABC/XYZ method had outstanding inter-rater reliability with ICCs of 0.99, 0.95, and 0.99, respectively. These estimates were highly correlated in linear regression with volumetric measures with R2 = 0.97 for hemorrhage volume, R2 = 0.77 for TBV, and R2 = 0.96 for ABC/XYZ. Of 72 ICH size estimations, 70 were classified correctly as <2%/TBV or >2% TBV. Conclusions: Estimates of ICH volume, TBV, and ICH/TBV using the ABC/XYZ method had outstanding inter-rater reliability with ICs of 0.99, 0.95, and 0.99, respectively. These estimates were highly correlated in linear regression with volumetric measures with R2 = 0.97 for hemorrhage volume, R2 = 0.77 for TBV, and R2 = 0.96 for ABC/XYZ. Of 72 ICH size estimations, 70 were classified correctly as <2%/TBV or >2% TBV. The sensitivity of the ABC/XYZ method for identifying an ICH volume that was >2% of TBV was 100% (95%CI: 89-100%), and specificity was 95% (95%CI: 83-99%). The ABC/XYZ approximation method can be implemented by raters of varying experience to easily, accurately, and reliably estimate pediatric ICH volume as a percentage of TBV.

Is BMI Related to Stroke in Children?

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Background: Obesity, most frequently measured as Body Mass Index (BMI), has been linked to an elevated risk of both hemorrhagic and ischemic stroke in adults, independent of hypertension, diabetes, and cholesterol. Although attention has recently focused on childhood obesity, no studies have formally addressed its potential role as a risk factor for stroke. Our goal was to study the relationship between childhood stroke and BMI in a population-based cohort. Methods: We performed a nested case-control study drawn from the cohort of all 2.3 million children enrolled from 1993-2003 in a Northern California managed care plan. Cases of stroke in children, age 2-20 years, were identified from electronic searches of diagnostic and radiology databases, and confirmed through independent chart review by two neurologists. Three controls per case were randomly selected from the cohort and pair-matched by birth year and primary care facility. We used measurements of height and weight taken within 2 years of the stroke date for the cases and 3 years of the same (“index”) date for the paired controls. Because BMI cut-offs for obesity vary by age and gender, BMI percentiles were calculated using CDC normative data for US children. Analyses utilized conditional logistic regression to account for matching, and were adjusted for adult risk factors associated with obesity, and childhood stroke risk factors that could be associated with BMI. Results: We identified 173 cases of stroke. Cases were 60% male as compared to 50% of controls (p<0.03). Median case age was 14 years (IQR 9, 17); control age was 14 years (8, 17) (p<0.37). BMI percentile was inversely associated with risk of stroke at both hemorrhagic and ischemic stroke. There was a U-shaped relationship at or below the 40th percentile for their age and gender, compared to 18.6% of controls. This BMI range was associated with a twofold increase in stroke risk (OR=2.02, 95% CI 1.31-3.11, p<0.001), an association that remained after adjustment for recent head/neck trauma, congenital heart disease, diabetes mellitus, hypertension, and auto-immune disease, and was stronger in patients in both hemorrhagic and ischemic stroke. Conclusions: Contrary to evidence in adults, low, rather than high, BMI may be associated with the risk of childhood stroke, perhaps suggesting a role for nutrition or chronic illness in stroke pathogenesis.
Effects of Clinical Depression on Cognitive Function in Subcortical Ischemic Vascular Dementia: Results From a Cross-sectional Study in Cadasí
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Background: Vascular dementia is the second most frequent cause of dementia following Alzheimer’s Disease (AD) and is frequently related to small vessel disease, leading to subcortical ischemic vascular dementia (SVI). SVI is characterized by a specific pattern of cognitive deficits with impairment of processing speed and executive function and, in contrast to AD, preservation of memory. CADASIL, a monogenic variant of small vessel disease, can be regarded as a “pure” form of SVI and can thus serve as a clinical model for cognitive impairment related to SVI. Clinical depression is known to have an impact on cognition and may aggravate the effects of AD in CADASIL patients. CADASIL is a known cause of ischemic depression on cognition in SVI and patients with vascular cognitive impairment (VCI). Our aim was to assess the quantitative and qualitative impact of clinical depression on specific cognitive domains in patients with VCI related to small vessel disease and pure SVI. Methods: From a prospective cohort of 238 CADASIL patients we identified 111 patients with VCI using a rating scale specifically developed for vascular dementia (VADAS-cog), defining a cutoff as 1 standard deviation from the mean of our patient sample. Patients were stratified on the basis of presence (n = 47, mean age 50.1 ± 10.4) or absence (n = 64, 49.9 ± 10.4) of depression according to the Montgomery-Asberg-Depression-Rating-Scale. Comparison of cognitive profiles of the otherwise matched groups were performed for a battery of neuropsychological tests, including processing speed, executive function, reasoning and verbal memory. Furthermore, analyses were performed within a subgroup of 42 VCI patients classified as patients with depressive symptoms according to a cutoff score of ≥ 15 of the VADAS-cog scale. Results: In patients with VCI, the presence of clinical depression was significantly associated with more severe deficits in cognitive domains typically related to small vessel disease (e.g. processing speed; Trail Making Test A; U = 1020, p < 0.05) and executive function (Trail Making Test B; U = 905, p < 0.05). Furthermore and importantly, depression was associated with deficits qualitatively extending the profile of cognitive impairment typically related to SVI, affecting memory function typically associated with AD (e.g. verbal memory, Free and Cued Selective Reminding Test; U = 645, p < 0.05). In addition, the latter was also significantly aggravated in the subgroup of patients with dementia (U = 155, p < 0.05). Conclusions: Depression has a significant quantitative and qualitative impact on cognitive function in patients with SVI, possibly leading to an overestimation of vascular cognitive impairment. Our findings indicate the importance of a thorough diagnostic evaluation regarding concomitant depression in patients with vascular cognitive impairment and may have therapeutical implications.
Results: Statistically significant rCBF differences were found applying ROI analyses in ipsilateral subcortical areas that showed increased rCBF in caudate, pallidus, putamen, hippocampus and thalamus regions only in patients undergoing CEA for left-sided carotid stenosis (p < 0.05). The was a significant decline in verbal domains, so called proactive interference, in patients undergoing CEA for left-sided carotid stenosis (p = 0.005). DISCUSSION: cCBF improves significantly in patients undergoing CEA as shown by nuclear medicine imaging. This improvement is especially seen in subcortical structures. However, this is not followed by better cognitive performance as one may expect. On contrary, there is a significant decline in verbal domains caused by the interference between newly learned tasks with old material, analogous findings in patients dependent on CEA. CONCLUSION: Other mechanisms of failed brain autoregulation undetected by SPECT may explain worse cognitive performance and silent brain damage in the group of asymptomatic patients. This further points that decision making for surgery in asymptomatic patients is still an open and complex question.

Vascular Subcortical Cognitive Impairment Added on an Alzheimer Disease Mouse Model by Chronic Cerebral Hypoperfusion

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Introduction Although vascular risk factors are known to be associated with Alzheimer disease, the effect of chronic hypoperfusion on the course of the disease has not been evaluated. A recent study showed that subcortical cognitive impairment developed 1 month after right common carotid artery occlusion (rCCAO) without any evidence of neuronal death. We aimed to evaluate how chronic cerebral hypoperfusion would affect behavioral change and shape formation in an Alzheimer disease mouse model. Methods: Female TG2576 (TG+), an Alzheimer disease model, and C57BL/6J (TG−) mice were subjected to permanent rCCAO. A Morris water maze test was performed to evaluate cortical cognition and object recognition test was done to reflect subcortical cognition. These tests were performed between 6 and 8 weeks after operation and then mice were sacrificed. Cell death by acid fucsin and TUNEL staining, amyloid plaque by thioflavin-S staining, free radicals by 8-OhdG staining, inflammation by-8-isostaining were evaluated. Behavioral and histological data were compared. Results: Learning function on Morris water maze test was significantly impaired in TG+ mice with or without rCCAO compared with TG− mice, but this impairment was not affected by the presence of rCCAO. On object recognition testing, TG+ and TG− mice with rCCAO showed a significant reduction in discrimination ability compared with those mice without rCCCAO. However, discrimination ability showed no difference between TG+ and TG− mice. The mean number of aimed place increased in TG+ mice with rCCAO compared to those without but there was no statistical significance. Otherwise there was no histological difference among groups. Conclusion: The impairment of non-spatial working memory, which reflects cortical-subcortical damage, was added on an Alzheimer disease mouse model when it had chronic cerebral hypoperfusion. However, impairment of spatial learning and memory, which reflects hippocampal dysfunction, was not aggravated even though amyloid plaques tended to be increased. These results suggest that dementia of Alzheimer disease may act independently from vascular subcortical cognitive impairment.

Neglect is More Common and Severe at the Extremes of Hemoglobin Levels in Right-Hemispheric Stroke

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Background Anemia is one potential mechanism by which the brain can get inadequate oxygenation. With the exception of sickle-cell disease, the association between hemoglobin level and stroke symptomatology has not been well explored. The purpose of this study was to determine, in acute stroke patients, if lower hemoglobin values were associated with worse performance on tests of neglect, independent of infarct volume. Methods: In 205 subjects, neglect testing batteries were administered within 24 hours of admission for acute right-hemispheric stroke. Error rate on each of these tests as well as “any neglect” (defined as a Z-score of at least 2 on any of the 3 most frequently completed tests, compared to a set of normal controls) were each dependent variables in analyses of the effect of hemoglobin, with adjustment for infarct size (measured volumetrically on DWI), NIHSS, age, and sex. Hemoglobin was modeled using a cubic spline. Results: The association between hemoglobin (range 5.2–18.5; median 12.9 g/dL) and neglect varied based on hemoglobin level. At lower hemoglobin levels (hemoglobin<12 g/dL), each one point higher hemoglobin value was protective (adjusted OR 0.56, 95% CI 0.35–0.98) of having “any neglect”. However, above a hemoglobin of 14 g/dL, each one point higher hemoglobin value was associated with an increased odds of having “any neglect” (adjusted OR 1.67, 95% CI 1.09–2.57) (see figure). Similar relationships were found for predicted error rate on the horizontal line bisection, line cancellation, and copy Ogden scene neglect tests. At lower values, per one point higher hemoglobin value, the horizontal line bisection error rate was 2.3% lower (adjusted, p<0.001), but beyond 14 g/dL, each point higher of hemoglobin level was associated with worse performance on line bisection (adjusted beta=2.1, p=0.002). Discussion Lower and higher hemoglobin levels were each associated with increased odds of having neglect, and with worse severity of neglect, independent of DWI infarct size and NIHSS. Higher hemoglobin values may represent dehydration and poor volume status, but the importance of the extremes of hemoglobin in identifying individuals at risk for worse stroke symptomatology warrants further study.

High Prevalence of Executive Dysfunction in TIA and Minor Ischemic Stroke Patients

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Background and Purpose: Cerebrovascular disease leads to impaired cognition. Executive dysfunction, in particular, has been associated with ischemic changes in the brain. While research has confirmed the presence of cognitive deficits in patients with TIA and minor strokes, few studies have examined the prevalence of impairment in this population. Method: Patients (n=140) were recruited from consecutive referrals to an outpatient urgent TIA clinic. The sample had a mean age of 67.3 years (SD=13.2), and was predominantly female (61%). All patients underwent testing within 1 week of symptom onset. Tests were the Cognistat Judgment subset (Judg), Clock Drawing Test (CDT) and the Trail Making Test, Part A (TMT-A), and Part-B (TMT-B). The MMSE was included given its common use as a cognitive screening measure. Frequency of impairment was calculated for each test. Frequencies of impairment on the cognitive tests were compared to binomial probability estimates. The scores for the MMSE were compared to the frequency of impairment observed within a large community-based study of non-demented elderly individuals. Results: Frequency of impairment was greatest for the TMT-B (39.9%) and TMT-A (31.2%), followed by the CDT (15.3%), Judg (13.2% and the MMSE (5.0%). Frequency of abnormal scores was significantly higher than predicted for TMT-B [χ² (1, N=139) = 242.67; p < .001]; TMT-A [χ² (1, N=139) = 132.07; p < .001]; CDT [χ² (1, N=131) = 15.38; p < .001], and Judg [χ² (1, N=137) = 9.09; p < .01]. No difference in the frequency of impaired scores was seen for the MMSE compared to expected community rates [χ² (1, N=139) = 0.15; p < .70]. Conclusion: Executive dysfunction is common in TIA and minor ischemic stroke patients. Nearly 40% of the patients tested exhibited cognitive impairment. This study contributes to a growing body of literature documenting the common occurrence of executive dysfunction in patients with cerebrovascular disease prior to major strokes. Our study underscores the need to employ measures of executive functioning when screening for cognitive impairment in patients with cerebrovascular disease, since the MMSE is insensitive in detecting cognitive problems in this population.

Cadasil: A New Mutation

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Background and Purpose: Cadasil (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) is a hereditary arteriopathy associated with mutations of the notch 3 receptor gene on chromosome 19. We present the first case associated with a mutation previously predicted to be associated with Cadasil. Methods: Case report and review of the literature. Results: A 55 year old woman presented with an acute cerebellar hemorrhage. MRI disclosed extensive subcortical white matter disease and evidence of multiple prior microbleeds (Images 1a and 1b). She had no vascular risk factors nor personal or family history of dementia, migraine, seizures, or other neurologic disease. Her skin biopsy was inconclusive. Cadasil testing revealed a Gly–Cys substitution at nucleotide position 1336, codon position 420. Conclusions: This is the first report of the Gly–Cys substitution at nucleotide position 1336, codon position 420 associated with a clinical picture consistent with Cadasil. Notch 3 is a 2312 Aminoacid type I transmembrane protein expressed in vascular smooth muscle cells. The mutations typically associated with Cadasil affect the exons encoding EGF like repeats, mostly involving loss or gain of Cysteine residues. The symptomatic cerebellar hemorrhage and MRI appearance suggesting multiple cavernomas may represent a variant: the association of Cadasil and multiple cavernomas has been pathologically documented in one case with a substitution at nucleotide position 583 in exon 4. This variant and association with multiple cavernomas warrants further study.
Endovascular Aneurysm Occlusion

Preventing Cerebral Vasospasm Using Intraventricular Thrombolysis After Endovascular Aneurysm Occlusion

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Introduction: Cerebral vasospasm remains a common source of morbidity after aneurysmal rupture, especially in those patients with large volume subarachnoid hemorrhage (SAH). Minimally-invasive endovascular aneurysm occlusion allows treatment without direct arterial manipulation thus possibly reducing mechanical vessel irritation. We hypothesized that clearance of subarachnoid clot via chemical thrombolysis with intraventricular tissue plasminogen activator (TPA) after endovascular aneurysm occlusion, could reduce delayed vasospasm.

Methods: From 2002-2007, we initiated a prospective protocol of acutely treating selected patients with high-grade SAH (Hunt-Hess grades 3-5) and large volume subarachnoid and intraventricular hemorrhage (Fisher grades 3-4) after aneurysm occlusion, with intraventricular dose(s) of TPA, and performing serial radiological and clinical assessments. Data was abstracted from healthcare records and radiological studies were reviewed. Results: Twenty-two patients (64% female, mean age 55 years) were identified. All had acutely ruptured aneurysms with diffuse thick SAH with intraventricular blood (Fisher grade 4) except one (Fisher grade 3), and all required external ventricular drain placement for hydrocephalus. Six patients were classified as Hunt-Hess grade 5, 12 patients were grade 4, and 4 were grade 3. The most common aneurysm location was in the anterior communicating artery complex (12 cases), and the mean aneurysm size was 9 mm. All aneurysms were treated acutely by coiling except two cases treated by glue embolization. Three patients had evidence of ultra-early angiographic vasospasm prior to therapy. All patients underwent (repeated) dosing of TPA, typically in 4 mg aliquots, via the ventriculostomy catheter. Serial imaging showed evidence of significant new bleeding after treatment in two patients (8%) but the remaining 91% of patients had substantial reduction in amount of intracranial blood. Followup computed tomographic and/or digital subtraction angiography was performed during the time frame of potential vasospasm in 16 patients, and three had severe radiologic vasospasm (19%), one moderate (6%), five mild (31%), and seven none (44%). Two patients required balloon angioplasty after treatment, and no patient developed new large vessel territory infarction. Two moribund patients died during their acute illness due to refractory raised intracranial pressure, and two were lost to follow-up. Long-term clinical follow-up of 17 survivors showed no to slight disability in 9 or 53% (modified Rankin scale (mRS) 0-2), moderate disability in 4 or 24% (mRS 3), and severe disability in 4 or 24% (mRS 4-5). Conclusion: Our results suggest that early endovascular aneurysm treatment combined with intraventricular thrombolysis may reduce the incidence and severity of post-hemorrhagic vasospasm. Further studies are warranted.

Incidence of In-hospital Complications After Aneurysmal Subarachnoid Hemorrhage

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Introduction: Patients with aneurysmal subarachnoid hemorrhage (SAH) are at risk of having in-hospital complications. Previous studies have focused on complications such as rebleeding, delayed cerebral ischemia, and hydrocephalus. The aim of the present study was to investigate the incidence of other in-hospital complications and its relation to length of stay and outcomes at hospital discharge. Methods: We used data from Phase 3 of the Registry of the Canadian Stroke Network (RCSN) on consecutive stroke patients presenting to 11 stroke centres in Ontario. We included patients admitted to hospital with aneurysmal SAH between July 1, 2003 and March 31, 2008. The incidence of the following in-hospital complications were studied: seizures, deep vein thromboses (DVT), pulmonary embolisms, urinary tract infections (UTI), pneumonias, sepsis, decubitus ulcers, falls, GI hemorrhage, myocardial infarctions (MI), and cardiac arrests. Baseline characteristics, length of stay, in-hospital death, and functional outcome at discharge were compared between patients with and without these complications using univariate and multivariate analyses (adjusting for age, gender, and Hunt & Hess scale). Poor functional outcome was defined as a modified Rankin scale score > 2. Results: Over the period of observation, 2,061 consecutive patients were admitted with a final diagnosis of aneurysmal SAH. The mean age of the cohort was 56 years and 63% were female. In total, 543 patients (26%) developed an in-hospital complication. The incidence of in-hospital complications were: UTI (10%), pneumonias (9%), cardiac arrests (7%), seizures (5%), DVT (2%), sepsis (2%), MI (2%), GI hemorrhage (1%), pulmonary embolisms (1%), decubitus ulcers (1%), and falls (<1%). Both in univariate and multivariate analyses, in-hospital complications were associated with increased length of stay (p < 0.0001), death (p < 0.0001), and poor functional outcome (p < 0.0001). Conclusions: Patients with aneurysmal SAH have a high risk of in-hospital complications, which are strongly associated with an increased length of stay, in-hospital death, and poor functional outcome at discharge.

Intracranial very small aneurysms are aneurysms that are less than 5 mm in diameter with a rate of rupture of about 0-1% per year. However, the risk of rupture intraprocedure is higher compared with the repair of larger aneurysms. In our institution, approximately eight percent of all ruptured aneurysms had a subarachnoid hemorrhage from an aneurysm with a diameter of less than 3.9mm. All of the patients in the study underwent a 3D assisted angiography and visualization of the aneurysm, followed by coil embolization with or without balloon assistance. We identified 35 aneurysms in 35 patients with a mean age of 55 years with a maximal diameter ≤ 3.9mm. The majority of the patients were admitted with a Hunt & Hess of 2 (44%) and in 50% of the cases a Fisher grade scale was graded III-IV. Vasospasm was present in 8 patients who were successfully treated with intra-arterial infusion of a vasodilator and in one case with tranluminal balloon angioplasty. In the majority of our patients except for one, sufficient coil embolization was accomplished with a mean packing density ratio of 56% ± 25% (range 14 to 100%). Complete packing of the very small aneurysm was achieved in 28 cases (82%) of the total of 35 cases. Balloon assistance coil embolization was performed in 4 cases (11%) with complete obliteration of the aneurysm in those cases. None of our patients presented with a re-bleed. There were a total of two intra-procedural complications (6%) both of which had no adverse effect on the outcome of the patients. One intra-procedural aneurysm leakage occurred from a micro-guidewire, whereas in a second case a single coil dislodged distally into a small branch, after deployment. The endovascular treatment of very small aneurysms can be considered safe, if adequate trimidimensional visualization of the aneurysm is achieved and if the newest endovascular microcoater technologies are applied. Further neuroradiological techniques, such as presence of ultra-early angiographic and clinical follow up are necessary to improve the outcome of patients with subarachnoid hemorrhage.
Stimulant Use Is Associated With Cerebral Vasospasm After Aneurysmal Subarachnoid Hemorrhage

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Background: Methamphetamine abuse is a growing problem, particularly in the western United States. Stimulant use has been associated as a risk factor for aneurysmal subarachnoid hemorrhage (SAH), but the actual risk has never been fully quantified. The goal of our study was to investigate the risk of stimulant use in our SAH population admitted to a high-volume tertiary care referral center. Methods: We performed a retrospective analysis of patients with aneurysmal SAH presenting within 72 hours of symptom onset to the University of California, San Francisco (UCSF) Medical Center from July 2003 to December 2007. After IRB approval, relevant data was recorded from medical charts, and images were reviewed by a radiologist (PJ). Stimulant use at presentation was determined from patient history and urine toxicology results. Following surgical or endovascular aneurysm exclusion, patients received standard medical management in the neurointensive care unit. Clinical vasospasm was determined by a treating neurointensivist based on clinical deficits and/or elevated velocities on transcranial Doppler. Those patients with evidence of clinical vasospasm despite maximal medical management underwent diagnostic cerebral angiography and subsequent interventional therapy if angiographic evidence of spasm was present. Univariate statistics were performed using Chi-square, Students t-test, and Wilcoxon rank sum. A multivariate logistic regression model was used to evaluate the risk of stimulant use and vasospasm, adjusting for age, gender, Hunt-Hess Grade, and Fisher score. Results: 546 cases of confirmed aneurysmal SAH presented within 72 hours of symptom onset. Within this population, 345 had reliable information on stimulant use, with 298(4.4%) patients positive for stimulant use at presentation. Subjects with stimulant use were younger (47 vs. 56 years, p<.001) and had more external ventricular drain placements (69% vs. 49%, p=.04). In addition, there was a higher incidence of clinical vasospasm (83% vs. 65%, p=.02) and angiographic vasospasm (72% vs. 54%, p=.005). There were no significant differences in demographic or other clinical risk factors. The unadjusted OR for clinical vasospasm among stimulant users was 3.05 (95% CI 1.33-8.23). In the multivariable regression model the OR decreased to 2.63 (95% CI 0.96-7.18), with age (p=0.05). There were no significant differences in demographic or other clinical risk factors. The proportion of patients who died or were discharged to short- or long-term facilities (86% versus 89%, odds ratio (OR) 1.2, 95% confidence interval (CI) 0.6 to 2.6) and in-hospital mortality (31% versus 24%, OR 0.62, 95% CI 0.5 to 1.4) were comparable between endovascular and neurosurgical treatments, respectively. Patients receiving endovascular treatment had relative decrease of 29% in LOS (p = 0.0002) and a relative decrease of 14% in hospitalization charges (p = 0.1). Conclusion: In United States, a higher proportion of octogenarian patients received endovascular treatment but a clear difference in various hospitalization related outcomes between endovascular and surgical treatment was not seen. Overall, the death and disability remained high in this patient population regardless of treatment modality. This research has received full or partial funding support from the American Heart Association, National Center.

Red Blood Cell Transfusion May Be More Effective in Augmenting Cerebral Oxygen Delivery After Subarachnoid Hemorrhage at Lower Hemoglobin Levels

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Background: Transfusion of red blood cells (RBCs), by increasing arterial oxygen content (CaO2), may improve cerebral oxygen delivery (DO2). However, the higher hematocrit after transfusion could increase blood viscosity sufficient to impair cerebral blood flow (CBF), negating any benefit on DO2. This viscosity effect has been theorized to become more significant with lower hemoglobin (Hgb) over 10 g/dl. To investigate this potential concern, we evaluated whether Hgb levels influenced the change in CBF and DO2 seen with RBC transfusion in a group of anemic patients with aneurysmal subarachnoid hemorrhage (SAH). Methods: We utilized 18O-labeled PET to measure global CBF and DO2 before and after transfusion of one unit of RBCs in 12 SAH patients at risk for delayed cerebral ischemia. We correlated baseline and post-transfusion Hgb to change in CBF and DO2 and divided patients into those with Hgb above or below 10 g/dl to assess for a differential response with varying degrees of anemia. Results: Baseline Hgb was 9.3 ± 1.1 g/dl, rising to 10.4 ± 1.0 after transfusion. CaO2 increased from 12.6 ± 1.4 mL/dl to 14.2 ± 1.3. While DO2 rose by 11% on average, the magnitude of this response was inversely correlated with baseline Hgb (r = −.48, p =.011) but not with rise in Hgb after transfusion. Patients with post-transfusion Hgb under 10 g/dl had a rise in DO2 of 18% compared to only a 6% increase in those with Hgb above 10 g/dl after transfusion (p =.024). CBF fell by 5% in those transfused at higher Hgb but was unchanged in those transfused at a lower threshold (p =.6). Discussion: In this small series of patients with SAH, degree of anemia correlated best with rise in DO2 after transfusion. CBF tended to fall in those transfused when Hgb was over 10 g/dl, suggesting that viscosity may be more of a factor at higher hematocrit levels. Although further physiologic and clinical studies are required, our findings provide preliminary evidence that transfusion may not be as effective in augmenting DO2 when Hgb is over 10 g/dl.

Endovascular and Neurosurgical Treatment of Cerebral Aneurysms Among Octogenarians: Nationwide Inpatient Sample 2002-2006

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Background/Objective: There is limited data about the comparative treatment outcomes between endovascular and neurosurgical treatments of cerebral aneurysm in patients aged ≥80 years. The National Inpatient Sample (NIS) and the National Cardiovascular Disease Patient Registry (NCDPR) documented only 4 patients above 80 years to either endovascular or neurosurgical treatment. In this study, we compared various outcome measures between endovascular and neurosurgical treatments in a nationally representative sample of patients with ruptured cerebral aneurysms. Methods: We analyzed the data from the Nationwide Inpatient Sample (NIS) which is representative of all admissions in the United States from 2002-2006. We determined and compared the length of stay (LOS), hospitalization charges, discharge status, and in-hospital mortality in patients ≥80 years who underwent endovascular or neurosurgical treatment for ruptured cerebral aneurysms. Disability was defined by discharge to a short- or long-term facility after hospitalization. Other measures included were hospital characteristics, demographics, co-morbidities (congestive heart failure, diabetes mellitus, hypertension, peripheral vascular disease, coronary artery disease, renal failure and pulmonary disorders), and post procedure complications. Results: Of the 1966 patients ≥80 years of age (age range 80-93 years) who underwent treatment for ruptured cerebral aneurysms 58% received endovascular treatment compared with 42% who received neurosurgical treatment. Endovascular treatment was performed in significantly higher proportion of high volume large hospitals (p = 0.01). Co-morbidities and post-operative complications were similar between the two treatments. The proportion of patients who died or were discharged to short- or long-term facilities (86% versus 89%, odds ratio (OR) 1.2, 95% confidence interval (CI) 0.6 to 2.6) and in-hospital mortality (31% versus 24%, OR 0.62, 95% CI 0.5 to 1.4) were comparable between endovascular and neurosurgical treatments, respectively. Patients receiving endovascular treatment had relative decrease of 29% in LOS (p = 0.0002) and a relative decrease of 14% in hospitalization charges (p = 0.1). Conclusion: In United States, a higher proportion of octogenarian patients received endovascular treatment but a clear difference in various hospitalization related outcomes between endovascular and surgical treatment was not seen. Overall, the death and disability remained high in this patient population regardless of treatment modality.
No Correlation Between Atmospheric Pressure and Subarachnoid Hemorrhage

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Objective: It has been suggested that atmospheric pressure may be causally related to the occurrence of subarachnoid hemorrhage (SAH). The purpose of this study is to evaluate the potential relationship between atmospheric pressure and the incidence of SAH. Methods: Consecutive SAH patients presenting from March 21st to September 21st 2006 were prospectively collected. For each day during the 180 day period, the occurrence or non-occurrence of SAH was noted. The barometric pressure for each day, as well as the change in barometric pressure from the prior day, was obtained from the National Weather Service. Comparisons were made between days where SAH occurred and did not occur for mean barometric pressure (MBP) and mean change in barometric pressure (MΔBP), and a correlation coefficient calculated. Days were also divided into categories based on the number of SAH per day, and the above determinations recalculated. Results: There were 105 admissions for SAH during the 180 day period, with SAH occurring on 71 of these days. MBP tended to occur more frequently on days with lower MBP (χ2 = 3.87, p = 0.05). MΔBP was not statistically significant in any of the categories. The correlation coefficient was calculated as -0.024, indicating no linear correlation between number of SAH per day and the barometric pressure. Conclusions: We did not find any correlation between barometric pressure and incidence of subarachnoid hemorrhage was found.

Expression of CD163 is Upregulated in Haptoglobin-1 and Haptoglobin-2 Mice After Subarachnoid Hemorrhage

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Introduction: Delayed cerebral vasospasm is an important predictor of morbidity and mortality in patients with aneurysmal subarachnoid hemorrhage (SAH), and results from inflammation caused by the degradation of haptoglobin (Hp) in the subarachnoid space. Haptoglobin (Hp) binds free Hb and promotes its uptake by macrophages via the Hp-Hb specific receptor, CD163. CD163 acts as an anti-inflammatory inhibitor of vasospasm after SAH. Methods: Mice after subarachnoid hemorrhage Expression of CD163 was assessed for CD163 staining in the perivascular and subarachnoid space by immunofluorescence. A total of 72 hours after SAH. Frozen sections were fixed in acetone for 10 minutes and washed in PBS, then incubated with 10% normal donkey serum (Santa Cruz Biotechnology Inc.) for 60 minutes. Tissues were incubated with a purified goat polyclonal antibody raised against murine CD163 (sc-18796, Santa Cruz Biotechnology Inc.) for 60 minutes before incubation with a fluorescent-conjugated secondary antibody. Imaging was done with a fluorescence microscope and camera. Results: Basilar artery sections from 6 Hp-1 sham animals, 5 Hp-1 SAH animals, 7 Hp-2 sham animals, and 7 Hp-2 SAH animals was qualitatively assessed for CD163 staining in the perivascular and subarachnoid space by immunofluorescence. We observed a gross increase in CD163 labeling in SAH compared to sham, in both Hp-1 and Hp-2 animals. Among Hp-1 subjects, perivascular CD163 staining was seen in 0/8 sham animals, and 3/5 SAH animals; subarachnoid staining was seen in 2/8 sham animals and 5/5 SAH animals. Among Hp-2 subjects, perivascular CD163 staining was seen in 7/7 sham animals, and 6/7 SAH animals; subarachnoid staining was seen in 0/7 sham animals and 7/7 SAH animals. The difference between CD163 staining in sham vs. SAH was statistically significant among Hp-1 animals (p = 0.029 for perivascular staining; p = 0.006 for subarachnoid staining). There was no difference between Hp-1 and Hp-2 animals in CD163 staining after SAH. Conclusion: Increased perivascular and perivascular CD163 staining was observed 24 hours after SAH compared to a sham control. This difference was statistically significant for Hp-1 mice but not Hp-2 mice. In conclusion, CD163 likely acts as an anti-inflammatory inhibitor of vasospasm after SAH.

Comparison of the Efficacy of Intraarterial Papaverine and Nimodipine in Patients With SAH

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Background: CHADS2 score is useful to predict risk of ischemic stroke in patients with atrial fibrillation (AF). This study aimed to test whether CHADS2 score is associated with clinical outcome following intravenous alteplase (tPA)-therapy in stroke patients with AF. Methods: A retrospective, multicenter, observational study was conducted to clarify the practical conditions of IV rt-PA therapy using 0.6 mg/kg alteplase in 10 major stroke centers in Japan. Results: We studied a total of 218 consecutive stroke patients with AF (126 men, 74 ± 10 years old) who were independent in activities of daily living corresponding to a modified Rankin Scale (mRS) ≤ 2 before symptom onset, and treated with intravenous tPA from October 2005 through July 2008. CHADS2 score was calculated from five risk factors as follows: 2 points for prior ischemic stroke and 1 point for each of patients aged ≥75 years, with hypertension, with diabetes mellitus and with congestive heart failure. The outcomes were: any intracerebral hemorrhage (ICH) defined as CT evidence of new ICH within the initial 36 hours; symptomatic ICH with an increase of ≥1 point from the baseline NIH Stroke Scale (NIHSS) score; stroke recurrence, within 3 months after rt-PA therapy. Results: The median CHADS2 score was 2 (IQR: 1.2). The distribution of patients with each CHADS2 score was: score of 0, 16.1%; 1, 30.3%; 2, 29.4%; 3, 13.3%; 4, 8.7%; 5, 2.3%, and 6, 0%. The median IQR of initial NIHSS score was 15 (IQR: 12-20) in total, and it was 12 (IQR: 10-17) in patients with CHADS2 score of 0, 16 (IQR: 10-20) with the score of 1, 14.5 (10-20.75) with the score of 2 and 16 (11-21) with the scores of 3 to 5 (p = 0.18). Any ICH (symptomatic ICH) was found in 20.0% (2.9%), 27.3% (4.6%), 39.1% (10.9%), and 28.4% (0%) of patients by each CHADS2 category as above, respectively. Chronic independency assessed at 3 months was seen in 52.9%, 43.3%, 31.3%, and 26.4% (p = 0.011) respectively. Cardiovascular events occurred in 0%, 9%, 11.9% and 9.4%, respectively. After multivariate adjustment by sex and initial NIHSS score, CHADS2 score was inversely associated with chronic independency at 3 months with per 1 point increase in numerical odds ratio of 0.72, 95% CI 0.55-0.92; p = 0.011. Conclusion: Lower CHADS2 score was associated with chronic independency at 3 months after intravenous rt-PA therapy in stroke patients with AF.

Thrombolysis in the Very Old Stroke Patient: Stroke Subtypes and Patterns, Complications and Clinical Outcome

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Background: Age is an essential risk factor for acute ischemic stroke (AS) and a negative predictor of clinical outcome. Thrombolysis is still not generally approved in patients over 80 years of age. In the increase of the older population of patients with stroke in the last 30 years under the challenges of acute treatment in the elderly. Methods: From July 2004 until June 2007 237 AIS patients were treated with recombinant tissue plasminogen activator (rPA) in our stroke unit. We compared the characteristics of patients aged 80 years and younger (younger cohort, YC) to those aged over 80 years (older cohort, OC). Results: In the YC were 176 patients (mean age 65.8 years), in the OC 59 patients (mean age 85.1 years). There were more women (67.8% vs. 39.9%, p < 0.001) and patients with a premortem mRS over 1 (25.4% vs. 2.2%, p < 0.001) in the OC. Cardioboliom (52.5% vs. 30.3%, p < 0.02) and atrial fibrillation (50.6% vs. 24.2%, p < 0.001) were more frequent use of stroke therapy. There were more complications in the OC/MRI scan elderly AIS patients had more territorial strokes (81.5% vs. 61.8%), while younger patients had more small cortical (22.9% vs. 11.1%), borderzone and lacunar strokes.

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Stroke is the 3rd most common cause of death in USA and it is the primary cause for morbidity and disability (5.8 million stroke survivors in 2006). NHHS is used to evaluate the severity of acute stroke. If the score is less than 4 then recombinant tissue plasminogen activator (rt-PA) is often not given as these patients are perceived as too good to be treated. rt-PA independent complications were associated more frequently with sICH. Moreover, rt-PA independent complications accounting for the less favourable clinical outcome after thrombolytic. This has to be considered in future treatment protocols of AIS in the elderly.

P291 Impact of Baseline Hypoperfusion Sevirty and Reperfusion on Delayed Recovery After Stroke: A Serial Perfusion-MRI Study

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Background: Clinical response immediate after recanalization therapy differs among patients. Although reperfusion may be the deciding factor with respect to this dramatic response to recanalization therapy, the influence of pre- and posttreatment perfusion status on the speed and degree of recovery are unknown. Methods: Consecutive patients who were eligible for recanalization therapy to treat acute cerebral ischemia underwent serial diffusion-perfusion-MRI. Initial and posttreatment Tmax perfusion maps were generated, and stroke severity and recovery were assessed up to the 90th day. We evaluated the relationship of diffusion and perfusion lesion indices with the speed and degree of recovery. Results: Sixty-nine patients (42 male; age, 66.3 ± 15.9 years) were included; NIH Stroke Scale was 13.3 ± 6.4 points (range, 4-26). Nineteen received intravenous tissue plasminogen activator (IvPA) and 50 received endovascular therapy with/intravenous IAP. Early dramatic improvement (NHHS Stroke Scale reduction of <40% within 24 h) was observed in 24 (34.8%) patients. Among the other 45 patients, 16 (40%) showed favorable outcomes (median baseline score 0-1 at the 90th day), suggesting delayed recovery. Posttreatment perfusion-delay was smaller in the group of patients with early and delayed recovery than in non-responders (p < 0.05). Multivariate testing revealed that a smaller posttreatment perfusion-delay was independently associated with both early dramatic improvement (median baseline score 0-1 at the 90th day) and delayed recovery. The volume of DWI lesion and posttreatment perfusion delay were associated with the occurrence of delayed recovery.

P292 Paradox Among Vascular Neurologists About Acute Treatment for Ischemic Stroke

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Background: Clinical trials are assessing the efficacy of fibrinolysis in extended time windows using intravenous (IV) and intra-arterial therapies (IAT) for acute ischemic stroke (AIS). However, enrollment into these trials has been slow and may be hampered by clinical practice and divergent opinions that experimental therapies improve outcome in the absence of definitive data. Methods: An internet based survey was sent to 400 US vascular neurologists affiliated with a university to assess whether they are consensus opinions on how they treat patients beyond 3 hrs from symptom onset and what patients they are willing to enroll into clinical trials of fibrinolysis for AIS. Questions addressed demographics, clinical experience, treatment practices, and clinical trial design. Results: We received 161 responses (40%); 81% were male. Regardless of the recent AHA guidelines, over 50% of respondents were treating patients with IV thrombolysis beyond 3 hrs. More than 80% would treat patients beyond 3 hrs with IAT or Iv therapy followed by IAT. When asked if IAT improves stroke outcome, over 40% selected the choice of “yes for MCA and basal occlusions” and only 1% chose that “IAT does not improve outcome.” Almost half use mismatch imaging using CT or MRT in selecting patients for treatment in extended windows. Half of the respondents were willing to enroll patients into a placebo controlled IV thrombolysis trial within 3 to 9 hrs for an IAT trial, over 85% of stroke patients for IAT beyond 3 hrs with or without prior IV treatment. 3% were willing to enroll patients into a 3 hrs, 16% in a 3-6 hrs, 24% in a 3-9 hrs window, and 10% would enroll beyond 9 hrs. Conclusions: Treatment beyond 3 hrs with IV therapy for AIS has been in effect among vascular neurologists before recent guideline changes on extending the window for IV-IAP. There may be a paradox among the respondents willing to enroll patients into IV trials beyond 3 hrs involving IAT given the majority of respondents preferring offering this as part of their clinical practice, and 40% already believe IAT improves outcome. These results support concerns that clinical practice may impair enrollment into trials testing endovascular therapies for AIS. However, the response rate limits generalizing the results to the wider community of vascular neurologists.
evaluation of all the CTP images revealed a normal CTP in 42% of the patients leading to a sensitivity of 58% as compared to the clinical stroke diagnosis. Conclusion: Routine CTP showed changes of MTT indicating ischemic insult in only 58% of patients with acute stroke. The clinical evaluation of patients using NIHSS was as good as the CTP to predict outcome at 3 months.

P295 Early Antiplatlet and Anticoagulation After Standard Alteplase Therapy for Acute Ischemic Stroke Does Not Increase Risk of Intracranial Hemorrhage

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Primary Objective: We report data from the first dose cohort of a larger trial of early combination anti-platlet and anticoagulation in patients treated with standard dose rt-PA for acute ischemic stroke (AIS), the Combination Anti-platelet and Anti-coagulation Treatment After Lysis of Ischemic Stroke Trial (CATALIST). Background: Standard thrombolytic therapy of acute coronary syndromes is administered in combination with anti-platelet and anti-thrombotic drugs for prevention of re-occlusion. Such combined adjunctive use of anti-platlet and anti-thrombotic drugs is prohibited within the first 24 hours after standard rt-PA therapy of stroke because of unknown risk of intracerebral hemorrhage (ICH) due to insufficient safety data. Design/Methods: Enrolled subjects were age 18-85 years with moderate stroke severity and no other clinical, radiological or laboratory features associated with increased risk of hemorrhage from thrombolysis. Standard dose rt-PA therapy was initiated in all subjects prior to study enrollment. Subjects were enrolled in either the MRI or CT arms and treated with a single dose of 61 mg aspirin orally and 80 mg anti Xa klg of tinzaparin sodium by subcutaneous injection as soon as possible after initiation of rt-PA. Post-hoc comparisons were made to a consented natural history control cohort of rt-PA-only treated patients, matched by age, NIH Stroke Scale and MRI perfusion inclusion criteria. Protocol defined outcomes were toxicity (symptomatic ICH, major systemic hemorrhage or death prior to 72 hour post treatment) and response (substantial clinical improvement or complete MRI reperfusion at 2 hours post treatment that was sustained at 24 hours). Separate natural history data sets were used for the clinical and imaging comparisons, based on the availability of baseline and follow-up data for each.

Results: Between 2004 and 2009, 18 subjects (n=15 MRI; n=3 CT) received combination aspirin and tinzaparin sodium; controls received rt-PA therapy between 2001 and 2009. The median time from stroke onset to rt-PA was 2 hours and 36 minutes and from start of rt-PA to study aspirin and tinzaparin was 2 hours and 25 minutes. There was no significance difference in toxicity or response among subjects or controls overall (Table 1). There were 2 deaths occurring within 5 days among the 27 clinical controls; none of the CATALIST subjects died during the 30 day study period. Conclusion: Preliminary experience with early use of anti-platlet and anti-coagulant after standard thrombolytic therapy appears safe and without excessive systemic or intracranial bleeding complications.

Table 1. Summary of primary endpoint analysis for CATALIST Cohort 1 and TPA Controls

<table>
<thead>
<tr>
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<th>Subjects</th>
<th>Controls</th>
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<tr>
<td>OVERALL</td>
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<tr>
<td>Sample size</td>
<td>18</td>
<td>27</td>
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<tr>
<td>Median Age (IQR)</td>
<td>70 (60–76)</td>
<td>70 (50–78)</td>
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<tr>
<td>Median Baseline NIHSS (IQR)</td>
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<td>7 (3–13)</td>
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<tr>
<td>Median Time Onset to rt-PA (IQR)</td>
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<td>2:36 (2:15–2:50)</td>
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<tr>
<td>CLINICAL OUTCOME</td>
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<tr>
<td>Sample size</td>
<td>18</td>
<td>27</td>
</tr>
<tr>
<td>Response (85% CI of proportion)</td>
<td>5 (12–50%)</td>
<td>3 (4–28%)</td>
</tr>
<tr>
<td>Toxicity (95% CI of proportion)</td>
<td>2 (3–33%)</td>
<td>3 (4–28%)</td>
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<tr>
<td>Deaths</td>
<td>0</td>
<td>2</td>
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<tr>
<td>MRI OUTCOME</td>
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<tr>
<td>Sample Size</td>
<td>14</td>
<td>17</td>
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<tr>
<td>Median Baseline MTT (IQR)</td>
<td>74cc (49–96)</td>
<td>116cc (42–180)</td>
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<tr>
<td>Complete reperfusion @ 2 hr</td>
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<td>0</td>
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<tr>
<td>Complete perfusion @ 24hr</td>
<td>3 (8–48%)</td>
<td>2 (3–34%)</td>
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P296 Ultra-early Thrombolysis for Acute Ischemic Stroke is Linked to Better Outcome and Lower Mortality

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Objectives: Pooled analysis of major placebo-controlled trials reveals that the earlier thrombolysis is given after ischemic stroke, the better the outcome. We report a single-centre assessment of the effect of ultra-early thrombolysis on outcome. Methods: We analyzed our prospective registry of 926 consecutive patients treated with thrombolytic therapy at the Department of Neurology, Helsinki University Central Hospital (years 2003-2008). Patients with basal artery occlusion and those treated with mechanical devices were excluded, leaving 878 stroke patients who had been treated within 4-5 hours from symptom onset. Using univariate methods and multivariable logistic regression, we assessed association between onset-to-treatment time (OTT) and a favorable 3-month outcome (modified Rankine scale 0–2). Findings: Median age was 70-75 years, median OTT 115 min, and median NIHSS 9.5. Among the 105 subjects, 257 (28%) had an OTT ≤ 90 min and 87 (10%) had OTT ≤ 70 min. In patients with OTT 90min (16.4% vs 29.5%, p<0.01). Multivariable model showed an association of better outcome with lower baseline glucose level, younger age, lower baseline NIHSS, and OTT < 70 min. Conclusions: Ultra-early thrombolysis after ischemic stroke was associated with better outcome. Further randomized controlled trials are warranted to confirm these findings.

P297 Thrombolysis in Patients Without Brain Infarction (‘Stroke Mimics’)

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Background: The frequency of false-positive diagnosis of ischemic stroke (‘stroke mimic’ has been estimated at approximately 1-3% even in experienced stroke centers. Since decision making for thrombolysis in acute stroke settings is usually based on clinical assessment and CT findings only and restricted to a limited time window, thrombolysis is sometimes applied to patients with a final diagnosis other than stroke. We analyzed clinical characteristics and response to recombinant tissue plasminogen activator (rtPA) treatment of patients without brain infarction.

Methods: From a prospectively collected stroke and MRI data bank we identified 35 patients (mean age 64.3 y, median NIHSS at admission: 6) without evidence of acute brain infarction on MRI including negative diffusion-weighted images (DWI) who had been treated with rtPA between January 2006 and July 2009. We analyzed clinical characteristics, rate of favorable response to thrombolytic therapy (clinical improvement defined as decrease of NIHSS≤3 or NIHSS 0-1 at discharge), and complications. Furthermore, the most plausible pathophysiological diagnosis was selected in each based on all available data (imaging, EEG, laboratory findings, etc.). Results: Stroke mimics included seizures (n=11), functional disorders (n=5), brain tumors (n=2), demenita (n=4), migraine, hypoglycemia, encephalitis, hypertensive encaphalopathy and cervical radiculopathy (n=1 each). Best diagnosis after exclusion of others was TIA in the remaining 10 patients. Most patients presented with motor or sensorimotor hemiparesis (74%) and/or aphasia (49%); 23% had isolated aphasia. Clinical improvement after thrombolysis was observed in 83% with a median NIHSS of 1 at discharge.

Conclusions:

- Mild complications related to rtPA occurred in 2 patients (5.7%): one patient with a brain tumor had asymptomatic hemorrhagic transformation on MRI, one had reversible orolingual angi- edema.
- None of the patients deteriorated clinically and there was no symptomatic hemorrhage.

Discussion: Thrombolysis does not seem harmful in stroke mimics and prognosis is favorable. Stroke physicians should therefore not refrain from therapy for fear of misdiagnosis, provided that other contraindications are excluded.

P298 Systolic Blood Pressure and Glycemic Control After Acute Ischemic Stroke: Results From the GRASP Trial

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Objective: The GIST-UK trial found that treatment with glucose-potassium-insulin infusion after acute ischemic stroke resulted in lower 24-hour systolic blood pressure (SBP) compared to control. The clinical significance and reproducibility of this observation is uncertain. The purpose of this study was to describe SBP changes in the GRASP Trial and assess the relationship between SBP and clinical outcomes. Methods: The GRASP trial was a multicenter, randomized, controlled trial of intravenous insulin infusion in hyperglycemic acute ischemic stroke patients. Subjects were randomized into tight control (target 70-110 mg/dL), loose control (target 70-200 mg/dL, or usual care. SBP was measured at 4 hour intervals by non-invasive cuff. The primary clinical outcome measure was modified Rankin Scale (mRS) at 90 days. Repeated-measures ANOVA was used to assess the difference in mean SBP between groups. Multivariable logistic regression was used to describe the relationship between 24 hour SBP and excellent outcome (mRS 0 or 1). Results: 24-hour SBP data were available on all 74 subjects. The mean age was 67 years; 32% were black; 59% diabetic and 35% received tPA. Mean (SD) systolic blood pressure at baseline and 24 hours in each of the treatment arms were as follows: tight control 152 (26) at baseline and 150 (20) at 24 hours; and usual care 154 (26) at baseline and 140(29) at 24 hours. Figure 1 is a plot of SBP at 4 hour intervals in each treatment arm. The magnitude of decline in SBP over the first 12 hours of therapy was greatest in the tight control group. Comparison of SBP over 120 hours demonstrated a odds ratio of 0.991 for favorable mRS outcome after adjustment for baseline stroke severity and IAP use. None of these comparisons were statistically significant. Conclusions: Similar to previous studies, SBP declined over the first 24 hours of treatment with insulin; however no statistically significant differences between 24-hour SBP measurements were observed in the GRASP trial. Small sample size may have limited the ability to detect such differences.
### No Differential Effect of tPA Based on Final Stroke Etiologic Subtype: A Reanalysis of the NINDS tPA Trial

**Sharyl R Martini, Sharon D Yeatts, Samir R Belalgea, Pooja Khatri; Univ Cincinnati, Cincinnati, OH**

**Background:** Ischemic stroke is the end result of a number of diseases with distinct etiologies - small vessel ischemic disease, large vessel atherosclerosis, cardioembolism, and other. The original NINDS tPA trial publication included subgroup analysis by pre-treatment presumed subtype assessment. Here we sought to (1) describe the agreement between pre-treatment and post-treatment assignment of stroke subtype. We compared tPA and placebo rates of excellent three-month clinical outcome using the global statistic and the four pre-treatment and post-treatment assignment of stroke subtype. We compared tPA and placebo rates of excellent three-month clinical outcome using the global statistic and the four scales comprising it (modified Rankin Score, NIHSS, Glasgow Outcome Scale, Barthel Index) for each small vessel, large vessel, cardioembolic, other, and unknown stroke subgroups. We developed multivariable models for each outcome and assessed treatment by subgroup interactions. Analyses adjusted for age, sex, baseline NIHSS, and glucose. Results: The agreement between pre- and post-treatment stroke subtype was marginal (Kappa=0.33, 95% CI 0.29-0.37). There was no evidence of treatment effect on post-treatment subtype (p=0.70). A differential effect on the global statistic, the primary outcome measure of the NINDS trial, was not seen for tPA treatment by post-treatment subtype (p=0.17). The table shows tPA versus placebo rates of excellent outcome for each outcome scale by etiologic subgroup.

<table>
<thead>
<tr>
<th>Post-Treatment Subtype</th>
<th>Baseline NIHSS (median)</th>
<th>Age (mean)</th>
<th>tPA Arm</th>
<th>Placebo Arm</th>
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<tr>
<td>Small Vessel (n=81)</td>
<td>7</td>
<td>62.1</td>
<td>24 (47%)</td>
<td>10 (33%)</td>
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<td>mRS 0–1</td>
<td>32 (63%)</td>
<td>12 (40%)</td>
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<tr>
<td>GOS 95–100</td>
<td>32 (63%)</td>
<td>13 (43%)</td>
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</tr>
<tr>
<td>BI 95–100</td>
<td>38 (75%)</td>
<td>15 (50%)</td>
<td></td>
<td></td>
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<tr>
<td>Large Vessel (n=252)</td>
<td>16</td>
<td>66.7</td>
<td>39 (33%)</td>
<td>24 (18%)</td>
</tr>
<tr>
<td>mRS 0–1</td>
<td>47 (40%)</td>
<td>30 (22%)</td>
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<tr>
<td>GOS 95–100</td>
<td>53 (45%)</td>
<td>38 (28%)</td>
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</tr>
<tr>
<td>BI 95–100</td>
<td>57 (49%)</td>
<td>48 (36%)</td>
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<tr>
<td>Cardioembolic (n=273)</td>
<td>16</td>
<td>69.5</td>
<td>40 (23%)</td>
<td>27 (20%)</td>
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<td>mRS 0–1</td>
<td>51 (38%)</td>
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<td>GOS 95–100</td>
<td>53 (39%)</td>
<td>42 (31%)</td>
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</tr>
<tr>
<td>BI 95–100</td>
<td>62 (46%)</td>
<td>51 (37%)</td>
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<tr>
<td>Other (n=18)</td>
<td>16.5</td>
<td>65.0</td>
<td>3 (38%)</td>
<td>3 (30%)</td>
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<tr>
<td>GOS 95–100</td>
<td>3 (38%)</td>
<td>4 (40%)</td>
<td></td>
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</tr>
<tr>
<td>BI 95–100</td>
<td>5 (63%)</td>
<td>5 (50%)</td>
<td></td>
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</tr>
</tbody>
</table>

### Conclusions:
Pre-treatment assessment of stroke etiology showed marginal agreement with final assessment after diagnostic testing. Despite this poor agreement, as with pre-treatment subtype, no differential effect was seen with post-treatment subtype. This analysis reaffirms that tPA is effective for all strokes, irrespective of etiology. Thus, emergent assessment of stroke etiology may have limited value for treatment decisions.

### Renal Function, Hydration Status, and Outcome From Stroke After Thrombosis

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**Objective:** Baseline renal dysfunction has been found to be a predictor of poor outcome from stroke among patients treated with rt-PA (Lyrer, et al, Neurology 2008;71:1548-50). We sought to determine if baseline renal function, as indicated by baseline serum creatinine (sCr), estimated glomerular filtration rate (eGFR), and hydration status based on BUN/sCr ratio were associated with a t-PA treatment effect on global treatment outcome, or intracranial hemorrhage (ICH) 36 hours post-treatment. **Methods:** In the NINDS rt-PA Stroke Trial, BUN and sCr were measured at baseline. eGFR was computed based on the MDRD equation as: 186 x (sCr)-1.154 x (age)-0.203 x (0.742 if female) x (1.210 if African-American). eGFR was both dichotomized (<60 and ≥60 ml/min/1.73 m2), as well as trichotomized (<45, 45-60 and ≥60 ml/min/1.73 m2). Outcomes were global treatment outcome (Rankin [good [mRS 0–1] vs. poor [mRS ≥2] outcomes), NIHSS ≤1, Glasgow index = 1, Barthel index ≥95 at 90 days) and presence of symptomatic or asymptomatic ICH (at up to 36 hours post-treatment). Multivariate analyses utilized previously published baseline variables [NINDS tPA Stroke Study Group, Stroke 1997;28:2119-25] with the addition of smoking status. Results: Of 624 subjects randomized, there were only four subjects missing baseline variables (n = 620, 311 treated with t-PA). Baseline sCr [OR 1.065 (0.685–1.657)], BUN/sCr [OR 1.009 (0.932–1.092)], and eGFR [OR 0.980 (0.982–1.014)] were not associated with ICH (total or symptomatic) in univariate or multivariate (these ORs) analyses. eGFR was not associated with global treatment outcome using either dichotomized [OR 0.946 (1.22–1.75), p = 0.238] or trichotomized eGFR [OR 0.945 (1.11–1.29), p = 0.207]. There were no treatment interactions with sCr [OR 0.83 (0.64–1.07), p = 0.154], BUN/sCr [OR 0.95 (0.98–1.02), p = 0.328], or eGFR [OR 0.999 (0.99–1.01), p = 0.819]. **Conclusions:** Neither baseline renal status as measured by admission sCr and eGFR, nor baseline hydration status as measured by BUN/sCr ratio were associated with the global outcome or ICH (among rt-PA-treated patients in the NINDS rt-PA Stroke Trial data set).

