Abstracts
Diagnosis

In Vivo Detection of Carotid Artery Thrombi by MRI and EP-2104R, a Fibrin-Targeted Imaging Agent


Background and Purpose: Emboli from carotid artery thrombi are a common underlying cause of ischemic stroke. The goal of this study was to determine the imaging efficacy of EP-2104R, a fibrin-targeted MR Imaging pharmacological agent, in a rabbit carotid artery thrombosis model. Methods: Adult rabbits (N = 4/dose) were sedated and anesthetized. A section of the carotid artery was isolated and a fixed stenosis placed distally using a needle and silk suture to induce a non-occlusive, mural arterial thrombus. The arterial section was occluded and endothelial damage induced by crushing the vessel with a hemostat. Approximately 3 min later, flow was re-established and thrombi were aged for 30 minutes. The neck region was imaged before and up to 45 minutes after, 1, 2, 5 µmol/kg EP-2104R injection. The MRI imaging sequence was a 30 gradient recalled echo with RF spoiling using a surface RF coil with chemical fat saturation as well as superior and inferior spatial band to null flowing blood. The signal intensity ratio (SIR) measured the thrombus S/M at each scan time. After imaging, animals were sacrificed and total Gd was measured in the clots and surrounding vessel. In addition, vessel measurements with a non-imaging paramagnetic analog (La-EP-2104R) was also performed. Results and Conclusions: MRI showed a dose-response relationship in the rabbit carotid artery thrombus model with thrombus to muscle SIRs of 1.0 ± 0.1, 1.6 ± 0.1, 2.1 ± 0.0 and 3.1 ± 0.1 for the pre-dose, 1, 2, and 5 µmol/kg EP-2104R, respectively, approximately 35 minutes after EP-2104R injection. The total amount of Gd in the clot and injured vessel correlated well to the enhancement seen on the images. EP-2104R also demonstrated specific binding to thrombus. In the displacement study, thrombus/muscle SIR dropped from 2.4 ± 0.2 to the near baseline value of 1.2 ± 0.1 within 30 minutes post-La-EP-2104R. The ability to readily detect small carotid thrombi in the rabbit indicates that MRI with EP-2104R has the potential to successfully image small, non-occlusive carotid thrombi in humans, and has potential for detecting an on-going source of emboli and rupturing unstable plaques.

A Portable, Noninvasive Acoustic Diagnostic System to Identify Ischemic and Hemorrhagic Stroke: A Phase II Study

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Background: Of 500,000 ischemic strokes annually, <3% of patients receive intravenous tPA. The current diagnostic tool, CT, does not confirm acute ischemia, requires an experienced reader, and is time consuming. Our phase I study suggested that a portable brain acoustics monitor can differentiate ischemic and hemorrhagic stroke. In this phase II study, we further refined the acoustics signal associated with each stroke subtype and explored the feasibility of using this system in ambulances. Methods: We monitored subjects with non-traumatic stroke presenting <12 hours from symptom onset. Acoustics data was acquired using a laptop device with non-invasive sensors applied to the patient’s radial artery and forehead for <15 seconds. Waveforms were categorized as ischemic, hemorrhagic, or normal by a signal analyst blind to clinical diagnosis. An abnormal signal, associated with ischemia, is defined as a difference of 10 dB between the head and arterial sensors in the range of 10–80 Hz. Hemorrhagic stroke had <10 dB difference. Clinical diagnosis and CT reading were confirmed by a blinded stroke neurologist. Results: To date, 181 subjects have full data sets for analysis: 91 ischemic and 18 hemorrhagic stroke, 10 pseudostroke (clinical findings inconsistent with stroke syndromes plus normal imaging), 25 TIA, and 37 controls. Sensitivity was 76% for ischemic stroke, 85% for hemorrhagic stroke (if monitored <6 hours from symptom onset and systolic blood pressure was <185 mmHg). Ischemic signals were detected in 85% of TIA and 80% of pseudostroke patients. We found use of the PDA BAM feasible for prehospital providers. Conclusions: These results suggest that our portable acoustics monitor may be promising as a more effective technology than CT to identify both ischemic and hemorrhagic stroke. TIA patients demonstrated ischemic signals despite normalization of their exams. Pseudostroke patients also showed abnormal signals. System sensitivity is higher when monitoring <6 hours from stroke onset. Therefore, our continued study concentrates on BAM testing in the prehospital setting. Funded by NIH 2944NS41843-02.

Increased Blood Volume Maintains Viability in Tissue With Isolated Focal Swelling on CT in Acute Stroke

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Introduction: Early ischemic changes on CT have been considered generally irreversible and used in the selection of patients for some acute stroke trials. The Alberta Stroke Program Early CT Score (ASPECTS) is a validated method of assessing ischemic changes. Parenchymal changes included in ASPECTS are focal swelling/sulcal effacement and hyper-attenuation. We tested the hypothesis that these signs have different underlying pathophysiology, by comparing CT with diffusion and perfusion-weighted imaging changes. Methods: MRI and CT were performed within, 2 hours of each other, in 29 patients <6 hours after symptom onset. Apparent diffusion coefficient ratios (ADC), relative cerebral blood flow (rCBF) and volume (rCBV) were calculated for individual cortical ASPECTS regions. Regional infarction was assessed on day 90 T2-weighted images, without reference to the acute studies. Results: Isolated focal swelling was seen in 13 ASPECTS regions from 4 patients. Hyper-attenuation was observed in 42 regions from 21 patients. Median ADC values were significantly lower in hypo-attenuated regions (0.79 [Inter-Quartile Range 0.65–0.91]) compared to those with focal swelling (0.90 [0.89–0.98]). Median rCBV was increased 123% (110–130) in regions with focal swelling, relative to tissue that appeared normal on CT (94% [61–114], p < 0.001). In contrast, rCBV was decreased in hypo-attenuated regions (53% [30–85], p < 0.001). Median rCBF in regions with focal swelling (56% [56–86]) was similar to that of normal tissue (72% [47–95]). In hypo-attenuated regions, rCBF was significantly decreased (39% [24–85], p < 0.002). Infarction on T2-weighted scans at 90 days occurred in all 42 acutely hypo-attenuated tissue regions. In 8 of the 13 regions with isolated focal swelling no infarction was evident, irrespective of reperfusion. Conclusions: Elevated (rCBV) and normal (rCBF) in tissue with focal swelling is consistent with complete reperfusion. This appears to preserve tissue viability, as rADC is higher than in hypo-attenuated regions. In some cases, these compensatory changes appear to protect the tissue from infarction. We therefore suggest that isolated focal swelling is a potentially reversible early ischemic CT change.

Glucose Is Persistently Elevated in Acute Stroke Patients

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Introduction: Although hyperglycemia is common in acute stroke and has an adverse effect on outcome, there are few studies of its natural history. We aimed to define the temporal profile of poststroke hyperglycemia using a subcutaneous Continuous Glucose Monitoring (CGM) system. Methods: CGM was performed in 56 ischemic stroke patients presenting within 24 hours of symptom onset. The CGM system recorded interstitial glucose every 5 minutes for 72 hours and was calibrated using capillary blood. Further measurement. Patients with subcutaneous insulin (<–8) were included in the descriptive analysis; 4 patients who received insulin infusions were excluded. The median glucose for each patient in 2 hour time epochs was calculated. Hyperglycemia was defined as a sensor glucose of ≥7 mmol/L. Results: CGM was performed for 69 hours (median, range 12–101) commencing 17 hours (5–44) post stroke. 37% of patients had pre-existing diabetes. Median glucose for the entire monitoring period was 6.4 mmol/L (2.2–22.2). During this period a median of 38% of patients were hyperglycemic; 67% at 8 hours and 37–60% at 60–86 hours post stroke. The peak median glucose level occurred at 8 hours (7.9 mmol/L), decreasing sequentially to a minimum of 5.7 mmol/L at 14 hours, followed by a plateau (5.6–8.6 mmol/L), until the occurrence of a secondary increase to a median of 7 mmol/L from 60–88 post stroke. Patients spent a median of 26% (0–100%) of the monitoring period in the hyperglycemic range. A third of patients (35%) were hyperglycemic for ~50% of the monitoring period. Multiple regression showed that diabetes (p = 0.001) and insular cortical ischemia (p = 0.01) were associated with higher glucose values. Conclusion: This comprehensive serial profile of the glucose response to stroke demonstrates that although glucose values decline hyper-acutely, a substantial number of patients remain hyperglycemic throughout the subacute phase of stroke, despite standard stroke unit treatment. Furthermore, the duration of hyperglycemia is greatly underestimated by random time-point glucose estimates. These results have significant implications for the duration and intensity of glucose lowering therapies in stroke.

Sensitivity of the ROSIER Scale in Diagnosis of Anterior and Posterior Circulation Stroke Subtypes

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Background and Purpose: Rapid intervention is crucial for acute stroke patients to maximise the benefit of treatment outcome. The ROSIER scale (Recognition Of Stroke In the Emergency
subtypes will be discussed. Conclusions: A combination of biomarkers including caspase-3, an apoptosis related biomarker, seems promising to make an urgent biochemical diagnosis of stroke. This approach will permit rapid referral of stroke patients to hospitals where acute treatments are available.

Acute Management

Association of Outcome With Early Stroke Treatment Using Abciximab in ABEStT: A Randomized Double-Blind, Placebo-Controlled Trial

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Introduction: Early treatment with reperfusion therapy, such as thrombolysis, is associated with an increased likelihood of favorable outcome. We hypothesized that a similar finding might be present with the administration of abciximab. To test this hypothesis we looked at the results of the Phase 2b ABEStT study. Methods: Data from 400 patients enrolled within 6 hours of stroke were analyzed. Patients were assigned either placebo or abciximab (1:1 ratio); 97% of the patient-based treatment > 3 hours after stroke onset. Odds ratio and 95% confidence intervals (CI/bootstrap) for favorable outcomes were calculated for all randomized patients using the interval from stroke until treatment. Results: Early treatment with abciximab was associated with an increased likelihood of favorable outcome (Figure). The point estimate of the odds ratio decreased at later intervals, but was favorable even after 6 hours (Odds ratio = 1.413, 95% CI 0.95–2.09, P = 0.046). The lower bound of the CT was at all timepoints before 5.25 hours (other than for the first time window). Conclusions: Our results suggest an association between early administration of abciximab and favorable outcomes among patients with acute ischemic stroke.

Microbubbles Administration Accelerates Clot Lysis During Continuous 2 MHz Ultrasound Monitoring in Stroke Patients Treated With Intra-venous Ipa

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Aim Experimental studies have shown that ultrasound-enhanced thrombolysis may be further enhanced by microbubbles (MB) administration, which lowers the threshold for cavitation. We aimed to evaluate the effects of galactose-based MB on the beginning, speed and degree of MCA recanalization during systemic thrombolysis and continuous 2 MHz pulsed wave TCD monitoring Methods We evaluated 103 consecutive stroke patients due to MCA occlusion treated with IV Ipa. Patients were allocated to receive Ipa plus continuous 2-h TCD monitoring (Ipa/US group), or Ipa plus placebo monitoring (Ipa group), or Ipa/US plus 3 doses of 2.5 g NINDS scapal Ipa US group, or Ipa/US plus 3 doses of 2.5 g NINDS plus 1 min Ipa US group. The beginning, speed, and degree of recanalization during the first 2 h of Ipa bolus were recorded. The speed of recanalization was calculated in seconds (1<19 min) stepwise (1–29 min) and slow (<30 min) reperfusion. NIHSS scores were obtained at baseline and 24 hours. Results Median pre-bolus NIHSS score was 18. Seventy-four (72%) patients had a proximal and 29 (28%) an distal MCA occlusion on TCD. Thirty-four (33%) patients received Ipa/US, 35 (34%) Ipa/USMB and 34 (33%) were treated with Ipa alone. Stroke severity, time to treatment, location of MCA occlusion and presence of carotid artery disease were similar among groups. Two-hour recanalization was seen in 12 (38.9%), 19 (68%) and 27 (76%) patients in the Ipa group, and Ipa/US/MB groups, respectively (p = 0.024). Two-hour complete recanalization rate was significantly (p = 0.038) higher in Ipa/US/MB group (54.5%) as compared to Ipa/US (40.8%) and Ipa (23.9%) groups. The time to beginning of recanalization after Ipa bolus was 26 ± 18 min in the Ipa-US and 19 ± 12 min in the Ipa-US/MB group (p = 0.12). Recanalization started after 1st, 2nd and 3rd MB dose in 9/25%, 14/25% and 3/19% patients, respectively. The combination of Ipa/MB increased in 2- 5-fold the rate of sudden recanalization as compared to Ipa/US (21.4% vs 10.7%) and Ipa/US/MB (21.4% vs 4.3%), respectively. At 24 h, 81%, 31% and 56% of Ipa, Ipa/US and Ipa/US/MB improved > 4 points in the NIHSS score. Conclusion MB administration further accelerates ultrasound-enhanced thrombolysis in acute stroke, leading to faster and more complete recanalization and better short-term outcome.
Hemorrhage in the Interventional Management of Stroke Study

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Introduction: Intracranial hemorrhage is the major complication of both intravenous and intra-arterial thrombolysis. In past studies, symptomatic hemorrhage occurred in 6–11% of patients treated with intravenous t-PA, and 10–15% of patients treated with intra-arterial t-PA. Mortality related to symptomatic hemorrhage ranges from 10% to 20% for patients treated with intra-arterial t-PA. Rates for asymptomatic hemorrhage range from 4 to 41%. Methods: The IMS study enrolled 80 patients in a pilot trial of combined intravenous and intra-arterial t-PA. Intra-venous t-PA at a dose of 0.6 mg/kg was administered within 3 hours of stroke onset following a 2-hour intra-arterial infusion of up to 22 mg in patients with residual thrombus to angiography. Intra-arterial hemorrhages within the first 36 hours were classified as PH1, PH2, H1 or H2 and all hemorrhages were reviewed and adjudicated by the study medical monitor. Symptomatic hemorrhage was defined as hemorrhage associated with any clinical deterioration. Clinical and angiographic factors predicting hemorrhage were explored. Results: Symptomatic hemorrhage within 36 hours occurred in 5 patients (6%) and asymptomatic hemorrhage in 34 patients (43%). By univariate analysis, baseline NIHSS score and edema or mass effect on CT were predictors of asymptomatic hemorrhage. There were no predictive factors for the small number of symptomatic hemorrhages. Location of arterial occlusion was a significant predictor for asymptomatic hemorrhage. Asymptomatic hemorrhage was 3 times more likely to stenosis or occlusion of the internal carotid artery (ICA) compared with similar lesions in the middle cerebral artery (MCA). ICA or M1: 9.1% (4–27.0); MCA or M2: 9.5% (4.3–19.6). Mean age (SD) was 66 (9.3) years; 51% were men; 67% had prior hypertension; 62% were smokers; and 65% of patients were treated with statins. Mean age (SD) was 66 (9.3) years; 51% were men; 67% had prior hypertension; 62% were smokers; and 65% of patients were treated with statins. The primary objective of PROTECT was to show non-inferiority of the low molecular weight heparin certoparin to standard prophylaxis with unfractionated heparin (UFH) for the prevention of thromboembolic complications in acute ischemic stroke. Method and results: PROTECT was multicenter, randomized, double-blind, active-controlled trial. The severity of the underlying stroke was defined by a score on the National Institute of Health Stroke Scale between 4 and 30 points. Patients had mild to severe paresis of a leg. Overall 545 eligible patients were randomized within 24 hours to treatment with certoparin (subcutaneous 3000 U anti-Xa once daily) (n = 272) or UFH (subcutaneous 5000 U three times daily) (n = 273). Duration of treatment was 12 to 16 days. Primary efficacy criterion was a composite outcome consisting of proximal deep venous thrombosis shown on Doppler venography, asymptomatic or symptomatic intracranial hemorrhage related to venous thromboembolism during the treatment period. CT scan was performed at entry, after 7 days and on clinical deterioration. Demographics were well balanced between treatment groups. The per-protocol analysis revealed 17 (7.0%) patients with an efficacy endpoint in the certoparin group as compared to 24 patients (9.7%) in the UFH group, thereby proving the non inferiority (p = 0.001), confirmed by intent-to-treat analysis (p = 0.0008). Fatality rates were identical in both treatment groups (2.6% during treatment). Major bleeding occurred in 3 patients allocated to certoparin (1.1%) and 5 patients allocated to UFH (1.8%). Conclusion: Certoparin (3000 U anti-Xa once daily) is as safe as UFH for prevention of thromboembolic complications in patients with acute ischemic stroke.

The ALIAS Phase I Trial: A Dose-Escalation and Safety Study of Albumin Therapy for Acute Ischemic Stroke

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Human albumin (ALB) therapy is highly neuroprotective in preclinical models of cerebral ischemia. Multiple mechanisms underlie ALB's efficacy: fatty-acid and transition-metal binding, antioxidant and anti-inflammatory, and act as a vehicle for delivery of co-factors and regulatory molecules. Objective: To design and conduct a dose-escalation study of a randomized, placebo-controlled Phase I trial of ALB infusion in patients with acute ischemic stroke. Design: This was a single-center, randomized placebo-controlled, dose-escalation study of ALB infusion following intravenous t-PA. The primary objectives were to determine the safety and efficacy of ALB administered at an optimal per-kg dose for the prevention of thromboembolic complications in acute ischemic stroke. The secondary objective was to determine the optimal per-kg dose of ALB for the treatment of acute ischemic stroke. Methods: ALB (5% solution) was administered at a rate of 20 g/m² over 2 hours to 24 patients (12 men, 12 women) randomized 1:1 to receive either ALB (n = 12) or placebo (n = 12). The first 4 subjects received 20 g/m² over 2 hours, followed by an escalating dose of ALB at 20 g/m² over 2 hours at 4-day intervals. End points of the study included mortality, morbidity, and changes in NIHSS score from entry to 72 hours after t-PA administration. The primary efficacy end point was a composite mortality-morbidity end point (a combined neurologic deterioration and death). Results: Six of 12 patients died; all had severe strokes (NIHSS > 38). Definitive pulmonary congestion was noted on chest x-ray in 4 of 12 subjects. ASPECTS score was 9 at 24 hours after t-PA administration in both groups. Conclusions: ALB at a dose of 20 g/m² over 2 hours is safe and could be explored in future Phase II trials investigating the efficacy of ALB in acute ischemic stroke. Algorithmic strategies are needed to define the optimal dose of ALB and to establish prespecified criteria for dose escalation. The ALIAS Phase II study is currently enrolling patients with acute ischemic strokes.

The Early Systemic Prophylaxis of Infection After Stroke Study: Final Results

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Background and Purpose- In mice subjected to focal brain ischemia, mucofilmacin prevents the development of infection and fever, and improves neurological outcome. Accordingly, preventive antibiotic treatment was recently proposed as a therapeutic approach to improve outcome in patients with acute stroke. The Early Systemic Prophylaxis of infection after stroke (ESPIAS) Study was started on April 18th, 2002, to elucidate whether early antibiotic prophylaxis decreased the incidence of infection at day 7 after acute stroke (primary end point). Secondary end points of ESPIAS included neurological outcome and mortality at 3 months. Methods- Randomized, double-blind, placebo-controlled, single-center study. ESPIAS required 120 patients per treatment group to observe a 50% risk reduction of infection (α = 5%, β = 80%) predicting an infection rate of 30% in the placebo group. Main inclusion criteria were ischemic or hemorrhagic stroke with symptoms lasting less than 24 hours, baseline NIHSS > 5, and written informed consent. Main exclusion criteria included pretreatment identification of infection based on clinical, imaging or biochemical data, or baseline temperature >37.7°C. Interventions- 1: randomization to i.v. Levofloxacin (500 mg/100 ml, for three days), or placebo. All conventional stroke therapies were allowed. Patients were managed in a Stroke Unit and followed for 3 months. Main outcome variable was defined as death at day 7, and 17.6, at 3 months, clinical details by treatment group will be provided at the conference.
Selective Involvement of Bcl-2 Family Members in Neuronal Hypoxia-Iscchma

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Neuronal hypoxic-ischemic injury is mediated in part by Bcl-2 family-dependent neuronal apoptosis. The Bcl-2 family consists of both pro- (e.g. Bax, Bad) and anti- apoptotic (Bcl-2, Bcl-X) proteins that regulate mitochondrial function, cytochrome c release and caspase activation. Back activation has been recognized as an important checkpoint for neuronal death in several models of brain injury, including neonatal hypoxia-ischemia. We hypothesized that modulation of Bcl-2 domain-only family members upstream of Bax would attenuate neuronal death following neonatal hypoxia-ischemia. Postnatal day 7 mice underwent neonatal hypoxia followed by increased reoxygenation after 2 hours. Infarct size was measured 48 hours after hypoxia. Bax-deficient mice were compared with wild-type littermates in each group. Results: Bax-deficient mice had reduced infarct size compared to wild-type mice (1.5±0.5% vs. 11.2±1.5%, p<0.05). Hippocampal Bax+ cells were decreased in Bax-deficient mice (20.4±3.7%, p<0.05) compared to wild-type littermates. Thus, activation of Bax may be a protective mechanism to prevent neuronal death following neonatal hypoxia-ischemia. These results suggest that Bax may be selectively involved in neuronal cell death following neonatal hypoxia-ischemia and may be a target for therapeutic intervention.
at baseline and following stroke. Activation of AMPK was reduced in nNOS−/− mice. Treatment with AMPK inhibitors led to dramatic neuroprotection (TTC at 24 hours) and reduction in AMPK phosphorylation. Conversely, AICAR treatment increased stroke damage. AMPK was also activated after OGD in slice cultures. **Conclusions:** AMPK activation is detrimental in stroke. Pharmacological inhibition of AMPK provides neuroprotection, an effect that may be mediated by AMPK-related stimulation of endogenous metabolic pathways that represent an important and novel target for neuroprotection demonstrated by our findings.

### Gender Differences in Neuronal Cell Death After Oxygen-Glucose Deprivation Injury in Organotypic Hippocampal Cultures

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**Background and Objective:** Increasing evidence has demonstrated striking sex differences in outcomes after acute neurological injury. Females are less vulnerable to acute cerebral ischemia. This endogenous female neuroprotection may not be due solely to hormonal influences. The objective of this study was to determine if there are gender differences in neuronal cell death in organotypic hippocampal cultures after oxygen glucose deprivation (OGD) injury and M-Methyl-d-Aspartic Acid (NMDA)-mediated excitotoxicity. We also addressed possible mechanisms by evaluating markers of nitrosative stress (nitrite and nitrate) and superoxide dismutase (SOD) activity in response to OGD. **Methods:** Organotypic hippocampal cultures were prepared from postnatal day 8 SD rat pups. Gender genotyping was accomplished by PCR for Sry gene. Cultures were subjected to OGD for 45min or exposed to 10mM NMDA for 1hr, in presence or absence of 30mM 7Ni (Nitrosindazole, a selective nNOS inhibitor), or 10mM 17β-estradiol (E2, applied 7 days prior to OGD). Neuronal death was quantified with propidium iodide (PI). Nitric oxide (NO) and products nitrite/nitrate and SOD activity were measured 4hr and 24hr of reoxygenation after OGD. Results: Baseline neuronal cell death in control, 7Ni, and E2 treated groups was equivalent in males and females. Cell death markedly increased after stimulation with OGD or NMDA (P<0.001) in both groups, but there was a significant increase in males (P<0.001–0.05). Treatment with 7Ni and E2 reduced neuronal damage induced by OGD and NMDA (P<0.001–0.05). Interestingly, this effect was more notable in males than in females after OGD (P<0.001). SOD activity was decreased after OGD in both groups, no significant gender differences were seen. The concentrations of nitrite + nitrate, nitrite or nitrate were increased after OGD in both sexes, with higher production of nitrite + nitrate in males (P<0.001). Conclusions: There is a consistent gender difference after OGD and NMDA toxicity, demonstrating endogenous neuroprotection in female cells. Dimorphisms in the management of N0 may underlie some of these differences in neuronal survival. Cells of both genders were responsive to E2 and 7Ni, with a more notable effect in males.

### Nursing and Rehabilitation Professions

#### Use-Dependent Cortical Reorganization After Modified Constraint-Induced Therapy

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Stroke-induced hemiparesis is problematic given its impact on valued activities. Modified constraint-induced therapy (mCIT), a reimbursable, outpatient intervention, aims to improve upper limb function and reduce shoulder pain but current evidence is inconclusive. We have undertaken a randomized controlled trial to evaluate a 4 week programme of mCIT to the shoulder following acute stroke. **Methods:** Patients admitted within 10 days of stroke were: medically stable, had no cognitive/language or previous upper limb impairment likely to influence assessments and had no contraindication to mCIT. Participants were randomised to receive mCIT or placebo in addition to stroke unit care. Outcome assessments were blinded. The primary outcome measure was arm function measured by the Action Research Arm Test (ARAT) 3 months after stroke. Secondary outcomes included other measures of arm function (subsections of the ARAT; Frenchay Arm Test (FAT)), impairment (Mobility Deficit Severity: timed 30-foot walks; Berg Balance Scale; Cardiovascular fitness: energy costs of hemiparetic gait (economy of gait) and VO2 peak;...
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Educational Intervention Reduces Occurrence of Depression in Community-Dwelling Stroke Survivors

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Background and Purpose Following a stroke, the emotional health of many stroke survivors is negatively impacted. Limited research has been reported assessing the long-term effectiveness of nonpharmaceutical interventions on emotional health. The purpose of this longitudinal, quasi-experimental intervention study was to determine what impact a structured, educational program would have on three aspects of emotional health of community-dwelling stroke survivors. We assessed the hypothesis that stroke survivors would experience less depression and an increase in hope and coping abilities as a result of participating in a structured educational program. Methods Our self-care model of nursing provided the conceptual basis for this study. Kozlowski’s principles of adult learning were utilized in developing the sixteen-hour structured, nurse-lead educational intervention. After signing an informed consent, each of the 41 study participants completed the following instruments: demographic form, Herth Hope Scale, Beck Depression Inventory and Ways of Coping CVA questionnaire. Participants were paired according to baseline scores. Each member of the pair was randomly assigned to control (n = 21) or intervention group (n = 20). Data was collected prior to the course, immediately following the course, at one year and at six years post-educational intervention. Data was analyzed using a repeated measures regression analysis. Results and Conclusion Six years after the educational intervention, the decline in depression scores remained significant (p = .02). Hope scores showed an initial improvement at year one following the intervention (p = .02). By the sixth year, hope scores had returned to baseline. Coping scores were unchanged by the intervention and further deteriorated over time (p < .04). The decrease in coping scores over time suggests that participants were having difficulty coping with the long-term consequences of stroke and were also using fewer methods to cope. In conclusion, a community-based, rehabilitation-focused education program can have a positive impact on some aspects of the long-term emotional health of stroke survivors.

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Stroke Survivors’ Behavioral and Psychological Symptoms of Depression: Infl uence of Informal Caregiver Mental Health

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Background and Purpose Informal caregivers, who serve a vital role in assisting stroke survivors living in the community, experience high levels of emotional distress, which can affect the quality and sustainability of community care. Stroke survivors’ behavioural and psychological symptoms (BPS) are becoming recognized as significant contributors to informal caregivers’ emotional distress. Unfortunately, the validity of these findings are threatened by methodological limitations (e.g., use of convenience samples, non-validated measures, and BPS measures). In the current study, we examined the association between caregiver distress and emotional health, and investigated the influence of informal caregiver mental health on the occurrence of BPS as a global construct. In addition, few studies have examined changes in caregiver distress over time. The objectives of this research were to determine: 1) changes in the level of informal caregiver emotional distress during the first year post-stroke and 2) the differential impact of the domains of BPS on informal caregiver mental health after controlling for important illness- and care-related factors. Method: A longitudinal cohort study of individuals who have survived their first ischemic or hemorrhagic stroke and their informal caregivers (IC) living in one of three Canadian cities was conducted. Stroke survivors (SS) and their IC completed standardized measures by telephone interview 1, 3, 6, and 12 months post-stroke. Individual Growth Curve models were used to examine changes in outcomes from baseline and fifteen SS/IC dyads participated (83% response rate). Overall, SS were 57% male, 68 (14.9 SD) years of age, and had an in hospital Canadian Neurological Scale score of 8.2 (2.52 SD). ICs were predominantly female (68%), aged 57 (14.7 SD) years, and married to the SS (59%). There was no significant change in caregiver emotional distress over time. Overall, IC reported more emotional distress when they were caring for SS exhibiting more BPS and more physical disability, and when IC were younger, experiencing more lifestyle interference, in poorer physical health, and reporting less mastery. In conclusion, initiatives to enhance the clinical management of stroke survivor depression, teach informal caregivers how to effectively manage BPS, and provide informal caregivers with lifestyle respite may enhance the community care of stroke survivors.
established and potential stroke risk factors in this anticoagulated population. Methods: The medical history and findings on physical examination were recorded for all 7329 SPORTIF participants at baseline. A central adjudication committee assessed possible events based on clinical findings and brain imaging. We selected the following variables for possible inclusion into a Cox-proportional-hazards model: coronary artery disease (CAD), smoking status; platelet count in peripheral blood (PB); plasma lipoprotein(a) (Lp(a)); ACE inhibitors. We used the quintile method to determine which of these factors were significant (P < 0.05), independent predictors of stroke. Results: There were 5 independent risk factors for stroke (table). None of them interacted with warfarin or intraluminal therapy. Conclusion: Smoking was the most important modifiable stroke risk factor in patients without warfarin prescription. Other significant stroke risk factors were CAD, increased platelet count, smaller BSA, and larger CHADS2 score.

### 31 Real-World Effectiveness of Warfarin Therapy for Stroke Prevention in Medicare Beneficiaries of All Races

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Background & Purpose: Randomized, controlled trials have demonstrated the efficacy of warfarin therapy in carefully-monitored patients who have atrial fibrillation (AF); compared to no antithrombotic therapy, adjusted-dose warfarin had a hazard ratio (HR) for ischemic stroke of 0.35 (relative risk reduction 65%). Participants in these trials tended to be white males who were carefully selected, with over 90% of patients with AF excluded from some trials. Thus, the effectiveness of warfarin therapy in patients receiving care in the real world is unknown. Methods: We used Medicare study record review compiled by Quality Improvement Organizations representing all 50 US states, we identified 16,744 white or Asian patients and 1425 black or Hispanic patients. We obtained information regarding comorbid conditions and warfarin prescription at hospital discharge, in medical records, in the pharmacy, and at proctoring outpatient (PT) monitoring of warfarin therapy from Medicare part A and part B claims. The primary endpoint was ischemic stroke based on ICD-9 codes. Results: In a Cox model that controlled for validated stroke risk factors, warfarin prescribed at hospital discharge had a protective effect in white and Asian patients HR 0.7; 95% CI 0.6–0.8 but no risk in Hispanic and Hispanic patients (HR 1.3; 95% CI: 0.8–1.9). During 1 year of follow up, gaps/loss of INR monitoring of 3 months or greater occurred in 19% of days in white and Asian patients and in 35% of days in African-American and Hispanic patients (P < 0.01). After adjusting for days of appropriately monitored warfarin therapy and stroke risk factors, warfarin had a protective effect in all racial groups: HR — 0.6 (0.5–0.7, P < 0.0001) and race-warfarin interaction was no longer statistically significant. Conclusion: Gaps in PT monitoring (and perhaps in warfarin therapy) resulted in inadequate stroke prevention, especially in Black and Hispanic patients.

### 32 Is Progressive Carotid Atherosclerosis a Risk Factor for Ischemic Stroke? The Atherosclerosis Risk Factors in Communities Study

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Background: Documented progression of carotid stenosis over time has been recommended as an indication for carotid endarterectomy. We determined the risk of ipsilateral ischemic stroke with progressive carotid atherosclerosis in a cohort. Methods: Data derived from the Atherosclerosis Risk in Communities study (ARIC) publicly available datasets, carotid atherosclerosis was quantified using intima media thickness (IMT) in a cohort of men and women, aged 45–64 years at baseline Doppler ultrasound examination. IMT was measured with a 7.5–10.0 MHz sector probe and 61 cm segments of common carotid, bifurcation and cavernous segments of the carotid artery was identified by repeat measurement of IMT performed after three years. Using Cox proportional hazard analysis, the relationship between progression of carotid atherosclerosis and risk of ipsilateral ischemic stroke over 9 years of follow-up was analyzed after adjusting for age, sex, race, smoking status, diabetes mellitus, body mass index, serum cholesterol, and systolic blood pressure. A second analysis evaluated the relation to progression of carotid atherosclerosis and risk of cerebral infarction. Results: Of the 22928 carotid arteries studied at baseline and 3 year follow-up, change in IMT was categorized in four quartiles: increase greater than 0.268, increase ranging from 0 to less than 0.268, decrease ranging from 0 to 0.067, and decrease greater than 0.067 mm. The incidence of ipsilateral stroke was similar for quartiles of decreasing severity: 2.0%, 0.3%, 2.0%, and 3.0%. Compared to the quartile with maximum decrease, the quartile with maximum increase in IMT did not have an increase risk of ipsilateral stroke (relative risk [RR] 1.1, 95% confidence interval [CI] 0.4–2.7) after adjusting for potential confounders in the second analysis. The maximum increase in IMT did not have an increased risk of brain infarction on MRI compared to the quartile with maximum decrease (odds ratio [OR] 1.0, 95% CI 0.7–1.4). Conclusions: We did not observe an increased risk for ipsilateral stroke or brain infarction on MRI with progressive carotid atherosclerosis. Further studies are required prior to considering progression alone as an indication for treatment of carotid atherosclerosis in middle aged patients.

### 33 Asymptomatic Carotid Stenosis and Risk of Stroke: Natural History Study

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The ACAS study has indicated that in patients with asymptomatic internal carotid artery stenosis greater than 60%, carotid endarterectomy (CE) reduces the stroke risk from 2% to 1% per year. Thus, approximately 20 operations need to be performed to prevent 1 stroke in 5 years. The aim of our study was to improve the current risk stratification using clinical and ultrasonic criteria additional to stenosis. Individuals (n = 1059) with asymptomatic carotid stenosis (50–99% ECST) were entered into the ACSRS natural history study. So far follow-up has been between 6 months and 7 years. Stenosis was 50–69% in 189 and 70–99% in 909 patients. There have been 307 (28%) cardiovascular events including 108 (9.8%) cardiovascular deaths and 145 (12.2%) cerebrovascular events including 110 (10%) were ipsilateral (AF – 44, strokes – 59, transient ischemic attacks – 9). Individual stenosis range was symptomless stenosis and severe stenosis (GS > 25) to areas of high level pixels (GS > 5) were (p < 0.004) were independent predictors of risk for ipsilateral stroke. Creatinine, history of contralateral TIA at least 6 months prior to admission, and silent ipsilateral CT brain infarcts were additional independent clinical predictors for stroke (p < 0.01). The relative risks ranged from 1.2 to 3.38. On the basis of our model 21% (20%) (upper quintile) could be identified as a high risk group having a 7 year cumulative stroke rate of 32% (4.6% per year). The remaining had a 5 year cumulative stroke rate of 3.3% (0.5% per year) (log rank p < 0.01). The high risk group included 33 (6%) of the patients. Using the above criteria only 6 operations need to be performed to prevent one stroke in 5 years.

### 34 Vitamin Intervention for Stroke Prevention Trial: An Efficacy Analysis of Patients More Likely to Respond to Therapy


Background: The Vitamin Intervention for Stroke Prevention (VISP) trial intention-to-treat analysis did not show efficacy of combined vitamin therapy for recurrent vascular events in patients with non-disabling strokes. Methods: We evaluated the potential for a combination of vitamin therapy based on subgroups of patients with severe angina, patients on warfarin therapy and patients on antiplatelet therapy. Results: Asymptomatic carotid stenosis was defined using color Doppler ultrasound (60%–90%). ISW were (P = 0.014). After adjusting for days of appropriately monitored warfarin therapy and stroke risk factors, warfarin had a protective effect in all racial groups: HR — 0.32 (0.28–0.37, P < 0.0001) and race-warfarin interaction was no longer statistically significant. Conclusion: Gaps in PT monitoring (and perhaps in warfarin therapy) resulted in inadequate stroke prevention, especially in Black and Hispanic patients.

### 35 Multivariante Linkage Analyses To Identify Genomic Susceptibility Loci For White Matter Ischemia and Brain Atrophy in Hypertensive Sibships

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Hypertension contributes to cognitive dysfunction, largely due to ischemic brain injury. Genetic susceptibility to ischemic brain injury has been demonstrated, but it is unknown whether the genes responsible are the same as those influencing blood pressure (BP). We conducted a genome-wide search to identify susceptibility loci for subclinical white matter ischemia (leukoaarosis) and brain atrophy in 488 non-Hispanic whites (183 men, 255 women; mean age = standard deviation) = 64.1 ± 7.2 years; 79% hypertensive) from 263 sibships, in which ≥2 members had essential hypertension diagnosed before age 60. Genotypes were measured at 366 microsatellite marker loci across the 22 autosomes; leukoaarosis volume was quantitated by magnetic resonance imaging and the difference between intracranial and brain volumes provided a quantitative measure of brain atrophy; BP was measured by random zero sphygmomanometer. The calculated mean arterial pressure (MAP) and pulse pressure (PP)
provided measures of steady-state level and pulsatile components of BP. After adjustment for sex and age, variance components models estimated significant heritability of leukoaraiosis volume ($\rho = 0.72$, $P < 0.001$) and of brain atrophy ($\rho = 0.52$, $P < 0.001$). There was little genetic correlation between leukoaraiosis and atrophy ($\rho = 0.06$). In contrast, leukoaraiosis was more genetically correlated with MAP ($\rho = 0.62$) and atrophy was more genetically correlated with PP ($\rho = 0.59$). Bivariate linkage analyses provided evidence for region on chromosome 5 with pleiotropic effects on MAP & leukoaraiosis (bivariate $\rho = 0.0009$) and of 2 regions with pleiotropic effects on BP & brain atrophy, one on chromosome 11 (bivariate $\rho = 5.1$ at 18 cM, $P < 0.00001$) and another on chromosome 16 (bivariate $\rho = 4.6$ at 124 cM, $P < 0.00003$). These results suggest that some of the genetic loci for hypertension-associated leukoaraiosis and brain atrophy may be the same as those influencing measures of BP.