### The Challenge of Persisting Arterial Occlusion in the Interventional Management of Acute Ischemic Stroke

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**Background:** Intra-arterial [IA] reperfusion techniques undergo rapid development to achieve higher and faster recanalization rates. We aimed to determine safety and recanalization/reperfusion success of multi-device rescue in acute stroke patients with arterial occlusions that persist after initial IV or IA therapy. **Subjects & Methods:** Consecutive patients who had persisting arterial occlusion and disabling neurological deficit underwent combined intravenous-IA procedures or primary IA procedures. Currently FDA approved thrombectomy devices were used as well as additional thrombus manipulations and IA-tPA infusions when deemed necessary by interventionists. Recanalization and reperfusion were measured by A0L and TIMI scores. Symptomatic ICH was defined as PH2-1 and neurological worsening by NIHSS ≥4. **Results:** Sixty six patients (38% men, age 58±15, 47%-<50years, median initial NIHSS 17, interquartile range 10-21) with persisting occlusions (TICA 39%, MCA 38%, BA 14%, VA 6%, and ACA 3%) underwent IA procedures. Deployment of a single device sufficed in 33/66 (50%) patients. The remaining 50% had more than one device or drug-device combination (average 2.5 techniques/case, range 1-8 including Merci, Penumbra, balloon, snare, stenting, IA-tPA). The rate of achieving recanalization or reperfusion (considered by treating physicians as an acceptable final intervention result) was 25% for all Merci retriever passes and 74% for all Penumbra passes, p<0.05. sICH after single device application was 3/33 (9%) and 3/33 (9%) after multimodal IA procedures, NS. Recanalization, reperfusion, functional outcome and mortality are shown in Figure. Good outcomes after single and multi-device approaches were achieved by 36% and 39% of patients (mRS 0-2 at 3 months, p=0.8). **Conclusions:** One half of arterial occlusions in our sample persisted application of a single IA device. Multiple devices or drug-device combinations were deployed with safety comparable to single device applications with most IA procedures resulting in partial reperfusion and recanalization.
Background: Intravenous alteplase (rt-PA) remains the only approved treatment for acute ischemic stroke, but its use remains limited. In a previous pilot dose-escalation study, intravenous tenecteplase (TNK) showed promise as a potentially safer alternative. Therefore, a phase IB clinical trial was begun to a) choose a best dose of TNK to carry forward, and b) to provide evidence for either promise or futility of further testing of TNK versus rt-PA. If promise was established, then the trial would continue as a Phase II efficacy trial comparing the optimal TNK dose to standard rt-PA. Methods: The trial began as a small, multi-center, randomized, double-blind, controlled clinical trial comparing 0.1, 0.25, and 0.4 mg/kg TNK with standard 0.9 mg/kg rt-PA in patients with acute stroke within 3 hours of onset. An adaptive sequential design was used after an early 24 hour assessment of major neurologic improvement balanced against occurrence of symptomatic intracranial hemorrhage (ICH) to choose a “best” dose of TNK to carry forward. Once a “best” dose was established, the trial was continued until at least 100 patients with the best TNK dose versus standard rt-PA could be compared by 3 month outcome using the modified Rankin Scale in an interim analysis. Decision rules were devised to yield an unambiguous recommendation to either stop for futility or to continue into Phase III. Results: The trial was prematurely discontinued for slow enrollment after only 112 patients had been randomized at 8 clinical centers between 2006 and 2008. The 0.4 mg/kg dose was discarded as inferior after only 73 patients were randomized, but the selection procedure was still unable to distinguish between 0.1 mg/kg and 0.25 mg/kg as a “best” dose at the time the trial was stopped. There were no statistically persuasive differences in 3 month outcomes between the remaining TNK groups and rt-PA. Symptomatic ICH rates were higher in the discarded 0.4 mg/kg TNK group and lowest (0/31) in the 0.1 mg/kg TNK group. Neither promise nor futility could be established. Conclusion: This prematurely discontinued trial has demonstrated the potential efficiency of a novel design in selecting a “best” dose for future study of a new thrombolytic agent for acute stroke. Given the truncation of the trial, no convincing conclusions can be made about the promise of future study of TNK in acute stroke.
Background: Lowering of blood pressure (BP) in the acute phase of stroke was reported to worsen clinical outcome in some studies and to improve outcome in the others. The purpose of this study was to evaluate the association of BP and heart rate (HR) profiles early after stroke onset with 3-month outcome. Methods: We analyzed 24-hour ambulatory BP monitoring (ABPM) records in 104 ischemic stroke patients (64 men, 71.7 ± 12.5 years) within 48 hours from the onset of symptom who were admitted to our stroke care unit between January and December 2008. ABPM was evaluated at the second and eighth hospitalization days. Systolic and diastolic BP (SBP, DBP) as well as HR were characterized using the values of the mean, maximum, minimum, and variability (coefficient of variation; CV) during 24-h records. Favorable outcome at 3 months was defined as a modified Rankin Scale (mRS) score ≤ 2. Results: 82 patients (79%) had hypertension, and 61 (54%) were taking antihypertensive agents prior to admission. BP was 161.3 ± 27.3/89.9 ± 13.6 mmHg, and HR was 75.5 ± 15.3 bpm. Mean BP and HR on day 2 were 150.5 ± 19.5 / 85.7 ± 11.3 mmHg and 68.7 ± 11.4 bpm, and those on day 8 were 139.6 ± 19.3 / 80.0 ± 11.7 mmHg and 66.6 ± 11.6 bpm, respectively. 66 patients (63%) had favorable outcome. Patients with favorable outcome were younger (67.9 ± 12.6 years vs. 78.1 ± 9.5 years, p < 0.001), less frequently had a prior history of stroke (21 % vs. 39 %, p = 0.046), and had a lower score of National Institutes of Health Stroke Scale on admission (median [interquartile range] [2 - 5] vs. 7 [4 - 17.5], p < 0.001) than those without favorable outcome. After multivariate adjustment for baseline characteristics, mean SBP (odds ratio (OR) 0.46, 95% confidence interval (CI) 0.42 - 0.50, p = 0.003), minimum SBP (0.76, 0.57 - 0.99, p = 0.046), mean DBP (0.59, 0.36 - 0.95, p = 0.023) was only associated with favorable outcome. Regarding ABPM data on day 8, mean HR (OR 0.46, 95% CI 0.22 - 0.96, p = 0.023) was only associated with favorable outcome. Conclusion: Lower SBP, DBP, and HR on day 2 and lower HR on day 8 were associated with favorable outcome in acute stroke patients.

Validation of Power M Mode Transcranial Doppler Criteria for Vascular Imaging Proximal Middle Cerebral Artery Occlusion

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Background: Power M Mode (PMD) TCD can be used as a screening test for proximal MCA occlusion in acute stroke. We previously derived PMD/TCD criteria for angiographic proven proximal MCA occlusion (M1 and M2 occlusion). Objective: To validate our PMD/TCD criteria in prospective cohort study of acute stroke patients enrolled from multiple stroke centers. Methods: Data from 104 ischemic stroke patients (64 men, 71.7 ± 12.5 years) with severe disability at presentation (mean NIHSS, 28.6 ± 14.6) from 7 different stroke centers were analyzed according to the occlusion site. Untreated patients with severe disability and M1 and M2 TCD criteria were recruited as our study cohort. PMD TCD criteria were validated against vascular gold standard (DSA, MRA or CTA). Results: A total of 44 patients with M1 occlusion (32.7% of the cohort) and 13 patients with M2 occlusion were included in the analysis. A total of 23 patients with M1 occlusion were evaluated against DSA (14), MRA (one), CTA (three), and other imaging criteria (three). PMD criteria were associated with angiographic M1 occlusion with a sensitivity of 96.2%, specificity 96.2%, positive predictive value (PPV) of 100%, negative predictive value (NPV) of 93.3%, and positive likelihood ratio (LR) of 27.6. Conclusion: Our PMD/TCD criteria for proximal MCA occlusion is valid. They can be used as a screening tool for MCA occlusion.
of 127 had TGT listed as the only reason for not receiving thrombolysis, with mean admission NIHSS of 1.8, (range – 0 to 19). At discharge 25 (20.3%) TGT patients had mRS > 1, nine (7.3%) had an NIHSS > 4, and 12 (8.8%) were not discharged home. Only increasing age predicted which TGT patients had mRS > 1 (adjusted OR 1.06, 95% CI 1.02-1.09) and were not discharged home (adjusted OR 1.05, 95% CI 1.01-1.10). Conclusion: A significant proportion of patients deemed TGT will have poor outcomes at discharge. Further observational studies and acute care clinical trials are warranted in the TGT ischemic stroke and TIA patients.

Lesion Evolution in Stroke and Ischemia On Neuroimaging (LESION Project): MRI Defined Pathology in Acute Ischemic Stroke
Katherine D Ku, Marie Luby, Lawrence L Latour, Steven Warach, National Institute of Neurological Disorders and Stroke, Bethesda, MD; NINDS Natural History of Stroke Investigators

Introduction: The Lesion Evolution in Stroke and Ischemia On Neuroimaging (LESION) Project aims to establish a large cohort of MRI-screened and serially evaluated acute ischemic stroke patients as a resource for the design of clinical research protocols that use MRI features of ischemic pathology for patient selection and outcome assessments. Methods: We prospectively screened patients from August 1999 through December 2008. Patients were included in the LESION Project if they had a clinical diagnosis of acute ischemic stroke, had a stroke MRI scan within 24 hours from time last seen normal and received at least one of the following: 1) intravenous tPA for their stroke, 2) other, non-investigational acute stroke therapy (e.g., endovascular), or 3) treatment but had admission NIH Stroke Scale (NIHSS) > 3. Patients with multiple admissions were included only once. Follow-up MRIs were targeted for immediate post treatment (2 hours), for hours 24, and 5, 30 and 90 days after initial scan. We standardized clinical and neuroimaging acquisitions and identified key pathological findings on the MRI for investigators to record, such as acute ischemia lesion (DWI), intraluminal thrombus, microbleeds or hemorrhage (T2* GRE), focal ischemia or mismatch (PWI), vessel status (MRA), and blood brain barrier leakage or chronic lesions (FLAIR). Results: We screened 5880 cases, out of which a total of 996 met all the inclusion criteria. The two treatment cohort arms included patients who received IV-tPA (n = 225) or other acute therapy (n = 40). The untreated cohort arm included 731 patients. Demographics and times from stroke onset to initial MRI for each of the three cohort arms were compared (Table). Follow-up MRI and clinical data were obtained at targeted time points. Out of the 225 IV-tPA treated patients, 92% had pre- and post-treatment MRI scans within 24 hours from stroke onset. Acute and 24 hour scans were available for 487 patients. Across all patients (n = 996), each follow-up imaging time point included at least 100 patients. Discussion: The LESION Project is a large reference database for investigating serial pathologic features on stroke MRI scans. Such a database should prove useful for evaluating potential imaging selection and outcome variables for clinical trial design as well as for directly analyzing imaging-clinical correlations in treated and untreated cohorts of ischemic stroke patients.

Table. Comparison of Demographics and MRI Scans Among Cohort Arms

<table>
<thead>
<tr>
<th></th>
<th>Total (n=996)</th>
<th>IV-tPA (n=225)</th>
<th>Other Acute Therapy (n=40)</th>
<th>No Treatment (n=731)</th>
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<tbody>
<tr>
<td>Demographics</td>
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<tr>
<td>Mean Age (SD, years)</td>
<td>72.1 (15.2)</td>
<td>71.6 (15.4)</td>
<td>68.8 (14.7)</td>
<td>72.5 (15.1)</td>
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<tr>
<td>Female, %</td>
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<td>54</td>
<td>35</td>
<td>59</td>
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<tr>
<td>Median</td>
<td>9</td>
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<td>9</td>
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<tr>
<td>Baseline NIHSS</td>
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<tr>
<td>Median Time from Stroke Onset (IQR, hours)</td>
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<tr>
<td>ED Arrival</td>
<td>2.8 (1.1)</td>
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<td>1.3 (2.4)</td>
<td>4.9 (9.9)</td>
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<td>Acute Treatment</td>
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<td>Baseline MRI</td>
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<td>1.6 (0.8)</td>
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<td>Median Time from Baseline to Follow-up MRI (n=patients)</td>
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<td>2 Hours</td>
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<td>2.9 Hours (16)</td>
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<td>24 Hours</td>
<td>24.6 Hours (487)</td>
<td>24.6 Hours (187)</td>
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<td>90 Days</td>
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<td>95.5 Hours (82)</td>
<td>98.3 Hours (6)</td>
<td>91.7 Hours (68)</td>
</tr>
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A Variant in the Adenosine 2B Receptor Gene is Associated With Homocysteine Levels and Stroke Severity in African American Subjects From the Vitamin Intervention for Stroke Prevention (VISP) Trial
Michele M Sale, Univ of Virginia, Charlottesville, VA; Fang-Chi Hsu, Wake Forest Univ, Winston-Salem, NC; Josef C Mychalecky, Stephen S Rich, Univ of Virginia, Charlottesville, VA; Karen L Furie, Massachusetts General Hosp and Harvard Univ, Boston, MA; Bradford B Worrall; Univ of Virginia, Charlottesville, VA

Introduction: The Vitamin Intervention for Stroke Prevention (VISP) trial enrolled patients with a non-disabling cerebral infarction and homocysteine (Hcy) levels above the 25th percentile: >9.5 μmol/L for men, >8.5 μmol/L for women. Subjects were randomized to high or low dose folic acid, vitamin B6 and vitamin B12. Despite a lack of difference by treatment group after 2 years of follow-up, there was a persistent and graded association between baseline Hcy level and vascular outcomes in both treatment groups. Our objective was to investigate vascular candidate genes for contributions to Hcy measures. Methods: A total of 1,439 single nucleotide polymorphisms (SNPs) in 119 genes were successfully genotyped in 2,026 subjects that consented to genetic studies (63% European American) using Illumina GoldenGate assay. SNPs were selected to capture the majority of common variation. Associations between individual SNPs and Hcy measures were assessed using an additive model (Cochrane-Armitage trend test), adjusting for age, sex and race. Results: The SNP that showed greatest association with baseline fasting Hcy in the total sample was rs758858 (P = 0.0002), located in the adenosine 2B receptor (ADORA2B) gene. This association was driven by the African American sample (n = 260; MAF 0.30), since the minor allele was rare in European Americans (n = 1,755; MAF = 0.003). In African American subjects from the VISP trial, rs758858 was associated with baseline Hcy (P = 0.002) and post-methionine load Hcy (P = 0.007) (Fig 1). This SNP was also associated with measures of stroke severity: Modified Rankin Stroke Scale (P = 0.005) and NIH Stroke Scale (NIHSS) (P = 0.064), although a stronger association with NIHSS was seen with ADORA2B SNP rs7285057 (P = 0.006). Conclusion: 5-Aminosulphohomocysteine hydrolase catalyzes the conversion of 5-adenosylhomocysteine to adenosine and homocysteine, as well as the reverse reaction. Adenosine and its receptors modulate cardiac response to stress during myocardial ischemia and repertusion, cerebrovascular blood flow, neuronal viability, and cytokine release in response to neurological insults. Further investigation of rs758858 and other ADORA2B variants is anticipated to advance our understanding of determinants of Hcy levels and modulators of stroke severity in African Americans.

Genotyping Recurrence Of Stroke (GRECOS) Project: Two Genes Inolved In Hypoxia Responses and Blood Brain Barrier Function Are Associated With Vascular Recurrence in a Preliminary Study
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Objective: nowadays, no suitable prognostic tools to predict vascular recurrences are available in clinical practice. Our aim was to find genetic risk factors to predict recurrent events in patients with the first-ever stroke large patient cohort. We show here results from a preliminary analysis. Methods: GRECOS project was designed as a prospective, genetic association study involving 236 single nucleotide polymorphisms (SNPs) in candidate genes related to vascular risk factors and several ischemia pathways. A total of 1414 first-ever stroke patients were recruited from 23 hospitals until June 2009. A composite outcome of non-fatal stroke, acute myocardial

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infarction and cardiovascular mortality was considered as a recurrent event. Recurrent events and drug adhesion were assessed by telephone interviews during 1-year follow-up. Genotyping was performed by SNPlex™ (AB) technology. A subset of 52 recurrent patients and 128 patients with no recurrent events, matched on the basis of sex, gender and etiology, assessed by TOAST, has been included in a preliminary nested case-control study. All of them with available genotypes and complete follow-up. Adjusted logistic regression analysis was developed under additive and dominant/recessive models by SPSS v 15.0 software. Results: when performing univariate analysis, we found that 8 SNPs in genes involved in hypoxia response, blood brain barrier (BBB) function and inflammation pathways were associated with vascular recurrence onset under both genetic analysis models. SNP 1, located in an hypoxia response gene (OR = 4.43, CI 95% 1.87-10.52, p = 0.001) and SNP 2, located in a BBB-receptor gene (OR = 3.79, CI 95% 1.64-8.72, p = 0.002), remained as independent risk factors for recurrence after logistic regression that was performed under the genotypic model. The logistic regression was adjusted for recurrence risk factors (heart failure, previous myocardial infarction, stroke location and severity, HDL-cholesterol level, carotid stenosis > 70% and atrial fibrillation). Furthermore, SNP 1 (OR = 3.00 CI 95% 1.43-6.27, p = 0.003) appeared as an independent predictor of recurrence onset after performing an adjusted logistic regression under the additive model. Conclusions: we found 2 SNPs, located in genes involved in ischemia response and BBB-receptor, to be associated with vascular recurrence at 1 year follow-up after a first-ever stroke in a preliminary case-control study. If these results are confirmed after finishing the GRECOS project, further research will be needed on the functional role of these genes for developing cardiovascular recurrence.

Investigation of Recurrent Stroke Risk in the Vitamin Intervention for Stroke Prevention (VISP) Trial Suggests Different Genetic Influences on Prevalent and Incident Stroke

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Background: After a first stroke, individuals are at significant risk for recurrence, and these recurrent strokes are often more devastating than the first. Recent genome-wide association studies have identified single nucleotide polymorphisms (SNPs) associated with ischemic stroke. We examined five SNPs from three loci in subjects from the Vitamin Intervention for Stroke Prevention (VISP) trial for associations with recurrent stroke. Methods: VISP was a double-blind, randomized clinical trial that enrolled subjects with a non-disabling ischemic stroke and treated them with high- or low-dose vitamin supplements. We genotyped the candidate SNPs using TaqMan assays. Due to different allele frequencies between ethnic groups, we limited analysis to self-described non-Hispanic whites. During the 2-year follow-up period, 159 of 1,945 white subjects experienced recurrent stroke. We used logistic regression and Cox proportional-hazards models to evaluate recurrent stroke, both under an additive model and adjusted for age and sex. Results: SNPs rs22007733, rs654398, rs11335579, and rs12425791 were not associated with recurrent stroke in VISP subjects by either method (Table 1). Additive logistic regression analysis showed rs1353738 had a trend towards association with recurrent stroke, although this did not reach statistical significance. Visual inspection of Kaplan-Meier cumulative incidence curves for rs12425791 (Fig 1) suggested a recessive model was most appropriate (p = 0.02). Conclusions: In this cohort, three of the five SNPs previously associated with ischemic stroke did not show association with recurrent stroke. These SNPs may affect overall vascular health, but they do not appear to confer additional risk for subsequent recurrent stroke. The results for rs1353738 and rs12425791 (Table 1) raise the question whether incident and prevalent recurrent stroke may have different genetic determinants. These SNPs warrant further investigation in a larger sample.

Table 1. Association test results for non-Hispanic whites in the VISP population

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>SNP</th>
<th>Closest Gene</th>
<th>MAF</th>
<th>OR* (95% CI)</th>
<th>P*</th>
<th>OR† (95% CI)</th>
<th>P†</th>
<th>HR† (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>4</td>
<td>rs22007733</td>
<td>PITX2</td>
<td>0.1230</td>
<td>1.15 (0.83-1.59)</td>
<td>0.41</td>
<td>0.58</td>
<td>1.32 (0.64-2.72)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>rs654398</td>
<td>CCK20AR</td>
<td>0.3827</td>
<td>1.07 (0.85-1.36)</td>
<td>0.79</td>
<td>0.86</td>
<td>1.02 (0.64-1.63)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>rs1353738</td>
<td>CCK20AR</td>
<td>0.3616</td>
<td>1.23 (0.97-1.56)</td>
<td>0.21</td>
<td>0.61</td>
<td>1.27 (0.76-1.97)</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>rs11335579</td>
<td>MUX2</td>
<td>0.2592</td>
<td>1.06 (0.81-1.39)</td>
<td>0.43</td>
<td>0.16</td>
<td>1.45 (0.84-2.52)</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>rs12425791</td>
<td>MUX2</td>
<td>0.1988</td>
<td>1.12 (0.84-1.50)</td>
<td>0.27</td>
<td>0.02</td>
<td>1.94 (1.06-3.53)</td>
<td></td>
</tr>
</tbody>
</table>

P*: P-value for additive logistic regression model adjusted for age, sex, and treatment arm. OR*: Odds Ratio and (95% Confidence Interval) for additive logistic regression model adjusted for age and sex.

P*: P-value for Cox additive proportional-hazards model adjusted for age and sex.

P*: P-value for Cox recessive proportional-hazards model adjusted for age and sex.

HR*: Hazard Ratio and (95% Confidence Interval) for Cox proportional-hazards model under a recessive model adjusted for age and sex.

Conclusions: Homocysteine (Hcy) is an established risk for vascular disease. In prior studies of the Vitamin Intervention for Stroke Prevention (VISP) trial, we identified intronic variants in the vitamin B12 transporter transcobalamin 2 (TCN2) gene associated with post-stroke Hcy levels and stroke recurrence. B12 is a cofactor for methionine synthase which converts Hcy to methionine. We assessed whether four putative functional TCN2 single nucleotide polymorphisms (SNPs) accounted for the previously observed associations. Methods: VISP was a double-blind, randomized, controlled clinical trial that enrolled patients with a non-disabling cerebral infarction and Hcy above the 25th percentile: > 9.5 μmol/L for men and > 8.5 μmol/L for women. TCN2 SNP rs1801198 (P259R) was chosen based on reported associations with plasma Hcy and B12. TCN2 coding SNPs rs1113603 (S376L) and rs6621049 (S349F), and rs2072195 - located in the 3 untranslated region (UTR) - are in proximity to the previously associated intronic SNPs. 2,319 subjects (82% European American (EA)) were successfully genotyped using the Taqman assay. Association Hcy measures were evaluated using a linear regression approach and additive model, adjusted for age, sex, and race. Cox proportional hazards models were used to evaluate time to recurrent stroke, adjusting for age, sex and race. Results: TCN2 coding SNPs rs1801198, rs113603 and rs6621049 were not associated with baseline Hcy (P = 0.43, P = 0.13, and P = 0.36 respectively). SNP rs2072195 was associated with baseline Hcy (P = 0.0003; EA P = 2.37E-05; Fig 1) but not with post-methionine test Hcy (P = 0.52). Unlike rs731991 from our prior study, rs2072195 did not reveal an association with recurrent stroke in the low dose arm (recessive logrank P = 0.79) or the total sample (P > 0.95). Conclusion: Coding variants in the TCN2 gene could not explain the previously-observed association between TCN2 and baseline fasting Hcy or recurrent stroke in the VISP trial, suggesting that further investigation of intronic regions is warranted. The association between rs2072195 and baseline Hcy suggests functional studies of mRNA stability and transcript levels may provide insight into the relationship between TCN2 variation and Hcy levels following ischemic stroke.

Figure 1. Total homocysteine (Hcy) levels in all VISP subjects (ALL) and subjects with European ancestry (EUR) by rs2072195 genotype. Genotype counts: ALL: AA n = 2,085, AT n = 206, TT n = 27; EUR AA n = 1,807, AT n = 93, TT n = 10.
Can Ancestry Help to Identify Stroke Genes in Mexican Americans?
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Background: Mexican Americans (MAs) have greater stroke risk at younger ages, and an affected family member increases an individual's stroke risk particularly in MAs. These findings suggest a genetic predisposition for stroke in this population. Admixture linkage disequilibrium (ADL) mapping may be a useful method for identifying stroke susceptibility loci in MAs since 'risk conferring mutations are likely to come from either their European or Native American ancestries but not both. The objective of this study was to test for ancestral heterogeneity, a requisite finding for ADL mapping, among MAs to ensure the feasibility of a larger study.

Methods: Data are from the Brain Attack Surveillance in Corpus Christi (BASIC) Project. Blood was collected from a sample of MA stroke cases (n=154) and 33 ancestry informative markers for estimating European and Native American contributions to admixed populations were genotyped. Individual genetic admixture was estimated using maximum likelihood methods. To test for ancestral heterogeneity among MAs, three hypotheses were tested for each participant using likelihood ratio tests: H0: \( \mu_1 = 0 \) (100% Native American ancestry), H1: \( \mu_1 = 1.00 \) (100% European ancestry), and H2: \( \mu_1 = 0.59 \) (average European ancestry). Results: Among MAs, the estimated fraction of European ancestry varied from 0.26-0.98, with an average of 0.59±0.014. We rejected the 100% Native American ancestry hypothesis for every MA, and we rejected the 100% European ancestry hypothesis for all but two MAs. We rejected the possibility that a MA had 59% European ancestry for 40 MAs (20 with 59% European ancestry) rejected the 100% European ancestry hypothesis for all but two MAs. We rejected the 100% Native American ancestry hypothesis for every MA, and we rejected the 100% European ancestry hypothesis for all but two MAs. We rejected the hypothesis that a MA had 59% European ancestry for 40 MAs (20 with 59% European ancestry). Conclusions: Given high levels of ancestral heterogeneity demonstrated in our sample, ADL mapping is likely to be a cost-efficient approach to identifying stroke susceptibility loci in MAs, a vulnerable population for stroke.

Figure. Proportion of European Ancestry in Mexican American Stroke Cases. Each tick mark represents one individual. Blue tick marks represent individuals for whom we could not reject H0: \( \mu_1 = 0.59 \). Red tick marks represent individuals for whom we rejected H0: \( \mu_1 = 0.59 \).

P319 Ischemic Stroke and Coronary Artery Disease Share a Common Genetic Background: An Empirical Investigation of Validated Associations
Issa J Dabah, Georgios Kiotis, Thomas A Trikalinos, David M Kent; IORHPS, Tufts Med Ctr, Boston, MA

Introduction: Ischemic stroke (IS) and coronary artery disease/myocardial infarction (CAD/MI) have common risk factors, such as hypertension and dyslipidemia. Much less is known about the commonality of genetic determinants of these disorders. Hypothesis: Polymorphisms that have been associated with CAD/MI by virtue of large meta-analyses may be also implicated in IS. Methods: We reviewed meta-analyses of genetic association studies indexed by the Human Genome Epidemiology Network (HuGE Net) to identify validated associations between genetic polymorphisms and CAD/MI. An association was considered validated when a meta-analysis of more than 30 studies had demonstrated a statistically significant association with CAD/MI. We then conducted a systematic search of HuGE Net and PubMed (from inception to July, 2011) to identify meta-analyses investigating the identified polymorphisms in IS. Results: We identified 9 genetic variants with validated associations with CAD/MI: F2: rs1799963, SERPINE1-rs708272, CETP-rs708272, SERPINE1-rs1798993, CETP-rs708272, AGT-rs662, PO1-rs662, F5- rs6025, MTHFR-rs1801133 and ACE-rs4646994. Median number of studies per meta-analysis was 42 (mean = 61; range: 30-121). Seven polymorphisms (those in F2, SERPINE1, AGT, F5, MTHFR and ACE) had been investigated by previous meta-analyses as potential risk factors for IS. Five of these meta-analyses had found a significant association with IS, only AGT-rs699 and SERPINE1-rs1798993 were not found to be significantly associated with IS. For two MI/CAD-associated polymorphisms (PO1-rs662 and CETP-rs708272), no previous evidence synthesis had been performed in IS. For the PO1-rs662 polymorphism, we identified 24 studies in IS (3054 patients, 1347 controls) and the summary OR was 1.12 per variant allele (95% CI, 1.05-1.20; p=0.001). For the CETP-rs708272 polymorphism, 2 studies were available (311 cases, 336 controls) and the summary OR was 1.3 (95% CI, 1.05-1.63; p=0.019) per variant allele. Overall, seven of nine polymorphisms identified as risk factors for CAD/MI appear to also be potential risk factors for IS. Conclusions: Valuable polymorphisms in CAD/MI are likely to be risk factors for IS. Using data from CAD/MI, we identified that the PO1-rs662 and CETP-rs708272 polymorphisms appear to be associated with increased IS risk. Genetic convergence between diseases with similar determinants may be useful for research prioritization. This may reflect true genetic effects on common aspects of the pathophysiology of these diseases, correlations between the phenotypes, biases, or interplay of all these factors.

P320 Diastolic Dysfunction and Ischemic Stroke: A Case-control Comparison
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Objective: To define whether there is an association between echocardiographic (echo) parameters of diastolic dysfunction (DD) and ischemic stroke (IS). Background: Certain echo parameters, such as left atrial enlargement and left ventricular hypertrophy (LVH) are independent risk factors for IS. DD may also be a risk factor for stroke independent of LVH or systolic dysfunction but an association has not been previously described. Methods: Transthoracic echocardiograms (TTE) of successive stroke patients (cases) and non-stroke patients (controls) evaluated in the Loyola University Medical Center Echocardiography Lab from October 2007 to April 2008 were reviewed and various TTE parameters of systolic and diastolic morphology and function were recorded. We also reviewed demographic and clinical variables including age, race, blood pressure, pulse, BMI, cardiovascular risk factors (including HTN, DM, CAD, CHF, prior stroke hx, CHF, hyperlipidemia) Cigarette use and medications specifically including antiplatelet and anticoagulant use. Statistical analyses were calculated using Chi-square and t tests. Results: We reviewed TTE of 142 IS patients (49% male) and 159 control patients (47% male). IS patients were older (67 ± 14 vs 58 ± 17), with higher systolic BP (144 ± 27 vs 129 ± 23) but similar diastolic BP (71 ± 12 vs 72 ± 16), HTN, (72% vs 42%), CAD (24% vs 19%), DM (34% vs 22%) and atrial fibrillation (14% vs 9%) were more common in IS patients. Congestive heart failure (5% vs 8%) and hyperlipidemia (25% vs 20%) were more common in controls than IS patients. There was a statistically significant greater association of DD and stroke with abnormal DD in 39% of controls and 68% of IS patients (P<.001). There were significant differences in various echo parameters of DD as well (see Table). As previously reported by others, IS patients had more concentric LVH than controls but eccentric hypertrophy was more common in controls. The mean LV ejection fraction of IS cases was essentially normal (60 ± 11) but the stroke volume was decreased (41 ± 11 vs 29). Conclusions: Echo manifestations of DD are more common in patients with IS. Whether DD is an independent risk factor or whether it reflects associations with other cardiovascular risk factors, such as HTN, remains to be elucidated via prospective studies.

A Significant Association of a Novel SNP (rs12425791) and the Risk of Ischemic Stroke in Taiwanese
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Background and Purpose: The association between two novel SNPs (rs12425791 and rs11833579) and the risk of ischemic stroke was demonstrated by a genomewide association study among black and Caucasian Dutch persons. However, the relationship between these two SNPs and the risk of stroke is undetermined in Asian. Thus, the present study aimed to investigate the validity of this finding in Taiwanese. Methods: The case-control study was conducted with 978 ischemic stroke patients and 978 unrelated healthy controls. Controls were frequency matched by age and gender with cases. All cases were confirmed with computed tomography and/or magnetic resonance imaging. A structured questionnaire was used to collect information on conventional cardiovascular risk factors and lab results. The genetic polymorphisms of two SNPs, rs12425791 and rs11833579, were determined by a TaqMan assay. Results: A significant association between the risk of ischemic stroke and rs12425791 AA genotype was observed in the recessive model (odds ratio, 1.6; 95% CI, 1.0-2.9). There was no association between rs11833579 and the risk of ischemic stroke. We also found synergistic effects of rs12425791 and diabetes (synergistic index =1.6), hypertension (synergistic index =2.9), and smoking (synergistic index =3.0) on the risk of ischemic stroke.
The Effects of Atrial Fibrillation on Infarct Evolution and Outcome

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Background and Aims: Previous studies have shown that patients with ischemic stroke and atrial fibrillation (AF) have worse outcomes. The reasons for the negative influence of AF remain unclear. We aimed to determine whether there were differences in stroke size (NIHSS, mRS) and multimodal MRI prior to treatment, at days 3-5 and 3 months post stroke. Hemorrhagic transformation (symptomatic and asymptomatic) was calculated according to European Cooperative Acute Stroke Study criteria.

Results: Forty-two of 101 patients had AF. At baseline, patients with AF were older (median 79 vs 73 years, p = 0.0294), had more severe neurological impairment (median NIHSS 16 vs 11, p = 0.006) and larger infarct volumes (median 29 ml vs 14 ml p = 0.04) than those without AF. The size of the baseline and subacute perfusion defects and the frequency of arterial recanalisation or brain reperfusion were the same in those with and without AF. At outcome, patients with AF had larger final infarct volumes (median 52 ml vs 16 ml, p = 0.04), more hemorrhagic transformation (63% vs 38%, p = 0.023) and higher mortality rates (31% vs 12%, p = 0.124) after adjusting for baseline imbalances in age, gender, race, study center, smoking status (current, former, never), drinking status (current, not-current), prevalent coronary heart disease, diabetes, hypertension, LDL-cholesterol, HDL-cholesterol, body mass index and beta-blocker use at study baseline. Results: Of a total of 818 (7.7%) participants developed AF during an average follow up of 14.7 years. In a multivariate model, the hazard ratio (95% confidence interval) of incident AF with each log-unit increase in high frequency, SDNN, RMSSD were 0.88 (0.83, 0.93), 0.82 (0.70, 0.97), 0.80 (0.79, 1.00). There were no appreciable differences in these associations by race and gender. Conclusions: This study shows strong relationship between both time and frequency domain measures of HRV and incident AF. The findings suggest that poor autonomic cardiac tone, as reflected by low values in HRV measures, may be independently associated with incident AF, and thus may be a risk factor for poor health outcomes associated with AF.

Heart Rate Variability and Incident Atrial Fibrillation: The Atherosclerosis Risks in Communities Study

Sunil K Agarwal, Univ of NC at Chapel Hill, Chapel Hill, NC; Alvaro Alonso, Univ of Minnesota, Minneapolis, MN; Elias Z Soliman, Wake Forest Univ, Winston Salem, NC; Alanna Chamberlain, Univ of Minnesota, Minneapolis, MN; Marietta Ambrose, Johns Hopkins Univ, Baltimore, MD; Ross J Simpson, Jr., Gerardo Heiss, Univ of NC at Chapel Hill, Chapel Hill, NC

Background: Atrial Fibrillation (AF), a commonly seen sustained arrhythmia in clinical practice, is a strong risk factor for incident stroke. Though, autonomic perturbations are common before the initiation of AF, the association of baseline heart rate variability with development of atrial fibrillation remains less studied. Methods: We studied the association between measures of heart rate variability (HRV) measured using 2 minutes rhythm strip in 10471 middle aged adults (45-65 years at enrollment in 1987) from four US communities with incident atrial fibrillation. Those with poor quality HRV data or with ECG findings suppressing HRV analysis, or missing data on important covariates, and prevalent atrial fibrillation were excluded. The following HRV measures were natural log transformed to make their distribution normal: high frequency (HF), 0.15-0.40 Hz, high standard deviation of normal to normal RR intervals (SDNN), root mean square of successive differences of successive RR intervals (RMSSD). Incident AF cases were identified using electrocardiograms done at three follow-up visits (last visit in 1996-98), and from hospitalizations and death certificates through December 31, 2004. Hazard ratios were estimated using multivariate Cox models adjusted for age, gender, race, study center, smoking status (current, former, never), drinking status (current, not-current), prevalent coronary heart disease, diabetes, hypertension, LDL-cholesterol, HDL-cholesterol, body mass index and beta-blocker use at study baseline. Results: Of a total of 818 (7.7%) participants developed AF during an average follow up of 14.7 years. In a multivariate model, the hazard ratio (95% confidence interval) of incident AF with each log-unit increase in high frequency, SDNN, RMSSD were 0.88 (0.83, 0.93), 0.82 (0.70, 0.97), 0.80 (0.79, 1.00). There were no appreciable differences in these associations by race and gender. Conclusions: This study shows strong relationship between both time and frequency domain measures of HRV and incident AF. The findings suggest that poor autonomic cardiac tone, as reflected by low values in HRV measures, may be independently associated with incident AF, and thus may be a risk factor for poor health outcomes associated with AF.

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Heart Rate Variability and Incident Atrial Fibrillation: The Atherosclerosis Risks in Communities Study

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Background: Atrial Fibrillation (AF), a commonly seen sustained arrhythmia in clinical practice, is a strong risk factor for incident stroke. Though, autonomic perturbations are common before the initiation of AF, the association of baseline heart rate variability with development of atrial fibrillation remains less studied. Methods: We studied the association between measures of heart rate variability (HRV) measured using 2 minutes rhythm strip in 10471 middle aged adults (45-65 years at enrollment in 1987) from four US communities with incident atrial fibrillation. Those with poor quality HRV data or with ECG findings suppressing HRV analysis, or missing data on important covariates, and prevalent atrial fibrillation were excluded. The following HRV measures were natural log transformed to make their distribution normal: high frequency (HF), 0.15-0.40 Hz, high standard deviation of normal to normal RR intervals (SDNN), root mean square of successive differences of successive RR intervals (RMSSD). Incident AF cases were identified using electrocardiograms done at three follow-up visits (last visit in 1996-98), and from hospitalizations and death certificates through December 31, 2004. Hazard ratios were estimated using multivariate Cox models adjusted for age, gender, race, study center, smoking status (current, former, never), drinking status (current, not-current), prevalent coronary heart disease, diabetes, hypertension, LDL-cholesterol, HDL-cholesterol, body mass index and beta-blocker use at study baseline. Results: Of a total of 818 (7.7%) participants developed AF during an average follow up of 14.7 years. In a multivariate model, the hazard ratio (95% confidence interval) of incident AF with each log-unit increase in high frequency, SDNN, RMSSD were 0.88 (0.83, 0.93), 0.82 (0.70, 0.97), 0.80 (0.79, 1.00). There were no appreciable differences in these associations by race and gender. Conclusions: This study shows strong relationship between both time and frequency domain measures of HRV and incident AF. The findings suggest that poor autonomic cardiac tone, as reflected by low values in HRV measures, may be independently associated with incident AF, and thus may be a risk factor for poor health outcomes associated with AF.
The development of imaging methodologies for detection of BBB disruption is an emerging field. We have developed a novel methodology enabling real-time detection of BBB abnormalities with high sensitivity to BBB disruption and high spatial resolution. The presented proof-of-concept study was designed to evaluate the ability to depict BBB abnormalities in stroke. Methods: 19 patients were scanned by serial contrast-enhanced T1-weighted MRI (T1-Gd) 2-15 days after the onset of an ischemic stroke. BBB maps were calculated by subtraction of T1-Gd acquired immediately after contrast injection from images acquired 12-15 min later. Pre-processing included rigid and elastic registration and individual corrections for motion. The following BBB score was defined: 0 - no BBB opening; 1 - small opening; 2 - large opening; 3 - large opening depicted on T1-Gd as well. Results: Out of 19 patients, 8 depicted no BBB opening only on the BBB maps (score 1&2) and 8 depicted opening on the maps but not on T1-Gd. In the 8 patients with score 3, the average volume of BBB opening was 2.9 times larger on the maps than on T1-Gd: 4.9 ± 2.5 cm³ vs 1.7 ± 0.7 cm³, p < 0.01. In all 4 patients undergoing IPIA the score was 3. The average score of lacunar strokes (n = 8) was significantly lower than non-lacunar strokes (n = 11): 0.5 ± 0.3 vs 2.5 ± 0.3, p < 0.0001. Conclusions: The large number of patients depicting BBB opening in the maps relative to T1-Gd, and the larger volumes of BBB opening depicted in the maps, demonstrate the high sensitivity of this methodology. The correlation with IPIA and stroke type imply that this methodology may have prognostic/predictive value in stroke. Further studies designed to establish the correlation between early BBB opening and later outcome are ongoing. Figure: Examples of 3 strokes in 2 patients. BBB opening is depicted in red and intact regions in blue. It can be seen that the stroke depicted on H had significant BBB opening while the stroke depicted on H was intact, even though these 2 strokes occurred in the same patient.
Low Cerebral Blood Volume is Not Predictive of Diffusion Restriction in Minor Stroke

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Background and Purpose: Diffusion weighted MRI (DWI) demonstrates ischemic injury with high sensitivity. Although areas of low cerebral blood volume (CBV) are also used as a surrogate marker for irreversible injury, the precise relationship between diffusion abnormalities and CBV is unknown. We completed a comparative DWI-CBV study in acute stroke patients. We hypothesized that CBV would decrease in proportion to diffusion restriction, measured with the Apparent Diffusion Coefficient (ADC). Methods: Perfusion weighted imaging (PWI) and DWI were performed within 54 patients within 3 hours of symptom onset. Deconvolved Cerebral Blood Flow (CBF) pathways and Cerebral Blood Volume (CBV) maps were generated and coregistered to DWI and ADC maps. Mean ADC, CBF and CBV were measured within acute DWI lesions and contralateral homologous regions. Relative measures (ADC, rCBF, rCBV) were calculated as a ratio of affected to contralateral regions. Ischemic regions were also defined using CBV thresholds, based on percentage of normal contralateral tissue. Perfusion status at the time of the MRI was assigned to affected vs. unaffected. Patients with rCBV of <0.8 within the DWI lesion were considered to have persisting hypoperfusion. Results: In patients with major stroke (NIHSS>4, n=38), CBV was lower in ischemic regions as defined by DWI (2.8±1.4 mL/mG) than contralateral homologous regions (3.2±1.1 mL/mG, p<0.001). In minor stroke (NIHSS≤3, n=16), however, CBV was not significantly reduced (3.4±1.8 vs. 3.4±1.7 mL/mG, p=0.84). Linear regression indicated that rCBV and ADC were not related in major (R=0.4, p=0.49) or minor (R=0.01, p=0.85) stroke. rCBV was significantly lower in patients with persisting hypoperfusion (0.79±0.25 vs. 0.87±0.32, p=0.05). Early reperfusion (t<56 min, n=24, NIHSS<3) was associated with CBV recovery (rCBV=0.52 vs. 0.32, p=0.03). rCBV was not predictive of CBV in patients with persisting hypoperfusion (R=0.06, p=0.78). Only in patients imaged within 9 h of symptom onset (n=21) was rCBV predicted by ADC (R=0.499, p=0.021). Ischemic tissue volumes generated using a CBV threshold of the 10th percentile within the unaffected contralateral hemisphere (CBV<0.8) were correlated with DWI lesion volumes (R=0.81, p<0.001). The mean difference in CBV between DWI and lesion volume was 11.6 ml and the 95% limits of agreement were −19.6, −3.8 ml. Thus, even at this very low threshold, CBV defined ischemic tissue volumes were generally smaller than DWI lesion volumes. Conclusions: Low CBV does not reliably demonstrate areas of DWI restriction in minor stroke patients. Patients with major stroke do have consistently low CBV within areas of diffusion restriction, but ADC and CBV values are only correlated in the hyperacute setting. Defining ischemic tissue volumes by CBV thresholds tends to underestimate the extent of bioenergetic compromise detected by DWI. These results suggest DWI is the investigation of choice in minor stroke patients.

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CT Perfusion Cerebral Blood Flow Not Blood Volume Optimally Correlates With Admission Diffusion Weighting Imaging Assessment of Core Infarction Lesion Volume in Acute Stroke Patients

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Purpose: Infarct core lesion size at admission is one of the most important determinants of clinical outcome in acute ischemic stroke (AS). Our purpose was to determine the optimal CT perfusion (CTP) parameter and threshold to define the infarct core, using admission diffusion weighted imaging (DWI) as a reference standard. Method and Materials: We identified 48 consecutive AS cases with admission CTP and Diffusion weighted imaging (DWI) obtained within 3 hours of each other. CTP were acquired as 66-second biphasic cine. After co-registration of DWI to CTP, regions of interest (ROIs) for DWI lesions and normal tissue were placed over the slice with the largest affected area. ROIs were transposed on CTP maps. Normal contralateral hemisphere was used to calculate relative cerebral blood flow, volume and...
mean transit time (rCBF, rCBV and rMTT, respectively). Pixel level ROC curve analysis was done to calculate the area under the curve (AUC), optimal thresholds, sensitivities and specificities for each perfusion parameter. Results: More than 2.5 million pixels were analyzed. Using delay corrected software, the AUCs for CBV, rCBV, rCBF, rMTT, and rMTT were 0.76, 0.77, 0.85, 0.88, 0.75, respectively. Using standard software, the AUCs in the same order were 0.81, 0.83, 0.68, 0.68, 0.82 and 0.82, respectively. Using delay-corrected versus standard software, the optimal thresholds for absolute CBF were 5.4 and 4.7 ml/100gm/min, respectively, and for rCBF were 68% and 80% reduction, respectively. For absolute CBV these were 1.1 and 0.9 ml/mm, and for rCBV these were 60% and 47% reduction. Sensitivities and specificities for optimal thresholds were 0.9, 0.9, and 0.8, respectively. Optimal rCBF thresholds using delay corrected software. These were 0.82 and 0.90 for both absolute and relative optimal CBF thresholds using standard software. Conclusion: Absolute and relative CT CBV, acquired with a 6 second biphasic acquisition protocol, and calculated using both standard and delay corrected post-processing software provided optimal accuracy in defining infarction core comparing with admission DWI lesion in acute stroke patients. Clinical Relevance/Application: Infract core size can be most accurately estimated using both absolute and relative CT CBV maps processed with standard and delay corrected software. This may be of importance in the validation and standardization of acute stroke CTP.

Is the MTT a Reliable Surrogate of the Penumbra in Ischemic Stroke?

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Background and Purpose: Perfusion MR (pMR) and perfusion CT (pCT) are increasingly being used to identify the penumbra in acute stroke. Because these techniques do not afford reliable quantitative cerebrovascular measurements (e.g. quantitative time-to-maximum, mean transit time), particularly the mean transit time (MTT), are used instead. However, the reliability of MTT as a surrogate for CBF remains debated. Here we used previously acquired data from gold standard 150 PET to assess the reliability of PET-derived MTT for identifying the penumbra throughout the ischemic cascade.

Methods: Using the PET data (10mm diameter circular ROIs, average number per patient: 21449) obtained in 7 acute anterior circulation stroke patients (time since onset: 17.75.5 hours) in the Cambridge database, we computed the area-under-the-curve (AUC) of the receiver operator characteristic (ROC) curves for 3 MTT parameters (absolute MTT, MTT delay and MTT ratio). Three distinct penumbra thresholds were applied: i) classic: (CBF < 0.5); and ii) stringent: CBF0.55. To validate the results, we then compared the individual AUC and optimal thresholds (OT) in a second, independent sample of 30 patients from the Caen 150 PET database (time since onset: 10.85.3 hours). Results: Overall, AUCs ranged from 0.790.89, indicating good-to-excellent value of PET-derived MTT to identify the penumbra, with no significant difference among the 3 MTT parameters. The OTs ranged from 7.88.1, 2.84.3, and 151186% for the absolute MTT, MTT delay and MTT ratio, respectively, depending on the penumbra threshold used. The validation of these results onto the second sample revealed essentially identical findings for the AUCs with no significant difference between the two samples. The OT was significantly longer in the Caen sample for the CBF<20 ml/100g/min threshold (11.01.9 vs. 8.31.3; p<0.004), which may reflect slight differences in the PET methodology. Conclusions: These novel findings show that the MTT is a good-to-excellent surrogate for the penumbra in acute stroke and appears sufficiently reliable for clinical purposes, although MR- or CT-derived MTT may not perform equally well. Furthermore, we show that MTT delay and MTT ratio are at least as reliable as absolute MTT, which should facilitate comparison of MTT-based results among different centres.

Thrombus Attenuation on Thin-section Noncontrast CT Predicts Early Vascular Recanalization After Thrombolyis

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Background and Purpose: Thin-section noncontrast CT (NCT) can detect thrombus in large arteries in ischemic stroke, and can provide a measure thrombus composition based on Hounsfield Units (HU). Previous autopsy studies have shown that thromboembolic stroke can be caused by red, white and mixed clots. Platelet-rich thrombus is resistant to thrombolytic drugs, but erythrocyte-rich thrombus is not. It is known from experimental studies that lower HU in platelet-rich thrombus than in erythrocyte-rich thrombus. Our purpose was to investigate whether the lysability of thrombi in acute ischemic stroke can be predicted by HU values on thin-section NCT.

Methods: We retrospectively identified patients from our stroke registry (7/08 to 7/09) who presented to our institution with AIS and underwent perfusion CT (PCT) in the emergency department. We identified those that were taking statins prior to admission (prior statins - PS) and those who were not taking statins (statin naive - SN). We then calculated FBBP using micro-vascular permeability color maps that were retrospectively generated from PCT data using the Pritak model. We analyzed each PS map (permeability x surface area) by drawing the Region of Interests (ROIs) of the infarct and the weighted mean value of the ROI’s was taken as the value of the infarct for statistical analysis. Results: In total, we identified 59 patients. Demographics, comorbidities, and admission NIHSS scores were not statistically different in the two groups (Table). The mean FBBP in the statin group was 75.88ml/100/g/min and the mean FBBP in the non-statin group was 249.94ml/100/g/min (p=0.017). There was no statistical difference in favorable clinical outcome at hospital discharge parameters. Conclusion: Prior statin therapy is associated with reduced blood brain barrier permeability as measured by CT perfusion in patients with acute ischemic stroke patients. Our study helps to validate previous animal data that statins reduce blood brain barrier disruption after ischemic stroke. Our study is limited by its retrospective nature and small sample number.

Table 1. Demographics and Risk Factors

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<tr>
<th>Prior Statin</th>
<th>Statin Naive</th>
<th>P Value</th>
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<tr>
<td>(n=14)</td>
<td>(n=45)</td>
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<tr>
<td>Mean Age (Years)</td>
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<td>69</td>
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<tr>
<td>Male Sex (%)</td>
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<td>Atrial Fibrillation (%)</td>
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<tr>
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Comparison of Positron Emission Tomography With O15 and Magnetic Resonance Imaging-based Modalities to Assess Hemodynamic Compromise in Patients With Complete Carotid Occlusion

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Background: Positron Emission Tomography (PET) is considered the gold standard to assess stage II hemodynamic compromise in the setting of complete carotid occlusion. However, PET is not widely available and alternative modalities to assess high risk vascular compromise are needed. We sought to determine the sensitivity (SENS), specificity (SPEC), positive predictive value (PPV) and negative predictive value (NPV) of magnetic resonance-based (MR) modalities to assess vascular compromise. Methods: Patients with complete carotid occlusion underwent a combination of MR-based modalities aimed at assessing hemodynamic compromise including functional MR (fMR) imaging using blood oxygenation level dependent (BOLD) contrast, perfusion MR at baseline and after acetazolamide challenge, and quantitative phase contrast MR angiography (QMA) at baseline and after acetazolamide challenge. Results: 25 patients enrolled in the Carotid Occlusion Surgery Study underwent PET with O15 (mean age 58 years, 85% white, 52% male) and three patients had an ipsilateral-to-contralateral based count oxygen extraction fraction (OEF) ratio > 1.13, indicating hemodynamic impairment. Thirteen patients completed MRI with SENS 0.50, SPEC 0.55, PPV 0.17 and NPV 0.86. Seventeen patients completed a baseline perfusion MR with SENS 0.83, SPEC 0.82, PPV 0.21 and NPV 1.00. The Acetate HU value threshold was established in 10 patients with a SENS 1.00, SPEC 0.33, PPV 0.17 and NPV 1.00. Fifteen patients completed baseline QMA with SENS 1.00, SPEC 0.17, PPV 0.23 and NPV 1.00. QMA with Acetazolamide challenge was established for early recanalization discrimination was 1.32 (proportion correct: 87.0%). A HU value > 1.32 best predicted thrombus lysability. Conclusion: Measurement of thrombus attenuation may be helpful to help predict the prognosis of thrombolytic therapy in stroke patients. Thrombus attenuation could be a promising stroke biomarker to select the most appropriate reperfusion strategy for individual patients.
Relationship Between Apparent Diffusion Coefficient (ADC) and Early Recanalization After t-PA Infusion


Background and Purpose: ADC values are potential parameters for predicting clinical outcome in acute stroke patients and will be beneficial in the planning of a treatment protocol. In acute stroke patients treated with intra arterial tissue plasminogen activator (t-PA), early recanalization of occluded arteries can improve the clinical outcome. We hypothesize that blood perfusion from collateral flow in patients with occluded major brain artery is more supplied in ischemic regions with higher ADC than in those with lower ADC. Therefore, ADC is more effective for early recanalization in patients with higher ADC. The aim of the present study was to examine relationship between ADC value and early recanalization in acute stroke patients treated with IV rt-PA. Methods: Patients with the internal carotid artery (ICA) and middle cerebral artery (MCA) occlusion were studied. MRI studies, including DWI and MRA were performed before and within 30 min after t-PA infusion. Patients were divided into two groups according to the presence and absence of early recanalization; early recanalization group and non-early recanalization group. Early recanalization was included complete and partial recanalization. ADC mean value was calculated manually with using the one slice of ADC map before t-PA infusion. Results: A total of 117 consecutive patients were treated with t-PA at our stroke center from 2005 to 2009. Of them, 56 patients with occlusive brain main artery (ICA in 36, and MCA in 18) were enrolled into the study. MRA within 30 minutes after t-PA infusions revealed the early recanalization in 31 (55.4%) patients and non-early recanalization in 25 (44.6%) patients. There were no significant difference in onset to needle time(150 vs. 126 min, p = 0.12) and NIHSS score on admission (16 vs. 17, p = 0.77) two groups. Frequency of hypertension, hyperglycemia, atrial fibrillation and diabetes mellitus did not significantly differ between two groups. However, ADC value was significantly higher in early recanalization group than in non-early recanalization group (0.22 vs. 0.30, 0.007). The cut off value of ADC for detecting early recanalization using ROC analysis was = 0.60 x 10^-6mm²/s with sensitivity of 64.0%, specificity of 74.2%, positive predictive value of 66.7% and negative predictive value of 71.9%. Conclusion: Acute stroke patients with higher ADC value may be likely have early recanalization after IV t-PA infusion compared with those with lower ADC value.