Vascular Pathophysiology/Thrombosis

Depletion of Krit1 Leads to Perturbation of $\beta 1$ Integrin-Mediated Endothelial Cell Angiogenesis in the Pathogenesis of Cerebral Cavernous Malformation

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Cerebral cavernous malformation (CCM) is an autosomal dominant disease mainly caused by mutations in KRIT1 and malcavernin, the genes at the CCM1 and the CCM2 loci. Clinical features include abnormal vascular sinusoids in the nervous system that predispose to seizures and hemorrhage. Little is known about the molecular and cellular functions of krit1 and malcavernin. We have previously shown that full-length krit1 interacts with icap1, a modulator of $\beta 1$ integrin signaling. Here, we have specifically silenced krit1 in cultured human endothelial cells and observed dramatic perturbations in endothelial cellular proliferation, motility, survival and angiogenesis. Each of these abnormalities correlates with alteration in the phosphorylation status and inferred activity of kinases and substrates that comprise specific components of $\beta 1$ integrin-modulated cellular signaling networks. Decreased phosphorylations in the MAP kinase cascade, known effectors of integrin-mediated cellular proliferation, was observed in krit1-depleted cells. Depletion of krit1 or icap1 reduces endothelial cell migration and invasion via the Rac1 signaling pathway. Depletions of krit1 and icap1 also inhibit $\beta 1$-integrin-mediated cell survival signaling via the ILK-AKT-BAD signaling pathway by increasing endothelial cell apoptosis in a caspase dependent manner. Further, depletion of krit1 or icap1 leads to increased number of disorganized focal adhesions with decreased interaction of ILK and FAK with the focal adhesion docking protein paxillin, providing a potential mechanism for regulation of phosphorylation along these signaling pathways. The synergistic effects of krit1 and icap1 on these signaling pathways can be explained by our observation that upon depletion of krit1, icap1 decreases in the cytoplasm and is no longer detected in the nucleus. These data suggest that krit1 both stabilizes and shuttles icap1 and thus modulates its regulation of $\beta 1$-integrin-mediated signaling. Further elucidation of the molecular and cellular functions of these interactions will yield more information about the molecular pathogenesis of CCM and may lead eventually to the development of rational therapeutic strategies.

Combined Inhibition of Cyclooxygenase-2 and Glutamate Induces Functional Recovery After Intracerebral Hemorrhage With Reduction of Brain Edema and Perihematomal Cell Death

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Background and Objectives: N-methyl-D-aspartate (NMDA) receptor antagonist, memantine and selective cyclooxygenase-2 (COX-2) inhibitor, celecoxib, have been reported to have anti-inflammatory, neuroprotective, and antioxidant effects, reducing the ischemic damage. In this study, we examined whether the combination treatment reduces cerebral inflammation, edema and perihematomal cell death after experimental intracerebral hemorrhage (ICH) and whether functional recovery is achieved. Methods: ICH was induced using stereotactic infusion of 0.23 unit of collagenase into the left basal ganglia of adult rats. Combination of memantine (Mem; 20mg/kg) and celecoxib (Cel; 20 mg/kg, in 5% DMSO) was administered intraperitoneally at 20 minutes after ICH induction and daily afterwards for 4 to 14 days (behavior test group only). Seventy-two hours after ICH induction, we checked hemorrhage content from spectrophotometric methods and water content in both hemispheres separately. TUNEL and activated caspase-3 staining was done for the perihematomal cell death, and myeloperoxidase (MPO) activity was analyzed for inflammation. Behavioral tests (rotarod, modified limb placing tests) were performed before, and 1, 7, 14, 21, 28, and 35 days after ICH, and the data was compared with ICH-only and celecoxib-only treatment groups. Results: The size of hemorrhage was decreased in Cel + Mem-treated group by 17% at 3 days after ICH (p<0.05). The brain water content of Cel + Mem-treated group decreased in both lesioned and non-lesioned hemispheres compared with ICH-only group. In the Cel + Mem-treated group, the number of TUNEL, MPO, activated caspase-3 or microglial cells was dramatically decreased in the perihematomal region. Combination of memantine and celecoxib (Cel + Mem) administered at 5 days post ICH via 35 days (p<0.05) in both rotarod test and MLPT, and the degree of functional improvement in combination treatment group was faster and better than that of celecoxib-only treatment group. Conclusions: Combination treatment of memantine and celecoxib induced better functional recovery than celecoxib-only treatment after ICH, which might be due to the combined effect of inhibition of COX-2 with neuroprotection from excitotoxic injury.

Quantification of Blood-Brain Barrier Opening in Stroke by a Magnetic Resonance Imaging Contrast Agent and Subsequent Confirmation by Using Its Radioactive Version

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Background and Purpose: Sadelomin-Dihydoethylenepiperazineacetic acid (Gd-DTPA) contrast enhanced magnetic resonance imaging (MRI) is the most commonly used technique for assessing blood-brain barrier (BBB) function in stroke. Some attempts have been made to refine and quantitate such MRI data by comparing it to other accepted markers of altered BBB permeability. Here we describe a method to quantitatively evaluate changes in BBB permeability using, for the first time, identical tracers for MRI and quantitative autoradiography (QAR). Methods: Custom-made 13C-labeled DTPA (Specific activity--30.69 mCi/mmol) was purchased from New England Nuclear (MA, USA). Unlabeled and radiolabeled versions of Gd-DTPA (400 mM) were prepared using published methods. Male Wistar rats (275–300 g; n=6) were subjected to focal cerebral ischemia using suture occlusion of the right middle cerebral artery for 3 h followed by reperfusion via suture withdrawal. MRI imaging of BBB function was performed using the unlabeled Gd-DTPA given as an i.v. bolus (0.025mM) at 2.5 hr of reperfusion. Immediately after MRI, the rats were injected with a bolus of [13C]DTPA (~75 µC). The tracer was allowed to circulate for 20 min (similar to the duration of the MRI study) and the brains were studied by QAR. Blood-to-brain influx constants for Gd-DTPA distribution were generated using Patlak plots by off-line processing of MR images. Similar estimates were also made from the autoradiograms. Results and Conclusions: Extravascular Gd-DTPA enhancement was observed by MRI indicating acute BBB opening in parts of the ischemically damaged tissue. The autoradiograms showed similar patterns of [13C]DTPA distribution confirming the MRI observations. The influx constants from MRI and QAR methods were virtually identical: 0.004±0.001 and 0.004±0.0009 ml/g/min (p=0.696, ns; slope--0.91, R=0.61, y-x=0.002), respectively. We conclude that using identical tracers in both MRI and traditional imaging studies and their analyses using Patlak plots will help in further refining of MRI thereby leading to quantitative, rather than empirical, information about BBB damage. With further substantiation, this approach may have potential future clinical applications in evaluating BBB injury in stroke.

Presence of DWI Lesion on Acute MRI in Minor Stroke and TIA Patients Predicts Recurrent Stroke and Clinical Outcome

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Background: Minor stroke and TIA herald significant risk with an estimated 10–20% of patients suffering a new stroke within three months. We sought to examine whether the presence of DWI lesions on acute brain MRI in minor stroke and TIA patients predicts the occurrence of subsequent stroke and functional outcome. Methods: Prospectively, consecutive patients with TIA or minor stroke symptoms (NIHSS <3) were examined in the emergency room within 12 hours of symptom onset. All patients had a stroke MRI scan within 24 hours of symptom onset. The imaging was assessed for the presence of a DWI hypointensity. Occurrence of new strokes during follow-up was recorded and functional dependence assessed at 3 months. Results: Among 104 patients enrolled in this study, 61 had a DWI lesion on a baseline brain MRI scan. Patients with a DWI lesion were at higher risk of having a subsequent stroke than patients without a lesion (17.6% versus 2.7%, adjusted absolute risk difference = 14.9%, p-value < 0.001, risks adjusted for baseline NIHSS score--figure 1). Among patients with a DWI lesion, 13.1% were functionally dependent at 90 days. In contrast, all patients without a DWI lesion were functionally independent at 90 days. Conclusions: The presence of a DWI lesion on an MRI in patients presenting acutely with a TIA or minor stroke is indicative of an increased risk of a future stroke and is predictive of subsequent functional dependence. Figure 1: Stroke-free survival curves for patients with a DWI lesion and for those without a lesion. Adjusted risks of stroke at 90 days are shown as percentages on the right-hand side above the curves.
Erythropoietin Increases Expression of CuZn Superoxide Dismutase in Endothelial Progenitor Cells

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Endothelial progenitor cells (EPCs) play an important role in repair of injured vascular endothelium and angiogenesis. Erythropoietin (EPO) is a pleiotropic cytokine with tissue protective functions including ability to protect neurons and vascular endothelial cells from ischemic and oxidative stresses. More recently, it has been shown that EPO enhances proliferation, differentiation, and mobilization of EPCs. We hypothesized that the beneficial effect of EPO is mediated in part by up-regulation of EPO antioxidant capacity. The human EPCs, outgrown from circulating mononuclear cells, demonstrated cobblestone morphology and expression of endothelial differentiation markers. Treatment with EPO (0.5, 1.0, and 10 U/mL) for 24 h caused a concentration-dependent increase in expression of CuZnSOD protein (38.6±20.9, 52.9±13.6, 66.5±8.66, and 79.7±20.82 relative densitometric unit, respectively). In contrast, the protein levels of manganese superoxide dismutase (MnSOD) and catalase were not affected by EPO. In the spleen (an important source of EPCs) of EPO mice, CuZnSOD protein levels were significantly increased compared to wild type controls (108.79±9.85, and 67.24±31.75 relative densitometric unit, respectively, n=5, P<0.05). MnSOD and catalase protein expressions in the spleen of transgenic mice were not affected by EPO. The results from these studies suggest EPO is an important molecular mechanism underlying vasoprotective effect of EPO.

Genomic Sequences Mediate Negative Regulation of CADASIL Gene, Notch3

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Background: Cerebral autosomal dominant arteriopathy with subcortical ischemic leukoencephalopathy (CADASIL) is caused by stereotyped mutations in Notch3. There are currently no therapies for this disorder, which leads to recurrent stroke and vascular dementia and is associated with Notch3 deposition in arterial smooth muscle of CADASIL patients. Since Notch3 appears to be dispensable for normal development, it is conceivable that inhibition of Notch3 protein levels could be beneficial for CADASIL patients. In this study, we have characterized mechanisms governing Notch3 transcription. In Part One, we address the hypothesis that Notch3 does not have significant function in human smooth muscle cells (HSM). In Part Two, we have cloned the flanking sequences of the Notch3 gene and characterized sequences regulating Notch3 transcription in HSM: we hypothesized that certain elements in these regions are important in the regulation of Notch3 transcription. Methods: Part One: To confirm that Notch3 does not have activity in HSM, Notch3 functional analysis was performed by transfecting the intracellular domain of Notch3 fused to GAL4 (along with a GAL4 reporter) into yeast, 293 cells, and HSM. Part Two: Notch3 transcriptional regulation was investigated by creating luciferase reporter fusions carrying defined portions of the Notch3 gene 1) between -1.5kb/-1.0kb (2) between -1.0kb/-1.0kb (3) between -1.0kb/-1.0kb (4) and visual (31%). One symptom occurred in 59% and only 8% had ≥3 symptoms. Duration was 11 hour in 68% and ≥12 hours in 9%. Overall rate of stroke after TIA was 74.7% with 7.5% at 1 week, 10.4% at 30 days, 13.8% at 60 days and 17.6% at 1 year. Most strokes (80%) were ischemic without cardioembolic source. Risk of stroke increase with age (HR 1.18, 95% CI 1.11–1.24) and the number of symptoms (HR 1.45, 95% CI 1.17–1.80). Subjects with visual symptoms, particularly transient monocular blindness, were less likely to develop a stroke (HR 0.6, p<0.001). Conclusions: Risk of stroke after first-ever TIA is high in this population-based sample and comparable to prior estimates, reiterating the need for urgent evaluation after TIA.Older age and multiple symptoms at presentation increase the risk of subsequent stroke.

Plasma C-Reactive Protein Is a Risk Factor for All Subtypes of Stroke: The Rotterdam Study

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Background and purpose: Increased plasma levels of C-reactive protein (CRP) are associated with atherosclerosis and cardiovascular disease, including stroke. Whether CRP levels are differently related to subtypes of stroke is unknown. We investigated the relation between CRP levels and risk of stroke and stroke subtypes in a large prospective population based cohort study. Methods: The study was based on 6430 participants of the Rotterdam Study who at baseline (1990–1993) were aged 55 years or over, stroke-free and had blood taken. Follow-up for incident stroke was continued until January 1, 2002. Strokes were classified as hemorrhagic, ischemic or unspecified. Ischemic strokes were further subclassified according to their presumed localization (lacunar, cortical) and according to the TOAST criteria. CRP levels were measured in 2004. Data were analysed with Cox proportional hazard models with adjustment for relevant confounders. Results: During 52,611 person years of follow-up (average: 8.3 years), 497 first-ever strokes occurred (275 ischemic, 48 hemorrhagic, and 171 undetermined). High CRP levels were associated with an increased risk of stroke (HR 1.14 per SD; 95%CI 1.04–1.24). The risk increase was similar for ischemic and hemorrhagic stroke (HR per SD 1.17 (95%CI 1.04–1.31) and 1.12 (95% CI 0.84–1.49)). The risk associated with high CRP levels was similar for lacunar and cortical strokes. Stroke risk increased across different stroke subtypes according to the TOAST classification. Reported hazard ratios are age and sex adjusted, adjusted for other vascular risk factors did not significantly alter any of these associations. Conclusions: Elevated plasma CRP is a risk factor for stroke and subtypes of stroke.

Apolipoproteins A1 and B and Risk of Incident Ischemic Stroke in a Large Cohort of Coronary Heart Disease Patients

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Purpose: extensive information exists on the relationship between Apolipoprotein A1 (Apo-A1) and Apolipoprotein B (Apo-B) and cardiovascular disease, but information about their relationship with stroke is sparse. We investigated whether Apo-A1, Apo-B and the ratio of Apo-A1 to Apo-B (Apo-A1/Apo-B) were associated with elevated risk for incident ischemic cerebrovascular disease in a large cohort of patients with preexisting atherothrombotic disease. Subjects and Methods: We followed up patients with coronary heart disease for 6–8 years. At baseline, vascular risk factors and blood lipids were assessed. Among 6,671 patients with measurements of Apo-A1 (range: 56–182 mg/dl) and Apo-B (range: 39–177 mg/dl), free of stroke, 43% developed an ischemic cerebrovascular disorder during follow-up. Among the latter, 270 (4.0%) had verified ischemic stroke or TIA. Results: Higher Apo-A1 and lower Apo-A1/Apo-B ratio were associated with increased risk for ischemic cerebrovascular disease, while no association was identified with Apo-A1. Adjusting for age, diabetes, hypertension, peripheral vascular disease, and smoking, New-York Heart Association functional class, the odds ratio (OR) for incident ischemic cerebrovascular disease...
associated with Apo-B was 1.92 (95% CI: 1.41–2.63; upper vs. lower quintile), and associated with Apo-A1/Apo-B was 1.80 (95% CI: 1.29–2.51; lower vs. upper quintile). Further adjustment for LDL-C did not change the results materially, with respective OR for Apo-B of 1.86 (95% CI: 1.31–2.65) and for Apo-A1/Apo-B of 1.67 (95% CI: 1.10–2.52). Similar trends appeared for the endpoint of verified ischemic stroke/TIA. **Conclusions:** These findings support the role of Apo-B and Apo-A1/Apo-B as markers for risk of ischemic cerebrovascular disease, beyond the risk conferred by blood lipid levels.

**Regional Differences in the Increased Stroke Mortality of African Americans: The Northern Manhattan Study**

Halina White, Annette Szumski, Bernadette Boden-Alba, Armistead D Williams, III, Mitchell S Elkind, Myunghee C Paik, Ralph L Sacco, Columbia Univ Med Ctr, New York, NY

**Objectives:** To determine the effect of total dietary fat intake on ischemic stroke risk.

**Background:** The relationship between total fat intake and ischemic stroke risk is unclear. A high intake of various fat subtypes has been previously reported as having protective, deleterious and neutral effects on ischemic stroke risk. However, based on increased vascular risk ATPIII recommends that fat intake constitute 25–35% of total caloric consumption.

**Method:** The Northern Manhattan Study (NOMAS) is a prospective cohort study designed to determine stroke incidence and risk factors in a multiethnic, urban population. Study participants completed a baseline modified Block dietary questionnaire, which measured portion size and intake frequency of 77 common foods. Total fat intake was calculated from questionnaire responses and subjects were divided into quintiles by total fat intake. Cox models were used to obtain Hazard ratios with 95% confidence intervals (HR, 95% CI) for each quintile, and for a separate dichotomous model of dietary fat intake greater or less than 65g (approximately 30% of calories based on a 2000 calorie diet - the AHA recommended fat intake limit). Results: Of 3,183 subjects, 63% were women, 21% were white, 24% were black and 52% Hispanic; mean age was 69.6 ± 10 years. They were followed for a mean of 5.5 years and 142 ischemic strokes occurred. Ischemic stroke risk was significantly greater in the quintile with the highest as compared to the quintile with the lowest total fat intake (HR=1.65, 95% CI: 1.01–2.71) after adjustment for age, gender, education, race-ethnicity, hypertension, heart disease, diabetes, moderate alcohol consumption, smoking, BMI, and physical activity. Total fat intake over 65g was also associated with a significantly increased risk of ischemic stroke (HR=1.64, 95% CI: 1.17–2.30). The effect was similar across all race and sex/ethnic/rural groups.

**Conclusions:** The results of this prospective cohort study support the current AHA dietary guidelines and strongly suggest that dietary intake of total fat above 65g can increase the risk of ischemic stroke.

**High Dietary Total Fat Intake Is a Risk Factor for Ischemic Stroke: The Northern Manhattan Study**

Halina White, Annette Szumski, Bernadette Boden-Alba, Armistead D Williams, III, Mitchell S Elkind, Myunghee C Paik, Ralph L Sacco, Columbia Univ Med Ctr, New York, NY

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**Conclusions:** The results of this prospective cohort study support the current AHA dietary guidelines and strongly suggest that dietary intake of total fat above 65g can increase the risk of ischemic stroke.

**Regional Differences in the Increased Stroke Mortality of African Americans: The Remarkable Stroke Burden of Being a Southern African American**

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**Background:** Nationally, at age 45 African Americans (AA) are at 4 times the risk of dying from stroke compared to whites. This excess mortality decreases with increasing age and at age 85 there is no difference in stroke mortality. Geographic variations in stroke mortality also exist with higher rates in the Southeastern US. In this analysis we assess if regional differences in the magnitude of the excess AA stroke mortality exist. **Methods:** State level data from vital statistics between 1995–2000 were used to calculate stroke mortality rates by gender and for (non-Hispanic) white residents. Twenty-one states had a sufficiently large AA population to provide reliable estimates of stroke mortality. The age specific AA-to-white stroke mortality ratio was calculated for these states. **Results:** At all ages (45 to 85+), there was a clustering of higher AA-to-white mortality ratios among 10 southern states that include the “stroke belt” states (NC, SC, GA, TN, AL, MS, AR, and LA) and non-stroke-belt states (FL and VA). These rates appeared for the endpoint of verified ischemic stroke/TIA. **Conclusion:** There were no significant differences between dissection cases, non-stroke controls or non-dissection cases in history of migraine, current use of OCPs, or family history of stroke.
management of stroke. We present results with a novel agent that enhances post-ischemic plasticity and restores sensory and motor function in animal models of stroke. Housing of animals in an enriched environment improves functional outcome after permanent middle cerebral arterial occlusion (MCAO) in the rat. The identification of molecular pathways that control the enhancement of functional recovery by environmental enrichment could lead to novel therapeutic approaches to long-term stroke treatment. We performed a detailed gene expression analysis of this model and determined the regional and temporal expression profiles of regulated genes in the enriched (i.e., increased social interaction, greater physical activity and expanded learning opportunities) vs. standard (i.e., two rats in standard cage environment). Significantly regulated gene sets (P < 0.01, enriched environment vs. standard environment) were found in all brain regions, with most expression changes in the frontal cortex. Regulated genes are involved in modulation of cell signalling, neurogenesis and plasticity. In addition, glial genes related to axonal growth and myelination were identified. These gene expression studies led to the identification of the sigma 1 receptor as an important determinant of functional recovery after ischemia. A high selective sigma 1 receptor agonist, ADY-94806, when first applied two days after permanent focal brain ischemia in rodents, significantly enhanced functional recovery in a number of sensory-motor tests. Based on these findings, this compound is starting clinical development for long-term stroke treatment.

Differential Neural Representation of Movements That Correspond to Different Stages of Recovery

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Background: Motor recovery following stroke follows a temporal sequence from the initiation of volitional movements with synergies to isolated movements unaffected by synergy. We used functional imaging studies to determine whether movement representation patterns in recovered stroke patients vary depending on whether the movement examined is representative of early or late recovery. Methods: We examined nine recovered, right-hand stroke patients and nine matched control subjects, for brain activation patterns produced by both a movement (pace at 1 Hz) that represented earlier recovery (wrist extension and flexion) and one that represented late recovery (isolated index finger movement). Five subjects had stroke in the right hemisphere and four in the left. Functional and anatomic data sets of these four subjects were flipped to allow group analysis. FMRI data was processed and analyzed using SPM99. Significant between group differences were determined for all movement conditions using a random effects model. Result: Between group comparisons (Patient—Controls) revealed greater activation in bilateral anterior superior parietal lobe (SPL) and superior central sensor-motor cortex (SMC) during movements (wrist and finger) of the recovered hand but not the unaffected hand. The index finger movements of the recovered hand resulted in significantly more activation in the SPL and the ipsilateral cerebellum, than wrist movements. In addition, the precentral activation observed during the recovered index finger task extended intero-laterally into the face area of the motor cortex. The supplementary motor area (SMA) was consistently more active in patients than controls for all tasks. Conclusion: Movement representations in recovered stroke subjects differ from that of normal subjects and depend on whether the movement examined is representative of early or late recovery. The anterior SPL and neighboring motor cortex (e.g., face area) may form a neural substrate for representation of movements of the recovered hand, more so for fine finger movements. The increased SMA activation for all movement tasks in patients is most likely due to increased motor planning or perceived level of difficulty in executing movements.

Safety and Effectiveness of Cortical Stimulation in Patients With Hemiparetic Stroke

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INTRODUCTION: Stroke is a leading cause of disability with limited treatment options for patients with moderate to severe hand/arm impairment. We report preliminary results of a randomized, prospective, multi-center safety and effectiveness study of subthreshold cortical stimulation concurrent with rehabilitation. METHODS: 24 patients with hand/arm motor deficit from ischemic stroke at least 4 months prior were randomized to 1) implant of an epidural electrode array and pulse generator designed to deliver subthreshold cortical stimulation concurrent with each rehabilitation session or 2) rehab activities alone. The electrode array was positioned in the hand/wrist motor cortex as determined by fMRI. Both groups underwent 6 weeks of intensive OT therapy with repeated measures of function including Arm Motor Fugl-Meyer (AMFM) and the Arm Motor Ability Test (AMAT). Safety was evaluated using predetermined criteria of function, seizure occurrence and other medical complications. Effectiveness was evaluated using modified Barthel Index (MBI) at baseline, 6 weeks and 12 weeks post-implantation. Results: MBI at 12 weeks was 20.5 ± 7.3 (control) and 34.4 ± 8.9 (investational) on a 66-point scale, scores indicative of a moderate to severe upper extremity impairment. Baseline AMAT-function scores were 1.8 ± 1.0 (control) and 2.4 ± 0.8 (investational) on a 5-point scale. Both groups showed improvement in upper extremity function as measured by AMFM and AMAT. The investigational group showed greater improvements in hand/arm function compared to controls at 4 weeks follow-up (AMFM: improvement 5.5 vs. 1.9 points, P < 0.03; AMAT: improvement 0.4 vs. 0.2 points, P < 0.2). A higher proportion of investigational subjects had clinically meaningful improvements (AMFM: > 3.5 points; AMAT: > 0.2 points) than controls (AMFM: 67% vs. 25%, P < 0.05; AMAT: 75% vs. 50%, P < 0.2; both criteria: 50% vs. 8%, P < 0.03). One investigational patient had a seizure the day after implantation that was unassociated with active stimulation. Otherwise, there were no significant adverse events. CONCLUSIONS: Cortical stimulation during six weeks of rehabilitation in stroke patients is safe. In addition, preliminary efficacy evaluation suggests that stimulation improves hand/arm function over what is achieved with intensive rehab alone.

Amphetamine-Enhanced Stroke Recovery Trial: Effect of Stroke Location and Severity on Recovery Rate and Outcome

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Background: AESR is a pilot clinical trial designed to collect data critical for the design of a full-scale clinical trial testing the efficacy of d-amphetamine combined with physical therapy to facilitate motor recovery following hemispheric ischemic stroke. Block randomization was used based on stroke severity and location anticipating these factors would affect both the degree and rate of recovery. Methods: Subjects were assigned to one of 4 blocks at the time of rehabilitation admission based on stroke location (cortical vs. subcortical) and severity (Fugl-Meyer score 0–35; severe; 36–79, moderate). Assessments were performed at baseline, the end of rehabilitation and at 90 days. The effect of randomization block on recovery rate was determined with repeated measures ANOVA. Analysis is based on completed patients enrolled in Phase 1 of the study. Results: The study population included 72 subjects (mean age 65 ± 2 yr; 55% male; 79% White, 58% partial anterior, and 4% total anterior circulation strokes (Oxfordshire)). Repeated measures ANOVA showed no Group × Time interaction for the CNS score (F = 0.97, P = 0.45; NIH-SS (F = 1.64, P = 0.14), 6-min Walk Speed (F = 0.94, P = 0.47) or distance (F = 0.73, P = 0.69). FIM Score (F = 0.89, P = 0.36) or the Stroke Impact Scale (F = 0.65, P = 0.59). Final outcome did not vary with stroke location for moderate severity strokes (Fisher LSD, P > 0.05 for each scale), but did vary with stroke location for impairment level scales (CNS, Fisher LSD P = 0.0002; NIH-SS, P < 0.0001). Those with more severe strokes at baseline had poorer overall outcomes at the end of rehabilitation on most scales. Conclusion: Recovery rate measured with a variety of scales was independent of stroke severity and location. Stroke location did not affect final outcome for those with moderate strokes at the beginning of rehabilitation, but did affect final levels of impairment among those with severe strokes.

Reducing Intersession Variability for Longitudinal fMRI Studies of Motor Recovery Following Stroke in Individual Patients

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Background: To improve efficacy of fMRI for longitudinal studies of stroke recovery in individuals, inter-session variability must be reduced. The laterality index (LI) of motor activity (contralateral minus ipsilateral divided by contralateral plus ipsilateral) changes during recovery and shows greater reproducibility compared to absolute measures (e.g. counting map pixels). Objectives: We investigated a technique to reduce inter-session variability using LI of motor cortex activity. The hypothesis was that combining intra-session runs would reduce inter-session variability. Methods: Four volunteers underwent 3 separate fMRI sessions. Each session consisted of 4 runs of visually paced finger flexion at 3 rates (0.75Hz, 1Hz, 1.5Hz, self-paced) randomized into nine blocks (12 sec task, 24 sec rest). Images were collected using a GE 3T scanner and analyzed using FSL. Motor cortex was identified with anatomical MRI. LI was calculated for each run, and average LI was calculated by successively including LI from each run (run 1, run 1 + 2, etc.). Inter-session variability was calculated as the standard deviation in LI. Results: As expected, LI varied between subjects, however, inter-session variability decreased as runs per session increased (see Fig. 1). Analysis revealed a significant effect of number of averaged runs (F(18) = 3.55, P = 0.02), where inter-session variability for all 4 runs combined was significantly lower (alpha < 0.05) than that measured for only 1 or 2 runs combined. Conclusions: We have developed a method to study stroke recovery of individuals by determining the number of runs per session required to detect changes in fMRI responses over the course of recovery.

Therapeutic Exercise and Depression After Stroke

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Objective: This study assessed the effect of a specific therapeutic exercise program on depression in subacute stroke survivors and determined the influence of baseline post stroke depression on the outcomes of therapeutic exercise. Methods: This is a planned secondary...
Joint Commission Primary Stroke Center Certification: Year One Experience

Provisioned staff education, or secondary stroke prevention measures. Six (30%) certified rates for certified centers ranged from 5–14% with symptomatic hemorrhage rates post-tPA program assessment.

The American Stroke Association’s Get With the Guidelines and Acute Stroke Treatment Program – the first group of hospitals that have undergone review.

Behavioral Recovery is Enhanced by Electrical Stimulation of Peri-infarct Motor Cortex During Rehabilitative Training

recovered to baseline (pre-infarct) performance levels, and rate of recovery. RESULTS While both groups benefited from the respective therapies, monkeys that received CS/RT showed a more rapid recovery and a greater magnitude of recovery than RT monkeys. CS/RT therapy produced significant improvements in task performance by week 2 of therapy compared to week 4 for RT therapy. CS/RT monkeys achieved benchmark performance goals by day 25 of therapy compared to day 30 for RT monkeys. Maximal recovery-to-baseline was 87% for CS/RT compared to 57% for RT alone. CONCLUSIONS. We conclude that a therapeutic strategy combining rehabilitative training with concurrent electrical stimulation of peri-infarct motor cortex is substantially enhanced recovery compared to rehabilitative therapy alone. These results suggest that clinical application of this technique would be a viable method for treatment of chronic motor disability following cortical ischemic injury.

Outcomes Research

The intervention-hospital and control groups were matched in terms of age, sex, vascular risk factors, stroke outcomes, and stroke severity. The PROTECT program was associated with improved cerebrovascular outcomes, 3 months after ischemic stroke / TIA hospitalization. Larger scale prospective randomized studies, conducted in a variety of different healthcare settings, are necessary to further evaluate the effectiveness and generalizability of the program.

Joint Commission Primary Stroke Center Certification: Year One Experience

Background/Purpose: Joint Commission Primary Stroke Center certification was developed to recognize hospitals providing evidence-based acute stroke care. We evaluated the outcomes of the first group of hospitals that have undergone review. Methods: Data were obtained through application materials and on-site review. The Brain Attack Coalition recommendations, the American Stroke Association’s Get With the Guidelines and Acute Stroke Treatment Program, and the Joint Commission Disease-Specific Care Standards provided a framework for stroke program assessment. Results: 60 primary stroke center applications have been submitted to the Joint Commission, of these 20 hospitals have been certified and the remaining 40 are in the process of review. Certified and applicant hospitals range in size from 250-1000 beds, with annual stroke admissions of 300-1200 patients. 10% of hospitals are academic medical centers. Using a denominator of all stroke admissions (ischemic and hemorrhagic), intravenous tPA treatment rates for certified centers ranged from 5–14% with symptomatic hemorrhage rates post-tPA treatment consistently reported at less than 6%. Five (25%) centers inconsistently documented stroke severity by NIH Stroke Scale on medical record validation; 4 (20%) centers could not demonstrate provision of 8 hours of continuing education for stroke caregivers; 1 (5%) center was found to inconsistently provide access to stroke team care; 1 (5%) center did not provide a program for thorough assessment of TIA with initiation of secondary stroke prevention measures; 18 (90%) centers inconsistently provided smoking cessation counseling. No relationship was noted between hospital size/type with tPA treatment rate, NIH scoring, provision of staff education, or secondary stroke prevention measures. Six (30%) certified programs were GWTG centers, 2 (10%) derived data from fully automated systems, 4 (20%) utilized "homegrown" databases, and 8 (40%) used a variety of data generating methods.

Conclusions: Joint Commission certified stroke centers deliver a higher rate of intravenous tPA safety to ischemic stroke patients compared to CMS data. While varying rates of compliance with sub-components exist, certified centers hold promise for improvement of acute stroke care.

Systematic In-Hospital Initiation of Secondary Stroke Prevention Therapies Is Associated With Improved Cerebrovascular Outcomes at 3 Months Posthospitalization

The PROTECT (Preventing Recurrence Of Thromboembolic Events through Coordinated Treatment) program systematically implements, at the time of acute tIA or ischemic stroke admission, eight medication / behavioral secondary prevention therapies that target the underlying atherosclerotic process. PROTECT has previously been associated with a substantial reduction in early stroke-related death and improved functional recovery, and improved adherence to national guideline goals for vascular risk factor management. We aimed to evaluate the impact of the program on the incidence of cerebrovascular events 3 months after stroke or TIA hospitalization. Methods: Clinical outcomes were compared between 50 consecutive patients, discharged over a period of 2.6 months from a PROTECT-intervention hospital with a diagnosis of ischemic stroke or TIA, and 50 ischemic stroke/ TIA patients consecutively discharged during a 3-month period from a comparison control hospital, which utilizes conventional care. Both hospitals were tertiary medical centers and university-affiliated. Day 90 follow up data were collected prospectively through clinic visits and/or telephone interviews of patients and/or their primary caregivers, and confirmation of events made with treating physicians or corresponding medical records wherever possible. Differences in outcome frequency data between the two hospital groups were analyzed using Chi-square test. RESULTS: The intervention-hospital and control-hospital groups were matched in terms of age, sex, vascular risk factors, stroke outcomes, and stroke severity. Using the American Stroke Association’s Get With the Guidelines and Acute Stroke Treatment Program as the gold standard, we assessed the accuracy of ICD-9 codes to identify the risk factors. Main Results: Medicare Part A data had variable sensitivity but high specificity for determining the nine risk factors: arterial peripheral embolism (sensitivity 0.20; specificity >0.99), heart failure (sensitivity 0.83; specificity 0.86), stroke/TIA (sensitivity 0.99; specificity 0.36); post-stroke depression (sensitivity 0.58; specificity <0.09), coronary heart disease (sensitivity 0.57; specificity 0.96), hypertension (sensitivity 0.83; specificity 0.99), diabetes mellitus (sensitivity 0.75; specificity 0.99), heart failure (sensitivity 0.83; specificity 0.86), and valvular heart disease (sensitivity 0.35; specificity <0.09). Conclusions: Using ICD-9 codes to identify the nine risk factors is suboptimal, with variable sensitivity and high specificity. Common risk factors (coronary artery disease, diabetes, hypertension, and stroke) can be identified from ICD-9 codes alone, but additional data (e.g. chart review, procedure codes, or medications) may be needed to identify rarer risk factors (arterial peripheral embolism, intracranial hemorrhage, deep venous thrombosis).

Accuracy of ICD-9 Codes for Identifying Stroke and Cardiovascular Risk Factors

Objectives: To determine which ICD-9 codes in Medicare Part A data identify stroke and cardiovascular risk factors. Design and Participants: A cross-sectional study comparing ICD-9 data to structured medical record review from 23,657 Medicare beneficiaries aged 20 to 105 years who had atrial fibrillation. Measurements: Quality improvement organizations used standardized abstraction instruments to determine the presence of nine cardiovascular and stroke risk factors. Using the American Stroke Association’s Get With the Guidelines and Acute Stroke Treatment Program as the gold standard, we assessed the accuracy of ICD-9 codes to identify the risk factors. Main Results: Medicare Part A data had variable sensitivity but high specificity for determining the nine risk factors: arterial peripheral embolism (sensitivity 0.20; specificity >0.99), heart failure (sensitivity 0.83; specificity 0.86), stroke/TIA (sensitivity 0.99; specificity 0.36); post-stroke depression (sensitivity 0.58; specificity <0.09), coronary heart disease (sensitivity 0.57; specificity 0.96), deep venous thrombosis (sensitivity 0.61; specificity >0.99), diabetes mellitus (sensitivity 0.75; specificity 0.99), hypertension (sensitivity 0.61; specificity 0.95), and valvular heart disease (sensitivity 0.35; specificity <0.09). Conclusions: Using ICD-9 codes to identify each of the risk factors is suboptimal, with variable sensitivity and high specificity. Common risk factors (coronary artery disease, diabetes, hypertension, and stroke) can be identified from ICD-9 codes alone, but additional data (e.g. chart review, procedure codes, or medications) may be needed to identify rarer risk factors (arterial peripheral embolism, intracranial hemorrhage, deep venous thrombosis).

How Valid Are Family Proxy Quality of Life Ratings?

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Background: Proxy respondents are required to measure functional and health-related QOL (HRQOL) outcomes in at least 25% of stroke survivors. In other conditions, proxies systematically rate HRQOL lower than patients, but whether this difference is observed in stroke and how it might affect outcome assessment in clinical trials is not well studied. Methods: We compared patient and family proxy HRQOL responses in patients (P) enrolled in a clinical trial for post-stroke depression. Half the patients were depressed and half were non-depressed and all had an enrolled family caregiver as the proxy (P-N = 182 P-P pairs) who saw the patient at least four days per week and performed at least two specific caregiving tasks.
Validation of a 4-Point Prediction Rule to Stratify Short-Term Stroke Risk

Trends in Cost and Outcome of Hospitalization for Stroke and Stroke Subtypes in the United States Over the Last Decade

Validation of a 4-Point Prediction Rule to Stratify Short-Term Stroke Risk

Background: Over the last decade, several new modalities have been introduced for treatment of stroke including intravenous and intrarterial thrombolysis for ischemic stroke, and endovascular treatments for intracranial aneurysm and cerebral vasospasm. We evaluated the impact of these new strategies by analyzing changes in mortality, morbidity, and cost incurred in patients aged 20 years and older hospitalized for stroke over the last 10 years.

Methods: National estimates of hospitalization for all strokes, ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage were obtained from the Nationwide Inpatient Sample using data from 986 hospitals and spanning a 20% stratified sample of US communities. All hospitals with an emergency department were surveyed to determine the incidence, mortality and disability associated with pregnancy from a large United States cohort. The Nationwide Inpatient Sample for the years 2000–2001 was queried for all inpatient care database in the United States and contains data from 986 hospitals.

Results: There were 1,736,351 admissions in 1990–1991 and 1,956,258 admissions for stroke in 2000–2001. There were 1,129,097 and 1,259,740 admissions for ischemic stroke for 1990–1991 and 2000–2001, respectively. The mean cost incurred for ischemic stroke was $10,500 in 1990–1991 and increased to $16,200 in 2000–2001 (expected increase based on inflation alone $13,700). There was a reduction in in-hospital mortality for ischemic stroke over the 10-year period from 8.3% to 5.3% (30% relative reduction). There were 148,004 and 157,498 admissions for intracerebral hemorrhage for 1990–1991 and 2000–2001, respectively. The mean cost incurred for intracerebral and subarachnoid hemorrhage in 1990–1991 was $6,300 and $37,400, respectively. The mean cost increased to $28,800 and $62,900 in 2000–2001 for intracerebral and subarachnoid hemorrhage (expected increase based on inflation alone $23,200 and $45,700). There was a 6% and 10% relative reduction in in-hospital mortality for intracerebral and subarachnoid hemorrhage. Conclusions: There has been an increase in the cost incurred for all subtypes of stroke admissions but what is predicted by inflation alone. There has been a reduction of in-hospital mortality predominantly for ischemic stroke.

Validation of a 4-Point Prediction Rule to Stratify Short-Term Stroke Risk

Background: In the Northern California TIA study, four independent risk factors were associated with risk of stroke during the 90 days after a TIA: age >60 years, diabetes, severe hypertension, and weakness with the spell. We created a risk score by summing the number of risk factors and evaluated it as a predictor of stroke risk in two independent cohorts derived from patients diagnosed with TIA in outpatient clinics and emergency departments.