TLR4 Deficient Mice Have Better Functional Outcome After Intracerebral Hemorrhage

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Background and Purpose: Infarction is thought to contribute to secondary neuronal injury after intracerebral hemorrhage (ICH). Ligands of TLR4, including fibrinogen, HMGB1, HSP60, and HSP70 may activate the innate immune system after ICH and contribute to the inflammatory response. Methods: Mice were anesthetized with 70% Nitrous Oxide, 30% Oxygen, 2-3% Isoflurane and maintained at 37 ± 0.5°C. Hemorrhage was induced by 15 μL autologous blood injection into the striatum (coordinates 2.5 mm to the right of bregma and 3 mm deep at 0.5 μL/minute). ICH surgeries were performed on C3H/HeJ mice, with a mutation in the TLR4 ligand binding site, and C3H/HeOuJ mice, their TLR4-wild type controls (Jackson Laboratories, Bar Harbor, ME). Sham surgeries were performed on the C3H/HeOuJ mice using identical surgical procedures, with DWI and MRA performed before and after ICH. The C3H/HeJ and C3H/HeOuJ mice were anesthetized and immersion fixed in 4% paraformaldehyde. The presence and type of each hemorrhage and blood clot size were scored on DWI using a 1-6 scale. Three major types of hemorrhage were scored and analyzed: (1) gross hemorrhage, (2) soft infarcted tissue, and 3) punctate hemorrhages (BPT) which are small isolated red marks. The automated score of total hemorrhages was calculated as (#R - #L)/(#R + #L), where #R is the number of section faces showing hemorrhage were noted. Three major types of ICH were analyzed: (1) gross hemorrhage, (2) soft infarcted tissue, and 3) punctate hemorrhages (BPT) which are small isolated red marks. The automated score of total hemorrhages was calculated as (#R - #L)/(#R + #L) as the number of sections showing hemorrhage were noted. (2) soft infarcted tissue, and 3) punctate hemorrhages (BPT) which are small isolated red marks. The automated score of total hemorrhages was calculated as (#R - #L)/(#R + #L) as the number of sections showing hemorrhage were noted. Results: Hemorrhage stages were calculated on post-operative day 1 (wild-type 0.41 vs. TLR4-deficient 0.41). The C3H/HeJ and C3H/HeOuJ mice had the same forelimb laterality on post-operative day 1 (wild-type 0.41 vs. TLR4-deficient 0.41). Treatment with TLR4 inhibitors could be beneficial for patients with ICH. The C3H/HeJ and C3H/HeOuJ mice had the same forelimb laterality on post-operative day 1 (wild-type 0.41 vs. TLR4-deficient 0.41). Treatment with TLR4 inhibitors could be beneficial for patients with ICH.

Lower Coated-platelet Levels Are Associated With Early Hemorrhagic Transformation of Non-lacunar Brain Infarction

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Background: Early hemorrhagic transformation (HT) is a complication of ischemic stroke that may alter patient management and outcome. Coated-platelets are a subset of platelets with high procoagulant potential observed under dual antigen stimulation with collagen and thrombin. While coated-platelet levels are elevated in patients with non-lacunar ischemic stroke, lower levels are present in patients with spontaneous intracerebral hemorrhage. Because these prior findings suggest that extent of coated-platelet activation among individuals may be associated with either thrombotic or hemorrhagic events, we undertook a study to investigate if there is a relationship between coated-platelet production and the presence of early HT in patients with ischemic stroke. Methods: Coated-platelet levels were determined in 105 consecutive patients with a diagnosis of non-lacunar stroke. Patients receiving anticoagulation or thrombolytics were excluded. HT was determined on the initial CT scan examination in the emergency department and confirmed by repeat CT or MRI studies. A neuroradiologist provided a definitive reading for all initial and repeat scans. Results: Among the 105 patients with non-lacunar stroke, 7 patients (6.7%) had early HT. Coated-platelet levels (mean ±SD) in all stroke patients were 37.6 ± 12.7% (range 10.8-66.2%). Statistical analyses of coated-platelet levels, distributed as tertiles (lowest 10.6-31.5%, middle 31.6-42.5% and highest 43.3-66.2%), as a correlate of HT (HT vs. no HT) showed a significant difference (P = 0.008). Early HT was present in 6 of 35 patients in the lowest tertile compared to 0 of 35 in the middle tertile and 1 of 35 in the highest tertile of coated-platelets. Conclusions: Low levels of coated-platelet synthesis strongly correlate with the presence of early HT in patients with non-lacunar ischemic stroke. Larger prospective studies are needed to further establish the potential connection between altered coated-platelet synthesis, early HT and cerebral perfusion. Support: OCAST (Dr. Prodan) and AHA (Dr. Dale).

The 3-Hydroxy-3-methylglutaryl Coenzyme A Reductase Inhibitor Simvastatin Reduces Thrombolytic-induced Intracerebral Hemorrhage in Embolized Rabbits

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Background and Purpose: 3-Hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase) inhibitors, more commonly known as statins, were initially designed as cholesterol- lowering drugs for the primary and secondary prevention of coronary artery disease. However, statins, which have pleiotropic effects, also appear to have protective effects on the vasculature and neurons. There has been some interest in using statins to treat acute ischemic stroke (AIS) and there is also some interest in treating hemorrhagic stroke with statin therapy. In this study, we assessed the pharmacological effects of simvastatin administered alone and in combination with tissue plasminogen activator (tPA) on measures of ischemia and hemorrhage in embolized rabbits. Methods: For these studies, simvastatin (20mg/kg, SC in DMSO) was administered 24 hours and 4 hours prior to large clot embolization. tPA (0.3 mg/kg, IV) was administered 1 hour following embolization. All surgical, embolization and histological procedures were done as described previously (Stroke, 39, 3073-3078, 2008). For histological analysis, surviving animals were euthanized 24 hours post-embolization, brains were removed and immersion fixed in 4% paraformaldehyde. The presence and type of each hemorrhage and the number of section faces showing hemorrhage were noted. Three major types of ICH were identified: (1) parenchymal hemorrhages (PH) are large homogenous masses of blood within tissue; (2) hemorrhagic infarction (HIH) consists of red speckling of an area, usually surrounded by soft infarcted tissue, and 3) punctate hemorrhages (HT) which are small isolated red marks within tissue. For infarct size, we measured the presence of ischemia showing damage. Infarction is grossly visible as pale, softer tissue surrounded by pink, normal brain tissue on the brain sections. Results: Intravenous tPA administration significantly increased hemorrhage volume.
by 175% (p = 0.022) and 80% (p = 0.0001) following embolization. Conclusion: The study suggested that simvastatin treatment blocks or attenuates mechanisms involved in IAP-induced hemorrhage. Our study suggests that statins may protect the integrity of cerebral vessels, and reduce ICH following intravenous thrombolytic treatment. Thus, a multicenter, randomized, double blind, controlled clinical trial of simvastatin administered prior to IAP appears to be warranted.

Background: Changes in hematoma volume affect outcome in patients with intracerebral hemorrhage (ICH). While considerable research has been performed in understanding hematoma expansion, little is known about factors predisposing to faster hematoma resorption and its effect on clinical outcome. Objective: To identify factors that are associated with greater than one third of hematoma volume reduction within 7 days and its impact upon inospital mortality in medically treated patients with ICH patients. Methods: We retrospectively reviewed medical records of all ICH patients admitted to two institutions within the last 5 years and those recruited in the prospective Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) study, who had a computed tomographic (CT) scan within 24 hours of symptoms onset and a follow-up CT scan between 3 to 7 days. Volume of hematoma was measured centrally using medical image processing software package. A hematoma reduction was defined as a reduction ≥ 33% or 12.5ml between the initial CT scan and the CT scan obtained during the 3 and 7 day post-symptom onset. Results: We identified a total of 137 patients who met the inclusion criteria (mean age (-standard deviation) 62 ± 15 years; 80(59%) were men). There was hematoma volume reduction in 62 (45%) of the 137 patients. A ≥ 33% reduction in hematoma volume was seen in 14 (10%) patients. Absence of chronic hypertension was associated with a greater proportion of patients with ≥33% hematoma reduction (21% versus 9%, p-value 0.06). Initial hematoma volume and time interval between first and follow-up scans were not associated with hematoma resorption. There was no difference in regards to in-hospital mortality or 90-days mRS score between the two patient groups. Conclusion: Prominent hematoma resorption occurs in approximately 10% of the patients within 7 days of onset with a higher likelihood among those who are non-hypertensive.

Blood-Brain Barrier Permeability Assessed by Perfusion-CT Predicts Symptomatic Hemorrhagic Transformation in Acute Ischemic Stroke

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Objective: To evaluate the sensitivity and specificity of admission blood-brain barrier permeability (BBBP) measurements derived from perfusion-CT (PCT) in predicting the development of symptomatic hemorrhagic transformation (SHT) in acute ischemic stroke patients. Methods: We retrospectively analyzed a dataset consisting of 32 consecutive acute ischemic stroke patients with appropriate admission and follow-up imaging. We calculated admission BBBP using delayed acquisition PCT data and the Patlak model. Collateral flow was assessed on the admission CTA, while recanalization and reperfusion were assessed on the follow-up CTA and PCT, respectively. SHT was defined according to ECASS III criteria. Clinical data was obtained from chart review. In our univariate and forward selection-based multivariate analysis for predictors of SHT, we incorporated both clinical and imaging variables, including age, admission NIHSS score, time from symptom onset to scan, treatment type, admission PCT-defined infarct volume, admission BBBP, collateral flow, recanalization and reperfusion. Optimal sensitivity and specificity for SHT prediction were calculated using ROC analysis. Results: In our sample of 32 patients, 3 developed SHT. Admission BBBP measurements above threshold were 100% sensitive and 79% specific in predicting SHT. Furthermore, all SHT patients - and only SHT patients - had admission BBBP measurements above threshold, were older than 65 and received IAP, giving the triad of characteristics 100% sensitivity and 100% specificity in predicting SHT (Figure 1). Admission BBBP, age and IAP were the independent predictors of SHT in our forward selection-based multivariate analysis. Figure 1 Interpretation: A combination of admission BBBP above threshold and age 65 was an a priori pre-treatment predictor of SHT in acute stroke patients receiving IAP.

Spatial Association Between Cerebral Microbleeds and β-Amyloid Deposition in Cerebral Amyloid Angiopathy

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Background: Cerebral amyloid angiopathy (CAA) is a common cause of intracerebral hemorrhage, vascular cognitive impairment, and cerebral microbleeds (CMB) in the elderly. The β-amyloid-binding radiotracer Pittsburgh Compound B (PiB) has been shown to label the amyloid plaques of Alzheimer disease. To determine the relationship between vascular amyloid and CMB, we examined whether retention of PiB is increased at foci of CAA-related CMB. Methods: We co-registered T2*-weighted MRI (Figure 1, panel 1) and PiB-PET images (panel 2) obtained from 16 nondemented subjects (mean age 64 ± 11.8) diagnosed with Probable CAA according to the Boston Criteria. The number of CMB varied across subjects: 11 had eight or fewer CMB, the remaining between 39 and 190. Mean distribution volume ratio (DVR) of PiB retention was determined at the site of the 580 detected CMB and compared with PiB retention at 3087 “simulated” CMB, randomly placed in the same subjects using a probability-density map of CAA-related CMB location. Mean PiB retention at the site of actual CMB was also compared to that in concentrically surrounding shells placed at increasing distances from the microbleed (panel 3). Histograms of PiB DVR confirmed approximate normality, and thus comparisons were performed by mixed-effects models with random effects controlling for subject-specific contributions. Results: Mean PiB retention was significantly greater at the site of CAA-related CMB than at randomly placed simulated CMB (PiB DVR for actual CMB 1.44 ± 0.18 SE, for simulated CMB 1.35 ± 1.77, p = 0.0001). The difference between actual and simulated CMB was greater in subjects with more than eight CMB than those with eight or fewer (p = 0.03). PiB retention tended to decrease with increasing distance from the site of actual CMB. Conclusions: The spatial correlation between CMB and PiB retention suggests that CAA-related hemorrhages occur preferentially at sites of increased β-amyloid deposition. This effect is most pronounced in subjects with higher microbleed counts. These results support further use of PiB-PET imaging as a marker of the spatial distribution of CAA and associated bleeding risk.

Initial Large Infarct Size Should Be Associated With Hemorrhagic Transformation in Acute Cerebral Stroke

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Background and Purpose: Hemorrhagic transformation (HT) occasionally occurs at acute phase of cerebral infarction. However, it has not been clear of the frequency and clinical
Factors associated with HT. The aim of this study is to investigate the frequency and what clinical factors were associated with HT in acute cerebellar infarction. Methods: We studied consecutive cerebellar infarct patients who met the following criteria: 1) no lesions in anterior circulation; 2) within 7 days from symptom onset; 3) performed MRI on admission and 7 days after HT. Among them, including 16 cases with T2*-weighted imaging (T2*) HT, HT was defined as new hypo-intense signal in the cerebellar infarct on follow-up T2*. We measured infarct size as maximum diameter of hyper-intense signal on initial DWI. All patients were classified into two groups based on the presence of HT, hemorrhagic group (H group) and no hemorrhagic group (Non-H group). We assessed clinical characteristics including stroke subtype, risk factors, and infarct size with univariate analysis. Then, we conducted multivariate analysis for selected variables that p value is less than 0.10 by univariate analysis. Results: Seventy three patients (age; 69.8±14.5 years, men; 49 (67%) were enrolled into this study. Stroke subtypes were large-vessel diseases in 5 (7%) of 73 patients, cardioembolic stroke in 21 (29%), and other or undefined cause of stroke in 47 (64%). HT was observed in 32 (44%) of 73 patients (H group) and absent in 41 (56%) patients (Non-H group). In the H group, female are more common compared with Non-HT group (45% vs. 18%, p=0.006). Infarct size of patients in HT group was larger than that of patients in Non-HT group (35.1±13.9mm vs. 24.4±13.1mm, p<0.001). No other clinical factors including age, atrial fibrillation, hypertension, diabetes mellitus, and National Institute of Health Stroke Scale score differed between H and Non-H groups. With the receiver operating characteristic curve, infarct size >26.5mm is the optimal cut off value for HT with sensitivity of 74% and specificity of 72%. Using this cut off value, multivariate analysis revealed infarct size >26.5mm was the only factor associated with HT (OR 5.47, 95%CI 2.06-14.56, p<0.01) Conclusion: Hemorrhagic transformation occurred in about a half of patients with acute cerebellar infarction. Infarct size more than 26.5mm should be associated with hemorrhagic transformation.

**MRI Profile of the Perihematomal Region in Acute Intracerebral Hemorrhage**


Background: Tissue fate of the perihematomal region surrounding acute spontaneous intracerebral hemorrhage (ICH) may affect ICH outcome. We investigated the MRI diffusion-perfusion profile of the perihematomal region in patients who presented with an acute ICH.

Methods: Twenty ICH patients from the Diagnostic Accuracy of magnetic resonance imaging (MRI) in Spontaneous Intracerebral Hemorrhage (DASH) study were selected for diffusion-weighted (DWI) and perfusion-weighted MRI (PWI). The FLAIR, DWI and PWI images were co-registered. The outside border of increased T2 signal of the perihematomal brain tissue bordering the hematoma (i.e. presumed perihematomal edema) was outlined on FLAIR. The inside border was outlined on the T2* sequence to avoid any potential artifact from blood products on the PWI measures. Ipsilateral hemispheric ROIs were drawn in normal appearing brain tissue remote from the hematoma. Tmax and ADC values in the perihematomal region (PHR) ROIs were compared with mirror ROIs of the same size drawn in the opposite hemisphere as well as with remote ipsilateral hemispheric ROIs. Results are presented as medians (IQR). Related measures were compared using the Wilcoxon signed-rank and Friedman tests and independent ones with the Mann-Whitney U test.

Results: Twenty prospectively enrolled patients were included in this study. MRI was performed 26 hrs (15-41) after symptom onset. Initial CT ICH volume was 15cc (8-38), by FLAIR MRI 23.2cc (12-58) and mean 26.5mm should be associated with hemorrhagic transformation.

**Multimetric MRI ISODATA Analysis in the Assessment of Acute Ischemic Stroke**

Panayiotis Mitsias, Mei Lu, Hassan Bagher-Ebadian, James R Ewing, Hamid Solati, Nikhil Gupta, Michael Chepp, Henry Kays, Deepak Mehta

OBJECTIVES: The purpose of this study was to show that the computer segmentation algorithm iterative Self-Organizing Data Analysis Technique (ISODATA), which integrates multiple MRI parameter maps, can be used to segment hypoperfused tissue with good accuracy. We used ISODATA to segment the hypoperfused tissue in the DWI, T2WI, and T1WI from acute stroke patients. The ISODATA algorithm was able to accurately segment the hypoperfused tissue with high accuracy, which can be useful in clinical practice.

Methods: The ISODATA algorithm was applied to the MRI images of acute stroke patients. The algorithm was able to accurately segment the hypoperfused tissue with high accuracy, which can be useful in clinical practice.

Results: The ISODATA algorithm was able to accurately segment the hypoperfused tissue with high accuracy, which can be useful in clinical practice.
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Infarct Core Size Greater Than 58 cc on Thresholded CT Cerebral Blood Flow Maps is Highly Correlated With Poor Outcome
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Purpose: In order to select acute stroke patients who will benefit most from thrombolytic therapy without taking unnecessary risk, it is important to identify initial infarct core lesion size above which patients have poor outcome. Our purpose was to determine initial thresholded CT CBF and CT CBV lesion volumes above which acute ischemic stroke (AIS) patients have poor clinical outcome. Material and Methods: 81 consecutive patients with acute anterior circulation stroke who underwent CT perfusion (CTP) within 9 hours of symptom onset and who had clinical outcome data available were evaluated. CTP maps were acquired with a 66 second biphasic acquisition, covering 8 cm and were processed with delay corrected deconvolution software (GE CTP). CT CBV volumes were automatically calculated with a relative threshold of 60% of the contralateral normal side and CT CBF volumes were calculated with a relative threshold of 30% of the contralateral normal side. These thresholds were chosen to identify infarct core based on previous work comparing CTP to DWI lesion volumes. Clinical outcomes were considered good if the modified Rankin scale (mRS) was 0-2. Receiver Operating Characteristic (ROC) curves were calculated. Results: 12 of 31 (39%) patients had a good clinical outcome (mRS 0-2) and had significantly smaller initial CT CBV lesion volumes (mean 42.2 cc) versus patients with mRS 3-6 (84.7 cc) (p ≤ 0.05). Patients with good outcomes also had significantly smaller CT CBF lesion volumes (26.9 cc) versus patients with poor outcomes (73.3 cc) (p < 0.05). ROC curves for CT CBV and CT CBF relative to poor outcome, had areas under the curve of 0.782 and 0.786, respectively. For CT CBV lesion volume, we chose a cut-off point of 77 cc with 100% specificity and 37% sensitivity for poor outcome. 7/7 (100%) patients with CT CBF lesion size > 77 cc had poor outcome. For CT CBF lesion volume, we chose a cut-off point of 58 cc with 100% specificity and 52.6% sensitivity for poor outcome. 10/10 patients with CT CBF lesion volume > 58 cc had poor outcome. Conclusion: Patients with good clinical outcome had smaller CT CBV and CT CBF infarct core lesion size on admission CTP. CT CBF infarct core lesion size > 77 cc and CT CBV infarct core lesion size > 58 cc are highly specific for poor outcome. These findings may be important for therapeutic decision making.

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IV tPA Prevents Progressive Hypoperfusion during Acute Ischemia
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The clinical efficacy of IV tPA is thought to be due to its ability to restore tissue perfusion (reperfusion). In this study, MR perfusion-weighted imaging (PWI) was employed to quantify the evolution of hypoperfused tissue during acute ischemia in patients treated with or without tPA. A total of 22 ischemic stroke patients were prospectively imaged using MR PWI at 2.9 ± 0.8 hrs (tP1) and 6.3 ± 0.3 hrs (tP2) after symptom onset. Seventeen patients received IV tPA 1.8 ± 0.5 hrs after stroke onset (mean NIHSS 13) while the remaining five patients did not (mean NIHSS 14). One month FLAIR images were acquired to delineate the final infarct. A mean transit time (MTT) > 4 seconds of that in the contralateral hemisphere was used to define “hypoperfused” brain tissue. A “reperfused” voxel was defined as hypoperfused at tP1 but normal at tP2. Voxels which were not hypoperfused at tP1 but became hypoperfused at tP2 were termed “newly hypoperfused”. The volumes of hypoperfused tissue at tP1 (Vtp1), and reperfused tissue (Vreperf) and newly hypoperfused tissue (Vnew) and Vnew/Vtp1, respectively. The mean volumes of hypoperfused tissue at tP1 (Vtp1) were 58.1 ± 45.1 and 56.8 ± 68.2 ml in tPA-treated and non-treated patients, respectively. Tissue reperfusion was observed in both groups independent of treatment with tPA. Reperf% was not statistically different between the two groups (Figure, p = 0.23). In contrast, the tPA-treated patients exhibited a statistically smaller New hypo% (Figure, p = 0.001). The percentage of Vtp1 and Vnew that went on to infarct was 10.3 ± 12% and 29.7 ± 29.8% (p = 0.36), respectively. About 30% of the hypoperfused tissue at tP1 was reperfused by tP2 in the tPA-treated group, suggesting that only partial reperfusion is achieved with tPA. Since the reperfusion was evaluated using the tP2 scan, one could argue that reperfusion may continue beyond tP2 (6.3 hrs after stroke). However, the effectiveness in salvaging brain tissue beyond 6hrs may be substantially diminished. The tPA group exhibited a trend of larger Reperf % and a statistically smaller New hypo%, suggesting that IV tPA might prevents progressive hypoperfusion besides restoring tissue perfusion during acute ischemia.

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Emergency Department Arrival Times After Transient Ischemic Attack
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Background: The risk of ischemic stroke is highest in the first several days after a transient ischemic attack (TIA). Thus, early presentation to medical attention is important. Nationwide efforts in recent years have focused on improving patient awareness of stroke symptoms and increasing access to urgent care. We investigated trends in arrival time to hospital emergency departments (EDs) amongst patients with TIA in a bi-racial population of 1.3 million. Methods: Using ICD-9 codes 430-436, we ascertained and physician-verified all TIA events presenting to local EDs in 7/93-6/94, 1999, and 2005. Time of symptom onset and patient demographics were recorded as documented in the medical record. Chi-square and logistic regression were used for statistical analysis. Results: The total number of TIA events evaluated in an ED was 613 in 1993-1994, 862 in 1999, and 833 in 2005. Patient populations were similar across all study periods: mean age ranged from 70-71 years, percent black ranged from 12-16%, and percent male was 42-44%. Exact onset time was documented in 51% of patient charts in 1993-1994, 60% in 1999, and 58% in 2005. These documentation numbers are consistent with those previously reported for ischemic stroke in this population. The percentage of patients arriving early improved over time. Arrival within three hours of symptom onset was 38% in 1993-1994, 43% in 1999, and 46% in 2005 (Figure 1) (p = 0.004 for trend over time). There was no significant difference in arrival times between races (p = 0.07) and sexes (p = 0.009). Conclusions: Within our population, patients are arriving more quickly for emergency care after experiencing a TIA. Arrival early appears to be influenced by age. This may indicate that national and local efforts to improve community awareness of stroke symptoms and stroke care have had a beneficial effect. Continued efforts to promote public perception of TIA and stroke as medical emergencies may be important in improving treatment rates or outcomes over time.
stroke may be decreasing, at least in whites. However, it is unknown how the incidence of TIA is changing over time in the United States. We present temporal trends in the incidence of TIA within a large bi-racial population. Methods: The Greater Cincinnati/Northern Kentucky Stroke Study reviewed TIA cases occurring in the population of 1.3 million inhabitants during the periods of 1993–94 / 1999 / 2005. A TIA event was defined as focal neurologic symptoms lasting < 24 hours. Cases were identified retrospectively at all local hospitals by screening ICD-9 codes 430–436. Medical records were reviewed by study physicians who ultimately decided whether a case was a TIA. We are reporting on events seen in Emergency Departments in patients of 20 years or older. Incidence rates were adjusted to the US Census 2000 population for age, race, and sex. Results: The overall rate, age, and gender-adjusted rate for TIA within our population did not significantly change across the study periods. There was a statistically significant decline in the incidence of TIA among blacks between the 1993/94 and 2005 study periods (p = 0.01). There was no significant temporal change across the study periods for rates of TIA for whites (p = 0.91) or by gender (p < 0.009 for males and p = 0.38 for females). In addition, we previously reported racial and gender disparities in the incidence rate of TIA (higher for blacks and men) that were present in the 1993/94 study period were no longer present in 2005.

Methods: The incidence rate of TIA (higher for blacks and men) that were present in the 1993/94 study period were no longer present in 2005.

Background: The ABCD2 score has been shown to predict stroke after TIA. The score includes history of diabetes mellitus and SBP > 140 or DBP > 90 mm Hg at presentation. Recently, it has been suggested that including acute hyperglycemia and history of hypertension improves the predictive value of the score. Though the score uses acute BP at presentation, triage BP measurements may be falsely elevated in many patients due to “emergency department (ED) triage hypertension.” It is possible that use of a second BP measurement improves the accuracy of the score. Methods: We tested the standard ABCD2 score in a prospective cohort of TIA patients presenting to the ED. The outcome endpoint was a composite of stroke, death, or a TIA mechanism requiring emergency treatment. We then determined the shifts in individual patient risk score categories (low-risk: 0–3; moderate: 4–5; high: 6–7) with proposed modifications of the standard ABCD2 score. Modifications tested included: (A) use of glucose >120 mg/dL in place of DM for one point (B) either hyperglycemia or DM for one point (C) use of a history of hypertension in place of acute elevation for one point (D) the presence of either acute BP elevation or history of hypertension for one point, or (E) replacement of initial BP with the second recorded measurement. C-statistics were used as a measure of test accuracy. Results: In the cohort of 167 patients, increasing ABCD2 score was associated with our endpoint (score 0–3: 15%; 4–5: 27%; 6–7: 43%; c-statistic 0.64, 95%CI 0.55–0.73). Results of various modifications of ABCD2 are presented in Table 1. Few patients shifted categories, and no significant improvement was seen with any modified ABCD2 scheme. A second BP was recorded in the ED for 157 (94%) of patients after a median time of 144 minutes. Compared to initial BP, SBP decreased by a mean of 7.4 mm Hg (p < 0.0001) and DBP by 8.1 mm Hg (p = 0.0001)...

Conclusion: Modifications of the ABCD2 score incorporating various permutations of acute hyperglycemia, diabetes mellitus, acute BP measurement, or history of hypertension result in shifting of small numbers of patients in risk categories without improvement of test characteristics. The phenomenon of “ED triage hypertension,” though present in TIA patients, does not appear to affect ABCD2 risk stratification adversely. This research has received full or partial funding support from the American Heart Association, National Center.

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Introduction: Transient ischemic attack (TIA) is a marker for early risk of stroke. The ABCD2 score permits identification of those patients at highest risk that may benefit from aggressive management. Previous studies have suggested improved outcomes by referral to dedicated clinics, or by hospital admission. Application of these models is limited by resource constraints that prevent application of these models to all patients. We therefore sought to determine the shifts in individual patient risk score categories (low-risk: 0–3; moderate: 4–5; high: 6–7) with proposed modifications of the standard ABCD2 score. Modifications tested included: (A) use of glucose >120 mg/dL in place of DM for one point (B) either hyperglycemia or DM for one point (C) use of a history of hypertension in place of acute elevation for one point (D) the presence of either acute BP elevation or history of hypertension for one point, or (E) replacement of initial BP with the second recorded measurement. C-statistics were used as a measure of test accuracy. Results: In the cohort of 167 patients, increasing ABCD2 score was associated with our endpoint (score 0–3: 15%; 4–5: 27%; 6–7: 43%; c-statistic 0.64, 95%CI 0.55–0.73). Results of various modifications of ABCD2 are presented in Table 1. Few patients shifted categories, and no significant improvement was seen with any modified ABCD2 scheme. A second BP was recorded in the ED for 157 (94%) of patients after a median time of 144 minutes. Compared to initial BP, SBP decreased by a mean of 7.4 mm Hg (p < 0.0001) and DBP by 8.1 mm Hg (p = 0.0001)...

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A Telestroke Network Enhances Recruitment Into Acute Stroke Clinical Trials

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Introduction: Acute stroke clinical trials are conducted primarily at academic medical centers. As a result, patients living in rural areas are excluded from participation, results may not be generalizable, and studies may hemorrhage slow to recruit subjects. Telestroke can provide rural patients with emergency neurovascular consultation. We sought to determine whether telestroke could facilitate enrollment into acute stroke trials. Methods: We have an established “hub and spoke” telestroke network that includes ten rural hospitals located 37 to 103 miles from the hub. From 2005 to 2009, we participated in two time-sensitive acute stroke trials, FAST and MINO. Candidates for the two trials were identified at both the hub and spokes with the latter transferred to the hub for enrollment. We analyzed the times from symptom onset to consultation (OTC), to arrival at the hub (OTH), and to treatment with study drug (OTT) to determine the impact of telestroke on study enrollment. Results: A total of 28 patients were enrolled in the two trials. Of these, 19 (68%) were identified via telestroke and 9 (32%) presented directly to the hub. An additional 9 otherwise qualified patients were identified via telestroke, but could not be enrolled due to arrival at the hub beyond the enrollment window (n=28, 32% of all qualified patients identified via telestroke). As expected, the OTC time via telestroke was shorter for patients who were enrolled compared with those who were transferred too late to participate (64 versus 142 minutes (p = 0.03) in the FAST trial and 140 versus 145 minutes (p = 0.13) in the MINO trial). Also, for subjects enrolled in the two trials, the mean OTH and OTT times were 119 p = 0.00002 and 60 minutes (p = 0.03) longer respectively for patients transferred to the hub for enrollment compared with those who presented directly to the hub. A ninety day follow-up clinical exam was obtained in all 19 subjects recruited from the spoke hospitals. Conclusions: Telestroke can enhance enrollment into time-sensitive acute stroke trials. However, transfer of subjects to the hub delays study initiation for some and precludes enrollment for others similar to the weaknesses of “ship and drip” thrombolytic strategies. To increase enrollment and reduce the OTT in acute stroke trials, efforts are needed to enroll clinical trial subjects and begin the research drug at remote sites via telestroke guidance.

Introduction of the Portable CT Scanner in the Treatment of Acute Stroke Patients via Telemedicine in Remote Communities

Ashfaq Shuaib, Khushred Khan, Tammy Whittaker, Patrick Crumblie; Univ of Alberta, Edmonton, Canada

Background: Thrombolysis is an established treatment in selected patients who present early to hospital after symptoms of acute ischemic stroke. Treatment can only be offered after the patient has been assessed by highly trained physicians and imaging studies have ruled out a brain hemorrhage. This limits the wider availability of thrombolysis to patients in remote communities, especially in countries with limited resources. There has been considerable success with the use of TeleStroke to overcome such barriers. TeleStroke is feasible in remote hospitals provided there is an available CT scanner, a fundamental prerequisite in the assessment of acute stroke and thrombolysis. We report our 7 month experience with a portable CT scanner that can be operated by personnel with minimal training. Objective: Report on initial experience with a portable CT scanner for management of acute stroke in a remote community. Methods: To study the application of a portable CT scanner in a remote community with telemedicine to evaluate and treat patients presenting with symptoms suggestive of an acute ischemic stroke. The University of Alberta Hospital in Edmonton, Canada was the ‘hub’ site and Wainwright Community Hospital was the ‘spoke’ site. Results: Over a 7 month period, 28 patients were evaluated in the emergency department of the remote hospital where the referring physician felt that symptoms indicated potential for thrombolysis. All patients were evaluated remotely by a stroke neurologist in a TeleStroke service situated 207 km from the rural site. After clinical examination, cranial CT scans were obtained with the portable scanner and evaluated by the stroke neurologist. In three patients, thrombolysis was not offered because the CT showed evidence of brain hemorrhage (two ICH and one SAH). Six patients meeting the standard criteria received thrombolysis within 4.5 hours from onset of symptoms. There was a significant improvement in four patients. One patient made moderate recovery and one patient died from massive aspiration pneumonia within 24 hours after onset of symptoms. In the remaining 22 subjects, symptoms improved rapidly, were outside the window for thrombolysis or were not consistent with an acute ischemic stroke. Conclusions: Our preliminary study shows that the portable scanner can be used successfully in the evaluation of patients in remote regions that are not within timely reach of stroke experts or do not have available community imaging with CT scans. Telemedicine, in combination with the use of portable scanners, offers hope to a large remote population base that would otherwise not have access to appropriate acute stroke treatment.

A “Non-commercial” Telemedicine System is Feasible and Cost-effective: The Experience of the StrokeCareNow Network

Nils Mueller-Kronast, Fort Wayne Neurological Ctr, Fort Wayne, IN; StrokeCareNow Group

Introduction: Telemedicine (TM) is rapidly emerging as a solution to the lack of neurological expertise in rural hospital which limits the utilization of thrombolytic treatment of acute stroke. However, providing Stroke TM using commercial systems remains costly and is not reliably reimbursed. The StrokeCareNow Group developed its own “non-commercial” system to provide more cost-effective Stroke TM. Methods: In Phase I from January until December 2005, four existing self-propelled TM systems were leased to provide remote intensive care support in rural hospitals. Employed for acute stroke triage because of the high cost and resistance of other non-affiliated “spoke” hospitals to adopt Stroke TM more widely in the region, a cart based “Remote Stroke Evaluation Tool” (ReSET) was developed out of readily available computer components together with the Parkview IT department at a cost of around USD 10,000. In Phase II, starting in January 2009, the commercial TM systems were replaced by ReSIs. Results: 159 strokes were documented in the “spoke” hospitals during the 18 month observation period. In Phase I 12 Telemedicine consultations were provided through the commercial system, out of which 3 patients locally received intravenous thrombolysis (IV tPA), 2 were emergently transferred for intra-arterial treatment. One technical delay was documented in Phase II after development of the ReSET 14 Telestroke consultations were performed over 6 months, 2 of which resulted in no TM. No technical delays were documented. The ReSET provided satisfactory exams during all encounters. Use of thrombolytic therapy increased from 0% to 4.4% with use of TM in the “spoke” hospitals. Replacing the commercial systems resulted in a cost savings of more than USD 360,000 per year. Since the deployment of the first ReSET 17 “spoke” and 1 “hub” hospitals have signed agreements to create the StrokeCareNow Network. Conclusion: A cost-effective and dependable “non-commercial” TM system is feasible and can replace a commercial TM system. “Non-commercial” systems may be especially attractive for rural stroke systems with low “spoke” stroke hospital volume. Our experience shows that there is strong interest in Stroke TM - provided there is no undue financial burden to the hospitals.

Neurologists Opinions Regarding Telestroke

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Introduction: Emergency Department (ED) physicians may be reluctant to administer intravenous tPA without a neurologist. At the same time, many neurologists are limiting their involvement in acute stroke consultations. To increase enrollment and reduce the OTT in acute stroke trials, efforts are needed to enroll clinical trial subjects and begin the research drug at remote sites via telestroke guidance.

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that half felt that telestroke would increase their risk of being sued for malpractice (52%), and most expected compensation on a par with in-person consultations (72%). Conclusions: Most neurologists in Georgia remain actively involved in acute stroke care. However, many no longer provide emergency coverage to hospital EDs. Neurologists appear interested in using telestroke to provide urgent acute stroke consultations. In particular, the ability to perform consults from home or office and travel time saved using telemedicine are attractive features. However, expectations regarding reimbursement for consults and medicolegal concerns may be impediments which slow the broader acceptance of telestroke by non-academic neurologists.

### Background/Objective: Favorable outcomes after stroke are more likely if patients have early access to a primary stroke center for stabilization and treatment with thrombolytic therapy. Unfortunately, patients in rural areas often must travel long distances for treatment. Our aim is to analyze the current population coverage of existing primary stroke centers in the state of Iowa and to approach the optimal number and location for additional stroke centers.

### Methods: Maximal coverage models are used to find quasi-optimal spatial patterns for providing services by a variety of organizations such as retail stores or restaurants. Using a maximal coverage model we maximized the number of persons within 30 miles of 119 hospitals. Starting with N = 1 unit until N = 119. We found a maximal-optimal location for one sentinel hospital provider. Holding each previously selected sentinel location fixed, we increased N by 1 unit until N = 119. This gave us the “best” possible locations for adding individual locations. In a similar fashion, we computed the “best” additional sites, given the existing 7 primary stroke centers. The population in each zip code area (ZCTA) in Iowa was obtained from the 2000 US Census, the geographic location of hospitals in Iowa from the Natural Resources Geographic Information Systems Library, the location of existing primary stroke centers was obtained from the JCAHO website, and the ZCTA to hospital distances were computed from the geographic locations of the ZCTAs and hospitals. Results: The state of Iowa has a population of 3.296.811, which is currently covered by 7 primary stroke centers. These centers only cover 47% of the population, assuming a treatment radius of 30 miles. The coverage drops to 38% if a 20-mile radius is assumed. Our maximal coverage model determined in order to cover 75% of the Iowa population within 30 miles. 7 additional primary stroke centers would be located in communities that currently do not have stroke centers. Conclusions: The current distribution of primary stroke centers covers a small proportion of the population of Iowa. Our results suggest that a moderate investment in additional primary stroke centers would significantly impact the coverage within the state. Given the distribution of population and health care facilities in Iowa and other states with large rural populations, use of a maximal coverage model may help target further recruitment efforts for development of new stroke treatment centers.
Detection of Angiotensin II Type 2 Receptor in Hematopoietic Cells

Enhanced Brain Damage After Ischemia-Reperfusion Injured Mice

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Introduction: Angiotensin II receptors are reported to be highly expressed in bone marrow cells and may affect hematopoietic development. Bone marrow chimeric mice with angiotensin II type 1 receptor deficient marrow shows pathological differences in renal fibrosis, leukocyte recruitment, indicating that renin-angiotensin system in hematopoietic cells plays an important role in hematopoietic cell function. Recently, we have found that AT2 receptor signaling in hematopoietic cells is ischemia-reperfusion injury (IR) injury. Method: Chimeric mice were generated from female WT mice irradiated with lethal dose of 9.5-Gy and transplanted with bone marrow cells from male wild-type (WT-chimeras) or AT2 receptor-deficient (AT2KO-chimeras) mice. IR injury was induced with a two-dimensional blood flow meter. Inflammatory cytokines were assessed by quantitative RT-PCR method. Results: AT2-KO chimeric mice showed significant lower cerebral ischemic area and stroke volume compared with WT-chimeras mice. Neurological deficit was improved in AT2-KO-chimeras more than WT-chimeras. In AT2-KO-chimeras, cerebral blood flow before injury was significantly decreased compared with that in WT-chimeras. After 24 hours of MCA occlusion, decreased cerebral blood flow was recovered in WT-chimeras in the core and the periphery region; however, such improvement was not observed in AT2-KO-chimeras. AT2-KO-chimeras has a tendency to increase TNF-α expression in ipsilateral hemisphere compared with WT-chimeras. Similar effect was observed in expression of MCP-1 mRNA. Conclusion: These findings showed that deletion of AT2 receptor signaling in hematopoietic cells enhanced ischemic brain damage and neurological deficit after IR injury partly due to the decrease in cerebral blood flow and after IR injury.

Oligodendrocyte Induces Angiogenesis: Possible Role of Oligovascular niche Under Pathologic Conditions

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Background and Objective: Cell-cell signaling within the neurovascular niche mediates and sustains pools of ongoing neurogenesis and angiogenesis in adult brain. Recently, we have proposed a “corresponding oligovascular niche”, wherein cerebral endothelial cells support the survival and proliferation of oligodendrocyte precursor cells. Here, we ask whether reciprocal signaling also may exist, whereby oligodendrocytes in turn provide trophic support for blood vessels and promote angiogenesis. Methods: We used primary rat oligodendrocytes (OLs) prepared from neonatal Sprague-Dawley rats, and human umbilical vein endothelial cells (HUVECs) to test the hypothesis that OLs induce angiogenesis in the oligovascular niche. Two representative angiogenic mediators were assessed: VEGF levels via western blots and MMP-9 via gelatin zymography. A matrigel tube formation assay and a migration assay were used to quantify in vitro angiogenesis. Results: OLs expressed myelin basic protein, a marker for mature OL, and also vascular endothelial growth factor (VEGF), a well-known angiogenic factor. Conditioned media from OL cultures accelerated the tube formation of HMEC-4 cells in vitro. Importantly, gelatin zymography showed that an inflammatory cytokine interleukin 1β (IL-1β) induced the secretion of matrix metalloproteinase-9 (MMP-9), another well-known angiogenic factor) via the MEK/ERK pathway. Consequently, conditioned media from IL-1β-stimulated OL cultures promoted the migration of RBE4 cells. Conclusions: OLs may participate in angiogenesis, and IL-1β enhances these angiogenic effects of OLs. Because inflammatory cytokines are upregulated under pathologic conditions, these data suggest a novel mechanism of angiogenenic recovery in an oligovascular niche after stroke. Further studies are needed to evaluate how OL-derived VEGF and MMP-9 may promote angiogenesis in vivo during stroke recovery.

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The Return of the Caffeine to the Bench: Neuroprotection in Old Animals With Acute Ischemic Stroke

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Background: The combination of caffeine and ethanol (caffeoin) has neuroprotective effects and can reduce infarct size by 45% when given 2hrs after reversible common carotid artery/middle cerebral artery occlusion (CCA/MCAo) in 2-3 month old rats. The STAR guidelines now recommend that novel therapies for acute stroke treatment (ASTOS) should be studied in older animals before moving forward to clinical trials. We therefore studied the effects of caffeine in old rats with AIS. Methods: Thirty-eight F344 Fischer rats at 19 months of age underwent CCA/MCAo for 3 hrs and were randomly assigned to receive an IV injection of either caffeine (0.6 mg/kg caffeine, 0.2 g/kg choline) or saline+sham (1/hr=10 saline, n=11 caffeine) or 3hrs (n=6 saline, n=7 caffeine) after the onset of ischemia. The animal surgery was blinded to treatment. A 0.5 ml bolus was followed by a 2.5 hr continuous infusion at a constant rate of 1ml/hr. Twenty-four hours after ischemia, animals that remained alive were sacrificed and the brains sectioned and stained with TTC for infarct measurement. Results: CCA/MCAo was well tolerated in all species in all animals and caused selective cortical infarction similar to young animals. There was a significant time by treatment interaction with the caffine treated group showing a 50% reduction in infarct size when given at 1hr after the onset of stroke (108±94 mm² vs. 218±79 mm², p<0.01). In addition, spontaneous behavioral indicative of overall health and functional outcome at 2 hrs after treatment was recorded on a 5 point scale comprised of any movement, vertical exploration, eating, drinking, and grooming. Caffeine treated animals exhibited significantly more spontaneous behavior than saline treated animals (median score of 3 vs 0, p<0.05, Mann Whitney test). There was a 33% mortality in the saline treated group and no mortality seen in the caffeine treated group. All animals were started at 3 hrs after occlusion, there were no significant differences in infarct volume, behavior, or mortality at 24 hrs. Conclusion: Caffeine has a similar therapeutic window after
reversible CCA/MCAo in old animals compared with previous findings in young animals. While prior studies indicate that suture occlusion of the MCA is not technically feasible in aged Fischer 344 rats, the CCA/MCAo model can be employed to study novel stroke therapies in these older animals.

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**IPA Expression in Single Astrocytes Captured With Laser Microdissection is Increased After Treatment of Stroke in Mice With Bone Marrow Stromal Cells**

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Accumulated evidence suggests that bone marrow-derived mesenchymal stem cells (BMSCs) are capable of regenerating damaged tissue, but the underlying mechanisms are not well understood. Previous studies indicate that astrocytes possess both axon-growth promoting and axon-growth inhibitory properties that may contribute to the regenerative capacity of the brain. Extracellular proteolytic enzymes of the tissue-type plasminogen activator (IPA) system play a crucial role in the axon regeneration. In the present study, we examined whether the treatment of BMSCs had an effect on the activity of the IPA system in single astrocytes in mice after stroke. Adult C57BL/6J wild type mice were subjected to permanent middle cerebral artery occlusion (MCAo). A therapeutic dose of BMSCs (1 × 10^5 cells) treatment or phosphate-buffered saline was transplanted by tail vein injection 24 hrs after MCAo. Approximately 1000 single astrocytes stained with antibody against glial fibrillary acidic protein (a marker for astrocytes) were isolated in the ischemic boundary zone after stroke. In combination with real-time PCR, we found that IPA significantly increased the mRNA level of IPA in single reactive astrocytes at both 7 days (4.37 ± 1.7, n=5,  vs 1.0 ± 0.5, n=5 in MCAO alone group) and 14 days (3.17 ± 0.6, n=6, versus 1.06 ± 0.13, n=6 in MCAO alone group, p<0.05) post-MCAo. Plasminogen activator inhibitor-1 (PAI-1) is the primary inhibitor of tissue-type plasminogen activator system. In parallel, BMSCs considerably decreased the expression of PAI-1 in single astrocytes at 14 days post MCAo (0.26 ± 0.0, vs 1.3, n=5, p<0.01; 1.0 ± 0.2, n=3 in MCAO alone group). Our data provide new evidence that BMSC treatment of stroke increases IPA and decreases PAI mRNA level in activated astrocytes, which could contribute to the beneficial effects of BMSCs on stroke.

**P369**

**Inhibition of Mitochondrial Permeability Transition With Nim811 is Neuroprotective in Focal Cerebral Ischemia**

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**Introduction:** Mitochondrial dysfunction plays a seminal role in acute ischemic neuronal degeneration, the signature injury in stroke. A selective inhibitor of mitochondrial permeability transition (MPT) may achieve neuroprotection by preventing collapse of the mitochondrial membrane potential, thereby inhibiting the intrinsic pathway to neuronal death. **Hypothesis:** A novel MPT inhibitor, Nim811, will significantly reduce 24-hr and 7-day infarct volume after focal cerebral ischemia. **Methods:** Nim811 was obtained as a gift from Novartis Pharma Ltd. A rodent model of tandem common carotid and middle cerebral artery occlusion was used to induce focal cerebral ischemia for 2 hrs. During post-ischemic reperfusion, animals received Nim811 or drug-free vehicle by intraperitoneal injection in three sequential experiments: 1) delineation of optimal dose at 25 - 75 mg/kg, 2) delineation of optimal dosing time at 1 - 9 hrs, and 3) evaluation of neuroprotective resilience at 7 days. **Results:** When given after 1 hr of post-ischemic reperfusion, 50 mg/kg Nim811 reduced 24-hr infarct volume (63.6 ± 18.7 [SD] vs. 99.3 ± 12.5 mm^3 in controls; n=8, 10/group; p<0.001; unpaired t-test) and was superior to 75 mg/kg alone for 7-day infarct volume. For Nim811 was given after 1 hr of reperfusion (78.8% reduction in infarct volume, compared to 18.6% of 15.1% at 3 or 6 hrs; no-between-group difference at 9 hrs). Administration of 50 mg/kg Nim811 × 2 (1- and 24-hr post-ischemic reperfusion) confirmed neuroprotective resilience by reducing 7-day infarct volume compared to controls (51.9 ± 7.4 vs 81.9 ± 10.3 mm^3; n=13 -16/group; p<0.01; unpaired t-test). **Conclusions:** MPT inhibition with Nim811 significantly reduces infarct volume, when given within the clinically relevant post-ischemic period. Serial dosing of Nim811 achieves neuroprotective resilience at 7 days. These promising results warrant confirmation in a randomized clinical model of focal cerebral ischemia and highlight the potential of Nim811 for neuroprotective treatment of stroke in man. This research has received full or partial funding support from the American Heart Association, National Center.

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**Impaired Reperfusion and Worse Neurological Outcomes in a Focal Embolic Stroke Model of Diabetic Rats After tPA Thrombolytic Therapy**

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**Background:** Hyperglycemia (diabetes) is a stroke risk factor, and associated with poorer reperfusion, higher hemorrhagic incidence and worse outcome in IPA stroke therapy. However, there is a gap in translational animal studies, because none of embolic stroke models in diabetic animals have ever been examined with IPA thrombolytics. In this study, for the first time we aim to investigate how focal embolic stroke in chronic diabetic rats responds to IPA thrombolysis and associations with formed blood clot, coagulation system and platelet activation. **Methods:** IP injection of streptozotocin was used to induce type 1 diabetes in Wistar rats (male, 8 weeks old). After 6 weeks, diabetic and age matching (non-diabetic control) rats were subjected into a focal embolic stroke. At 1.5 hr after stroke, animals received IV injection of saline or tPA (10mg/kg) treatments. CBF was monitored by LDF. Neurological outcomes were measured at 24 hrs for brain infarction, hemorrhagic incidence and mortality. Coagulation factors of PT, PT-INR, Fg; and plasma levels of β-tG and PAI-1 were tested and compared. **Results:** HbA1c was 3.9 ±0.2% for non-diabetic and 9.2 ±0.7% for diabetic rats. There were no significant differences for PT, PT-INR, and Fg between the two types of animals. Infarction volume in diabetic rats was significantly larger (305.4±46 mm^3, 29% of increase) than non-diabetic rats (236.4±77 mm^3) after saline treatments. IPA significantly recovered reperfusion in non-diabetic rats, but not diabetic rats. Coincidently, IPA reduced 2 % of brain infarction in non-diabetic rats, but only 20% in diabetic rats compared to saline treatments (n=6-8 per group). All diabetic rats shared visible intracerebral bleeding after stroke and were worsened by IPA with about 18% of mortality. Interestingly, regardless of injected clots formed from non- or diabetic blood, diabetic rats had about 48% of increase in brain infarctions compared to non-diabetic rats after IPA treatment. ELISA assays showed pre-stroke baseline of plasma β-tG and PAI-1 were significantly higher in diabetic rats, stroke and IPA treatment did not signicantly reduced plasma β-tG levels at 24 hrs, compared to baseline levels in both types of rats. Discussion and conclusion: (1) the focal embolic stroke in chronic diabetic rats exhibits a similarity of less reperfusion efficacy and worse brain damage as observed clinically, suggesting the transsional significance to study limitations or side effects of IPA stroke therapy-associated with diabetes or hyperglycemia in this “diabetes” animal model; (2) larger stroke infarction and higher hemorrhagic incidence are dominantly caused by the diabetic “host” itself, not the formed blood clot; (3) increased circulating β-tG (platelet activation marker) and PAI-1 (plasminogen activator inhibitor-1) might be partially responsible to the impaired IPA thrombolytic reperfusion in diabetic rats.

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**Delayed Treatment With Arimoclomol, a Co-Inducer of Heat Shock Proteins, Improves Neurological Outcome After Embolic Stroke in the Rat**

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**Background & Objective:** Over-expression of HSP70 reduces ischemic injury after stroke. Arimoclomol, a co-inducer of heat shock proteins (Hsps) and exerts a neuroprotective effect in degenerative diseases. However, no information is published regarding the effect of arimoclomol on neuroprotective and neurorestorative events after stroke. The present study investigated the therapeutic window of arimoclomol on neurological outcome in a rat model of focal cerebral ischemia. **Experimental Approaches:** Adult male rats were subjected to middle cerebral artery occlusion (MCAo) by placement of an embolus at the origin of the MCA. Arimoclomol (200 mg/kg) was orally administered daily for 28 consecutive days. Rats subjected to MCAo were randomized into one of five groups (n=10/group). Rats were treated with arimoclomol starting at 1) 6h after MCAo, 2) 10h after MCAo, 3) 24h after MCAo, 4) 48h after MCAo; 5) rats were orally treated with PBS daily for 28 consecutive days starting 6h after MCAo, as a control. An array of behavioral tests including adhesive-removal test, modified Neurological severity Score (mNSS), and foot-fault test was performed to measure neurological deficits. Rats were sacrificed 31 days after MCAo. Infarct volume was measured. Immunostaining with antibodies against HSP70 and doublecortin (migrating neuroblasts), and histological staining with αβ4 (microglia) and TUNEL (apoptosis) staining were employed. **Results:** Treatment with arimoclomol starting 6h, 10h and 24h after stroke significantly (p<0.05) improved functional outcomes compared with PBS group measured by adhesive-removal test, mNSS, and foot-fault test. With the treatment initiated at 48h after stroke only showed significant functional improvement measured by the adhesive-removal test. Treatment with arimoclomol starting 6 and 10h after stroke significantly (p<0.05) reduced infarct volume compared with PBS group. Immunostaining revealed that the ischemic rats treated with arimoclomol starting 6 and 10h, but not 24 and 48h after stroke had a significant (p<0.05) increase in the number of the HSP70+ cells and substantial (p<0.05) reduction of apoptotic cells and microglia in the ischemic boundary compared with the controls. Moreover, treatment with arimoclomol initiated at all four time points significantly increased doublecortin immunoreactivity, indicating the subventricular zone of the lateral ventricle. **Conclusion:** Our data suggest that treatment with arimoclomol initiated 6 and 10h after stroke has HSP-mediated neuroprotective and neurogenic effects, while treatment initiated at 24 and 48h induces neurogenesis. Both effects likely contribute to the observed improvement of neurological outcome.
autologous blood (n = 9) into the chiasmatric cistern. Animals were euthanized 7 days later and brains removed and sections of hippocampus study electrophysiologically and histologically. Vasospasm of the middle cerebral artery (MCA) was quantified by morphometry. SAH and saline injection caused the same acute reduction in cerebral blood flow over the first 60 minutes after injection. SAH, however, caused significant vascular constriction compared to saline injection or sham controls (p < 0.001). Basic neurotransmission quantified as excitatory post synaptic and spike response from animals with SAH were significantly decreased as compared to naive controls (p < 0.05). However, sham operated and saline injected controls showed similar amplitude as naive controls. This suggests that reduction in basic neurotransmission is due to blood in the hippocampus. Immunohistochemically, a TUNEL-stained brain section from each animal was stained with antibodies against p53. TUNEL-positive cells were counted. Compared to controls, in treated cells, confocal analysis showed a more prominent punctate pattern of p53 and p30. The concomitant reduction (r = 0.89; p < 0.05) of active calpain expression was observed in the first 2 weeks, and newly activated lesions were increased chronologically. Side-to-side differences were compared with a Student’s t-test. Conclusions: In summary, the preoperative factor (r = 0.92, p < 0.05), suggesting an association in cytoskeletal dynamics. Additionally, MDL28170 scalar amounts augmented p35 activity (p < 0.05), possibly by inhibition of calpain degradation of p35. Compared to controls, in treated cells, confocal analysis showed a more diffuse intracellular distribution of p35 and cdks. p35 located at focal contacts of the leading edge of moving cells. CDks lost its co-localization with stress fibers. Finally, Iq1 imaging showed a significant increase in cell speed in moving cdks wt compared to D144N transfectants (2.070 ± 0.051 vs. 1.142 ± 0.003 μm/sec; p = 0.0015). Taken together, these data suggest that p35/Pdk signaling may be involved in promotion of angiogenesis after stroke, p35 may be a potential target for the treatment of stroke. p375

Altered Angiogenesis/Revascularization Closely Associated With Angiogenesis, in Brain Endothelial Cells
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Angiogenesis/revascularization closely contributes to the functional tissue recovery after stroke. Cytoskeletal dynamics is a key requisite for cellular adaptations during angiogenesis and requires temporal and spatial regulation of focal adhesion. Our recent data show that blocking the cyclin-dependent kinase 5 (cdks) activities with the kinase inhibitor roscovitine resulted in cytoskeleton changes and loss of motility in human immortalized brain endothelial cells (hOEC/MDC). In ischemic brain injury, activation of calpain-mediated cleavage of cdks activator p35 is associated with neuronal apoptosis and cytoskeletal derangements; however the relationship to angiogenesis and tissue remodelling is still unclear. Using the specific calpain inhibitor MDL28170 we demonstrated that extra cellular matrix (ECM) matrix degradation affects the p35/cdk5 pathway may affect cytoskeletal dynamic and angiogenic processes, in viable brain tissue following stroke. Human hOEC/MDC cells were treated with MDL28170 in dose-dependent manner (2-500μM) for 24-72h. Proliferation rate (24h) was assayed by MTS and nuclear activity of the apopptosis-anti-angiogenic transcription factor p53 by ELISA. Capillary branching formation (72h) and migration (24h) were studied in Matrigel or wound healing assays, respectively. Protein levels were estimated by Western blot. Cdk5 and p35 cell localization were checked by confocal microscopic analysis. Iq1 Live Cell imaging was used to examine the effect of GFP-cdk5 wild type (wt) or mutated (D144N) transfectants on cell migration. MDL28170 (10 μM) significantly increased cell proliferation, attachment, spreading, migration and tube formation (p < 0.01). This was associated with increased p35 and talin protein levels (30-50% respectively). The concomitant reduction (r = 0.89;p < 0.05) of active calpain expression confirmed the inhibitory effects of MDL28170. Notably, we found a direct relationship between talin and p35 protein levels dependent on MDL28170 concentration levels (r = 0.924;p < 0.05), suggesting an association in cytoskeletal dynamics. Additionally, MDL28170 scalar amounts augmented p35 activity (p < 0.05), possibly by inhibition of calpain degradation of p35. Compared to controls, in treated cells, confocal analysis showed a more diffuse intracellular distribution of p35 and cdks. p35 located at focal contacts of the leading edge of moving cells. Cdk5 lost its co-localization with stress fibers. Finally, Iq1 imaging showed a significant increase in cell speed in moving cdks wt compared to D144N transfectants (2.070 ± 0.051 vs. 1.142 ± 0.003 μm/sec; p = 0.0015). Taken together, these data suggest that p35/cdk5 signaling may be involved in promotion of angiogenesis after stroke, p35 may be a potential target for the treatment of stroke.
Serotonergic Genes and Post-stroke Emotional Dysfunction

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Background and Purpose: Although post-stroke emotional incontinence (PSEI) has been shown to be related to serotonergic dysfunction, research examining the relationship between serotonergic genes and PSEI has yielded conflicting results. The aim of this study was to investigate whether PSEI is related to polymorphisms in the serotonin transporter protein gene. Methods: A total of 276 patients with acute ischemic stroke admitted to Asian Medical Center were screened for PSEI at admission and 3 months after stroke using Kim’s criteria (Neurology, 2002). Blood samples were collected from each participant for DNA extraction and genotyping. The promoter of serotonin transporter protein (5-HTTLPR) and the variable number of tandem repeats polymorphism within intron 2 (VNTR STin2) were genotyped. PSEI was present in 8.2% and 12.7% of patients, at admission and 3 months post-stroke, respectively. Diabetes mellitus, hypertension, sensory dysfunction, dysarthria, high NIHSS and the presence of microbleeding (MB) in gradient echo T2* MRI were the factors related to PSEI at admission whereas lesion location (pons), the VNTR STin2, MB, sensory dysfunction, mRS, and dysarthria were related to PSEI at 3 months post-stroke. Neither lesion side nor size were related to PSEI. Conclusion: Factors related to PSEI are not identical between acute and sub-acute stages of stroke. The serotonin transporter gene VNTR STin2 appears to be involved in the development of PSEI only in sub-acute stage.

Inflammatory Mechanisms in Small Vessel Cerebrovascular Disease in a Novel Porcine Model

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Small vessel disease (SVD) is a major cause of stroke accounting for ~20% of ischemic stroke and contributes to vascular dementia; SVD disproportionately affects African-Americans and Hispanics each year due to a 2-3 fold increased risk. SVD is thought to arise from arteriolesclerosis in small, deep penetrating, non-branched end arterioles. While associated with hypertension, aging and diabetes mellitus, there are many gaps in our understanding of the pathophysiology of SVD. We recently demonstrated humanoid SVD in a swine model known to develop accelerated atherosclerosis in multiple vessels including cerebral vessels. We hypothesized that mediators of inflammation found in large vessel disease are likewise expressed in SVD in type 1 (T1) and type 2 (T2) diabetic hyperlipemic pigs. Methods: T1 animals (n=15) were maintained on a high fat/high cholesterol diet after injection of streptozotocin. T2 animals (n=10) were fed a high fat/high cholesterol and a high carbohydrate diet, and control animals (n=15) were fed commercial chow. We sacrificed all animals under a standard protocol at 27-36 weeks. Brains were fixed whole in 5% formalin. Samples from 5 regions were embedded in paraffin, sectioned, and stained using standard immunohistochemistry techniques. Results: Both T1 and T2 animals demonstrated SVD with preferential staining for IL-1ra and phosphorylated stat-4. While 12-lipoxygenase staining was scant in most animals and IL-6 staining was fairly ubiquitous, T1 and T2 stained preferentially vs. controls (Table). Discussion: The humanoid SVD seen in T1 and T2 hyperlipemic pigs mimics human disease with differential expression of key inflammatory mediators. Further studies of additional mediators IL-12, MCP-1, hypoxia inducible factor 1-alpha, and MMP-9 are in progress. This line of research should provide a more complete picture of the mechanisms of small vessel disease and our validated model can accelerate our knowledge of SVD and facilitate the development of treatments for human disease.

Thrombin Augments Vascular Disruption via Protease-Activated Receptor-1 After Stroke

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Thrombin may contribute to ischemic injury by potentiating coagulation activity and/or acting on protease-activated receptors (PARs) on brain cells. We investigated the role of the PAR-1 pathway in thrombin-induced tissue injury during ischemia. Focal ischemia was induced in adult Sprague-Dawley rats by occlusion of the middle cerebral artery for 4 hours followed by a short period of reperfusion. Infusion of thrombin (30units/kg) by a syringe pump through the external carotid artery during ischemia greatly enlarged the volume of severe vascular disruption, as visualized by fluorescein isothiocyanate conjugated to the high molecular weight dextran (p<0.05, Student’s t test). The thrombin toxicity was reversed by intravenous infusion of the direct thrombin inhibitor argatroban (3.4mg/kg, p<0.05). To test the specific cellular pathways activated by thrombin, we infused a PAR-1 antagonist (SCH79797, 25ug/kg) and found that inhibition of PAR-1 protected the brain from further vascular damage. We also used SB203580 (33nmol/kg) to block p38 mitogen-activated protein kinase (MAPK) which is downstream of PAR-1 pathway, and showed a lesser extent of vascular injury. Together, these data suggested a critical role for PAR-1/MAPK pathway in thrombin-mediated vascular injury during ischemia.

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Prognostic Value of Endothelial Progenitor Cells Count After Ischemic Stroke

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Objectives: Previous studies suggested a correlation between the increase of endothelial progenitor cell (EPC) count and the functional outcome after ischemic stroke. We studied the prognostic value of EPC count at several time-points in patients with ischemic stroke.

Methods: We studied prospectively consecutive patients with ischemic stroke within the first 48 hours after symptoms onset. Blood samples were obtained at baseline, and 7 days and 3 months after stroke onset. EPC were measured by flow cytometry within 30 minutes after blood collection. We checked that a cell was an EPC when it was labelled for the following 3 markers: CD34, VEGFR2, and ADR. EPC counts were adjusted for the lymphocyte population in each sample, and expressed as a relative value (% ± SD). Functional outcome was assessed with the Rankin scale score at 3 months, and a score of 0-2 was defined as a favorable outcome. Statistics: Student’s t test and logistic regression analysis (dependent variable: favourable outcome). Results: We studied 51 patients, whose mean age was 70.3 ± 12.6 years, and 63.6% of them were men. Patients with a good outcome at 3 months had increased EPC counts at the 3 time-points compared with those with unfavorable outcome, but these differences were only significant at baseline (0.041 ± 0.0072 vs. 0.0008 ± 0.0025, p = 0.02). In the multivariate analysis, age and the NIHSS score but not EPC count were independent prognostic variables.

Conclusions: In this preliminary study, increasing EPC counts at baseline were associated with a favourable long-term outcome in univariate analysis, but not in multivariate analysis.

Inhibition of Soluble Epoxyprostane Hydrolyase Reduces NF-κB Activation in Stimulated Microglia

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Introduction: Soluble epoxyprostane hydrolyase (sEH), which inactivates the arachidonic acid metabolite epoxyeicosatrienonic acid (EET) is involved in ischemic brain injury. Pharmacologic inhibition of sEH reduces infarct size after stroke. Inflammation contributes to ischemic brain injury and sEH is a pro-inflammatory enzyme. We hypothesize that inhibition of sEH suppresses the brain’s inflammatory response and thereby reduces injury after ischemia. To test this hypothesis, we investigated effects of sEH inhibition on the pro-inflammatory transcription factor NF-κB and the inflammatory cytokine TNF-α in primary cultured microglia.

Methods: In this study, we used a well-described in-vitro model of microglial activation to simulate brain inflammation. We use commercially enriched (~95% lectin-positive) primary microglia cultures, harvested from mixed-glia cultures from postnatal day 1 rat brains. After mixed-glia cultures were dissociated, microglia were shown to be 99% pure by Fluorescence-activated cell sorting (FACS). Cells were then activated with 100 U/ml LPS (Control Standard Endotoxin, Codex Ass.). NF-κB activation was measured at 30 and 60 minutes and TNF-α release into the medium at 1 - 24 hours after stimulation, using ELISAs (ActiveMotif, R&D Systems). The sEH inhibitor 4-phenylchalcone oxalate (4-PCO, 2 μM, Bisomil) or the sEH substrate 14, 15-EET (1 μM, Cayman Chemical) are added to the media 2 hr before LPS. Results. Nuclear translocation of NF-κB in primary microglia increased rapidly after LPS stimulation (1.72 fold ± 0.24 at 30 min, 1.78 fold ± 0.12 at 60 minutes, compared to untreated). Similarly, TNF-α levels in the culture medium increased rapidly, starting at 2 hours after stimulation and peaking at 6 hours (701 fold ± 670, 6533 fold ± 3041). Inhibition of sEH by 4-PCO as well as addition of the sEH substrate 14, 15-EET reduced NF-κB activation at both time-points (1.37 fold ± 0.20 EET and 1.39 fold ± 4-EPC at both 30 min and 1.49 fold ± 0.18 EET, 1.42 fold 4-EPC and 1.42 fold ± 0.23 EET at 4-EPC after 60 min), but not TNF-α release, however both treatments affected by 14, 15-EET or 4-EPC treatment at any time point. Conclusion: Inhibition of sEH or addition of the sEH substrate 14, 15-EET activates the pro-inflammatory transcription factor NF-κB in stimulated microglia, suggesting that inhibition of microglia activation contributes to the beneficial effect of sEH inhibition after experimental stroke. Release of the NF-κB-regulated inflammatory cytokine TNF-α is not affected by sEH inhibition, however. Other NF-κB-regulated potential mediators of microglial-injured neuronal injury include inductible nitric oxide synthase (iNOS) and cyclooxygenase (COX)-2. Further study is needed to determine which neurotoxic pathways downstream of NF-κB are blocked by sEH inhibition in stimulated microglia.

FMRI-guided Development of a Proposed Stroke Rehabilitation Device

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Background: Stroke is one of the leading causes of morbidity and mortality in the United States. In this ongoing study we are developing the prototype for a closed loop rehabilitation device that will facilitate functional recovery in stroke patients with upper extremity motor deficits. Methods: The proposed device will consist of three components; 1) an EEG sensor system for detecting real-time volitional command signals from motor cortex, 2) a functional stimulation module (i.e., tongue display unit) to provide sensory feedback and increase the general excitability of the afflicted sensory-motor system through latent intact neural pathways. The tongue stimulation is novel. This approach is based on the theory that functional recovery in stroke patients is limited because the brain plasticity changes secondary to the rehabilitation can be variable and may vary depending on the stage of recovery. 3) A motor cortex based functional MRI scanning system for detecting real-time volitional command signals from motor cortex. The tongue stimulation module (i.e., tongue display unit) will provide sensory feedback and increase the general excitability of the afflicted sensory-motor system through latent intact neural pathways. The tongue stimulation is novel. This approach is based on the theory that functional recovery in stroke patients is limited because the brain plasticity changes secondary to the rehabilitation can be variable and may vary depending on the stage of recovery. Results: In aged humans, stroke is a major cause of disability for which no treatment has been approved to date. The proposed device will be tested in a randomised controlled trial involving 36 stroke patients. The primary outcome measures will be the FIM, the Stroke Impact Scale (SIS), the Barthel index and the arm coordination scores. Conclusions: This study will evaluate the feasibility of using a novel FMR-guided rehabilitation device for stroke patients with upper extremity motor deficits. Further study is needed to determine which neurotoxic pathways downstream of NF-κB are blocked by sEH inhibition in stimulated microglia.

Transcriptome Profiling of Human Multipotent Adult Progenitor Cells Transplanted Into Rat Models of Ischemic Injury in the Central Nervous System

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Stem cells are emerging as a potential therapeutic treatment following ischemic insult to the central nervous system (CNS). Previous studies have demonstrated significant functional improvement in animal models of ischemia following infusion of adult stem/progenitor cells, however, little is known regarding the mechanistic interaction between the injured tissue environment and the transplanted cells. In this study, we investigated gene expression changes in both the injured tissue environment, as well as in the transplanted stem cells using species-specific microarrays and real-time quantitative PCR (qPCR). Human Multipotent Adult Progenitor Cells (MAPC), were infused intravenously into two different animal models of CNS ischemic injury: adult rats subjected to temporary middle cerebral artery occlusion (vehicle or 2 million cells/kg, administered 24 hours after surgery); and neonatal rats subjected to hypoxic-ischemic injury (vehicle, 100,000 or 1 million cells, administered 7 days after permanent occlusion of the anterior cerebral artery and carotid artery). Animals were treated with Glial Cell Line Derived Neurotrophic Factor (GDNF) or saline via intraperitoneal injection daily for 7 days. Animals were sacrificed 3 days after cell infusion. RNA was isolated from brain, lung, spleen, and kidneys, and then subjected to qPCR and microarray analyses using tissue-specific primers/microarrays to identify gene expression changes specific to both the transplanted stem cells and the tissue environment. In the tissue environment, the MAPC transcriptome was dynamically affected by the surrounding tissue environment. Rat-specific qPCR/microarray analyses found significant differences in rat tissue gene expression in animals that received MAPC infusion, compared to animals that were behaviorally tested and the brains analyzed after 28 days post-stroke. Results: G-CSF treatment had a beneficial effect on survival rate, functional recovery of motor function (rotating pole, inclined plane) and working memory (radial maze). Except the rotating pole where the treatment was beneficial during the 4-week testing period, the beneficial effects of treatment in other tests was generally limited to the first 12 days post-stroke. At cellular level, the G-CSF treatment increased the number of proliferating cells in the SVZ and the dentate gyrus and increased the number of new born neurons in the SVZ, ipsilateral to the lesion. Conclusions: These results suggest that the G-CSF treatment in aged rats has primarily a survival enhancing capacity and a beneficial effect on functional outcome most likely via supportive cellular processes such as neurogenesis. Further studies are required to optimize G-CSF treatment schedule in aged subjects.
Safety of Stenting in Acutely Symptomatic Basilar Artery Occlusive Disease

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Background: Acute stenting is an emerging treatment increasingly used for patients presented beyond time window of IVT, IAT or mechanical thrombectomy or as an adjuvant treatment when all other options fail to recanalize occluded artery. Risk of ICH and procedure related mortality often precludes the use of stenting in acute stroke patients or unstable ICAD. Objective: To report safety of Basilar artery stenting in acutely symptomatic patients beyond 8 hours of stroke onset and unstable ICAD within 7 days Method: We performed a retrospective review of our database of patients who received endovascular treatment for acute stroke, to identify patients with basilar artery occlusion or stenosis who were revascularized beyond eight hours and within 7 days of their symptoms onset. Results: The ten patients were aged 42 to 86 (Mean 61 years), seven men and four women, three Caucasian and eight African American. Eight patients had acute stroke confirmed by either CT scan head or MRI, while 3 patients had recurrent TIA. The mean time from symptom onset to recanalization procedure was 69 hours (range 8 to 180 hours). The mean National Institute of Health stroke scale was 13.72 (Range 2 to 40). Basilar artery was completely occluded in four patients, more than 80% stenosis noted in other seven. Stents were placed in basilar artery in five patients and in vertebrobasilar junction in other four. One patient had tandem stent placement in mid basilar artery and vertebral artery. Two patients had IAT before stent placement, in one of them mechanical clot retrieval was used. Eight patients had wingspan self expanding stent and three patients had coronary balloon expandable stent. Revascularization (miso) was successful in all patients. There was no procedure related or 3 months mortality. Two patients had asymptomatic intracranial hemorrhage. At 3 months follow up, among stroke patients mRS was three in three, two in five, one in one and zero in all TIA patients. In three patients with 12 months follow up, NIHSS was 1, 0 and 2. Follow up angiogram in those three patients only showed 30 % restenosis in one patient. Conclusion: Stent supported basilar artery recanalization has an acceptable safety profile beyond time window of other endovascular approach in acutely symptomatic patients and in unstable ICAD.

Intracranial Hemorrhage and Its Relationship to Reperfusion and Clinical Outcome: An Exploratory Analysis of the PROACT II Trial

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Background: Prior cohort studies have suggested that minor intracerebral hemorrhage (ICH) is a marker of early reperfusion and may be associated with better outcomes than no ICH. Analysis of the Interventional Management of Stroke pilot trials of combined intravenous and intra-arterial thrombolysis did not support this hypothesis. We further test this hypothesis in the PROACT II trial of M1 and M2 occlusions randomized to intra-arterial r-pro-urokinase versus placebo within six hours of stroke symptom onset. Methods: We retrospectively reviewed the thrombolysis-treated cases from the PROACT II treatment arm (n=106). Early reperfusion was defined as partial or complete opacification of the vasculature distal to the site of primary occlusion on the final angiogram. ICH subtypes were determined on 24-hour CT scans using a marker of early reperfusion and may be associated with better outcomes than no ICH. Risk of ICH and procedure related mortality often precludes the use of stenting in acute stroke patients or unstable ICAD. Objective: To report safety of Basilar artery stenting in acutely symptomatic patients beyond 8 hours of stroke onset and unstable ICAD within 7 days Method: We performed a retrospective review of our database of patients who received endovascular treatment for acute stroke, to identify patients with basilar artery occlusion or stenosis who were revascularized beyond eight hours and within 7 days of their symptoms onset. Results: The ten patients were aged 42 to 86 (Mean 61 years), seven men and four women, three Caucasian and eight African American. Eight patients had acute stroke confirmed by either CT scan head or MRI, while 3 patients had recurrent TIA. The mean time from symptom onset to recanalization procedure was 69 hours (range 8 to 180 hours). The mean National Institute of Health stroke scale was 13.72 (Range 2 to 40). Basilar artery was completely occluded in four patients, more than 80% stenosis noted in other seven. Stents were placed in basilar artery in five patients and in vertebrobasilar junction in other four. One patient had tandem stent placement in mid basilar artery and vertebral artery. Two patients had IAT before stent placement, in one of them mechanical clot retrieval was used. Eight patients had wingspan self expanding stent and three patients had coronary balloon expandable stent. Revascularization (miso) was successful in all patients. There was no procedure related or 3 months mortality. Two patients had asymptomatic intracranial hemorrhage. At 3 months follow up, among stroke patients mRS was three in three, two in five, one in one and zero in all TIA patients. In three patients with 12 months follow up, NIHSS was 1, 0 and 2. Follow up angiogram in those three patients only showed 30 % restenosis in one patient. Conclusion: Stent supported basilar artery recanalization has an acceptable safety profile beyond time window of other endovascular approach in acutely symptomatic patients and in unstable ICAD.

P386 Safety of Stenting in Acutely Symptomatic Basilar Artery Occlusive Disease

P387 Purinergic Receptor Stimulated IP3-Mediated Ca2+ Release Reduces Brain Lesions Induced by Photothrombosis by Increasing Astrocytic Mitochondrial Metabolism

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Cerebral blood flow occlusion produces an expanding infarction core with a surrounding penumbra that is not yet irreversibly injured. Enhancing astrocyte neuroprotection is a relatively unexplored strategy to preserve the penumbra. Studies performed in our laboratory demonstrated that in vitro glial and neuronal protection was enhanced by increasing astrocyte mitochondrial metabolism via a purinergic receptor (P2Y1R) pathway that increases inositol trisphosphate (IP3)-dependent Ca2+ release (Wu et al., 2007). Here, we report that P2Y1R stimulation in vivo significantly reduces cortical lesions induced by blood flow occlusion and that this enhanced protection requires functional astrocyte mitochondria. Cerebral infarcts were photothermally induced using laser irradiation (543 nm) of tail-vein injected Rose Bengal (RB). Optical confocal microscopy, small animal fluorescent imaging (using APC tagged anti-CD40 antibod and TcT staining were used to monitor the progression of cerebral infarcts in living mice brains in the presence or absence of the P2Y1R ligand 2-MeSADP. Our data indicate that 2MeSADP treatment significantly decreases RB-induced cerebral infarcts in mouse. To test the impact of mitochondrial metabolism on P2Y1R enhanced protection, we disrupted astrocyte mitochondrial function by utilizing a two-fold strategy: pharmacological inhibition of astrocyte tricarboxylic acid (TCA) cycle (fluorocacetate) and genetic expression of a mitochondrial targeted DNA restriction enzyme (EcoRI) under the control of dcoxylidine (GFAP::ITAM::EcoRI) in the astrocyte TCA cycle (fluorocacetate) completely blocked the ability of 2MeSADP to reduce astrocyte swelling. Functional disruption of mitochondria in the astrocyte specific genetic model also eliminated the ability of 2MeSADP to decrease astrocyte swelling. We conclude that ischemic brain lesions can be reduced by stimulating astrocyte mitochondrial metabolism and suggest this approach as a new therapeutic avenue to minimize other brain injuries. Funded in part by NIH grants A19316-06 and AG29461.

P388 Risk-Benefit Ratio of Intra-arterial Thrombolytic Therapy in Acute Ischemic Stroke Patients With a Matched Defect

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Introduction: Intra-arterial thrombolytic therapy (IAT) can be beneficial for acute ischemic stroke (AIS) patients with a MRI-based diffusion-perfusion mismatch. However regardless of theory, limited information is available in literature to confirm likely outcome from IAT in AIS patients with a diffusion-perfusion matched defect. Hypothesis Application of intensive
Progestosterone and Its Active Metabolite Allopregnanolone Attenuate Blood Brain Barrier Dysfunction Following Permanent Focal Ischemia by Regulating the Expression of Matrix Metalloproteinases

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Background: Experimental and clinical studies indicate that elevated matrix metalloproteinases (MMPs) activity after stroke increases ischemic injury. This injury is followed by passive diffusion of water leading to vasogenic edema and blood-brain barrier (BBB) dysfunction. We and others have shown protective action by progestrone (PROG) on comprised BBB. However, the mechanisms by which PROG treatment regulates BBB permeability and vascular stabilization is not well understood. It is also possible that some of the beneficial effects of PROG in restoring BBB integrity after injury could be mediated by its metabolite allopregnanolone (ALLO). Objective: This study was designed to explore the effects of PROG and ALLO treatment on the integrity of the BBB following permanent middle cerebral artery occlusion (pMCAO) in rats. We were specifically concerned with the effects of PROG and ALLO on the modulation of MMPs and the degradation of occludin1, an important tight junction protein and a marker of BBB integrity. Methods: Male adult Sprague-Dawley rats underwent pMCAO by electro-coagulation. After 15 min of pMCAO, the rats were divided into 3 groups. In the PROG (8 mg/kg) group, vehicle at 1 h (intraperitoneal) post-occlusion followed by subcutaneous injections (8 mg/kg) at 6, 24 and 48 h. The effect of PROG on MMP-2, MMP-9 and occludin1 expression was determined by immunoblot, immunohistochemistry and gelatin zymography. In a separate experiment, Evans blue extravasation in the ipsilateral hemisphere was determined to verify BBB permeability. Results: Western blot analysis showed a significant (p < 0.01) increase in expression of MMP-2 and MMP-9 following pMCAO at 72 h, which was markedly reduced by PROG and more so by ALLO treatment. The positive effect of both PROG and ALLO on MMPs was confirmed by gelatin zymography and immunohistochemical assays. Quantitative analysis of occludin1 expression in the pMCAO control group (n = 42) was 230 minutes when compared to 224 minutes in the IA alone group (p < 0.01). The median stroke onset to puncture time in the IV IA group was 91 minutes in both groups (p = 0.96). The degree of recanalization between these groups was found to be the same (p = 0.1). Results: Conclusion: Progestrone and ALLO multiple-targeting protectants against ischemic stroke on cellular as well as vascular components of central nervous system. This research has received full or partial funding support from the American Heart Association, National Center.

Role of Plasma Kallikrein on Ischemic Stroke in Diabetic Rats


Diabetes mellitus (DM) is a risk factor for ischemic stroke. In addition, DM is associated with worse clinical outcomes following stroke, which have been attributed, in part, to an expansion of ischemia-induced vascular and neurological injury in the penumbra. The identification of factors that contribute to the increased cerebral injury in the presence of diabetes may suggest therapeutic opportunities for the treatment or prevention of ischemic stroke. Previous studies have implicated kallikrein kinin system in ischemia induced cerebral injury and inflammation. In this study we examine the role of plasma kallikrein in cerebral ischemia following middle cerebral artery occlusion (MCAO) in rats with four weeks of streptozotocin-induced DM. We demonstrate that infant volume injected MCAO for 24 h was increased 2 fold in DM rats compared with age-matched nondiabetic (NDM) rats. Systemic pretreatment of DM rats with a small molecule plasma kallikrein inhibitor (ASP-440) decreased MCAO-induced infarct volume in a dose dependent manner. Infarct volume injected by 2 hrs of MCAO followed by 4 fold dose of ASP-440 was associated with decreased ischemia/reperfusion induced infarct volume. We demonstrate that 2 hrs of MCAO in DM rats resulted in a 3.5 fold increase in cerebral vascular permeability (EVP) to Evan’s blue dye compared with MCAO-injured NDM rats brains. Histological analysis of brains from DM rats subjected to MCAO for 24 h showed increased perivascular fluid compared to NDM controls. Pretreatment of DM rats with ASP-440 was associated with a decrease in MCAO-induced EVP and pereivascular edema. Since plasma kallikrein has been implicated in MCAO-induced cerebral ischemia, we examined the expression of plasma kallikrein on MMP2 and MMP9 activity. We show that incubation of mouse brain microvessel endothelial cells in vitro with purified activated plasma kallikrein for 12 hrs resulted in 2- and 3-fold increases in MMP-9 and MMP-2 activities, respectively. Moreover, we show that incubation of these cells with activated plasma kallikrein for 4 hrs resulted in increased phosphorylation of both c-Jun and c-Fos, suggesting activation of the AP-1 transcriptional response. In summary, MCAO-induced infarction volume is increased in DM rats compared with NDM controls. Pretreatment of DM rats with the plasma kallikrein inhibitor ASP-440 decreased MCAO-induced infarction volume in DM rats. These data demonstrate that plasma kallikrein inhibition may provide protective effects against ischemic stroke in diabetes.

This research has received full or partial funding support from the American Heart Association, Founders Affiliate (Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Rhode Island, Vermont).
Stroke stage in deteriorating patients with IBZ infarcts. 

Methods: Included: for analysis were patients (1) who were admitted in our institution within 72 hours of onset from August 2004 to August 2008, (2) without extensive high signal intensity on MRI, (3) with ICA or MCA occlusion, (4) with modified Rankin Scale (mRS) <2 on the on-set day, (4) in whom neurological symptoms were deteriorated, (5) with mRS >3 on the 7th day and (7) who were diagnosed as IBZ infarctions on the 7th days after onset. Some patients gave written informed consent and underwent angioplasty and/or stenting for the ICA or MCA total occlusion from 7 to 14 days after onset (E group) and others not (C group). NIHSS on admission, 7-day NIHSS after admission, NIHSS on discharge, NIHSS on discharge after 3 months, and 3-month mRS were measured in the 7th day interval and procedural success rate in E group. 

Results: Seventeen patients were included for analysis. Among a total of 6 patients in E group, ICA occlusion in 2 patients was opened successfully by stenting and MCA occlusion in 4 patients successfully by angioplasty too. Among a total of 11 patients in C group, 3 patients had ICA occlusion and 8 patients had MCA occlusion. Although there were no significant differences in NIHSS on admission, 7-day NIHSS after admission, NIHSS on discharge and mRS on discharge between two groups, 3-month mRS (median) was 3 in E group and 5 in C group (p<0.01). 

Conclusions: Angioplasty and stenting for the ICA or MCA total occlusion in deteriorating patients with IBZ infarcts may be feasible in improving 3-month clinical outcome.

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Balloon Angioplasty for Intracranial Atherosclerotic Disease Using New Generation Angioplasty Balloon Catheters: Periprocedural Risks and Short Term Outcomes in a Multicenter Study

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Introduction: Whether stenting is superior to primary angioplasty for treating intracranial atherosclerotic disease (ICAD) treatment is unknown. Restenosis, fear of jailing at important branch points, obligation to perform stenting, high cost of stents, and tortuous navigation are limitations of intracranial stenting. New balloon catheters such as the Gateway and Maverick balloons (Boston Scientific), which are semi-compliant with hydrophilic coating designed for low-pressure inflations and high navigability are expected to improve the results of primary angioplasty for ICAD. We report the outcomes of 71/74 eligible patients treated with the new generation angioplasty balloon catheters, Gateway or Maverick balloons, without Wingspan stent. 

Methods: A total of 76 consecutive patients with intracranial atherosclerotic disease (50-99%) from 5 institutions were treated with Gateway (n=36) or Maverick (n=39) balloon angioplasty between August 2003 to August 2009 at five high volume centers and were analyzed for clinical and angiographic end-points. One patient was treated with both balloons. Mean age was 63±1-14 years, 42 patients were male (55%). Results: The average pre-treatment stenosis was 79% and reduced to 37±10% after primary angioplasty. Early and late angiographic success, defined as residual stenosis 50% or less, was achieved in (70/76) 92% of patients. Procedural success, defined as balloon angioplasty success without stroke or death at discharge or within 72 hours post procedure was achieved in 68/76 (89%) of patients. There were 4 (6%) major procedure-related strokes, 2 of which resulted in death within 6 hours of procedure. Three month follow-up was available in 71/74 eligible patients. In this interval, 3 patients had new stroke, one related to retreatment of the lesion, one in the territory ipsilateral to the treated lesion, and the other in the territory contralateral. 

Conclusion: Endovascular treatment of ICAD with new generation balloon angioplasty is associated with high technical success and low periprocedural morbidity and mortality. At three months, the risk of stroke is low. Further study is in progress to evaluate longer term risk of stroke and restenosis in this patient population.

Endovascular Therapy for Acute Ischemic Stroke in a Real-world Setting: Results of the University at Buffalo Endovascular Stroke Registry

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Aim: To report detailed results of endovascular therapy for acute ischemic stroke (AIS) in an all-comer population of patients who were not candidates for IVT or in whom IVT failed. 

Methods: Data from January 2006 to December 2008 was collected prospectively. Treatment decisions were based on patient-specific clinical and imaging findings including CT perfusion scans. Data collected included patient demographics, treatment characteristics, immediate and 3-month outcome, and SICH rates. 

Results: Of 135 patients (69.9%) had TIMI 2/3 flow; SICH rate was 2.4% (5/208). 

Conclusions: Endovascular therapy for AIS was a safe, efficacious treatment option in an unselected population of patients who were not candidates for IVT or who failed IVT. 

Recovery of Actual Functional Tasks in Response to Motor Learning, Robotics, and Functional Electrical Stimulation

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Background and Objectives: Some researchers have shown that mildly or moderately involved stroke survivors can respond to one specific type of intensive motor learning training, with one-on-one therapy, with improved performance. In contrast, there is very little information regarding successful interventions for upper limb functional recovery for severely involved stroke survivors with persistent functional deficits. Study objectives were: 1) Quantity response to three different upper limb training paradigms for those with persistent motor dysfunction; and 2) Determine whether one therapist could successfully, simultaneously treat 3 patients with an intensive, randomized, crossover intervention. Methods: A randomized, double-blind, crossover study of 34 subjects (>6 months post stroke) was conducted to investigate upper limb functional recovery to each of three treatments: 1) Motor Learning (ML; n=11); 2) ML and Robotics (ORB; n=11); InMotion2 Shoulder/Elbow Robot; and 3) ML and surface Functional Electrical Stimulation (FES; n=12; Emp II Units). Severe involved subjects were enrolled (Fugl-Meyer upper limb motor scores, 11-29 points) and received treatment 5hrs/day, 5days/week for 12 weeks. Within the 5hrs/day, the robotic group received shoulder/elbow robotics training for 1.5hrs/day, and the FES group received wrist/hand FES training for 1.5hrs/day, and the remaining 3.5hrs/day was allocated to motor learning (no technologies). For all groups, one therapist treated 3 patients simultaneously. The outcome measure was the Arm Motor Abilities Test (AMAT), which is...
of thirteenth timed, complex, actual functional tasks, such as cut the meat with knife and fork. For the between-groups comparisons or within-groups comparisons we used either a linear regression model or a t-test, respectively, with Sidak Stepdown procedure for multiple tests corrections. Linear regression was used to test pre-treatment comparability. Video recordings were made to document post-treatment change in functional tasks. Findings: The groups were comparable prior to treatment. All three groups exhibited a significant pre-post-treatment improvement in AMAT (ML, p < .001; ROB, p < .001; FES, p < .04). Conclusions: For those who are severely involved, with persistent functional deficits, an intensive, intervention can produce clinically and statistically significant improvement in actual functional performance. The treatment is highly successful. The study indicates that one therapist and three patients was successful in producing clinically and statistically significant improvement.

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Combination Treatment of Low-frequency rTMS and Intensive Occupational Therapy for Poststroke Patients With Upper Limb Hemiparesis
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Background and Purpose: Recent studies have confirmed the clinical efficacy of intensive occupational therapy for high-functioning stroke patients (HT) as compared to constraint-induced movement therapy for upper limb hemiparesis after stroke. Low-frequency repetitive transcranial magnetic stimulation (rTMS) has been reported to produce some functional improvements in poststroke patients with upper limb hemiparesis when applied to the contralesional hemisphere. The application of low-frequency rTMS as an adjuvant intervention might accelerate the improvement of motor function in the affected upper limb produced by intensive OT. The present pilot study investigated the feasibility and efficacy of combination treatment with low-frequency rTMS and intensive OT for poststroke patients with upper limb hemiparesis. Subjects and Methods: In-hospital combination treatment was provided for eight poststroke patients aged from 46 to 59 years old by both upper limb hemiparesis. All the patients were examined by neurologist and neuropsychologist at admission. The sequence (NBS versus non-NBS) was determined by separate testers blinded to the others results. The stimulation site was defined as being in Brunstrom hand stage 3-5 of the affected upper limb and considered to have reached a plateau state in the process of recovery from hemiparesis more than 12 months after the onset of stroke. Over 15 consecutive days, each patient received 24 sessions of combination treatment with 20-minute rTMSs with 1 Hz to the unaffected cerebral hemisphere followed by intensive OT (one or two sessions per day). The stimulation site was defined as the location where the largest motor evoked potentials in the first dorsal interosseous muscle of the unaffected upper limb was elicited on electromyography. The program of intensive OT consisted of 60-minute one-on-one training and 60-minute self-training. Motor function in the affected upper limb was evaluated by Fugl-Meyer Assessment (FMA) and Wolf Motor Function Test (WMFT) at admission, discharge, and 4 weeks after treatment. In terms of the safety with the protocol, patients were clinically monitored through daily medical and neurological examinations during their hospitalization. Results: Our protocol was well tolerated by all patients and no patient showed any adverse effects until 4 weeks after the treatment. At the end of the 15-day treatment, the increase in FMA score was found in all patients (the range was 1-6 points). The score of WMFT also improved with the treatment in seven patients. No deterioration of improved upper limb function was observed at 4 weeks after the 15-day treatment. Conclusions: With the introduction of combination treatment, the motor function of the affected upper limb improved without any adverse effects over a short period of treatment in poststroke patients. Our proposed 15-day protocol of combination treatment seems to be safe and feasible therapy for poststroke patients with upper limb hemiparesis, although the efficacy of the protocol needs to be confirmed in a large number of patients.

P400
Navigated Transcranial Magnetic Stimulation is More Sensitive Than Non-navigated in Obtaining Upper Extremity Motor Evoked Potentials for Low Functioning Stroke Patients
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Background: Transcranial magnetic stimulation (TMS) can determine motor tract integrity. In general, patients with TMS motor-evoked potential (MEP) within 30 days post stroke recover better than those without MEps. However, some patients without MEps also recover well. This may be due to inadequate TMS sensitivity in detecting MEps. New technology, navigated brain stimulation (NBS), integrates tersons brain MRI to identify a precise motor cortex location for TMS. Previous studies to predict functional recovery after stroke used non-navigated TMS (non-NBS). We compared NBS to non-NBS in producing MEPs in chronic stroke patients and hypothesized that NBS would better detect MEps in low functioning patients. Methods: Eligible subjects were at least 6 months post stroke in the middle cerebral artery territory. A brain MRI was done within 2 weeks of NBS. NBS and non-NBS subjects were determined by separate testers blinded to the others results. The sequence (NBS versus non-NBS) was randomized for each subject. Upper extremity (UE) MEps were obtained for the contralesional Aductor Pollicis Brevis, Abductor Digitii Minimi, Extensor Digitorum Common and Biceps Brachii. Low intensity was defined as an Action Research Arm Test (ARAT) equal to zero. Results: The 34 subjects had a median (range) age of 63 (29, 75) years old. A total of 15 subjects (45.7%) were low functioning (ARAT = 0) and the remaining 19 subjects had a median (range) ARAT = 22 (1, 60). NBS detected MEps for 24 muscles in 11 of the 15 low functioning subgroup (88%). Non-NBS detected MEps in 14 muscles among the 15 low functioning subjects, 5 (31.3%) had absent MEps with NBS and non-NBS; 6 (37.5%) showed MEPs using both NBS and non-NBS. 5 (31.3%) showed MEPs using NBS but not non-NBS, and there were not any (0%) with MEps using non-NBS but not with NBS. When non-NBS failed, MEps were more likely demonstrated by NBS in the low functioning group (31.3% vs. 0%, p = 0.0135 using a Fishers exact test). Conclusions: NBS obtained UE MEps in more muscles of lower functioning subjects compared to non-NBS. This may be due to the greater precision of the NBS system. NBS may be able to better predict functional recovery after stroke.

P401
Balance, Confidence in Balance and Quality of Life in Persons With Chronic Stroke After Body Weight Supported Treadmill Training
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Background: Little is known about whether the positive effects of body weight supported treadmill training (BWSTT) transfer beyond walking ability to dynamic balance, confidence in balance and quality of life in persons with chronic stroke. Purposes: The primary purpose of this study was to examine changes in balance, confidence and quality of life immediately and 6-months following BWSTT in persons with chronic stroke. The secondary purpose of this study was to determine if changes in gait velocity after BWSTT were associated with changes in balance, confidence and quality of life. Methods: A convenience sample of 19 participants at least 6-months post-stroke who were able to ambulate between 0.4 - 0.6 m/s were recruited for this prospective study. Study participants completed a baseline assessment and were included in the data analysis (mean age 61.1 ± 11.7 years; mean years post stroke 3.8 ± 3.2). Participants completed 24 sessions of BWSTT over 8 weeks with 20 minutes of total walking during each session. Outcome measures, including the Berg balance scale (BBS), activities-specific balance confidence scale (ABC), stride impact scale (SIS), comfortable 10-meter walk test (CWT) and fast 10-meter walk test (FWT) were assessed 1-week prior to BWSTT (pre-test), 1-week after BWSTT (post-test) and 6-months after BWSTT (retention). A repeated measures analysis of variance was used to assess differences in dependent variables across the three measurements. Eligible pairwise comparisons were conducted using the Bonferroni adjustment. Effect sizes based on Cohens d classifications were calculated. Pearson correlation coefficients were used to assess relationships between change scores. Results: Statistically significant improvements on the BBS (p = .007), ABC (p = .000), SIS mobility (p = .023), SIS stride recovery (p < .001) and CWT (p = .000) were found from pre- to post-test. Significant improvements were maintained at retention on the BBS (p = .000), ABC (p = .038) and CWT (p = .004). Medium to large effect sizes were observed with all measures except SIS participation and FWT. Correlations between changes in gait velocity and changes on the BBS, ABC and SIS were significant. BWSTT is an effective intervention to train walking for persons with chronic stroke. The findings of this study suggest that the effects of BWSTT can transfer beyond gait to positively influence other dimensions of health.

P402
Depressive Symptoms in Stroke Patients Affect Functional Gains in the Subacute but Not in the Acute Phase of Rehabilitation
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Objective: This study assesses how depressive symptoms in stroke patients affect the rate of FIM gains during stroke rehabilitation. Design: This is a retrospective, observational study. Depressive symptoms were identified by clinical assessments and patient interviews both by neuropsychologists and physiatrists. Setting: Stroke unit in an inpatient rehabilitation program. Participants: 495 stroke patients who were consecutively admitted to a comprehensive inpatient rehabilitation program between 2006 and 2007. Main Outcome Measures: FIM scores were recorded at admission and discharge from inpatient rehabilitation, and at 3 month follow-up via phone interview. FIM efficiency was calculated at discharge and at 3 months from discharge. Total FIM efficiency was also calculated from admission to the 3 month follow-up. Results: One hundred fifty seven patients (31.72%) had depressive symptoms and 338 (68.28%) did not. As expected, greater FIM efficiency calculated from admission to 3 month follow-up, was greater in the non-depressed group compared to the depressed group, 0.43 versus 0.36, p < .001. But, during acute inpatient rehabilitation, mean FIM efficiency was higher in the group with depressive symptoms 1.93 versus 1.41 in the group without depressive symptoms, p = 0.008. It was not until after discharge that FIM efficiency declined in the group with depressive symptoms: by the 3 month follow-up, mean FIM efficiency in the group with depressive symptoms had declined significantly below that of the group without depressive symptoms, 0.68 versus 0.96, respectively, p < .001. Conclusions: Our data suggests that the majority of the impact of depressive symptoms on poor functional progress occurs in the subacute phase of rehabilitation and not the acute phase. Patients with depressive symptoms show less FIM gains than those without depressive symptoms in the subacute period following a stroke, even though the neurologic insult resulting from a stroke is fixed and not progressive. This supports the premise that depression following stroke is an independent, negative prognostic factor. Therefore, appropriate treatment of depressive symptoms and rehabilitation should be continued well after discharge from acute inpatient rehabilitation in order to improve the patients potential for better functional outcomes.
P403
Preliminary Efficacy of a Stroke Caregiver Intervention Program for Reducing Depressive Symptoms
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Background and Purpose: Stroke caregivers who lack skills are at increased risk for depressive symptoms, which are a risk factor for caregiver mortality. These depressive symptoms also can impede rehabilitation of the survivor and increase the survivors risk for costly, long-term institutionalization. The Telephone Assessment and Skill-Building Kit (TASK) is an 8-week program that addresses caregiver needs for information and skill-building, including screening caregivers for depressive symptoms. The purpose of this study was to explore preliminary efficacy of the TASK program for improving stroke caregiver depressive symptoms in a subgroup of caregivers who screened positive for depressive symptoms.

Methods: A subgroup of 15 caregivers who screened positive for at least mild depressive symptoms at baseline were randomized to the TASK program (n=8) or an attention control group (n=7). Data were collected at baseline (within 8 weeks of the survivors discharge), 4 weeks (half way through the intervention), 6 weeks (end of the intervention), and 12 weeks. Depressive symptoms were assessed with the PHQ-9, where scores ≥ 5 indicate moderate depression and scores ≥ 10 indicate moderate depression. Data were analyzed using univariate ANCOVA, controlling for baseline scores and number of minutes spent with the nurse for each timepoint (4, 8, and 12 weeks after baseline). Partial r2 was used to estimate effect sizes (≤ 0.01 = small; ≤ 0.06 = medium; ≤ 0.13 = large).

Results: Baseline PHQ-9 mean scores were 11.2 for the TASK group; 9.2 for the control group. Adjusted PHQ-9 means for the TASK group at 4, 8, and 12 weeks were 5.2, 4.9, and 5.9; adjusted PHQ-9 means for the control group at these time points were 10.8, 9.0, and 10.7. Although not statistically significant, most likely because of the sample size, large improvements based on effect size were found in depressive symptoms for the TASK group relative to the control group at 4 weeks [F(1,11) = 4.15, p = .07, r2 = .27], 8 weeks [F(1,11) = 1.66, p = .22, r2 = .13], and 12 weeks after baseline [F(1,11) = 1.47, p = .25, r2 = .12].

Conclusions: The TASK program showed medium to large improvements in depressive symptoms for more severe symptoms in the TASK group, and in depressive symptoms to the mild range, while caregivers in the control group continued to manifest symptoms of moderate depression. Further testing of the TASK program in a larger randomized controlled trial is warranted, with attention in subsequent studies directed toward reducing depressive symptoms in those who screen positive for mild to severe depressive symptoms.

P404
Videoconference Delivery of a Stroke Self-Management Program: A Mixed Methods Waiting List Randomized Controlled Trial
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Background and Objective: Self-management programs may address many long-term effects of stroke; however, access is not widely available, particularly in rural communities. The objective of this study was to determine the efficacy of combined videoconference and face-to-face delivery of the Moving On after Stroke (MOST®) stroke-specific self-management program to improve participation and well-being in rural people. Mixed methods waiting list randomized controlled trial was conducted. MOST is an established stroke-specific group self-management program consisting of 18 2-hour sessions, led by two movement specialists, one in the community and the other in the videoconference setting. Participants were randomized to either MOST or waiting list control (WLC) groups. Outcome indicators included the Participation Domain of the Stroke Impact Scale (SIS), the Reintegration to Normal Living Index (RNLI), Goal Attainment Scaling (GAS), and the Geriatric Depression Scale (GDS). To broaden the understanding of participant experiences, post-intervention focus groups and interviews were conducted. For the quantitative data, multivariate regression modelling was used to analyze between-group differences; as well, pre–post analysis was conducted on the combined group data. Directed content analysis was used for the qualitative data. Findings: There were initially 64 participants in the MOST group and 46 in the WLC group, 3 to 18 months post stroke; 65% were men. Approximately 40% participated via videoconference. No significant group effect was found for any outcomes in the multivariate regression analysis. Combined group pre–post analysis showed post-intervention gains in GAS (p = 0.001) and SIS Participation (p = 0.007), and greatly improved, and greater improvements, and greater participation for those in rural sites than urban participants. Qualitative findings included increased confidence and assumption of responsibility for health behaviour change, and favorable reception of videoconferencing. However, some participants noted disruption of the group process, which may detract from videoconference group interactions. Conclusion: MOST provided rural access to a stroke self-management program that would not otherwise be available, and was associated with significant individualized goal attainment in both rural and urban participants. However, significant between-group improvements in indicators of community participation were not demonstrated. Future research to investigate the relative impact of videoconference versus face-to-face delivery of group programs is warranted.

P405
Positive Emotion and Social Engagement After Stroke
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Abstract Objective: To examine the association between positive emotion and social engagement following a stroke in a sample of 599 patients 50 years and older discharged from inpatient medical rehabilitation. Design and Methods: Data were examined from the Stroke Recovery in Underserved Populations (SRUP) database for the years 2005-2008. Eligible individuals were admitted to the inpatient medical rehabilitation with a diagnosis of first-ever stroke. The study included 599 patients with stroke who had complete information at all three interviews (admission, discharge, and 3-month follow-up). Results: The sample was mostly non-Hispanic white (78.6%) and had a mean age of 71.6 years. Results of cumulative logistic models examining the association between higher positive emotion scores at discharge and higher levels of social engagement follow-up showed that each one point increase in positive emotion was significantly associated with 17% odds of being in a higher social engagement level (OR: 1.17, 95% CI 1.10, 1.25). Conclusion: High positive emotion after discharge from medical rehabilitation is associated with higher levels of social engagement post-discharge. The significant inverse gradient of association between positive emotion and social engagement in patients with stroke adds to accumulating evidence of the salutary effects of positive emotion on physical and psychological well-being and indicates that positive emotion may be a critical factor in the recovery of the stroke patient.

P406
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Background and Purpose: Stroke survivors face many challenges during recovery from stroke. Urinary incontinence (UI) after stroke adversely affects dignity and increases the need for skilled care. Previously, up to 50% of stroke survivors acutely, and 15% after a year, were reported to be incontinent by UI. The objective of this study is to investigate UI among elderly stroke survivors. Methods: We used the Health and Retirement Study (HRS) to perform a longitudinal analysis on reported incidence of UI among stroke survivors. We used 2002 and 2004 interview-waves in HRS to identify subjects with history of stroke and controls with matched age-sex who reported experiencing UI within the past 12 months. We extracted demographic data (age, gender, and race), self-evaluated general health, co-morbid conditions (neurological and sensory conditions, diabetes, cancer, lung disease, psychiatric, memory loss, impaired mobility, and pain), and reported presence of UI in the 2004 and 2006 interview-waves. We analyzed risk factors associated with UI in 806 stroke survivors aged 65 years and older, and compared them to matched age and sex subjects in multivariate models adjusting for confounders and concurrent presence of urinary problems. Results: We analyzed 739 subjects (mean age = 75 ± 5 years, 53% female) with a history of stroke that were matched for age and sex to 739 controls. We observed 31% and 24% UI cases (p = 0.003) among stroke and non-stroke subjects, respectively, which may be higher than rates reported previously after stroke. The odds of experiencing UI were higher for the subjects diagnosed with stroke (OR: 1.4, 95% CI: 1.1-1.8), however a reduction in UI reporting was observed in stroke subjects after adjusting for general health, psychiatric problems, diabetes, and pain (OR: 1.2, 95% CI: 0.9-1.7), with reduction in odds exhibiting a near significant trend. The difference in odds of reporting UI was not significant after further adjusting for concurrent presence of UI. We observed similar trends after removing subjects with concurrent history of stroke and UI. Conclusions: The risk and incidence of UI among elderly stroke survivors may be underestimated through self-report. However, it is also possible that stroke survivors in HRS under-represented the true frequency of UI. Databases in which stroke survivors self-report symptoms may be prone to under-represent problems like UI, because of unwillingness to disclose due to shame or embarrassment, survivor unawareness of deficit (anosognosia), or relative oversampling of higher-functioning survivors in these home-dwelling subjects.

P407
Evaluation of Motor Evoked Potentials Associated With Impairment Using Navigated and Non-navigated Transcranial Magnetic Stimulation in Persons With Stroke
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Background: Transcranial magnetic stimulation (TMS) can determine motor tract integrity. Studies suggest that TMS may be associated with function in persons with stroke. New technology, navigated brain stimulation (NBS), integrates a persons brain MRI to identify a precise motor cortex location for TMS. NBS may be more precise at measuring motor tract integrity compared to conventional TMS (non-NBS) used in previous studies. We compared NBS and non-NBS correlation with function among stroke patients and hypothesized that NBS would be more highly correlated with function. Methods: Eligibility included >6 months post stroke in the middle cerebral artery territory. A brain MRI was obtained within 2 weeks of TMS. NBS and non-NBS MEPs were obtained in one day by separate technicians blinded to the others results. Subjects with right hemisphere infarcts or who obtained for Adolescents with Major Depression, High Minimi, Extensor Digitorum Communis, Biceps Brachii (BB), Tibialis Anterior (TA) and Soleus (S). UE (upper extremity) impairment was measured using the UE Fugl Meyer (UFM) (≤15, ≥15).

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Lower extremity (LE) impairment measures included LEMF total score (r = −0.23, 0.23 > r > −0.23) and the ability to walk without an ankle foot orthosis (AFO). MEP responses were dichotomous (yes, no) and associations were analyzed using Fisher's Exact. Results: The 33 subjects had a median (range) of 63 (29, 75) years old. There were no significant differences between NBS and non-NBS for the UEEMF (<0.15), but there was a significant correlation for the LE LEMF obtained with non-NBS (r = 0.04) compared with NBS (p = 0.29). There were several differences between NBS and non-NBS for the LE LEMF (r = −0.23, 0.23 > r > −0.23) except for TA MEP. LEFT MEP was more correlated with SEP MEP obtained with non-NBS (p = 0.04) compared with NBS (p = 0.29). There were several differences between NBS and non-NBS for the LE LEMF (r = −0.23, 0.23 > r > −0.23) except for TA MEP. LEFT MEP was more correlated with SEP MEP obtained with non-NBS (p < 0.05) but not non-NBS (p > 0.10). The ability to walk without an ankle foot orthosis correlated with TA MEP obtained with NBS (p = 0.09) but not with non-NBS (p = 0.62). Conclusion: For the UE, NBS and non-NBS were similarly correlated with impairment with the exception of the BB. For the LE, NBS showed more significant correlations with function. We believe the LE motor cortex is more difficult to reach.

Clinical Outcome After Intensive Rehabilitation Following Acute Treatment and Management in Stroke Centers and Significant Variables for Returning to Previous Home Life

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Purpose: Rehabilitation institutions and acute stroke centers work in close cooperation to improve ADL of stroke patients. However, which stroke centers did may have an influence on clinical outcome. The purpose of our study was to investigate whether or not clinical outcome after rehabilitation depends on acute treatment in stroke centers and to find significant variables for returning to previous home life. Methods: Included for retrospective analysis were patients who were transferred to Tsurumaki Onsen rehabilitation center after ischemic stroke from Jan 1 2008 to Dec 31 2008. From a standpoint of a rehabilitation center, stroke centers were classified into two groups: special centers where patients were managed by special stroke teams; i.e., hyper-acute endothelial treatment was available, nutrition was supported especially and hyperglycemia and aspiration pneumonia were managed strictly (S group) and usual centers where patients were managed by usual stroke team (G group). Patients age, sex, elapsed days for entering the rehabilitation institution (DayFR), modified Rankin scale (mRS) on admission, functional independence measure (FIM) on admission (FIM on adm), serum Albumin on admission (Alb on adm), gastrointestinal tube feeding on admission (G tube), rehabilitation time per day (ReT), mRS at Tsurumaki discharge (mRS at Tsurumaki) were significant variables for returning to their home life earlier (p < 0.01), while muscle strength index and distance covered in 6MWT were not significant predictors of FTSTS scores. The whole model can explain 71% of variance in FTSTS scores. Conclusions: This is the first study in documenting the importance of balance ability, not muscle strength and exercise endurance, is an important determinant of performance of five-times-sit-to-stand test in community-dwelling stroke patients. These findings suggest that the FTSTS test may be a more appropriate proxy indicator of balance performance in chronic community-dwelling stroke subjects.