Methods: We identified all patients diagnosed with TIA in the emergency department or in urgent care outpatient clinic appointments at one of 16 facilities that managed TIA in Northern California, March 1998 - February 1999. Records were selected at random to obtain samples of approximately 1000 patients from each setting who were seen for a new TIA within 7 days of symptom onset. Characteristics of the patient, the TIA, and treatment were abstracted by means of a structured case report form. Patients undergoing diagnosis after discharge from a variety of sources, including those of out-of-hospital patients, and were adjudicated independently by two physicians. Results: Entry criteria were met by 1084 patients diagnosed in the emergency department, of whom 116 (10.7%) experienced a stroke during 90-day follow-up. Risk score stratified by score ranged from 0% among patients with zero score to 15.4% among 91 with all four risk factors (p < 0.001 for trend by rank-sum test: c statistic 0.60). In the clinic cohort, 966 met entry criteria, of whom 60 (6.2%) experienced a stroke during 90-day follow-up. Stroke risk was 2.6% among 39 with a score of zero and 11.6% among 43 with four (p < 0.001 for trend; c statistic 0.64). Conclusions: A simple 4-point risk rule–one point for age >60, diabetes, severe hypertension, and weakness with the spell--may be a useful tool in managing patients presenting within 1 week of a TIA. Validation of the rule should be repeated in a different clinical setting.

Peripartum Stroke: Incidence, Mortality, and Outcomes

Background: Peripartum stroke is an infrequent but potentially devastating event. Population-based studies of stroke incidence in pregnancy have been done, but little is known about stroke-related morbidity and disability in these women. Objective: To estimate stroke incidence, mortality and disability associated with pregnancy from a large United States cohort.

Methods: The Nationwide Inpatient Sample for the years 2000–2001 was queried for all pregnancy-related discharge codes (antepartum, cesarean or vaginal delivery, or postpartum). Strokes were classified as hemorrhagic (ICD 9 431, ischemic (434 and 436), cerebral vein thrombosis (325), or pregnancy-related cerebrovascular event (674). Discharge destination codes were considered as a measure of disability and compared for women with and without strokes. Counts, rates and standard errors were calculated using methods accounting for the survey design. Results: Of the 8,326,972 discharges with a pregnancy delivery code, there were 2,850 stroke discharges (rate 34.2/100,000 deliveries). The rate of ischemic stroke was 9.2/100,000 deliveries, hemorrhagic 6.5/100,000, cerebral vein thromboses 0.6/100,000, and pregnancy related cerebrovascular events 15.9/100,000. There were a total of 117 stroke-related deaths, for a rate of 1.4 per 100,000 deliveries and a case fatality rate of 4.1%. The majority of the fatal strokes were hemorrhagic (72.6%). The risk of stroke was 2 times higher after age 35 (58.4/100,000) than before age 35 (26.2/100,000). Twenty-two percent of stroke survivors were discharged to a skilled nursing facility as opposed to only 3% of all pregnancy-related discharges. Conclusion: Although administrative data are limited by possible coding inaccuracies, these data suggest that the incidence of peripartum stroke was higher than previously reported and that there was a dramatic increase in the rate of maternal and neonatal death. In addition, of women who survive the stroke, one fifth were discharged to facilities other than home, likely reflecting stroke-related disability. Prospective studies are needed to understand which women are at risk and which prevention strategies may reduce the likelihood of this devastating event.

Diagnosis

Defining the Ischemic Penumbra by Acute Stroke Magnetic Resonance BOLD Imaging

Background: The ischemic penumbra is defined as the “penumbra”. The “mismatch” concept–appling perfusion–(PWI) and diffusion-weighted (DWI) imaging is only a weak approximation of the underlying electro-physiological tissue status. Therefore we searched for an additional parameter reflecting the present metabolic state of the threatened brain tissue. Such a parameter is deoxy-Hb as an indicator of the oxygen extraction fraction which can be visualized by T2*-based “BOLD-imaging” (blood oxygen level dependent). We hypothesized that deoxy-Hb should be considerably increased in the penumbra. Material and methods: We analyzed data from 32 patients with acute stroke in the territory of the middle cerebral artery. Acute stroke MRI within the first 6 hours after symptom onset included FLAIR, DWI, PWI, TOF-angiography, quantitative T2- and T2*-imaging. Follow-up imaging was performed at day 1 and day 5–8. We calculated 1/T2’ = 1/T2’/T2, i.e. T2’ corrected with T2 spin-spin effects. Changes of T2’, representing the deoxy-Hb effect, were recorded in both hemispheres. Fullwidth of all images to an identical 3-D space revealed the following “regions-of-interest” (ROIs): ADC lesion day 0 (L0), TTP lesion day 0 (TTP0), final infarct size day 7 (FLAIR7), “lesion-growth” (L0-FLAIR7-L0) and “surviving tissue” (ST-TTP0-FLAIR7). Results: In the L2-images a clear signal loss in the infarcted hemispheres (L2) and “L0” was detected in the non-infarcted ROIs. The arithmetic mean of all 32 patients showed the most pronounced loss of signal intensity in “L0” (12.23%), followed by “L0” (9.06%) and “ST” (7.73%). Discussion: As expected, T2’ was shortened in “L0” (the “penumbral region”) which is a result of actual deoxy-Hb increase due to electro-physiological changes but is not strictly impaired neurons. These changes are noticeable in the reconstructed 2D-images and serve as a marker for the real penumbra region. However, the ischemic core defined by ADC decrease showed even more T2’-shortening which could be explained by previously produced deoxy-Hb which can’t be removed from the ischemic core due to highly reduced cerebral blood flow.

Metabolic Patterns Behind the Mismatch: A Comparative Study With DWI/DWI-MRI and PET in Acute and Subacute Ischemic Stroke

Background: In cerebral ischemia, diffusion weighted (DW) and perfusion weighted (PW) MRI differentiates tissue compartments based on neuronal integrity and perfusion (i.e. DW lesion, mismatch, oligemia). It remains unclear, whether these compartments correspond to the classical definition of penumbra. Using multitracer position emission tomography (PET) we defined the metabolic patterns of MRI based tissue compartments and tested the hypothesis that the concept of mismatch reflects the concept of penumbra. Material and Methods: In 14 patients (mfxbody/median 6; range 3–11) DW-MRI and PW-MRI were performed in addition to (a) arterial spin labeled blood flow (ASL, blood oxygen metabolism (CMRO2) and oxygen extraction (OEF) was performed (median 100 min MRI to PET). First, a region of interest analysis assessed the PET values in the following MRI compartments: (i) DW lesion (> 125% of relative DWI signal intensity); (ii) Mismatch DW lesion but with relative PW signal intensity < 50% of PW signal intensity; (iii) Oligemia: DW lesion but with relative PW signal intensity < 50% of PW signal intensity but TTP delay below 4 s); and (iv) contralateral reference. Then, a volumetric analysis compared the mismatch with the penumbra (relative OEF increase of > 150%) Results: Acute and subacute values did not differ significantly. DWI lesions showed low CMRO2 (< 60 μmol) and low OEF (<40%). Mismatch areas had preserved CMRO2 (>60 μmol) and normal or elevated DEF (range 43 to 70%). Oligemic areas had normal CMRO2 and normally elevated DEF (35
Clinical Predictors of False-Negative Diffusion-Weighted Imaging in the Emergency Assessment of Suspected Ischemic Stroke

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A SDE were 99% for DWI and 97.3% for SDE. However, SDE was superior to DWI in the prediction

p /H11021 /H11021 /p .0001) were significantly higher in these patients. Both

imaged

associated with a faster SDE. Ten patients developed a malignant MCA infarction (6

in Local Cerebral Blood Flow and Glucose Metabolism

Emergency Assessment of Suspected Ischemic Stroke

Clinical Predictors of False-Negative Diffusion-Weighted Imaging in the Emergency Assessment of Suspected Ischemic Stroke

A high speed of DWI

Speed of Diffusion-Weighted Imaging Lesion Expansion Within 3 Hours From Stroke Onset Predicts Evolution to Malignant MCA Infarction

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Aim: The speed of DWI lesion expansion (SDE) from stroke onset to ultra-early imaging may be used as a surrogate mark of the velocity of recruitment of the ischemic penumbra. We aimed to evaluate whether SDE predicts the evolution to malignant MCA infarction within 3 and 6 hours after acute intracranial ICA or MCA occlusion. Methods: From 152 hyperacute (<6h) patients who underwent a multiparametric stroke-MRI, 82 with an intracranial ICA or MCA trunk occlusion documented by MR-angiography were finally included after exclusion of patients in whom the exact time of stroke onset was unknown. Time-to-peak (TTP) maps and DWI lesion volumes were obtained. SDE was estimated by the ratio (DWI cc)/(time from onset to MRI). Admission NIHSS score, temperature, blood pressure and glycemia, and day 80 modified Rankin Scale (mRS) score were recorded. Results: 45 patients were imaged ≤3 hours and 37 between 3–6 hours. DWI and TTP volumes did not differ significantly between both groups. Median SDE was 6.4 cc/h, interquartile range (IQR) Q2.8–25.9. SDE correlated with baseline NIHSS (p = 0.44, p = 0.001) and day 90 mRS (p = 0.36, p = 0.001). Hypertension (p = 0.33), >1 risk factor (p = 0.23), right hemisphere (p = 0.05), and younger age (p = 0.02) were associated with a faster SDE. Ten patients developed a malignant MCA infarction (6

76 Speed of Diffusion-Weighted Imaging Lesion Expansion Within 3 Hours From Stroke Onset Predicts Evolution to Malignant MCA Infarction

Conclusions - False-negative DWI is associated with very early (<3 hours, mild NIHSS < 4), or brainstem-only strokes. These associated factors may relate to a smaller lesion size and/or less DWI hypointensity relatively to more severe and later strokes. In these circumstances, a negative DWI may not rule out ischemic stroke in patients with persistent clinical symptoms.

74 Transient Diffusion-Weighted MRI Lesions in Poststroke Seizures: Changes in Local Cerebral Blood Flow and Glucose Metabolism

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BACKGROUND AND PURPOSE: Following seizures, focal abnormality may be observed tran-
siently on diffusion-weighted MRI (DWI). Detailed mechanisms of such transient high signal intensity (THL) manifestation have yet remained unclear. In order to clarify the clinical significance and pathogenetic mechanism of THL, we performed SPECT/ PET studies combined with MRI in patients with post-stroke seizures. METHODS: During the last 6 years, 58 patients with post-stroke seizures underwent MRI studies combined with Tc-99m HMPAO SPECT and/or F-18 FDG PET in the ictal and/or perictal phases. In 14 of them (6 males, mean age 61.2 yrs). THL were observed on DWI. Results: 3 patients had subcortical diffusion defects and 2 were associated with current histopathological hypothesis for the DWI lesion and for the oligemia. However, the mismatch volume overestimated the volume of the penumbra and therefore the true risk at

70 Safety and Efficacy of Intravenous TPA Stroke Treatment in the 3- to 6-Hour Window Using a Multimodal MRI Selection Protocol

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Background: Growing data points towards IV TPA benefit beyond the 3 hours window in selected patients. Methods: We studied consecutive patients with acute MCA occlusion. Patients within 0–3h from symptom onset (A) were treated according to standard CT based criteria. Inclusion criteria for patients within 3–6h (B) were defined according to a multimodal MR protocol (12h, DWI, MRA, PWI). Complete TCD monitoring assessed clot location and recanalization criteria. NIHSS at 24h assessed neurological improvement/favouring (<4 points) and mRS<3 functional independence at third month. Results: From the 135 studied patients 56 were in the 3–6h window. Only 13 (23%) patients in the 3–6h window did not meet the MIR inclusion criteria. Finally 122 patients were treated with IVPA: A.789(65%); B.43(35%). Median time to treatment was: A; 140 minutes (range 60–360) 2.B 210(185–360). There were no differences in demographic parameters, baseline NIHSS (A17; B17 p = 0.89) and occlusion location (proximal MCA: A65.8%; B74.4% p = 0.28). Recanalization rates at 2h were similar (A44.3%; B55.2% p = 0.33) as were the hemorrhagic transformation rates (asymptomatic A15.7%; B3.7% p = 0.43; symptomatic A3.7%; B2.3% p < 0.05). The degree of neurological improvement at discharge was similar in both groups (NIHSS dropped A.63 points Vs B.61 p = 0.86). However the number of patients who benefit from treatment was slightly higher in the 3–6h group (A53.2%; B76.2% p = 0.05) while the same rate of patients worsened (A11.4%, B 7.1% p = 0.46). At three months the rate of independent patients was A42% Vs B38% (p = 0.74) Conclusions: TPA treatment can be safely and effectively extended to the

78 Transient Diffusion-Weighted MRI Lesions in Poststroke Seizures: Changes in Local Cerebral Blood Flow and Glucose Metabolism

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89 Spreading Excitotoxicity Can Result in the Evolution of Infarction Beyond the Penumbral Area in Patients With Acute Ischemic Stroke

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Background: Although it is generally accepted that DWI lesion growth occurs as a result of the evolution of the penumbral zone, it remains unknown whether the penumbra is the only tissue at risk of becoming infarcted. The aim of this descriptive study is to determine whether DWI lesion growth is limited to the penumbral zone and if it is, which clinical, radiological and molecular factors might be related to the extension of the DWI lesion volume beyond the initial hypoperfused area (penumbral -PP- zone). Methods: We studied 74 patients with an acute hemispheric infarction within the first 12h of symptoms. First DWI and PWI (MTT,4

68 Diffusion-Weighted Imaging Lesion Expansion Within 3 Hours From Stroke Onset Predicts Evolution to Malignant MCA Infarction

A high speed of DWI

Methods - We analyzed patients from a large (n = 356), representative sample of patients with clinically suspected acute stroke referred from emergency physicians to the acute stroke team. DWI scans were independently interpreted by four blinded clinicians to clinical and other imaging information (CT, MR angiography, MR perfusion). A positive DWI diagnosis of ischemic stroke required at least 3 of the blinded readers to concur. To determine the false negative rate, the blinded DWI interpretations were compared to the final diagnoses (ischemic stroke, hemorrhage, TIA, or stroke mimic) of the unblinded clinical team recorded in the medical record.

Multiple logistic regression was performed using the following variables: age, stroke severity by admission NIHSS score, stroke location (brainstem vs. other), and time from onset of symptoms to MRI. Results - A high speed of the DWI expansion (SDE) was confirmed as ischemic stroke by the clinical team. Logistic regression analysis revealed a significant association of false-negative DWI with: brainstem stroke (OR 7.3; 95% CI 2.2–25.0), time from onset of symptoms to scan less than 3 hours (OR 5.8, 95% CI 2.3–14.9), and NIHSS score less than 4 (OR 3.2–95%, CI 1–7.9). A total volume of DWI > 60 cc was found better than DWI or age. Of the 32 false-negative DWI scans, the clinical team had prospectively identified 23 of them as positive (false-negative rate: 9 of 190, 5%). A post-hoc analysis found an ischemic defect on perfusion MRI in 48% cases of false-negative DWI, suggesting that combined DWI and perfusion MRI may have a greater diagnostic yield than DWI alone

Conclusions - False-negative DWI is associated with very early (<3 hours, mild NIHSS < 4), or brainstem-only strokes. These associated factors may relate to a smaller lesion size and/or less DWI hypointensity relatively to more severe and later strokes. In these circumstances, a negative DWI may not rule out ischemic stroke in patients with persistent clinical symptoms.
In-Hospital Treatment

Silent Cerebral Ischemic Lesions After Carotid Artery Stenting With Cerebral Protection
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PURPOSE: To evaluate by diffusion weighted MRI (DW-MRI) ischemic, silent cerebral lesions produced after carotid artery stenting (CAS) with distal cerebral protection in patients with ICA stenosis ≥70. METHODS AND MATERIALS: From August 2003 to July 2004, 96 (CAS) were performed. Mean age of the patients was 67.3 (range 37–82)(74 male), and 72 (75%) were symptomatic. All patients wee on aspirin and clopidogrel for at least three days, and heparin 24 hours before CAS. Four different types of cerebral protection systems were used: EPI 18 (18.8%), SPIDER 18 (18.8%), EZ 50(S2), Acceun 9 (9.4%) Emboshield 1%. The mean length of the whole procedure was 22.2 minutes (range: 8–110). Transient occlusion of the filter occurred in three cases. Every patient had a MRI of the brain (T1, DP-T2, FLAIR, FFE-T2 and DWI) done in the three days before CAS and DW-MR (eco planar single shot, b= 1000 mm2/s) in day 1 after CAS. RESULTS: There were no minor stroke, major stroke, death, or myocardial infarction in the 30-day post-CAS period. Only transient ischemic attack was observed. DW-MRI after CAS showed 30 new silent ischemic foci in 14 patients (14.6 %). An isolated lesion was seen in 7 patients, whereas they were multiple in the others (range 2–6). Lesions were seen mainly in the ipsilateral medial cerebral artery (27); 2 in the posterior fossa, and 1 in the contralateral medial cerebral artery CONCLUSIONS: The use of cerebral protection devices seems safe, however, cerebral lesions due to distal emboli could be observed after CAS in 15% of the patients. Although clinically asymptomatic, their immediate and late consequences should be tested through neuropsychological test. Diffusion weighted image has a high sensitivity in the detection, localization, and counting of this ischemic-related lesions.

Systemic Thrombolysis in German Stroke Units Before and After Approval of rtPA
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Background: Systemic thrombolysis with rt-PA within 3 hours after onset of focal cerebral ischemia was approved in Germany in August 2000. The aim of this study was to investigate changes in patient selection and outcome compared to the time when thrombolysis was not yet approved for this indication. Methods: 11 Neurology departments with acute stroke units participated in the German Stroke Study Collaboration before (1998–99, N =4160) and after (8/2000–3/2002, N=3663) approval of rt-PA in Germany and consecutively registered all patients with acute ischemic stroke. A predominantly central follow-up 100 days after admission assessed functional outcome and death. Results: Frequency of systemic thrombolysis in patients admitted within 3 hours after symptom onset increased from 11.6% before approval to 18.1% after approval of rt-PA. The thrombolysis rate among all acute ischemic stroke patients was 9.8% before and 12.9% after approval of rt-PA. The proportion of patients over 75 years among those treated with rt-PA increased substantially from 9.9% to 19.4%. There were no further significant differences in baseline characteristics, complications or outcome between both study periods. Conclusions: While proportionally more and partially younger patients could be treated with systemic thrombolysis after official approval of rt-PA for treatment of acute ischemic stroke, there was no significant increase in complications or change in outcome in the two study periods. This may be explained by greater legal security as well as a learning curve of patient selection. Outcome distribution in both study periods was comparable to those of randomised studies.

Real Time Wait Times for Carotid Endarterectomy in a Canadian Teaching Hospital
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Background: Recent analyses of data from the randomized trials of carotid endarterectomy (CEA) for symptomatic carotid stenosis show that the benefit from CEA is highly dependent on the time between the ischemic event and surgery. In general, the greatest benefit is derived when surgery is performed 6 hours after the ischemic event. In most centers, the time between the decision for surgery and CEA was 1.9 weeks (range 0–51). For 61 patients with a prior ipsilateral event (n=64), the median time between the decision for surgery and CEA was 1.9 weeks (range 0–51). Conclusion: Most patients who underwent CEA for symptomatic carotid stenosis at our hospital in 2003 had the operation outside the time frame of benefit demonstrated by the best available evidence from randomized trials. Despite thorough review of all documentation, the date of symptom onset could not be determined in one fifth of the cohort. There were long delays in the patient reaching the surgeon. There were also shorter, but substantial, delays between surgical consultation and operation. Further work is required to improve data quality and to understand and rectify the many possible causes of these delays if the full benefit of CEA is to be realized.

Routine Electrocardiographic Telemetry After Acute Cerebral Infarction Improves Detection of Arrhythmias
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Abnormal ECG’s are frequently recorded in patients with acute stroke, and may contribute both to identification of the patient’s risk factors of stroke as well as to identification of cardiac co-morbidity. The aim of this study was to investigate if ECG telemetry added to the information from a 12-lead ECG on admission. Patients and methods: The analysis was based on 692 patients with acute cerebral infarction (diagnosis based on clinical findings and CT-scan in all patients) who were admitted within 6 hours after symptom onset. ECG in 12 leads was recorded on admission and ECG telemetry was continued for the first 12 - 24 hours after admission. The ECG’s were analysed according to general guidelines by one observer (FC) who was blinded to all other information. Results: In 41.6 % of patients, we observed ECG abnormalities in the telemetry recording that was not identified by ECG in 12 leads on admission. This included findings that need urgent cardiac intervention: asystolia (> 2 sec). was found in 61.1 % of patients, ventricular fibrillation in 2.2 % of patients, and ST-depression in 0.6 % of patients. Tachycardia with HR > 120 bpm (in 13.3 % of patients) and bradycardia with HR < 45 bpm (in 7.7 % of patients) were frequent findings, and 1.9 % of patients had episodes of both tachycardia and bradyarrhythmia, suggesting a sick sinus syndrome. Conclusion: The use of ECG-telemetry after acute cerebral infarction is well justified by the observed diagnostic yield as intervention in these cases may reduce mortality and morbidity.

Safety Outcomes of Alteplase in Ischemic Stroke Patients With Special Characteristics
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Objective: To examine whether patients in special subgroups (i.e., >70 years old, with NIHSS score >20, diabetes, congestive heart failure (CHF), and of Hispanic origin) have a higher risk of intracranial hemorrhage (ICH) than patients without these characteristics. Methods: Four prospective observational studies were identified and combined for this analysis, which included the Standard Treatment With Alteplase To Reverse Stroke Study (STARS, N=399), Epidemiology Study Of Ischemic Stroke (EIS, N=133), University Of Texas Houston Stroke Study [UT, N=241], and Canadian Activase For Stroke Effectiveness Study [CASES, N=1135]. The risk of ICH was calculated for all patients and for each of the five subgroups separately. Results: Overall the risk of symptomatic ICH was 4.7% (95%CI: 3.8–5.8%) and the risk was similar among patients with and without each of the five characteristics. See Fig. 1. In addition, the ICH risk was comparable to findings reported in the pivotal trial conducted by the National Institute of Neurological Disorders and Stroke (6.4% [95%CI: 4.0%–9.7%], NEJM 1995). Conclusions: Results from this analysis of a largest dataset suggest that subgroups of patients are not at increased risk of ICH compared to the overall indicated patient population.

Transient Ischemic Attack: Misperception and Missed Opportunity
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Background and Purpose: It is well known that there is a time-dependent risk of stroke and other vascular events with transient ischemic attacks (TIA). Nevertheless, TIA is perceived as a much less serious condition than stroke by the public and professionals. The evaluation and management of TIA varies considerably. We hypothesized that hospitalized TIA-patients receive less diagnostic testing, therapy and teaching, than stroke patients. Methods: Patients consecutively admitted with TIA (n=91) or Stroke (n=94) from 2/1/04–6/1/04 at a regional medical center were studied. Demographics, Risk factors, diagnostic testing, medications, and patient education data were compared using Chi- square test for categorical variables, t-test (normally distributed), or Wilcoxon Rank sum test (non- normal) for continuous variables. The patients were admitted by primary care physicians and neurologists were consultants. Results:
Stroke Protection by Farnesyltransferase Inhibitors Is Mediated by Ras-p21

Seventy-two hours after the stimulation and 24 hours after MCAO animals were euthanized, brains removed, dissected or sliced, and levels of UCP4 and mRNA in the areas corresponding to the core, penumbra and unaffected cortical areas were evaluated. FN stimulation increased membrane via farnesyl group. Since cerebral ischemia leads to excitotoxicity and increased ROS levels we investigated whether the brain damage induced by an excitotoxic stimulus could be modified by pre-treatment with farnesyl transferase inhibitors (FTIs). Mouse neuronal cortical cells survival was assessed measuring the cellular reduction of [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] (MTT) by mitochondrial dehydrogenase. Farnesylation inhibition was measured in brain tissue homogenates by western blot analysis with monoclonal anti-pan Ras antibody pointing out the shift from the membrane-bound p21 Ras to a free cytosolic p21-Ras. ROS production was measured in brain tissue by the hydroethidine method. Excitotoxic lesions were produced by unilateral intraarterial injection of N-methyl-D-aspartate 75 mM (NMDA) with or without the farnesyl transferase inhibitors FTI-277 (20 μ M) or FTI-180 (180 nm). The brain necrotic area was evaluated staining the tissue with thionine. In cultures, pretreatment with FTI-I significantly increases the percentage viability of cortical neurons following 3 different doses of oxidative stress 7.5%: 3%, 32%: 15%, 1%: vs control 48%: 48%, 31%: 3%, 8%: 0.5% respectively (p < 0.05). Pretreatment with FTI-I caused the accumulation of non-pretreated inactive Ras in the cytosolic fraction of the brain homogenate tissue. In brain tissue, pretreatment with FTI-277 reduced brain injury by 65%: 2.3 m3/mm3 (n=5) vs control 38: 4.3 m3/mm3 (n=5) and FTI-I by 40%: 32.2: 1.2 m3/mm3 (n=6) vs control 54: 2.2 m3/mm3 (n=6) (p < 0.05), respectively. Thus FTIs inhibit injury: decrease oxidative stress and reduce excitotoxic brain damage. Considering the important role that oxidative stress and excitotoxicity play in the mechanisms of ischemic brain injury, farnesyltransferase inhibitors may be a novel neuroprotective strategy for the treatment of ischemic stroke.

Neuroprotective Stimulation of the Cerebellar Fastigial Nucleus Modifies Expression of Uncoupling Protein 4

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Excitatio of the cerebellar fastigial nucleus (FN) neurons affords prolonged neuroprotection through the unknown mechanisms. Our data suggest that FN stimulation increases mitochondrial tolerance against damaging insults. Mitochondria play a key role in the mechanisms of the ischemic cell damage. Mitochondrial membrane potential partially regulated by UCPs determines mitochondrial stability and functioning. It was demonstrated that UCP2 might be involved in the ischemic preconditioning neuroprotection. We hypothesized that stimulation of FN might affect expression of brain-specific UCP4. In Sprague Dawley rats we compared levels of UCP4 (Western blot and immunocytochemistry) and UCP4 mRNA (dot blot and in situ hybridization) in the cortex of naïve rats, rats after permanent middle cerebral artery occlusion (MCAO), and rats received FN or cerebellar dentate nucleus (DN) stimulation 72 hours prior to MCAO. Seventy-two hours after the stimulation and 24 hours after MCAO animals were euthanized, brains removed, dissected or sliced, and levels of UCP4 and mRNA in the areas corresponding to the core, penumbra and unaffected cortical areas were evaluated. FN stimulation increased
levels of specific mRNA by 55%±15% (p<0.05, n=4) as well as UCP4 (22.1±1%, p<0.05, n=8) throughout the cortex. After MCAO alone mRNA levels slightly decreased in the core (−7.2%, p<0.05, n=4) and were unaffected in all other areas. However, UCP4 increased in the core area by 16.8% (p<0.05, n=5) and slightly elevated in the penumbra and unaffected cortices (−7.2%). When MCAO was preceded by FN stimulation mRNA levels did not change in the core or penumbra but dramatically increased in the unaffected ipsilateral cortex (85.2±21%, p<0.01, n=4). Surprisingly levels of UCP4 decreased by 17.3% (p<0.05, n=4) in these areas. Our results demonstrate a consistent significant increase in the UCP4 expression in the FN stimulated animals. Combination of FN stimulation and MCAO significantly boosted levels of specific mRNA expression in the ipsilateral to the occlusion cortex. These findings suggest that FN-evoked neuroprotection might involve modification of UCP4 expression, which can exert neuroprotective effect by rendering mitochondria more tolerant to ischemic insult.

### Matrix Metalloproteinase Induction by EMMPRIN Is Not Affected by Recombinant Tissue Plasminogen Activator in Experimental Focal Cerebral Ischemia

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Recombinant tissue plasminogen activator (rt-PA) is successfully used in human ischemic stroke. The main drawback is the development of hemorrhage related to microvascular basal lamina damage. Matrix metalloproteinases (MMP) are critically involved in the degradation of the basal lamina after ischemia, their activity is coregulated by a MMP inhibitor protein (EMMPRIN). We investigated the effects of rt-PA on the MMPs and EMMPRIN. Experimental cerebral ischemia in rats was induced for 3 h and followed by 24 h reperfusion (suture model). Each group (n=6) received either treatment (18 mg rt-PA/kg body weight) or saline (control) at the end of ischemia period; 6 animals were sham-operated. EMMPRIN expression was measured by Western blot of the ischemic and non-ischemic basal ganglia and cortex separately. Zymography was used to detect MMP-2. Compared with the control area, EMMPRIN expression was significantly increased in the ischemic hemisphere: 158%±16% (-0.05) cortex; 128%±22% (p<0.05). As shown previously the high dose rt-PA resulted in an activation of MMP-2, but no significant further increase was observed. rt-PA administration (figure). EMMPRIN, as a MMP activation system, is shown to be relevant in cerebral ischemia. These results suggest that the expression of EMMPRIN is responsible for known increased content of MMPs following cerebral ischemia and reperfusion. The increased MMP-2 content after rt-PA administration is independent from EMMPRIN, which might be attributed to another activation pathway.

### Hemorrhage

#### Magnesium Sulfate in Aneurysmal Subarachnoid Hemorrhage: A Randomized Controlled Trial

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Background and Purpose: Magnesium reverses cerebral vasospasm and reduces infract volume after experimental subarachnoid hemorrhage in rats. We aimed to assess whether magnesium reduces the frequency of delayed cerebral ischemia (DCI) in patients with aneurysmal subarachnoid hemorrhage (SAH). Methods: Patients were randomized within 4 days after SAH. Magnesium sulfate therapy consisted of a continuous intravenous dose of 64 mmol/day, to be started within 4 days after SAH and continued until 14 after occlusion of the aneurysm. The primary outcome DCI (defined as the occurrence of a new hypodense lesion on CT compatible with clinical features of DCI) was analyzed according to the 'on-treatment' principle. For the secondary outcome measures 'poor outcome' (Rankin > 3) and 'non-excellent outcome' (Rankin > 0) we used the 'intention-to-treat' principle. Results: 283 patients were randomized. Magnesium treatment reduced the risk of DCI by 34% (hazard ratio 0.66, 95% confidence interval 0.53–0.81). After three months the risk reduction for poor outcome was 23% (risk ratio 0.77; 95% CI 0.54–1.09). At that time 18 patients in the treatment group and 6 in the placebo group had an excellent outcome (RR for non-excellent outcome 0.91; 95% CI 0.64–0.98). Conclusions: This study strongly suggests that magnesium has a neuroprotective effect in patients with SAH. Magnesium reduces DCI and subsequent poor outcome, but the results are not yet definitive. A next step should be a phase III trial to confirm the beneficial effect of magnesium therapy, with poor outcome as primary outcome.

#### Phenylpropanolamine in Cold Remedies and Risk of Hemorrhagic Stroke: Acute Brain Bleeding Analysis Study


Objectives: Phenylpropanolamine (PPA) in appetite suppressants has been suggested as an independent risk factor for hemorrhagic stroke in young women. However, the risk of low dose
In cold remedies remains to be clarified. We performed a study to assess the risk of cold remedies containing low dose PPA for hemorrhagic stroke in Korean population. Methods: Patients with hemorrhagic stroke were prospectively recruited from 33 hospitals in Korea between October 2002 and March 2004. Eligibility criteria for patients include non-traumatic acute hemorrhagic stroke confirmed by neuroimaging studies, aged 30 to 84 years, absence of a history of stroke or hemorrhage-prone brain lesions, and the ability to complete the interview within 30 days after the onset. Each case was matched to 2 controls (hospital and community) on age and sex. Pre-trained interviewers obtained information including drugs taken within 2 weeks before the onset of stroke. Results: There were 940 patients and 1880 controls. All PPA-containing drugs reported were cold remedies. The rates of PPA exposure within 2 weeks were 1.7% for hemorrhagic stroke patients and 0.7% for controls. The PPA dose per day for hemorrhagic stroke patients was 73.4±57.0 mg/day (12–240 mg/day). The unadjusted odds ratio (OR) of PPA exposure for hemorrhagic stroke was 2.46 (95% CI, 1.15–5.24). After adjusting for age, hypertension, a history of stroke, and recent upper respiratory infection, ORs were 2.14 (95% CI, 0.94 – 4.84) for all subjects, 3.86 (95% CI, 1.08 – 13.80) for women, and 1.75 (95% CI, 0.45 – 4.15) for men. For all subjects, ORs significantly increased with the recent exposure (≤ 3 days between exposure and onset, p = 0.017 on likelihood ratio test for trend) and longer duration of exposure (> 3 days, p = 0.037). For women, OR also increased with higher dose (> 75mg/day, p = 0.023). According to the stroke type, ORs were 1.68 (95% CI, 0.58 – 4.89) for intracerebral hemorrhage and 3.96 (95% CI, 0.97 – 16.08) for subarachnoid hemorrhage. Conclusions: This study suggests that low dose PPA in cold remedies may increase the risk for hemorrhagic stroke, especially in women.

Outcome Following Intracerebral Hemorrhage Defined by Location: A Population-Based Study
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Background: Morbidity and mortality following intracerebral hemorrhage (ICH) have been reported in small population-based studies. We present the largest population-based study of outcome following ICH to date, with stratification by location of hemorrhage. Methods: All patients >20 hospitalized with nontraumatic ICH in the Greater Cincinnati area were identified from 5/87 to 7/01 and 8/02 to 4/03. Mortality was plotted using actuarial methods. Differences in mortality were assessed using the log-rank test and pairwise comparisons. Morbidity among patients surviving at least 1 month, defined as the last available modified Rankin Scale (mRS) score within 30 days of ictus, was assessed with the Kruskal-Wallis test. Results: There were 1,051 ICHs identified. Cases in Asian Americans (8), a Hispanic American (1), and of unknown location (4) were excluded, leaving 1,038 cases (823 white, 215 black). Survival curves are presented in the figure. The log-rank test showed a difference in survival by location (p = 0.0158). Survival was no different for lobar and deep cerebral ICH (p = 0.2044) or lobar and brainstem ICH (p = 0.0965), but worse for lobar than cerebellar ICH (p = 0.0159). After adjusting for age, race, and sex, survival after ICH was better than brainstem ICH (p = 0.0213). Among survivors, the median last available mRS did not differ by location (p = 0.1529). Conclusions: Mortality did not differ between deep cerebral and lobar ICH in this large population-based study. Survival is best for cerebellar ICH. Short-term functional outcome among survivors did not differ by location.

Microemboli Contribute to Subarachnoid Hemorrhage–Associated Cerebral Ischemia
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Background and Purpose: Cerebral ischemia commonly complicates subarachnoid hemorrhage (SAH) and has been traditionally associated to vasospasm. However, the determinants of cerebral ischemia commonly complicates subarachnoid hemorrhage (SAH) and has been traditionally associated to vasospasm. However, the determinants of cerebral ischemia are not well understood as many patients with vasospasm do not develop ischemic complications. This study was conducted to evaluate the role of microemboli in SAH-related ischemia. Methods: Aneurysmal SAH patients with a secured aneurysm on or before day 4 after SAH were prospectively monitored clinically for cerebral ischemia and ultrasonographically for vasospasm and microemboli on a daily basis until day 14 or discharge. Vasospasm was defined as an intracranial to extracranial carotid ratio of ≥ 3 and a mean flow velocity of ≥ 120 cm/s. Both middle cerebral arteries were monitored for 30 minutes for microembolic signals (MES) which interrupted the middle cerebral artery M-mode spectrum in a time-defined manner and were ascertained by two observers. Cerebral ischemia was assessed by a stroke neurologist blinded to the ultrasonographic data. Chi-square analysis was used to identify ultrasonographic data that was associated with cerebral ischemia. Results: Of the 22 patients studied, 8 (36%) had MES detected 6 days (range 2–13) after SAH. Ischemia was noted in 7/8 with MES and 4/14 without MES (p = 0.201), and in 7/11 with vasospasm and 4/11 without vasospasm (p = 0.201). Using both MES and vasospasm as markers for clinical ischemia did not improve diagnostic accuracy (0.77). The presence of a proximal aneurysm to the vessel with MES, the mode of securing the aneurysm or the simultaneous occurrence of vasospasm in the monitored vessel was not associated with the occurrence of MES. Conclusions: Microembolism is a common phenomenon in SAH and may represent a novel mechanism of ischemia in this condition. There does not appear to be a synergistic effect of microemboli and vasospasm on the development of ischemia, although this finding could be influenced by the small sample size. Further studies should determine the origin and composition of MES in SAH. Acknowledgement: This work was supported by an AHA Florida Affiliate Grant 03535287.

Simvastatin Attenuates Serum Markers of Vasospasm After Aneurysmal Subarachnoid Hemorrhage
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INTRODUCTION: Cerebral vasospasm is a major source of morbidity following aneurysmal subarachnoid hemorrhage (SAH). Early reduction of vasoconstrictive injury occurs in patients developing cerebral vasospasm. We previously demonstrated that simvastatin, a 3-hydroxy-3-methylglutaryl coenzyme reductase inhibitor, exerts anti-inflammatory effects in the injured central nervous system, and prevents cerebral vasospasm and delayed ischemic deficit in a murine model of SAH. Based on these preclinical data, we hypothesized that simvastatin would reduce serum markers of inflammation, central nervous system (CNS) and vascular injury in a clinical population of patients with aneurysmal SAH. METHODS: Patients with SAH were randomized to receive 80 mg/day simvastatin (n = 9) or placebo (n = 8) for 14 days. Plasma AST, ALT, and CPK were recorded daily to evaluate the occurrence of hepatitis or myositis. Plasma markers, including von Willebrand factor (vWF), a member of the TNF superfamily and an inflammatory marker, were recorded daily. Patients underwent serial TCD and clinical examinations to assess for the occurrence of vasospasm. RESULTS: Two patients developed clinically insignificant transmetits with simvastatin treatment. No patients developed CKP elevation. Plasma vWF, S-100, and TWEAK were markedly decreased 3 - 10 days after SAH (p < 0.05) in patients receiving simvastatin versus placebo. TCD evidence of vasospasm (velocity > 140 cm/sec) occurred in 38% (3/8) of placebo versus 0% (0/9) in simvastatin treated patients. CONCLUSION: The use of simvastatin as prophylaxis against delayed cerebral ischemia following aneurysmal SAH is a safe and effective treatment for cerebral vasospasm.
well-tolerated intervention. Its use attenuates surrogate markers of endothelial damage and inflammation that predict vasospasm, and may decrease the incidence of vasospasm.

De Novo and Regrowth Cerebral Aneurysm on Follow-up Screening: Retrospective Assessment of DSA or CT at Time of Initial SAH

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Patients who are clipped for a ruptured intracranial aneurysm are at risk for a rebleed from a newly formed aneurysm. To prevent rebleeding, screening on new aneurysms might be useful. If new aneurysms are found with screening, the question arises whether these positive findings developed after the SAH or whether they are retrospectively visible. - Purpose: to compare aneurysms detected with CT screening with the initial postoperative subtraction angiography (DSA) and/or CT angiography (CTA). Methods: 494 patients with a clipped ruptured intracranial aneurysm, admitted between 1983 and 2000 were screened by means of multislice CTA. One hundred patients had 136 positive findings, either at the clip site (23) or at a different location in the circle of Willis (113). Of 313 patients with an initial postoperative DSA was available, we were not present after the operation. Of the 63 aneurysms at a different location than the clip site, 18 (29%) were not present at time of the initial SAH. 45 aneurysms (71%) were retrospectively visible and 12 of these aneurysms (27%) had enlarged since the initial SAH. Five of the 18 new aneurysms were <3 mm, 11 were 3–5 mm, 1 was 6–10 mm and 1 >10 mm. Eleven of the retrospectively visible aneurysms with a stable size were <3 mm, 20 were 3–5mm and 2 were 6–10 mm. Increase in size of retrospectively visible aneurysms was seen in 8 aneurysms of 3–5mm and of 6–10 mm size. [2] More than half of the missed aneurysms were located at the carotid artery where differentiation with infundibulum or atherosclerotic blebs can be difficult.

Conclusions: De novo aneurysms are found in 4% and missed aneurysms in 9% in screening CTA of patients with past history of SAH. More than one quarter of the missed aneurysms have grown since the initial scan or DSA.

Acute Management

New York State Department of Health Stroke Ctr Designation Project

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Objective: To determine if stroke center designation and selective triage of acute stroke patients improves quality of care. Background: Many hospitals lack the infrastructure required to treat acute stroke patients. The Brain Attack Coalition (BAC) published guidelines for the establishment of primary stroke centers (PSC). Methods: The New York State Hospital Emergency Medical System (EMS) and NYSDOH collaborated on this study involving 32 hospitals serving Brooklyn and Queens. Baseline medical record review was performed on all stroke admissions (based on ICD-9 codes) from March - May 2002. Hospitals were invited to meet BAC guideline-based criteria. Adherence was verified by on-site visits. Designation took effect on May 5, 2003. Remeasurement data was collected from August - October 2003. Results: We abstracted 1598 cases at baseline vs. 1464 at reevaluation, with 57% admitted to the 14 designated stroke centers. An ED diagnosis of stroke was made in 970 patients (76% ischemic) at baseline vs. 918 (72% ischemic) at remeasurement. Median door to physician contact time decreased from 25 to 15 min overall (p<.05) and 10 min in stroke centers (p<.05). Median door to CT time decreased from 125 to 95 min overall (p<.05) and 65 min in stroke centers (p<0.05). Among potential ITPA candidates, it decreased from 65 (n=169) to 53 min (n=206) overall (p<.05) and 32 min (n=162) in stroke centers (p<.05). Median door to ITPA time decreased from 105 (n=18) to 98 min (n=38) overall (ns) and 95 min (n=32) in stroke centers (p<.05). IV ITPA utilization increased from 2.4% (1873) to 5.2% (378/75) overall (p<.05) and 7.7% (32/416) in stroke centers (p<.05). Select ITPA protocol violations decreased from 11.1% (218) to 7.9% (33/478) overall (ns) and 6.3% (2/52) in stroke centers (ns). Conclusions: AHA and NYSDOH collaboration facilitated stroke center designation which improved the quality of stroke care and access to timely thrombolytic therapy. This data provides evidence to support stroke center designation and selective triage of acute stroke patients.

“Get With The Guidelines—Stroke” Improves Acute Intervention in Patients Hospitalized With Ischemic Stroke or TIA

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Background: There have been several national registries developed recently with a goal of improving stroke care. Get With The Guidelines (GWTG)-Stroke is the American Stroke Association program to improve the practice of acute stroke care in metropolitan areas in the U.S., or TIA. Methods: We used inter-hospital collaborative meetings, best practice sharing and an Internet tool for data collection, reporting and decision support in a cohort of 21,563 clinically identified patients from 99 participating hospitals. Data collection comprised baseline (collected prior to 4/03) and four consecutive quarters (4/03 to 3/04). Patients from 3 CDC-funded Paul Coverdell acute stroke registry prototypes (MA, OH, GA) were included if the hospitals used the GWTG tool for data entry and GI during all 4 quarters after baseline. We focused on increasing use of t-PA, generated descriptive data on documentation of eligibility (why no ITPA) in patients who arrived <2 hr (<ED–2 hr + ITPA) or <3 hr (ED–3 hr < ITPA) after symptom onset, with an emphasis on use of ITPA within 60 min (ITPA–60 min), monitoring symptomatic systemic or intracranial hemorrhage (IV ITPA Comp) and antithrombotics within 48 hours when appropriate (Rx AT 48hr). Compliance (% was recorded at each quarter and compared to baseline; trends over time were assessed by Mantel-Haenszel chi-square test. Results: Clinically meaningful improvement occurred in 4 measures with significance achieved by Q1 for all 4 measures. There was no increase in the rate of bleeding after ITPA. There was also no increase in early IV ITPA use. Conclusion: GWTG-Stroke implementation was associated with dramatic improvement in rates of acute antithrombotic and IV thrombolytic therapy in appropriate patients and occurred without increased complications. By Q4, only 15% of all acute stroke patients were without any evidence of consideration for IV ITPA. Opportunities for improvement remain and ongoing performance needs to be monitored. Reduced door-to-needle time is a priority and will require new strategies.

94 Results from the First 2200 Patients in the Safe Implementation of Thrombolysis in Stroke Registry: Symptomatic Intracranial Hemorrhage Still at Low Rate


The SITS registry, based on internet and daily updated automatic feed-back reports, includes over 350 centers in 26 countries. An increasing proportion of these centers had no experience of i.v. thrombolysis of stroke patients before they joined the SITS registry. An analysis of the first 652 patients, one year ago, with almost entirely experienced centers participating, indicated that the rate of symptomatic intracranial hemorrhage (SICH), defined as a clinical deterioration of 4 points on the NIHSS combined with large intracerebral haemorrhage (PH2) was less than 2%. The corresponding rate of any post-treatment haemorrhage combined with any clinical deterioration was 4.6%, compared to 8.6 % in randomised controlled trials. In August 2004, with more than half of the centers lacking previous experience, and with more than 2200 patients included in the registry, the rate of SICH is still below 2%. To confirm correctness of reporting SICH events, source data monitoring independence of imaging scans have been performed, and in-depth audits at a number of centers are planned later in 2004. Although SITS data suggest a learning curve for inexperienced centers for logistics, e.g. for door-to-needle time, accumulating data indicate that the rate of SICH is still low even with a large proportion of centers with limited earlier experience of the treatment. This is encouraging in the perspective of broad implementation of the treatment, but close monitoring should continue.

Geno-ITP: A Pharmacogenomic Approach to Identifying Polymorphisms Modifying Safety and Efficacy of Thrombolysis for Acute Stroke

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Background and Objective: Individual response of similar stroke patients [i.e. Middle Cerebral Artery (MCA) occlusions] to I-PA treatment may be very different ranging from complete recanalization associated with total recovery to dramatic brain bleedings with high mortality and morbidity. Methods: Among the studied genes those that decreased recanalization associated with t-PA infusion by 30% or more were selected from previous studies. Results: t-PA infusion in patients with a clipped ruptured intracranial aneurysm resulted in symptomatic intracranial hemorrhage in 158 patients (n=158) who were included in the study. Among the studied genes those that decreased recanalization rates by the end of t-PA infusion (evaluated at six hours post t-PA) were: ACE I allele (51% vs. 91% - p<0.001), TAFI
homocytotes (22.2% vs 65.5%, p = 0.011) and A<sub>v</sub>Thr312 fibrinogen allele (44% vs 72%, p = 0.047). Regarding hemorrhagic transformation FXII Leu24 influenced the appearance of symptomatic haemorrhages (12.5% vs 3%, p = 0.025) and this allele was also associated with higher mortality rates (22.2% vs 8.3%, p = 0.021). **Conclusions:** Genetic background of stroke patients greatly conditions their individual response to thrombolytic therapy. In the future a pharmacogenomic test might increase t-PA safety and efficacy.

### Clinical-CT Mismatch Is Not Useful in Selecting Acute Stroke Patients More Likely to Benefit From Thrombolytic Therapy

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**Background:** Mismatch between clinical deficits and imaging lesions in acute stroke has been proposed as a method of identifying patients who may have hypoperfused but still viable brain, and may be especially apt to respond to reperfusion therapy. We explored this hypothesis using the ASPECT scores on CT scans in a combined database including 4 major thrombolytic therapy clinical trials (NINDS, ATLANTIS A and B, and ECASS 2). Methods: To determine what the radiological correlates of a “matched” functional deficit are, we reviewed a sample of patients without significant mismatch. We therefore calculated the relationship between the ASPECT score of the 24-hour (follow-up) CT scan and the 24-hour National Institute of Health Stroke Severity (NIHSS) score on the sub-sample with ASPECT scores done at this time (n = 820). Based on this empirical relationship, we computed the absolute difference between the observed baseline ASPECT score and the “expected” score (i.e. matched) based on baseline NIHSS for all patients (n = 2131). We tested whether patients with better than expected baseline ASPECTs were more likely to benefit from rt-PA. Results: At 24 hours, there was a strong, linear negative correlation between NIHSS and ASPECTs (r-square = 0.33, p < 0.0001); on average, an increase of 10 points on NIHSS corresponded to a decrease of about 3 points on ASPECTs. At baseline, the average degree of mismatch between the observed and “expected” ASPECTs was 2.1 points (inter-quartile range 1.0 to 3.4). The degree of this difference between observed and expected ASPECTs did not predict who would benefit from rt-PA therapy (p-value for the interaction = 0.72). Multiple secondary analyses failed to reveal any consistent relationship between the degree of clinical-CT mismatch at baseline and a patient’s likelihood of benefit from rt-PA. Conclusion: Clinical-CT mismatch using ASPECT scoring does not reliably identify patients more or less likely to benefit from rt-PA.

### Who Is Most Likely to Benefit From t-PA? The Perfusion-Diffusion and Clinical-Diffusion Mismatch Models Disagree


**Background:** Different diffusion-weighted MRI (DWI) based models have been proposed to identify stroke patients who are most likely to benefit from t-PA beyond the established 3-hour time-window. A perfusion weighted MRI (PWI)-DWI mismatch model, defined as the PWI lesion volume exceeding the DWI lesion volume by at least 20% is used by some. Others have suggested the use of a Clinical-DWI mismatch model defined as a National Institutes of Health stroke scale score (NIHSSS) ≥ 8 and a DWI lesion volume of <25ml. We sought to determine if these two models identify the same group of patients. **Methods:** NIHSSS, DWI and PWI were obtained in 44 acute stroke patients in whom an MRI could be obtained between three and six hours after symptom onset. All patients were treated with tPA following their MRI as part of an NIH sponsored study. DWI and PWI lesion volumes were measured by one investigator (VT). For each patient the presence of a PWI-DWI mismatch and a Clinical-DWI mismatch were determined. Agreement between the two mismatch models was described as a raw percentage and as Cohen’s kappa. **Results:** PWI was of sufficient quality to determine a PWI lesion volume in 39 of 44 patients (89%). The two models agreed in 23 of 39 cases (59%; 95% CI 42 to 74%) giving a kappa statistic of 0.04 (95% CI -0.28 to 0.35), indicating no significant agreement beyond chance between the two models. **Conclusion:** Two previously proposed mismatch models identify very different groups of patients when applied to a cohort of prospectively enrolled acute stroke patients. Therefore, these models can not be used interchangeably. Future studies are needed to determine which, if any, model accurately predicts a favorable response to t-PA.

### Outcomes Among Ischemic Stroke Patients Not Treated With t-PA Due to Mild or Improving Deficits

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**Background:** Many patients not receiving IV t-PA due to mild or improving stroke (“MILD”) symptoms still have poor outcomes. We used data collected at a single center in the Paul Coverdell National Acute Stroke Registry and Get with the Guidelines-Stroke pilots to retrospectively compare the outcomes of MILD patients to both tPA and non-tPA treated stroke patients. **Methods:** From 01/02–03/02 and 01/03–03/04, 445 patients with ischemic stroke arrived at the ED; 14 patients who received IA therapy without IV therapy were excluded. Data on the remaining patients (n = 431) were abstracted from the medical record by a trained research coordinator and included demographics, medical history, initial NIH Stroke Scale (NIHSS) and contraindications to t-PA. A neurologist evaluated all patients. **Results:** Of the 121 (28%) arriving ≤3 hours after onset, 50 (41%) received IV t-PA (40 with IV t-PA alone and 10 with IV t-PA followed by IA thrombolysis) and 71 did not. Contraindications to IV t-PA were documented in 69 of these 71 (97%); the most common were improving deficit (n = 24, 33%), mild deficit (n = 17, 24%), CT abnormality (n = 7, 10%) or lack of time (n = 6–9%). There were no differences in outcome between patients with mild vs. improving stroke. Mean NIHSS in the 41 “MILD” patients was similar to the 340 non-tPA treated patients (4.4 ± 4.7 vs. 5.7 ± 6.2), but lower than the 50 IPAl-treated patients (4.4 ± 4.7 vs. 15.6 ± 6.2, p < 0.001). “MILD” patients were more likely to be discharged home than the IV t-PA treated (p < 0.001) or the non-IA/PA treated patients (p < 0.001). After adjustment for age and NIHSS, “MILD” patients were more likely to be discharged home than non-IA/PA treated patients (OR 3.7, 95% CI 1.5–9.1, p = 0.004); the difference between “MILD” and tPA treated patients was not significant. Additional adjustments for diabetes, previous stroke, and atrial fibrillation did not change the results. Even so, among the “MILD” patients 12 (29%) were not discharged home; 9 “MILD” patients were non-ambulatory and 2 died. **Conclusions:** Patients with mild or rapidly improving symptoms did better than other patients who did not receive tPA, but still suffered substantial short-term disability. The possibility that tPA would have benefited this population should be studied in a randomized design.
Recanalization After Cervicocephalic Arterial Dissection: The Cleveland Clinic Experience

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Objectives: As endovascular options for treatment of cervicocephalic dissections improve, a better understanding of the natural history and risk factors for poor outcome are important. We endeavored to describe our experience with cervicocephalic dissections to identify these features and the impact of various medical treatments upon vessel healing. Methods: The Cleveland Clinic radiology dictation database from 1997–2001 was queried for the term “dissection” and medical records reviewed to include patients with imaging confirmed cervicocephalic dissection of determinable onset. Data collected included imaging features of severity of stenosis (moderate 50–69%, severe ≥70%), recanalization (improvement to <50% stenosis), presence of pseudoaneurysm, pseudoaneurysm healing (complete or near complete resolution), and time to recanalization or healing. Results: There were 76 patients, 57% women, mean age of 45.8 years (range 14 – 80) followed for a total of 341 visits. Ninety-three dissected vessels were analyzed and 78 vessels had at least 1 follow-up visit. At baseline, there were 28 occluded vessels, 39 with severe stenoses, 3 with moderate stenoses and 26 with pseudoaneurysms. Sixty percent of vessels recanalized spontaneously, 79% in the first 6 months and 90% within the first year. The median time to recanalization was 134 days for the anticoagulation group (n=22) versus 25 days for the antithrombotic group (n=4) (p=0.016). In contrast, 47% of pseudoaneurysms healed spontaneously, 13% in the first 6 months and 50% within the first year with a median time to healing of 362 days. Conclusions: While spontaneous recanalization of a dissection occurs primarily within 6 months, healing of pseudoaneurysms has a delayed course and neuroradiologic monitoring should be tailored to these observations. Our data suggest that anticoagulation may delay recanalization and this warrants further investigation.

Predictors of Vessel Occlusion in Acute Ischemic Stroke

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Abstract: Background and purpose: We tested the hypothesis that there is an association of the National Institute of Health Stroke Scale (NIHSS) score and the presence - or absence - of a visible vessel occlusion on arteriography performed within the first hours after symptom onset in ischemic stroke. Methods: We analyzed NIHSS score on hospital admission and clinical and radiological data of 226 consecutive patients (94 women, 132 men; mean age 62 ± 12 years) with acute ischemic stroke who underwent IA-DSA within 6 hours of symptom onset in anterior circulation (carotid territory) stroke and within 12 hours in posterior circulation (vertebrobasilar territory) strokes. Patients were divided into 6 groups according to the location of the arterial occlusion. Results: Median NIHSS was 14 (mean 15.7, range: 3–38 ). The interval from stroke onset to hospital admission was 155 ± 97 minutes and interval from stroke onset to ISA-DA study was 245 ± 100 minutes. Median NIHSS in the basilar artery (BA group, n = 27) was 20 (range: 11–36), 17 (range 7–25) in the internal carotid artery (ICA group, n = 49), 18 (range 5–24) in the M1 segment of the middle cerebral artery (M1 group, n = 67), 14 (6–25) in the M2 segment of middle cerebral artery (M2 group, n = 28), 12 (range 7–20) in the anterior cerebral artery (ACA group, n = 3), 10 (range 3–18) in the branches of middle cerebral artery group (M3/4, n = 23), 9 (range 9–20) in the posterior cerebral artery group (n = 3) and 8 (range 4–27) in patients without vessel occlusion on arteriography (n = 26). In the anterior circulation strokes 97% of patients with NIHSS score ≥10 showed arterial occlusions, and in patients with posterior circulation strokes 96%. When NIHSS score was less than 10, arteriograms showed occlusions in 54% of patients only. In a multivariate regression analysis of older age, male gender, NIHSS score subitems such as “level of consciousness questions” and “motor leg” and “sensation” were independent predictors for vessel occlusion. Conclusions: The NIHSS score is associated with the site of vessel occlusion in patients with an acute ischemic stroke. An NIHSS score ≥10 strongly predicts that a vessel occlusion will be seen on arteriography both in patients with stroke in carotid artery and vertebrobasilar artery territories.

Conventional T2*-Weighted Susceptibility Images for Detection of Intraluminal Thrombus in Acute Stroke

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Background: Susceptibility-induced signal change in the MCA trunk has been reported to represent an acute thrombosis on echo-planar susceptibility-based perfusion-weighted MR images (PWI). We sought to determine the diagnostic utility of conventional T2*-weighted susceptibility images (T2*WI) in detection of arterial thrombosis in acute stroke relative to CT, CTA and MRA. Methods: Thirty-eight patients with acute ischemic stroke who underwent MR and CT examinations within the first 12 hours of symptom onset were studied. T2*WI, PWI, DWI, MRA or CTA, and CT were obtained in each patient. The presence of susceptibility was visually assessed and defined as a signal void that exceeded the diameter of contralateral corresponding vessel on T2*WI and, PWI. Arterial hyperintense sign on CT and vascular patency

on CTA and MRA were also assessed. Results: Susceptibility changes consistent with thromboembolism were identified in 63% (n = 24) of all patients on T2*WI and 39% (n = 15) on PWI. The hyperdense artery sign was present in 32% (n = 12) patients on CT. T2*WI was positive in all patients who had thromboembolism identified by PWI or CT. The site of occlusion on MRA or CTA overlapped with T2*WI findings in 21 cases. MRA or CTA failed to display occlusion in 3 patients who all had distal MCA occlusions (M3) on T2*WI. Using CTA or MRA as a gold standard and excluding M3 occlusion, sensitivity/specificity of T2*WI, CT, and PWI were seen in the Table. The sensitivity of T2*WI (91%) was higher than CT (52%, p < 0.01) or PWI (61%, p < 0.05). None of the 14 patients who did not exhibit signal changes consistent with thromboembolism on T2*WI had thromboembolism upon either PWI or CT criteria. Conclusion: T2*WI appears at least as sensitive as other non-contrast imaging techniques and deserves further evaluation tool in detecting acute thromboembolism in major cerebral arteries. The sensitivity/specificity of T2*WI, PWI, and CT for detection of intraluminal thrombus

Identification of the Site of Acute Occlusion in All Major Cerebral Arteries by High-Resolution Gradient Echo T2*-Weighted Images

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Background: In acute stroke magnetic resonance imaging (MRI), the effect of vascular obstruction is readily demonstrated by indirect signs such as lack of flow signal on magnetic resonance angiography (MRA) or the area of altered perfusion on perfusion weighted MRI (PWI). T2*-weighted magnetic resonance imaging has been shown to locate the site of acute vessel occlusion in the middle cerebral artery (MCA). This study was performed to determine the ability of T2*-weighted MRI to identify the site of occlusion in all major cerebral arteries. Methods: We analyzed the MRI data of 23 patients who presented with acute onset stroke symptoms (mean 5.4 h) due to occlusion of cerebral arteries with respect to T2*WI, DWI, and PWI findings. Results: Hypointensity on high resolution gradient echo T2*-weighted images was identified at the site of vessel occlusion in ischemia of the anterior cerebral artery 2/23, posterior cerebral artery 2/23, MCA 10/23, posterior inferior cerebellar artery 9/23. Hypointensity was either slightly larger than the affected vessel diameter or was present over a short vessel segment. Confirmatory evidence of vessel obstruction was the lack of flow signal on MRA and the respective hyperperfused vascular territory on PWI (Fig.1). Conclusion: High resolution gradient echo T2*-weighted images can identify the site of acute occlusion in all major cerebral arteries. This phenomenon is possibly caused by endothelial damage and bleeding or calcified embolic material. Especially in patients with occlusion of the PICA - a vessel not clearly definable on MRA - the combination of T2*WI and PWI helped to achieve the diagnosis of persistent vessel pathology.
P6

Intracranial Stenosis Predicts Higher Risk of Vascular Events in Caucasians With Asymptomatic Carotid Stenosis

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Background: Extracranial atherosclerosis (EA) is more frequent in Caucasians, and intracranial stenosis (IS) is thought to be less frequent than in Asians, African-American and Hispanics; therefore, it is not often considered in Caucasians. Purpose: We sought 1) to determine the frequency of intracranial stenosis in patients with asymptomatic internal carotid stenosis> 60% (ACS), and 2) whether IS predicted adverse vascular outcome in this high-risk group. Methods and Materials: 327 patients with ACS were enrolled between June 2000 and August 2004. All patients underwent a thorough transcranial Doppler study (PMD 100 M-Mode Transcranial Doppler). Mean velocities and pulsatility index (PI) were recorded. IS was diagnosed in vessels in which peak and mean velocities were elevated, and/or PI was decreased. Results: 118 (36.2%) had intracranial stenosis; among those cases 73 (61.9%) were male; mean age was 68.9 years (50 - 84.2). 31 patients (26.3%) were diabetic and 28 (23.7%) were smokers. IS was more common (25% vs. 14%) in patients with diabetes (p = 0.05). Events (stroke/death/endarterectomy) occurred in 15/118 (12.7%) patients with IS, vs. 15/208 (7.2%) without; in multiple regression, intracranial stenosis was a significant predictor of stroke/death/endarterectomy after adjustment for age, sex, cholesterol, systolic pressure and c-reactive protein (p = 0.017). Conclusions: IS is not uncommon in Caucasians, and its presence predicts an increase risk of stroke at two years. TCD detection of IS may be useful for identification of patients who warrant more intensive therapy. It may be worth exploring new approaches to treatment of patients with asymptomatic IS.

P7

Resolution of “Dense Dot Sign” After Acute Ischemic Stroke Is Associated With Better Outcome

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Background: A number of studies indicate that asymmetric dense vascular signals on CT scan correlate with underlying carotid stenosis. We followed the progression of dense dot signs in the MCA and basilar artery on pre-treatment and 24 hour post-treatment CT scans in consecutive patients participating in a Phase I safety study of abciximab and heparin in patients ineligible for intravenous ASA. Most had moderate to severe strokes and had received anticoagulation or had aspirin/ASA. We assessed if positivity of the dense dot sign reversed as ICP decreased. Methods: Patients admitted to a participating center underwent CT and MRA on admission and then at 24 hours. Thirteen out of 23 patients demonstrated reversal of the dense dot sign (Group 1). The mean decrease in HU in ROI of this group was -2.83 ± 2.14. Six of thirteen (46%) had reversal of resolution of the dense dot sign to Group 1, 3 in group 2, and 2 in group 3. There were 3 parenchymal hematoma with mass effect in this group. Conclusion: Resolution of dense dot sign may predict reversal of outcome in patients with acute stroke. The effect of therapy on reversal of this sign will be explored prospectively in follow up studies.

P8

Validity of ICD-9 Procedure Code and CPT Codes for Thrombolyis in Patients With Ischemic Stroke

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Background: Recently, new International Classification of Diseases Ninth Revision (ICD-9) procedure code and Current Procedural Terminology (CPT) codes were designated for injection or infusion of thrombolytic agents. Although the introduction of ICD-9 and CPT codes allow estimation of national and regional use of thrombolytic therapy, the accuracy of the codes in use is unknown. Methods: We determined the accuracy of ICD-9 procedure code 99.10 and CPT codes 37201 and 37202 for use of thrombolytics in a consecutive series of patients admitted to a University Hospital with ischemic stroke admitted over a 12 month period. The sensitivity, specificity and predictive values of diagnosed use of thrombolytics in patients with ischemic stroke. Results: Intra-arterial or intravenous thrombolytics were used in 51 (12.3%) of the 415 patients with ischemic stroke admitted during the study duration. The sensitivity, specificity, positive and negative predictive value of the CPT code 37201 was 99%, 88%, and 94%, respectively. Sensitivity, specificity, positive and negative predictive value of the CPT code 37202 was 93%, 99%, 87%, and 94%, respectively. When ICD-9 or CPT codes were used to identify use of thrombolytics, the sensitivity, specificity, positive and negative predictive values were 84%, 99%, 90%, and 98%. Conclusions: The use of ICD-9 and CPT codes alone may underestimate the use of thrombolytics using national and regional databases. Best results are achieved when combinations of ICD-9 and CPT codes are used to identify the use of thrombolytics.

P9

Markedly Reduced Regional Cerebral Blood Volume Pretreatment: A Predictor of Hemorrhagic After Thrombolysis

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Background and Purpose: Accurate assessment of the risk of hemorrhage could help to improve the patient selection for thrombolytic therapy and reduce hemorrhagic complications, particularly beyond the 3-hour time window or in cases in which time of onset is unknown but other imaging parameters look favorable. Hemodynamic MRI using bolus contrast is frequently used for definition of tissue-at-risk of infarction but it may also provide important information for predicting tissue-at-risk for hemorrhage. Methods: Bolus contrast and diffusion MRI was performed prior to intravenous Tissue Plasminogen Activator (TPA) therapy in 19 patients presenting with acute stroke symptoms within the first 6 hours following symptom onset. Hemorrhage was assessed on CT or MRI scans obtained within 24-72 hours of therapy by two independent observers. Regions defining the hemodynamically abnormal region in each patient were drawn using calculated Mean Transit Time and blood volume maps. Regions defining the hemorrhage location and extent were drawn on follow-up imaging studies aligned to the acute study. Results: Of the 19 patients studied, 5 had detectable hemorrhage on follow-up scans. Blood volume maps demonstrated virtually no signal within much of the hemorrhagic region indicating contrast did not arrive by the end of the imaging series (80s). A threshold of 126 voxels with blood volume less than 5% of contralateral gray matter within the hemodynamically abnormal volume separated hemorrhagic patients from non-hemorrhagic with a sensitivity of 100% and a specificity of 71% (p<.001). All subjects with hemorrhage were at least partially reperfused following thrombolysis while most false positives did not reperfuse (p<.05). Number of low blood volume voxels of individual patients correlated with the number of voxels with T2* values below 55.0106 –6 mm2/s (r=0.76, p<0.03) another previously proposed predictor of hemorrhage. Conclusions: Extremely low or complete absent contrast arrival may indicate tissue at risk for hemorrhage prior to TPA administration, aiding in risk-benefit assessments, particularly in patients treated in the extended time window. Occurrence of hemorrhage within at risk areas may be dependent on tissue reperfusion.

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Microbleeds on T2*-Weighted Gradient Echo Images of Patients With Acute Ischemic Stroke: Association With Occurrence of Parenchymal Hemorrhage After Thrombolysis Treatment

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Purpose: To evaluate the relationship between microbleeds (MBs) seen on pretreatment T2*-weighted gradient echo MR (GE) images and occurrence of parenchymal hemorrhage in acute ischemic stroke patients after intravenous (IV) and/or intra-arterial (IA) thrombolysis. Materials and Methods: A total of 39 patients with terminal ischemia/infarction of the anterior circulation treated with IV and/or IA thrombolysis were included. The number and location of MBs were assessed with GE images. The patients were categoriezed into three groups according to the number of MBs: Group 1 (28 patients without MBs), group 2 (6 patients with MBs = 4), and group 3 (5 patients with MBs ≥ 5). Follow-up GE images were obtained two to five days after thrombolytic treatment. The frequency and location of parenchymal hemorrhage (defined as new dark signal on GE images regardless of the amount) were evaluated on the follow-up images. Results: Parenchymal hemorrhage was observed in 9 in group 1, 3 in group 2, and 2 in group 3. There were 3 parenchymal hematoma with mass effect in this group. Conclusion: Hemorrhage occurred only in patients with MBs. There was no statistical difference in the frequency of hemorrhage between the groups. In terms of the location of the parenchymal hemorrhage, all of the new dark signals were noted at the different sites remote from the sites where MBs were. Conclusion: In the thrombolytic treatment of acute ischemic stroke, MBs noted on GE images are not associated with the occurrence of parenchymal hemorrhage regardless of the number of the MBs. Larger sample size is required to obtain higher level of evidence.
Identifying Vasogenic Edema by Diffusion-Weighted MRI in Patients With Early-Blood-Brain Barrier Disruption After Intraarterial Thrombolysis

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Background and purpose: Intraparenchymal hyperdense areas are commonly observed on postthrombotic CT scans taken immediately after intra-arterial (IA) thrombolysis. Angiographic dye extravasation into disrupted blood-brain barrier (BBB) has been suggested as a mechanism for BBB breakdown and subsequent development of vasogen edema or hemorrhagic transformation on these areas has been reported. We sought to evaluate diffusion MR parameters to identify vasogenic edema in the areas of disrupted BBB after IA thrombolysis.

Methods: Fifteen patients with acute middle cerebral artery occlusion were studied with postthrombotic CT and serial follow-up at immediate post-thrombolysis, and 1 day and 7 days of symptom onset. Areas of parenchymal hyperdensity were defined as hypere attenuation on postthrombotic CT where no hemorrhage were observed on post-thrombolysis gradient echo (GRE) MRI taken before CT scan. Regions of interest (ROIs) on CT scans were transferred to follow-up GRE images (2 s/mm², 80 mm image matrix and a significant diffusion factor of anisotropy (A)) maps. Isotesional/contralesional intensity ratio of ROIs on images and ADC maps were analyzed.

Results: Eighty percent (12/15) of patients had parenchymal hyperdense areas on postthrombotic CT. Among these patients, parenchymal hematoma or perichemal hemorrhage were located in 60% of cases. Mean intensity ratio of hyperdense area were significantly higher than diffusion MRI-positive lesion without parenchymal hyperdensity at immediate, 1 and 7 day after IA thrombolysis (1.29 vs 1.09, p<0.01, 1.46 s 1.27, p<0.01, 1.49 vs 1.32, p<0.05). Mean intensity ratio of ADC were significantly lower at day 1 in diffusion MRI-positive lesion without parenchymal hyperdensity (0.92 vs 0.78, p<0.05). Baseline relative intensity before thrombolysis for both ROIs and ADC maps were not statistically different (1.02 vs 1.07, 0.79 vs 0.85). Conclusion: Diffusion-weighted MRI can reliably differentiate early vasogenic edema from cytotoxic edema after IA thrombolysis. Treatment directed to prevent further BBB breakdown might be beneficial in selected patients after IA thrombolysis.

Anatomy of Neurogenic Cardiac Injury


Background: The neuroatomic basis of stroke related myocardial injury is not well understood. We sought to identify regions of the brain that might be associated with myocardial damage when infarcted. Methods: Out of 730 consecutive patients with acute ischemic stroke, we selected 50 patients with elevated troponin and no recent MI or cardiac surgery. The control group consisted of 50 randomly selected, age and sex matched stroke infarct patients without troponin elevation. DWI images with outlines of infarction were coregistered to a template in both groups, averaged and then subtracted in order to find voxels that differed. A non-parametric permutation test was used in order to determine voxelwise p-values. Results: The groups did not differ in prior history of coronary artery disease, ejection fraction, TOAST subtypes, or frequency of right and left MCA involvement. The figure demonstrates those regions more frequently infarcted in patients with troponin elevation compared to the control group. Conclusions: The insular cortex shows significant predicted tropinin elevation with 26% sensitivity and 88% specificity. Infarction in specific brain regions including the right insula are associated with myocardial injury. Accurate identification of neuro-anatomic correlates of myocardial injury by MRI may help identify patients at risk of cardiac adverse events.

Left Insular Stroke, Not Right Insular Stroke, Is Associated With Adverse Cardiac Outcomes

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Background: 10% of stroke victims suffer adverse cardiac outcomes due to an underlying coronary artery disease or cardiac pathophysiologic derangements induced by stroke itself. Left and right insular strokes have been reported to be associated with cardiac autonomic changes that may lead to these outcomes. Method: We performed a prospective study of 141 stroke/TIA patients: 84 with non-insular stroke/TIA (group 1: reference group), 32 with left insular stroke (group 2), and 25 with right insular stroke (group 3). Adverse cardiac outcomes including cardiac death, myocardial infarction, angina and heart failure were assessed within 1 year. Results: On univariate analysis, group 2 had relative risk (RR) = 1.75 for adverse cardiac outcomes compared to group 1 (95% CI: 1.02–3.00, p = 0.05) and group 3 had RR = 1.23 (95% CI: 0.62–2.44, p = 0.56). On multivariate analysis, left insular stroke was an independent predictor of the outcomes with odds ratio (OR) = 2.79 (95% CI: 1.11–7.04, p = 0.03) but right insular stroke was not (OR = 1.29, 95% CI: 0.47–3.59, p = 0.50). Sensitivity analysis excluding TIA patients from the reference group and excluding angina as an outcome showed similar results. When results were stratified by symptomatic coronary artery disease (SCAD), group 2 had RR = 4.06 (95%CI: 1.83–9.01, p = 0.003) compared to group 1 among patients with SCAD. For those with SCAD, RR = 0.36 (95%CI: 0.06–2.13 P = 0.14). Survival analysis demonstrated stronger association between left insular stroke and outcomes among those without SCAD (p = 0.002) than when the analysis was performed without considering SCAD status (p = 0.06). Conclusion: Left insular stroke, not right insular stroke, is associated with an increased risk of adverse cardiac outcomes compared to stroke in a non-insular location and TIA. The association is even stronger among those without SCAD. A possible mechanism is impairment of the parasympathetic tone favoring the sympathetic system. In patients with SCAD, the cardioprotective effect of medications, especially beta-blockers, taken at the time of the stroke, and ischemic preconditioning phenomenon may explain lack of association between left insular stroke and adverse cardiac outcomes in this subgroup.
nism. Left and right insular stroke are associated with cardiac autonomic dysfunction that may lead to neurogenic stunned myocardium. Method: A prospective study of 141 stroke/TA patients: 84 with non-insular stroke/TA (group 1: reference group), 32 with left insular stroke (group 2), and 25 with right insular stroke (group 3). TEE was done to assess abnormal myocardial contraction. Result: In group 2, 27 had TCD and 12 (44%) had abnormal myocardial contraction (p = 0.16, group 2 vs. group 1). In group 3, 20 had TEE and 8 (40%) had abnormal contraction (p = 0.37, group 3 vs. group 1). Analysis was further done by stratifying symptomatic coronary artery disease (SCAD). For those without SCAD, in 24 group 2 had TEE and 11 (46%) had the abnormality whereas in group 1 had TEE the abnormality (p = 0.009, group 2 vs. group 1). In group 3, 13 had TEE and 3 (23%) had the abnormality (p = 0.62, group 2 vs. group 1). In multiple logistic regression, left insular stroke was an independent predictor of abnormal myocardial contraction (OR = 2.07, 95% CI: 0.87–9.4, p = 0.44) while right insular was not (OR = 1.51, 95% CI: 0.49–4.65, p = 0.68). In a model adjusted for interaction between left insular stroke and TAC, OR for left insular stroke = 4.15 for those without SCAD (95% CI: 1.36–12.63, p = 0.01). Conclusion: Left insular stroke is associated with abnormal myocardial contraction compared to stroke in a non-insular location and TAC. Among those with TAC, the association was stronger. Similar results of SCAD and autonomic dysfunction mechanism may be activated sympathetic tone upon the heart. Patients with SCAD are less affected possibly due to cardioprotective effects from medications or ischemic preconditioning phenomenon.