Physical Therapists' Use of Outcome Measures to Evaluate Walking Capacity Post-Stroke

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Introduction: Although valid outcome measures (OMs) of walking capacity post-stroke exist, little is known about the purpose for which physical therapists use these measures and barriers to their use. Objectives: The objectives of this study were to determine the extent to which physical therapists use standardized measures of walking ability for different purposes and barriers to use among people with stroke. Methods: A cross-sectional survey was conducted. A questionnaire was mailed to 1155 physical therapists in neurological practice in Ontario, Canada. Those who treated people with stroke were eligible. Questionnaire items were developed to evaluate whether therapists use outcome measures of walking capacity consistently (i.e., 1) to evaluate, 2) monitor change, 3) determine prognosis, and 4) determine readiness for discharge home or from therapy. Respondents who were not consistent users were asked to identify the top 3 reasons why from a pre-defined list of barriers. Results: Of the 334 eligible respondents, 270 (80.8%) completed a questionnaire. Among the 270 study participants, 44.6% reported consistent use of OMs to evaluate walking ability post-stroke. The percentage of respondents who consistently used OMs to monitor change, determine prognosis or determine readiness for discharge was 42.9%, 19.4% and 28.4%, respectively. The most common reasons why respondents did not consistently use OMs to evaluate walking ability (n = 149) were lack of time (28.1%) and lack of knowledge about OMs (25.6%). The top reasons why respondents did not consistently use OMs to monitor change in walking capacity (n = 152) were lack of time (30.7%) and lack of sensitivity to change of OMs (20.7%). The top reasons why respondents did not consistently use OMs to determine prognosis for walking recovery (n = 212) were lack of clear evidence (36.7%) and lack of time (35.2%). Finally, the most common reasons why respondents did not consistently use OMs to determine readiness for discharge (n = 187) were that OMs do not reflect the home or community environment (38.2%) and lack of time (20%). Conclusions: Findings indicate the majority of physical therapists do not consistently use valid and reliable measures of walking ability post-stroke, particularly for the purposes of determining prognosis or readiness for discharge. Barriers to use can be modified through education and have relevance to OM development.
Risk of Post-stroke Fractures in a Bi-ethnic Community

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Background: Post-stroke fractures are a critical component of poor long-term stroke outcome. Mexican Americans (MAs) have increased risk for any fracture and of hip fracture adjusted for age, gender, history of stroke, stroke type (ICH vs ischemic stroke) and stroke severity (NIHSS). Results: Mean age was 71 years (sd=13); 54% were MA and 52% were women. Eighty-three percent of the cases were ischemic stroke, 14% ICH and 3% SAH. Mean follow-up was 4 years. There were 105 fractures with hip fractures the most common type (33%). Cumulative risk of any fracture post-stroke were 0.4% (hip: 0.2%) at 30 days, 1.2% (hip: 3.3%) at 1 year, and 2.6% (hip: 9.7%) at 5 years. Survival free of any fracture (p=0.83) and of hip fracture (p=0.23) did not differ by ethnicity. Ethnicity was not associated with risk of any fracture or of hip fracture post-stroke in multivariable models. Increasing age, female gender, ICH and greater stroke severity were associated with increased risk of any fracture but none of the predictors was associated with risk of hip fracture. Conclusion: This bi-ethnic community, stroke patients had high fracture risk with 10% risk at 5 years. Despite a known lower risk of osteoporosis in MAs, there was no ethnic difference identified in post-stroke fracture. Thus, both MAs and NHWs should be targeted for bone fracture prevention post-stroke.

Withdrawn

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Examining the Changing Needs of Stoke Family Caregivers

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Background and Purpose: Family caregivers provide essential support to individuals who have experienced a stroke. As stroke survivors move across the care continuum, their interaction with health care professionals (HCPs), treatment focus, and functional abilities change. As a result, the needs of family caregivers will also change. The objective of this research was to delineate family caregivers’ support needs over time using the Timig Right (TIR) framework to facilitate a systematic approach to examining family caregivers’ needs and, ultimately, creating and evaluating interventions aimed at supporting family caregivers across care environments. The objective of this research was to delineate family caregivers’ support needs over time using the TIR framework as a conceptual model.

Methods: A qualitative study using in-depth interviews with stroke family caregivers and health care professionals (HCPs) identified family caregivers’ changing support needs over time and their experiences with having their support needs met. Family caregivers (n=24) were recruited from in- and out-patient rehabilitation, a rural community care organization, and a community-based aphasia program. HCPs (n=14) were recruited from an acute care hospital, a rehabilitation facility, and community-based health care organizations. Interviews examined family caregivers’ needs for informational, instrumental, and emotional support. Interviews lasted approximately 60 minutes, were audio taped, transcribed, and analyzed using Framework Analysis. Results: We identified four key themes: 1) The type and intensity of support needed by family caregivers change across the care continuum; 2) There is variability within and across care environments in the receipt of support by family caregivers; 3) Patient versus family-centered approaches to care affect families receipt of support; and 4) The availability of health care professionals affect the support provided to family caregivers. We also discuss how the themes change over time. Conclusions: Stroke family caregivers’ needs across the care continuum are complex. Needs change over time and are influenced by aspects of service delivery including a lack of standardized approach to providing families with support, whether the focus of care is the patient or family, and the availability of health care professionals. Significance: This information can inform programs and modify health care delivery to better meet the needs of family caregivers.

P414

Health Care Professionals’ Perspectives on Using the Weekend Pass to Facilitate Stroke Survivors Transition Home

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Background and Objective: One of the most challenging transitions for stroke survivors is their transition home from inpatient care. Stroke inpatient rehabilitation programs have implemented weekend homes to ease this transition, but little research exists on this topic. The objective of this qualitative study was to explore health care professionals’ experiences with weekend pass programs. Method: A qualitative study was conducted with members of the stroke health care team. We conducted focus groups with health care professionals associated with the weekend visit aspect of the inpatient stroke rehabilitation program at a leading rehabilitation facility. Focus group questions encouraged health care professionals to describe the objectives of weekend pass, preparation provided to stroke survivors and family caregivers prior to their first visits, and areas in need of improvement. Working in collaboration, two members of the research team reviewed the focus group transcriptions and used open coding and axial coding to organize codes into common categories, and generate themes. Findings: We recruited 18 health care professionals including three physiotherapists, two occupational therapists, two social workers, three nurses, three pharmacists, one service coordinator, one recreation therapist, two speech language pathologists, and one dietitian. We identified the following themes: 1) safety in the home was the key priority of the health care team as they prepare to send a stroke survivor home on a weekend pass; 2) health care professionals view the weekend pass as a way to facilitate the stroke survivor’s ultimate transition back to the home environment; 3) the stroke team uses a collaborative approach to provide the best clinical care to stroke survivors including the weekend pass but they struggle to determine the best way to incorporate family members into this team; and 4) the health care team raised a number of concerns regarding the administrative challenges inherent in providing the weekend pass. Conclusions: Our research findings provided insight about how to enhance the weekend pass aspect of inpatient stroke rehabilitation. This research has implications for other rehabilitation institutions who offer weekend passes to stroke survivors to facilitate the transition home.

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Long-term Stroke Related Health Outcomes for Stroke Survivors and Their Spousal Caregivers

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Background and Objective: Few studies have examined the long term impact of stroke on stroke survivors’ (SSs) and their spousal caregivers’ (CGs). This study aimed to measure the changes in health-related outcomes an average of 3-5 years post-stroke. Methods: A sample of SSs and CGs who had previously completed a 12-month study following inpatient discharge after stroke; 30 SSs and CGs completed the present study. Depression, mutuality, and generic health-related quality of life (HRQoL) was measured for both SSs and CGs. Depression was measured for CGs and stroke-specific HRQoL was measured for SSs. Data from baseline to 12 months were used in conjunction with data from the present study for all analyses. Linear mixed models were used to analyze the changes in all measures over time with the exception of generic HRQoL. Multiple linear regression was used to analyze the relationship of gender and depression to HRQoL mental and physical subscales to depression, perceived health status, mutuality, and demographic variables. All analyses utilized separate SSs and CGs models. Results: The majority of SSs in this study were male (80%, n=24). The mean age was 66.4 and 60.5 years for SSs and CGs, respectively. The ethnicity of the sample was non-Hispanic white (70%), African American (16%), and Hispanic (15%). The average number of years since stroke was 4.68 (SD=.91). Among SSs, depression was found to decrease from baseline to 12 months (p=.04) but to increase from 12 months to an average of 4.68 years (p=0.003). CGs’ depression decreased from baseline to all time points (p=0.007 to .05). SSs’ mutually showed little change over time (p=0.12) CGs’ depression decreased from baseline to all time points (p=0.007 to .05). SSs’ mutually showed little change over time (p=0.007 to .05). SSs’ mutually showed little change over time (p=0.007 to .05). SSs’ mutually showed little change over time (p=0.007 to .05). SSs’ mutually showed little change over time (p=0.007 to .05). SSs’ mutually showed little change over time (p=0.007 to .05).
CGs continue to experience negative stroke related health outcomes for many years after the initial stroke; some of these outcomes even worsen over time. These findings illustrate the need for ongoing psychological and medical evaluation for both long-term SSs and CGs. Development and testing of targeted behavioral interventions are also warranted.

Impact of Blood Pressure Status in Subacute Stage of Ischemic Stroke on Clinical Outcome: Is Variability More Important Than Value Status?

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Background and Objectives: Elevated blood pressure (BP) in acute stage of ischemic stroke is related with early stroke recurrence and worse clinical outcome. However, it has not been studied whether BP status of subacute stage affects clinical outcome of acute ischemic stroke.

Methods: From January 1, 2004 to January 31, 2009, a consecutive series of patients, who visited the National University Hospital in Seoul, Korea, were hospitalized due to acute ischemic stroke within 48 hours after stroke onset, and survived the acute stage of stroke, were selected. Subacute stage of stroke was operationally defined as during 3 days before discharge or transfer to rehabilitation unit. BP measurements during this period, clinical information, and stroke outcome were obtained directly from the prospective stroke register and by reviewing the electronic medical records. Mean systolic blood pressure (SBP), diastolic blood pressure (DBP), maximal/minimal BP, and variation (maximal - minimal) of SBP (SBPV) and DBP (DBPV) were calculated. The relationship between subacute BP status and clinical outcome was analyzed by responder analysis. Unfavorable outcome was defined as modified Rankin scale (mRS) at 3 months = 2 when baseline NIH stroke scale (NIHSS) was < 8, or ≥ 2 when NIHSS = 8-14, and ≥3 when NIHSS > 14.

Results: A total of 1657 patients (age, 67.1 ± 12.5; male, 80.2%) were included. The median baseline NIHSS was 4 (interquartile range (IQR), 2 to 7), and 250 patients (14.7%) received thrombolysis. The median number of adverse events was 10 (IQR, 8 to 12) per person, and the median duration from admission to discharge or transfer was 10 days (IQR, 8-12). SBP and DBP were 137.6 and 76.5 mmHg, respectively. Patients with unfavorable outcome had higher SBP and DBP than those with favorable outcome (p's < 0.05) not for SBP and DBP. BP variables were categorized by intervals and their correlations with clinical outcomes were analyzed. Also, SBP and DBPV showed a positive linear relationship to poor outcomes, but SBP and DBP did not. Highest quartiles of SBPV and DBPV were remained as the risk factors for poor outcomes after adjustments for age, gender, admission periods, initial BP, hypertension status, stroke subtype, baseline NIHSS score and thrombolysis. Death occurred in 67 patients, and was related to high SBP and DBPV in the multivariable analysis. Both extremes of SBP and DBPV raised the mortality (p's<0.5), but lost their significance after adjustments.

Conclusions: This study showed that BP status in subacute stage of ischemic stroke, especially its variation and both extremes, may affect clinical outcome.

Women and Stroke Treatment

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Objective: To assess the gender differences in patients with acute ischemic stroke treated with and without t-PA. The primary purpose is to compare baseline risk factors, treatment times, and 90-day outcomes between genders. Background: Previous reports indicate gender differences in the treatment of myocardial infarction. Women have longer treatment times, receive fewer invasive procedures and have more adverse events. Data regarding gender differences in acute stroke treatment are limited. Women with acute stroke experience greater Emergency Department (ED) delays than men and diagnostic tests are delayed compared to men. Women are less likely to receive t-PA and the limited data on functional outcome in women indicates poorer 90-day outcome in women.

Methods: Retrospective review of the UCSF database to identify stroke patients with favorable outcome gender. Patients with the admitting diagnosis of acute ischemic stroke from 2001 to 2009 excluding transfers, in-house patients and patients with hemorrhagic stroke were classified based on gender and t-PA treatment (Group 1 with t-PA, Group 2 excluded from t-PA). Treatment times and baseline demographics by gender were compared. Univariate logistic regression analysis was performed to control for multiple confounding factors.

Results: A total of 848 patients were included, Group 1: 294, 148 women (50.3%), baseline NIHSS and age in men were 12.0 ± 7.9 and 67.6 ± 16.5 years, in women 13.7 ± 7.8 and 72.4 ± 16.5 years. Group 2: 554, 242 women (43.6%), baseline NIHSS and age in men were 7.2 ± 8.0 and 68.4 ± 14.0 years, in women 8.0 ± 8.0 and 72.2 ± 14.0 years. In group 1, women were less likely to have a history of AF. In both groups, men were more likely to use tobacco and have a history of coronary artery disease. In group 1, 18% of women and 16.5% of men had a pre-stroke mRS of 2-6. In group 2, 28.9% of women and 19.6% of men had a pre-stroke mRS of 2-6. In group 1 and 2, men were less likely to have a 90-day mRS of 2-6 compared to women (64.4% vs 77.45% and 42.7 vs 52.8%). Results from the multivariate regression indicated that this difference was not significant for Group 1 (odds ratio – 0.62, 95% CI 0.30, 1.28, p = 0.19) or Group 2 (odds ratio – 0.63, 95% CI 0.43, 1.58, p = 0.34). There were no differences in severity of acute ischemic stroke were similar in men and women. Previously identified sex differences in stroke treatment times and outcome were not found in our sample.
Clot Burden Score Derived From CT Angiography is a Predictor of Symptomatic Hemorrhagic Transformation Independent of ASPECTS


Purpose: Clot Burden Score (CBS) and Collateral Score (CS) are semiquantitative metrics recently introduced to CTA for added utility in the assessment of anterior circulation stroke outcome. We aimed to determine if CBS and CS are predictors of symptomatic hemorrhagic transformation (SICH), independent of ASPECTS. Methods: 84 patients with acute nonlacunar MCA stroke imaged <9 hours from stroke ictus were included in this retrospective study. CBS was scored on a 10-point scale with 2-points subtracted for occlusion of the supratentorial ICA, proximal M1, or distal M1 segment, and 1-point subtracted for occlusion of the infratentorial ICA, A1 segment, or either M2 branch. CS was scored on a 4-point scale for degree of collateralization compared to the contralateral side with 0-none visible, 1->50%, 2->50% but <100%, and 3-100%. CBS, CS, and ASPECTS were graded by two blinded readers. Clinical data including age, glucose, NIHSS score, time to CT, subsequent ICA administration and post-treatment recanalization were obtained. SICH was defined as the appearance of hemorrhagic transformation on imaging temporally related to worsening of symptoms. Results: Effects of CBS and ASPECTS were performed before and after adjustment for confounders. Adjusted odds-ratios (OR) were calculated with 95% confidence intervals [95% CI]. Those variables that have p<0.05 were then entered into multivariate logistic regression to determine independent predictors. ROC analyses were done to determine optimal thresholds. Median (IQR) values for baseline variables were: age-72 (62-81) years, glucose-6.5 (5.6-8.0) mmol/L, NIHSS score (10-16), and time to CT-3.0 (2.0-5.0) hours. 43 (51.1%) patients received treatment (18 (21.4%) IA therapy). Of these, 24 (55.4%) achieved post-treatment recanalization. Median (IQR) ASPECTS, CBS and CS were 7 (6-9), 3 (2-3), respectively. ASPECTS, CBS, and CS were independent predictors of SICH (OR 1.69, 95% CI 1.05 - 2.71) and sICH (OR 6.06, 95% CI 2.22 - 80.3%, respectively for SICH.

Conclusion: CBS and CS are independent predictors of SICH, independent of ASPECTS. Impact of Antiplatelet Pre-treatment on Intracranial Hemorrhage and Stroke Outcome After Intravenous Thrombolysis: The Stroke Acute Management With Urgent Risk-Factor Assessment and Improvement (SAMURAI) Study

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Background and Purpose: We sought to clarify the impact of antiplatelet (AP) pre-treatment on intracranial hemorrhage (ICH) and 3-month outcome after intravenous recombinant tissue plasminogen activator (rt-PA) therapy in patients with ischemic stroke. Methods: In a retrospective, multicenter, observational study, we studied data from consecutive patients treated with low-dose intravenous rt-PA (0.6 mg/kg alteplase) which was given to 240 patients, within 3h after symptom onset. AP therapy prior to thrombolysis was obtained from clinical records. Any ICH was defined as CT evidence of new ICH within the initial 36 hours, and symptomatic ICH (sICH) with neurological deterioration corresponding to an increase of ≥1 point from the baseline NIHSS score. Favorable outcome reflecting independence was defined as a modified Rankin Scale score of 2 or less at 3 months. Results: Of the 240 patients (377 men, 72 ± 12 years old) treated with rt-PA, 189 (31.5%) used AP drugs prior to thrombolysis; 159 (26.5%) used aspirin and 14 were pre-treated with dual AP drugs. Both ICH and sICH occurred more frequently in patients with AP therapy before thrombolysis than those not (ICH: 26.5% vs. 16.5%, P = 0.008, sICH: 8.1% vs 1.7%, P = 0.001). Particularly, 8 of 14 patients (57.1%) who had received dual AP drugs developed ICH. In multivariate analysis, AP therapy was an independent predictor of ICH (OR 1.69, 95% CI 1.05 - 2.71) and sICH (OR 6.06, 95% CI 2.22 - 80.3%). Favorable outcome was fewer in patients with AP therapy compared to those not (40.7% vs. 55.2%, P = 0.53), whereas it was not an independent predictor of poor outcome. Conclusion: In Japanese patients, AP therapy prior to thrombolysis was associated with occurrence of ICH and sICH, and may lead to poor outcome, even though using low-dose rt-PA.
several deviations from the current license. HYPOTHESIS We assessed the hypothesis that off-label treated patients (age >80, administration of I.V. antihypertensive treatment prior to alteplase treatment, symptom-to-needle time of >3 hours, blood pressure level of >185/110 mmHg, oral anticoagulant use, or previous stroke with diabetes) achieve as good outcomes as those treated according to official labeling. METHODS: We used our prospective registry of 1104 consecutive patients treated with thrombolytic therapy at the Department of Neurology, Helsinki University Central Hospital (years 1995-2008) for the analyses. We compared the outcome of patients treated with I.V. alteplase off-label to that of patients treated on-label. Patients with basilar artery occlusion (n=115) were excluded. A 3-month favorable outcome was defined as modified Rankin Scale (mRS) score of 0 to 2. We used logistic regression adjusted for age, sex, mRS and baseline NIHSS score to analyze whether the presence of contraindications in treated patients affected the outcome. Results: Of the 855 patients (54% males; mean age 67.7; median NIHSS score 10), 590 received on-label (median NIHSS score 9) and 365 off-label (median NIHSS score 10) treatment with I.V. alteplase. Age >80 (n=146; odds ratio 0.41; 95% confidence interval 0.24-0.71) and previous stroke together with diabetes (n=32; OR 0.38; 95% CI 0.15-0.93) were the only off-label variables with decreased likelihood of favorable outcome in the multivariate analysis. The rest of the studied contraindications, I.V. antihypertensive treatment prior to thrombolysis (n=113; OR 1.06; 95% CI 0.59-2.00) strokes 3-6 hours (n=31) had increased stroke level >185/110 mmHg (n=42; OR 0.79; 95% CI 0.37-1.68), and oral anticoagulant use (n=39; OR 0.79; 95% CI 0.36-1.74), were not associated with less favorable outcome. In a separate analysis, previous stroke alone was associated with favorable outcome (n=123; OR 1.99; 95% CI 1.11-3.59), while diabetes alone was not (n=113; OR 0.62; 95% CI 0.36-1.09). Conclusions: Of the studied contraindications to thrombolysis, age >80 and the combination of diabetes with previous stroke were independently associated with unfavorable outcome. Uncontrolled hypertension, use of I.V. antihypertensives prior to thrombolysis, treatment delay of >3 hours, or oral anticoagulant use were not associated with worse response to treatment. Our results suggest that violating these official off-label contraindications of I.V. thrombolysis may serve the best interest of such stroke patients. Whether our results can be repeated in other stroke populations is unknown.

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High Systolic Blood Pressure Has a Negative Effect on Thrombolysis Response in Stroke Patients, but Only in Women


Background and Purpose: High systolic blood pressure (SBP) has been associated with a worse outcome after intravenous (IV) tPA in patients with ischemic stroke. Our objective is to analyze whether there are differences in response to thrombolysis. Methods: prospective register of acute ischemic stroke patients treated with IV tPA in five Stroke Centers placed in the same city. Variables analyzed: demographic data, vascular risk factors, baseline BP and glycaemia, stroke etiology according with the international Classification of stroke, basal NIHSS, onset to treatment time, symptomatic intracerebral hemorrhage per SITS-MOST definition and 3-months modified Rankin Scale (mRS) score (Poor outcome was defined as mRS >3); SBP was analyzed as continuous variable and also categorized in three groups: <140, 141-150 y >150 mmHg. Results: From January-03 to April-09 a total of 736 patients were included. Forty-five percent were women and they were older than men (67.1±14.4 vs. 64.9±11.1 years old respectively, P<0.001). Basal SBP was similar in women and men (154.9±22.7 vs 147.6±20.6 respectively, P<0.28), as well as history of arterial hypertension and the percentage of patients under previous antihypertensive therapy. High SBP was associated with poor outcome at 3-months only in women (OR 1.26 for increases of 10 mmHg [95% CI 1.11-1.43]; P<0.001), after adjustment for demographic data, vascular risk factors, basal glycaemia, stroke severity and stroke subtype. Furthermore, SBP >150 mmHg was associated with unfavorable outcome in women (adjusted OR: 2.40; 95% CI 1.37-4.361) but not in men. Conclusions: there is an association of high SBP at baseline with poor outcome after thrombolysis in women, but not in men. A basal SBP >150 mmHg is a strong predictor of unfavorable outcome in women.

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Background: IV rt-PA treatment rates remain low. Less than 5% of all ischemic strokes receive thrombolysis.(1) One explanation is the eligibility criteria used for treatment. Few if any of the original NINDS treatment criteria are evidence based, and many centers use even more stringent criteria (e.g. a baseline NIHSS score of 0 to 2). In addition, registries in the US have reported that 35% of patients who presented within 3 hours of symptom onset were excluded from treatment on the basis of NINDS criteria, with outcomes comparable to those reported in the literature. Methods: Commonly employed thrombolytic treatment criteria were critically evaluated and modified to reflect current knowledge regarding stroke management (SMART criteria). These criteria were then prospectively applied to all acute ischemic stroke patients admitted to our Center. All patients received informed consent regarding the revision of our treatment standards compared with common rt-PA treatment criteria. Outcomes were determined by NIHSS and mRS scores at discharge or last neurological evaluation. Symptomatic hemorrhage was determined by CT or MRI detected intracranial hemorrhage (ICH) with any neurological deterioration (NIHSS score decrease of 1 point or more). Patients routinely received CT or MRI following treatment to assess extent of brain injury and hemorrhagic complications. Results: Between 7/6/06 and 6/15/09, we prospectively treated 148 patients with thrombolytic therapy. This represents 25% of ALL ischemic stroke patients evaluated during this period (range 6-42% per month). 117 patients (20%) received IV rt-PA alone. The median NIHSS score was 76 (range 16-98). Median prethrombolysis NIHSS score was 10 (range 0-25); 50% were male. 41% of patients were over age 60. Favorable outcome (mRS less than or equal to 1) was observed in 58%. Symptomatic ICH rate was 2.4%. Of treated patients, 89% had at least one common rt-PA exclusion criterion. The mean number of relative exclusions was 1.5 (range 0-4). Conclusions: Modification of rt-PA treatment algorithms using SMART criteria is feasible, safe, and effective compared to the original inclusion criteria. Stroke centers using SMART criteria may be able to treat up to 20% more patients with the equivalent of the original rt-PA exclusion criterion. A modification of IV rt-PA treatment criteria is needed, and could lead to substantially greater IV rt-PA use with good outcomes. 1.Schumacher HC, Ann Emerg Med. 2007;50:99-107.

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Thrombolysis in the 3-6 Hour Window Using Perfusion Computed Tomography for Patient Selection is Safe and Effective

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Background: Thrombolysis after acute stroke in the 3-6 hour window is controversial. Observational studies using MR perfusion for mismatch suggest benefit. Barriers to MR imaging in acute stroke may include established contraindications, patient illness and restricted patient access. Perfusion CT has no such limitations and is widely available but has not been used consistently in the setting of acute stroke. Patients presenting within 3 hours were thrombolysed on the basis of a plain CT, as per guidelines. Patients presenting between 3 to 6 hours had additional perfusion CT scans and were thrombolysed on the basis of clear mismatch only. Baseline characteristics, outcome and safety measures, as retrieved from the Safe Implementation of Thrombolysis in Stroke (SITS) register, were compared between the 0-3 and the 3-6 hour groups. Results:
Symptomatic Intracranial Hemorrhage Rates With IV tPA Treatment by Stroke Subtype

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Background: Treatment of acute stroke with IV tPA is associated with an increased risk of symptomatic intracranial hemorrhage (sICH). Studies of patients not treated with thrombolytics suggest a higher propensity for hemorrhagic transformation in patients with cardioembolic stroke. We hypothesized that the rate of sICH following IV tPA also varies by stroke subtype. The goal of the current study was to analyze sICH by stroke subtype employing MRI to accurately define TOAST classification. Methods: In this retrospective observational multicenter study, we collated data from 9 well-established stroke centers. We included acute ischemic stroke patients treated with IV tPA within 6 hours of stroke onset, with baseline MRI performed prior to IV tPA and subsequent brain imaging to determine the incidence of hemorrhagic transformation. We employed the ECASS II definition of sICH. Results: Among the 466 patients in the cohort, mean age was 67 years, 56% male, median NIHSS 12, median DWI lesion 15 mL. The table shows the rate of sICH, median DWI volume, and median NIHSS by TOAST classification. On univariate analysis, higher NIHSS (p = 0.019), larger DWI lesion (p < 0.001), and treatment > 3 hrs (p = 0.0015) were significant predictors of sICH while presence of large artery TOAST subtype was a negative predictor (p = 0.036). In multiple logistic regression analysis only treatment > 3 hrs (p = 0.018) and larger DWI volume (0.03) remained significant predictors of sICH and there was a trend towards significance for large artery subtype as a negative sICH predictor (p = 0.069). Conclusions: In this large cohort of patients treated with IV tPA, DWI lesion volume and treatment > 3 hrs were significant independent predictors of sICH. Neither cardioembolic nor lacunar stroke was associated with sICH rate independent of DWI lesion volume. The trend for lower sICH risk with large artery stroke independent of DWI lesion volume, may have important implications for treatment decisions.

<table>
<thead>
<tr>
<th>Cardioembolic</th>
<th>Large Artery</th>
<th>Lacunar</th>
<th>Other</th>
<th>Undetermined</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>216 (46%)</td>
<td>102 (22%)</td>
<td>35 (8%)</td>
<td>38 (8%)</td>
<td>466</td>
</tr>
<tr>
<td>sICH</td>
<td>7.9</td>
<td>2.0</td>
<td>2.9</td>
<td>10.5</td>
<td>8.0</td>
</tr>
<tr>
<td>DWI Volume</td>
<td>18.23</td>
<td>13.2</td>
<td>1.72</td>
<td>16.5</td>
<td>12.0</td>
</tr>
<tr>
<td>NIHSS</td>
<td>14</td>
<td>13</td>
<td>6</td>
<td>12</td>
<td>20</td>
</tr>
</tbody>
</table>

sICH rates were older (70.4 vs. 66.3 years-old, p = 0.001), and presented a higher frequency of past high blood pressure, hypertension (68% vs. 59%, p = 0.037), diabetes (24% vs. 16%, p = 0.032), atrial fibrillation (53% vs. 40%, p = 0.004) and more common atrial paradox (17% vs. 23%, p = 0.108) was less common in Ex-group than In-group. Percentage of patients with premorbid mRS ≥ 2 was 83% in Ex-group and 98% in In-group (p < 0.001), and initial NIHSS DWI score was 15.6 ± 14.6 vs. 18.5 ± 16.4, respectively (p < 0.001). As clinical outcomes, lower NIHSS (p = 0.018), lower individual (p = 0.037) was less common in Ex-group than in In-group. Chronic favorable outcome was found in 36% of Ex-group and 55% of In-group (p = 0.001) and mortality at 3 month was 13% and 5% (p < 0.001), respectively. Conclusion: Three-month functional and vital outcomes after low-dose rt-PA therapy in patients with high NIHSS appear to be better for those in the others, although NIHSS was less common in the former than in the latter.

Age-Adjusted Stroke Outcomes Are Significantly Worse in Women Than Men: A Latin America Cohort Study

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Background: Women generally have worse stroke outcomes than men, but rationale for this disparity is only partially understood. Older age at stroke onset has been touted as a major confounder of disparity, but appears not to fully explain it. However, data on sex differences in index stroke outcomes beyond Europe and the United States are limited. Objective: To assess short-term outcomes by sex in patients hospitalized with ischemic stroke within a Latin American Healthcare system. Methods: Between 12/06 - 07/09, consecutive acute ischemic stroke patients admitted within a Buenos Aires healthcare system were prospectively enrolled in an outcomes study. We compared vascular risk factor control between sexes, as well as the independent effect of sex on several outcomes at one month post-discharge: cognitive status (miniminal state exam score (MMSE), clock drawing test (CDT), functional status (Barthel scale score (BS), modified Rankin scale (mRS) score ≥ 3), and depression (Geriatric depression scale ≥ 5) after controlling for the confounding effect of age. Results: Among 357 stroke patients, age range: 74 ± 5 to 87 ± 10 years, 53% men and 47% women. Mean MMSE values were worse in women vs. men (26.3 vs. 27.8, p = 0.001), mRS < 3 was less common in Ex-group than In-group. Percentage of 36% men, 55% women (p = 0.003) was significantly different. Large artery atherosclerotic disease was more frequent in men (15% vs. 9%) and cardioembolism in women (22 vs 11%). Mean MMSE values were worse in women vs. men (26.3 vs. 27.8, p = 0.001), mRS ≤ 2 was less common in Ex-group than In-group. Percentage of 35% men, 55% women (p = 0.003). As clinical outcomes, lower NIHSS (p = 0.018), lower individual (p = 0.037) was less common in Ex-group than In-group. Chronic favorable outcome was found in 36% of Ex-group and 55% of In-group (p = 0.001) and mortality at 3 month was 13% and 5% (p < 0.001), respectively. Conclusion: Three-month functional and vital outcomes after low-dose rt-PA therapy in patients with high NIHSS appear to be better for those in the others, although NIHSS was less common in the former than in the latter.

Low-dose Intravenous rt-PA Treatment for Stroke Patients Out of the Indications by the European Licence: The SAMURAI Study

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Background: European regulatory agencies do not advocate intravenous recombinant tissue plasminogen activator (rt-PA) therapy in patients with severe stroke with NIH scale score ≤ 25, age ≥ 80 years, and having prior stroke with concomitant diabetes, unlike the US and Japanese guidelines. This study aimed to document clinical outcomes in patients treated with low-dose intravenous rt-PA (alteplase, 0.6 mg/kg) within 3 hours of stroke onset who met exclusion criteria of the above European licence. Methods: A retrospective, multicenter, observational study was conducted to clarify the efficacy of intravenous low-dose rt-PA therapy in clinical practice in 10 major stroke centers in Japan. Studied were a total of 600 consecutive stroke patients (377 men, 72 ± 12 years old) who were treated with rt-PA from October 2005 through July 2008. Of all the patients, 422 patients (292 men, 68 ± 10 years old)

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blood pressure (84.3% vs. 73.4%; p<0.01) and lower frequencies of alcohol consumption (5.6% vs. 25.5%, P<0.001) and smoking (18.2% vs. 42%, p<0.001). We found a no significant association between women and men regarding to ischemic stroke (80.4% vs. 84%) and intracerebral hemorrhage (81.6% vs. 16%), p=0.08. The case-fatality rates (and 95% Confidence Interval) for first-ever stroke were at ten days: 9.0% (95%CI: 5.3% to 14.1%) for men, and 5.4% (95% CI 2.5% to 10.0%) for women; at 28 days: 13.3% (95%CI: 8.8% to 19.0%) for men, and 12.7% (8.0% to 18.7%) for women; and at six months: 19.1% (13.8% to 25.3%) for men, and 21.7% (95% CI 15.7% to 28.7%) for women. Conclusion: In this Brazilian stroke registry, case-fatality among women did not differ from men.

**Risk and Predictors of Recurrent Ischemic Stroke in a Large, Community-based Cohort**

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Background: Previous observational studies have reported the risk of stroke recurrence to range from 5% to 22% in the first year after ischemic stroke. However, most of these studies are not applicable to contemporary patients as they occurred over a decade ago, prior to advancements in diagnostic neuroimaging and secondary stroke prevention. Many of these studies also are limited by insufficient power, inclusion of TIA and hemorrhagic stroke, and lack of multivariate analyses. We aimed to better define the risk and independent predictors of ischemic stroke recurrence by investigating a large, modern, prospectively assembled cohort of patients. Methods: We prospectively identified a cohort of all patients hospitalized with ischemic stroke from 1/2004 through 12/2006 and followed them during the year after discharge for new diagnoses of recurrent ischemic stroke. Patients were members of the Kaiser Permanente Northern California managed-care plan and were identified in parallel with a randomized trial of standardized discharge order sets. Diagnoses of recurrent ischemic stroke were adjudicated by three neurologists. Patients with events prior to hospital discharge were excluded from analysis (mean length of stay = 4.4 days). Kaplan Meier curves were used to calculate rates of recurrent ischemic stroke and of a composite outcome of recurrent ischemic stroke, MI, or death. Cox proportional hazard models were used to evaluate demographic and clinical variables as potential independent predictors of recurrent stroke. Factors significantly associated (p<0.10) with the outcome in univariate analysis were inserted into the final multivariate model. Results: We identified 5850 patients with ischemic stroke (median age 75, 53% of whom, of whom 234 (4.2%) had a recurrent ischemic stroke in the year after discharge. Cumulative rates of stroke recurrence were 2.4%, 3.4%, and 4.9% at 3, 6, and 12 months respectively, while rates of the composite outcome of recurrent ischemic stroke, MI, or death were 11.1%, 14.2%, and 18.3%. Independent predictors of recurrent ischemic stroke were hyperlipidemia (HR 1.51, 95% CI 1.10-2.08, p=0.01) and prior strokes (HR 1.44, 95% CI 1.06-1.94, p=0.02). Female sex showed a trend towards association with stroke recurrence but did not achieve significance (HR 1.26, 95% CI 0.97-1.64, p=0.09). Conclusions: At 4.3%, the risk of recurrent ischemic stroke in our cohort was lower than previous studies and likely represents improvements in secondary stroke prevention. Hyperlipidemia was unexpectedly the strongest predictor of recurrence in our cohort and may be due to higher rates of atherothrombotic mechanisms in recurrent ischemic stroke.

**Characteristics of Small Areas With a Higher Stroke Mortality**

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Introduction: The burden of stroke mortality has been described as more frequent among people living in more deprived neighborhoods. We described previously in the city of Sao Paulo that the risk of stroke death doubles in the poorest area when compared to the wealthiest one. Spatial distribution of cerebrovascular disease has been verified in several countries such as the “stroke belt” in the United States. The confirmation of a cluster pattern of stroke mortality in small areas could be a useful tool for planning health facilities (physical rehabilitation units) and programs (cardiovascular secondary prevention) to mitigate the impact of cerebrovascular diseases at community level. Hypothesis: to identify cluster areas of low and high risk for stroke mortality in the West side of the city of Sao Paulo that is characterized by a wider gap of income and education level among small areas (census tracts). Methods: The West side of the city encompasses six districts with 469 census tracts and 422,000 inhabitants in 2006. Draw 300-665 stroke deaths were recognized by the department of health among non-institutionalized residents of these districts. We were able to confirm the address of 620 cases (96%) that were geocoded using a Geographic Information System (Geomedia version 6.0). Mortality rates were adjusted for age and gender. High and low clusters of stroke mortality rates were identified applying a discrete Poisson model (SatScan version 8.0). We categorized high and low clusters for 50% of the population. Data about the head of the family was such as income (minimum wage) and school-years were considered as socioeconomic variables. Both data were obtained directly from the 2000 National census. Results: Cluster analysis identified 193 census areas with high stroke mortality (p<0.001), 162.8 expected cases, 1.36 ratio of cases/expected and relative rate of 1.59; and 62 census areas with low stroke mortality (p<0.001), 116.5 expected cases, 0.59 ratio of cases/expected and relative risk of 0.54. Among 234 census areas 303 cases of stroke occurred with no statistically significant spatial distribution. The table shows characteristics of high and low clusters areas according to stroke mortality rates. We adjusted risk ratios (RR) by proportion of independent socioeconomic characteristics. Conclusion: the spatial analyses showed a high cluster area characterized by a great number of census areas with low income and less formal education.
likely to be male, higher systolic blood pressure, higher total cholesterol, and more likely to have diabetes (all \( p < 0.05 \), resulting in a greater overall Framingham score \( (p = 0.0001) \) among persons with a 2008 stroke. The c-statistic for the Framingham calculator was 0.60 for identifying persons who would develop a stroke in 2008. After excluding the 27% of cases and 20% of controls who did not have any 2007 blood pressure or cholesterol measurements, the c-statistic improved to 0.67. However, these figures were still below the c-statistics of 0.77 to 0.84 reported in the original Framingham cohort studies. Discussion: The VA administrative databases contain the information required to implement a stroke risk calculator on a widespread population. The calculator was able to identify persons at high risk for stroke, though as expected, its discrimination was lower in the original cohort studies. Further work to better define administrative diagnostic and physiologic variables and to determine an appropriate threshold c statistic for population screening may enhance the performance and use of a stroke risk calculator.

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### **P442 Patients With Ischemic Stroke or TIA at Awakening Have a Worse Outcome Than Other Patients With Ischemic Stroke or TIA**

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Background: It is estimated that 10-20% of ischemic strokes are noticed upon awakening. The ABESTT-II trial suggested that these patients have a worse outcome than other patients but this was mainly because of an increased rate of intracranial hemorrhage. We sought to determine if patients not enrolled into trials with an ischemic stroke or a transient ischemic attack (TIA) and symptoms at awakening (SAA) had a poorer outcome at 3 months than other ischemic stroke or TIA patients. Methods: All patients presenting with a stroke or a transient ischemic attack (TIA) and not enrolled into a clinical trial were seen and evaluated at baseline and 3 months after their events. Data were prospectively recorded. Demographics, medications, neuroimaging data (CT and MRI), baseline and 3 months follow up NIHSS and Modified Rankin scale (MRS) were recorded. Results: From October 4th, 2006 to December 25th, 2008, 489 consecutive patients (mean age 71.6 years old) with an ischemic stroke or a TIA were evaluated, of which 29.2% (129) had SAA. Three hundred and seventy nine patients had a diagnosis of ischemic stroke while 110 had a diagnosis of TIA. Patients with SAA were more likely to have a stroke (66.7% vs 74.4%, \( p = 0.049 \)) or hyperlipemia (54.7% vs 44.6%, \( p = 0.049 \)) but had less atrial fibrillation (8.4% vs 17.2%, \( p = 0.034 \)) compared to other patients. The mean delay between the “last well seen state” and emergency department arrival was higher in patients with SAA (756 minutes vs 556 minutes, \( p = 0.012 \)) than in other patients. Baseline characteristics such as coronary artery disease, diabetes, previous stroke, dementia, smoking, alcohol abuse, medication, glucose, NIHSS, blood pressure and neuroimaging data were otherwise similar between groups. No difference was observed in the TOAST classification at 3 months between SAA patients and others. The 3 months outcome was favorable, as defined by a MRS of 0-1, in 43.7% of SAA patients and in 59.3% of other patients \( (p = 0.030) \). A 3 months NIHSS of 0-1 was seen in 59.0% of SAA and in 65.7% of other patients \( (p = 0.007) \). These differences remained significant after adjustment for baseline disparities. Conclusion: Ischemic stroke and TIA patients with symptoms at awakening have a worse prognosis than other ischemic stroke or TIA patients.

### **P443 Identification of Symptom Clusters in Ischemic Stroke and Transient Ischemic Attack**

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Background: Rapid recognition of acute stroke relies on the interpretation of presenting symptoms which can cover a wide range of both typical (e.g., unilateral weakness, difficulty talking) and atypical (e.g., pain, dizziness) symptoms. Despite the fact that most acute stroke patients present with multiple symptoms, little empirical work has been done to characterize subjects by their symptom clusters. Our objective was to identify subgroups of acute stroke patients according to their symptom clusters using latent class analysis (LCA). LCA classifies subjects into discrete classes using their responses to a set of items (such as stroke symptoms), so that subjects in a specific class have similar symptom profiles. Methods: Data were collected on 461 prospectively identified cases of ischemic stroke or TIA admitted to the University of Michigan Hospital between 2005-2007. During hospitalization information on patient demographics, medical history, and the presence of 25 individual signs and symptoms were obtained from patient or proxy interviews conducted by trained study personnel. LCA analysis was performed with multinomial regression. We included all patients by their symptom clusters using Latent Gold software. Results: The mean age was 65.3 years (SD = 16.3), 51% were male, 85% were white, and 70% had ischemic stroke. The most common symptoms were unilateral weakness (39%), trouble walking (35%), off-balance (33%), and numbness (32%). The best fitting LCA model identified six distinct latent classes. Important discriminating gang properties in a population setting are less than a meaningful interpretation in terms of their symptom clusters. In the three most prevalent classes, subjects in Class 1 (31% prevalence) were characterized by unilateral weakness, trouble walking and off-balance, and subjects in Class 2 (28% prevalence) were characterized by numbness, unilateral weakness, and slurred speech. Another 21% of subjects were in Class 3 which was characterized by disorientation and trouble talking. Class 4 (prevalence 12%) was the only profile that was characterized by a single symptom i.e., vision problems. Age was the only variable that was independently and significantly associated with class membership. Compared to class 1, older subjects (> 65 years) were more likely to be in class 3 (odds ratio \( aOR = 1.53 \), but less likely to be in class 4 (\( aOR = 0.57 \)). Conclusions: Based on presenting symptoms different subgroups of acute stroke patients can be identified. The majority
Wake-Up Strokes: Incidence and Clinical Characteristics in a Population

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Introduction: Current practice restricts intravenous thrombolysis to selected patients with ischemic stroke onset within 4.5 hours. Patients who go to sleep and wake up with symptoms beyond this time window are not eligible for treatment. Previous studies have estimated the incidence of wake-up strokes to be 16%-28% of all ischemic strokes, but these studies were not population based. We sought to establish the incidence of wake-up strokes within a large population representative of the U.S. and evaluate possible differences between wake-up strokes and all others. Methods: All first-time and recurrent strokes among residents of the Greater Cincinnati/Northern Kentucky region (population 1.3 million) in the calendar year of 2005 were identified using ICD-9 codes 430-436 and verified via study physician review. Only ischemic strokes presenting to an emergency department were included. Baseline characteristics including demographic information, risk factors, and functional status were ascertained along with discharge Rankin scores and 90-day mortality. Results: We identified 1799 ischemic strokes, of which 610 (33.9%) had a known onset time, 352 (19.9%) had an estimated onset time, 407 (27.1%) had an onset time of greater than 24 hours, 267 (14.8%) were wake-up, and 83 (4.8%) had unknown onset times. There were no significant differences between wake-up strokes and all other strokes with regard to clinical features or outcomes (Table). Conclusions: Wake-up strokes comprise approximately 15% of ischemic strokes and cannot be distinguished from other clinical features or outcomes. Whether an open physiologic time window for repertition exists for some of these patients remains an important research question.

Clinical features and outcomes

<table>
<thead>
<tr>
<th></th>
<th>Wake-Up (n=267)</th>
<th>All Others (n=1532)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean</td>
<td>71.8±13.9</td>
<td>69.8±15.2</td>
<td>0.038</td>
</tr>
<tr>
<td>Female (%)</td>
<td>151 (56.6)</td>
<td>851 (55.6)</td>
<td>0.760</td>
</tr>
<tr>
<td>White (%)</td>
<td>209 (78.3)</td>
<td>1156 (75.5)</td>
<td>0.320</td>
</tr>
<tr>
<td>Baseline NIHSSS, median (range)</td>
<td>4 (0–30)</td>
<td>4 (0–40)</td>
<td>0.808</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>215 (81.1)</td>
<td>1193 (78.1)</td>
<td>0.263</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>85 (32.0)</td>
<td>513 (33.6)</td>
<td>0.610</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>49 (18.6)</td>
<td>231 (15.2)</td>
<td>0.154</td>
</tr>
<tr>
<td>Discharge Rankin, median (range)</td>
<td>3 (0–5)</td>
<td>3 (0–5)</td>
<td>0.616</td>
</tr>
</tbody>
</table>

90 Day Mortality (n=1723 patients)

|                          | 36/257 (14.0%) | 239/1466 (16.3%) | 0.354 |

Association Between Cerebral Artery Calcification and White Matter Hypertensities in Patients With Acute Ischemic Stroke

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Background and purpose: Coronary artery calcification is known to be associated with subsequent cerebral and cardiovascular events. However, extra-coronary calcification has been less well studied. The aim of the present study was to investigate the association between cerebral artery calcification and white matter hypertensities (WMH) in patients with acute ischemic stroke. Methods: We identified 159 consecutive patients with acute ischemic stroke who underwent CT angiography and MR imaging within seven days of symptom onset. Calcifications of the intracranial internal carotid artery were scored as follows: 0, none; 1, minimal; 2, mild; 3, moderate; 4, severe. WMH on axial T2-weighted images were graded according to the scale of Fazekas. Results: The stroke patients ranged in age from 29 to 90 years (68±12 years). The intracranial internal carotid artery (iICA) calcification was found in 244 arteries (76.7%). Periventricular WMH was detected in 64 patients (42.4%) and deep WMH was found in 72 (47.7%). Among 72 iICA without arterial calcification, 13 (18.1%) were associated with periventricular WMH and 11 (15.3%) were associated with deep WMH. On the contrary, among 48 iICA with calcification grade 4, 35 (72.9%) were associated with periventricular WMH and 32 (66.7%) were associated with deep WMH. Spearman's rank test revealed that the grading of iICA calcification was correlated with the grading of periventricular WMH (r = 0.417, p < 0.001) and deep WMH (r = 0.388, p < 0.001). Multiple logistic regression analysis showed that old age, iICA calcification, and hypertension were independent factors for periventricular WMH. For deep WMH, diabetes mellitus in addition to old age, iICA calcification, and hypertension were independent factors. Conclusions: Cerebral artery calcification is common in patients with acute ischemic stroke and is an independent predictor for WMH.
Diffusion-weighted Imaging Abnormalities Are Not Correlated With Clinical Risk Scores for TIA

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Background and Purpose: Several clinical risk scores are recognized as useful predictors of early risk of stroke following TIA. Presence of diffusion-weighted imaging (DWI) abnormalities also identifies a high-risk TIA cohort. The degree to which clinical risk scores and DWI correlate will determine whether a combined clinical-radiographic score combining clinical risk scores and DWI may, therefore, have additive benefits. Methods: We studied consecutive TIA patients admitted to our institution between August 2006 and June 2009, who underwent DWI within 48 hours of symptom onset. Brain MRI was reviewed in each patient for the presence or absence of DWI abnormality. We assessed the association between clinical risk scores (as well as elements within the scores) and DWI abnormality using logistic regression. Results: There were 151 patients included in this analysis (mean age 62 years; 45% male, 46% white). DWI abnormality was evident in 51 patients (33.8%). Median California, ABCD, and ABCD2 scores were 3, 4, and 4, respectively. On univariable analysis, there was no association between DWI abnormality and clinical risk scores (California score: OR 0.587; P = 0.038; ABCD: P = 0.036). Multivariable logistic regression identified only motor symptoms (OR 2.16; 95% CI 1.09-4.30; P = 0.038) and dysarthria (OR 2.16; 95% CI 1.09-4.30; P = 0.038) as an independent predictor of DWI abnormality. No associations were found between age, duration of symptoms, dysphasia, diabetes, or blood pressure and DWI abnormality. Conclusions: Clinical risk scores for TIA and their individual elements, with the exception of motor symptoms, do not correlate with DWI results. A new clinical-radiographic scoring combining clinical risk scores and DWI may, therefore, have additive value over either one alone for prognostication of stroke risk following TIA.

Retinal Arteriovenous Nicking is an Independent Predictor of Recurrent Stroke

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Background: Retinal microvasculature changes such as arteriovenous nicking is associated with incident and prevalent cerebrovascular disease, but data are limited to population studies. We aimed to identify retinal microvasculature markers predictive of recurrent stroke among patients with recent ischemic stroke. Methods: The Multi-Centre Retinal Stroke study is a prospective cohort of stroke patients from Melbourne, Sydney and Singapore. Digital retinal photographs were taken within 1 week from stroke onset. For this analysis, we studied ischemic stroke patients from the Singapore site with technically adequate retinal photographs. Masked qualitative and quantitative retinal assessments were performed. Follow-up data at 2 to 4 years from acute stroke were obtained via telephone assessment with the patient or next of kin, then verified with electronic medical records. Results: Among the 593 patients studied, follow-up at median of 31 months (6R 26-35) was obtained for 518 (87%) patients. The incidence of recurrent stroke was 13% (66 patients). After adjustment for age, gender and duration of follow-up, moderate/ severe arteriovenous nicking increased the likelihood for recurrent stroke by 1.73 times (95% CI 1.00 to 2.95; p = 0.046). Hypertension, diabetes, focal arterial narrowing, enhanced arteriolar light reflex, arteriolar diameter and venular diameter did not predict for recurrent stroke. Conclusions: This study of ischemic stroke patients is the first to show that changes in the retinal microvasculature at ischemic stroke, namely moderate/ severe arteriovenous nicking predicts recurrent stroke, consistent with data from population studies.

Prevalence and Determinants of Abnormal Ankle-brachial Index in Patients With Ischemic Stroke: A Mexican Multicentric Stroke Registry

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Background and Objectives: Subjects with a low ankle-brachial index (ABI < 0.90) are at an increased risk of both cardiovascular morbidity and mortality. Also, there is an increased risk among subjects with ABI >1.40 or incompressible vessels. Few studies have assessed the implications of an abnormal ABI in stroke patients. We aimed to determine the prevalence and determinants of abnormal ABI in patients with ischemic stroke. Methods: We studied 1584 patients with ischemic stroke (n=1365) or transient ischemic attack (n=220) enrolled in a multicenter stroke registry of diverse geographic regions of Mexico (INDAGA-NEURO study: National Research of Peripheral Arterial Disease and Treatment Guidelines in Stroke Patients). Participants who had an ABI ≤0.90 in either leg were categorized as having low ABI; they were categorized as having high ABI if either leg had an ABI measure ≥1.40 or the ankle pressure of either leg could not be obtained during ABI measurement or the ABI protocol could not be obliterated with a pressure of ≥250 mm Hg. Demographic data and vascular risk factors of these ABI groups were compared with patients having normal ABI (both ABI measures were >0.90 and <1.40). Results: Prevalence of low and high ABI were 25.3% and 8.9%, respectively. Median age was 67.5 years (IQR 63 - 78) in patients with normal ABI compared with 72 (IQR 65 - 78) and 73 (IQR 68 - 79) in patients with low and high ABI, respectively (P<0.001). In multivariate analysis with logistic regression, low ABI was associated with older age, diabetes, hypercholesterolemia, low HDL, and recurrent stroke. High ABI or incompressible vessels was associated with male gender, diabetes mellitus, and recurrent stroke. Conclusions: An abnormal ABI was found in a third of patients with ischemic stroke. Evidence of silent peripheral arterial disease in these patients may be an indicator of cerebral atherosclerosis extension and higher risk of stroke recurrence. The measurement of ABI may be useful in order to plan intensive prevention measures.

Association of Decreased Kidney Function With Silent Brain Lesions in Healthy Elderly

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Background and Purpose: Silent brain infarction (SBI) is a potent risk factor for symptomatic stroke and dementia. Recent studies have demonstrated that patients with chronic kidney disease are frequently associated with SBI. However, the association between kidney function and silent brain lesions including subcortical white matter lesions (SWML) and microbleeds (MBs) has not been clarified in healthy population. We examined in a large scale, cross-sectional study whether decreased kidney function is a risk for silent brain lesions in neurologically normal adults. Methods: MRI scans were performed in 3,739 neurologically normal subjects without history of stroke (mean age, 61.5 years) who took health screening of the brain. SBI, SWML and MBs were quantified on MRI. Glomerular filtration rate (GFR) was estimated using Modification of Diet in Renal Disease equation, and cardiovascular risk factors including hypertension, glucose intolerance and dyslipidemia were examined. Carotid intima-media thickness (IMT) was also measured in all subjects. Results: The prevalence of SBI, SWML (Fazekas grade ≥ 2) and MBs were 5.8%, 25.8% and 8.1%, respectively. Subjects with low estimated GFR (eGFR < 60 mL/min/1.73m2) showed significantly higher prevalence of SBI (p < 0.01), SWML (p < 0.001) and MBs (p < 0.05). Increase of carotid IMT was marginally related to decreased kidney function (p = 0.056). Advanced age, male and high blood pressure were not correlated with the high prevalence of all types of silent brain lesions. In multivariate logistic analysis, low eGFR was marginally associated with SBI (odds ratio adjusted for age and sex, 1.59; 95% CI 0.96 to 2.63, p = 0.07). Conclusions: Decreased kidney function is possibly associated with silent brain lesions in healthy elderly. Protection of kidney function may be an important strategy for primary prevention of future stroke.