Multiple logistic regression

<table>
<thead>
<tr>
<th>OR</th>
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<th>p</th>
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<td>Left insula</td>
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<td>1.04–7.94</td>
</tr>
<tr>
<td>Right insula</td>
<td>1.51</td>
<td>0.49–4.65</td>
</tr>
<tr>
<td>SCAD</td>
<td>5.37</td>
<td>2.06–14.01</td>
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<td>Age</td>
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Cardiovascular Ultrasound Above and Below Age 50 in Embolic Stroke

P17


Introduction: The diagnostic strategy in suspected embolic stroke still varies due to insufficient evidence of the relative usefulness of various techniques, particularly in relation to age at index event. Some authors have stated that echocardiography and especially transesophageal echocardiography(TEE) should be done only in patients younger than 50 years old. Hypothesis: TEE has a high yield of relevant findings in all age-groups and age –50 years is not a valid reason to exclude a patient from TEE. Methods: We evaluated the diagnostic yield in relation to age below or above 50 from carotid duplex ultrasound (CDU), transthoracic echocardiography (TTE) and transesophageal echocardiography in consecutive patients referred for evaluation of possible embolization from the heart as a cause of ischemic stroke. Results: In all, 867 patients (196 below age 50) were investigated by CDU and TTE. 453 of these (130 below age 50) also by TEE. TEE was less often performed in patients with known ischemic heart disease and those having diuretics. Cardiovascular medication, ischemic heart disease, hypertension, diabetes mellitus and atrial fibrillation were more common above age 50 among those with TEE as well as without. Patient paraenome as well as atrial septal aneurysm were more common in younger subjects. On the other hand, left atrial thrombus and spontaneous contrast, akinisia, a low ejection fraction and presence of valvular defects were essentially limited to the patients above age 50, and in this group the prevalence of carotid plaques was 5-6 fold that of younger patients. In the TEE group, patients above age 50 also had significantly higher serum cholesterol, blood glucose and C-reactive protein, and 3-4 times more prevalent proximal aortic plaque. Findings of complex proximal plaques in patients below 50 years of age and diabetes mellitus, atherosclerosis, atrial fibrillation and hypertension were more common below 50 years. Relevant findings on TEE were rare especially in patients without previously known ischemic heart disease. Conclusion: Age –50 years is not a valid reason to exclude a patient from TEE since recent TEE findings in stroke patients are considerably more prevalent in patients –50

Almost Perfect Concordance Between Simultaneous Transcranial Doppler and Transesophageal Echocardiography in the Study of Patent Foramen Ovale

P18

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Background and Purpose: Transesophageal echocardiography (TEE) and transcranial Doppler (TCD) are the methods of choice to study patent foramen ovale (PFO), but there are discrepancies between the two concerning PFO detection and right-to-left shunt (RLS) quantification. As there are no established cut-off values for the hemodynamic situations of the Foramen ovale (FO) and the Valsalva manoeuvre (VM) in each one differ. We assessed the hypothesis that concordance between TEE and TCD in PFO detection and RLS quantification is almost perfect when performing both tests simultaneously. Methods: We prospectively included consecutive patients with ischemic stroke or TIA treated with TCD ultrasound and transthoracic echocardiography (TTE). Two microbubbles (mb) were diagnosed by TCD and TTE. mb were detected in the left atrium within 3 heartbeats after opacification of the right atrium. We applied the TCD protocol of the Consensus Conference (Venice 1999). The study was performed with two VM. PFO quantification was: 1) TCD: minimum (−10mb), moderate (−5mb), and maximum (−mb); 2) TEE: minimum (−3mb), moderate (−10mb) and maximum (−30mb). Statistics used were contingency tables, Chi-square and Cohen’s Kappa test. Quantification concordance was considered as slight, K < 0.2; fair, K = 0.21–0.40; moderate, K = 0.41–0.60; substantial, K = 0.61–0.80; or almost perfect, K = 0.81–1.00. Results: We studied 110 patients whose mean age was 56.7 ± 12.1 year and 61% were men. PFO was detected at first VM in 30% of patients with TCD, and in 31.8% with TEE. At second VM both methods detected the same patients (32.7%). PFO was minimum (n = 14), moderate (n = 5) and massive (n = 17) in TCD, and accountable (n = 13), moderate (n = 3) and countless (n = 20) in TEE. There was an almost perfect concordance in PFO quantification (K = 0.928, p < 0.001) with only 4 discrepancies, all due to TCD underestimation in moderate and countless echocardiographic PFO. Conclusions: In conclusion, simultaneous study with TCD and TEE showed an almost perfect concordance in PFO detection and RLS quantification.

Predicting Stroke Clinical Outcome in the Nondominant Hemisphere Using MRI

P21

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Background: The National Institutes of Health Stroke Scale (NIHSS) is a widely used and validated tool for assessing clinical outcome following ischemic stroke. The correlation between
MRI-based surrogates (specifically, infarct volume) and NIHSS has been shown to be only moderate ($r = 0.3$–$0.6$), particularly in the non-dominant hemisphere. Because infarct location is also important in determining the severity of a clinical deficit, we hypothesized that a method that utilized both location and size would improve the correlation between imaging and NIHSS.

**Methods**: We generated a stroke Hazard Atlas in which each voxel is weighted according to multiplying each voxel in each coregistered, binarized ($1$ = infarct, $0$ = normal) imaging dataset within 2 weeks of their stroke. Lesion location was determined by the Cerefy 3 dimensional, encephalopathic, non substance abuse prone people who were tested with the 16 domain FNS within 2 weeks of their stroke. Lesion location was determined by the Cerefy 3 dimensional, digital, coxial brain atlas identifying 6 regions of cerebral interest including 1) frontal, 2) subcortical grey matter, 3) subcortical white matter, 4) subcortical, 5) temporoparietooccipital and 6) multiple regions. Lesion location was assessed with the NIHSS and infarct volume measured in cubic centimeters. Results: In young stroke people for analysis ($n = 445$, mean age $44$, after exclusions, people with FNS included (120/325) with a final diagnosis of transient ischemic attack (TIA), ischemic stroke (ISCH) or intracerebral hemorrhage (HEM) were included in the analysis, which was based on a county-wide hospital-based stroke registry. Apart from baseline variables, data on risk factors, lesion location, and the initial neurological deficit and time from symptom onset to hospital admission were available. Results: In total, 11328 patients (56.4%) suffered from a left and 8769 patients (43.6%) from a right-sided cerebrovascular event ($p < 0.001$). In a subgroup analysis, this difference was significant for patients with TIA and ISCH (both $p < 0.001$), but not for patients with intracerebral hemorrhage ($p = 0.085$). In a multivariate regression analysis, the left side preponderance was found to increase with increasing age and to decrease with increasing stroke severity. In addition, the non-symmetrical distribution was particularly prominent in patients admitted within the first 3 hours after symptom onset. Conclusion: The strikingly non-symmetrical distribution of ischemic events in our large multi-center stroke registry, particularly in patients with transient or mild deficits, suggests widespread underrecognition (or misinterpretation) of symptomatic right hemisphere ischemia.

**Background and Purpose**: The key neural substrates of hemispheric neglect are currently being hotly debated. While earlier studies implicated the right parietal lobe, particularly the temporo-parieto junction (TPJ), an influential recent study argued that the right superior temporal gyrus is the critical neural substrate, while the temporo-parieto junction (TPJ) comprised of ischemic stroke not due to typical etiologies of atherothrombosis, cardiac embolism, or penetrating artery disease. We studied this OTH classification in our own acute stroke population.

**Methods**: We overlapped the MRI scans of 27 right-hemispheric stroke patients, 15 with and 12 without neglect. All patients were assessed using the NIH Stroke Scale and underwent structural 3D T1 MRI scans. Results: Of 1251 patients with acute ischemic stroke reviewed, 102 (8.1%) were included with the OTH classification, and 822 (65.7%) had typical determined etiologies (TYP). The different etiologies noted within the NIHSS category are listed in the table. The reported on the OTH patients was $47.0$ ($\pm$ 24.2), compared to 68.2 ($\pm$ 14.0) for TYP patients ($p < 0.0001$).
Of OTH patients, 61.3% were women, compared to 45.5% of TYP patients (p < 0.001). There were significant differences in the frequencies of all stroke risk factors, especially hypertension, present in 30.3% of OTH and 70.4% of TYP patients (p < 0.001). Clinical severity and frequency of improvement were similar for OTH and TYP patients, although OTH patients had a higher percentage of posterior circulation deficits (26.8% vs 15.0%, p < 0.0001).

Conclusions: Patients presenting with acute ischemic stroke to TOAST—OTH classification tend to be younger, more often female, and have lower frequencies of stroke risk factors. Arterial dissection is the most common etiology in the OTH classification.

Specific Diagnoses in TOAST—OTH Category

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Percent</th>
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<td>Noninflammatory</td>
<td>Dissection</td>
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<tr>
<td>Vasculopathy</td>
<td>Unruptured Aneurysm</td>
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<tr>
<td>Vasculopathy</td>
<td>Moy-a-Moya disease</td>
</tr>
<tr>
<td>Vasculopathy</td>
<td>Other Vasculopathy</td>
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<tr>
<td>Inflammatory</td>
<td>Systemic Vasculitis</td>
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<td>Vasculopathy</td>
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<td>Vasculopathy</td>
<td>CNS Aspergillosis</td>
</tr>
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</tr>
<tr>
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<td>Mitochondrial stroke</td>
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Sites of Intracranial Hemorrhage in Adult Moyamoya Disease and Associated Angiographic Findings

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BACKGROUND AND PURPOSE: Adult moyamoya disease often present with intracerebral hemorrhages (ICHs), but their sites and cause have not been fully studied. We sought to determine sites of ICHs and detect specific angiographic findings. MATERIALS AND METHODS: 165 patients aged over 19 years were diagnosed with this disease in our institution from 1988 to 2001. Subjects were 61 patients whose CT scans at the onset of ICH and cerebral angiograms performed within 60 days of CT scans were available. According to the origin of ICH on CT scans, they were classified into 6 groups: 4 groups with parenchymal involvement including the basal ganglia, thalamus, periventricular white matter, and subcortical white matter; 2 groups without parenchymal involvement including ventricular system (confined within lateral and/or third ventricle) and subarachnoid space. The border between periventricular and subcortical white matter was defined as imaginary line 1.5 cm from the ventricular wall. In cases with ICH extending to both periventricular and subcortical white matter, the primary site of ICH was regarded as subcortical. In order to detect specific angiographic findings presumptive to the ICHs, angiograms of the 61 patients were retrospectively reviewed. RESULTS: ICH sites were basal ganglia in 26 (43%) patients, thalamus in 11 (18%), periventricular white matter in 6 (10%), subcortical white matter in 5 (8%), ventricular system in 10 (16%), and subarachnoid space in 3 (5%). Among 48 patients of parenchymal involvement groups, 29 (48%) proved to have associated intraventricular hemorrhage (IVH). Angiograms revealed small aneurysms along dilated perforators (basal moyamoya) distributed to the sites of ICHs near ventricles in 4 patients. Two of them disappeared on follow-up angiograms and were judged as pseudo-aneurysms. CONCLUSIONS: ICHs in moyamoya frequently had primary IVHs or secondary IVHs deriving from parenchymal ICHs. Intra-arterial thrombus and small aneurysms were frequent complications of ICHs. With these angiographic and clinical features were analyzed. RESULTS: One hundred and four patients (50.7%) had the index of comma/wedge shape, and 101 patients (49.3%) had round shape infarct. Among the 104 patients with comma/wedge shape infarct, 77 had a parent artery stenosis (92%) and 11 of 101 patients with round shape infarct (p < 0.001). The diameter of comma/wedge shape infarct (19.7 mm) was also significantly larger than that of the round shape (12.5 mm) (p < 0.001). Neurologic deficit at admission and after 7 days were more severe in the patients with comma/wedge shape infarct than the patients with round shape infarct (p < 0.001, respectively). Hypertension was more prevalent in patients with comma/wedge shape infarct (89.4%) than those with round shape (73.3%) (p < 0.003). Multivariate analysis revealed that the infarct shape is independently related to the parent artery stenosis (p < 0.01). Conclusions: In the patients with deep penetrating arterial territory infarct, comma/wedge shape infarct has more underlying artery stenosis than the round shape infarct. The infarct shape can be a clue in the classification of ischemic stroke mechanism.

The Patterns of Acute Ischemic Stroke in Moyamoya Disease

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BACKGROUND: It has been considered that the presumed cause of cerebral ischemia among patients with moyamoya disease is a gradually progressive hypoperfusion secondary to occlusion of the major vessels. However, the pathogenesis of acute ischemic stroke in patients with moyamoya disease is a gradually progressive hypoperfusion secondary to occlusion of the major vessels. However, the pathogenesis of acute ischemic stroke in moyamoya disease. It could provide different therapeutic views of acute ischemic stroke in moyamoya disease.

METHODS: Thirty neurologically asymptomatic SCD adult patients (9 males; mean age: 26.7 ± 11.23 yo) underwent a complete neurological examination prior to TCD and MRI studies. MR imaging was evaluated to examine the presence of lacunar infarction, encephalomalacia, leuкоencephalopathy and brain atrophy. MRI studies were performed to identify possible intracranial arterial stenosis (IAS) and occlusion or major arterial tortuosity. The highest mean flow velocity (maxVf) detected during TCD examinations was also recorded and correlated with the hematocrit performed at the same day. Results: The overall frequency of MR imaging abnormalities was 66.7% (leuкоencephalopathy=53.3%, brain atrophy=30%, lacunar infarct=10%, encephalomalacia=3.3%) and they were correlated with IAS or arterial tortuosity (p < 0.01). MRI was abnormal in 53.3% and IAS was observed in 13.3%. The highest maxVF (mean =147.75 cm/s) was found in patients with lacunar infarct (p = 0.07) or IAS (p = 0.01). There was a correlation between IAS demonstrated on MRA and lacunar infarct (p = 0.004). Conclusions: Prevalence of acute ischemic brain imaging abnormalities in SCD adult patients is higher than that described for children. Although lower than in children with SCD, the max VF in adult SCD patients is correlated with neuroimaging findings. Lacunar infarct seems to be correlated with IAS. In conclusion, TCD findings together with MRI abnormalities may help to identify high risk adult SCD patients that should be enrolled in further stroke prevention trials.
of the discrete lesions on DWI-T was 0.7 ± 0.9 ml and 51% were restricted to the cortical gray matter ribbon. **Conclusions:** Improved conspicuity, particularly of cortical lesions, was attributed to improved SNR and reduced partial volume effects. Numerous lesions were not easily identified on routine DWI. The prevalence of lesions evident on DWI-T in the cortical gray matter ribbon was unexpected and exploratory studies are underway to examine the underlying pathophysiology.

**Figure 1.** Multiple ischemic lesions appearing on DWI-T in the vicinity of an acute stroke patient.

### Patterns of Stroke in Patients With Severe Hemodynamic Impairment

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**Background and Purpose:** Severe hemodynamic impairment has been proven as an independent risk factor for subsequent stroke in patients with symptomatic carotid artery occlusion. The purpose of the present study was to investigate the specific pattern of the BZ infarct stroke and to correlate it with clinical and radiological features. **Methods:** This was a retrospective investigation of data recorded for the St. Louis Carotid Occlusion Study, a prospective, blinded study of the role of hemodynamics in ischemic stroke. On enrollment, 81 patients with complete carotid artery occlusion underwent measurements of oxygen extraction fraction (OEF) were derived using positron emission tomography. During a mean follow-up period of 3.1 years, 13 patients had ischaemic ischaemic strokes. Eleven of the 13 patients had increased OEF, a marker of severe haemodynamic impairment. For the present investigation, clinical records and radiological images related to the endpoint event were reviewed by a stroke neurologist. The location of the stroke on imaging was characterized as borderzone or territorial, based on the studies of van der Zwan. Clinical events were reviewed for evidence of associated hypotension and for nature of deficit. **Results:** Eleven clinical strokes occurred in the 13 patients with increased OEF. Clinical deficits: One was retinal and two were large fatal hemorrhagic strokes. The clinical deficits in the remaining 9 patients were consistent with middle cerebral artery territory deficits. **Conclusions:** The present findings support experimental results of Li et al. showing that the DWI detectability of ischemic lesions following transient focal cerebral ischemia is biphasic.

### The Significance of Focal Hyperperfusion During Migraine With Aura

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**Background:** Hemispheric hyper- and hypoperfusion have been described during different phases of migraines with and without aura. Perfusion-CT has not been used yet to study blood flow in patients with migraines with aura. Methods: Over a 2 year period, 16 patients with acute or subacute neurological symptoms of a focal neurological deficit were identified. Vascular events were excluded. Perfusion-CT (PCT) during the attack. Follow-up neurological exam and MRI or CT was obtained in all subjects. **Results:** Clinically, all deficits resolved within 7 days and no infarct was found at follow-up imaging. 14 patients had normal perfusion during migraine with aura. In 2 patients, PCT showed hyperperfusion unilaterally in the frontal and subcortical regions and 2 patients showed hypoperfusion unilaterally in the posterior frontal regions. **Conclusion:** Focal hyperperfusion can also be seen in several other processes, including demyelination, abscess, and tumors.

### Spinal Cord Infarction Demonstrated by Line-Scan Diffusion MRI: Clinical and Radiological Aspects in 15 Cases

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**Objective:** To establish the value of LSDI (Line Scan Diffusion MR Imaging) in detection of SCI (spinal cord infarction). **Methods:** Fifteen patients with clinical and radiological findings consistent with SCI underwent LSDI in an attempt to identify areas of decreased diffusion suggestive of infarction. MR was performed on a Signa 1.5T imaging system on either the sagittal or axial plane using a phased-array spine coil (GEMS) with the following approximated sequence parameters: 3860/75/9.1/3 (TR/TE/excitation); 3.5cm field of view; 129 x 256 imaging matrix; 3-5mm slice thickness; of b 5 and 750 s/mm2, with the maximum b value applied in 3 directions. The ADC measurements for the normal spinal cord and for the areas of infarction were calculated from the trace ADC maps by using the average value of five distinct ROIs (area 0.043–0.864 cm2) positioned over the spinal cord avoiding the inclusion of CSF. **Results:** Ten patients were female. Age ranged from 11 to 82 (mean 64). 8 infarcts were spontaneous; 5 related to aortic aneurysm (AA) surgery; 1 related to AA; and 1 related to hypotension during non-SSA anesthesia. 2 infarcts were cervical; 5 thoracic; and 8 were in the thoracic/commarginal/conus region. **Conclusion:** LSDI was obtained between 5 hours and 8 days after the event. ADC ranged between 0.46 and 0.63 x 10-3 mm2/s and progressed to higher values on repeat LSDI. **Conclusion:** LSDI is feasible and probably the most reliable technique to diagnose spinal cord infarction in the acute setting. Thus, LSDI may provide the diagnostic means for the employment of therapeutic trials in the hyperacute phase of spinal cord infarction. The potential application of DWI in the spinal cord to distinguish acute ischemic from non-ischemic lesions still requires further investigation since in the brain decreased diffusion can also be seen in several other processes, including demyelination, abscess, and tumors.

### Biphasic Manifestation of Ischemic Lesions on Diffusion-Weighted Images Following Transient Ischemic Attacks

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**Background:** Focal ischemic lesions can be detected by diffusion-weighted imaging (DWI) until 2–3 weeks following transient ischemic attacks (TIA). Little, however, has yet been known as to the DWI detectability of ischemic lesions in the early post-ischemic period, such as 0–12 hours after TIA. Experimental studies of transient focal ischemia by Li et al. (2004) indicated that the DWI detectability was biphasic showing the poor sensitivity at the early post-ischemic phase. The aim of our study is to clarify whether such a biphasic change can be seen in the DWI detectability after TIA. **Method:** DWI films in 78 consecutive TIA patients who underwent MRI (1.5 Tesla) within 2 weeks after TIA in the carotid artery territory were reviewed in a retrospective manner. Patients were divided into 7 groups according to the time of DWI from the end of TIA episode, such as intra-ischemic (n=4), 0–3 hours after TIA (n=11), 3–12 hours after TIA (n=16), 12–24 hours after TIA (n=13), 1–3 days after TIA (n=6), 3–7 days after TIA (n=6), and 7–14 days after TIA (n=15). Threshold-analysis using a previously described method (Wintermark et al, Ann Neurol 2002) showed that this hypoperfusion can be easily identified on routine DWI. The prevalence of lesions evident on DWI-T in the cortical grey matter ribbon was significantly higher than that on DWI-T in the subcortical region. **Results:** Ischemic lesions were detected in 22 of 78 patients (28%). The frequency of DWI-positive lesions was 50% (2/4) in the intra-ischemic period. The frequency decreased to 0% (0/11) at 0–3 hours after TIA, and remained low (13%, 2/16) at 3–12 hours after TIA. The frequency increased to 31% (4/13) 12–24 hours after TIA and remained the same thereafter showing 38% (3/8) at 1–3 days after TIA, 36% (4/11) at 3–7 days after TIA and 47% (7/15) at 1–2 weeks after TIA. The average duration of ischemic symptoms was longer in the intra-ischemic group (9.8 hours) and shorter in the 12–24-hour group (0.4 hours) but was the same in all the other groups (1.2–5.1 hours). In 3 of 17 patients with serial DWI studies, the first DWI within 12 hours failed to depict lesions, while the second DWI at 1–8 days detected ischemic lesions successfully. **Conclusion:** The present findings support experimental results of Li et al. showing that the DWI detectability of ischemic lesions following transient focal cerebral ischemia is biphasic.

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Background & Objectives: Analysis of basal/acetazolamide brain perfusion single photon emission computed tomography (SPECT) using statistical parametric mapping (SPM) and statistical probabilistic anatomic map (SPAM) could give objective information about the cerebral perfusion and cerebral vascular reserve. By basal/acetazolamide brain perfusion SPECT using SPM and SPAM, we investigated the changes in brain perfusion and cerebral vascular reserve after stenting, and efficacy of endovascular stenting for symptomatic cerebral artery stenosis.

Methods: Fifteen patients, undergone endovascular stenting for symptomatic middle cerebral artery (MCA), intracranial or extracranial internal carotid artery stenosis (ICAS), and twelve age-matched healthy volunteers were studied with SPECT-EC basal and acetazolamide brain perfusion SPECT. Using SPM and SPAM analysis, we compared between pre- and post-stenting SPECT of the two groups for each basal/acetazolamide image, and assessed the changes of perfusion and vascular reserve in MCA stenting and ICA stenting. Results: The SPM analysis between patients and control group showed significant improvement in basal perfusion in the ICA territory. The vascular reserves by basal and acetazolamide SPECT image were significantly improved from pre-stenting state, but remained regions of decreased perfusion reserve were also observed. The improvement of basal perfusion and perfusion reserve were more obvious in the patients with ICA stenting than MCA. Conclusions: The objective analysis of basal/acetazolamide SPECT using SPM and SPAM demonstrated significant improvement in cerebral perfusion and vascular reserve by endovascular stenting in symptomatic MCA or ICAS stenosis, and showed efficacy of endovascular stenting treatment.

Superficial Temporal Artery Duplex Ultrasonography for Evaluating Improved Cerebral Hemodynamics After Extracranial-Intracranial Bypass Surgery

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Purpose: Recently, extracranial-intracranial (EC-IC) bypass trial has revealed a benefit of EC-IC bypass for preventing stroke. The purpose of the present study is to investigate the availability of superficial temporal artery (STA) duplex ultrasonography (STDU) for evaluating the cerebral hemodynamics after EC-IC bypass. Methods: This study included 48 consecutive patients who underwent EC-IC bypass for the treatment of occlusive cerebrovascular disease with severe cerebral hemodynamic failure (regional cerebral blood flow (rCBF) <32.0 ml/100g/min and acetazolamide (ACZ) reacticity <10%) in the ipsilateral middle cerebral artery (MCA) territory. STDU was performed to measure the flow velocity, pulsatility index (PI; a parameter reflecting vascular resistance), and diameter of the operated STA before, 14 days and 3 months after EC-IC bypass. Using transcranial color-coded sonography (TCCS), the flow velocity and direction of the ipsilateral MCA were also evaluated. The rCBF and ACZ reactivity of the ipsilateral MCA territory were evaluated by quantitative single photon emission computed tomography. Results: On 14 days after EC-IC bypass, STA mean flow velocity (MFV) (29.8 ± 8.4 to 60.4 ± 16.7 cm/sec, p <0.0001) and diameter (1.52 ± 0.19 to 2.25 ± 0.45 mm, p <0.0001) increased and PI value (1.82 ± 0.54 to 0.90 ± 0.26, p <0.0001) decreased in comparison with the baseline values. On 14 days after EC-IC bypass, STA MFV in 11 patients with retrograde flows of the MCA horizontal portion was higher than STA MFV in 37 patients with antegrade flows of the MCA (64.3 ± 18.4 vs 53.8 ± 16.7 cm/sec, p <0.05). STA MFV was correlated with the rCBF 14 days after EC-IC bypass (R = 0.51, p <0.0001). The cut-off value of post-surgical STA MFV over 66.8cm/sec yielded the highest diagnostic accuracy (sensitivity, 80%; specificity, 90%; for acceptable rCBF value (<40/ml/min) after EC-IC bypass. Between 14 days and 3 months after EC-IC bypass, changes in STA MFV correlated with changes in rCBF (R = 0.44, p <0.001). Conclusions: Changes in STDU parameters could indicate the patency of the bypass flow via STA. Development of the bypass flow via STA was associated with the direction of the STA flow. STDU were available for evaluation of post-surgical rCBF of the ipsilateral MCA territory.

Platelet GIIb/IIIa Inhibitors as Adjunctive Therapy in Endovascular Treatment of Large Artery Occlusion

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Objective: To evaluate the safety of platelet GIIb/IIIa inhibitors administered as adjunctive therapy in patients with large artery occlusion (LAO) refractory to thrombolysis with intratrabem thromboplastin (ITPA) and balloon-mediated clot disruption. Background: LAO tends to be refractory to ITPA. Intraarterial TPA and mechanical therapies have had limited success. We hypothesized that the addition of intratrabem thromboplastin GIIb/IIIa inhibitors might enhance recanalization with acceptable safety. Methods: Criteria for addition of GIIb/IIIa therapy included failure to recanalize after administration of TPA (intrastrabem ≤ intravenous), with or without balloon-mediated clot disruption. Results: Twenty-one (mean age 62 years, range 29–88 years) patients were treated, 11 with dominant hemisphere, 2 with nondominant hemisphere, and 8 with vertebrobasilar system LAO. All patients received ITPA.Twelve had received ITPA initially without recanalization. Nine were not candidates for ITPA. Balloon-mediated clot disruption was performed in 18 patients. GIIb/IIIa inhibitors were administered after the above intervention–intratrabem in 16 patients, intravenous in 3 (as rescue to maintain patency) and both in 2. Complete or partial recanalization was achieved in 17 patients. After treatment, 15 patients were improved clinically. Three sustained asymptomatic intracranial hemorrhage (2, 2.5, 8.7 ml). There were no other significant procedure-related complications, and no patient worsened in relation to treatment. At mean 8.5 month follow up,13 patients were functionally independent (modified Rankin score 0 to 3) and 8 were disabled or dead. Conclusion: As part of an escalating endovascular protocol that includes intratrabem TPA and balloon-mediated thrombolysis, the addition of GIIb/IIIa inhibitors has a low risk of significant hemmorrhage and may prove to be a useful adjunct for achieving recanalization.

Combined Systemic Thrombolysis With Recombinant Tissue Plasminogen Activator and Abciximab in Patients With Occlusion of the Middle Cerebral Artery in the 3- to 6-Hour Time Window

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Background: In ischemic stroke due to occlusion of the middle cerebral artery (MCA) intravenous administration of recombinant tissue plasminogen activator (rtPA) is the recommendation for therapy within the 3–6 h time window. Intravenous treatment using pro-urokinase is recommended but not every time and everywhere available. The goal of our ongoing pilot study is to assess the feasibility and safety of systemic thrombolysis with rtPA at half standard dose combined with Abciximab (a platelet glycoprotein IIb/IIIa receptor inhibitor) in patients with MCA-occlusion within the 3–6-hour time window. Methods: From December 2002 to August 2004, we prospectively and consecutively treated 15 patients with ischemic stroke due to occlusion of the MCA within the 3–6-hour time window with intravenous administration of rtPA (0.45 mg/kg) and Abciximab (0.25 mg/kg bolus, followed by 0.125 µg/kg/min x 12h). We performed transcranial ultrasound immediately and every 6 hours after start of treatment to register recanalization of the MCA. Cranial computed tomography was performed at admission and day 1 to detect intracranial haemorrhage. National Institute of Health Stroke Scale (NIHSS) was assessed on admission and at discharge. Results: Recanalization of the MCA could be observed in 7 patients (47%) within the first 8 hrs and in 4 patients (27%) within 24 hrs. One patient suffered symptomatic intracranial haemorrhage and went to surgery. No other serious side effect occurred. Two patients (one with and one without recanalization of the MCA) developed malignant brain oedema and went to decompressive surgery. The mean NIHSS improved from 14.2 (range 6–24) to 9.9 (range 1–27) at day 5. Conclusions: Combined systemic thrombolysis with rtPA at half standard dose and Abciximab seems to be a safe treatment option in patients with occlusion of the MCA within the 3–6-hour time window. The relatively high rate of MCA-recanalization is promising. But general use of this therapeutic regime cannot be recommended until safety and efficacy have been proven. Further prospective clinical trials are necessary.
Safety of Thrombolyis Given Both Inside and “Out of the NINDS Box”

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Background and Purpose: Increasing confidence with intravenous (IV) thrombolyis as treatment of acute ischemic stroke (AIS) may have led to an increasing number of patients being treated outside current protocol. Aim of this study is to assess the safety of thrombolyis performance either within or outside current guidelines in patients with AIS in a community setting.

Methods: We prospectively studied 142 consecutive patients with AIS treated with thrombolysis in a Canadian teaching hospital between April 2002 and April 2004. Treated patients were defined by adherence to the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA protocol or by inclusion in off-label protocols: Results: Of 142 treated patients, 51 (36%) received thrombolysis outside NINDS guidelines: 31 received alternative thrombolytic treatment other than, or in addition to, IV tPA while 20 patients received systemic thrombolysis with tPA in the presence of contraindication to treatment. Median (range) baseline NIH Stroke Scale was 13 (5–22) in the group treated “on protocol”, and 16 (6–42) in the “off-label” group. Symptomatic hemorrhage developed in 2/91 (2.2%) patients treated with IV tPA according current guidelines. In the “off protocol” group no symptomatic hemorrhage was observed in those treated with IV tPA only, while 4/31 (13%) patients who received alternative thrombolytic treatment had symptomatic bleeding. Patients treated “off protocol” were (not significantly) more likely to be older (OR 1.6, 95% CI 0.4–5.7). The proportion of patients dead or dependent at 3 months was not significantly higher in the “off label” group (75% vs 46%) in the univariate analysis and after adjusting for baseline risk (OR 1.6, 95% CI 0.5–5.2). The highest mortality (40%) was observed in patients treated with IV tPA only outside current guidelines, despite the absence of hemorrhagic complications.

Conclusions: The risk of death, dependency and symptomatic hemorrhage is as expected in those who meet NINDS criteria. Risk increases (not significantly) for patients whose presentation and course necessitate additional off-label intervention.

The CLEAR Stroke Trial: Blinded Results From the First Dose Tier

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Introduction: The Combined approach to Lysis using Eptifibatide And rt-PA (CLEAR) Stroke trial is a multi-center, sequential, dose-escalation, double-blind, randomized safety study evaluating the risks and benefits of combining a glycoprotein IIb/IIIa antagonist, eptifibatide, with recombinant tissue plasminogen activator (rt-PA) in 100 acute ischemic stroke patients treated within 3 hours of onset.

Methods: The two dose tiers will contain 40 and 60 patients respectively. Patients are randomized 3:1 to the combination of IV eptifibatide plus low-dose rt-PA, vs. standard dose rt-PA. The low-dose rt-PA for dose tiers one and two are 3 mg/kg and 0.45 mg/kg respectively. The eptifibatide dose is a bolus of 75 mcg/kg and an infusion of 0.75 mcg/kg/min for 2 hours for both dose tiers. The primary safety endpoint is the incidence of symptomatic hemorrhage. The eptifibatide dose is a bolus of 75 mcg/kg and an infusion of 0.75 mcg/kg/min for 2 hours for both dose tiers. The primary safety endpoint is the incidence of symptomatic hemorrhage.

Results: As of Aug 1, 2004, 34 patients have been randomized. Patients are currently being enrolled at slightly greater than one patient per week. By May 2005 we will have completed dose tier one and 3-month follow-up. We will present the enrollment and blinded safety data. Of the 34 patients enrolled to date, 18 (52%) are male, 8 (24%) are African American, 25 (74%) are Caucasian, and 1 (3%) is American Indian. Age, NIHSS and time to treatment were similar between the two dose tiers. Two patients have suffered a symptomatic PH. Early Fibrinogen Degradation Product (EFDP) in the FDP (at 2 hours) was not a predictive factor of HI in univariate analysis. No other parameter concerning coagulation, at any time, was predictive.

Conclusions: Little is known about the coagulation factors in the prediction of cerebral bleedings in IV thrombolysis. An Early Fibrinogen Degradation Coagulopathy (EFDPC), consisting in the increase of Fibrinogen Degradation Products (FDP) at 2 hours, has been shown by us to be predictive of early (<24 h) parenchymal hematoma.

Methods: Consecutive patients were included in the Lyon rt-PA protocol. Early hemorrhagic infarcts (within 24 hours), diagnosed on the ECASS angiography radiological basis (1 and 2), were considered for the study. The fibrinogen and FDP were assessed at entry, 2 and 24 hours after the beginning of thrombolysis. Fifty three variables, etiological, clinical, biological and baseline radiological, were also studied. Results: Of hundred fifty seven patients, 31 had early hemorrhagic infarcts (HI) (19.7%), 11 had early parenchymal hematomas (PH) (7%), and 115 had no bleeding (73.2%). Conversely to early PH, Early Fibrinogen Degradation Product (FDP at 2 hours) was not a predictive factor of HI in univariate analysis. No other parameter concerning coagulation, at any time, was predictive.

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thrombolysis for acute ischemic stroke. Methods: Consecutive ischemic stroke patients treated within three hours of symptom onset with full dose IV tPA who had at least one of the following within one hour of treatment: no improvement clinically, no recanalization, or early arterial reocclusion were taken for IA therapy. All patients were evaluated in the Emergency Department with Transcranial Doppler (TCD) using standard protocol and validated criteria. Results: Of 62 patients (56 male, 16 female) within the last 15 months (age 40–93 years, range 8–98 years, 26 women) had median pre-treatment NIHSS 18 (range 6–39, 95% with > 10). IV tPA bolus was given at ≥12 ± 37 (median 121) minutes and IA therapy started 296 ± 61 (median 289) minutes. IA treatment was administered with Retaplace (n=46), Alteplase (n=7), and Urgten (n=9) with an average dose of 2.5 units (0.35–8), 8.5 mg (4–18) and 10,000 units (50,000–1,000,000) respectively. Adjunctive mechanical therapy was frequently used. Symptomatic intracerebral hemorrhage [Parechymal Hemorrhage (PH2)] occurred in 5/62 (8%) including three fatal bleeds. Recanalization (TIMI 2&3) was achieved in 45 (72%), favorable outcome (mRS 0–2) in 38 (61%), and survival (mRS 0–6) in 11 (18%) patients who had persistent occlusion and/or lack of clinical improvement appears safe compared to rates of symptomatic ICH reported with IV therapy alone. A high rate of recanalization and favorable outcome can be achieved.

P48 Outcome of IV Thrombolysis Within 6 Hours of Acute Middle Cerebral Artery Stroke in MRI-Selected Patients: Results of a German Multicenter Study Compared With Pooled Data of the rPA Stroke Trials

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Background: In a multicenter approach we studied outcome of intravenous thrombolysis within 6 hours of symptom onset in patients selected by MRI and compared our data with the pooled data of the stroke rPA trials (ATLANTIS, ECASS and NINDS). Methods: In three german stroke centers patients with acute MCA stroke were examined by perfusion and diffusion weighted imaging (PWI and DWI) within 6 h of symptom onset. In a retrospective analysis, all patients treated with thrombolysis presenting with a PWI/DWI mismatch of at least 25% were selected. Neurological deficit at admission was assessed using the National Institutes of Health Stroke Scale (NIHSS). Outcome was assessed after 90 days using the modified Rankin scale (mRS). Data were compared with the pooled data of ATLANTIS, ECASS and NINDS rPA-trials. Results: 146 patients with PWI/DWI-mismatch were treated with IV-thrombolysis (70 ±35(35) [median (range)] min after symptom onset. Thrombolysis was performed within 3 h in 59.9% and after 3–6 h in 40.5% of patients. A favorable outcome [mRS 0–1] was reached by 48% of patients in our study, compared to 33.4% in the placebo group and 39.6% in the rPA group of the pooled rPA-trials data. Mortality at day 90 was 7.7% in our group compared to 12.3% in the placebo group and 3.3% in the rPA group. Conclusion: IV thrombolysis within 6 hours of symptom onset in patients selected by diffusion and perfusion weighted MRI appears to be better than in the pooled analysis of the large clinical rPA-trials. Our study does not substitute a randomized controlled trial of MRI guided IV-thrombolysis within 6 hours. Nevertheless it provides some evidence, that stroke MRI may help selecting patients for safe and effective IV-thrombolysis within a 6 hours time window. With the use of MRI as a tool for patient selection, onset to treatment time appears to play a less important role, than in unselected patients.

P49 Recanalization Rates and Clinical Outcomes in Patients With Tandem ICA/MCA and Isolated MCA Occlusions

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Background: Patients with isolated MCA and tandem MCA/ICA occlusion often show similar severe cerebrovascular obstruction and low recanalization rates were reported for both ICA and MCA occlusions. We aimed to determine MCA recanalization rates and clinical outcomes in patients treated with systemic thrombolysis for tandem and isolated lesions. Methods: MCA occlusion was identified using the CLOTBUST trial protocol by abnormal TBI 0–3 flow grades on transcranial Doppler. Complete recanalization was defined by TBI 5 grade 2 or 3 hours after t-PA bolus (TIMI score ≤2) confirmed before min 30 postbolus, ≤30, 60, 120 min and 24 hours after IA thrombolysis. Early neurological improvement (ENI) was defined by reduction of NIHSS ≥10 or total NIHSS ≤3 points. Good outcome at 3 month after onset was modified Rankin Score (mRS) ≤2. Results: Among 126 patients, 33% of patients have tandem ICA/MCA and 67% isolated MCA occlusions. Mean age was 61 year (30–93) with 15 ischemic lesions and 21 with tandem lesions before TPA bolus (ns). Complete recanalization rate of isolated MCA occlusions was 38% vs. 17% with tandem lesions, p=0.015. Partial recanalization was seen in 25% and 39% respectively (ns). ENI at 24 hours occurred in 42% of patients with isolated MCA occlusions and in 22% with tandem lesions, p=0.027. Despite this, 30% of patients with tandem lesions achieved good outcomes at 3 months compared to 39% with isolated MCA lesions (ns). Symptomatic hemorrhage rates were 6% and 3% respectively (ns). Conclusion: Despite having lower recanalization and early clinical recovery rates compared to isolated MCA occlusions, a substantial proportion of patients with tandem lesions recover at 3 months. Partial recanalization and collateral flow improvement may be potential mechanisms how systemic thrombolysis may impact tandem lesions, and the presence of concomitant ICA obstruction should not be used as an exclusion standard from IA therapy in the first 3 hours of stroke.

P50 Tpa Argatroban Stroke Study (TARTS)


Background: rt-PA benefit in acute stroke is linked to artery recanalization. However, only 20% of patients will have complete recanalization by 2 hours, and 34% with recanalization will re-occlude. Argatroban is a direct thrombin inhibitor that safely augments the benefit of rt-PA in animal stroke models. Design: TARTS is an ongoing, prospective, single-arm, dose escalation, safety and activity trial of the use of Argatroban and rt-PA measuring the incidence of symptomatic intracerebral hemorrhage (SICH) and rates of re-occlusion. Methods: Fifteen patients with early vessel recanalization were studied. Baseline NIHSS was 66.5 year (30–184) vs control median 137 min). PH-2 occurred in one patient, symptomatic ICH occurred in 5/62: 36% M1, 64% M2 occlusions. Baseline median NIHSS was 14 (range 3–25) with 64% patients treated within 3 h and those treated after 3–6 h (48.9% vs. 46.7%). Conclusion: Low dose Argatroban combined with IV rt-PA may produce faster reperfusion by thrombolysis. Evaluation of ischemic threshold measured by ADC ratio may provide important data for information clinical decision making of thrombolytic therapy.

P51 Thrombectomy in Middle Cerebral Artery Embolism Trial

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Rationale: Thromboembolic occlusion of the MCA in patients with acute ischemic stroke is often resistant to rapid recanalization and intravenous or intra-arterial thrombolysis. We developed and tested two versions of a MCA thrombectomy device based on the AngioJet™ thrombectomy system. Two versions of a core thrombectomy specific AngioJet™ thrombectomy device were employed in 25 patients with acute thromboembolic occlusion of the M1 or M2 segments of MCA within 6 hours of stroke onset. Median time from symptom onset to activation of the device was 5 hours, 0 minutes. The first version employed a high operating pressure and a relatively stiff catheter shaft. Version 2 accessed the lesion in 4 of 9 patients and achieved TIMI 2 or 3 recanalization in 1 of 4 patients assessed by angiography 60 minutes post procedure;
in 2 patients radiographic evidence of perfusion was identified. Because of perfusions, a modified second version employed a lower operating pressure and a more flexible shaft.

Version 2 accessed the lesion in 11 of 20 patients and achieved TIMI 2 or 3 recanalization in 11 of 20 patients; 10 patients did not need IA tPA and had excellent outcomes (row 2 in table). The 50 patients who received IV/IA tPA9 did not have a treatment modifying effect on good outcome but showed a trend to lower mortality at 90 days with tPA (RR 0.67 95%CI 0.41–1.06, p = 0.10). ASPECTS 8–10 was associated with a trend to larger benefit of rt-PA compared to placebo. Conclusion: There was no evidence of treatment effect modification by the baseline ASPECTS value in the NINDS rt-PA Stroke Study. Therefore, exclusion of patients for thrombolysis within three hours of symptom onset based on EC is not supported by our data. There is a trend to reduced mortality and increased benefit of rt-PA if the baseline CT scan is favourable (ASPECTS ≥ 8).

Pre-activation of plasminogen to plasmin prior to thrombolysis may occur more slowly than previously suspected. Activation may actually occur after blood has passed the target clot as blood flow limits their efficacy and increases the risk of hemorrhagic complication. From years of thrombolytic treatment, we have noticed that the rate of thrombolysis is greatest in a vessel that is completely occluded and diminishes substantially as flow is reestablished. However when the thrombolytic agent is pre-mixed with the patient’s blood and re-infused, a markedly increased rate of clot lysis and distal reperfusion is observed. We have designed an experiment that investigates various thrombolytic combinations that increase both thrombolytic activity and rate of reaction by pre-activating plasminogen. Controls were established for quantity, time, position and angle. Calibrated IV pumps were pre-loaded with NaCl 0.9%, rt-PA (Alteplase) and rFg, Luminex, Lausanne Stroke Index (LSI=penumbra/penumbra + infarct) and vessel patency were compared by delayed neuroimaging. Clinical assessment was quantified by admission and 24-hour NIHSS and 3-month mRS. Univariate factors with a p < 0.20 were forced in a multivariate stepwise logistic regression model in order to find predictors of final infarct size, symptomatic and asymptomatic ICH (SICH, AICH) and total recovery (mRS < 2) at 3-month follow-up. Thresholds of final significant PCT-data were studied by ROC curves. Results: 8 patients were excluded due to inappropriate contrast injection. 66 patients (mean age 65 years ± 14.3, 39 males) underwent PCT and CTA within a mean of 120 min (SD ± 4.2) and rt-PA was initiated within 154.7 min (± 33.5). Mean admission NIHSS was 15.5 ± (5.42), 25 (38%) patients had favorable outcome. SICH occurred in 4 (6.1%), and AICH in 7 (10.6%) patients. MCA-branches were occluded in 30 (45.5%) patients, ICA in 1 patient (1.5%) in the NABSI team and 14 patients (20%) in the CTA. Average for the ICA and MCA-branches occurred in 4 (10.8%) and 20 patients (54%), respectively, and this was a positive outcome predictor (p = 0.05). No correlation was found between mean admission LS5 and outcome (p = 0.52). Conversely, we found a strong correlation between initial global ischemic perfusion volume and final infarct size among patients without recanalization (p = 0.0043). Furthermore, increased MTT in the estimated penumbra was a predictor of AICH, with a specificity of 81.8% and sensitivity of 71.4%, with a threshold of 12.6 sec (p = 0.035). Preliminary analysis of a limited number of patients (4) indicated a higher risk of symptomatic hemorrhage within the estimated global hyperperfused area on PCT with rFg over 63.65 ml/100 g tissue/sec (sensitivity 75%, specificity 80%). Conclusion: PCT and CTA are useful methods for estimation of outcome and risk of ICH in patients with ischemic stroke treated with rt-PA within the 3-hour time window.

Outcomes of Patients Receiving 0.6mg/kg IV tPA with and without IA tPA

<table>
<thead>
<tr>
<th>Patient Groups</th>
<th>% Mortality in hospital</th>
<th>% Symptomatic Hemorrhage</th>
<th>Median NIHSS on admission</th>
<th>% NIHSS ≤4 at discharge</th>
<th>% NIHSS ≤2 at discharge</th>
<th>Median length of stay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole cohort: IV only</td>
<td>N = 133</td>
<td>12</td>
<td>6.9</td>
<td>7.5</td>
<td>12</td>
<td>62</td>
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<tr>
<td>IV-only and N = 44</td>
<td>6</td>
<td>3.6</td>
<td>9</td>
<td>71</td>
<td>63</td>
<td>4</td>
</tr>
<tr>
<td>NINDS 5-9</td>
<td>5.6</td>
<td>1.9</td>
<td>11</td>
<td>6</td>
<td>67</td>
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<td>NINDS 10-14</td>
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<td>14</td>
<td>14</td>
<td>48</td>
<td>24</td>
<td>7</td>
</tr>
</tbody>
</table>

Conclusion

Low dose IV tPA at 0.6mg/kg is safe and effective. Using a lower dose may increase the comfort level of practitioners reluctant to administer IV tPA.

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Importance of Early Ischemic CT Changes Using ASPECTS in NINDS rtPA Stroke Study

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Background: The importance of early ischemic change (EC) on baseline CT in the decision to thrombolise the acute ischemic stroke patient has been controversial. ASPECTS is a semi-quantitative scale which scores the extent of EC within the MCA territory. We examined whether ASPECTS could be a treatment modifier by systematically reviewing the CT scans in the NINDS rt-PA Stroke Study. Methods: 608 of the 624 CT scans were available and of sufficient quality. One of two teams (n=3) of each expert ASPECTS readers evaluated each scan for an ASPECTS value using a consensus score approach. Each team was blind to all clinical and outcome information except stroke symptom side and as well as to follow-up imaging results. ASPECTS values were stratified prior to analysis. Multivariable logistic regression was used to determine if an ASPECTS by treatment interaction existed on treatment response, outcome, and ICH risk. Results: 57.2% (348/608) of scans showed EC with an ASPECTS <10. ASPECTS dichotomized into 0–9 and ≥10 did not have a treatment modifying effect on good outcome but showed a trend to lower mortality at 90 days with tPA (IRR 0.67 95%CI 0.41–1.06, p = 0.10). ASPECTS 8–10 was associated with a trend to larger benefit of IA with a number needed to treat (NNT) of 5 versus ASPECTS 3–7 with a NNT of 8. Patients with ASPECTS ≥8 were infrequent (5%) but associated with a trend to poorer outcome and increased mortality with rt-PA compared to placebo. Conclusion: There was no evidence of treatment effect modification by the baseline ASPECTS value in the NINDS rt-PA Stroke Study therefore, exclusion of patients for thrombolysis within three hours of symptom onset based on EC is not supported by our data. There is a trend to reduced mortality and increased benefit of rt-PA if the baseline CT scan is favourable (ASPECTS >7).

Accelerated Thrombolysis by Preactivation of rtPA (Alteplase) With Plasminogen

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Introduction All currently available plasminogen activators are associated with drawbacks that limit their efficacy and increase the risk of hemorrhagic complication. From years of intra-arterial thrombolytic experience, we have noticed that the rate of thrombolysis is greatest in a vessel that is completely occluded and diminishes substantially as flow is reestablished. However when the thrombolytic agent is pre-mixed with the patient’s blood and re-infused, a markedly increased rate of clot lysis and distal reperfusion is observed. We postulated that activation of plasminogen by plasmin may occur more slowly than previously suspected. Activation may actually occur after blood has passed the target clot as blood flow is reestablished, resulting in ineffective thrombolysis. Methods We have designed an experiment that investigates various thrombolytic combinations that increase both thrombolytic activity and rate of reaction by pre-activating plasminogen. Controls were established for quantity, time, position and angle. Calibrated IV pumps were pre-loaded with NaCl 0.9%, rt-PA (Alteplase) and rt-PA premixed with plasminogen. Fixed volumes of each solution were infused over the clots at a constant rate. Hemoglobin was then extracted from the thrombolysed effluent and analyzed using light spectrophotometry. Results The results at the time of submission of this abstract showed a statistically significant increase in thrombolysis of the rt-PA premixed with autologous plasminogen when compared to the NaCl control (n=4 patients, 8 samples, p = 0.0001) and when compared to rt-PA alone (n=4 patients, 8 samples, p = 0.0004). No statistically significant difference was noted when comparing rt-PA and NaCl controls (n=4 patients, 8 samples, p = 0.087). Conclusion Pre-activation of plasminogen to plasmin prior to thrombolysis has shown a statistically significant increase in clot lysis when compared to rt-PA alone and the NaCl control. This method of pre-activation of plasminogen to plasmin with rt-PA represents a clinically significant new method of thrombolysis. This may also apply to other thrombolytic drugs and may have a variety of clinical applications.
Intraarterial Thrombolytic With Tissue Plasminogen Activator in Acute Ischemic Stroke With Persistent Arterial Occlusion

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Background and Purpose: Intra-arterial thrombolytic therapy with pro-urokinase has been shown to be effective when given within 6 hours of symptom onset in patients with acute ischemic stroke (AIS). We evaluated the clinical efficacy and safety of thrombolysis with intra-arterial recombinant tissue plasminogen activator (rt-PA) within first 6 hour in patients with AIS.

Methods: The medical records of patients with AIS who received intra-arterial tPA at our institution between October 1999 and March 2003 were reviewed. The National Institute of Health Stroke Scale (NIHSS) and modified Rankin’s scale (mRS) scores were collected at admission, 24 hours and on discharge. The NIHSS was scored at discharge for the patients who underwent transcranial Doppler (TCD) and CT angiography to determine the site of occlusion prior to treatment. Patients who had occlusion of major intra-cerebral vessels were treated with intra-arterial tPA. Recanalization was achieved in 3/4 patients receiving rescue IA lytics, recanalization was achieved in 2/3. Recanalization occurred in 10/16 (63%). In patients unresponsive to IA tPA receiving rescue IA mechanical clot retrieval, thrombolysis and influence on outcome with respect to recanalization.

Results: Recanalization was achieved in nearly two-thirds of patients and fair to good clinical outcomes in more than one third.

Conclusions: This series expands the worldwide reported experience with intra-arterial thrombolysis and mechanical clot retrieval based therapy for acute ischemic stroke. The degree of recanalization required to achieve good outcome remains uncertain. We reviewed our stroke database of consecutive acute ischemic stroke patients treated with IV or with IV/IP tPA over six years. Trained interventional neuroradiologists blinded to outcomes reviewed angiograms assessing rate of recanalization using modified TIMI criteria. Grade 0 – no penetration beyond the occlusion, grade 1 – penetration but not perfusion, grades 2 – partial perfusion with incomplete distal branch filling of < 50% (Ci) or > 50%–99% (Sh) of the expected territory respectively, grade 2c – near complete perfusion without visible thrombus but TIMI remaining at Grade 0 –1 in 27 patients with 18 (66%) having poor outcome before treatment. Presence and location of MCA occlusion was assessed using the TIBI flow grading system. TIMI occlusion was defined according to validated criteria. Patients were continuously monitored with TCD during 2-hour IP infusion. NIHSS scores were obtained at baseline and 24hr. mRS score was used to assess outcome at 3 months. Results: Median pre-bolus NIHSS score was 17. On TCD, 138 (69%) patients had a proximal and 59 (31%) a distal MCA occlusion. Severe carotid artery stenosis (>70%) or occlusion ipsilateral to the MCA occlusion was noted in 31% of patients. Although revascularization therapy in time to treatment were similar in patients with and without TIMI occlusions. Thirty (33.8%) patients with and 107 (68.8%) without TIMI lesions achieved a MCA recanalization at 2-h of IP bolus (p = 0.001). The independent contribution of TIMI lesions on poor outcome (mRS score > 2) at 3 months. However, the independent contribution of TIMI lesions on poor clinical outcome varied depending on the location of MCA occlusion. TIMI occlusions predicted poor outcome in patients with proximal (OR 4.3 95% CI: 1.32–14.6), but not in those with distal (OR 1.2 95% CI: 0.78–18.9) MCA occlusion. Conclusion: TIMI occlusion independently predicts poor outcome after IV thrombolysis. However, its impact on poor outcome varies depending on the location of the occlusion and independent carotid ultrasound plus TCD examinations may improve the selection of patients for more aggressive reperfusion strategies.
Previously been formally studied. Methods: Consecutive acute ischemic patients undergoing intra-arterial fibrinolytic or mechanical embolectomy interventions for acute circulation outcomes between 1996–2004 were identified from the UCLA Stroke Registry. Pretreatment angiographic runs were analyzed to determine the most proximal and most distal extensions of thrombus on late arterial and capillary phase images. Average diameters of intracranial vessels were taken from standard postmortem studies. The volume of clot burden was calculated as measured length of clot x (vessel radius)^2 x pi. Degree of reperfusion achieved after endovascular therapy was rated employing the anterior perfusion sub item of the Recanalization in Brain Ischemia (RBI) scale. Results: 67 patients had full angiographic runs available for analysis. Clinical NIHSS were: carotid T 316 cc, ICA - 265 cc, M1 - 90 cc, M2 - 31 cc, M3 - 18 cc. Interventions consisted of IA fibrinolytics alone in 52, clot retrieval alone in 6, combined fibrinolytics and embolectomy in 9, IA fibrinolytics and clot retrieval in 3, and, in 2, other treatments. Clot burden was less in patients treated with chemical fibrinolytics (81 cc) than in patients treated with mechanical interventions (166 cc). Successful reperfusion was achieved in 67% of cases. Achievement of reperfusion was more frequent across all patients when the initial target clot burden was small (<0.05), and especially so in patients treated with pharmacologic fibrinolytics (p<0.02). Conclusions: The volume of obstructing thrombus in acute ischemic stroke is strongly related to clot location, increasing with more proximal sites of obstruction. An extensive burden of clot increases the likelihood of failure of endovascular recanalization therapy, especially for pharmacologic fibrinolytic interventions.

Clinical Predictors of Angiographic Collaterals in Acute Ischemic Stroke

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Background and Purpose: The clinical variables associated with collateral blood flow in the cerebral circulation remain undefined. We sought to determine the frequency of these angiographically demonstrated events and their impact on functional outcomes following treatment. Methods: Clinical data and angiographic images derived from three prospective studies, the Buffalo intra-arterial treatment regimen, the US EXOS Microlysol® trial, and one institutional study were analyzed. The rates of distal occlusion (defined as a persistent occlusion in a distal vessel segment not adjacent to the segment with the target occlusion) and reocclusion (defined as a partial or complete initial recanalization with occlusion recurring at the same site as documented by angiography) during the endovascular treatment were determined. The effect of distal occlusion and reocclusion on favorable outcome defined by a modified Rankin scale score of 0–2 at one to three months was determined using a logistic regression model adjusting for age, gender, time to treat, and initial National Institutes of Health Stroke Scale (NIHSS) score. Results: In these three studies, 78 patients were treated for ischemic stroke (mean age 67±16 years, 43 men). Initial NIHSS ranged from 5 to 42, and mean time interval between symptom onset and treatment was 4.7±1.9 hours. Initial severity of occlusion was categorized as Qureshi grade 0 (n=3), grade 1 (n=4), grade 2 (n=9), grade 3A (n=17), grade 3B (n=17), grade 4A (n=11), grade 4B (n=17), and grade 5 (n=8). The frequency of distal occlusion and reocclusion were 23% (n=18) and 22% (n=17), respectively. Reocclusion was associated with a reduced rate of favorable outcome at 1–3 months (Wald chi-square 4.5, p=0.03) after adjusting for potential confounders. No relationship was observed between distal occlusion and outcome. Conclusions: Distal occlusion and reocclusion in the high risk areas of the M1 and M2 posterior circulation are associated with poorer functional outcomes. Reocclusion but not distal occlusion is associated with a worse outcome following thrombolysis.

The Rapid Anticoagulation Prevents Ischemic Damage Study in Acute Stroke: Final Results From the Writing Committee of RAPID

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Background: Unfractionated heparin (UF) has demonstrated neuroprotective effects after transient focal brain ischemia in rats. However, the role of high-dose weight-adjusted UF in acute ischemic stroke has not been well tested. Methods: The Rapid Anticoagulation Prevents Ischemic Damage (RAPID) Trial is an academic, open label, randomized, parallel, phase 4 study of the clinical safety and efficacy of UF (levels of 0.3 to 0.5 U/mL), and ASSA (300 mg/day), in patients with suspected nonacunar ischemic stroke and symptoms lasting less than 12 hours. The primary endpoint is the Modified Rankin Scale < 2 at 3 months. Results: RAPID was stopped for the estimated target of 1184 patients had been reached because after 30 months of study only 67 patients had been recruited. Accordingly, RAPID is not adequately powered to reject the estimated difference of 8% between UF and ASSA with regard to the percentage of patients with favourable outcome. However, RAPID remains as the largest UF trial to date in ischemic stroke patients. Anticoagulation showed a trend (p=0.09) toward more efficacious prevention of stroke recurrence than ASSA without increasing the risk of hemorrhagic worsening. Hemorrhagic worsening, and ischemic worsening, were associated to excessive (p<0.01) or insufficient (p<0.01) heparin levels, respectively. Greater neurological impairment at the time of randomization associated with hemorrhagic worsening was stronger in ASSA (p=0.04) than in UF-treated patients (p=0.96). Conclusions: Weight-adjusted IV UF unlike other anticoagulation regimens previously evaluated in acute ischemic stroke trials tended to reduce stroke recurrence without increasing the rate of serious bleeding. Inadequate UF levels were associated with untoward clinical effects reinforcing the relevance of tight drug monitoring. Further details will be provided during the conference.

The Third International Stroke Trial: Baseline Characteristics of Patients Recruited in the Expansion Phase

Ingrid Kane, Peter Sandercoc, Clinical Neurosciences, Edinburgh, United Kingdom; Richard Lindley, Western Clinical Sch, Sydney, Australia; Staff Lewis, Clinical Neurosciences, Edinburgh, United Kingdom; IST-3 Collaborative Group

Background: Recombinant tissue plasminogen activator (rt-PA) is approved in many countries for use in highly selected patients with acute ischemic stroke who can be treated within 3 hours of onset of symptoms. The Third International Stroke Trial (IST-3) seeks to determine whether a wider variety of patients may benefit. This analysis describes the characteristics of the patients randomised in the initial phase of the study. The main trial (2005–2009) aims to involve up to 6000 patients from up to 400 centres worldwide. Design: IST-3 is an international multi-centre, randomised, controlled trial of intravenous recombinant tissue plasminogen activator (maximum dose 90mg) versus control, in patients with acute ischemic stroke who can be enrolled and treated within 6 hours of symptom onset. The full protocol is available at www.ist3.com. Results: The study began in May 2000 and by 12th August 2004, 253 patients had been recruited from 18 centres in 7 countries. The median time to randomisation was 3.8 hours. At baseline: 69% of patients were aged over 70; 35% were in atrial fibrillation; 55% of patients had hypertension; 40% had diabetes; 23% of patients were female; 17% had a history of smoking; and 10% reported a history of hypertension, diabetes mellitus, coronary artery disease, atrial fibrillation, and peripheral vascular disease. At 3 months, 62% had been discharged to home, 33% had been discharged to rehabilitation, and 5% were still in hospital. Conclusions: The current literature is limited to case reports. We sought to determine the safety and efficacy of thrombolysis after cerebral ischemia. METHODS: Angiographic collaterals were graded on the pre-thrombectomy injection of collateral routes in MERCI (n=120), blinded to clinical data. Baseline demographics, co-morbidities, and other clinical parameters were obtained from the trial database. Multivariate logistic regression analyses determined clinical predictors of collateral grade for all cases and based on site of vascular occlusion or collateral flow pattern. Results: Baseline demographics including age, gender, and ethnicity demonstrated no correlation with the extent of angiographic collaterals. History of hypertension, diabetes mellitus, coronary artery disease, atrial fibrillation, and peripheral vascular disease were also unrelated to collateral grade. More robust results were noted when patients with a current or past smoking history (p=0.001) and peripheral vascular disease (p=0.087), whereas dyslipidemia was associated with impaired collaterals (p=0.105). Prior carotid revascularization, transient ischemic attack, and stroke were not predictive of collateral status. Baseline mRS and NIHSS scores were also unrelated to the extent of angiographic collaterals. Admission laboratory data: including platelet count (p=0.031) and INR (p=0.076) predicted poorer collaterals, whereas blood glucose and hematocrit were unrelated. Clinical predictors of angiographic collaterals varied based on the site of occlusion and corresponding nature of collateral anastomoses. Conclusions: Angiographic collaterals in acute ischemic stroke may not be predicted by most clinical variables. Current smoking may induce collateral development due to angiogenic stimuli including hypoxia. Further characterization of collateral blood flow and associated clinical factors in acute ischemic stroke may reveal novel therapeutic strategies.

Thrombolysis for Strokes After Cardiac Catheterization

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BACKGROUND: Thousands of patients suffer strokes after cardiac catheterization annually. Despite the optimistic clinical setting, the role of thrombolysis is unclear due to safety concerns and the poorly characterized mechanisms of these strokes. The current literature is limited to case reports. We sought to determine the safety and efficacy of thrombolysis after cardiopulmonary bypass. METHODS: The current trial was a multi-centre, multi-national, randomised, controlled trial of thrombolysis in patients with acute cerebral ischemic strokes who were similar between groups. Median baseline NIHSS score was 12 in the IPA group and 6 in the non-IPA group (p=0.02). The median change in NIHSS from baseline to 24 hours, comparing IPA to non-IPA cases was the Wilcoxon rank sum test. We also collected all bleeding events. RESULTS: We identified 48 cases: 10 (21%) were treated with IPA, including 4 by intra-arterial route. A detailed analysis of thrombolysis in patients with acute ischemic strokes is planned. There were no significant between-group differences in the primary outcome measure was median change in NIHSS from baseline to 24 hours, comparing IPA to non-IPA cases with the Wilcoxon rank sum test. We also collected all bleeding events.
no were symptomatic intracranial hemorrhages and 6 minor asymptomatic hemorrhages, 3 in the IPG group. There were 5 patients with minor puncture site bleeding, 1 in the IPG group and none requiring transfusion. There were no other significant bleeding events. CONCLUSIONS: Thrombolyisis appears to improve early outcome of stroke after cardiac catheterization, and seems relatively safe in this context. This study has the limitations inherent in its design, as well as a small sample. Post-catheterization patients may be ideal thrombolysis candidates, and further prospective study is warranted.

"Drip and Ship": A Retropective Review of the Use of IV TPA in Rural Hospitals Within the OSF Stroke Network

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Background IV TPA is the only FDA approved thrombolytic agent for acute ischemic stroke within 3 hours. However, only about 2–20% of stroke patients can benefit from it. One main reason for the low usage is the lack of timely neurological coverage at small or rural hospitals. Within the 24-hospital OSF Stroke Network, 90% are in rural areas. All have given IV TPA. The ER physicians at these rural sites give TPA without neurologist on-site but with consultation from a Network center on-call neurologist. Once TPA given, patients are transferred to the center. Method This is a retrospective study. From 01/2002-7/2004, all patients who had TPA at the Network sites with transfer were reviewed. Demographics recorded. Time of symptom onset to ER, door to CT, door to lab, to door IV TPA, mode of transfer, TPA stroke subtypes, intracerebral hemorrhage rate, NIHSS, discharge destination and mortality were recorded. Result Forty-nine patients had TPA at 18 rural hospitals. No consistent documentation in some elements. Lifeflight (93%) was the main transport. Twenty-eight (55%) were male, 46 (94%) were white, Average age was 69.4 (range: 39–89) years. The average NIHSS on admission was 14 (2-28), 6 (0 –15) at discharge. Eight (18%) had large vessel were 34%, small vessel 20%, cardiogenic 30%, unknown 16%. Eight (18%) had symptomatic ICH. The average NIHSS on admission was 14 (2–28), 6 (0–15) at discharge. Five patients (10%) died, 22 (44%) went home, 12 (24%) to rehabilitation and 11 (22%) to nursing home. Conclusion Rural hospitals can give TPA effectively with good outcome and acceptable mortality/complication rates. The NINDS recommended timelines for rapid diagnosis/ treatment are met. The key to success is to help rural hospitals establish a stroke team, follow protocols, give timely feedback and reliable consultation.Rural ER physicians are more confident giving TPA. Their fear of hemorrhage lessens with consultation and subsequent protocols. The study is limited by an inconsistent data documentation. Nevertheless, this “drip and ship” model shows improved acute stroke care in rural areas and IV TPA can be appropriately administered without a neurologist on site.

Intraarterial Thrombolytic Therapy in the Postangiography Cerebral Stroke

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Introduction: Intra-arterial thrombolysis (IAT) in the treatment of post-coronary angiography (CA) angiography stroke may be safe and efficacious. However, IAT may increase the risk systemic or intracranial hemorrhage (ICH). We report our experience with IAT following CA. Methods: A retrospective case series from three university hospitals. All cases of IAT following CA were identified. Demographics, stroke severity, angiographic findings, thrombolytic agent used, modified Rankin’s Scale (mRS), ICH, and mortality were determined. Results: Twenty-four patients with stroke following CA were treated with IAT (mean age 67.8 years ± 13.5). Left CA was performed in 2187.5%) for coronary artery disease and right CA for electrophysiological studies in 3 (12.5%) cases. Occlusion sites were M1 in 5 (21%), M2 in 3 (12.5%), PCA in 3 (12.5%), V1 in 1 (4%), and VA in 1 (4%). We administered tissue plasminogen activator (tPA), urokinase and a combination of tPA and urokinase in 11 (45.8%). The mean time to therapy was 119.8 ± 43.7 minutes. Tissue plasminogen activator was used in 11 (45.8%) and urokinase in 13 (54.2%). The mRSs ≥ 2 occurred in 13 (54.2%) patients. Younger patients, right CA, and shorter time to IAT were more likely to have complete recanalization and clinical recovery. IAT occurred in 3 (12.5%) cases, none had a complete recanalization. Four (17%) patients died; two were unrelated to IAT. Conclusions: Younger age, shorter time to IAT, and patients with right CA may be more likely to respond to IAT. The risk of ICH and death is not different than the previously reported clinical studies.

Cost and Outcomes of Thrombolysis in the United States: Data From the Nationwide Inpatient Survey, 2000–2001

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Introduction: Intravenous (IV) tissue plasminogen activator (tPA) has been available since 1995, and intraarterial (IA) thrombolysis since 1981. We compared differences between these and untreated patients from 2000 to 2001, registered in the Nationwide Inpatient Survey, which provides a 20% cross section of United States community hospitals. Methods: We divided all ischemic stroke patients into nonvascularized, intravenously and endovascularly treated groups and compared hospital and discharge data between them. We used anography as a surrogate marker for endovascular treatment as the NS data set relies on International Classification of Diseases (ICD-9) coding, and without Food and Drug Administration endorsement for IA thrombolysis or mechanical thrombectomy, no ICD-9 code exists. We compared rates of good outcomes (home or short term rehabilitation discharges) versus bad outcomes (in house mortality and nursing home discharges) by performing two way chi-square analyses. Results: Between 2000 and 2001, 1,160,046 patients were admitted with ischemic strokes for which complete data is available. Results are tabulated below. Conclusions: Compared to the untreated and IV TPA groups, patients who received endovascular therapy had the highest procedural costs and rates of adverse outcomes, including low rates of non-traumatic SAH and non-traumatic ICH (p<0.001). This group of patients also had less in house mortality than patients treated intravenously.
Validity of Real Time Perfusion CT in Acute Stroke

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Background: Perfusion CT (pCT) offers rapid evaluation of tissue perfusion in acute stroke. Previous studies have relied on post-processing of data to define perfusion parameters. We sought to establish whether visual analysis of studies using software available on the CT console provided valid information on tissue viability.

Methods: Retrospective analysis of prospectively collected data. Selection criteria were: 1) pCT+ 24h after onset; 2) final diagnosis of hemorrhagic stroke; 3) follow-up plain CT at 24–72h; pCT was acquired as 4 contiguous 5mm slices. Colour scale maps of time to peak (TTP) and cerebral blood volume (CBV) were analysed. Four-slice lesion volumes were determined by manual tracing of baseline pCT images (regions of prolonged TTP or reduced CBV) and 24–72h infarct. Arterial occlusion site and recanalisation were defined by CT angiography, conventional angiography or TCD. NIHSS at baseline and at 24h was recorded.

Results: 17 patients (mean age 64±16 years, median baseline NIHSS 15) fulfilled criteria, 12 received rtPA. 13 had proximal, 4 distal, MCA occlusions. With recanalisation CBV maps at the time of pCT provides a valid indication of tissue viability in acute stroke.

Conclusion: CBV maps at the time of pCT provides a valid indication of tissue viability in acute stroke.
discharge or at three months and six months post-SAH. However, SAH patients whose CBF fell below critical thresholds were more likely to have poor long-term outcome.

Recovery

Motor System Activation After Subcortical Stroke Is Related to Cortico-Spinal Tract Integrity


Movement related brain activation patterns after stroke are characterized by relative overactivations in secondary motor areas compared to controls, so more in patients with poorer outcome. We hypothesized that this recruitment occurs if the functional integrity of the direct cortico-motorcortical (CMN) pathway between contralateral primary motor cortex (M1) and spinocerebellar cortico spinal neurons mediates these overactivations. We measured the relationship of brain activations and a measure of functional cortico-spinal tract integrity (CST) in six chronic stroke patients (33–74 years, mean 56) 6 to 36 months after first stroke. Lesions were all subcortical (3 right and 3 left sided). Patients performed a dynamic isometric hand grip task with the affected hand during functional magnetic resonance imaging. Transcranial magnetic stimulation was performed within 2 days of scanning. Motor evoked potential recruitment curve slopes were obtained for contralateral first dorsal interosseus muscle (FDI) from both the affected (RC) and unaffected (RCU) hemispheres. RC/RCU was taken as a measure of functional CST. Images were processed and analysed using SPM2, and were flipped such that all lesions were right-sided. Using a multi-subject fixed effects model, we examined for brain regions in which there was a linear correlation between size of activation for the main effect of hand grip and CST. A negative correlation between these parameters was seen in contralesional M1 (r2 = 0.50) and dorsolateral premotor cortex (PMD, r2 = 0.47), ipsilesional PMD (r2 = 0.46), ventrotemporal premotor cortex (r2 = 0.43) and supplementary motor area (r2 = 0.46). A positive correlation was seen in ipsilesional M1 (r2 = 0.63) and primary sensory cortex (r2 = 0.92). In conclusion, these preliminary data provide direct evidence that recruitment of secondary motor systems (including contralesional M1) occurs in response to reduced functional integrity of direct CMN pathways. Conversely, those in whom this pathway is functionally intact can rely primarily on ipsilesional primary sensorimotor cortex. Thus lesion induced cerebral reorganization is dependent on the functional integrity of the remaining motor system.

Inability to Anticipate Arm Biomechanics Contributes to Reaching Deficits in Mild Hemiparesis

John W Krakauer, Leila B Bagaez, Pietro Mazzoni, Columbia Univ, New York, NY

BACKGROUND AND PURPOSE: The nature of the underlying arm control deficit in stroke-induced hemiparesis is not well understood. We hypothesized that patients with hemiparesis are impaired in their ability to take account of their arm’s biomechanical properties when reaching, and that this is due to a motor learning defect. We tested this in patients with mild chronic hemiparesis. We reasoned that these patients, because they have minimal to no weakness, are optimal to investigate deficits in motor control and motor learning. METHODS: We tested 6 patients with mild chronic right hemiparesis (Upper limb FM score 55) and 6 controls, all right-handed and age-matched. Subjects made planar reaching movements with their right arm, supported by a frictionless air-jet system, to targets in 16 directions. Hand grip and target location were randomly jittered to control for any motor learning effects. Visual feedback was removed during movement. The hand path was shown after each movement. Each subject performed 2 sessions separated by 15–30 minutes. Errors in movement distance are expected to vary with movement direction if the arm’s biomechanical properties are not taken into account. RESULTS: For contralateral movement directions, patients showed greater errors in movement distance than controls (P < 0.01). These errors were target-direction dependent in both groups (P < 0.01). Modulation of distance by movement direction was greater in patients (P < 0.01). Movements were hypermetric for elbow-only directions (low inertia) and hypometric for elbow-shoulder directions (high inertia). This dependence on inertia was captured by a significant relationship between movement distance and peak acceleration in patients but not in controls. Direction-dependent modulation of error decreased in the second session for controls (P < 0.01), but not for patients. CONCLUSIONS: Reaching errors in mild hemiparesis can in part be explained by impaired anticipatory control of arm inertia. This is not explained by weakness as the patients performed the task at similar speed to controls and had normal elbow flexor strength. Lack of improvement of anticipatory control with short-term practice shows a learning deficit that may underlie the observed impairment in the control of limb biomechanics in mild hemiparesis.

Impaired Cerebral Vasoactivity Affects the IMRI Motor Activation Pattern in the Opposite Hemisphere in Patients With Unilateral Large-Vessel Disease


Background and purpose: Functional reorganization has been shown to occur following hemiparesis from stroke. We recently demonstrated atypical ipsilateral motor activity in the hemisphere opposite a hemodynamically significant high-grade carotid stenosis or occlusion in the absence of stroke. We now examine in a larger group whether normal vs. impaired vasoactivity affects this process. Methods: Thirteen patients with ICA or MCA high-grade stenosis or occlusion but no stroke (6 had TIA) and 10 age-matched normal controls underwent CBF testing with 2-minute, 5% CO2 inhalation and continuous transcranial Doppler monitoring of bilateral MCA mean flow velocities (MFV). Abnormal CBF was defined as < 20% increase in MFV per mmHg PCO2. In IMRI, all patients and controls performed a unilateral hand closure task in synchrony with a 1 Hz metronome tone during 7 alternating 20-second rest and activation periods (128 x 128 image matrix, FOV = 19cm, TR = 4000ms, TE = 60ms, FA = 60°, 4.5mm thick slices, 0mm gap. For left eccentric targets, subjects were seated with their right upper arm resting on a frictionless support). Images were normalized to the MNI template, smoothed to 6mm gaussian kernel, then entered into a "random effects" model for group analysis, or “fixed effects with conjunction” model for subgroup analysis with < .10 patients (SPM99). Results: All patients and controls had normal neurological function. Controls and 5 patients had normal CBF; 9 patients had unilateral abnormal CBF. Group analysis (patients - controls) for movement of the hand contralateral to the affected body part (left hand in controls) showed unique motor activation in ipsilateral dorsal premotor cortex and SMA. Subgroup analysis of patients with abnormal CBF showed ipsilateral activation whereas those with normal CBF had typical contralateral activation. There was no difference in degree of atonia between patient subgroups. Conclusion: Impaired CBF in large vessel disease alters functional motor networks in the opposite hemisphere in the absence of stroke, supporting the hypothesis that cerebral hemodynamics plays an independent role in determining functional activation pattern. Yet unexamined is whether symptoms (TIA) in the setting of hyperperfusion are required for functional reorganization.

Early Depressive Symptoms After Stroke: Neuropsychological Correlates and Lesion Characteristics

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Objective To examine the relation between specific cognitive functions and depressive symptoms in patients with a recent stroke, and to examine associations with lesion characteristics. Methods We studied 126 out of 183 consecutive patients within three weeks after a first-ever symptomatic stroke (mean interval, 8.3 ± 4.3 days). Seventy of depressive symptoms was assessed with the Montgomery Åsberg Depression Rating Scale. Neuropsychological functioning was examined by means of a detailed neuropsychological examination covering six cognitive domains. A healthy control group (N = 75) was included to obtain normative data for the neuropsychological examination. Functional impairment was measured with the Barthel Index and the modified Rankin Scale. Symptomatic and pre-existent lesion characteristics were determined on CT or MRI. Results Of the included patients, 40% demonstrated mild and 12% moderate to severe depressive symptoms. Severity of depressive symptoms was related to lesion volume (p < 0.008), functional impairment (all p < 0.004), and degree of overall cognitive impairment (p < 0.005). After adjusting for lesion size, a specific neuropsychological profile emerged in patients with moderate to severe depressive symptoms, affecting primarily memory, visual perception and language (all p < 0.05). No association was found between severity of depressive symptoms and lesion location, pre-existent lesion characteristics (white matter lesions and silent infarcts) and demographic factors (age, education and gender). Conclusions Severity of depressive symptoms in the early stage post-stroke is associated with specific cognitive impairment, larger lesion size, and poorer functional status. We suggest that early depressive symptoms in stroke patients are, at least in part, a reactive manifestation to severe and acute cognitive and functional deficits.

Amphetamine-Enhanced Stroke Recovery Trial: Concurrent Validity of the Stroke Impact Scale

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Purpose: AESR is a pilot clinical trial designed to collect data critical for the design of a full-scale clinical trial testing the efficacy of d-amphetamine combined with physical therapy to facilitate motor recovery following hemispheric ischemic stroke. One of the secondary ESR goals is to assess the utility of stroke outcome measures that could be used in this type of trial. Background: The Stroke Impact Scale (SIS) was designed to assess stroke related impairments, disability and handicap affecting quality of life. Methods: Outcome measured with the SIS 90 days after completion of poststroke rehabilitation was correlated with a variety of outcome measures based on data collected during Phase 1 of the AESR trial. Results: The study population included 72 subjects (mean age 65 ± 2 years, 55% male; 79% White, 13% Black) of whom 37% had lacunar, 58% partial anterior, and 4% total anterior circulation strokes (Oxfordshire). The SIS score was correlated (all p < 0.001) with 6 min walk speed (r = 0.672), distance (r = 0.623), CNS score (r = 0.513), NIH-SS (r = 0.418), FIM motor score (r = 0.82), Fugl-Meyer Arm (r = 0.403) and Leg (r = 0.575) scores and Rankin Index (r = 0.622). Conclusion: The SIS score is strongly correlated with other impairment, disability and handicap measures supporting its concurrent validity as used in the context of a clinical rehabilitation trial.
Prevention

Does “Get With The Guidelines” Improve Secondary Prevention in Patients Hospitalized With Ischemic Stroke or TIA?  
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Get With The Guidelines-Stroke is an American Stroke Association program to improve hospital care of acute ischemic stroke or TIA patients. Methods: The program used collaborative meetings, best practice sharing, and an Internet tool for data collection, reporting and decision support, to assist 99 hospitals in their treatment of 21,563 identified patients. Data for eight measures of secondary prevention: antithrombotics, anticoagulation for atrial fibrillation, lipid measurement and treatment for LDL >100 (LDL100) or no documented LDL <100 (LipidRO), diabetes treatment, and applicable counseling for smoking cessation and weight management, were collected at baseline (collected prior to 4/03) and four consecutive quarters (4/2003 to 3/2004). Patients from 3 Paul Coverdell Acute Stroke Registry prototypes (MA, OH, GA) were included from hospitals that used the Internet tool for baseline data entry and for all 4 subsequent quarters of QI. Performance improvement was determined by comparison of each quarter to baseline; trends over time were assessed by Mantel- Haenszel chi-square. Results: Clinically and statistically significant improvement over time occurred in all measures. Significant improvement was seen by Q1 for all measures except smoking cessation and weight management counseling. While substantial improvement occurred in weight management and lipid treatment, lipid and BMI determinations were done in only half of the patients. Lipid therapy was more likely to be given in those patients with LDL measured in the hospital, OR 2.7, 95% CI [5.35–6.16]. Conclusion: GWTG-Stroke was associated with significant improvement in all measures in those patients entered into the Internet tool. These data demonstrate that defined secondary prevention measures can be initiated in the hospital, but there is opportunity for additional improvement. Measurement of risk parameters such as LDL cholesterol produced higher treatment rates and should also be emphasized in the hospital care of these patients.