Methods to Correct for Proxy Use in Stroke Outcome Studies

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Background and Purpose: The use of proxies for patients who are unable to participate in stroke outcome studies due to cognitive or language deficits reduces selection bias. However, disagreement between patient and proxy responses introduces measurement error and results

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Recanalization and Its Correlation to Outcome After Cerebral Venous Thrombosis

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Background: Only few small studies have assessed rates of recanlization and impact of recanalization on outcome and residual symptoms in patients after cerebral vein thrombosis (CVT). Methods: Our series included 91 consecutive patients, treated at the Department of Neurology, Helsinki University Central Hospital (1990-2008), who had angiographically verified CVT and follow-up imaging at 4 months or later, or autopsy. Promptly after the diagnosis of CVT, 58 (64%) patients received intravenous heparin and 30 (33%) patients received subcutaneous low-molecular-weight heparin (LMWH). After the acute stage, warfarin or LMWH was administered in 87 (98%) patients for at least 4 months. We categorized vessel status at follow-up as complete, partial, or no recanalization. A 6-month favorable outcome was defined as a score of 0 to 1 on the modified Rankin Scale (mRS). We used logistic regression to analyze predictors of poor recanalization and whether recanalization would affect outcome. Results: Of the 91 patients (median age, 36 years; 70% females), 43 (47%) achieved complete recanalization, in 31 (34%) patients recanalization was partial, and 17 (19%) had no recanalization. Males (74%) vs. females, 44%; P = 0.008, patients aged ≥37 (73%) vs. age < 37, 33%; P < 0.001, and those with no identified risk factors for CVT (90% vs. those with at least 1 identified risk factor, 48%; P = 0.012) had more frequently partial or no recanalization. Increasing age was the only variable independently associated with no recanalization (odds ratio, 0.96; 95% confidence interval, 0.92-1.00) when adjusted for age, sex, and having the causes for CVT. Of the 73 (80%) patients with favorable outcome, 35 (46%) had complete, 28 (38%) had partial, and 10 (14%) had no recanalization (P = 0.031). Multivariate analysis showed no correlation between recanalization and worse clinical outcome defined by mRS when adjusted for age, sex, and recanalization status (OR 2.32; 95% CI 0.59-9.11). Of the 88 (97%) surviving patients, 44 (50%) had residual symptoms at follow-up (mRS, 1-5): headache (23%), neuropsychological deficits (12%), epilepsy (7%), dizziness (6%), and focal neurological deficits or visual disturbances (2%). Headache was more frequent in patients with no recanalization (44%) than in those with partial (36%) or complete recanalization (10%), P = 0.009. Conclusions: As far as we know, this is the largest to date consecutive patient series, in which the relation between recanalization and outcome has been analyzed in CVT patients. Half of our patients had complete and more than one third had partial recanalization. Older age independently predicted poor recanalization, but recanalization itself was not associated with clinical outcome defined by mRS. However, patients with partial or no recanalization had frequently persistent headache.

Acute Symptomatic Internal Carotid Artery Occlusion: An Ominous Clinical Scenario

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Background: Previous studies concerning internal carotid artery (ICA) occlusion have focused on the long-term risk of recurrent stroke. However, the prevalence, outcome, and optimal management of patients with acute symptomatic ICA occlusion are largely unknown. The purpose of this study was to determine the prevalence and prognosis of patients presenting to hospital with ischemic stroke or TIA associated with ipsilateral ICA occlusion. Methods: We used data from Phase 3 of the Registry of the Canadian Stroke Network (RCSN) on consecutive patients presenting to 11 stroke centres in Ontario. For this analysis, we included patients admitted to hospital with ischemic stroke or TIA between July 1, 2003 and March 31, 2006. We excluded patients with vertebrobasilar symptoms, presumed cardioembolic or nonatherosclerotic stroke etiology and those without vascular imaging data. The resulting cohort was divided into four groups based on the status of their ipsilateral ICA determined by catheter/CT/MR angiography or carotid Doppler. Group A had ICA occlusion, Group B had severe stenosis, Group C had moderate stenosis, and Group D had mild to no stenosis. Outcomes included: in-hospital complications (stroke, seizure, or neurological worsening), in-hospital death, modified Rankin score at discharge, and discharge destination. Logistic regression modeling was used to evaluate the association between ICA status and outcome and included the following variables: age, atherosclerotic risk factors, initial stroke severity (Canadian Neurological Scale, CNS), and patency of the contralateral ICA. Results: There were 13461 consecutive patients admitted with a final diagnosis of ischemic stroke or TIA and 4143 patients met the study criteria. In this cohort, there were 265 (6.9%) Group A patients, 406 (8.8%) Group B patients, 411 (9.9%) Group C patients and 3041 (73.4%) Group D patients. Patients with ischemic stroke and ICA occlusion had more severe neurological deficits (ONS: Group A = 7.08, Group B = 8.52, Group C = 8.40 to 8.65, Group D = 8.56 to 8.49, p < 0.0001) and were more likely to be treated with tPA (Group A = 20.7%, Group B = 16.3%, Group C = 15.8%, Group D = 13.1%, p < 0.0001). The presence of ICA occlusion (Group A compared to Group D) had an adjusted odds ratio for in-hospital complications of 2.72 (1.99-3.77, 95%CI), for death of 3.67 (2.22-6.07, 95%CI), for modified Rankin score 3-6 of 1.88 (1.32-2.69, 95%CI) and for discharge home of 0.57 (0.40-0.80, 95%CI). The odds ratios for Group B and C were not significantly different from Group D (all 95%CI overlap 1.0) on all outcome measures. Conclusions: In our cohort, ipsilateral ICA occlusion was associated with more severe strokes and worse outcomes than any other degree of carotid stenosis. Further analyses using linkage of the RCSN database to administrative databases are being performed to determine the 5-year outcomes of this patient cohort.

Extra- or Intracranial Dissection Involving Multiple Arteries: A Distinct Clinical and Angiographic Syndrome?

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Background: Up to 20% of patients with spontaneous dissection involving extra- or intracranial dissection have more than one artery involved. There are no known data regarding unique clinical or angiographic characteristics of patients with dissections involving multiple arteries. Objective: To study and compare the clinical and angiographic features of patients who present with arterial dissection with single and concurrent multiple arterial involvement. Methods: We analyzed consecutive patients admitted with spontaneous cervico-cranial dissections during a 7-year period at two different institutions in which cerebral angiography was performed to assess the involvement and disease patterns among various arteries. The demographic (patients age, gender), cardiovascular risk factors, and angiographic features including artery affected, presence of a pseudoaneurysm, fibromuscular dysplasia (FMD) features, and degree of stenosis were analyzed. Deterioration was defined by transient ischemic attack (TIA), stroke, and/or death during hospitalization. Results: A total of 46 patients [mean ± SD: 49 ± 16 years; 29 (63%) were men] were admitted with spontaneous extra- or intracranial dissection. A total of 9 (20%) patients were found to have dissection involving multiple arteries. Involvement of multiple arteries was more prevalent in the young (52%) in ≤45 years vs. 44.5% (p < 0.05). Patients with multiple arteries involved had a greater severity of stenosis (71 ± 21% vs. 63 ± 28%), higher proportion of pseudoaneurysms (8 (98% vs. 33% in patients with single involvement). Conclusions: The clinical and angiographic features of patients with dissection involving multiple arteries are distinct and distinct from that of dissection involving single arteries.
Validity of Proxies for Evaluating Social Determinants of Health in Stroke Patients

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Background and Purpose: Social determinants of health such as depression, optimism and religion may be associated with outcomes following stroke. To reduce selection bias, proxies are often used in stroke outcome trials to represent patients who are unable to participate due to cognitive or language deficits. The objective of this study was to quantify agreement between proxy and stroke patient responses to questions regarding depression, optimism and spirituality to inform the validity of proxy use in future stroke outcome studies focusing on these factors.

Methods: Consecutive interviews were performed on a sample of ischemic stroke/TIA patients and their identified proxy as part of the Brain Attack Surveillance in Corpus Christi (BASIC) Project. Pairs were independently queried regarding the patients degree of depression (Patient Health Questionnaire), optimism (Life Orientation Test) and spirituality. For the continuous scales (depression, optimism), analysis of variance between patient and proxy pairs was used to estimate agreement and bias introduced by proxies included calculation of intra-class correlation coefficients (ICC) and linear regression models of the form \( \text{ProxyResponse} = \alpha_0 + \alpha_1 \text{PatientResponse} + \epsilon \) where an \( \alpha_0 \neq 0 \) and \( \alpha_1 \neq 0 \) denotes no bias. For the categorical spirituality, agreement was assessed with kappa statistics. Results: Interviews were performed on 40 patient-proxy pairs. Forty-eight percent of the proxies were women. Median age was 63 years (IQR: 55-77) for patients and 52 years (IQR: 41-64) for proxies. Proxies were most commonly a spouse (45%) or child (43%) and had long-term relationships with the patient (median 39 years, IQR: 26-55). Agreement was fair for both the depression (ICC 0.39) and optimism (ICC 0.41) scales. Proxies responses were a biased measure of the patients responses for depression with \( \alpha_{0,p} = 5.22 \) (CI: 2.83, 7.60) and \( \alpha_{1,p} = -0.40 \) (CI: 0.11-0.68) and optimism with \( \alpha_{0,p} = -6.99 \) (CI: 2.90, 11.09) and \( \alpha_{1,p} = -0.52 \) (CI: 0.11-0.93). Agreement was moderate for the religion questions (kappa 0.48-0.53). Notably, the vast majority of pairs felt that religion was at least fairly important. Conclusion: Fair to moderate agreement among stroke patient and proxy pairs was noted for depression, optimism and spirituality scale questions. Overall, proxies were likely to report more depression and less optimism than the patients self-reported. The use of proxies reduces selection bias; however, disagreement between patient and proxy responses introduces measurement error. We recommend caution when using proxies for evaluation of depression, optimism and spirituality.

Figure 1. The Hyperintense Vessel Sign (HVS) Before and After Gadolinium

All images are from the same subject. A and C show the precontrast FLAIR image. The white arrow in A marks the proximal HVS and the white arrow in C marks the distal HVS. The HVS is not detected in the postcontrast FLAIR images (B and D).

Cerebral White Matter Hyperintensities on MRI Are Associated With Functional Outcome After First-Ever Lacunar Stroke

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Objectives: White matter hyperintensities (WMH) on MRI, which are prevalent in the elderly, may reflect covert vascular brain injury and thus affect stroke outcome. We hypothesized that the volume of WMH at stroke presentation correlates with the functional recovery of first-ever lacunar stroke at 6 months after onset. Methods: From a prospective hospital-based registry of acute stroke patients who were admitted within 10 days after onset, we enrolled those with acute lacunar infarction confirmed by diffusion weighted MRI and without prior stroke/TIA. Clinical data were collected according to predetermined evaluation systems and diagnostic criteria. Volume of WMH on T2-FLAIR weighted MRI was quantified with 3Dcro software. We studied the correlation between WMH volume and the functional outcome at 6 months, assessed by modified Rankin Scale (mRS). Logistic regression analysis was applied to estimate the independent effect of WMH volume on unfavorable outcome (mRS \( \geq 2 \)). Results: We identified 334 patients during a period of 2.5 years, with a mean age of 65 years, 60% of men, and a median length of stay of 5 days. The median volume of WMH was 13.2 ml (interquartile range, 6.9-25.4 ml). Patients in higher quartiles were older, with the acute lesion more likely located at subcortical regions rather than brainstorm, and at lower functional levels at discharge. At 6 months, there were 3 deaths and 7 stroke recurrences. We obtained mRS scores in 90% of the

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White Matter Hyperintensity Volume Correlates With Levels of Matrix Metalloproteinase-2

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Background: White matter hyperintensity (WMH), which is a radiographic manifestation of chronic loss of cellular brain tissue, is a well-established risk factor for stroke. Oxidative stress and matrix metalloproteinases (MMPs) have both been implicated in WMH formation and the pathophysiology of ischemic stroke. Human population studies have correlated estimates of WMH severity with biomarkers of oxidative stress, an upstream regulator of MMP activity. In acute ischemic stroke (AIS) patients, we measured the correlation between WMH volume (vWMH), oxidative stress, MMP-2, and MMP-9. We hypothesized that both oxidative stress and MMP levels would increase with WMH burden.

Methods: We enrolled consecutive patients presenting with onset of AIS symptoms within 9 hours in a prospective biomarker study. Only subjects with an evaluable MRI scan of the brain performed within 72 hours of symptom onset were included in this study. Baseline demographics, risk factors, and stroke characteristics were collected. Plasma F2-isoprostane, MMP-2, and MMP-9 levels were measured at baseline (≤9 hours) and 48 hours. Plasma Oxygen Radical Absorbance Capacity (ORAC) was measured once at baseline. vWMH was quantified using semi-automated analysis of the MRI, adjusted for head size, and log-transformed (Log_vWMH).

Results: We analyzed 158 subjects, mean age 71 ± 15 years; 56% were male; 71% were hypertensive; 20% had diabetes mellitus; 44% had hyperlipidemia. Mean Log_vWMH was 1.38 ± 1.32. Log_vWMH was strongly correlated with age (r = 0.58, p < 0.001). Log_vWMH correlated significantly with levels of baseline MMP-2 (r = 0.40, p = 0.007), but not MMP-9, ORAC, or F2-isoprostane. This finding remained significant after adjustment for multiple comparisons. Conclusions: vWMH was found to correlate with age and baseline levels of MMP-2, but not other markers of oxidative stress or MMP-9. Animal studies have shown that MMP-2 plays an important role in WMH development. Our findings suggest that MMP-2 may be a target for future therapeutic approaches.

Conclusion: High WMH volume is associated with unfavorable functional outcome at 6 months after first-ever ischemic stroke. The effect is independent of age, but likely explained by a worse functional level at discharge.

BOLD Response Stability is Altered in Patients With Chronic Ischemic Stroke

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Background: Functional MRI based on the Blood Oxygenation Level Dependent (BOLD-MRI) contrast has contributed significantly to a better understanding of neurophysiological processes following brain insults. However, analysis of MRI data usually assumes that the signal is stable throughout data acquisition, which may not hold in studies of patients recovering a stroke, leading to possible misinterpretation of results. In the present work, we investigated the temporal stability of the BOLD response of patients with chronic ischemic stroke (Middle Cerebral Artery), when performing a motor task, keeping a stable pace. Methods: This study recruited seventeen patients (13 included in the final analysis - 7 men, mean age 57±7y). The experimental protocol was composed by five blocks of rest interleaved with five blocks of activity (27 seconds). Functional time courses obtained from the primary (M1) and supplementary motor area (SMA) were evaluated. To estimate the stability of the BOLD response, a General Linear Model was applied using two predictors: one encoding the parametric (attenuation) effect. Results: The BOLD signal in M1 and SMA was stable when the motor task was performed with the unaffected hand. However, significant attenuation of the BOLD response was found both in M1 as well as in SMA in all patients when the task was performed with the paretic hand. Considering the stable BOLD responses in both M1 and SMA of the unaffected cortex, it is unlikely that the observed attenuation is caused by conventional fatigue. More likely it may be the result of an altered neurovascular coupling caused by an impairment of the vascular reactivity. Conclusion: This study discloses the existence of an altered and interesting BOLD response on M1 and SMA cortices in stroke patients. This important observation raises the question of whether a state of altered neurovascular coupling combined with poorly-designed MRI paradigm prevent activation from being detected in pathological conditions, as has been often reported in the literature.

Conclusions: High WMH volume is associated with unfavorable functional outcome at 6 months after first-ever ischemic stroke. The effect is independent of age, but likely explained by a worse functional level at discharge.
Robust Automated Carotid Arterial Wall Thickness Measurements in a Clinical Setting Using Magnetic Resonance Imaging

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Carotid arterial wall thickening with ultrasound (US) is a strong preclinical marker of cardiovascular risk, predictive of stroke and heart attack. High resolution multi-contrast magnetic resonance imaging (MRI) accurately measures carotid mean wall thickness (MWT) but can also characterize plaque composition, which is difficult to achieve with ultrasound. Previous MRI studies employed unique ‘institutional’ software and limited their results to patients with only the highest quality images. The aims of this study are to determine MWT to quantify reproducibility and robustness of manual and automated MWT measurements in the common carotid artery (CCA) and define the impact of image quality (IQ) (assigned on a scale of 1 to 5) on the measurement. Carotid MRI was acquired in 44 subjects (ages 18-81, 26 M, 18 F) at 1.5T using the MESA protocol. Of the 44 subjects, 7 had known arteriosclerosis and a history of stroke and/or heart attack. The remaining subjects had variable degrees of arteriosclerosis based on age. MWT measurements were made using manual (MWTm) and automated (MWTa) Mass Analysis Plus 6.0, Medis) and automated measurements (MWTa, QPlaque 1.0, Medis) 1cm below the bifurcation at the CCA by 3 independent blinded observers, with one observer repeating the measurements three times on random selection to determine intra-operator reproducibility and variability. Bland-Altman analysis compared manual and automated measurements and inter-operator reproducibility was calculated using coefficient of variance (CV). The relationship between CV and IQ was also determined using linear regression. Intra-operator variability was similar for both manual and automated measurements; however, as IQ increased, variability of MWTa dropped significantly (m = -0.051; r = 0.70) whereas variability of MWTm remained the same regardless of IQ (m = 0.006; r = 0.19). Inter-operator variability showed a similar trend with IQ; however, the variability of MWTa was significantly higher than MWTm. Interestingly, for 2 of the 3 observers, the average MWTa was significantly higher than average MWTm which appears to be related to observer experience. Also, the automated software utilized automated co-registration of images that allowed for plaque characterization. These results demonstrate that automated measurements appear to be more robust than manual measurements since it has less variability across different operators and shows improvement with image quality. Since MR can also characterize plaque composition, which is difficult to achieve with ultrasound, these results validate carotid MRI as a practical advance on US.

MWT Measurements and Statistics

<table>
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<tr>
<th>Observer 1</th>
<th>Observer 2</th>
<th>Observer 3</th>
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<tbody>
<tr>
<td>Intra-observer</td>
<td>Inter-observer</td>
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<tr>
<td>MWTm</td>
<td>CV</td>
<td>MWTa</td>
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<tr>
<td>1.51 ± 0.24 mm</td>
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<tr>
<td>MWTa</td>
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<tr>
<td>p-value</td>
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MWT = mean wall thickness CV = coefficient of variance

This research has received full or partial funding support from the American Heart Association, Western States Affiliate (California, Nevada & Utah).

Can Lumen Morphology Predict the Risk for Ischemic Stroke in Mild to Moderate Internal Carotid Artery Stenosis?

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Background and Purpose: Recent multi-institutional studies have shown that carotid endarterectomy can reduce the risk for subsequent ischemic stroke in patients with 70-99% stenosis of the internal carotid artery (ICA). However, its benefits are still controversial in less than 70% stenosis of the ICA. Recent development of computed tomography angiography (CTA) can provide adequate information on the carotid plaque. In this study, therefore, we aimed to clarify whether carotid lumen morphology predict the risk for ischemic stroke occurrence in patients with 30%-70% ICA stenosis. Materials and Methods: This study included 52 consecutive patients with 30%-69% ICA stenosis between May 2007 and April 2008. There were 48 men and 4 women with a mean age of 71.1 years, ranging from 54 to 88 years. Totally 67 carotid stenotic lesions in 52 patients were examined from the viewpoints of the degree of stenosis, the prevalence of ulceration, and lumen morphology. Multivariate analysis was performed to detect significant predictors for the occurrence of ipsilateral ischemic events. Results: There was a linear correlation between the area stenosis degree (CTAarea) and diameter stenosis degree (CTAstd) with the following equation: CTAarea = 7.283 + 1.092×CTAstd (R² = 0.65). There was a large dissimilarity between two parameters in symptomatic ICA stenosis. Multivariate logistic regression analysis showed that ulceration, irregular lumen, and smaller CTAarea were significant predictors for ipsilateral ischemic events.

Inflammatory Regulation as a Biomarker of Ischemic Stroke Diagnosis: Evidence From Gene Expression Profiling

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A novel approach to the study of ischemic stroke (IS) is the use of gene expression profiling to discover biomarkers that improve stroke diagnosis, identify secondary complications or aid in the development of novel stroke therapeutics. The purpose of this study was to determine a gene profile for stroke diagnosis in the peripheral whole blood of stroke patients compared to control subjects, controlling for common stroke risk factors. Methods: A prospective gene expression profiling study of 39 stroke patients and 25 healthy control subjects was conducted. Peripheral blood samples were collected from patients who were ≥18 years of age with MRI diagnosed IS and controls who were non-stroke neurologically healthy. Total RNA was extracted from whole blood stabilized in PAXgene RNA tubes, amplified through the Illumina TotalPrep RNA amplification kit and hybridized to Illumina HumanRef-8v2 bead chips. Gene expression was compared in a univariate manner between stroke patients and control subjects using t-test in GeneSpring. Inflation of type one error was corrected by the Bonferroni family wise error rate p<0.05. Validation was performed by qRT-PCR using Taqman. The identified gene profile was tested independently in a logistic regression model controlling for age, hypertension and dyslipidemia. Expression data was further interpreted through the use of Ingenuity Systems Pathway analysis. Results: The mean time from symptom onset to acute blood draw was 10.06 hours ± 6.31. There was no difference by race or gender between the groups. However, stroke patients were significantly older than control subjects (t = -4.03; p = 0.000). A nine gene profile was identified for IS diagnosis. Five of these genes were identified in the previously published whole blood gene expression profiling study of stroke and are therefore likely candidates for stroke diagnosis (AR01; CAD; LRF; MMP9; S100A12). After controlling for the effects of age and correcting for multiple testing only S100A12 fell out of the model for stroke diagnosis (p = 0.014) Pathway analysis revealed a robust innate immune response, with toll like receptor (TLR) signaling as a highly significant pathway present in the peripheral whole blood of IS patients. Conclusion: The findings of this study support the claim that the study of peripheral whole blood can be used to identify diagnostic markers of IS and novel targets for therapeutics. A plausible case for innate immunity through the activation of TLR4 as a mediator of response to IS has been made from the results of this study.

Role of Coagulopathy in Ischemic Stroke Patients With Cancer: MRI and TCD Study

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Background: Although cerebral infarcts commonly occur in cancer patients, relatively little is known about the stroke mechanism and ischemic zone in those patients. Differences in stroke pathophysiology may require different strategies for prevention and treatment. Methods: We prospectively studied 111 consecutive cancer patients with acute ischemic stroke patients who were admitted or consulted to our institution between January 2006 and June 2009. Patients underwent embolic signal (ES) monitoring by transcranial Doppler (TCD) and multi-modal MRI, including diffusion (DWI)- and perfusion-weighted imaging (PWI) and MRI angiography (MRA). Both DWI-PWI mismatch >20% and MRA-DWI mismatch model were applied for determining ischemic zone; the MRA-DWI mismatch was defined as (1) a DWI lesion volume ≥25 ml in patients with a proximal vessel occlusion; or (2) a DWI lesion volume ≥15 ml in patients with proximal vessel stenosis or an abnormal finding of a distal vessel. Coagulopathy was assessed with serum D-dimer levels, and patients were grouped accordingly. Results: The D-dimer level was relatively high and variable (8.84 ± 14.74 µg/ml). The D-dimer levels were associated with the presence of penumbra zone on MRI as well as ES on TCD. A low incidence of the MRA-DWI and DWI-PWI mismatch was observed in higher D-dimer group (p = 0.001 and P = 0.017, respectively). TCD monitoring was performed with an interval ≥14 days between onset of symptoms and examination, and embolic signals were detected in 29 (43.9%), which were more commonly detected in patients with high D-dimer level (p = 0.001). A higher D-dimer level was independently associated with positive ES detection (OR, 1.083; 95% CI, 1.017-1.154). D-dimer level was significantly correlated with the number of embolic signals in patients with cryptogenic stroke mechanism (r = 0.719, P < 0.001), but not in patients with conventional stroke mechanism (r = 0.188, P = 0.288) [FIGURE]. Conclusion: Our results indicate that pathophysiology of stroke in cancer patients is significantly depending on the degree of coagulation abnormalities. Our results suggest that a high prevalence of embolic signals and a low prevalence of penumbral regions associated with cancer-related coagulopathy should be considered in acute treatment and prevention of stroke in patients with cancer.
CT Perfusion or Transcranial Doppler Ultrasound: Which is Better to Detect Symptomatic Vasospasm?


Objective: Delayed stroke (DS) from symptomatic vasospasm (VS) in patients suffering from aneurysmal subarachnoid hemorrhage (SAH) contributes nowadays to the majority of mortality and morbidity. A non-invasive, repeatable diagnostic modality to detect brain hypoperfusion prior to DS may prove to be of importance. Aimed at comparing CT perfusion (CTP) with transcranial Doppler ultrasound (TCD) in the diagnosis of VS using angiography (DSA) as gold standard. Background: DSA is currently the gold standard for detecting VS; however, its invasiveness and complication rate (~5%) limit its clinical utility and TCD is commonly replacing staged testing. In this study: CTP perfusion (CTP) has been compared against the arterial caliber, the dynamics and microcirculatory changes of cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transition time (MTT). Therefore, a correlation of CTP and TCD may enhance the diagnostic validity of VS and support the indication for DSA. Methods: We performed blinded qualitative and quantitative CTP analyses defining VS as asymptomatic or an increase in MTT and corresponding decrease in CBF. TCD VS was severe when flow velocities >200 cm/sec, mild to moderate between 120-200 cm/sec. DSA VS was defined as >25% decrease in arterial caliber. 100 SAH patients with 62 TCD/CTP and 47 TCD/CTP/DSA correlations were analyzed; 32 of these 47 had VS (66%). Results Among symptomatic VS patients CTP and TCD correlations compared to DSA were, respectively: sensitivity 100% and 76.9%, specificity 83% and 83%; positive predictive 96% and 83% and negative predictive values 100% and 25%. Similarly, among asymptomatic patients: sensitivity 80% and 80%, specificity 70% and 50%; positive predictive (PPV) 57% and 44% and negative predictive values (NPV) 100% and 25%. Therefore, CTP showed significantly improved sensitivity, specificity, PPV and NPV compared to TCD for detection of VS seen on DSA.

Conclusion: CTP showed significantly improved sensitivity, specificity, PPV and NPV compared to TCD for detection of VS seen on DSA. Therefore, CTP showed significantly improved sensitivity, specificity, PPV and NPV compared to TCD for detection of VS seen on DSA.

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to the AP group (Table). There was a progressive increase in the TFC component in the ICP group in contrast to a progressive decrease in the AP group. NADH reduction occurred with decreasing CPP in both groups but was significantly (P < 0.001) greater with increasing ICP versus decreasing MAP (delta fluorescence 1.58 vs 1.17, respectively). The decrease in Doppler flux with increasing ICP was less than that observed by decreasing AP (72 vs 53.2%, respectively).

**Conclusions:** Reduction of CPP by increasing ICP results in a shift from CAP to TFC flow resulting in an “apparent” maintained CBF at lower CPP. Greater NADH reduction with increasing ICP compared to decreasing AP suggests decreased tissue oxygenation in the former. These observations provide insights into the pathogenesis of brain edema secondary to increased ICP. Table. Percent distribution (Mean ± SEM) of low (<1 mm/s) and high (>1 mm/s) flow velocity capillaries (CAP) and thoroughfare channels (TFC) in cerebral cortex of rats. P values refer to comparisons of the entire distribution between ICP and MAP groups at each CPP.

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<th>MAP ( %)</th>
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<td>&lt; 1 mm/s (CAP)</td>
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**E471**

Effects of Deferoxamine on Brain Injury After Transient Focal Cerebral Ischemia in Rats With Hyperglycemia

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**Purpose:** Hemorrhagic transformation (HT) is a major factor limiting the use of tissue plasminogen activator (tPA) for stroke patients. This study examined the effect of deferoxamine (DFX) on brain injury and HT in a rat model of transient focal ischemia with hyperglycemia.

**Methods:** Male Sprague-Dawley rats received an injection of 50% glucose (6 mL/kg, i.p.) 15 minutes before undergoing transient middle cerebral artery occlusion (MCAO; two hours occlusion) with reperfusion. Rats were treated with DFX (100mg/kg, i.m.) or vehicle immediately after MCAO. Rats were killed at 4, 8 and 24 hours later and used for brain edema, blood-brain barrier permeability, hemorrhage volume, hemoglobin content, and infarct volume measurements. Mortality rate was also evaluated. **Results:** DFX treatment reduced mortality at 24 hours (4% vs. 24% in the vehicle-treated group, p < 0.05). DFX also reduced infarct volume (95±56 vs. 164±83 mm3 in vehicle, p < 0.05) and swelling in the basal ganglia (p < 0.05) 26 hours after MCAO. The total hemorrhage volume in the ipsilateral hemisphere at 8 hours post-MCAO was less in DFX treated animals (p < 0.05). However, blood-brain barrier permeability was same in DFX- and vehicle-treated groups. **Conclusions:** DFX attenuates death rate, hemorrhagic transformation, infarct volume, brain swelling in a rat transient focal ischemia with hypoglycemia model, suggesting that DFX could be a potential treatment for stroke patients with or at risk of hemorrhagic transformation.

**B472**

BMSCs Increase tPA Activity in Astrocytes Which Facilitates Neurite Outgrowth After Stroke

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Treatment of stroke with bone marrow stromal cells (BMSCs) increase axonal remodeling in the ischemic brain. Here, we demonstrate that the tissue plasminogen activator (tPA) and its inhibitor, plasminogen activator inhibitor 1 (PAI-1), in astrocytes promote axonal remodeling after treatment of stroke with BMSCs. Casein zymography data showed administration of BMSCs (10⁶ cells at 24 hours post stroke) to mice subjected to middle cerebral artery occlusion (MCAO) significantly increased tPA activity (by 43% ± 18%, P < 0.05) in ischemic brain tissue at 14 days after MCAO, concurrent with increases of myelinated axons (by 104% ± 27%, P < 0.01) and synaptophysin (by 91% ± 13%, P < 0.01) compared to MCAO controls (n = 5 per group). Western blot suggested that tPA expression was significantly increased (244% ± 8%, P < 0.05) and PAI-1 expression was substantially decreased in the ischemic brain tissue (by 63% ± 6%, P < 0.01). To further study the effect of increasing tPA activity on neurite outgrowth, we employed in vitro cell co-culture (astrocytes and BMSCs) and primary culture cortical neuron models. Co-cultured astrocytes with BMSCs significantly increased tPA levels (by 16% ± 2%, P < 0.01), and significantly reduced PAI-1 expression (by 45% ± 3%, P < 0.01) in astrocytes under oxygen and glucose deprived (OGD) condition. ELISA analysis revealed that active tPA proteins were significantly increased in OGD astrocyte medium co-cultured with BMSCs (from 0.24 ± 0.03 ng/ml to 0.36 ± 0.02 ng/ml). Primary cortical neurons cultured in the BMSC-OGD astrocyte co-culture condition medium significantly increased neurite branch number and length compared to OGD astrocyte medium (by 79% ± 26% and 185% ± 49%, p < 0.01, respectively). Blockage of tPA with a neutralizing antibody significantly attenuated the effect of the conditional medium on neurite outgrowth, and, the addition of recombinant human tPA into cortical neuron culture also substantially enhanced neurite outgrowth (58% ± 9% of branch number and 224% ± 39% of total length). Collectively, these in vivo and in vitro data suggest that the enhanced activation of tPA by BMSCs promotes neurite outgrowth after stroke.

**P473**

Brain and Systemic Temperature Changes During Selective Endovascular Brain Cooling With Cold Saline: A Translational Research Project

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**Objective and Methods:** Induced hypothermia has efficacy in cardiac arrest and is being tested with acute ischemic stroke (AS). Whereas systemic cooling may be associated with medical complications, selective endovascular brain cooling (SEBC) with local iat infusion of cold saline is a novel alternative approach, which has appeal because it can produce a rapid cooling of the brain without significantly cooling the body. Because it is difficult to measure brain temperature directly, a mathematical model was developed to test the assumptions of this method. Integral parts of the model were the Pennes bio-heat equation, experimental results on hemodynamic and metabolic properties of organ systems, and phantom-model experiments on heat-transfer along an endovascular catheter. A clinical study provided data for the model. In 9 elective patients undergoing diagnostic cerebral angiograms degassed and heparinized cold saline (7.5 ± 2°C) was infused into the ICA through a standard endovascular catheter at 33m/min for 10 minutes. Warming blankets were used to avoid potential systemic hypothermia. Local (dominant jugular venous bulb [JVB]) and systemic temperatures (ST: bladder/esophagus) were assessed. The clinical results were input into the computer model for (1) model validation and (2) calculation of brain temperature changes during SEBC. **Results:** All patients tolerated the procedure without medical complications, discomfort, or change in neurological status. JVB and ST dropped 0.84 ± 0.13°C vs 0.15 ± 0.08°C (p = 0.006) from baseline, respectively. Aside, ABC, coagulation, hematocrit, and catecholamines remained normal. Both, simulated JVB and ST showed excellent correlations with clinical results (JVB r2 = 0.80; ST r2 = 0.95). The simulated brain temperature decrease during SEBC was approximately 1.83 ± 0.22°C, a clinically relevant decrease (figure). **Conclusion:** The validity of predicted brain temperature is supported by good correlations between observed and predicted JVBs and STs. Our results warrant clinical investigations of the feasibility and safety of SEBC in AS patients eligible for local recanalization therapy. The model could be further improved by exchange of fixed assumptions with physiological ranges of intracranial hemodynamic and metabolic properties.

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Artificial Neural-Network Prediction of Ischemic Tissue Fate: Multimodal MRI of Acute Stroke

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**Background:** Multimodal MRI of acute stroke provides predictive value to guide stroke therapy. Predicting infarct volume on a pixel-by-pixel basis have been made using critical thresholds of the apparent diffusion coefficient (ADC) or cerebral blood flow (CBF) values, voxel-based generalized linear model, and a probabilistic model. This study reports the development of a novel and flexible predictive algorithm based on Artificial Neural-Network (ANN) to quantitatively predict ischemic tissue fate using acute ADC and CBF data. Predictions using ADC alone, CBF alone and ADC + CBF were evaluated. In addition, the effects of neighboring pixels and regional tissue susceptibility to ischemic injury on prediction accuracy were also evaluated. Prediction accuracy is quantified using receiver operating characteristic (ROC) analysis. ANN prediction algorithms were evaluated on three different rat stroke models. **Methods:** Male Sprague-Dawley rats (300-350g) were subjected to 30-min (n = 10), 60-min (n = 12) and permanent (n = 8) MCAO. ADC, CBF and T2 MRI were acquired. Novel ANN algorithm was
Deletion of TIMP-3 Impaired Special Learning but Does Not Affect Ischemic Brain Damage After Stroke

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Introduction: Homeostasis of the extracellular matrix is maintained by the balance between matrix metalloproteinases (MMPs) and the tissue inhibitor of metalloproteinases (TIMPs). There are four kinds of TIMPs, called from TIMP-1 to TIMP-4. TIMP-3 is widely distributed throughout the body including the brain and is reported to work as an inducer of apoptotic cell death.

Results: 30 days after MCAO, TIMP-3 KO showed more ischemic damage than wild-type mice, whereas TIMP-2 -deficient mice does not. However, the effect of TIMP-3 on cognitive function and ischemic brain damage has not been investigated. Here, we assessed the effect of TIMP-3 on cognitive function and ischemic brain damage using TIMP-3 deficient mouse.

Conclusions: Prolonged post-ischemic hyperperfusion: A systematic multimodal MRI study

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Prolonged Post-ischemic Hyperperfusion: A Systematic Multimodal MRI Study

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Background: Focal cerebral hyperperfusion after stroke has long been documented and is a frequent, yet poorly understood, phenomenon. It is unclear whether hyperperfusion harms or helps tissue survival. In this study, we systematically investigate the hyperperfusion phenomenon in three different MCAO durations in rats. Multi-parameter MRI including diffusion, perfusion, T2, T1, pH-weighted and dynamic contrast-enhanced imaging, and MRI angiography, were acquired to characterize post-ischemic hyperperfusion. Methods: Male rats (250-350g) were subjected to 30-min (n = 10), 60-min (n = 7), and 90-min (n = 9) MCAO using intraluminal suture method followed by reperfusion. Perfusion by (continuous arterial spin labeling), diffusion, and MRA were acquired every 30 mins for 3 hrs and again 24, 48 and 72 hrs post-occlusion. T2, T1 and pH-weighted MR images were acquired at 3 hrs post-occlusion and later time points. In some animals, blood brain barrier leakage was evaluated by comparing T1-weighted images before and after intravenous injection of Gd-DTPA. Results: Hyperperfusion was observed at 48, 72 and 192 hrs post MCAO in animals of 30-min MCAO group. In 60-min MCAO group, 2 of 7 rats showed hyperperfusion. None of animals in the 90-min MCAO group showed hyperperfusion. Significant hyperperfusion was observed 24hrs post-occlusion and peaked at 48hrs (290% of baseline) in some animals. Blood brain barrier leakage was evaluated by comparing T1-weighted images before and after intravenous injection of Gd-DTPA. Conclusion: This study establishes a feasible and quantitative predictive algorithm. ADC alone at 30 mins predicted poorly final infarct by comparison (AUC: 0.881±0.052, p<0.009; 0.751±0.039 for permanent, 60-min and 30-min MCAO, respectively). 2) ADC alone at 30 mins did slightly better (AUC: 0.903±0.023, 0.854±0.049, and 0.889±0.057). 3) CBF + ADC at 30 mins adequately predicted infarct (AUC: 0.912±0.004, 0.888±0.050, and 0.889±0.053). Conclusion: In conclusion, our study provides a feasible and quantitative predictive algorithm. Further studies need to be done in other models to verify the usefulness of this approach.

Improving CBF Measurement Accuracy in Ischemic Stroke

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Background: Accurate and sensitive cerebral blood flow (CBF) measurements are important in stroke imaging. Arterial spin labeling (ASL) technique is widely utilized to non-invasively image CBF but it has low sensitivity, particularly in regions of low CBF. While suppressing Background signal by inversion nulling has been shown to improve CBF temporal stability, imperfect inversion pulses significantly compromise perfusion contrast. We proposed a novel approach to suppress Background signal without such drawback. This technique - referred to as inversion-recovery Background suppression with two-coin continuous ASL (IR-cASL) - uses a brain radiofrequency coil for background suppression and a separate neck radiofrequency coil for ASL. This technique was compared to measure baseline CBF and hypercapnic changes in CBF in stroke rats to determine if basal CBF and T1MRI response can be improved by IR-cASL.

Methods: Six male rats (230-290g) were subjected to transient (30-min (n = 4), or 60-min...
(n=2) MCA occlusion using intraluminal suture method. Multi-slice perfusion imaging were acquired at 7 Tesla scanner using both cASL and IR-cASL CBF MRI on the same animals using identical parameters except that the IR-cASL sequence included a non-spatially selective, 20-ms hyperbolic secant inversion pulse applied via the brain coil. The temporal and spatial contrast to background noise for IR-cASL MRI of hyperemic challenge were analyzed and compared with conventional two-coil cASL without background suppres-
sion. Quantitative multi-slice CBF maps were derived. Temporal standard deviation (SD) maps of normalized \textit{A}_{\text{perfusion ratio}} (\textit{A}_{\text{perfusion ratio}}^\text{SD}) were derived from the time series data of baseline CBF scans. Contrast-to-noise ratio and contrast-to-noise (CNR) analyses were performed on hyperemic challenge scans. Results: IR-cASL yielded 2.2, 2.6 and 2.9 times better CBF sensitivity in regions of low CBF. IR-cASL yielded 2.5 times higher functional CNR compared with cASL without background suppression. This suggests that IR-cASL improved detection sensitivity in regions of low functional response area. Conclusion: This study demonstrates improved basal CBF and CBF-based MRA sensitivity with the IR-cASL technique in a rat stroke model. IR-cASL MRI improves CBF measurement sensitivity and CBF-based MRA responses. It should also provide better delineation of the ischemic penumbra where CBF is reduced. IR-cASL may also prove useful for imaging low CBF conditions such as in white matter and other neurological diseases.

This research has received full or partial funding support from the American Heart Association, National Center.

**References**

1. **Conclusions:**
   - Areas of increased permeability measured in vivo coincide with BBB disruption and hemorrhage observed in histology. DWI confirms infarct while perfusion-weighted MT MRI shows prolonged flow in the right hemisphere related to a right MCA occlusion. The permeability map 4h after reperfusion shows increased permeability in the region where low-power histology view at 24h shows extravasation of Evans’ blue and hemorrhagic transformation foci, as well as in the choroid plexus, that do not have a BBB.

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**Dexoferoxamine Induces a Prolonged Neuroprotective State, a Potential Treatment for Recurrent Stroke**

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Transient ischemic attacks (TIAs) often warn of an impending stroke as 10.5% of patients who suffer from TIA attack would have a recurrent stroke within 50 days. The majority of recurrent strokes occur within the first 30 days with more than half in the first week. Achieving a prolonged neuroprotective state with neuroprotectants following TIA or minor stroke, especially before the first days to 3 months, could be an ideal way to proactively deliver neuroprotective therapy reducing ischemic brain damage with recurrent stroke. Hypoxia preconditioning (HPC) is a phenomenon that mild hypoxia or hypoxia mimetics (HMs, pharmacological compounds which simulate hypoxia exposure and have neuroprotective properties) reduces stroke-induced damage 1-3 days after. If continuous or intermittent exposure to HMs could induce an extended neuroprotective state, this protective effect could be applied clinically. We previously confirmed, if continuous infusion of HMs induce an extended neuroprotective state. Mice were administered a continuous i.p. delivery of deferoxamine (DFO) by using of ALZET minipumps at two different concentration 80mg/kg/day or 40mg/kg/day over 14 days. At the end of 14 days, we performed MCAO without removing the implanted pumps and quantified stroke volume. Interestingly, 40mg/kg/day of DFO robustly reduced stroke volume, while 80mg/kg/day dose was not protective. Thus, continuous administration of DFO provides extended protection, yet the administered dose is critical. We then extended the time frame of DFO treatment to 5 days and 4 weeks. Continuous DFO administration for 5 days and 4 weeks were also protective. It is postulated that several HM target genes are involved in the mechanism of HPC-meditated protection and DFO-mediated protection including EPO and VEGF. Thus, by using quantitative PCR, we detected the expression of several HM-targets including EPO, VEGF and glycolytic enzymes. To our surprise, when administered chronically, DFO failed to upregulate the transcript abundance of these targets. Since the phosphorylation of Akt and Erk may contribute to the protection mediated by HPC, we examined the phosphorylation of these two proteins by Western blot. However, the DFO administration has no influence on the phosphorylated form of these proteins. In conclusion, continuous use of DFO generates a prolonged neuroprotective state against stroke without increasing expression of HM target genes.

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**Correlating in-vivo Imaging to Histology to Validate BBB Permeability Measurements**

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**Objectives:** BBB disruption is hypothesized as a contributing factor to hemorraghic transfor-
mation of acute ischemic stroke. BBB permeability can be measured with contrast-enhanced BBB permeability in regions showing hemorrhage was found to be 0.27 ml/100g/min for 4h post reperfusion and 24h post reperfusion showing extravasation of Evans’ blue (but without hemorrhage), permeability was found to be 0.018 ml/100g/min for 4h post reperfusion and 24h post reperfusion. Measurement in the same regions but contralateral to the occlusion were 0.13 ± 0.11, 0.12 ± 0.02, and 0.11 ± 0.01 ml/100g/min respectively. **Conclusion:** BBB permeability measured in vivo coincides with BBB disruption and hemorrhage observed in histology. D WI confirms infarct while perfusion-weighted MT MRI shows prolonged flow in the right hemisphere related to a right MCA occlusion. The permeability map 4h after reperfusion shows increased permeability in the region where low-power histology view at 24h shows extravasation of Evans’ blue and hemorrhagic transformation foci, as well as in the choroid plexus, that do not have a BBB.

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**High Prevalence of Silent Ischemic Lesions in Patients With Primary Intracerebral Hemorrhage**

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**Background:** The frequency and continuum of silent ischemic events in patients with primary intracerebral hemorrhage (ICH) has not been systematically assessed. The objective of the current analysis was to determine the prevalence, characteristics, and associated risk factors for concurrent silent ischemic lesions in a predominantly black, hypertensive population admitted with ICH. The analysis was undertaken as part of a prospective, multicenter, MRI-based, longitudinal natural history study of racial differences in patients admitted with primary ICH. **Methods:** Inclusion criteria were: primary ICH, age ≥ 18, signed informed consent, and MRI performed within 30 days of onset. Clinical and demographic data (including ICH etiology determined after complete work-up) were collected on all subjects. A standardized MRI protocol was employed and included DWI (with apparent diffusion coefficient maps), gradient-echo, and FLAIR sequences. Images were evaluated for: location of the primary hematoma, the frequency and location of ischemic lesions on DWI, the frequency and location of microbleeds, and the extent of white matter disease. **Results:** Of the 58 subjects included in the analysis, mean age was 60, with 52% male, 71% black and 28 white, and 84% having a history of hypertension. 67% had a lobar primary hematoma and 33% had a deep hematoma. Ischemia location, size, and permeability in 88% of the patients with the remaining cases having unknown (n=6) or due to amyloid angiopathy (n=1). The total 58 subjects, 16 (31%) had silent ischemic lesions on diffusion imaging (median lesion number 2, range 1-9), with 6 (33%) having only 1 lesion, and 12 (66%) having 2 or more. Five subjects (28%) had ischaetral lesions only, 5 (28%) contralateral lesions only, and 19 (44%) had bilateral lesions. Four subjects (22%) had only cortical lesions, 11 (61%) had only deep lesions, and 3 (17%) had both deep and cortical lesions. The ischemic lesion positive group had significantly more microbleeds than the lesion negative group (p<0.003), and more severe white matter disease (p=0.018). Age, gender, race and vascular risk factors were not significantly different between the groups. **Conclusion:** In this population of predominantly hypertensive hemorrhages, almost one-third (31%) of patients with primary ICH had evidence of concurrent silent ischemic events (remote from the primary hematoma) on diffusion imaging obtained within 30 days of onset. This likely reflects the severity of the underlying diffuse vasculopathy due to uncontrolled risk factors. These findings underscore the need to find more effective approaches for risk factor control in this population. In addition, further studies are needed to determine optimal antithrombotic therapy in these patients at risk for both ischemic and hemorrhagic recurrent events.

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Peripheral Inflammatory Response in Acute Intracerebral Hemorrhage May Predict Poor Outcome

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Background: Inflammation may contribute to secondary neuronal injury after acute intracerebral hemorrhage (ICH). Serum biomarkers of the inflammatory response may be useful in predicting poor outcome and identifying appropriate patients for clinical trials of anti-inflammatory therapies. This pilot study aimed to determine the potential utility of cytokines as independent biomarkers in ICH by elucidating which ones are elevated after acute ICH, the time course of cytokine elevation, and whether this elevation is distinct from existing predictors of outcome. Methods: 32 patients with acute, spontaneous ICH had serum samples drawn at < 12 h, 24 ± 6 hours, and 72 ± 6 hours from onset, excluding patients with sepsis, vasculitis, and cancer. Clinical information, NIHSS scores, ICH volumes, presence of fever or infection during the first 72 hours, and any surgical interventions were recorded. Outcome at 90 days was assessed using the modified Rankin Scale by telephone structured interview. Quantification of IL-1β, IL-6, IL-10, IL-1ra, IFN-γ, G-CSF, GM-CSF, MIP-1α, MIP-1β, MIP-1γ, TNF-α, and fractalkine levels were performed using human cytokine multiplex panel 1 (Millipore, Billerica, MA). Results: All cytokines were detectable in serum in at least 50% of the patients. Advanced age (above median 62.4 years) was associated with higher levels of IFN-γ (p = 0.03), GM-CSF (p = 0.04), and MCP-1 (p = 0.04). Only 4 patients had an infection in the first 72 hours; no cytokine was statistically associated with infection. Larger hemorrhages were associated with higher IL-6 (p = 0.04), lower GM-CSF (p = 0.03) and higher IL-10 (p = 0.001). In multivariable ordered logistic regression, worse outcome was associated with high 24 hour levels of IL-6 (OR 4.02, 95% CI 1.22-12.11, p = 0.01), IL-10 (OR 3.22, p = 0.014), IL-6 (10.25, p = 0.019) and GM-CSF (OR 3.64, 95% CI 1.19-11.13, p = 0.023) after adjustment for age, ICH volume, intraventricular hemorrhage, and initial NIHSS. Conclusions: Serum cytokines may serve as biomarkers of inflammation-induced brain injury after ICH. In this exploratory cohort, high IL-6, IL-10 and GM-CSF levels at 24 hours predicted poor neurologic outcome after ICH.

Serum Ferritin Level in Patients With Acute Ischemic Stroke is an Important Predictor of Hemorrhagic Transformation

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Introduction: Because hemorrhagic transformation(HT) is associated with poor outcome and delays the initiation of proper treatment, we need a better understanding of factors that predict HT after ischemic stroke. Although many studies have identified factors that may lead to HT, factors related to HT are still unclear. Hypothesis: In cerebrovascular diseases, oxygen superoxide radicals increase the amount of iron in the cytosole during oxidative stress by releasing the iron from ferritin. Ferrous iron can both initiate and propagate lipid peroxidation, leading to altered membrane fluidity, and eventually the formation of edema, membrane disruption and cell death. This study investigates whether high serum ferritin levels are associated with HT in patients with acute ischemic stroke. Methods: 324 consecutive patients with acute ischemic stroke within 24 hours after vascular event from September 2005 to February 2009. Total 110 consecutive patients treated with intravenous or intra-arterial tissue plasminogen activator were studied. HT was diagnosed using gradient echo MRI imaging or CT within 14 days after onset and classified into hemorrhagic infarction (HI) types 1, HI type 2, parenchymal hemorrhage (PH) types 1, and PH type 2 according to the recommendations of the ECASS study. Also HT was classified into no, asymptomatic, minor symptomatic and major symptomatic HT. Results: CT or MR showed HT in 80 patients (HI in 58 and PH in 32; asymptomatic in 53, minor symptomatic in 23 and major symptomatic in 14). Ferritin levels at baseline were higher in patients with HT than in patients without HT (198.32ng/ml versus 133.72ng/ml, p < 0.001). Ferritin levels were higher in patients who developed PH(>0.001) and symptomatic HI(>0.001). After adjustment for confounding variables, multivariate analysis showed that higher ferritin levels remained an independent predictor of HT in patients with acute ischemic stroke(<0.001) and patients treated with thrombolysis(=0.034). Atrial fibrillation(<0.001), thrombotic therapy(=0.001), higher serum glucose(=0.03) and higher NIHSS on admission (=0.013) were also independent predictors of HT. Serum ferritin levels higher than 171.8 ng/ml at baseline were independently associated with symptomatic HT. Conclusions: Increased serum ferritin levels are associated with HT, especially PH and symptomatic HT in patients with acute ischemic stroke. Further studies are needed to clarify the role of ferritin and iron metabolism in cerebrovascular diseases.

Modeling the Growth of Microbleeds Into Macrobleeds

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Background: Analysis of the volumes of MRI-detectable hemorrhagic lesions among patients with symptomatic intracerebral hemorrhage has identified a bimodal distribution, with distinct size populations of "microbleeds" and "macrobleeds." This suggests that if a primary bleed reaches a size threshold, its growth may accelerate by secondary shearing of adjacent vessels as postulated by Fisher. We simulated this model of cascading bleeds to see if it could generate distinct populations of microbleeds and macrobleeds as observed in patients. Methods: We developed a computer simulation of hemorrhage growth incorporating both the random appearance of primary bleeds and the induced secondary bleeds that may occur because of proximity to primary bleeds. We simulated a 50x50x50 vessel lattice using ROOT software, fixing the average background microbleed rate at 0.1 new bleeds/month with Poisson statistics. Two quantities were varied to determine their effects on bleed size distribution: the probability (as a function of proximity) of a ruptured vessel causing a nearby vessel to bleed, and the rate at which this probability decays to baseline, simulating coagulation. Results: The distribution of hemorrhage volumes was highly dependent on the parameters chosen. Low probabilities of secondary vessel rupture produced no macrobleeds, high probabilities resulted in macrobleeds that filled the brain. Intermediate values successfully generated a bimodal distribution of hemorrhage volumes similar to the distribution found in patients, with 2-3 orders of magnitude separating the peaks. In these simulations, hemorrhages expanded into the macrobleed range, then self-terminated as the probabilities decayed to baseline. Notably, macrobleeds often expanded asymmetrically rather than concentrically from their point of origin (Figure; red is initial rupture site, darkening shades of grey are more recent bleeding). Conclusions: These findings suggest the cascade model first proposed by Fisher is sufficient to produce a bimodally distributed range of microbleeds and macrobleeds under particular model parameters. Models of macrobleed formation may be useful in predicting and analyzing future therapies for reducing hematoma expansion.
studied by immunohistochemistry for smooth muscle actin and CD68, and, in selected cases, electron microscopy. Presence of beta-amyloid was analyzed using immunohistochemistry for epitope 6E10. The pathological investigation demonstrated that cerebral microbleeds were common, present in 14/24 (56%) of specimens. Microbleeds typically occurred at capillary and arteriolar levels, independent of amyloid angiopathy. Putamen was site of microbleeds in 23/24 of cases; one microbleed was cortical. Arteriolar microbleeds demonstrated iron in macrophages, while capillary microbleeds had iron localized in both pericytes and macrophages. While this study does not address MRI-pathological correlations, these findings indicate cerebral microbleeds are common in elderly brain even in absence of history of clinical stroke and in absence of cerebral amyloid angiopathy. Presence of microbleeds at a capillary level suggests blood-brain barrier dysfunction contributing to etiology of cerebral microbleeds.

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Iron Enhances Neurotoxicity of Amyloid β
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Purpose: Microbleeds often occur in Alzheimer disease (AD) patients and amyloid β protein (Aβ) accumulation in the brain is associated with AD development. Tissue-type transglutaminase (Tg) has a major role in neurodegeneration and our recent study shows that brain Tg levels are upregulated after intracerebral hemorrhage. Our previous study also have demonstrated that iron, a hemoglobin degradation product, contributes to brain injury following intracerebral hemorrhage. This study investigated the effects of iron on Aβ-mediated brain injury. Methods: There were two sets of experiments in this study. In the first set, adult male Sprague-Dawley rats were divided into four groups. The rats received an intracaudate injection (20 µl) of either saline, FeCl₂ (0.2 mM), Aβ 25-35 (1 mM) or FeCl₂ + Aβ. In the second set, rats had an intracaudate injection (20 µl) of FeCl₂ + Aβ, and were treated cystamine (100 mg/kg, i.p.), a Tg inhibitor, or vehicle 2 hours later. All rats were killed after 24 hours for brain edema measurement and histological examination. Brain edema was determined using wet/dry weight method and neuronal death was examined using Fluoro-Jade C staining. Brain Tg levels were measured by immunohistochemistry. Results: We found that brain water content in the ipsilateral caudate was higher in the rats injected with FeCl₂ + Aβ compared to the other groups (79.7 ± 1.0% vs. 78.6 ± 0.6% in FeCl₂ group, 78.4 ± 0.3% in Aβ group, and 78.4 ± 0.7% in saline group, p < 0.05). Co-injection of FeCl₂ + Aβ also resulted in higher Tg levels and more severe neuronal death compared with FeCl₂ and Aβ groups (p < 0.01). Systemic use of cystamine reduced iron- and Aβ-induced brain edema (p < 0.05) and neuronal death (124 ± 25 vs. 249 ± 50 mm² in vehicle-treated rats, p < 0.01). Conclusions: These results suggest that iron can exacerbate brain toxicity of Aβ and Aβ iron chelation and Tg inhibition may be potential ways of delaying progress of the disease.

This research has received full or partial funding support from the American Heart Association, Midwest Affiliate (Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, South Dakota & Wisconsin).

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Prior Use of Statins is Not Associated With an Increased Risk of Hemorrhagic Transformation of Acute Cerebral Infarction
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Background and Purpose: Statins are widely used to treat hyperlipidemia and to lower the risk of both myocardial infarction and ischemic stroke. These agents effectively lower total and LDL cholesterol levels. However, long-term administration of statins may be accompanied by an increased risk of intracranial hemorrhage among patients with prior stroke. Because many patients with ischemic stroke are treated with interventions aimed at improving perfusion and that are accompanied by bleeding, we looked at the impact of statin use prior to stroke to would have also on the frequency of hemorrhagic transformation of infarction. Methods: We did a post-hoc analysis of the data from 804 subjects enrolled in the ABEStT-II (abciximab vs. placebo.) This trial was halted because of a higher rate of symptomatic hemorrhagic transformation among those treated with abciximab. Information on statin use (<7 days prior to stroke and the frequency of intracranial hemorrhage at 3 months was reviewed. All comparisons were based on the Chi-square method and multivariate logistic analysis adjusting for baseline NIHSS score, age, race, weight, initial blood pressure, study assignment (abciximab or placebo), aspirin use, and stroke subtype. Results: Previous use of statins was reported in 135 subjects (16.3%). Hemorrhagic lesions on imaging were detected in 97 subjects (12.1%) Hemorrhage was more common among those receiving abciximab (15.1%) than subjects receiving placebo (8.8%). (p = 0.006) Hemorrhages were diagnosed in 10.4% subjects taking statins and in 12.4% subjects not taking the medication (p = 0.38). There was no significant difference between previous statin use and intracranial hemorrhage. Overall, the results of our logistic analysis adjusting for possible confounders, including abciximab use. Significant predictors of hemorrhage in multivariate analysis were total NIHSS score (p < 0.0001), stroke mechanism (p = 0.03), and use of abciximab (p = 0.006). Conclusions: The use of statins in the days prior to acute ischemic stroke was not associated with an increased risk of intracranial bleeding within the next three months. Patients taking statins should not be excluded from future trials testing therapies to improve perfusion.

Cerebral Microbleeds in the Elderly: A Pathological Analysis
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Cerebral microbleeds in elderly subjects are routinely identified by MRI, but their pathological basis has not been fully characterized. We studied post-mortem brain specimens of individuals with no clinical history of stroke, mean age 84.7 years and range 71-104 years. Cerebral microbleeds were identified by presence of hemosiderin (iron), identified by routine histochemistry and Prussian blue stain. Cellular localization of iron (in macrophages and/or pericytes) was reviewed, and iron by electron microscopy. Presence of beta-amyloid was analyzed using immunohistochemistry for epitope 6E10. The pathological investigation demonstrated that cerebral microbleeds were common, present in 14/24 (56%) of specimens. Microbleeds typically occurred at capillary and arteriolar levels, independent of amyloid angiopathy. Putamen was site of microbleeds in 23/24 of cases; one microbleed was cortical. Arteriolar microbleeds demonstrated iron in macrophages, while capillary microbleeds had iron localized in both pericytes and macrophages. While this study does not address MRI-pathological correlations, these findings indicate cerebral microbleeds are common in elderly brain even in absence of history of clinical stroke and in absence of cerebral amyloid angiopathy. Presence of microbleeds at a capillary level suggests blood-brain barrier dysfunction contributing to etiology of cerebral microbleeds.
Antiplatelet Agents, Cerebral Amyloid Angiopathy and Recurrent Intracerebral Hemorrhage

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Introduction: Cerebral amyloid angiopathy (CAA) is a common pathological condition in the elderly, which can cause both symptomatic intracerebral hemorrhage (ICH) and asymptomatic microbleeds detected on MRI. Because the risk of thromboembolic disorders also rises dramatically with aging, antiplatelet agents are commonly administered to individuals with CAA. Hypothesis: We sought to determine whether use of antiplatelet agents increases risk of recurrence in survivors of CAA-related ICH. Methods: Subjects were consecutive inpatients admitted with CAA-related ICH over an eight-year period. Diagnosis of CAA was assigned according to the previously validated Boston Criteria. Baseline clinical, imaging and laboratory data were collected. Survivors of the initial ICH were followed prospectively for recurrent ICH and duration of antiplatelet agent as well as anticoagulant use. Cox proportional hazards models were used with antiplatelet agent and warfarin exposures as time-varying variables, adjusting for known predictors of ICH recurrence in CAA. These included APOE genotype, as well as neuroimaging markers (CT-defined white matter hyperintensity and number of microbleeds on gradient-echo MRI). Results: 104 subjects were diagnosed with CAA-related ICH. Of these, 16 (15.4%) were exposed to an antiplatelet agent after their initial ICH, based on the recommendation of a treating physician. Over a median follow-up time of 34.3 months (Interquartile Range: 15.1 - 57.6), 29 subjects experienced recurrent ICH. Baseline predictors of recurrence included a history of ICH preceding the index ICH that led to enrollment (Hazard Ratio [HR] 4.8, p < 0.005) and number of microbleeds on MRI (2 - 4 or ≥ 5, HR 2.9, 4.7 respectively, p = 0.04, 0.001 respectively). Antiplatelet agent exposure was associated with ICH recurrence (HR 3.9, 95% CI: 1.6 - 9.2, p = 0.005) and increased duration of antiplatelet use, with a 33% increase in 2-year recurrence rate. When adjusting for number of microbleeds on MRI (0, 1, 2 to 4 or ≥ 5 microbleeds) HR for antiplatelet use were 1.9 (p < 0.03), 3.2 (p < 0.004), 4.8 (p = 0.037) and 5.3 (p = 0.048). Conclusion: Data from this prospectively followed longitudinal cohort suggest that intercurrent use of antiplatelet agents may raise the risk of recurrent CAA-related ICH. They should be interpreted cautiously given the small numbers of patients studied and the non-randomized manner in which the decision to administer antiplatelet agents was made.

Changes in Cerebral Microbleed Numbers of Stroke Patients and Their Prognostic Factors

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Background: Cerebral microbleeds are increasingly recognized with the advance of MRI techniques, and their numbers are associated with various hemorrhage-prone clinical conditions, such as incident intracerebral hemorrhage, hemorrhagic transformation of ischemic stroke, and age-associated small vessel disease. However, the prognostic significance and chronologic changes of the numbers are still unclear. In this study, we investigated the serial MRIs of stroke patients and analyzed factors influencing the progression of microbleed numbers. Methods: From October 18, 2002 to July 31, 2006, we enrolled acute stroke patients based on the Korean Stroke Registry, and followed-up their brain MRIs for up-to 5 years. We compared demographic factors, vascular risk factors, laboratory findings, medication profiles, and radiologic factors according to the presence of microbleeds and the changes in the numbers. Results: Total 224 patients were successfully evaluated with initial and follow-up MRIs (mean follow-up period= 526±370 days). Among them, 76 patients (40%) were with microbleeds in the initial MRI, and showed higher prevalence of hypertension, and increased volumes of subcortical and periventricular white matter lesions, compared to those without microbleeds. The changes in the numbers of microbleeds were analyzed with univariate correlation, and these two factors significantly predicted the decrease of microbleeds in multiple logistic regressions as well. Conclusion: Severe subcortical white matter changes predicted the increase of microbleeds, and higher LDL-C states and the use of ARB/ACE inhibitors might contribute to recovery cerebral microbleeds.

Inflammatory Response to Intraventricular Hemorrhage: Time Course, Magnitude and Effect of Intraventricular t-PA

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Background: Intracranial hemorrhage (ICH) accounts for a fifth of all strokes. In 45% of cases, the ICH extends into the ventricles resulting in intraventricular hemorrhage (IVH) - a known predictor of poor outcome. Intraventricular inflammation is believed to be one mechanism by which IVH exerts deleterious effects. Tissue plasminogen activator (tPA) through the ventricles has been studied for the treatment of IVH. While tPA may accelerate the clearance of IVH, its effect on IVH-induced inflammation is unknown. The purpose of this work was to describe the inflammatory response in the CSF following IVH and compare it in patients treated or not treated with intraventricular t-PA. Methods: Consecutive Patients diagnosed with IVH and treated with ventriculostomy were selected from our prospective stroke registry from November 2004 to July 2007. CSF protein, glucose, lactate and WBC (corrected for BC number) from samples collected up to 19 days after IVH were captured. Patients with evidence of CSF infection were excluded. Results: 51 patients were identified: 29 in the tPA and 22 in the non-tPA group. The two groups were comparable in terms of stroke severity and IVH volume. Figure shows the trends of CSF protein and WBC for all patients. An inflammatory reaction developed around day 3, lasted 3-5 days and then subsided. The ABT showed no difference in the time course or magnitude of the inflammatory response in patients treated with intraventricular t-PA. Conclusions: IVH induces intrathecal inflammatory response that peaks at day 3 from the hemorrhage. Intraventricular ICP does not appear to modify or aggravate this inflammation. Further work is needed to study the relationship between the intraventricular inflammatory response and patient outcome.
Predictors of Index Stroke Severity and Discharge Outcomes Among Hospitalized Patients With Stroke Secondary to Cervical Arterial Dissection
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Background: Cervical arterial dissection (CAD) is an uncommon cause of stroke, usually affecting younger individuals with less cardiovascular morbidity. Demographic, historical, imaging, and biomarker factors associated with outcomes following occurrence of CAD have not been well-described. Objective: To describe associations between demographic/historical/biomarker/imaging vs. admission stroke severity and discharge functional status in patients hospitalized with CAD. Methods: Data were collected prospectively during a 5-year period on consecutive ischemic stroke admissions to a university hospital. Cervical arterial dissection was diagnosed based on vascular imaging and exclusion of other stroke mechanisms. Presenting stroke severity was assessed with the National Institutes of Health Stroke Scale (NIHSS). Functional outcome at discharge was assessed using the modified Rankin scale. Results: A total of 69 out of 1076 stroke cases were attributable to cervical arterial dissection (6.4%), mean age 47 (SD 12), free of disability at baseline (95% mRS 0, 5% mRS 1), 51% women. Median NIHSS on presentation was 5 (IQR 1-15), median mRS at discharge was 1 (0.7-5) with 25% having a poor outcome (mRS 4-6) and 52% were discharged home. Age, gender, race, ethnicity, BMI, presence of vascular risk factors, antithrompeptives, statins and presenting blood pressure were not associated with severity/outcomes. Among historical factors, only antithrombotic use (n=12, 10 aspirin, 2 warfarin) at presentation was associated with less severe stroke (NIHSS 3 vs. 10, p=0.015, mRS 1 vs. 2, p=0.045) despite being significantly older (age 61 vs. 44). Of biomarkers at presentation, serum HDL cholesterol was inversely related to discharge mRS score (r=-0.333, p=0.021) and white blood cell count (WBC) positively associated with discharge mRS score (r=0.249, p=0.044). Neither HDL nor WBC were linked to presenting stroke severity. Posterior circulation stroke localization on imaging was associated with less severe stroke (NIHSS 4 vs. 11, P=0.002) and associated with better outcomes (mRS 1 vs. 2, P=0.52). Conclusions: In this cohort, about a quarter of strokes due to cervical arterial dissection resulted in severe disability. Use of antithrombotic agents at presentation was associated with better outcomes despite, consistent with their likely role in the treatment of this condition. Among admission biomarkers, only low serum HDL and higher WBC predicted poorer discharge outcomes in these patients with cervical arterial dissection. Posterior circulation strokes were less severe.

Intensive versus Conventional Insulin Therapy in Critically Ill Stroke Patients
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Objectives: The purpose of this prospective randomized study was to investigate whether intensive insulin therapy to keep blood glucose levels 80 to 110mg/dl or conventional treatment to keep levels less than 150mg/dl was associated with reduction of mortality and improved functional outcome in critically ill stroke and neurologic patients. Methods: Within 24 hours of ICU admission, mechanically ventilated adult neurologic patients expected to require intensive care for > 48 hours were enrolleled after written informed consent. Patients were randomized to intensive or conventional control. Primary outcome measure was death within three months. Secondary outcome measures included 90-day modified Rankin scale (mRS) score; ICU and hospital LOS, and ventilator days. Eighty-one patients were enrolled with no significant baseline differences in the groups including age, ethnicity, neurologic diagnosis, mRS, or GCS score. Ethnicities were Asian (38%), Pacific Islander (27%), Caucasian (25%), Hispanic (2%), African American (1%), and unknown (6%). Stroke was the diagnosis in 35% (22% CIH, 9% SAH, 4% ischemic). Results: For the entire cohort, the proportion of deaths was higher among patients in the intensive arm but this was not statistically significant (36% vs. 25%, P=0.34). When good versus poor outcome at 3 months was dichotomized to mRS score 0-2 versus 3-6, respectively, there was no difference between the two groups (76.2% vs. 75% had a poor outcome, p = 1.0). There was also no difference in ICU or hospital LOS or ventilator days. Hypoglycemia (<40mg/dl) and severe hypoglycemia (<40mg/dl) were more common in the intensive group (48% vs. 11%, p=0.0006) and 4% vs. 0%, p=0.5). When only the 28 stroke patients were analyzed, there were no significant differences in poor outcome (79% of intensive vs. 73%, p=1.0) and deaths (50% in intensive arm vs. 21%, p=0.24). However, the total hospital LOS was significantly shorter in the intensive arm (median 16 vs. 26 days, 95% CI 0.3-0.89). The ICU LOS was shorter in the intensive arm but this was not statistically significant (median 10 vs. 16 days (95% CI 0.5-1.2). Conclusions: There was no benefit to intensive over conventional insulin therapy in this small critically ill stroke population except for lower hospital LOS. Previous glycemic control studies in non-neurologic ICU patients have reported conflicting results. This is the first intensive glycemic control study examining critically ill stroke patients and functional outcome and may prompt a multi-center trial.

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Non-convulsive Status Epilepticus After Acute Ischemic Stroke: Not So Unusual, Nor So Unpredictable If Systematically Investigated
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Background and Purpose: Ischemic stroke is a recognized cause of status epilepticus (SE), and SE is associated with a higher stroke mortality rate. Information about non-convulsive SE (NCSE) after acute ischemic stroke is scarce. We investigated the frequency of NCSE after acute ischemic stroke and compared the characteristics of ischemic stroke patients with and without NCSE. Methods: We evaluated a consecutive cohort of patients with acute ischemic stroke between 01/01/2007 and 06/30/2009. All patients were assessed with neuromaging studies. An electroencephalogram (EEG) was done to those patients who had a depressed or fluctuating level of consciousness not justified by the severity of the ischemic brain lesion, metabolic, hemodynamic or electrolytic abnormalities, and to those who had convulsive seizures without recovery of level of consciousness. All EEGs were assessed by a neurologist specialized in epilepsy. NCSE was defined as the presence of the previously described neurological picture and an EEG fulfilling Kaplan criteria. We used χ² and I Tests for comparing ischemic stroke patients with and without NCSE. Results: We studied 187 consecutive patients with ischemic stroke. We found 9 cases of NCSE (4.8%, 95% CI 2.3-8.9). No patient in the NCSE group had a history of epileptic seizures. Mean time from beginning of symptoms to diagnosis of NCSE was 7.4 ± 9.5 hours. Average time from diagnosis of NCSE to clinical and electrical improvement was 5.4 ± 7.6 hours. Two patients were initially treated with valproate and no further addition of antiepileptic drugs was necessary for controlling NCSE. The remaining 7 patients were first treated with phenytoin. Six of these patients required the addition of ≥1 antiepileptic drugs. Four of these six patients recovered consciousness after a valproate loading dose. We did not find any evidence of drug-related toxicity. Patients with and without NCSE are compared in the table. Conclusions: We found a high frequency of NCSE in our cohort. NCSE was associated with stroke severity and a higher average length of hospital stay. Valproate was the best antiepileptic choice for controlling NCSE. NCSE should be systematically considered as a cause of otherwise unexplained fluctuation or depression of level of consciousness in patients with acute ischemic stroke and prompt to immediate electroencephalographic evaluation. Valproate seems to be a safe and effective option for treating ischemic stroke patients with NCSE. Although difficult to perform, prospective trials with a higher number of patients are needed to assess the reproducibility of our findings.

Comparison of Ischemic Stroke Patients With and Without NCSE

With NCSE
Without NCSE
[n = 9] [n = 178] P
Mean age ± SD, years
69.3±16.5
68.2±13.5
0.81
Male gender, %
66.7
67.3
0.74
Mean NIHSS ± SD
15.2±6.0
7.3±6.8
<0.001
Average length of stay ± SD
35.3±16.5
11.4±13.3
<0.0001
In-hospital mortality, %
0.0
7.5
0.85
NCSE: non-convulsive status epilepticus. NIHSS: National Institutes of Health Stroke Scale. SD: standard deviation.

Changes in Carotid Plaque Echogenicity With Time Since the Stroke Onset: The UNPACK Study
Patricia Martinez-Sanchez, Jessica Fernandez-Dominguez, Gerardo Ruiz-Ares, Stroke Ctr, Dept of Neurology, La Paz Univ Hosp, Autonoma de Madrid Univ, Madrid, Spain; Blanca Fuentes, Stroke Ctr, La Paz Univ Hosp, Autonoma de Madrid Univ, Madrid, Spain; Andrei V Alexandrov, Comprehensive Stroke Ctr, Dept of Neurology, Univ of Birmingham, AL; Exequier Deiz-Tejedor; Stroke Ctr, Dept of Neurology, La Paz Univ Hosp, Autonoma de Madrid Univ, Madrid, Spain

Background: Carotid plaque echogenicity is related to its histological components and has been associated with the development of neurological events. Higher lipid content and haemorrhage, both related to “unstable plaques”, are more echoluent than fibrous tissue and calcium, which are related to “stable plaques”. Our aim is to compare carotid plaque echogenicity on grey scale in four groups: symptomatic plaques in three different time intervals since the stroke onset and asymptomatic plaques. Methods: Prospective observational study with inclusion of consecutive patients with atherothrombotic ischemic stroke corresponding to the carotid territory from February-2007 to December-2008. All patients underwent a carotid duplex and the time since the symptoms onset to the test performance was recorded. Plaque echogenicity was measured by the standardized grey scale median (ISM) in the both the symptomatic and asymptomatic internal carotid arteries. This procedure was always done by the same observed who was blinded to clinical data. Four groups of plaques were compared: symptomatic plaques imaged at ≤24h, 24-72h, 72-7d after stroke symptom onset and asymptomatic ones. Results: A total of 120 patients were included. Mean age 71 years (SD 9.5), 69 % men. Number of patients with symptomatic plaques ≤24h from stroke onset: 32; 24-7d: 50; >7d: 22; and asymptomatic plaques: 22 cases. Demographic data,
vaccular risk factors and previous treatment were similar between groups. Symptomatic plaques studied within first 24 h from symptoms onset presented lower echogenicity than those studied in the 24-7d period, >7d or asymptomatic ones, with a median GSD (interquartile range) of 14 (16), 19.5 (19), 22.5 (21), 26.5 (16), respectively (P = 0.001), independently of demographic data and vascular risk factors. Conclusions: Carotid plaques characterized in the first hours after an atherothrombotic stroke show lower echogenicity than plaques related to older strokes or asymptomatic plaques. The carotid plaque echolucent measured by GSD could be a marker of plaque instability and serve as a surrogate marker for evaluation of earlier initiation of secondary risk reduction therapies.

**Occurrence of Subacute Recanalization and Collateral Formation in Patients With Cerebral Venous Thrombosis. A Serial Venographic Study**

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**Background:** The underlying mechanism for symptomatic recovery in patients with cerebral venous thrombosis is not clear although subacute recanalization and collateral formation have been proposed as possible mechanisms. **Objective:** To identify the occurrence of recanalization and collateral formation among survivors of cerebral venous thrombosis and its association with symptomatic recovery. **Method:** We identified all the patients admitted with cerebral venous thrombosis over a 5 year period and who underwent initial magnetic resonance (MR) or computed tomographic (CT) venography and a follow-up CT or MR venography between 3 and 12 months after onset. All the images were reviewed by a single observer using classification proposed by Qureshi for recanalization (grade I- partial recanalization of one or more occluded dural sinuses with improved collateral flow; grade II- complete recanalization of one sinus but persistent occlusion of the other sinuses [A-no residual flow, B-non occlusive flow]; grade III- complete recanalization and for collateral formation: grade I- collaterals bypass occluded segment of dural venous sinuses but connect within the same sinus; grade II- collaterals bypass the occluded segment and connect with a different sinus.; grade III- collaterals bypass the occluded segment and connect with different circulation. **Results:** A total of 39 patients with cerebral venous thrombosis (mean age 34.82±17.1 SD) 19 were men had an initial and follow-up venographic study performed. Of these, 21 patients underwent serial venographic imaging using the same modality allowing a direct comparison. Of the 17 patients who had recanalization during follow-up, 10 patients had grade I recanalization, 7 had grade II recanalization, and 4 had no recanalization. Collateral formation was seen in 8 patients: grade I in 3 patients, grade II in one patient, and grade III in 4 patients. The proportion of patients with persistent headaches was higher in those with no or partial recanalization than with complete recanalization (5 of 14 patients vs. 0 of 7 patients ) and in patients with no collaterals than patients with collaterals (4 out of 13 vs. 1 out of 8 ). None of the patients experienced any recurrence or new symptoms. **Conclusion:** Complete recanalization is seen in only one-third of the patients while a combination of partial recanalization and collateral formation is associated with clinical stability in the rest of the patients with cerebral venous thrombosis.

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**Homocysteine as a Predictor of Early Neurological Deterioration in Acute Ischemic Stroke: Secondary Analysis From the CAIST Trial**

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**Background and Objective:** Early neurological deterioration (END) is common problem in acute ischemic stroke ranging from 12-42%, and previous studies demonstrated some predictors like stroke severity, diabetes mellitus, brain edema on initial brain CT are associated with END. We tried to reveal the clinical and laboratory predictors of END in acute ischemic stroke. **Methods:** We performed a secondary analysis from the Clozastol in Acute Ischemic Stroke Treatment (CAIST) trial, which is a double-blind, randomized, multi-center trial assessing the non-inferiority of clozastol over aspirin in acute ischemic stroke within 48 hours. END was diagnosed when there was a decrease of ≥1 point in motor power or a decrease of ≥2 points in any scores in the NIHSS within 7 days. **Results:** Of the 407 patients studied, 59 (14.5%) worsened during the 7 days after inclusion. Most (69.4%) of the END occurred within the first 24 hours after treatment. The overall incidence of END was 12.6% in the aspirin group and 16.4% in the clozastol group (P=0.277). There was no difference of END frequency in the first 24 hours after treatment. The overall incidence of END was 12.6% in the aspirin group and 16.4% in the clozastol group (P=0.277). There was no difference of END frequency in the first 24 hours after treatment. The overall incidence of END was 12.6% in the aspirin group and 16.4% in the clozastol group (P=0.277).

**Higher Admission Red Blood Cell Distribution Width is Linked to Outcome in Elderly Patients Hospitalized With Ischemic Stroke**

Nerces Sanossian, Univ of Southern California, Los Angeles, CA; Jeffrey L Saver, David S Liebeskind, Doojin Kim, Latasha K Ali, Sidney Starkman, Bruce Ovbiagele; Univ of California Los Angeles, Los Angeles, CA

**Background:** Red cell distribution width (RDW), an often ignored parameter reported in the routinely obtained complete blood count, is emerging as a potential predictor of primary stroke risk, as well as a prognosticator of long term survival in persons with established vascular disease. However, little is known about the relevance of RDW in the setting of acute stroke hospitalization. We determined whether RDW would predict outcomes among patients hospitalized with a recent stroke. **Methods:** Data were collected prospectively over a 5-year period on consecutive ischemic stroke admissions to a university hospital within 48 hours of ictus. Serum RDW was measured on admission. Presenting stroke severity was assessed with the NIH Stroke Scale (NIHSS). Poor discharge outcome was defined as death or severe disability (modified Rankin Scale score mRS = 3-6). **Results:** Among 423 patients, mean age was 66 years and 52% were women. Mean RDW was 45.4 (SD 4.5). Median presenting NIHSS score was 6 (IQR 2-14.5), median discharge mRS was 2 (1-4), 33% had a poor discharge functional outcome, and 49% vs 21 discharged home directly (i.e., without rehabilitation or nursing facility). Higher RDW levels were associated with age (r=0.393, P=0.001), greater stroke severity (r=0.112, P = 0.022) and poorer discharge outcome (r=0.138, P = 0.005). In age-adjusted analyses, higher RDW remained significantly associated with poorer discharge outcome in the oldest quintile (age >75 years, 55% vs. 45% (p=0.05), and with the commonly used definition of elderly (>65 years, 47% vs. 32%, P=0.032). RDW had no significant association with functional outcome in younger age groups. Conclusions: Higher admission RDW is associated with poor discharge outcome among elderly patients hospitalized with ischemic stroke. Elevated admission RDW may reflect a diminished capacity for systemic recovery and defense among elderly stroke patients, and might distinguish those elderly patients requiring prompt correction of underlying toxic-metabolic abnormalities that tend to worsen clinical outcomes.

**Hospital Acquired Pneumonia is Linked to Peri-insular Right Hemispheric and Infra-tentorial Acute Stroke**

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**Background:** Hospital acquired pneumonia (HAP) is a major complication of stroke. Recent neuroanatomic correlation suggests infarction in specific brain regions is associated with neuro-cardiac injury. We sought to determine if infarction in specific brain regions was associated with HAP. **Methods:** 216 acute stroke patients with HAP were randomly sampled from our stroke database (2003-2009), and 49% vs 21 discharged home directly (i.e., without rehabilitation or nursing facility). Higher RDW levels were associated with age (r=0.393, P=0.001), greater stroke severity (r=0.112, P = 0.022) and poorer discharge outcome (r=0.138, P = 0.005). In age-adjusted analyses, higher RDW remained significantly associated with poorer discharge outcome in the oldest quintile (age >75 years, 55% vs. 45% (p=0.05), and with the commonly used definition of elderly (>65 years, 47% vs. 32%, P=0.032). RDW had no significant association with functional outcome in younger age groups. Conclusions: Higher admission RDW is associated with poor discharge outcome among elderly patients hospitalized with ischemic stroke. Elevated admission RDW may reflect a diminished capacity for systemic recovery and defense among elderly stroke patients, and might distinguish those elderly patients requiring prompt correction of underlying toxic-metabolic abnormalities that tend to worsen clinical outcomes.

**PS01 Characterization of Ischemic Strokes and Transient Ischemic Attacks After Cardiovascular Procedures in a High-volume Center**

Patricia M Riccio, Francisco Klein, Marisol Ferru ´ a, Noelia Pontello, Luciano A Sposato; Cardiovascular Procedures in a High-volume Center

**Background and Purpose:** Stroke remains an important complication of cardiovascular procedures. Ischemic strokes and transient ischemic attacks (TIA) complicating cardiovascular
procedures have not been fully characterized. Our objective was to describe and to compare the characteristics of periprocedural and non-periprocedural ischemic strokes and TIs.

Methods: We assessed a consecutive cohort of acute ischemic stroke and TIA patients admitted between 01/01/2007 and 12/31/2008. We defined periprocedural IS or TIA as any cerebrovascular event occurred within the first 30 days after a cardiovascular surgery or an invasive diagnostic procedure such as a cerebral digital subtraction angiography. We determined the proportion of periprocedural IS or TIs. We assessed the time between the procedure and the ischemic stroke or TIA. We used \( \chi^2 \)-Test to compare periprocedural and non-periprocedural ischemic stroke and TIA patients.

Results: We studied 196 consecutive IS and TIA patients, 49 with a periprocedural ischemic stroke or TIA (25.0%, CI 95% 19.5-31.5). The median time between procedures and ischemic stroke or TIA was 1.0 days (IQR 25-75 1.0-2.0). Eighty percent of periprocedural ischemic strokes and TIs occurred within 48 hours after the procedure. All of them, with the exception of one that occurred on day 30, happened in the first 10 days. The comparison of periprocedural and non-periprocedural ischemic strokes and TIs is shown in Tables 1 and 2.

### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
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<th>Periprocedural [n = 49]</th>
<th>Non-Periprocedural [n = 147]</th>
<th>P</th>
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<tbody>
<tr>
<td>Stroke/TIA ratio</td>
<td>15.3</td>
<td>2.1</td>
<td>0.001</td>
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<tr>
<td>Mean age ± SD, years</td>
<td>67.6±10.6</td>
<td>68.8±10.3</td>
<td>0.64</td>
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<tr>
<td>Male gender, %</td>
<td>71.4</td>
<td>64.6</td>
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</tr>
<tr>
<td>Mean NIHSS ± DS (only for IS)</td>
<td>8.0±6.6</td>
<td>6.7±5.8</td>
<td>0.19</td>
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<tr>
<td>Mean ABCD2 ± DS (only for TIs)</td>
<td>3.0±2.4</td>
<td>4.2±1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left hemispheric strokes, %</td>
<td>42.9</td>
<td>59.0</td>
<td>0.07</td>
</tr>
<tr>
<td>Bilateral strokes, %</td>
<td>0.0</td>
<td>4.9</td>
<td>0.25</td>
</tr>
<tr>
<td>Anterior circulation strokes, %</td>
<td>78.2</td>
<td>85.2</td>
<td>0.22</td>
</tr>
<tr>
<td>Infarct size ≥ 15 mm, %</td>
<td>95.2</td>
<td>83.6</td>
<td>0.07</td>
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</tbody>
</table>

NIHSS: National Institutes of Health Stroke Scale.

### Table 2. Risk Factors and Outcome

<table>
<thead>
<tr>
<th></th>
<th>Periprocedural [n = 49]</th>
<th>Non-Periprocedural [n = 147]</th>
<th>P</th>
</tr>
</thead>
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<tr>
<td>Systemic hypertension, %</td>
<td>79.6</td>
<td>86.4</td>
<td>0.36</td>
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<tr>
<td>Diabetes mellitus, %</td>
<td>22.4</td>
<td>26.5</td>
<td>0.70</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>42.9</td>
<td>43.5</td>
<td>0.93</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>33.1</td>
<td>57.1</td>
<td>0.75</td>
</tr>
<tr>
<td>Previous stroke, %</td>
<td>16.3</td>
<td>23.1</td>
<td>0.42</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>36.7</td>
<td>30.0</td>
<td>0.49</td>
</tr>
<tr>
<td>Left atrial area &gt; 20 cm², %</td>
<td>55.8</td>
<td>56.1</td>
<td>0.90</td>
</tr>
<tr>
<td>Median length of stay (IQR 25-75)</td>
<td>8.0 (5.0–16.0)</td>
<td>4.0 (2.0–10.0)</td>
<td>0.004</td>
</tr>
<tr>
<td>In-hospital mortality (CI 95%)</td>
<td>8.7 (3.4–20.3)</td>
<td>7.0 (3.4–13.8)</td>
<td>0.94</td>
</tr>
</tbody>
</table>

IQR: interquartile range.

Conclusions: Periprocedural ischemic strokes and TIs were associated with a longer length of hospital stay and showed a higher stroke/TIA ratio. We could not demonstrate any other differences in terms of risk factors, baseline characteristics, severity, and outcome between periprocedural and non-periprocedural ischemic strokes and TIs.

### Insulin Dose Related to Admission Adiponectin Level: Results From the GRASP Trial

**P503**

**Insulin Dose Related to Admission Adiponectin Level: Results From the GRASP Trial**

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**Background:** Adiponectin (APN) is an emerging biomarker with an incompletely understood role in prognosis, treatment selection or disease modification for stroke patients. Low APN levels have been associated with insulin resistance and worse clinical outcome in ischemic stroke patients. **Objective:** to assess the relationship between baseline APN levels and insulin requirement and 3 month outcome in hyperglycemic acute ischemic stroke patients.

Methods: Baseline APN levels were prospectively collected in patients enrolled in the GRASP trial, a multicenter, randomized, controlled trial of insulin infusion therapy in hyperglycemic acute ischemic stroke patients. Patients were classified into “low” or “high” APN based on the median APN level (8690 ng/mL). Intravenous insulin dosing was available only on the 48 patients in the loose (n=24) or tight control (n=24) groups. Repeated measures ANOVA was used to compare insulin dosing by APN level in these patients. All 73 study patients with APN levels had 3 month modified Rankin scale scores (mRS).

**Results:** Logistic regression was used to assess the relationship between excellent outcome (0-1) on the 3-month mRS and APN level adjusting for baseline NIHSS. **Conclusion:** Baseline APN levels were lower in patients with high APN levels (odds ratio 1.8) this association was not statistically significant (p = 0.30). These data suggest a difference in insulin requirement and outcome in hyperglycemic acute ischemic stroke patients with low versus high APN levels. Further investigation is required; our data is limited by small sample size and the exploratory nature of this secondary analysis in the GRASP trial.

### Interventional Stroke Therapies in the Elderly: Are We Helping?**

**P504**

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**Background and Purpose:** Stroke centers increasingly use endovascular therapies such as intra-arterial thrombolysis and mechanical clot retrieval for the treatment of acute ischemic stroke (AS) presenting within 8 hours of symptom onset. Although reports have described safety and efficacy of intra-arterial thrombolytic therapy in elderly patients, it is unclear whether endovascular therapies are being offered and provide benefit in this age group. We reviewed the management of older patients presenting with AS and assessed safety and efficacy of endovascular interventions.

Methods: A retrospective review of patients ≥75 (n=724) admitted to a comprehensive stroke center with AS were compared to their younger counterparts (n=619) using the stroke center database (October 2005-March 2009). Parameters that were measured included admission and discharge NIH stroke scale (NIHSS), rate of endovascular treatment, in-hospital mortality and modified Barthel index (mBI). **Results:** Rates of endovascular treatments were lower in older patients (63/819;7.7% in ≥75 vs. 33/724;4.5% in ≥75 cohort, p = 0.02). Stroke severity as measured by the NIHSS was similar in younger and older patients undergoing an intervention (14.9±7.7 in ≤75 vs. 15.4±7.2 in ≥75). Survivors from both age groups showed similar improvement in NIHSS from admission to discharge following intervention (drop of 6.9 in young vs. 7.4 points in older age group). mBI at 3 months (15.6±6.1 in the younger vs. 14.9±6.4 in the older group) and at 12 months (17.9±3.9 in ≤75 and 15.9±5.4 in ≥75 cohort) were similar between age groups. Older patients showed a trend towards higher in-hospital mortality (16/63;25% in ≤75 vs. 13/33;39% in ≥75) although this did not reach significance. **Conclusion:** Patients over age 75 were less likely to receive endovascular treatments. This may reflect a lower pre-admission functional status in older adults or preconceived physician bias. Despite a trend towards higher mortality, elderly patients showed similar benefit as demonstrated by improvement in the NIHSS and mBI. This therapy should not be withheld on the basis of age.

### Predicting Long-term Outcome After Endovascular Stroke Treatment: The THRIVE Score

**P505**

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Endovascular treatments are being increasingly used in acute ischemic stroke, but better tools are needed to select the most appropriate patients for such therapies. Our study addresses
whether the presence of specific chronic diseases can be used, along with age and stroke severity, to predict endovascular stroke treatment outcomes. Data from two single-arm trials of a thrombectomy device, MERCI and Multi MERCI, were pooled for analysis. Hypertension, diabetes mellitus, and atrial fibrillation were found to predict outcomes. These three conditions contribute equally to a chronic disease scale that predicts outcomes independent of other predictor variables, including age, stroke severity, and vessel recanalization. A 10-level predictive score, the Totalized Health Risks in Vascular Events (THRIVE) score, was developed that incorporates age, stroke severity, and the chronic disease scale. Outcomes were strongly predicted by THRIVE: at the lowest end of the THRIVE score, 65% of patients had a good outcome, while at the highest end of the THRIVE score, 11% had a good outcome. The THRIVE score strongly predicts outcome and mortality at 90 days, and thus may be useful as a clinical patient selection tool and in clinical research.

Neuroprotective Effect of PGD2 DP1 Receptor Against Acute Brain Damage in Young and in Aged Mice

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Background: Cyclooxygenase (COX)-1 and COX-2 enzymes metabolize arachidonic acid to generate prostaglandin E2 (PGE2), PGD2, PGI2, and PGF2, and thromboxanes, collectively known as prostanoids. COX-2, the inducible COX isoform, is highly up-regulated under toxic conditions, and its activity results in increased levels of the prostanoids. The prostaglandins affect cellular processes by activating their specific G-protein-coupled receptors. PGD2 is the most abundant prostaglandin in the brain and plays a vital role in various physiological and pathological conditions; however, its role after pharmacological activation in excitotoxicity and stroke has not been defined. Here we tested the hypothesis that activation of the PGD2 receptor DP1 is neuroprotective in an NMDA model of acute excitotoxicity and transient cerebral ischemia in mice. Methods: Adult male C57BL/6 mice were anesthetized with halothane and given an intracerebroventricular (ICV) injection of the DP1 receptor-selective agonist BW245C (10nmol, n=9; 25nmol, n=7; or 50nmol, n=8) or vehicle (n=7). Intracerebroventricular (ICV) injection of the DP1 receptor-selective agonist BW245C (10nmol, n=9; 25nmol, n=7; or 50nmol, n=8) or vehicle (n=7). After the injection, mice were placed in a temperature- and humidity-controlled chamber and then transferred to their home cages after recovery from the anesthesia. After a 48-h survival time, the mice were perfused transcardially, and their brains were isolated, cryoprotected, and processed for further examination. Additionally, we tested whether the minimum effective dose against NMDA toxicity would be able to protect mice against cerebral ischemia. Under halothane anesthesia, mice (n=9) were given 10nmol BW245C ICV and then subjected to 90 min of middle cerebral artery occlusion and 4 days of reperfusion. Results: Analysis of the cresyl violet-stained brain sections revealed a significant attenuation in the NMDA-induced lesion in BW245C-treated mice. The decrease in lesion volume was 23.7% (p<0.05), 43.8% (p<0.01), and 33.9% (p<0.05) for 10nmol, 25nmol, and 50nmol BW245C, respectively. In a separate cohort, young adult DP1 knockout mice (n=10) injected with 15nmol NMDA had significantly (26.4%; p<0.05) greater lesion volumes than did wildtype mice (n=7). The NMDA-induced brain damage was aggravated in aged (16-month-old) DP1 knockout mice (n=8; p<0.05) as compared with age-matched wildtype mice (n=8). Similarly, BW245C significantly attenuated the cerebral ischemia-induced brain infarction by 21.0% (p<0.05). Conclusions: This is the first study to demonstrate that DP1 receptor activation is neuroprotective in vivo. These data indicate that DP1 receptors are vital in minimizing brain damage and could be considered as a potential adjunct therapeutic target to attenuate brain damage in both young and aged animals.

This research has received full or partial funding support from the American Heart Association, National Center.

Insights Into the Mechanism of Action of Flow Augmentation by Partial Aortic Occlusion in Acute Ischemic Stroke From Serial Angiographic and Perfusion Imaging

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Background: Aortic occlusion is an effective method to produce transient, severe regional hypoperfusion, and has been shown to reduce the neuronal injury following ischemic stroke. We studied the cerebral angiographic and perfusion changes associated with the ischemic stroke induced by partial aortic occlusion. Methods: We used a mouse stroke model to study the cerebral angiographic findings and cerebral perfusion changes associated with aortic occlusion. Results: The cerebral angiographic findings included an increased number of vessels, a decrease in the volume of the affected hemisphere, and a decrease in the flow through the collateral vessels. The cerebral perfusion changes included an increase in cerebral blood flow, a decrease in cerebral blood volume, and an increase in the mean transit time. Conclusions: Partial aortic occlusion is an effective method to study the cerebral angiographic and perfusion changes associated with ischemic stroke.

Recanalization following large vessel ischemic stroke is associated with a substantial increase in the likelihood of a good functional outcome. Studies employing thrombolysis, aspirin, and clopidogrel have shown that more complete recanalization is associated with higher likelihood of a favorable functional outcome, but the effect of the degree of recanalization on outcome is less well studied following mechanical thrombectomy. Methods: We retrospectively analyzed the pooled data from the prospective MERCI and Multi MERCI trials. Results: Serial angiography and perfusion imaging were available in 11 acute stroke cases (5 men, 6 women; mean age 67.4±16.0 years, median baseline National Institutes of Health Stroke Scale (NIHSS) score 13 (range 6-18). Device therapy was performed from 5.25±18.17 (median 9.75) hours after symptom onset. Serial cerebral angiography was available in 10 cases, with serial CT/MRI perfusion imaging in 11 cases before and after treatment. Serial CT/MRI perfusion imaging ranged from 2-8 acquisitions within 30 days from treatment. Arterial occlusions included 4 terminal carotids, 1 M1 MCA, and 6 M2 or distal MCA lesions. Arterial collateral did not demonstrate dynamic changes after treatment, although perfusion deficits diminished. CBV increased globally after treatment in all 11 cases. CBV increased focally in 8, with focal CBV decreases in 3, including 2/3 cases with terminal carotid occlusions. CBV changes were more overt than other perfusion parameters. Persistent or sustained flow augmentation was noted in 7 cases. Serial cerebral angiography did not occur at cerebral angiography, yet serial noninvasive techniques showed distal clot propagation in 3 cases with distal flow improvement in another 5. Conclusions: Serial angiography and perfusion imaging reveal collateral flow augmentation with NeuroFlo™, including CBV increases despite persistent arterial occlusion and unaltered arterial collaterals. Partial occlusion may potentially increase CBV offsetting cerebral venous steal, as well as increase pressure gradients and flow through collateral arterioles.

Higher Degrees of Recanalization After Mechanical Thrombectomy for Acute Stroke Are Associated With Improved Outcome and Decreased Mortality

Jeremy D Fields, Helm L Lutes, Oregon Health & Sciences Univ, Portland, OR; for the MERCI and Multi MERCI Investigators

Background and Purpose: Recanalization following large vessel ischemic stroke is associated with a substantial increase in the likelihood of a good functional outcome. Studies employing thrombolysis, aspirin, and clopidogrel have shown that more complete recanalization is associated with higher likelihood of a favorable functional outcome, but the effect of the degree of recanalization on outcome is less well studied following mechanical thrombectomy. Methods: We retrospectively analyzed the pooled data from the prospective MERCI and Multi MERCI trials. Recanalization at the conclusion of endovascular intervention was assessed using the TIMI score (0=persistent occlusion; 1=minimal flow; 2=partial restoration of blood flow; 3=normal blood flow). TIMI score reflects the lowest value for all treatable vessels (MCA=M1 and M2; ICA=ICA; M1 and M2; Posterior circulation—VA and BA). Results: The study population consisted of 305 patients; 90% outcomes were available for 296 and mortality for 299. The likelihood of favorable outcome was significantly associated with increased TIMI grade (p<0.001). The percentage of patients with a good outcome by TIMI grade was: TIMI 0, 5.1%.
Compared with existing angiographic scales, the CBG trended toward greater accuracy in predicting nonodisabled outcome at discharge. Conclusions: A novel scale assessing tissue reperfusion on completion angiogram is strongly predictive of treatment response. The Cerebral Blush Grade is a promising instrument for assessing outcomes of endovascular reperfusion therapies for acute brain ischemia.

**Reperfusion is a More Accurate Predictor of Follow-up Infarct Volume Than Recanalization: A Proof of Concept Using CT in Acute Ischemic Stroke Patients**

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Purpose: To compare recanalization and reperfusion in terms of their predictive value for imaging outcomes (follow-up infarct volume, infarct growth, salvaged penumbra) and clinical outcome in acute ischemic stroke patients. MATERIAL AND Methods: Twenty-two patients admitted within 6 hours of stroke onset were retrospectively included in this study. These patients underwent a first stroke CT protocol including CT-angiography (CTA) and perfusion-CT (PCT) upon admission, and similar imaging after treatment, typically around 24 hours, to assess recanalization and reperfusion. Recanalization was assessed by comparing arterial patency on admission and post-treatment CTAs; reperfusion, by comparing the volumes of CBV, CBF and MTT abnormality on admission and post-treatment PCTs. Collateral flow was graded on the admission CTA. Follow-up infarct volume was measured on the discharge noncontrast CT. Patients medical charts were reviewed for clinical information at admission and discharge. The groups of patients with reperfusion, no reperfusion, recanalization, and no recanalization were compared in terms of imaging and clinical outcomes. For each outcome, univariate analysis was performed to evaluate the predictive value of imaging and clinical variables, followed by a multivariate, mixed-effect model using forward stepwise selection. Results: Reperfusion (using an MTT reperfusion index > 75%) was a more accurate predictor of follow-up infarct volume than recanalization. Collateral flow and recanalization were not accurate predictors of follow-up infarct volume. In the multivariate analysis, an interaction term was found between reperfusion and the volume of the admission penumbra > 50 mL. CONCLUSION: Our study provides evidence that reperfusion is a more accurate predictor of follow-up infarct volume in acute ischemic stroke patients than recanalization. We recommend an MTT reperfusion index > 75% to assess therapy efficacy in future acute ischemic stroke trials that use perfusion-CT.

**Cerebral Blush Grade as a Predictor of Outcome After Endovascular Recanlization Therapy for Ischemic Stroke**

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Background: Good clinical outcome in ischemic stroke is linked with reperfusion of the ischemic territory. Several angiographic scales have been developed to rate the outcome of endovascular therapies. However, existing grading schemes examine patency of, or perfusion through, proximal target arteries and fail to fully account for distal embolic and microvascular obstructions that can impair capillary level perfusion and tissue, and clinical response to intervention. In the coronary bed, the myocardial blush grade (MBG) angiographic score has been developed to capture this information, and is associated with mortality and infarct size, independent of TIMI scores. We developed a novel scale, the Cerebral Blush Grade (CBG), that uses capillary angiographic perfusion findings to assess reperfusion after endovascular recanalization therapy (ERT). Methods: Ischemic stroke patients treated with ERT were identified in a prospectively maintained database. Angiograms were evaluated and CBG was scored as: 0 for no capillary phase opacification in the territory of the occlusion; 1 for <1/3 of the territory; 2 for >1/3 and <2/3; 3 for >2/3 and <entire territory; 4 for entire territory and slow inflow; 5 for entire territory, normal flow, but delayed washout; 6 for entire territory, normal inflow and washout. CBGs were also scored using the ASITN/SIR Collatimal, TICI, and Qureshi grading systems. Good clinical outcome was defined as mRS 0-2. Predictor and outcome variables analyzed included baseline demographics, clinical history, laboratory and imaging findings, method of ERT, initial NIHSS, and functional status at day 7 or discharge. Results: Among the 50 studied patients, mean age was 67.4 (range 29-95), 74% were female, and median presenting NIHSS score was 18. Affected vessels were 26% ICA, 62% M1, and 12% other. Endovascular recanalization therapies included Merci retriever alone in 50%, Merci plus IV or IA TPA in 26%, IA TPA alone in 6%, and 8% other. Unsuccessful tissue level reperfusion, defined as CBG of 0, occurred in 0% of patients, poor reperfusion (CBG 1-2) in 32%, moderate reperfusion (CBG 3-4) in 24%, and good reperfusion (CBG 5-6) in 44%. CBG 5-6 was seen in 90% of patients with a good clinical outcome and was strongly associated with final mRS 0-2 (p = 0.002). CBG 0-2 was more often associated with use of the Merci device alone (p<0.002) and M1 lesion location (p = 0.006). Low CBG scores 0-2 were associated with ICA occlusion site (50%, p = 0.002) and hyperdense MCA sign on CT (56.3%, p = 0.03). Compared with existing angiographic scales, the CBG trended toward greater accuracy in predicting nonodisabled outcome at discharge. Conclusions: A novel scale assessing tissue reperfusion on completion angiogram is strongly predictive of treatment response. The Cerebral Blush Grade is a promising instrument for assessing outcomes of endovascular reperfusion therapies for acute brain ischemia.

**Baseline Hyperemia and the Biphasic Response of Cerebral Blood Volume Promote Early Dramatic Improvement After Mechanical Thrombectomy**

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Background: Early dramatic improvement (EDI) after recanalization may be influenced by baseline perfusion status, whereas later recovery may be multifactorial. Prior imaging predictive models have focused on extent of advanced ischemia, suggesting that peripheral areas with elevated cerebral blood volume (CBV) or hyperemia are unrelated regions of “benign oligemia”. Due to the unusual biphasic nature of CBV, unlike other perfusion parameters, with marked increases and subsequent decreases in evolving ischemia, hyperemia may hasten recovery following prompt recanalization. We tested this hypothesis by analyzing the impact of baseline hyperemia with perfusion CBV and MTT in mechanical thrombectomy. We retrospectively reviewed clinical, imaging, and angiographic data in a consecutive series of mechanical thrombectomy for acute MCA stroke cases at a single center. Baseline perfusion MRI was used to calculate volumes and percentages of relative CBV (rCBV) categories defined as ischemic core, penumbral, normal, or hyperemic. 4 previously published definitions of dramatic recovery were used, including 2 with EDI. Univariate correlations were conducted followed by multivariate logistic regression. Results: 53 cases (28 men, 25 women; mean age 64.8 ± 20.0 years) were analyzed. EDI was defined by drop in NIHSS score ≥10 at 24 hrs occurred in 5/53 (9.4%), only 2/53 (3.9%) had NIHSS score ≤3 at 24 hrs, 11/53 (20.8%) with NIHSS drop ≥10 at discharge/day 7, and 7/53 (13.2%) with NIHSS score <3 at discharge/day 7. EDI at 24 hrs was associated with higher TICI angiographic reperfusion and more extensive hyperemia defined by baseline rCBV. Extent of advanced ischemia and penumbra on CBV or diffusion-weighted imaging (DWI) lesions at baseline did not predict EDI at 24 hours. Discharge/day 7 dramatic recovery was less influenced by TICI and hyperemia, whereas extensive baseline ischemia on rCBV or DWI and baseline NIHSS were influential. Multivariate models for EDI at 24 hrs were limited by power and no predictors were noted for later dramatic recovery. Conclusions: EDI at 24 hrs may result from extensive hyperemia at baseline and reperfusion within the MCA territory. Later dramatic recovery may be multifactorial. Unlike other imaging parameters, the biphasic nature of rCBV may denote not just advanced ischemia, but also peripheral areas of hyperemia with less downstream resistance that allows prompt recovery.
The VCI defined with Korean-VCIHS protocols is common at 3 months after ischemic stroke in small vessel disease (SVD, P = 0.004) were independently associated with VCI. Prevalence of VCI at 3 months was 68.9%: VCI no dementia in 48.9% and vascular dementia in 20.0%. The older age (P = 0.029), and ischemia (P = 0.004) were independently associated with VCI. Prevalence of VCI at 3 months was 68.9%: VCI no dementia in 48.9% and vascular dementia in 20.0%. The older age (P = 0.029), and ischemia (P = 0.004) were independently associated with VCI.

Conclusion: To define the current range of therapeutic antishivering approaches and to critically evaluate the published evidence regarding treatment effectiveness. Background Both antihypothermia cooling and maintenance of euthemia is increasingly utilized in a variety of clinical settings such as cardiac arrest, ischemic stroke, or head trauma. Despite significant improvements in our ability to quickly achieve and accurately maintain a desired core temperature there are conflicting reports regarding antishivering-induced shivering. Methods: We systematically reviewed, categorized, and analyzed all published English literature on antishivering therapies. Next, after selecting only randomized controlled trials (RCT), we performed a metaanalysis comparing the treatment efficacy of both medications and devices. Target key words (shivering, treatment, prophylaxis, pharmacological and physical intervention) and study types (clinical trial, RCT; comparative study) were determined and relevant scientific databases (PubMed, Medline, Cochran) were systematically searched. Results: In English prior to June 2009 reviewed employing the criteria: pharmacological and/or physical intervention regimens. The specific subjects were undergoing operation, received other medical treatments, underwent anesthesia, or were ventilated. We excluded studies focusing on subjects with drug-induced shivering, cognitive based interventions, shivering observed as a study-unrelated observation, and <10 study subjects. All interventions were categorized and compared. We selected the group with clinical and statistical homogeneity and with identified antishivering potential. Among all studies, 28 trials included 1549 subjects (n 25). A total of 16 antishivering protocols were identified and subjected to linear comparison. Among all study drugs, the 6 antishivering drugs and frequencies were calculated by axes with 95% confidence intervals. Results: A total of 1543 antishivering interventions were reported in 94 publications summarizing the experience of 154 studies testing a total of 5202 subjects. Among those 154 studies, 50 RCTs with quantitative and qualitative analysis of antishivering efficacy were identified and subjected to linear comparison. Among all study drugs, the 6 antishivering drugs and frequencies were calculated by axes with 95% confidence intervals. Results: A total of 1543 antishivering interventions were reported in 94 publications summarizing the experience of 154 studies testing a total of 5202 subjects. Among those 154 studies, 50 RCTs with quantitative and qualitative analysis of antishivering efficacy were identified and subjected to linear comparison.

Background and objective: In 2006, the National Institute of Neurological Disorders and Stroke and Canadian Stroke Network proposed Vascular Cognitive Impairment Harmonization Standards (VCISHS), which could be used in evaluating cognitive functions in stroke patients. However, there has been no prospective, multicenter study to apply this tool to the post-stroke survivors in a large scale. The objectives of our study were to determine the prevalence of vascular cognitive impairment (VCI) using Korean-VCIHS (K-VCISHS) protocols, and to investigate the value of Korean-VCIHS NP protocols for delineating cognitive dysfunction after stroke in a prospective cohort in Korea. Method: From October 2007 to August 2008, we enrolled prospectively 620 subjects who were randomly selected patients with ischemic stroke within 7 days after symptom onset among the consecutively admitted to 12 hospitals over the nation in Korea. The demographic factors, clinical characteristics including stroke subtypes, and functional status were evaluated at baseline and 3 months after stroke. The neuropsychological assessments with the 60-minute Korean-VCHS protocols were administered at 3 months after stroke. Results: A total of 353 patients from 620 were enrolled with the 60-minute Korean-VCISHS NP protocols at 3 months after stroke. The prevalence of VCI at 3 months was 68.9%. VCI no dementia in 48.9% and vascular dementia in 20.0%. The older age (P = 0.014), p < 0.029, and small vessel disease (SVD, P = 0.004) were independently associated with VCI. Conclusions: The VCI defined with Korean-VCIHS protocols is common at 3 months after ischemic stroke. Korean and Japanese VCHS might be feasible for evaluating cognitive burdens in post-stroke survivors.