Optimizing Secondary Risk Reduction Therapy in the Ischemic Stroke Population

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Objective Cerebrovascular disease necessitates aggressive risk factor modification. This has not traditionally been perceived as a priority in the non-corporate population. A program of risk factor identification and evidence-based treatment guidelines, used successfully with cardiovascular disease inpatients, was implemented in the hospitalized cerebrovascular population. Methods: Patients admitted with a diagnosis of cerebrovascular disease were prospectively identified on the physician census screen with a “heart icon” alert. This includes parameters such as LDL cholesterol produced higher treatment rates and should also be emphasized in the hospital care of these patients.

Percentage of Cerebrovascular Patients Per Pharmacologic Therapy

<table>
<thead>
<tr>
<th>Medication</th>
<th>Pre-Reach 6 Months</th>
<th>2 Years Post-REACH (N=554)</th>
<th>P Value</th>
<th>Relative Increase (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>69.7(n=229)</td>
<td>83.9(n=466)</td>
<td>0.0001</td>
<td>20</td>
</tr>
<tr>
<td>ACE/ARB</td>
<td>33.9(n=111)</td>
<td>42.8(n=238)</td>
<td>0.004</td>
<td>26</td>
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</tbody>
</table>

Does Aspirin Interruption Increase Risk of Brain Ischemic Stroke?

Alexandre B Maulaz, Patrik Michel, Daniel Bezerra, Bartolomei Plechowski-Jozwiak, Julien Bogossoulassky, CHU, Lausanne, Switzerland

Background: Aspirin (ASA) is widely used in the prevention of ischemic cardio- and cerebrovascular diseases. It is unclear whether stroke may be associated with ASA discontinuation. Clinical and experimental data suggest the occurrence of a rebound effect < 4 weeks from ASA interruption. We studied ASA discontinuation as a risk factor for ischemic stroke (5). Methods: From all patients with IS or TIA admitted to our University Department between January 2002 and April 2004, we selected those on long-term ASA before their index event. As controls we selected patients with a > 6 months history of IS or TIA that were put on long-term ASA. We compared the frequency of ASA discontinuation within 4 weeks before IS, or a control visit. We used Mann-Whitney test for comparison of risk factors. We calculated odds ratio using logistic regression analysis, p<0.05 was considered significant. Results: Among 978 patients with ischemic stroke, we selected 308 cases were on regular ASA therapy. We matched them with 308 controls under antithrombotic therapy without stroke but who had similar prevalence of risk factors, including hypertension, diabetes, dyslipidemia, smoking, coronary heart disease, cardiobiemic source peripheral vasculopathy. There were 13 patients stroke patients versus 4 controls who had discontinued ASA within 4 weeks of admission. ASA interruption yielded odds ratio for IS/TA of 3.25 (95% CI 1.07–10.56 p < 0.005). Conclusion: Stopping ASA therapy may carry a risk of stroke. Our results highlight the importance of ASA compliance and show potential risks of ASA discontinuation.

Aspirin-Based Antithrombotic Regimen Is Associated With Less Severe Stroke

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Background: Some, but not all, prior studies have suggested that prestroke aspirin use is associated with better outcome from an index stroke. However, few studies have analyzed aspirin’s effects on the presenting severity of index stroke and few have investigated whether aspirin has specific severity-lessening effects distinct from other antithrombotic agents. Methods: Data was collected on 260 consecutive patients presenting within 24 hours of ischemic stroke onset. Stroke severity on presentation was indexed using the NIH Stroke Scale (NIHSS). Patients were categorized according to pre-morbid antithrombotic use as aspirin-inclusive (aspirin alone, aspirin plus dipyridamole, aspirin plus clopidogrel), non-aspirin-inclusive (clopidogrel, ticagrelor, warfarin), and no antithrombotic. Results: Among the 260 patients included, age was 69.6 and 52% were male. The median NIHSS was 6, range 0–35. Patients receiving aspirin prestroke had a lower median presenting NIHSS than those on other antithrombotic regimens. Stopping ASA therapy may carry a risk of stroke.
Progressing Stroke in Acute Ischemic Stroke Patients

Response to ADP. There was a trend for a decreased response in men, those undergoing retrospective analysis without concerning therapy during acute stage, these results suggest 95%CI:0.67–0.97). Conclusion: The second significant predictor for outcome next to severity above 9 at admission showed OR as 15.6 (95%CI :13–19), and OR of older age above 70 years with therapeutic INR (4 vs. 7).

The quartile with the highest level of platelet aggregation, i.e. least response to clopidogrel, had 41(21%) versus 8(4.1%). Among those intervention, and those with higher WBC. This group may be at increased risk for ischemic events and deserves further study.

Pretreatment With Antiplatelet Therapy May Reduce Risk for Progressing Stroke in Acute Ischemic Stroke Patients

Background/It has been reported that neurological deterioration within 48 hours after admission observed in about 20% of patients with ischemic stroke. It is not known whether pretreatment of anti-thrombosis (aspirin or warfarin etc) can reduce a risk for progressing stroke or not. We investigated predictors for progressing stroke using data from Japanese stroke data bank. Our JSJRS started from 2001 and more than 19000 patient’s data were registered up to now. Method: We selected 4723 ischemic stroke patients (mean age 71 years), admitted within 24 hours. All patients were examined with CT and MRI. Severity of stroke was scored using NIH Stroke Scale (NIHSS). Outcome at discharge was evaluated by modified Rankin scale (mRS). We studied the relationship between neurological deterioration within 48 hours after admission and pretreatment anti-thrombosis using multivariate logistic analysis. Anti-thrombosis therapy included antiplatelet using in 17%, anticoagulant in 6% and both in 2% of all subjects. Result: 1) For poor outcome at discharge (mRS > 2), neurological deterioration after admission showed the second highest odds ratio (OR) as 6.2 (95%CI:5.1–7.5), NIHSS above 9 at admission showed OR as 15.6 (95%CI:13–19), and OR of older age above 70 years was 2.7 (95%CI:2.3–3.2). Pretreatment of anti-thrombosis showed mild but significant risk reduction against poor prognosis (OR=0.81,95%CI:0.68–0.98). 2) For neurological deterioration after admission, NIHSS at admission showed highest OR as 1.95 (95%CI:1.6–2.2) and pretreatment of anti-thrombosis showed mild but significant risk reduction (OR=0.803, 95%CI:0.72–0.89). Conclusion: Our study demonstrated that the significant outcome of stroke is neurological deterioration within 48 hours after admission. Although, our study was retrospective analysis without considering therapy during acute stage, these results suggest that pretreatment of anti-thrombosis may have high risk reduction for progressing stroke.

P89 Clonidine Unresponsiveness Is Common In Patients With Cerebrovascular Disease

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Background/Purpose: Studies have shown that insufficient platelet inhibition with clonidine is associated with recurrent MI in patients undergoing PCI. Platelet response to clonidine has not been studied in patients with cerebrovascular disease or those who undergo cerebral interventions. Methods: We retrospectively collected demographic, clinical, and laboratory data of all patients who underwent measurement of platelet aggregation while on clonidine for the treatment of cerebrovascular disease. Platelet aggregation in response to ADP and arachidonic acid was measured with an optical platelet aggregometer (Helena Inc.). Results: Eighty-one patients, mean age 65.5yrs, were identified. Forty-two(52%) were male, 61(75%) were white, 18(22%) were African American. Fifty-eight(72%) were treated for stroke, 17(21%) for TIA, and 6(7%) for asymptomatic arterial stenoses. Thirty-five(43%) patients had an endovascular intervention, Sixty-seven(83%) were also on aspirin. The mean levels of platelet aggregation in response to ADP and arachidonic acid were 338% ± 17% and 255% ± 18%, respectively. Among those taking both aspirin and clonidine, response to ADP and arachidonic acid stimulation were correlated at the 0.11 level (p<0.01). There was a correlation between aggregation and WBC count, r = 0.12 (p = 0.01), but not with platelet count. Dividing the patients into quartiles based on their level of platelet aggregation showed 20 had 52–81% aggregation, 20 had 40–50% aggregation, 20 had 26–38% aggregation, and 21 patients had 3–25% aggregation. The quartile with the highest level of platelet aggregation, i.e. least response to clonidine, had more men (4/20; 70%) and more interventions (10/20; 50%) than the other quartiles, p = NS. Conclusion: Of patients on clonidine 25% had <50% inhibition of platelet aggregation in response to ADP. There was a trend for a decreased response in men, those undergoing
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than AT2-formation suppressing agents, including beta-blockers and ACE inhibitors. Agents, including ARBs, thiazides, and Ca-channel blockers, may reduce stroke severity more.

There was a non-significant trend towards lower stroke severity in favor of the AT2-increasers in the median NIHSS model. On multivariate analysis, the adjusted median NIHSS was 45 (45, 45) for AT2-suppressors, 16 on AT2-formation increasers. The unadjusted median NIHSS was not significantly different between the two regimens.

Within 24h of first-ever ischemic stroke over an 18-month period were studied. Subjects were female; median presenting NIHSS was 6 (range 1–32). 48 patients were on AT2-formation suppressors, 16 on AT2-formation increasers.

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Stroke Risk Factors

Baseline stroke risk factors were compared between the two groups using student t-tests and chi-square analysis. The effect of statin therapy on the risk of ipsilateral stroke, any stroke, and death was analyzed. Results: Twenty of the 117 patients were on a statin agent at the time of enrollment and CBF measurement. Complete quantitative measurements of CBF were obtained in 17 of the 20. Quantitative CBF measurements were obtained in 78 of the 97 patients not on a statin agent. No difference in mean CBF measured ipsilateral (i) or contralateral (c) to the occluded carotid artery was found between groups: statins - mean CBF (SD) in ml/100gm/min = 38.8 (16), cCBF = 43.4 (14); no statins - mean CBF = 38.5 (12), cCBF = 44.2 (12). The two groups were similar on baseline stroke risk factors assessed except for significantly lower LDL levels and higher HDL levels in the statin group. No significant difference in outcome between the two groups was seen for any stroke or ipsilateral stroke.

A significant difference in death was present (0 of 20 patients on statins compared to 16 of the 97 patients not on a statin (p = 0.04). Fisher exact test). Conclusions: Baseline CBF study in asymptomatic stroke patients, these data find no evidence for significant increase in CBF in humans. A significant reduction in the risk for death, but not stroke, was observed.

Antiangiotensin 2 Receptor Activity and Ischemic Stroke Severity

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Background: Recent studies have suggested that drugs that increase angiotensin 2 (AT2) formation, including thiazides, calcium channel blockers and angiotensin receptor blockers (ARBs), may be more effective at reducing stroke severity than those that suppress AT1 receptors, such as angiotensin converting enzyme inhibitors and beta-blockers. However, no prior study has examined whether AT2-formation-increasing drugs might reduce incident stroke severity, compared to AT2-formation-suppressive drugs.

Methods: Consecutive patients presenting within 6h of first-ever ischemic stroke over a 10-month period were studied. Analysis was only included if they were on only AT2-formation increasers, only AT2-formation suppressors, or on no antihypertensive agents. NIHSS score at presentation was used as the index of stroke severity. Demographic data, risk factors, admission blood pressures, other medications, and stroke mechanisms were controlled for across the three groups using least absolute deviation linear regression. Results: 172 individuals met study criteria. Mean age was 67.4 yrs ± 14.5% were female; median presenting NIHSS was 6 (range 1–32). 48 patients were on AT2-formation suppressors, 16 on AT2-formation increasers. The unadjusted median NIHSS was not significantly different among the three groups. Age at admission, atrial fibrillation, previous antithrombotic use, cardioembolic and large vessel atherosclerotic mechanisms, mean SBP and mean DBP were significant univariate predictors of presenting NIHSS and were adjusted for in the median NIHSS model. For multivariable analysis, the adjusted median NIHSS was significantly lower in the AT2-increasers (median = 2.2, p = 0.055) and trended lower for AT2-suppressors (median = 4.4, p = 0.074) compared to the “no” group (median = 6.9). There was a non-significant trend towards lower stroke severity in favor of the AT2-increasers compared to AT2-suppressors (p = 0.123). Conclusions: Pretroke use of antihypertensives is associated with reduced severity of incident ischemic strokes. AT2-formation increasing agents, including ARBs, thiazides, and Ca-channel blockers, may reduce stroke severity more than AT2-formation suppressing agents, including beta-blockers and ACE inhibitors.

Intracranial Arterial Stenosis

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Background and Purpose: It is well established that control of hypertension reduces the risk of stroke. However, it is still common practice to maintain higher blood pressures in patients with intracranial stenosis to theoretically increase perfusion to the brain and thus decrease the risk of stroke. We sought to determine whether higher systolic blood pressure (SBP) decreases the risk of stroke recurrence in patients with known intracranial arterial stenosis. Methods: Data on 569 patients enrolled in the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial were analyzed. The time to stroke was compared in patients with mean SBP < 140 mmHg vs. mean SBP ≥ 140 mmHg during follow-up. The comparison was done for patients with and without hypertension and for patients with and without previous stroke. Results: Among the 91 patients without a history of hypertension, there was a trend for a
greater risk of any stroke for patients with \( \text{SBP} > 140 \) or \( \text{OR} = 1.30 \pm 0.39 \), which persisted after additional adjustment for cigarette smoking, hypertension, and diabetes (OR 1.9, 95% CI = 1.1–3.3). No association was seen among Caucasians (OR 0.8, 95% CI = 0.3–2.4). Haplotypic analyses did not provide additional information. Conclusions: We identified a novel PDE4D SNP associated with stroke in African American females, providing the first support for association of this gene with stroke in non-Icelandic populations.

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Five-Lipoxygenase Activating Protein Polymorphisms and Risk of Cerebral Infarction in a Biracial Population: The Stroke Prevention in Young Women Study

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Background and Purpose: Five-lipoxygenase activating protein (FLAP) is necessary for the synthesis of leukotrienes, inflammatory leukotriene mediators. Nine genetic variants in the FLAP gene (ALOX5AP) have been associated with increased risk of myocardial infarction and stroke in some populations. However, these associations have not been consistently reproduced. The Stroke Prevention in Young Women Study, is a population-based case-control study in young women. We compared 5 variants in the gene encoding FLAP with stroke risk in white and biracial populations.

Methods: Fifty-one hospitals in the greater Baltimore-Washington area participated in the sample population. Cases were young women with stroke, 15 to 49 years of age, identified through the Stroke Prevention in Young Women (SPYW) Study. Control subjects were population-based, young women recruited among the patients of age-stratified physicians. All patients were confirmed stroke-free by structured interview. One hundred and four sibling pairs from the Siblings with Ischemic Stroke Study (SWISS) were used in linkage analyses, and 341 individuals (217 cases and 124 controls) from the Ischemic Stroke Genetics Study (ISGS) and the Mayo Stroke Genetics Data Bank (MSGD) were used in association analyses. The two cohorts were combined for association analyses. A maximum LOD score of 0.14 (at marker S6113114) was reached for both PDE4D and ALOX5AP polymorphisms. The maximum LOD score for both PDE4D and ALOX5AP was 0.70. Haplotype analyses did not provide additional information. Conclusions: This study provides the first evidence that ALOX5AP is associated with stroke risk in young African American women.

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Failure to Confirm That Either Phosphodiesterase 4D or 5-Lipoxygenase Activating Protein Is a Major Risk Factor Gene for Ischemic Stroke

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Background and Purpose: Ischemic stroke risk is mediated by environmental and genetic factors. While several environmental exposures have been implicated, less is known about the genetic basis of predisposition to this disease. Studies in Iceland demonstrated two putative genetic risk loci for ischemic stroke: phosphodiesterase 4D (PDE4D) and 5-lipoxygenase activating protein (ALOX5AP). We attempted replication using one sibling pair cohort and two case-control cohorts. Methods: All affected individuals had World Health Organization-defined symptomatic strokes confirmed to be ischemic by computed tomography or magnetic resonance imaging. All unaffected individuals were confirmed stroke-free by structured interview. One hundred and four sibling pairs from the Siblings with Ischemic Stroke Study (SWISS) were used in linkage analyses, and 341 individuals (217 cases and 124 controls) from the Ischemic Stroke Genetics Study (ISGS) and the Mayo Stroke Genetics Data Bank (MSGD) were used in association analyses. Conclusions: The two cohorts were combined for association analyses. A maximum LOD score of 0.14 (at marker S6113114) was reached for both PDE4D and ALOX5AP polymorphisms. The maximum LOD score for both PDE4D and ALOX5AP was 0.70. Haplotype analyses did not provide additional information. Conclusions: This study provides the first evidence that ALOX5AP is associated with stroke risk in young African American women.

Community/Risk Factors: Genetics, Race and Risk Factors

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Phosphodiesterase 4D Polymorphisms and Risk of Cerebral Infarction in a Biracial Population: The Stroke Prevention in Young Women Study

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Background and Purpose: Linkage and association studies in Iceland demonstrated that polymorphisms within the phosphodiesterase 4 gene (PDE4D) are associated with ischemic stroke risk. Previous studies in non-Icelandic populations have not been reported. Using data from the Stroke Prevention in Young Women Study, we conducted a search for novel genetic variants in PDE4D and determined the association of these variants with stroke risk. Methods: A population-based case-control study of stroke among women aged 15–49 identified 300 cases of first ischemic stroke (52.2% African-American) and 225 age-comparable control subjects (44.2% African-American). Based upon Visualization Tools for Alignments (VISTA) results, a systematic polymorphism search in the highly evolutionary conserved regions of PDE4D was performed on 48 African-American and 46 Caucasian participants. Polymorphisms were confirmed in the entire study population and assessed both for association with stroke and for linkage disequilibrium. Results: A total of 41 novel and previously known polymorphisms with a major allele frequency greater than 0.05 were found in PDE4D among the sample population. Among the 17 polymorphisms analyzed to date, the A allele (frequency = 0.12) of a novel SNP, PDE4D-229902-AG, located in intron 1, was found to be significantly associated with stroke using an additive model (OR 1.7, 95% CI = 1.1–2.6). Age-adjusted race-stratified analysis demonstrated significant association among African-Americans (OR 1.7, 95% CI = 1.0–3.0), which persisted after additional adjustment for cigarette smoking, hypertension, and diabetes (OR 1.9, 95% CI = 1.1–3.3). No association was seen among Caucasians (OR 0.8, 95% CI = 0.3–2.4). Haplotypic analyses did not provide additional information. Conclusions: We identified a novel PDE4D SNP associated with stroke in African American females, providing the first support for association of this gene with stroke in non-Icelandic populations.

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Association of PDE4D With Ischemic Stroke

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Introduction: A previous study in Iceland reported association of an ischemic stroke with a putative susceptibility gene, phosphodiesterase 4D (PDE4D), on 5q12. Its validation in other populations is needed to confirm the role of PDE4D in the pathophysiology of ischemic stroke. We tested the association of 6 coding single nucleotide polymorphisms (SNPs), which showed
Atrial Natriuretic Peptide Polymorphisms and Risk Gene Is Associated With Higher Glutamate Concentrations and Brain Injury

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Objective: Mutations in the glutamate transporter EAAT2 gene may play a role in the differential regulation of expression of this gene and in glutamate levels during acute cerebral ischemia. Our aim was to identify novel polymorphisms in this gene associated with higher plasma glutamate concentrations and greater brain injury. Methods: We studied 94 patients with ischemic hemispheric stroke of 4-12 h duration and 94 controls. Plasma glutamate was determined on admission, at 24 and 72 h by high-performance liquid chromatography. Neurological deterioration was defined as an increase of >5 points in the NIHSS between admission and 72 h. Infarct and ischemic volumes were measured by DWI and PWI at the same intervals. Genomic DNA was isolated from peripheral blood samples. EAAT2 promoter polymorphism screening was performed by single-strand conformation polymorphism (SSCP) analysis and sequencing. Transcriptional activity was investigated in cultured rat astrocytes by luciferase assay. Results: A novel polymorphism was identified in the promoter region of the EAAT2 gene, an A to C change at -181 bp from the transcriptional start site. The prevalence of allele C was similar in stroke patients (0.40) and in general population (0.30). Median [quartiles] glutamate levels on admission were higher in patients with mutant allele C (74.3 [46.2–219.8]) than in those without (69.5 [39.8–100.3]) (p = 0.068), and remained higher at 24 h (p = 0.073). In patients included within 3 h (n = 60) these differences were significant both on admission and at 24 h (p = 0.037 and p = 0.017). Thirty percent of patients with allele C had neurological deterioration compared to 16% of wild type allele (p = 0.198). In a general linear factorial model, these findings could not be attributed either to differences in stroke severity nor to DWI and PWI lesion volumes on admission. In astrocyte cultures, the mutant construct showed a 4-fold increase in promoter activity compared to wild type. Conclusions: The A/C promoter polymorphism in EAAT2 gene is associated with higher glutamate plasma levels after acute stroke, and with decreased activity in cultured astrocytes. Taken together, our results suggest that this prevalent mutation might be associated with susceptibility to glutamate-mediated brain injury.

Methylenetetrahydrofolate Reductase 677 C to T Polymorphism and Risk of Ischemic Stroke: Results of a Cumulative Meta-analysis

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Background: Data are conflicting concerning the risk for ischemic stroke associated with a common polymorphism in the gene encoding 5,10-methylenetetrahydrofolate reductase (MTHFR 677C>T), which predisposes to hyperhomocysteinemia. This may be related to ethnic variation or inclusion in some studies of stroke subtypes unlikely related to hyperhomocys-teinemia. Method: Systematic review and cumulative meta-analysis of studies examining risk of ischemic stroke associated with this polymorphism, to update a previous analysis in 2002. Searches of MEDLINE, Science Citation Index from 1966 to March 2004. Exposure was defined as the presence of the MTHFR TT genotype. Outcome was defined as ischemic stroke with or without neuroimaging, or silent brain infarction on MRI. Studies (case-control, cross-sectional, cohort design) with reported or calculable odds ratios (OR) associated with genotype exposure were included. Exclusion criteria were absence of calculable OR, outcome other than ischemic stroke, and studies confined to stroke in those below 18 years of age. Statistical analysis for between study heterogeneity, publication bias, and pooled risk estimates were performed using Stata software(). Subgroup analyses examined risk stratified by ethnicity and stroke mechanism. Results: Among 42 included studies (7,404 stroke cases and 11,974 controls), the pooled OR associated with the MTHFR TT genotype was 1.26 (95% CI 1.13–1.46, p = 0.001). To exclude the potential confounding influence of non-ischemic leukoaraiosis, the analysis was repeated after exclusion of 5 studies examining silent brain infarction. For the remaining studies, the pooled risk was 1.27 (95% CI 1.08–1.47, p = 0.005). When examined by ethnic origin, the previously observed 1.29 (95% CI 1.04–1.57, p = 0.20) studies in Asian ethnicity and 1.23 (95% CI 1.08–1.53, p = 0.05) in those of non-Asian ethnicity. Among studies the pooled OR was 1.61 (95% CI 1.03–2.54, p = 0.05) for lacunar infarction. Conclusion: These data support an association between MTHFR TT genotype and ischemic stroke, in Caucasian and Asian populations, supporting experimental and clinical data suggesting that mild-moderate hyper-homocyst(e)inemia is an important risk factor for cerebrovascular disease.
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α-1 Antitrypsin Gene Deficiency in Patients With Stroke and Spontaneous Cerebral Artery Dissection: Correlation With Connective Tissue Abnormalities on Electron Microscopy of Skin Biopsy

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Introduction and Objectives: we previously reported an association between low plasma levels of alpha-1 antitrypsin (A1AT) in patients with spontaneous cerebral artery dissections (sCAD). Moreover, more than a half of german patients with sCAD have connective tissue abnormalities in skin biopsy. However, recent studies performed in that population failed to show a high prevalence of deficient genetic forms of A1AT. In this study we evaluated the prevalence of genetic A1AT deficiency in a series of patients with stroke and sCAD and their role in the pathogenesis of elastic and collagen fiber abnormalities.

Methods: Thirty two patients with sCAD were included in the study. All patients were diagnosed by angiography (sonographic or conventional) and MRL. Deficient genotypes of A1AT (P2 and P5) and plasma levels of A1AT (performed in the chronic phase) were evaluated in all subjects. Twenty six patients had available information of electro microscopic study of skin biopsies. Pathologists looked for collagen and elastic abnormalities in the skin. In the A1AT deficient group, the plasma level of A1AT deficiency in sCAD patients was compared with asymptomatic controls of our mediterranean demographic area.

Results: Deficient forms of A1AT (P5) were detected in 8 sCAD patients (25%) whereas the prevalence in controls was 6% (p<0.01). As expected, patients with P5 had lower plasma levels of A1AT than patients without A1AT genetic deficiency (107 mg/dL versus 129 mg/dL: p<0.02). Abnormalities of connective tissue were found in 13 patients (50%): 3 with P5 genotype but 10 without genetic A1AT deficiency.

Conclusions: In our population a genetic deficiency of A1AT may predispose to sCAD. Although dermal abnormalities in our population are as frequent as detected in german population, it seems that low levels of the proteolytic inhibitor A1AT do not explain that pathological findings in sCAD patients.

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Serum Biomarkers in Patients With Carotid Atherosclerosis Using ProteomicTechniques

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Background: Atherosclerosis is known to be a chronic inflammatory disease, yet specific serum markers for symptomatic carotid atherosclerotic disease remains undefined. In an effort to find biomarkers predictive for increased risk of ischemic stroke due to atherosclerosis, we have begun examining protein expression profiles from a cohort of consenting subjects in an IRB approved protocol (n=21) undergoing carotid endarterectomy, 11 of which were undergoing carotid endarterectomy. Strain (% change in diameter), stiffness B [ln (Systolic BP / Diastolic BP) / Strain], distensibility (IMT) and elastic abnormalities blinded respect to the A1AT genotype. The prevalence of A1AT deficiency in sCAD patients was compared with asymptomatic controls of our mediterranean demographic area.

Results: Deficient forms of A1AT (P5) were detected in 8 sCAD patients (25%) whereas the prevalence in controls was 6% (p<0.01). As expected, patients with P5 had lower plasma levels of A1AT than patients without A1AT genetic deficiency (107 mg/dL versus 129 mg/dL: p<0.02). Abnormalities of connective tissue were found in 13 patients (50%): 3 with P5 genotype but 10 without genetic A1AT deficiency.

Conclusions: In our population a genetic deficiency of A1AT may predispose to sCAD. Although dermal abnormalities in our population are as frequent as detected in german population, it seems that low levels of the proteolytic inhibitor A1AT do not explain that pathological findings in sCAD patients.

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Heritability of Carotid Artery Distensibility Among Caribbean Hispanics in the Northern Manhattan Family Study

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OBJECTIVE: The objective of this study was to estimate heritability of carotid distensibility among a high vascular risk Caribbean Hispanic population of the Northern Manhattan Family Study. BACKGROUND: Arterial distensibility is a measure of arterial expansion and contraction with cardiac cycle and has been introduced as a novel risk factor for atherosclerosis. We have previously reported a significant heritability of approximately 40% for carotid intima-media thickness (IMT). The heritability of carotid distensibility is largely unknown. SUBJECTS AND METHODS: The cohort consisted of 515 subjects from 84 Caribbean Hispanic families enrolled to date. Mean age was 49±18 years; 63% were women. Carotid distensibility and intima-media thickness were measured by high-resolution B-mode carotid ultrasound. The diameters for the right CCA were measured from 5 B/M-mode registrations and averaged. Strain (% change in diameter), stiffness B [ln (Systolic BP / Diastolic BP) / Strain], distensibility (IMT) and elastic-strain elastic modulus EM (SBP - DBP) / Strain were calculated. The carotid IMT was calculated as the mean of the 12 carotid intima-media thickness measurements and the car and the far wall in CCA, bifurcation, and ICA bilaterally. Variance component methods were used to estimate age- and sex-adjusted heritability for these parameters. Bivariate analyses were conducted to test for genetic and environmental correlations between distensibility parameters and IMT. RESULTS: A significant heritability of 25% was found for distensibility (p<0.002), 16% for strain (p=0.03), 14% for stiffness (p=0.04), and 18% for EM (p=0.01). The mean strain was 10%, mean stiffness 7.16, mean distensibility 1.55, and mean EM 96.23. The total model was 0.61 ± 0.06 mm. Only distensibility parameter was moderately correlated with IMT (ranged from -0.09 to -0.15). Bivariate analyses did not reveal significant genetic correlations between IMT and any of the four distensibility parameters. CONCLUSIONS: These results suggested that genetic factors explained a moderate proportion of the variability of carotid distensibility. There were no substantial correlations between distensibility and IMT. There may be different underlying genes for carotid distensibility and carotid IMT.

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Age and Subject Selection for Stroke Genetics Research

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Background: The target population for stroke genetics studies remains an enigma. Familial clustering of stroke at younger ages suggests that age may be a useful selection criterion. Studies that have investigated the relationship between age at onset and family history of stroke have not taken into account ischemic stroke subtype, which is a potential confounder in this relationship. The objective of this study was to determine the association between age at stroke onset and family history of stroke adjusted for stroke subtype.

Methods: A total sample of 302 families were identified using the entire case set of the Northern Manhattan Stroke Family Study. A sample of ischemic stroke cases from the Brain Attack Surveillance in Corpus Christi Project, identified between January 1, 2000 and December 31, 2002, was investigated regarding family history of stroke (n=407). Stroke subtypes were classified according to the previously published modified TOAST criteria that include the addition of a category of non-lacunar stroke, comprised of large strokes that had insufficient evidence for categorization into large artery atherosclerosis or cardioembolism. Logistic regression was used to test the association between age and a positive family history of stroke adjusting for stroke subtype, race-ethnicity, and sex.

Results: Age was categorized and variables created based on the quartiles of the distribution. RESULTS: The sample was 48% non Hispanic white and 52% Mexican American; 59% were female. Median age was 74 years. Forty percent of cases reported a family history of stroke at the first degree relative. Age was associated with family history of stroke adjusting for stroke subtype. Individually, ischemic stroke (age 73 were roughly twice as likely (age 45–64: OR=1.98 95% CI 1.03–3.79; age 65–73: OR=1.94 95% CI 1.03–3.65) to have a family history of stroke compared to those with stroke at or after age 80. The association between stroke subtype and family history of stroke was borderline significant (p=0.056). Conclusion: A higher percentage of family history occurs in younger patients with ischemic stroke, adjusting for stroke subtype. This finding implies a strong advantage of focusing on young stroke patients for initial stroke genetics studies.

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Interleukin-1 Receptor Antagonist Gene Polymorphism in Ischemic Stroke

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Background & Purpose: Ischemic stroke is a frequent manifestation of cerebrovascular atherosclerosis. Genetic determinants of ischemic stroke remain to be diagnosed. We report an association of an inflammation marker, the interleukin-1 receptor antagonist (IL-1Ra) gene (rs17570), with ischemic stroke.
fully elucidated. Genes coding for inflammatory mediators hold promise as candidates. We previously found an association between carotid atherosclerosis and allele 2 of the 86-bp variable number tandem repeat (VNTR) polymorphism of the interleukin-1 receptor antagonist gene (ILRN). Here, we determine whether ILRN genotype is associated with ischemic stroke overall or symptomatic large vessel (LV) atherosclerotic disease in particular. Methods: DNA was obtained from the SWISS (sib-pair design), ISGS (multi-site case-control) and MSGD (single-site case-control) studies. All samples were analyzed blinded to clinical status. DNA was PCR-amplified and genotyped for the 86-bp VNTR of ILRN. We compared allele frequencies by case/control and symptom status using contingency tables and logistic regression models. Results: DNA was available for 217 cases and 124 controls; all were successfully genotyped. Presence of ILRN allele 2 (ILRN*2) was 94/217 in cases and 62/124 controls (P = 0.23). The frequency of ILRN*2 homozygotes was similar in cases (9/217) and controls (3/124, P = 0.41), as was the frequency of ILRN allele 1 homozygotes (114/217 vs. 59/124, P = 0.38). Adjustment for age, sex, DNA source and conventional risk factors did not alter the results. In SWISS, 46/110 (43.0%) probands, 52/106 (49.1%) affected siblings (P = 0.37 vs. proband), and 24/42 (57.1%) unaffected siblings (P = 0.12 vs. proband) had at least one copy of ILRN*2. Subgroup analyses were performed across all 3 studies on those with and without LV stroke as their mechanism of stroke. The presence of ILRN*2 was 34/80 with LV stroke compared to 147/177 with non-LV stroke (P = 0.22). When variation due to other risk factors was included in the logistic regression model, the independent effect of the 2 allele was significant (P = 0.04, odds ratio = 1.90). Conclusion: ILRN genotype was not associated with ischemic stroke. However, presence of ILRN*2 appears to increase the risk of large vessel disease - a finding consistent with our previous observation that ILRN*2 was associated with carotid atherosclerosis but not ischemic events.

The Northern Manhattan Stroke Study Risk Score: A Stroke Prediction Tool for Clinical Use Among Multiethnic Populations

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Objective: To design a risk score for stroke based on a multi-ethnic, urban prospective cohort using easily accessible risk factor information. Background: The Framingham stroke scale (FSS) is widely used for stroke prediction, but its accuracy has not been well validated by race-ethnicity. Alternative prediction tools may be needed for stroke prevention among African Americans and Hispanics. Design/Methods: Using the prospective NOMAS cohort, Cox models predicting stroke were fitted from baseline risk factors. Risk scales by gender were constructed taking a weighted average of Cox coefficients. Scores were weighted and predictability of the scores evaluated using hazard ratios estimated via Cox models where risk score was a covariate categorized by score quartiles. To compare the accuracy of the NOMAS stroke risk scale to that of the FSS, the same method was applied to the FSS. Results: The NOMAS cohort consisted of 2386 randomly selected subjects. Covariates used for NOMAS scores for men were age, systolic blood pressure, former/current smoking, diabetes (fasting glucose >126 mg/dl), cardiovascular disease, physical activity, moderate alcohol intake (~2 drinks/day); waist circumference (>35 inches) was added for women. Mean risk scores were similar for men (12.89 SD 5.6) and women (12.86 SD 5.2). The scores strongly predict increasing risk of stroke for second, third, and fourth score quartiles for men and women (HR 2.27, 3.39, 17.36, p < 0.01; 4.79, 7.02, 11.04, p < 0.01). Among men, a significant hazard ratio difference between the second and fourth quartiles (p = 0.05) and marginally significant difference between the third and fourth quartiles (p = 0.1) suggest discrimination between groups of moderate risk, intermediate and high risk of stroke. The FSS, which includes AF and LVH by DX, was predictive of stroke (HR 1.75, 4.49, 5.73, p < 0.01; woman 3.34, 6.82, 10.52, p < 0.01). Hazard ratio differences between third and fourth quartiles for Framingham scores were not significant in each gender. Conclusions: Our NOMAS stroke risk scale offers an alternative to the FSS scale that may be suitable for clinical practice. The addition of alcohol, physical activity, and waist circumference may increase stroke discrimination among urban, multi-ethnic subjects.

High-Sodium Diet Is a Risk Factor for Ischemic Stroke: The Northern Manhattan Study

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Objective: To determine the effect of dietary sodium intake on the risk of ischemic stroke in a prospective cohort. Background: An independent relationship exists between sodium intake and blood pressure. Few studies have supported a relationship between sodium intake and the risk of ischemic stroke, particularly among multi-ethnic cohorts with greater risks of stroke and hypertension. Design/Method: The Northern Manhattan Study (NOMAS) is an ongoing, prospective cohort study designed to determine stroke incidence and risk factors. Sodium intake was calculated by participants completing a modified Block food frequency questionnaire. Subjects consuming 4 or more grams, 2.4–4 grams, and 2.4–3 grams of sodium per day were compared to those who consumed the recommended 2.4 or fewer grams of sodium per day. Adjusted hazard ratios (HR) and 95% confidence intervals for each group were obtained using Cox univariate and multivariate models. Results: Of 3,193 participants, 318 developed stroke. Cox proportional hazards analysis was used to identify the relative risk (RR) of cardiovascular disease with higher sodium consumption among diabetic patients. The increased risk of ischemic heart disease associated with higher sodium consumption among diabetic patients warrants further investigations.

Adverse Effect of Overweight on Stroke Risk in Women

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The prevalence of overweight is increasing in all segments of the population but the level of cerebrovascular risk associated with a given body mass may vary with race, gender, and age. Obesity is listed as a potentially modifiable risk factor for stroke but the effect of body mass on stroke mortality remains unclear. The Black Pooling Project consists of nine studies and includes 9,820 women, 7,175 black men, 27,606 white women and 37,415 white men who were followed for vascular disease events from 1950–1992. We examined the association between overweight (BMI >25 kg/m²) and stroke mortality, calculating the crude age-specific stroke mortality rates. The prevalence of overweight was greater for black than white women at all age groups and in white than black in all but the oldest men. Stroke mortality rates were consistently greater for black men and women compared to whites across age categories. Across all ages, stroke mortality rates were higher in normal weight black and white men and increase the risk of ischemic stroke. This supports the American Heart Association recommendations for limiting sodium consumption.
Are Both Low and Elevated Serum Levels of Uric Acid Predictive of Long-Term Fatal Stroke? A Follow-up of 9000 Men

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Background: Increased serum uric acid (SUA) levels are linked to obesity, dyslipidemia, diabetes, and hypertension. Whether SUA carries a risk for coronary heart disease (CHD) and stroke remains uncertain.