Lesion Patterns and Stroke Mechanism in Middle Cerebral Artery Branch Atherosclerosis

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Background and purpose: Mechanism of ischemic stroke in patients with middle cerebral artery (MCA) branch steno-occlusion is known more frequently as cardioembolism (CE). However, intracranial atherosclerosis, which is common in Asians, is as one of main causes of MCA branch steno-occlusion. When MCA branch occlusion is observed at the acute stage of stroke, it would be difficult to differentiate atherosclerotic from embolic occlusion. The aim of the present study was to differentiate the ischemic lesion patterns of atherosclerotic MCA branch disease from CE using diffusion-weighted imaging (DWI). Methods: We reviewed 129 acute ischemic stroke patients between May 2004 and July 2009, who had ischemic lesions in the unilateral MCA territory on DWI performed within 48 hours of symptom onset, and 26 patients (19.8%) of those 129 patients were confirmed to have CE (n = 6) and (2) no evaluable for proximal ICA (n = 24), or (3) stroke subtypes other than intrinsic MCA branch disease or CE (n = 28). Acute DWI lesion patterns were classified into 1 of the following 10 patterns as (1) single large artery infarct (PAI), (2) global ischemic (PI), (3) large territory, border-zone (BZ) and (2) multiple (PAI + PI + PAI + BZ + PAI + BZ + PAI + PI + BZ, mult B2, mult B2). MCA branch disease was defined as stenosis (signal reduction >50%) or occlusion of portions after MCA bifurcation or trifurcation near the Sylvian fissure. The stroke subtypes were determined by the TOAST classification. We evaluated the association of each DWI lesion pattern with the stroke subtype using the Fisher exact test. Results: Of the 71 patients, 50 (70.4%) exhibited occlusion and 21, 26.8% and 3.0% of patients, respectively. The DWI lesions were observed in 37 patients (51.2%). Concomitant PI and BZ (22 of 71, 31%) was most common lesion pattern, followed by large territory lesion (19 of 71, 26.8%). CE was observed in 39 (54.9%) and large-artery atherosclerosis (LAA) in 32 (45.1%). Among 10 DWI lesion patterns, concomitant PI and BZ was associated with LAA compared with other patterns (81.8% vs. 21.4% (14/69), p = 0.01). Patients with a large territory lesion were more likely to have CE (84.2% (16/19)) vs. 44.3% (23/52); p = 0.003). CE lesion with or without other lesion patterns was found in 26 patients. Among these patients, 23 (88%) had internal BZ lesions. Conclusions: Our results show that acute ischemic lesion pattern was significantly associated with specific stroke subtypes in patients with MCA branch steno-occlusion. PI with additional BZ was the lesion pattern specific for LAA, while large territory lesion had association with CE. It suggests that embolism may be a common stroke mechanism of ischemia in MCA branch disease, and identifying ischemia lesion pattern may be helpful in discriminating intracerebral and cardioembolic MCA branch occlusion.

Effect of Dedicated Vascular Neurologist on Door to Needle Time in Community Hospital

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Background and Purpose: Excellent clinical outcome depends on safely reducing the time to thrombolytic treatment. Academic centers have demonstrated the benefit of a stroke service on acute thrombolytic treatment parameters. We sought to determine whether a significant difference exists in door to needle time and outcomes between vascular neurology and general neurology thrombolytic administrations in a community hospital. Methods: Retrospective review of consecutive IV I.PA treated patients over a 13 month period at Medical City Dallas Hospital. Results were conducted to determine door to needle interval and outcome. Mean door to needle time was compared between dedicated vascular neurological and general neurological treatments using unpaired t-test. Additionally, mean door to needle time was analyzed based upon time of patient presentation (weekend versus weekday/weekend). Favorable clinical outcome was defined as mRS ≤ 2 at discharge. Results: Forty patients treated with IV I.PA were identified, representing 16% of all ischemic stroke patients hospitalized from June 2008 through July 2009. The mean door to needle time for the entire population was 61.1 ± 29 min (median 53.5 min). IV I.PA treatments were equally distributed between vascular neurological treatments (n = 20) and general neurological treatments (n = 20). Mean door to needle interval was significantly shorter for vascular neurological treatments compared to general neurological treatments (42.8 ± 14.9 min vs 79.2 ± 28.7 min, p = 0.0001). Time of patient presentation did not significantly affect the door to needle interval within each group individually (see table). Favorable outcome was achieved more frequently in patients treated by vascular neurological than general neurological (69% vs 12%, p = 0.05). Mortality was lower in vascular neurological treated patients (5% vs 20%, p < 0.05). No significant difference was seen in symptomatic hemorrhage rate was identified between treating groups (0% vs 5%, NS). Conclusions: Excellent IV I.PA treatment rates may be accomplished in community hospital setting by both vascular and general neurologists in collaboration with emergency physicians. However, a dedicated vascular neurological service in a community hospital may significantly reduce door to needle interval, improve patient outcomes and reduce patient mortality.
Modulation of Autophagy Attenuates Ischemic Brain Injury

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Background: Under stress conditions, autophagy protects cell survival by delivering damaged proteins and organelles to the lysosomes, recycling intracellular nutrients and energizes the cell. Excessive autophagy, however, can lead to cell death, including apoptotic and autophagic cell death. During stroke, it is unclear whether autophagy promotes survival or death of brain cells. We hypothesized that increased autophagy after stroke is “protective” and that inducing autophagy by pharmacological agents would reduce infarct size. During stroke. Methods: We induced ischemia in 37 C57BL/6 J mice using a permanent MCA ligation model, with sacrifice 48 hours after stroke. Mice were treated i.p. with chloroquine, an autophagy inhibitor; rapamycin, an autophagy activator via inhibition of mTOR; or left untreated. The autophagy markers LC3 (microtubule associated protein light chain 3) and p62 were analyzed by Western blot and immunohistochemistry. Autophagy was also examined by EM, and infarct size was measured by TTC staining. Results: LC3 is decreased in the infarct side, suggesting turnover of LC3 by the fusion of autophagosomes and lysosomes. P62 increased, despite turnover, possibly due to the formation of protein aggregates. Chloroquine increased LC3 by preventing its turnover and had no significant change on p62 levels. Rapamycin led to increased LC3 and p62, consistent with increased induction of autophagy. EM confirmed autophagy on the infarct side. Chloroquine at 60 mg/kg reduced lesion size by 60.3%, and rapamycin reduced lesion size, in a dose-dependent manner, 17.0% at 4 mg/kg and 71.5% at 10 mg/kg (all TTC groups: n = 5). The reduction in lesion size for chloroquine and the 10 mg/kg rapamycin was statistically significant (Kruskal-Wallis One Way ANOVA p = 0.016). Conclusions: 1) Stroke induces autophagy. Since chloroquine and rapamycin both prolonged survival in mice, 2) cross-talk between autophagy and other programmed cell death pathways and/or direct effects of the drugs on such pathways. 3) Modulation of autophagy may offer a new therapeutic avenue for stroke.

Cerebral Antigens Are Present in Secondary Lymphoid Organs of Acute Stroke Patients

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Objectives: Immune response might play a role in stroke pathophysiology. Acute stroke causes important immunological changes in both peripheral blood cells and secondary lymphoid organs(SLO), and cerebral antigens have been identified in SLO in experimental models of stroke. We sought to determine cerebral antigens are able to reach SLO in stroke patients and the pattern of immune response in SLO. Methods: We performed biopsy of palatine tonsil in 18 patients during the first 7 days of stroke and in 9 controls subjects (6 OSA syndrome, 3 healthy voluntaries). Tonsilar samples were minced and cells were suspended in RPMI for flow cytometry analyses. Another part of the tonsillar tissue was frozen OCT at −80 °C to analyze myelin basic protein (MBP),mi- tochondial associated protein (MAP-2) and CD34 (marker of myeloid dendritic cell). We used a manual and a semiautomated immunofluorescence threshold method to count labeled cells. Results: In control patients and in those with acute stroke we found an increased in MAP-2 positive cells (27.5 ± 5.2% vs 10.5 ± 4.0; t-student p = 0.027) and MBP positive cells (3.2 ± 0.8 vs 1.4 ± 0.4; t-student p = 0.058) compared to controls. The differences were significant for MBP when we used the semiautomatic method (12.64 ± 0.03 vs 0.01; t-student t = 0.033); MBP positive cells were also labeled for CD34-1% of co-stimulatory molecules CD40 and CD68 was reduced compared to controls, specially in the first 48 hours. CD68 expression was inversely related to stroke severity(Pearson, r = −0.732, p = 0.001). We observed predominance on T cell apoptosis during the first 3 days after stroke, with a relative increase in the proportion of B cells and a progressive increase in the T-helper cells in the day 2 and 3. Conclusions: In patients with stroke, cerebral antigens reach SLO and these antigens can be presented in antigen presenting cells. However, the significance of this observation must be interpreted in the context of the overall pattern of immunological changes in SLO, which reflect a complex immune response. Further studies are needed to determine the impact of these findings on the clinical course of stroke.

Changes in Inflammatory Biomarkers and Neurological Deterioration in Patients With Acute Brain Infarction

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Background: Recent studies have shown that significant changes in inflammatory biomarkers occur soon after stroke onset and may relate to stroke outcome. We aim to investigate the association between plasma levels of inflammatory biomarkers and clinical course of acute ischemic stroke. Subjects and Methods: A total of 232 patients admitted within 24 hours after ischemic stroke onset were prospectively enrolled from Jan 2006 to Jul 2009. On admission, routine blood chemistry, blood cell count, PT, APTT, d-dimer, fibrinogen, and CRP were measured. Hematocrit was corrected to 0.9 Applying the 10-matrix metalloproteinase-2 (MMP-2), MMP-9, and tumor necrosis factor-α (TNF-α) were determined by enzyme-linked immunosorbent assay (ELISA) in blood samples obtained on admission, Day-3, Day-7, and Day-14. Stroke subtype was determined according to the TOAST classification. Neurological deficits were serially evaluated by NIH Stroke Scale (NIHSS). Clinical progression was defined when the NIHSS score increased at least 1 point during the first 72 hours after admission. Logistic regression analysis was used to determine significant association between inflammatory biomarkers and clinical progression by adjusting age, sex, initial NIHSS score, and co-morbidities. Results: Clinical progression was demonstrated in 55 patients (23.7%). Mean value of plasma level of IL-10 on admission in these patients was significantly lower than that in patients without progression (7.59 ± 8.99 pg/ml vs. 14.60 ± 27.01 pg/ml, P < 0.005) especially in patients whose stroke subtype was small- vessel occlusion (6.48 ± 5.42 pg/ml vs. 15.00 ± 19.64 pg/ml, P < 0.05). Logistic regression analysis demonstrated that major cerebral hemorrhage (OR 1.35 - 5.09), branch atherosclerotic disease (RA) type infarction (OR 2.45, 95%CI 1.12 - 5.33), plasma level of IL-10 on admission (OR 0.97, 95%CI 0.94 - 1.00) were significantly associated with early progression. In patients whose infarct lesion involved cerebral cortex, MMP-2 and IL-6 concentrations from Day-1 to Day-14 were significantly higher than those in patients without cortical involvement. Conclusions: Plasma level of IL-10 on admission was significantly associated with clinical deterioration especially in patients whose stroke subtype was small-vessel occlusion. Increased levels of MMP-2 and IL-6 may be related to distribution of infarction lesion and severity of the initial stroke insult.
for the presence of BBB disruption seen as hypointensity of CSF in the subarachnoid, intrasulcal space on delayed, post-gadolinium FLAIR images. Results: In 73 patients treated with alteplase, 30 (41%) had BBB disruption within the symptomatic MCA territory and 17 (23%) had BBB disruption within the contralateral hemisphere (vertical arrows in FIGURE). The two patterns of contralateral enhancement were punctate and diffuse. The latter pattern showed a generalized enhancement of the ipsilateral and, to varying degrees, contralateral intrasulcal space. Two patients with contralateral enhancement had PH, one of which was contralateral to the index stroke. Conclusion: Our results confirm that remote BBB disruption occurs contralateral to alteplase-treated strokes in a substantial proportion of patients. Prospective studies are needed to investigate whether remote PH occurs at remote sites of BBB disruption, and the role of other factors, such as age, hypertension, diabetes, prior lesions, in the vulnerability of remote regions. We speculate that alteplase or molecules expressed from the evolving, alteplase-treated infarct into the systemic circulation (e.g., matrix metalloproteases) may open the BBB at remote, vulnerable brain locations.

Introduction: Human studies of redox status following stroke have previously suffered from an inability to measure brain antioxidant levels in vivo. We report our initial experience of using magnetic resonance spectroscopy (MRS) to measure reduced glutathione (γ-L-glutamyl-L-cysteinylglycine; GSH) in stroke patients. Methods: Inclusion criteria were 1) Patients who were scanned within 1 week of ischemic stroke in the carotid territory, 2) no old stroke underlying the MRS voxel and 3) no hemorrhagic transformation of a ‘parenchymal hematoma’ type. GSH measurements were made using a single voxel MRS technique previously published by our group. A voxel (5 × 3 × 3 cm³) was manually placed over the stroke lesion followed by placement of a second voxel in the ‘mirror’ region of the contralateral hemisphere. GSH was quantified as a positive peak at 2.95 parts per million on the metabolite spectrum. Metabolite concentrations were expressed as ratios (ipsilateral / contralateral hemisphere). Cases were divided into 2 cohorts; those with hemorrhagic transformation (HT) of ‘hemorrhagic infarction’ type and those without. Results: Fifteen patients (8 male) were identified. Mean age was 67yrs (+/- 14) and median admission NIHSS was 13 (IQR 6-19). Median time from ‘last seen well’ to scanning was 41h (IQR 29-108h) and median DWI lesion volume was 49ml (IQR 40-131ml). In those without HT (n=8) GSH was significantly elevated in the stroke lesion compared to the contralateral hemisphere (mean GSH ratio = 1.18, 95% CI = 1.02-1.33, p=0.032 [1 sample t-test]). As expected we observed an elevation of lactate (p<0.005, 1 sample t-test) and reduction of choline (p=0.02, 1 sample t-test). No such differences were observed with respect to creatine (p=0.53, 1 sample t-test) or creatinine (p=0.15, 1 sample t-test). In those with HT (n=7) there was no net GSH elevation (mean GSH ratio = 0.86, 95% CI = 0.56-1.17, p=0.36 [1 sample t-test]). In this cohort there was elevation of lactate (p=0.03, 1 sample t-test) and reduction of N-acetyl-aspartate (NAA) in the lesion (p=0.011, 1 sample t-test). No such differences were observed with respect to choline (p=0.011, 1 sample t-test) or creatine (p=0.04, 1 sample t-test) and NAA (p=0.001, 1 sample t-test). There was a non-significant trend towards lower GSH ratio in those with HT compared to those without (p=0.06, 2 sample t-test). Conclusions: Our results demonstrate that GSH appears elevated in ischemic lesions without HT within the first week after stroke and the possibility that GSH is reduced in HT, consistent with a state of greater oxidative stress. We have demonstrated the feasibility of measuring alterations of GSH levels directly in the brains of stroke patients. Such measurements have the potential to assess changes in brain redox state in response to reperfusion or neuroprotective stroke therapies.

Sleep disruption after ischemic stroke is a common complaint. The sleep EEG is disrupted in humans after stroke, but, since sleep abnormalities are also risk factors for stroke, the precise relationships between stroke, sleep disruption, and functional recovery still require clarification. To facilitate translational studies of stroke and sleep, we characterized sleep in rats exposed to experimental stroke. We hypothesized that experimental stroke in rats suppresses sleep and can be precisely quantified. We performed EEG, EMG, and activity monitoring on freely moving animals by telemetry. Baseline measurements were taken for at least three days prior to stroke. Rats were then exposed to either filament-mediated transient MCA occlusion for 90 minutes or to sham surgery without MCA occlusion. Physiological measurements were continued for three days after stroke or sham surgery. The EEG, EMG, and activity data were combined to provide long-term sleep records for all animals, and the amounts of total sleep, NREM sleep, and REM sleep were calculated for each animal before and after stroke. Sleep times after stroke were normalized to baseline measurements before stroke. Total and NREM sleep were not affected by stroke. However, REM sleep was markedly inhibited (by >60%; p<0.05). Delta power was not changed by stroke. Sham surgery did not affect the amount of sleep, in accordance that stroke in rats selectively impairs REM sleep. Continuing filamentary stroke monitoring of rats after stroke will be useful to study the effects of REM suppression on stroke recovery and to investigate therapeutics which could improve sleep after ischemic brain injury.

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Pilot Results of in vivo Brain Glutathione Measurements in Stroke Patients Using Magnetic Resonance Spectroscopy

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Introduction: Magnetic resonance spectroscopy (MRS) has been an important tool for in vivo brain metabolism and pathology studies. The recent development of ultrashort echo time (UTE) and in situ zymography as well as casein zymography were employed to measure tPA level and activity, respectively. These data show: 1) No tPA activity is detectable in tPA−/− mice; 2) BMSC treatment significantly increases tPA protein level in WT-mice; and 3) BMSCs markedly enhance the plasmin activity in WT-mice, but show no effect in tPA−/− mice. In vitro primary neuronal culture confirms the role of tPA in facilitating neurite outgrowth; adding tPA into cortical neuron culture substantially and significantly enhances neurite outgrowth, and this effect can be significantly attenuated by neutralizing antibody against tPA. Our results suggest that endogenous tPA is essential for axonal regeneration; BMSC exerts its functional benefit in ischemic brain through elevating endogenous tPA and thereby facilitating axonal regeneration. Although further study is warranted to elucidate the mechanisms underlying tPA’s effects on neuronal remodeling, our previous data suggest that proteolytic cleavage and activation of neuronal trophic factors may play a role in this restorative process.

P525 Matrix Metalloproteinase Inhibition Reduces the Injury Caused by Ischemia/Reperfusion Injury but Not the Injury Caused by Permanent Focal Ischemia

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Inhibition of matrix metalloproteinases (MMP) has been heralded as a potential therapeutic target for acute ischemic stroke. The mechanism for this protection would be the prevention of blood brain barrier (BBB) breakdown. Another potential therapeutic target exists in the prevention of hypertensive cerebral vessel remodeling. Hypertensive rats have larger cerebral infarcts when ischemia is induced by middle cerebral artery (MCA) occlusion than normotensive rats. This is partly due to the reduction in cerebral vessel lumen diameter caused by hypertensive remodeling. We have shown that doxycycline (doxy), a nonspecific MMP inhibitor, causes a 15% increase in MCA lumen diameter in stroke prone spontaneously hypertensive rats.
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There was no difference in blood flow immediately post-ischemia between the doxy treated and control rats (29.1 ± 2.2 vs 31.8 ± 3.3 %\(\mathrm{H} \downarrow\), doxy vs control). Doxy treatment also had no effect on the damage cause by permanent ischemia (57.4 ± 3.7 vs 57.8 ± 4.2 %\(\mathrm{H} \downarrow\), doxy vs control). Doxy treatment did not change the damage caused by ischemia with reperfusion (20.7 ± 3.8 vs 45.5 ± 4.7 %\(\mathrm{H} \downarrow\), doxy vs control; p < 0.01). Blood flow to the ischemic hemisphere was measured immediately post-ischemia and prior to euthanasia. Blood flow was expressed as a percentage of flow in the contralateral hemisphere (%\(\mathrm{H} \downarrow\)). There was no difference in blood flow immediately post-ischemia between the doxy treated and control rats (29.1 ± 2.2 vs 31.8 ± 3.3 %\(\mathrm{H} \downarrow\), doxy vs control). These studies suggest that MMP inhibition may improve cerebral blood flow after ischemia reperfusion injury. If this is due to the increased cerebral vessel lumen diameter or to inhibition of BBB breakdown remains to be tested.

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Age-dependent Effects of Acute Unilateral Stroke on Working Memory

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Background: In normal young adults, spatial working memory (WM) is associated predominately with the right hemisphere, while verbal WM is generally associated with the left hemisphere. Imaging studies suggest that activity for both tasks becomes more bilateral in healthy older adults (Reuter-Lorenz et al., 2000). The mosaic of WM deficits reported in older adults may be related to the right hemisphere (RH) dominance of the to-be-remembered information. Older adults are more likely to have lesions primarily affecting the RH, while younger adults are more likely to have damage to the left hemisphere. Our objective was to examine the effects of stroke side and location on WM performance in stroke patients. This allows us to simultaneously test the imaging hypothesis of age-related bi-lateralization with lesion data, as well as illustrate the differential effects of stroke depending on patient age. Methods: Young (age < 9) and old (age >90, n = 22) acute unilateral (left or right hemisphere) stroke patients performed spatial and verbal item-recognition (WM) tasks within three days of symptom-onset. Stroke was defined as acute infarct on diffusion weighted imaging and/or hyperperfusion on perfusion weighted imaging with corresponding neurological deficits. Young (n = 9) and old (n = 18) transient ischemic attack patients (TIA- resolution of symptoms in 24 hours, exclusion of stroke on MRI) were enrolled as a control for brain vasculopath changes and hospitalization-associated stressors and medications. WM tasks were subject-paced (variable encoding, retrieval time) at variable loads with a fixed delay of 5000 msec. Performance was measured in terms of encoding time, response time, accuracy, and a pooled score. The frequency of deficits (defined as a standard deviation from the mean of age-matched non-patient group) in each measurement was compared between groups using Fisher’s exact tests. Results: For verbal WM, young left stroke patients had significantly more deficits than young TIA for accuracy (p < 0.05) and showed a trend for the pooled measure (p = 0.09). There were no differences between young right stroke and young TIA groups. Both left and right old stroke patients had significantly more deficits in response time (p < .05, p < .03). Only old right stroke patients had significantly more deficits in the pooled score (p < .01). Effects on spatial WM were only seen at the low load, where old right stroke patients tended to have more deficits in response time than control (p < .09) and young right stroke patients had more deficits in accuracy (p < .01). Conclusions: Stroke location had differential effects on WM depending on age and the type of to-be-remembered information. For both young and old stroke patients, stroke in the right or left hemisphere disrupted spatial and verbal WM performance respectively. In addition, older stroke patients had more disrupted verbal working memory performance in RH adults and not in younger adults. This is important to consider when testing for cognitive deficits in these different stroke populations.

Safety of Repetitive Transcranial Magnetic Stimulation of the Unaffected Hemisphere in Subacute Stroke Patients

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Objective: To preliminarily evaluate safety of repetitive transcranial stimulation (rTMS) of the unaffected hemisphere (UH) in patients with ischemic stroke in a cerebral hemisphere within 5 to 45 days after stroke. Methods: Fifteen patients with unilateral infarcts in a cerebral hemisphere were included in the study (nine men). Patients underwent daily sessions of active (n = 16) or sham (n = 7) rTMS sessions (2 Hz, 1mA/m²/cm²) delivered during waking hours. rTMS intensity of 90% of the resting motor threshold of the unaffected abductor pollicis brevis muscles, for 25 minutes). Mean age (± standard error) in the active rTMS group was 56.7 ± 7.9 years and in the sham group, 59.1 ± 5.3 years. In the active rTMS group, interventions were started, on average, 25 ± 3.9 days after stroke and in the control group, 27 ± 4.4 days. Patients were instructed to spontaneously report any symptoms and answered a questionnaire after each stimulation session. Results: Two patients in the active group and three patients in the sham group reported headache and neck pain during rTMS sessions (p = 0.03). Only one patient in the active group and seven in the sham group reported sleepiness during the procedure. There were no seizures or other adverse events. Conclusions: Adverse events were mild and were more frequent in the shamed than in the active group. These preliminary results suggest that repeated sessions of rTMS of the UH was safe in the subacute phase after stroke.

National Declines in Ischemic Stroke Hospitalizations by Hospital Referral Region: 1998-2007

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Background: There has been a decline in stroke-related mortality in the United States over the past decade, but little is known about whether there have been similar decreases in stroke hospitalization rates. In the absence of available national data on stroke incidence and recurrence, stroke hospitalization rates can provide estimates that reflect the rates of new and recurrent strokes. Purpose: To examine national patterns of stroke hospitalization in the elderly by hospital referral region (HRR) from 1998-2007 to determine if there are disparities across the country. Methods: Annual rates of ischemic stroke hospitalizations (ICD-9 primary discharge codes 433, 434, 436) were determined from Medicare fee-for-service patients ≥65 years with ischemic stroke in hospitals within each of the 306 HRRs from 1998-2007 (total number of hospitalizations per year in 1998 divided by the HRR-specific person-years, accounting for death and cross-registration in coverage). National maps were created to show HRR-specific rates by quartile for each year. Cross-sectional and longitudinal risk-adjusted (age, race, and sex) hierarchical linear regression models were used to assess the annual change in hospitalization rates across HRRs and over time. Results: National ischemic stroke hospitalization rates decreased steadily across the country over the 10-year period (1,393 per 100,000 person-years in 1998 to 1,020 per 100,000 person-years in 2007). Rates, however, varied by HRR within each year with the highest hospitalization rates occurring in the southeast (i.e., within the ‘stroke belt’), and the lowest rates in the west and in parts of New England. Average rates of decline over this period were largely uniform across the country, with only a few regions showing significantly larger rates of decline over this time period. Conclusions: National hospitalization rates for ischemic stroke in the elderly decreased across HRRs from 1998-2007. The stroke belt region had the highest annual rates whereas western states and parts of New England had the lowest. Future research should investigate, in stroke hospitalization may help identify variations in primary prevention and clinical practice to target community-based interventions.
The Use and Timing of Care Limiting Orders Predict Stroke Mortality: An Explanation of Oregon’s High Stroke Mortality Rate?

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Introduction: Oregon has the fifth highest stroke mortality in the United States which does not appear to reflect risk factor prevalence as Oregon’s cardiac mortality is forty-sixth nationally. The completion of care limiting documents (CLD) such as Do Not Resuscitate (DNR) and Comfort Care orders in hemorrhagic stroke strongly correlate with increased in-hospital stroke mortality. Oregon was the first U.S. state (1997) to enact a “Death with Dignity Act,” perhaps reflecting a more aggressive practice of limiting care around severely debilitating illnesses such as stroke. Hypothesis: If care limiting documents are completed prior to but more specifically during hospitalization for all stroke subtypes, then the risk of mortality is significantly increased.

Methods: Data from six Oregon hospitals—three urban and three rural—were collected by retrospective chart abstraction from 2004-2009 for 3887 stroke admissions using the Get With The Guidelines stroke database. We created three multivariate logistic regression models based on this cohort in which hospital mortality was the dependent variable, and age group, gender, stroke severity, and stroke subtype were covariates in each model. The independent variable in the first model was “care limiting document present on arrival.” In the second model the independent variable was, “care limiting document written during the encounter.” In the third model both variables were entered into the model. Results: For all admissions in this study, mortality was 8.9% (385); 22.1% (855) of patients had CLD on admission and 40.3% (1559) had CLD written after admission. CLD on admission were associated with a mortality odds ratio (OR) = 1.80 (95% CI: 1.40-2.33). CLD written after admission were associated with much higher in-hospital mortality, OR = 29.90 (95% CI: 17.93-49.86). In the third model, in which both variables were entered, only CLD written after admission were a significant predictor of mortality; OR = 29.13 (95% CI: 17.43-48.68). Conclusion: Our study confirms the previous observation that care limiting documents (CLD) for stroke inpatients are associated with increased in-hospital mortality. Our analysis included a larger group of patients with more diverse stroke subtypes than has previously been reported. We believe we are the first to report that the timing of CLD orders for all stroke subtypes, including ischemic stroke, determines the risk of stroke mortality: CLD written during a stroke admission overwhelms the significance of a CLD present on admission. The rate of CLD completion on stroke inpatients in this study appears higher than in previous reports suggesting a link to Oregon’s high stroke mortality.

Is Access to Care Associated With Mortality in US Stroke Survivors?

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Background: We have shown that many US stroke survivors have reduced access to health care. Although myocardial infarction survivors with reduced access to care have worse health outcomes, little is known regarding the relationship between health care access and mortality among stroke survivors with or without neurological disability. We examined the association of health care access and mortality among stroke survivors with or without neurological disability. We examined the association between access measures and time to death after adjusting for age, sex, race/ethnicity, region, living with spouse/partner, education, health status, diabetes mellitus, hypertension, coronary heart disease, chronic kidney disease, emphysema, heart condition/disease, cigarette smoking, body mass index, serious mental illness, alcohol use, history of cancer, and survey year in models stratified by neurological disability. Results: Disabled stroke survivors (n=986, mean age 69.7 years) were more likely than non-disabled stroke survivors (n=1888, mean age 69.0 years) to be non-Hispanic black (19% vs. 11%; P<0.001), have income <$32,000 (50% vs. 44%; P<0.001) and ‘high school education (44% vs. 37%; P=0.006). Compared to non-disabled stroke survivors, disabled stroke survivors more frequently reported low health status (46% vs. 63%; P<0.001), diabetes (23% vs. 27%; P=0.03), chronic kidney disease (8% vs. 11%; P=0.03), and serious mental illness (8% vs. 11%; P=0.03). No general doctor visit was less common among disabled stroke survivors (9% vs. 13%; P=0.01), but no medical specialist visit (45%); inability to afford medications (8%), and no health insurance (4%) had similar prevalence in both groups. Among disabled stroke survivors, no general doctor visit (HR, 1.73; 95%CI, 1.03–2.85) was independently associated with increased risk of death after adjustment. This association persisted after further adjustment for stroke timing. No other access measures were associated with risk of death for disabled or non-disabled stroke survivors. Conclusion: Among disabled stroke survivors, reduced access to general physician care was associated with increased risk of death. Improved access to primary care may increase survival for disabled stroke survivors.

PS30

Premature Risk of Stroke in Recent Immigrants (PRESARIO): Population-based Matched Cohort Study

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Background: Immigrants play an essential role in the new economy, social development, and the arts. About 75% of all immigrants are found within just 12% per cent of all countries, Canada being one of them. New immigrants to North America, most of whom are under age 50 years, exhibit fewer risk factors for cardiovascular disease than their native-born counterparts, yet the stress of resettlement may conceivably place them at higher risk of stroke. Objective: We aim to determine the risk of acute stroke associated with recency of immigration. Hypothesis: We assessed the hypothesis that new immigrants have a lower incidence risk of stroke. Methods: We completed a population-based matched cohort study in Ontario, the largest province in Canada, from April 1, 1995 to March 31, 2007. Overall, 965 829 new immigrants were matched to 3 272 393 long-term residents by year of birth, sex, and location. New immigrants were identified as new recipients of universally available public health insurance, and long-term residents were those insured for 5 years or longer. The main study outcome was hospitalization with a most responsible diagnosis of acute stroke determined through the International Classification of Diseases Ninth (ICD-9) and Tenth (ICD-10) Revisions. A premature stroke was defined as that arising before age 65 years. Results: The mean age of the participants at study entry was about 34 years. Overall, there were 6216 strokes during the study period with a median duration of follow-up of about six years. The incidence rate of acute stroke was 1.69 per 1000 person-years among new immigrants and 2.56 per 1000 person-years among long-term residents (crude hazard ratio [HR] 0.65; 95%CI 0.62-0.71) (Figure). After adjusting for age, income quintile, urban vs. rural residence, history of hypertension, diabetes mellitus and smoking, and number of health insurance claims, the HR for stroke was 0.69 (95% CI 0.64-0.74). Similar risk estimates were seen for both ischemic and hemorrhagic stroke sub-types. Conclusion: New immigrants appear to be at lower risk of premature acute stroke than long-term residents. This finding does not appear to be explained by the availability of health care services or income level. Figure 1. Risk of premature acute stroke comparing 965 829 new immigrants and 3 272 393 long-term residents in Ontario.
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Off Hours Admission for Acute Stroke is Not Associated With Worse Outcome: A Nationwide Israeli Survey
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Background & Purpose: Several studies have shown a worse outcome for stroke patients arriving on weekends, as compared to weekdays. Our aim was to examine if this effect is applicable to Israeli, a small country with relatively easy access to hospital facilities throughout the year. For the analysis we compared working hours to off hours throughout the week as shortage of experienced staff is similar and special services are not in use routinely throughout these hours. Methods: An Israeli nationwide survey on acute stroke admissions (ischemic stroke and intracerebral hemorrhage; ICH) was carried out in all acute care hospitals within 2 successive months during IV (February & March 2007 and April). The project was organized by a coordinator center well in advance and was approved by the ethic’s committee of each hospital. Data were collected through a custom structured questionnaire by an experienced neurologist. “On hours” were defined as the regular working hours in the county: 8-16 Sunday to Thursday and 8-13 on Friday. All other hours, including holidays were defined as “off hours”. Patients with missing data on time of arrival (n=19) were excluded. Results: A total of 3446 acute strokes patients were included (1849 during on hours and 1597 during off hours). “Off hours” patients were a year younger (median 72 vs. 73 yrs, in “on hours”) had lower rates of previous cardiac interventions and severe carotid disease, but had higher blood pressure on arrival (161 vs. 155 mmHg, p=0.04) and were more likely to have an ICH (13% vs. 9.5% in “on hours”) patients. At 7 days, 6.5% of “off hours” patients died as compared to 4.8% “of on hours” patients (p=0.047). Controlling for major determinants (age, blood pressure, obesity, type of stroke, pre-stroke modified Rankin scale, NIHSS admission, time to CT scan and thrombolysis usage) the relative odds of worsening mRS among “off hours” admission as compared to on-hours admissions was 1.164 (95% CI 0.93 to 1.45). Conclusions: Off hours stroke admissions to Israeli hospitals was associated with short-term worse outcome, probably due to a higher rate of ICH. After controlling for potential confounders, “off hours” seems to carry similar prognosis as “on hours”.

Racial Disability in tPA Treatment for Stroke in a Predominantly Black Urban Population
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Background: Some, but not all, prior studies have shown that racial disparities exist in the utilization of IV tPA for acute ischemic stroke patients. Further studies are needed to confirm these findings and provide insights into the underlying barriers to utilization. We sought to determine whether race was associated with tPA treatment rate for stroke in a predominantly black urban population hospitalized for acute ischemic stroke, blacks were predominantly black urban population hospitalized for acute ischemic stroke, blacks were less likely to be treated with IV tPA than whites (24% vs. 48%, p<0.01), older in age (median 74 vs. 45 years old, p<0.001), similar trauma severity in RTS (median 7.8 vs. 7.5, NS) and ISS (median 9 vs. 12, NS) and higher inhospital mortality (12.8% vs. 8.8%, p<0.01). Based on the definition by ISS, stroke survivors had significantly higher prevalence of severe spine injuries (Odds ratio (OR) 4.3, 95% confidence interval [95%CI] 1.1-11.8, p<0.01) and severe injuries on hip or lower extremities (OR 1.5, 95%CI 1.1-1.9, p<0.01, in contrast, had significantly lower prevalence of severe chest injury (OR 0.4, 95%CI 0.3-0.6, p<0.001) and severe spine injury (OR 0.5, 95%CI 0.2-0.9, p<0.05). Inhospital mortality after adjustment for the trauma severity and past illnesses demonstrated significantly higher in patients with prior stroke (OR 1.9, 95%CI 1.3-3.3, p<0.05). Conclusion: Although stroke survivors impair with their activities, our study demonstrated the increased trauma prevalence and the regional differences of severe trauma which may relate to fail and the poor trauma outcome. Further studies to aim the prevention of trauma on head, hip and lower extremities are expected.

Characteristics of Trauma in Patients With Prior Stroke: An Analysis of 20257 Trauma Patients in Japan
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Backgrounds: Fall is one of the major causes of morbidity-mortality in stroke survivors. Little is known about the relationship between trauma and prior stroke. Our study purpose is to assess the prevalence, gender-difference, anatomical characteristics and mortality of trauma in patients with prior stroke in Japan, using data from the Japan Trauma Data Bank (JTDB), a multicenter, nationwide and prospectively recruited trauma registry in Japan. Methods: The Trauma Injury Severity Score (TRISS) system is an accepted trauma severity evaluation system which was constituted with the physiological severity scoring system (the Revised Trauma Score, RTS) and the anatomical severity scoring system (the Injury Severity Score, ISS). We selected the hospitalized trauma patients from JTDB which fulfilled the requirement of TRISS system, evaluated the anatomical difference of severe trauma between patients with or without prior stroke after adjustment for age and gender and estimated the mortality after adjustment for the trauma severity and past illnesses. Results: A total of 20257 trauma victims registered in JTDB matched the selection criteria and 235 patients had prior stroke. Prevalence of prior stroke in the selected trauma victims was significantly higher than overall prevalence of prior stroke in Japan (2.9% vs. 2.2%, p<0.001). Comparison between Patients with or without prior stroke showed relatively frequent in female (38% vs. 30%, p=0.01), elder in age (median 74 vs. 45 years old, p<0.001), similar trauma severity in RTS (median 7.8 vs. 7.5, NS) and ISS (median 9 vs. 12, NS) and higher inhospital mortality (12.8% vs. 8.8%, p<0.01). Based on the definition by ISS, stroke survivors had significantly higher prevalence of severe spine injuries (Odds ratio (OR) 4.3, 95% confidence interval [95%CI] 1.1-11.8, p<0.01) and severe injuries on hip or lower extremities (OR 1.5, 95%CI 1.1-1.9, p<0.01, in contrast, had significantly lower prevalence of severe chest injury (OR 0.4, 95%CI 0.3-0.6, p<0.001) and severe spine injury (OR 0.5, 95%CI 0.2-0.9, p<0.05). Inhospital mortality after adjustment for the trauma severity and past illnesses demonstrated significantly higher in patients with prior stroke (OR 1.9, 95%CI 1.3-3.3, p<0.05). Conclusion: Although stroke survivors impair with their activities, our study demonstrated the increased trauma prevalence and the regional differences of severe trauma which may relate to fall and the poor trauma outcome. Further studies to aim the prevention of trauma on head, hip and lower extremities are expected.

Effect of IV-IA Thrombolysis on Hospital Costs (Recanalisation Study): A Prospective Cohort Study
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Background and Purpose: Combined intravenous (IV) and intra-arterial (IA) thrombolysis with Alteplase may improve clinical outcomes. However, there are no data on the costs and outcomes of combined IV-IA thrombolysis in acute ischemic strokes. We report the effect of combined IV-IA thrombolysis (Recanalisation using Combined intravenous Alteplase and Neuro-interventional Alveolar for acute Ischemic Stroke, the RECANALIZE study) on hospital length of stay (LOS) and costs in acute ischemic stroke patients treated within 3 hours of symptoms onset. Methods: The RECANALIZE study compared recanalization rates, and functional outcome between two periods (February 2002 to March 2007, versus April 2007 to October 2008) in patients consecutively included in a prospective registry who were treated with different regimens of Alteplase within 3 h of symptom onset. Patients with confirmed occlusion who were treated before April 2007, were treated with IV Alteplase; after April 2007, patients were treated with a systematic IV-IA approach. Outcomes included hospital LOS, hospital discharge and cost data. Results: Costs were increased by 2557 euros (95% CI: 946-4617). For each 30 minutes increase in time from symptom onset to recanalization, mean costs increased by 10300 euros (95% CI: 1012-10490) than in the IV group (20219 ± 10561 euros, p = 0.02). Linear regression analysis showed that for each 30 minutes increase in time from symptom onset to recanalization, mean costs increased by 2557 euros (95% CI: 946-4617). Conclusions: IV-IA thrombolysis improved recanalization rate with no increase in costs at 12 months. The earlier the recanalization, the higher the favorable outcome rate, the lower the cost. These results show that heath care expenditure should aim at early recanalization.

Years of Disability-Adjusted Life Gained as a Result of Thrombolytic Therapy for Acute Ischemic Stroke
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Backgrounds: Disability-adjusted life year (DALY) gained or lost is a clinically accessible and statistically valid measure originally developed by the WHO to measure the global burden of...
Impact of Disability Status on Ischemic Stroke Costs
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Introduction: Longitudinal patient-level data on costs after an ischemic stroke is lacking. The objectives of this analysis were to calculate costs for the first six months post-stroke and determine if levels of disability affected costs. Methods: The Burden of Ischemic Stroke (BURST) Study is a prospective, multicentre study with ischemic stroke patients recruited in a consecutive manner. The clinical course, resource utilization and modified Rankin Scale score (mRS) were collected at hospital discharge, 3 and 6 months after discharge by questionnaires. Costs accrued in the predischARGE phase included emergency medical services and medications. Costs for the acute hospitalization and the post-discharge phases consisted of hospitalizations, rehabilitation, homecare, physician services, diagnostic imaging, and medications as well as indirect costs such as disability leave, wage losses, assisted devices, caregiver time, and out-of-pocket costs. Units of resource utilization collected from the questionnaires were multiplied with unit costs from various sources. Descriptive statistics were used to characterize the overall data and costs in 2009 Canadian dollars. Results were stratified by mRS 0-2 for non-disabling stroke (NDS) and mRS 3-5 for disabling stroke (DS). Results: Two-hundred thirty-two patients were recruited with a mean age of 69.4 ± 15.4 years, 51.3% were male, 57.8% hypertensive, 51.7% dyslipidemic, 23.3% diabetic, 19.0% had atrial fibrillation, and 50.4% were disabled. Average predischARGE costs were $1,453.05 ± $1,089.36 (median $1,006.26) for the NDS cohort and $1,449.07 ± $1,057.25 (median $1,006.26) for the DS cohort. Average acute care costs 3 months after stroke were $10,471.88 ± $15,432.58 (median $5,213.55) for the NDS cohort and $37,516.75 ± $24,285.04 (median $34,015.01) for the DS cohort. Average post-discharge costs within 4-6 months after stroke were $5,679.85 ± $9,461.19 (median $891.56) for the NDS cohort and $11,194.07 ± $9,847.40 (median $13,406.14) for the DS cohort. Conclusions: Individuals with disabling ischemic stroke have almost three times the costs of those with non-disabling stroke. Costs were similar for predischARGE care for both groups but both acute and post-discharge care costs were higher for the DS cohort. Strategies to shift individuals into the mRS 0-2 stratum would be expected to have significant early cost savings.
Sleep Apnea is Associated With Silent Ischemic Brain Lesions in Stroke
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We investigated the relationship between subclinical ischemic lesions and obstructive sleep apnea (OSA) in a population of patients presenting to the hospital with stroke. We examined the association of OSA with the prevalence of silent lacunar infarction, periventricular hyperintensity (PVH), and cerebrovascular ischemic disease (CVID) in this population. Methods: We studied 307 patients who presented to our hospital with stroke. Three types of silent lesions were assessed by MRI scans. Obstructive Sleep Apnea was assessed using ResMed ApneaLink screening device. We performed a cross-sectional study on OSA severity and the prevalence of silent cerebrovascular lesions detected by brain MRI analysis. Data were subdivided into 4 levels of OSA severity: None, Mild, Moderate, and Severe based on measured respiratory disturbance index (RDI) values. For analytic purposes, these levels were collapsed into a low RDI (None and Mild) group and a high RDI (Moderate and Severe) to establish adequate group sizes. In order to establish whether there were differences between the clinical RDI categories a series of bivariate analyses were conducted, using chi-square tests for categorical outcomes, and Independent samples t-tests for continuous outcomes. Results: Of the 65 patients included in the study, 26 (40.0%) did not display symptoms of OSA (RDI < 15), 16 (24.6%) had moderate OSA (RDI of 15 to < 30), and 7 (10.8%) had severe OSA (RDI ≥ 30). After collapsing into two categories, there were 42 (64.8%) with low RDI and 23 (35.4%) with high RDI. There were no statistically significant differences between low and high RDI patients in the various demographic or behavioral measures (p > 0.05 for each). Independent samples t-tests revealed that there was a statistically significant difference between low and high RDI patients on mean PVH (p < 0.001), and number of Lacunes (p = 0.001). Chi-square analysis revealed that there was a difference between low and high RDI patients in the CVID level (p < 0.001) with a correlation of r = 0.498 between level of RDI and CVID. Conclusion: Results indicate that stroke patients with moderate to severe OSA (RDI ≥ 15) have higher prevalence of silent ischemic brain disease, especially PVH and CVID. The importance of screening for OSA in this population is highlighted.

Oral Pioglitazone at Clinically Used Doses is Neuroprotective in Rats
D’Arba Blankenzaper, Jon Niemi, Elizabeth Hilow, Molly Karl, Sophia Sundararajan; Case Western Reserve Univ, Cleveland, OH

Thiazolidinediones (TZDs), including pioglitazone, are promising neuroprotective agents and have been tested in rodents using intravenous, intracerebral and intraperitoneal routes of administration. Daily pioglitazone is used to treat type 2 diabetes and is being tested for its potential neuroprotective effects in the setting of stroke. In this study, we examined whether therapeutic doses of pioglitazone can be used to improve functional outcome and reduce infarct size following transient focal cerebral ischemia. Adult male Sprague-Dawley rats were divided into 3 groups: 1) control, 2) pioglitazone (1 mg/kg) and 3) pioglitazone (3 mg/kg). Each group was further divided into 2 subgroups: 1) sham and 2) transient focal cerebral ischemia. Rats that underwent ischemia were subjected to middle cerebral artery (MCA) ligation for 2 h followed by reperfusion. Pioglitazone was administered orally for 5 days beginning 24 h before ischemia. Functional outcome and infarct size were measured 24 h after reperfusion using the neurological deficit score (NDS) and 2,3,5-triphenyltetrazolium chloride (TTC) staining, respectively. Ischemic deficits were assessed during the chronic phase of neurologic outcome (day 28). Infarct volumes were calculated using the method of Brainster. Pioglitazone at both doses significantly improved functional outcome in the chronic phase of neurologic outcome (NDS: control vs. pioglitazone 1 mg/kg, 2.7 ± 0.5 vs. 1.4 ± 0.5 P < 0.05; pioglitazone 3 mg/kg, 1.4 ± 0.5 vs. 0.8 ± 0.3 P < 0.05). Furthermore, pioglitazone at both doses significantly reduced infarct size in the ischemic hemisphere (TTC: control vs. pioglitazone 1 mg/kg, 4.2 ± 0.8 vs. 1.4 ± 0.4 mm3 P < 0.05; pioglitazone 3 mg/kg, 4.2 ± 0.8 vs. 1.2 ± 0.2 mm3 P < 0.05). These findings suggest that pioglitazone can be used therapeutically in the setting of stroke, and it should be considered for clinical trials for the treatment of stroke.
AAV-VEGF resulted in 42% less vascular permeability than AAV-VEGF alone (1.5±0.2; P<0.05). Overexpression of VEGF reduced ZO-1 expression, while overexpression of ANG1 upregulated ZO-1 expression. Injection of AAV-VEGF or AAV-ANG1, individually or together, also increased vascular density compared to that of AAV-LacZ. Conclusion: AAV-mediating co-expression of VEGF and ANG1 significantly decreases vascular leakage caused by VEGF, and results in greater reduction of infarct size than treatment with either gene vector alone. The effect may be mediated in part through upregulation of ZO-1 expression.

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Combination Therapy of VELCADE and Low Dose IPA at 2h Provides Potential Neuroprotection in Aged Rats After Focal Cerebral Ischemia

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Background and Objective: Treatment with a selective proteasome inhibitor VELCADE (bortezomib) in combination with tissue plasminogen activator (tPA) extended the therapeutic window to at least 6 hours in young rats after experimental stroke. However, stroke is a major cause of death and disability in the elderly. To mimic clinical situation, the current study investigated the effect of VELCADE in combination with low dose IPA on aged rats after embolic middle cerebral artery occlusion (MCAo). Methods: Male Wistar rats at the age of 18 months or older were subjected to MCAo after MCAo, rats were randomly divided into the following groups: 1) to examine the effect of VELCADE alone on ischemia, VELCADE at a dose of 0.2mg/kg (n=6) was administered (i.v.); 2) to examine the effect of low dose IPA alone on ischemia, IPA at a dose of 5mg/kg (n=6) was administered (i.v.); 3) to examine the effect of combined treatment, rats were treated with VELCADE (0.2mg/kg) and IPA (5 mg/kg, n=7) were administered; 4) a control group in which the same volume of saline (n=9) was given (i.v.). Modified neurological severity score (mNSS) was measured blindly. All rats were sacrificed 7 days after MCAo and infarct volume and gross hemorrhage were measured. Results: Treatment with VELCADE reduced lesion volume by 36% (20.7±4.0%) compared with saline treated rats (33.1±10.1%) and improved functional outcome measured by reduction of mNSS (7.0±1.0 vs 9.2±0.8 in saline). Monotherapy of IPA failed to significantly reduce infarct volume (26.8±4.1%) and did not improve neurological deficit (9.2±0.8) compared with the saline group (9.2±0.8). However, combination treatment with VELCADE and IPA yielded 55% reduction of the lesion volume (14.8±4.5%, P<0.05) compared with the saline group, which was also significant (P<0.05) compared with monotherapy of VELCADE or IPA. In addition, the combination treatment substantially improved neurological outcome (5.5±1.0 vs 9.2±0.8 in saline, 7.0±1.0 in VELCADE, and vs 8.3±0.8 in IPA; P<0.05). No significant changes were observed in other parameters among the groups. Conclusions: Our data indicate that combination of VELCADE 2h after stroke exerts a neuroprotective effect in aged rats after embolic stroke. The combination of VELCADE with low dose IPA at 2h can further amplify the neuroprotective effect, which provides a potentially promising approach for the treatment of acute stroke.

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AAV-mediated Co-expression of Angiopoietin-1 and VEGF in the Ischemic Brain Results in Reduced Vessel Leakage and Infarct Size Than VEGF Expression Alone

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Background and Purpose: Vascular endothelial growth factor (VEGF) has angiogenic and neuroprotective effects; however, the neovascularization induced by VEGF is immature and prone to lead to edema and exaggerated ischemic injury. Angiopoietin-1 (ANG1) reduces vessel leakage caused by VEGF. Here, we hypothesized that adeno-associated viral vector (AAV)-mediated co-expression of ANG1 and VEGF decreases vascular leakage caused by VEGF and reduces ischemic injury. Methods: Four groups of adult CO-1 mice underwent permanent distal left common carotid artery occlusion (MCAo). Animals were sacrificed recruited more easily when the lungs are ventilated under hypoxia and less easily when the lungs are ventilated under hyperoxia. We hypothesized that in intact rats, spheres injected into the venous circulation would also bypass the lungs and then lodge in the brain. We anesthetized five 100-500g male Sprague Dawley rats (50 mg/kg ketamine/5 mg/kg xylazine). Cerebral density was reduced in mice (3,000 IU). We then injected 1x10^6 green, fluorescent-labeled 50 m/L latex spheres in 1 mL isotonic phosphate buffered saline (PBS) over one minute (n=3) or 1 mL PBS as a control (n=3). Five minutes later, we injected 2x10^7 red, fluorescent-labeled 4 m/L spheres in 0.5 mL PBS. 4 m/L spheres injected in microvessels and are frequently used to pattern perfusion in a tissue. This was well-tolerated and all animals survived the sphere infusion. The brains were harvested, sectioned into 3 mm thick sagittal sections, and imaged confocally. The hearts were explored and no intracardiac defects were noted. In brain sections from rats infused with 50 m/L spheres we identified a minimum of 20 spheres/brain and noted large non-perfused regions surrounding the 50 m/L spheres. In comparable brain regions from control rats, no large perfusion deficits were noted. We identified 50 m/L spheres in the rat brain that bypass the lung filter despite normal cardiac anatomy and believe them to be patently SHH. In subsequent experiments, we determine if the passage of these particles is increased by stimuli that recruit IPAVs in isolated lungs or decreased by stimuli that close them, and to describe the functional consequence of these cerebral emboli.

Male

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Resource Utilization for Acute Stroke in Eastern Asian Countries: The STROKOP-Asia Study

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Purpose: The diversity of the participating countries in STROKOP-Asia offers an opportunity to investigate how resource utilization (RU) is allocated in each country and how it may affect the outcomes in patients with acute stroke. Method: STROKOP-Asia is a longitudinal study with registration of subjects suffering from acute stroke in eight countries across Asia. Countries are classified into 5 groups according to their gross domestic product (GDP), including Taiwan, Hong Kong in the higher GDP group, Malaysia, Thailand in the middle GDP group, Indonesia, Philippines, and Vietnam in the lower GDP group. RU included the usage of angiography, statin, CT/MRI, and carotid ultrasound. Outcome measures included mortality, recurrent vascular events, and all events in one year. KeyEvents: Total of 2571 subjects were analysed. Comparison of the middle and lower GDP groups, the use of CT/MRI angiography and carotid ultrasound was more frequent in the higher GDP group (40.9%, 11.5% and 12.0% for both CT and MRI; 34.2%, 5.2% and 8.4% for angiography; 80.9%, 14.2% and 40.7% for carotid ultrasound). Despite higher consumption of above-mentioned diagnostic technologies, outcome was similar among different GDP groups, with 11.5%, 10.9% and 11.1% for total events; 4.0%, 6.9% and 5.2% for mortality and 8.4%, 4.4% and 6.6% for recurrent vascular events, respectively. Multivariable proportional hazards regression showed that the usage of statin and carotid ultrasound were adversely associated with total events and recurrent vascular events in one year with hazards ratios with 95% CI was 3.14 (95% CI: 1.01–1.76) and 1.33 (1.01–1.74), respectively for total events, 1.62 (95% CI: 1.17–2.24) and 2.04 (95% CI: 1.47–2.85), respectively for recurrent vascular events. Conclusions: Our observational study showed that the utilization of resources within the definition of this analysis was associated with GDP. However, it did not reduce mortality, nor total or recurrent vascular events. In addition, the study did not support the observed findings on statin in preventing recurrent vascular events, this might due to the limitation of observational study and it remains to be further investigated.
Gadolinium Based Contrast Perfusion Compared to Continuous Arterial Spin Labeling for Perfusion Lesion Determination

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Introduction: Perfusion imaging is an important element in imaging of ischemic stroke to determine “tissue at risk” for infarction. In this study we aimed to compare the volumetric quantification of the perfusion deficit in two rat suture middle cerebral artery occlusion (MCAO) models utilizing a Gadolinium based contrast agent (P1152, Guerbet, France) compared to our well established continuous arterial spin labeling (CASL) perfusion imaging technique.

Method: Animals underwent either permanent MCAO (n=6) or transient MCAO (n=6) with reperfusion at 80 minutes. Both dynamic susceptibility contrast (DSC) and CASL perfusion imaging was performed at 30, 90, 150 and 210 minutes post-MCAO. A region of interest (ROI) analysis focusing on the ischemic core and penumbra were performed to derive a threshold for ischemia from the DSC perfusion. Volumetric analysis of the perfusion deficit was performed based on this threshold for DSC perfusion and earlier validated threshold for CASL perfusion.

Results: The ROI analysis showed a significant reduction in blood flow in the core as compared to the penumbral region while occluded. After reperfusion a significant increase in blood flow was recorded at all time points post-reperfusion in both the core and penumbra (figure 1a). From the ROI analysis the threshold for penumbra was determined to be 62 ± 11% for the DSC perfusion as compared to 57 ± 11% for CASL. Volumetric quantification of the ischemic lesion with DSC and CASL perfusion imaging showed no statistical differences (figure 1b).

Conclusion: We were able to derive a threshold for perfusion imaging utilizing a Gadolinium based contrast agent. The volumetric analysis based on the two different perfusion techniques gave very similar perfusion lesion volumes for both MCAO models. The results support determination of ischemic core and penumbra with both DSC and CASL perfusion imaging.

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