Subjects and Methods: Of an original cohort of 10,232 middle-aged workers, examined in 1963 and followed-up for 23 years, 9125 men, free of CHD, are included in this report. Subjects were divided into quintiles according to baseline SUA levels. Hazard ratios (HR) for all-cause, CHD, and stroke mortality were estimated in SUA quintiles, with the 3rd quintile serving as the reference category. Results: During the follow-up period, 2883 deaths were recorded, including 830 (29%) ascribed to CHD, and 292 (10%) to stroke. The HR for all-cause and CHD mortality were significantly increased in the upper SUA quintile (1.22 (95% CI: 1.00–1.47), and 1.29 (95% CI: 1.05–1.58), respectively). Fatal stroke showed a U-shape relationship, with both the lowest and highest SUA quintiles being at increased risk (1.43 (95% CI: 0.98–2.08), and 1.48 (95% CI: 1.02–2.17), respectively). Adjusting for confounding risk factors reduced the HR associated with the upper SUA quintile somewhat to 1.20 (95% CI: 1.07–1.34) for all-causes, 1.17 (95% CI: 0.95–1.43) for CHD, and 1.33 (95% CI: 0.90–1.95) for stroke, but did not alter the HR for stroke in the lowest SUA quintile (1.45 (95% CI: 1.00–2.01)). Correction for regression dilution increased these HR slightly (Figure). Conclusion: In addition to findings supporting an increased mortality in the upper SUA quartile, we have identified a strong association between low SUA levels and fatal stroke, which requires further investigation.
disease risks associated with this level of blood pressure are even less evident for black men and women. The Black Pooling Project includes nine follow-up cohort studies with 37,413 white males, 27,606 white females, 7,175 black males and 8,920 black females. Cardiovascular mortality rates were determined for the four race-sex groups with the four classifications of blood pressure: normal - SBP <120 and DBP < 80; prehypertension - SBP 120–129 or DBP 80–89; stage 1 hypertension SBP 140–159 or DBP 90–99; and stage 2 hypertension SBP ≥160 or DBP ≥100. While black men and women were more likely to be hypertensive, the rates of prehypertension were greater among white men and women (white men 30.3%, black men 15.8%; white women 32.7%, black women 14.5%). Stroke mortality rates increased with blood pressure level among all four race-sex groups. However, stroke rates were consistently higher for black men and women at each category of blood pressure compared to white men and women. These results emphasize the racial disparity in rates of hypertension and stroke risks, and identify the new classification of prehypertension as a category of increased disease risks for whites and blacks.

Age-adjusted stroke mortality rates per 10,000 person years

<table>
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</table>

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Early Identification of African Americans at Increased Risk for Stroke

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Background and purpose: African Americans (AA) have approximately twice the rate of stroke compared to Whites. Previous population-based studies have shown that about 4% of community dwelling AA have extracranial carotid stenosis. Patients with established ischemic heart disease (IHD) would be expected to have an increased frequency of carotid atherosclerosis. Early identification of these patients would provide an opportunity for primary stroke prevention. We assessed the hypothesis that about 10% of AA patients with established IHD would have >50% extracranial carotid artery stenosis. Methods: Patients were identified from the cardiology clinic of a University medical center and were required to have a diagnosis of MI or angina within the previous two years. Previous TIA/stroke excluded patients from the study. Demographic and past medical information was obtained. Carotid ultrasound was performed according to standardized methods by two technologists. Results: 101 patients (51% male) with a mean age of 59.8 years underwent extracranial carotid duplex scanning. The frequency of risk factors were as follows: hypertension (86%), diabetes mellitus (36%), current or previous smokers (59%), and hyperlipidemia (65%). 39% of patients had undergone previous CABI. Overall, the frequency of at least unilateral carotid stenosis of >30%, >50%, and >70% carotid stenosis was 21%, 11%, and 5%. Age greater than 60 years (21% vs. 3%, p<0.01) and diabetes (22% vs. 5%, p<0.01) were predictors of unilateral carotid stenosis of >50%. Hypertension, sex, and risk factor combinations (2, 3, or 4 factors) were not predictors of carotid stenosis. Conclusions: In patients with established IHD, approximately 11% of AA patients have >50% carotid stenosis on DUS. This figure is higher than community dwelling AA and is comparable to other studies of Whites and Asians with established IHD. Early identification of these patients provides an opportunity for intensified medical therapy in all patients and endarterectomy in select patients. Screening of AA patients with IHD and with either age greater than 60 or diabetes may be cost effective but further studies are needed to support this recommendation. Study supported by Blue Cross and Blue Shield of Michigan Foundation.

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Associated Vascular Risk Factors for Extra- and Intracranial Atherosclerosis in Korean Patients

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Background: Besides race-ethnicity, the role of other risk factors that can be related to the distribution of cerebral atherosclerosis has been controversial. Objective: We determined if there were vascular risk factors associated with the extra- and intracranial atherosclerosis in Korean stroke patients. Methods: We studied 856 consecutive patients with ischemic stroke admitted to our two hospitals over a 5-year period. We excluded patients who had potential cardiogenic source of embolism. We determined the location and severity of atherosclerotic lesions on MR angiography (MRA). The presence of atherosclerotic lesion in intracranial cerebral arteries and extracranial carotid artery was defined as 50% or more narrowing of luminal diameter or occlusion on MRA. The information about potential vascular risk factors such as age, sex, arterial hypertension, diabetes mellitus, hyperlipidemia, cigarette smoking, alcohol consumption, was obtained from medical records. Results: Three hundred fifty-five patients (41.5%) had intracranial atherosclerotic lesion on MRA. Sixty-one patients (7.1%) had steno-occlusive extracranial carotid artery disease, and 78 (8.1%) had combined extracranial carotid and intracranial atherosclerotic lesions. Multivariate logistic regression models showed that hyperlipidemia were significantly associated with the extracranial carotid atherosclerosis (OR, 4.12; 95% CI, 1.21 - 9.11, p<0.01), but diabetes mellitus was only associated with intracranial atherosclerosis (OR, 3.26; 95% CI, 1.45 - 6.52, p<0.01). Conclusions: Our data suggest that the risk factors for extra- and intracranial artery lesion are different. Diabetes mellitus may be associated with the development of intracranial atherosclerosis, which disease is predominant in Korean patients.

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Lipoprotein (a) and Stroke Events in Postmenopausal Women: The Chin-shan Community Cardiovascular Cohort Study

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Background and Purpose: Women are well-known to lag behind men about 10 years in cardiovascular disease (CVD) morbidity and mortality. Due to the aging population, the risk of CVD increases with age in postmenopausal women. However, there is limited information about the risk factors for CVD incidence in postmenopausal women in Chinese. And, the relation between baseline lipoprotein (a) level and the future incidence of stroke is still unclear. Methods: This report describes the factors, including traditional risk factors and lipoprotein (a), and their contribution to stroke incidence after average 8.6 years’ follow-up in 1137 postmenopausal women in the Chin-Shan Community Cardiovascular Cohort (CCCC) Study. Results: At the end of 2002, 70 stroke incidence cases were identified from medical records and death certificates. Multiple Cox proportional hazard regression models were used to evaluate the predictors for new onset of stroke. Age ≥65 years, hypertension, and diabetes were found as the three important risk factors for stroke incidence. After controlling age ≤65 years, hypertension, diabetes, smoking, obesity (body mass index ≥35Kg/m2), low-density lipoprotein cholesterol ≥160 mg/dL, and cholesterol ≥5.0 mmol/L, upper quartile levels of lipoprotein (a) (≥19.06 mg/dL) was identified as a significant predictor for stroke incidence (HR=1.73, 95% CI=1.02–2.92). Conclusions: In addition to hypertension, diabetes and age ≥65 years, levels of lipoprotein (a) were found as important risk factors for stroke incidence in postmenopausal women. Lipoprotein (a) levels may serve as a new emerging risk factor for stroke events in postmenopausal women.
Feasibility of a Population-Based Study of Childhood Stroke

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Background: A recent report from the National Institute of Neurologic Disorders and Stroke cited the critical importance of more studies of childhood stroke. Our goal was to assess pediatric stroke rates in a bi-ethnic population-based study in order to determine the feasibility of studying childhood stroke in a single community. Methods: This work is part of the Brain Attack Surveillance in Corpus Christi (BASIC) project. The community of 325,000 is located in southeast Texas and is composed of approximately equal numbers of Mexican Americans (MA) and non-Hispanic Whites (NHW). Discharge diagnosis codes from all hospitals in the county were used to identify cases of childhood stroke (age < 20) in 2002 and 2003. ICD-9 codes included ischemic stroke, intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), and venous sinus thrombosis, but excluded codes related to trauma and perinatal ischemia/hemorrhage. Incidence rates of stroke were calculated with 95% confidence intervals for the entire population, and by ethnicity using 2000 census data as the denominator. A rate ratio comparing MA with NHW was calculated. Results: There were a total of 8 cases of childhood stroke identified during the two years of the study (age 2 months to 18 years). There were 4 cases of SAH, 3 cases of ICH, and 1 TIA. Annual stroke incidence rate per 100,000 was 4.03 (95% CI 1.74, 7.93) overall, 4.68 (1.72, 10.20) for MAs, and 3.54 (0.43, 12.77) for NHWs. The rate ratio for stroke comparing MAs with NHWs was 1.32 (0.27, 6.55). Conclusions: Given the low incidence of pediatric stroke, case control studies may be more appropriate than cohort studies to assess risk factors for stroke in children. A large, cooperative project is needed with cases and controls reflecting the general population rather than academic referral populations.

Hemorrhage

Intraoperative Hypothermia and the Risk of Cardiac Injury and Dysfunction in Patients With Subarachnoid Hemorrhage

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The Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST) demonstrated no beneficial effect of mild hypothermia (33°C) on neurologic outcome in patients with SAH undergoing microsurgical aneurysm clipping. However, in previous non-neurosurgical studies, intraoperative hypothermia has been associated with an increased risk of myocardial ischemia. The aim of this IHAST substudy was to determine whether intraoperative hypothermia affects the risk of developing myocardial necrosis (release of cardiac troponin I [cTNI] or left ventricular dysfunction. Methods: Seven IHAST centers participated in this substudy. In addition to the procedures for the parent study (randomization to intraoperative hypothermia vs. normothermia), each patient had serum collected for measurement of cTNI and an echo within 24 hours prior to surgery. These procedures were repeated 8–24 hours after surgery. For each echo, a blinded observer measured the left ventricular ejection fraction (LVEF) and the LV regional wall motion score (RWMSS) for each of 16 LV segments. The mean change in cTNI, LVEF, and RWMSS was compared by randomization status using Wilcoxon ranksum tests. The proportion of patients in each group with an increase in cTNI and RWMSS was compared using chi-square and Fisher’s exact tests.

Results: Complete data was obtained on a total of 62 patients. Their mean age was 52 ± 13 years, 37 (58%) were women, and the majority were World Federation of Neurological Societies (WFNS) grade II (77% vs. 3% for grade 2 and 3% for grade 3). The results are shown in the table. Conclusions: SAH patients receiving intraoperative hypothermia during aneurysm surgery were less likely to have additional myocardial necrosis post-operatively. Hypothermia did not significantly affect post-operative left ventricular function.
female (81.4 ± 0.5 % vs. 80.1 ± 0.3 % in vehicle treated rats, n = 5, p < 0.05) but not in male rats suggesting that ER-alpha activation during ICH is protective in female rats. Administration of exogenous 17beta-estradiol to male (but not female) rats significantly attenuated brain edema (79.1 ± 0.6 % vs. 81.8 ± 0.9 % in the vehicle, n = 5, p < 0.05). Neurological deficits (p < 0.05) and ICH-induced changes in HO-1 (Western blot analysis: 1536 ± 345 pixels vs. 1251 ± 531 pixels, p < 0.05) when given two hours after ICH. The effects of exogenous 17beta-estradiol were via an ER-alpha independent mechanism because the degree of 17beta-estradiol-induced protection was similar in ICH 182,760 and vehicle-treated male rats. Conclusions: This study has shown that female rats have less ICH-induced injury than male rats due to an ER-alpha-dependent mechanism. ICH-injury in male rats can, however, be reduced by administration of exogenous 17beta-estradiol through an ER-alpha independent mechanism that may involve modulation of HO-1 and iron-induced toxicity. Since delayed 17beta-estradiol treatment was effective in male rats, it could be a potential therapeutic agent for ICH.

Intracranial Hemorrhages Associated With Intravenous Platelet Glycoprotein IIb/IIIa Receptor Inhibitors in the United States

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Background: Rates of intracranial hemorrhages among patients treated with platelet glycoprotein IIb/IIIa inhibitors for coronary interventions and acute coronary syndromes have been studied within clinical trials but not in routine practice. We evaluated the rates of intracranial hemorrhage associated with use of platelet glycoprotein IIb/IIIa inhibitors in routine practice in United States. Methods: National estimates of intracranial hemorrhages associated with platelet glycoprotein IIb/IIIa inhibitors use, in-hospital outcomes, and mortality were obtained from National Hospital Discharge Survey. Records were matched to International Classification of Diseases-9-Clinical Modification (ICD-9) procedure and diagnosis codes. Results: There were 367,294 patients aged 18 years or greater who were treated with platelet glycoprotein IIb/IIIa inhibitors between 2000 and 2002 in United States. Intracranial hemorrhage was observed in 479 (0.13%) of the 367,294 patients. The mortality among patients who developed intracranial hemorrhage was 100%. Intracranial hemorrhages related to glycoprotein IIb/IIIa inhibitors comprised 0.12% of the total number of intracranial hemorrhages (n = 479) observed in the United States between 2000 and 2002. Conclusions: Intracranial hemorrhages related to platelet glycoprotein IIb/IIIa inhibitors are uncommon but are associated with exceedingly high mortality. Further strategies are required for identification of high-risk patients and rapid reversal of platelet inhibition in patients receiving glycoprotein IIb/IIIa inhibitors.

Clinical Outcome After First and Subsequent Hemorrhage in Patients With Untreated Brain Arteriovenous Malformation

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Background: The neurological morbidity from primary intracranial hemorrhage (ICH) is well known, but that for hemorrhage from untreated brain arteriovenous malformations (BAVMs) has not been studied within clinical trials but not in routine practice. We evaluated the rates of intracranial hemorrhage during clinical follow up in patients who developed intracranial hemorrhage associated with use of platelet glycoprotein IIb/IIIa inhibitors in routine practice in United States. Methods: National estimates of intracranial hemorrhages associated with platelet glycoprotein IIb/IIIa inhibitors use, in-hospital outcomes, and mortality were obtained from National Hospital Discharge Survey. Records were matched to International Classification of Diseases-9-Clinical Modification (ICD-9) procedure and diagnosis codes. Results: There were 367,294 patients aged 18 years or greater who were treated with platelet glycoprotein IIb/IIIa inhibitors between 2000 and 2002 in United States. Intracranial hemorrhage was observed in 479 (0.13%) of the 367,294 patients. The mortality among patients who developed intracranial hemorrhage was 100%. Intracranial hemorrhages related to glycoprotein IIb/IIIa inhibitors comprised 0.12% of the total number of intracranial hemorrhages (n = 479) observed in the United States between 2000 and 2002. Conclusions: Intracranial hemorrhages related to platelet glycoprotein IIb/IIIa inhibitors are uncommon but are associated with exceedingly high mortality. Further strategies are required for identification of high-risk patients and rapid reversal of platelet inhibition in patients receiving glycoprotein IIb/IIIa inhibitors.

Role of NAD(P)H Oxidase in Pathogenesis of Cerebral Vasospasm

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Background and Purpose- Existing evidence suggests that increased production of superoxide anions plays an important role in narrowing of cerebral arteries after subarachnoid hemorrhage (SAH). NAD(P)H oxidase is one of the most important enzymatic source of superoxide anion in arterial wall. The present study was designed to determine if NAD(P)H-oxidase may contribute to increased formation of superoxide anions and development of chronic cerebral vasospasm. Methods- Autologous arterial blood (1 ml/kg) was injected into cisterna magna to induce vasospasm in the rabbit basilar arteries. Forty-eight hours after SAH, vasospasm was confirmed by angiography. Vasomotor function of isolated basilar arteries was studied by isometric force recording. Expression of the NAD(P)H-oxidase protein was determined by western blotting of p47phox subunit. Protein nitration at tyrosine due to chemical antagonism between nitric oxide (NO) and superoxide anion (and subsequent production of peroxynitrite) was determined by western analysis of 3-nitrotyrosine. Results- SAH caused significant narrowing of basilar artery (55 ± 11%, n = 18, p < 0.05). The expression of p47phox protein expression (n = 8, P < 0.05) and associated increase in 3-nitrotyrosine levels (n = 3, P < 0.05) were detected in spastic basilar arteries. Consistent with high production of peroxynitrite, inducible nitric oxide synthase (iNOS) protein levels and enzymatic activity (n = 8–5, p < 0.05) were also elevated in spastic arteries. Conclusions - The results of our studies demonstrate that SAH stimulates expression and enzymatic activity of NAD(P)H-oxidase and NOX in vivo, providing molecular basis for tyrosine. It is likely that prolonged protein nitration is an important contributor to irreversible impairment of vascular smooth muscle function leading to chronic cerebral vasospasm.

Intracranial Hemorrhage Risk in Children versus Adults With Brain Arteriovenous Malformations

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Background: Brain arteriovenous malformations (BAVMs) in children are said to be at higher risk for intracranial hemorrhage (ICH) than those in adults. Although this notion affects treatment decisions, the evidence to support this claim is limited. Methods: To compare rates of ICH in children and adults with BAVMs, we collected clinical data for all cases of BAVMs evaluated at the University of California, San Francisco (1/2000 to 1/2004; n = 391), and Kaiser Permanent Northern California (1/1993 to 1/2000; n = 853). We evaluated each patient’s history and subsequent ICH rates. Conclusions - Children with BAVMs do not appear to be at increased risk for a “subsequent” ICH compared to adults. As BAVMs diagnosed in children appear less likely to be diagnosed incidentally, the higher rate of hemorrhagic presentation may be due to selection.
Phenyltoin Exposure Is Associated With Functional and Cognitive Disability After Subarachnoid Hemorrhage

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Many patients with subarachnoid hemorrhage (SAH) have a prior history of hypertension (HTN) and left ventricular hypertrophy (LVH). The objective of this study was to test the hypothesis that LVH may occur in SAH patients without a history of HTN and may resolve during the acute hospitalization. Methods: A prospective cohort study enrolled a consecutive series of patients admitted with aneurysmal SAH. An echocardiogram was performed on the day of enrollment and was repeated five days later. For each study, left ventricular mass index (LVMi) was measured by a blinded observer using the truncated ellipsoid method. LVH was defined as an LVMi >90 gm/m². For each subject, a prior history of HTN was also noted as well as the systolic (SBP) and diastolic (DBP) blood pressure during each echo. Results: A total of 253 patients were included in the study. LVH was present on the initial echo in 137 (75%) of cases. 71 (29%) of these patients had a prior history of HTN. Patients with LVH and no prior history of HTN had a mean SBP of 147 ± 24 mmHg vs. 155 ± 27 in patients with HTN (t-test p = 0.056) and the DBP was 74 mmHg in both groups. Among all patients with LVH, the mean LVMi decreased from 109 ± 14 on the initial echo to 102 ± 24 on the follow-up study (t-test p = 0.003). There was no difference between the mean SBP (166 ± 30) in SAH in patients with and without a prior history of HTN, even without a prior history of HTN, and may improve or resolve during the acute hospitalization. These findings suggest that an increase in LV mass may occur as an acute manifestation of neurogenic injury. Myocardial edema is one possible mechanisms for transient LVH after SAH.

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Anxiety Screening After Surgical Treatment for Ruptured Aneurysms

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Background - Patients who survive after subarachnoid hemorrhage (SAH) are at risk for new intracranial aneurysm formation and recurrent SAH despite successful treatment of the ruptured aneurysm. We studied the field of screening for new aneurysms in these patients. Methods - We screened 610 patients with CT-angiography (CTA) who had been admitted between 1985 and 2001 for SAH and in whom the ruptured aneurysm had been clipped. In patients with an aneurysm ≥ 3 mm conventional angiography was performed. Detected aneurysms were treated by clipping, coiling or followed by yearly CTA. Results - With screening we found 143 aneurysms in 115 of the 610 patients (19%). Twenty aneurysms in 20 patients were located at the clip site of the previously treated aneurysm, 64 aneurysms in 52 patients were located at new sites, 39 aneurysms in 36 patients were in retrospect visible on the initial angiogram but not identified at that time and 25 aneurysms in 19 patients had already been visible on the initial angiogram at the time of the SAH. Conclusion - The field of screening for new aneurysms in patients who have been treated by clipping after a SAH has a high yield. The risks and benefits of screening should be carefully weighed, for example in a decision analytic model.

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Phenyltoin Exposure Is Associated With Functional and Cognitive Disability After Subarachnoid Hemorrhage

Andrew M Naidech, Kurt T Kreiter, Nazli Janjua, Noeleen Ostapkovich, Augusto Parra, Juan M Zaroff, UCSF, San Francisco, CA

The peak PHT level was higher in patients with functional disability (19.9 ± 7.8, p = 0.001) after correction for admission Glasgow Coma Scale, fever, stroke, age, NIH Stroke Scale ≥10, hyperhomocysteinemia, chronic vasospasm, and aneurysm rebleeding. Seizure in hospital (OR 4.1, 95% CI 1.1–1.1, P = 0.002) was associated with functional disability in 14 days (odds ratio 1.5 per quartile, 95% CI 1.3–1.8, P = 0.001); the effect remained (OR 1.6 per quartile, 95% CI 1.2–2.1, P = 0.001) after correction for admission Glasgow Coma Scale, fever, stroke, age, NIH Stroke Scale ≥10, hyperhomocysteinemia, chronic vasospasm, and aneurysm rebleeding. Seizure in hospital (OR 4.1, 95% CI 1.1–1.1, P = 0.002) was associated with functional disability in a univariate model only. Forcing in length of stay did not change the results. Higher quartiles of PHT burden were associated with worse TICS scores at hospital discharge (P < 0.001) and at three months (P = 0.003). Conclusions. Burden of exposure to PHT, but not seizures, predicts poor functional and cognitive outcome after SAH. In prophylaxis of seizures after SAH, the treatment may be worse than the disease.
dichotomous variable (abnormal if ≤50% on any study). Each echo was also assessed for the presence of regional wall motion abnormalities (RWMA) of the LV. The proportion of subjects with each cardiac abnormality was compared between arg/arg homozygotes and a combined group of heterozygotes and gly/gly homozygote using Fisher’s exact and Wilcoxon ranksum tests. Results: The study included 167 patients with a mean age of 56 and a mean Hunt-Hess grade of 2.3; 71% of the subjects were women. See table. Conclusions: Genetic variation in the B1AR sensitivity of the B1AR appears to modulate the risk of cardiac injury (CtI release) after SAH. These data support the hypothesis that cardiac dysfunction after SAH is a form of neurocardiogenic injury.

### Cardiac Injury & Dysfunction by SNP Status

<table>
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<th>Genotype</th>
<th>cT1 &gt; 1.0 mg/L</th>
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<th>Arg/Gly or Gly/Gly BIAR</th>
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<tr>
<td>Genotype</td>
<td>P Value</td>
<td>Genotype (N=95)</td>
<td>Genotype (N=72)</td>
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<tr>
<td>cT1 &gt; 1.0 mg/L</td>
<td>16 (17%)</td>
<td>11 (12%)</td>
<td>4 (6%)</td>
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<td>Mean LVEF</td>
<td>62±11</td>
<td>64±11</td>
<td>64±11</td>
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<td>LVEF &lt; 50%</td>
<td>11 (12%)</td>
<td>15 (19%)</td>
<td>4 (6%)</td>
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<tr>
<td>RWMA</td>
<td>25 (26%)</td>
<td>13 (18%)</td>
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</table>

#### Role of Oxidative Stress in MMP-9 Induction in Astrocytes After Cerebral Hemorrhage

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Background: Peri-hematoma edema contributes to deleterious sequelae after intracerebral hemorrhage. Matrix metalloproteinase-9 (MMP-9) is an inducible gene that may degrade vascular matrix and basal lamina, thus mediating brain edema. In this study, we examined the profiles of MMP-9 regulation using in vivo and in vitro models of cerebral hemorrhage. Methods: Homologous blood (30 ul) was infused into the striatum of CD-1 mice (male, 10–12 weeks old) as a model of intracerebral hemorrhage. Immunohistochemistry was used to survey the cellular distribution of MMP-9 at 24 and 48 hrs post-hemorrhage. In parallel, mouse cortical astrocytes were cultured and exposed to hemoglobin as an in vitro model of hemorrhage. Gelatin zymography was used to measure MMP-9 levels in conditioned media. The role of oxidative stress was histomorphologically assessed using various anti-oxidants. Results: In mouse brain, MMP-9 was up-regulated in cells surrounding the hematoma at 24 and 48 hrs post-hemorrhage, whereas signals primarily centered on the astrocytes under GFAP. In primary mouse astrocyte cultures, exposure to hemoglobin induced a dose (0.5–10 μM) and time (1–24 hrs)-dependent increase in active-MMP-9 within conditioned media. Treatment with the lipoxygen antioxidant U68663E (10–40 μM) significantly decreased active MMP-9 levels at 24 hrs after exposure to 2.5 μM hemoglobin. MMP-9 (fold-increase, mean ± SD): 11.9 ± 5.7 for hemoglobin alone, 3.0 ± 2.6 for hemoglobin plus 10 μM U68663E, 1.6 ± 0.3 for hemoglobin plus 40 μM U68663E (n=4 per group, P<0.05). However, no effects were observed with the iron chelator deferoxamine (25–200 μM). Conclusion: Reactive astrocytes surrounding an intracerebral hemorrhage upregulate MMP-9. This process may be mediated by hemoglobin-induced oxidative stress.

#### Cardiovascular Predictors of Vasospasm & Death

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Early Deterioration of Intracerebral Hemorrhage in Patients Treated With Antiplatelet Agents

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BACKGROUND AND OBJECTIVE: Although antiplatelet agents have been reported to be included in higher incidence of acute intracerebral hemorrhage (ICH), Relationship between antiplatelet therapy and early deterioration (ED) of ICH remains unknown. We performed the current study to address the issue. METHOD: We reviewed 406 consecutive patients admitted within 24 hours of onset of acute ICH from January 1999 to December 2003. We excluded 32 patients who had been on anticoagulant therapy and analyzed the other 374 patients. We defined ED, if hematoma enlarged, surgical treatment was performed or a patient died within 48 hours of onset. CT was followed 24–48 hours after the onset or when symptoms deteriorated. When hematoma volume was 1.4-fold larger than that in the baseline CT, the hematoma was considered to have enlarged. We divided the 374 patients into either ED group, 84 patients with ED (52 men, 66.8±13.2 years old), or into control group, the other 290 patients (164 men, 66.6±12.4 years old). We compared backgrounds between the two groups.

RESULTS: The ED group had more frequently antiplatelet therapy (27.4% vs. 12.1%, chi square test, p=0.006), shorter time-interval from onset to admission (median 1.5 vs. 2.0 hours, p=0.0013), more frequent liver disease (19.0% vs. 10.0%, p=0.032), and heart disease (21.4% vs. 14.8%, p=0.149), and higher systolic blood pressure (BP) on admission (184.0 vs. 180.0 mmHg, p=0.05) than the control group. There were no differences in diabetes mellitus, hypothyroidism, current smoking, age and gender between the group. The multiple logistic regression analysis revealed that antiplatelet therapy (OR 3.11, 95%CI 1.60–6.06; p=0.0008), time from onset to admission (OR 0.93, 95%CI 0.86–0.99; p=0.048), liver disease (OR 3.06, 95%CI 1.50–6.26; p=0.020), systolic BP on admission (OR 1.01, 95%CI 1.00–1.02; p=0.013) were independent factors for ED. CONCLUSION: Antiplatelet therapy may independently promote the early deterioration of ICH.

#### Antithrombotic Therapy Is Associated With Early Deterioration of Intracerebral Hemorrhage

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Background and Purpose: Enlargement of intracerebral hemorrhage (ICH) often results in neurological deterioration early after stroke onset. The influence of antithrombotic therapy before admission on early ICH enlargement has not been elucidated fully. The aim of this study was to address this issue. Methods: We reviewed 416 patients with ICH admitted within 24 hours after the onset (246 male, 170 female; age, 67.4±12.4 years). CT scan was performed on admission and within 24–48 hours after the onset or when symptoms deteriorated. Hematoma enlargement was defined as hematoma volume on CT 1.4-fold larger than the baseline. Patients who died or were operated before the follow-up CT and who had hematoma...
Experimental Ischemia

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To test whether eNOS regulates growth factor expression, SVZ progenitor cell proliferation, neuronal migration and neurological functional recovery after stroke, eNOS−/− mice and wild-type C57Bl/6J mice were employed and subjected to MCAo. Adult male eNOS−/− mice and wild-type mice were subjected to MCAo and sacrificed at 7 days after MCAo. Ischemic brain extracts were obtained and VEGF, bFGF and BDNF ELISA assays were performed. To test whether eNOS induces neuronal migration in vitro, cortical explants obtained from eNOS−/− and wild-type mice postnatal cortical were cultured for 7 days (n = 5/group) and neuronal cell migration was measured. Functional tests show a significant attenuation in eNOS−/− mice compared with wild-type mice at 1, 3 and 7 days after MCAo (p < 0.05). BrdU and DCX reactive cells significantly decreased in the SVZ of the ipsilateral hemisphere in the eNOS−/− mice (BrdU: 71.0 ± 1.3; DCX: 10 ± 3%; p < 0.05). These data indicate that eNOS regulates BDNF expression in the ischemic brain, mediates progenitor cell proliferation and neuronal cell migration, and affects functional recovery after stroke.

Increased Expression of a DNA Replication-Licensing Factor, Minichromosome Maintenance-2, in Subventricular Cells After Stroke

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As a member of DNA replication-licensing factor, minichromosome maintenance 2 (MCM-2) is an essential factor for initiation of DNA replication in early G1 of cell cycling. Using immunohistochemistry, we examined the distribution of MCM-2 in the subventricular zone (SVZ) of adult stroke rats. Rats (n = 35) were sacrificed at 0 (as non-ischemia), 2, 4, 7, 14, and 28 days after embolic stroke. Stroke significantly (p < 0.05) increased the numbers of MCM-2+ cells in the isipilateral SVZ at 2 (251.5 ± 10.1; 4) (354.4 ± 8.5; 7) (506.9 ± 12.9; 14) (413 ± 11.6) and 28 days (345 ± 6.9) compared to the non-stroke rats (182 ± 7.6) (p < 0.01). Interestingly, 2 days after stroke, rats did not exhibit a significant increase of numbers of BrdU+ cells (202.9 ± 10.3) when compared with non-ischemic SVZ (182.5 ± 10.6). Double immunostaining revealed that approximately 90% of MCM-2+ cells were BrdU+ 4 days after stroke. However, the numbers of MCM-2+/BrdU− declined to 57% and 49% at 14 and 28 days after stroke respectively. The decrease of BDNF (p < 0.05) was significantly increased at 7 days after stroke. These data suggest that MCM-2 is involved in stroke induced neurogenesis and MCM-2+ cells represent both actively proliferating cells (neural progenitor cells) and cells with proliferating potential (neuronal stem cells). Furthermore, targeting on MCM-2+ cells could be a potential therapeutic approach for enhancing neurogenesis.

A Role for EphB2 in Stroke-Induced Neurogenesis

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A subclass of the large ephrin protein family, the EphB receptors and their Ephin-B ligands play roles in physiological events varying from neural crest migration and vascular development, to angiogenesis, axonal guidance and tumor invasion. Yet, to date, information concerning functions of ephrin-B in stroke is scarce. Intravenous administration of EphB2 results in disruption of mural nitric oxide synthase (NOS) migration of subventricular zone (SVZ) progenitor cells, and increases neurogenesis within the SVZ of uninjured brain. As similar NOS migration disruption and SVZ proliferation follows cerebral ischemic insult, we hypothesized that EphB2 may be a key factor in SVZ alterations following cerebral stroke. Employing qualitative PCR and quantitative real-time RT-PCR, we demonstrate that subventricular EphB2 mRNA increases 3.5 fold 7 days post middle cerebral artery occlusion (MCAo) in mice. Similarly, immunocytochemistry indicated an increase in SVZ EphB2 expression ipsilateral to infarct. SVZ progenitor cells isolated from the uninjured brain and treated with 2ug/ml recombinant EphB2 significantly (p < 0.05) upregulated proliferation by MIT, and Brdu incorporation in progenitor cells was increased by flow cytometry. Interestingly, expression of two genes indicated as neurogenic regulators Notch1 and Zic1 were reduced by EphB2 (0.1 fold and 2.2 fold, respectively). Cultured cells isolated from the SVZ ipsilateral to infarct similarly demonstrated increased proliferation as compared to contralateral. These data suggest that EphB2 may activate neurogenesis after stroke via regulation of the Zic1 and Notch1 genes.
agoint treatment reduced infarct volume by 45% (p<0.01) with dose response. In PPAR-γ agonist-treated group, neuroprotection / microglial infiltration, ischemic cell death in the ischemic penumbra area were reduced, eNOS expression was increased in the ipsilateral hemisphere by western blot and immunohistochemistry analysis. Cerebral atrophy was also reduced and behavior tests showed better recovery starting from 2 weeks after ischemia (p<0.05).

Conclusions: In this study, we provide evidences that PPAR-γ agonist rosiglitazone induces long-term functional recovery in focal ischemic model, which might be due to the induction of ischemic tolerance.

Spreading-depression-like peri-infarct Depolarizations Originate at Multiple Sites Including Striatal Regions After MCA Occlusion in Cats

Rudolf Graf, Masao Umegaki, Yannic Waerzeggers, Yasuhiro Sanada, Gerhard Rosner, Wolf-Dietrich Heiss, MPP for Neurological Resch, Cologne, Germany

Spreading-depression-like peri-infarct depolarizations (PIDs) characterize and possibly deteriorate penumbral conditions in cortical border zones of experimental focal ischemia. To investigate the relevance of PIDs in subcortical ischemic regions, we used Calomel electrodes to simultaneously measure the activity in the striatal and cortical penumbra. In early and late stages of ischemia, we observed 11 anesthetized cats after permanent occlusion of the middle cerebral artery. Additionally, platinum electrodes measured regional cerebral blood flow (rCBF). Cats demonstrated moderate to severe reductions of rCBF in NC (24.6±5.6% of control), Negative DC shifts >10 mV were obtained in 10/11 cats. The spreading depression-like depolarization (SDDL) occurred in 5/11 cats: 5.2±1.22 min duration; 23.3±4.2 mV amplitude) were predominantly found in medial and longer depolarizations (LDs in 4/11 cats: 6.4±7.45 min duration; 25.0±1.13 mV amplitude) in lateral NC showing that the lateral NC belongs to the ischemic core. Terminal depolarizations (TDs in 6/11 cats: >1 min duration) were found in the lateral NC beyond the final stage of ischemia acquisition or at a final stage documenting then a malignant course of infarction. In individual cases, propagation of depolarizations from lateral to medial NC was observed with a velocity of around 2–3 mm/min. Furthermore, parallel measurements in cortical penumbra revealed also TDs, which were, however, temporarily independent from those in striatum. We conclude that PIDs originate and propagate at multiple sites including cortical as well as striatal penumbra. They are most likely relevant for progressive deterioration of penumbra conditions and may finally lead to malignant infarction.

Brain Infarction After Transient Focal Cerebral Ischemia in Mice

Rudolf Graf, Masao Umegaki, Yannic Waerzeggers, Yasuhiro Sanada, Gerhard Rosner, Wolf-Dietrich Heiss, MPP for Neurological Resch, Cologne, Germany

Background: Integrin-associated protein knockdown reduces neutrophil infiltration and brain damage after transient focal cerebral ischemia by comparing IAP knockdown mice and wild-type littermates. Methods: Integrin-associated protein knockdown reduces neutrophil infiltration and brain damage after transient focal cerebral ischemia by comparing IAP knockdown mice and wild-type littermates. Methods: Integrin-associated protein knockdown reduces neutrophil infiltration and brain damage after transient focal cerebral ischemia by comparing IAP knockdown mice and wild-type littermates. Methods: Integrin-associated protein knockdown reduces neutrophil infiltration and brain damage after transient focal cerebral ischemia by comparing IAP knockdown mice and wild-type littermates. Background: Integrin-associated protein (IAP/CD47), a cell surface transmembrane Ig superfamily member, is an extracellular ligand for signal regulatory protein (SRP-alpha). Interactions between IAP and SRP-alpha regulate neutrophil (PMN) transmigration in vitro. Neutrophil infiltration is known to aggravate cerebral ischemic damage. In this study, we examine the role of IAP in mediating neutrophil infiltration and brain damage after transient focal cerebral ischemia by comparing IAP knockdown mice and wild-type littermates. Results: Compared with wild-type mice, IAP knockout mice had smaller numbers of extravasated neutrophils in the ischemic cortex. IAP knockouts showed a 33% reduction of extravasated neutrophils in the ischemic cortex. Effects of IAP and SIRP-alpha regulate neutrophil (PMN) transmigration in vitro. Neutrophil infiltration is known to aggravate cerebral ischemic damage. In this study, we examine the role of IAP in mediating neutrophil infiltration and brain damage after transient focal cerebral ischemia by comparing IAP knockdown mice and wild-type littermates. Results: Compared with wild-type mice, IAP knockout mice had smaller numbers of extravasated neutrophils in the ischemic cortex. IAP knockouts showed a 33% reduction of extravasated neutrophils in the ischemic cortex.
**Statistical Prediction of Ischemic Tissue Fates Based on Quantitative Perfusion and Diffusion Imaging During the Acute Phase**

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**Background:** Early changes in ADC and CBF could predict tissue fates in ischemic brain injury. This study aimed to develop a statistical means to predict, on a pixel-by-pixel basis, the probability of tissue becoming infarcted based on early ADC and CBF information. **Methods:** Quantitative perfusion and diffusion data (200x200x150 μm, 8 slices) were acquired every 30min for 3hrs on 12 rats subjected to MCAO. Probability of infarct (P) contour plots were computed using the ADC & CBF data of 6 rats by determining the percentage of pixels at each grid that migrated to ischemia core (at 3hrs) as defined by an improved ISODATA cluster analysis. Prediction of infarct was made on another 6 rats using only their 30-min data: ADC alone, CBF alone and ADC + CBF data. Receiver operating characteristic (ROC) and correlation between predicted lesion volume (LV) and 24-hr TTC infarct volume were analyzed to evaluate the prediction accuracy. **Results:** Predicted maps showed excellent spatial correspondence with ISODATA-derived LV at 3hrs. Predicted LV with ADC alone (18.7±64 mm³) was consistently underestimated, with CBF alone (206±43 mm³) consistently overestimated, whereas with ADC+CBF (185±44 mm³) most closely approximated the TTC infarct volume (190±51 mm³). For CBF alone, ADC alone, and ADC + CBF, respectively, the correlation coefficients were 0.88, 0.92, and 0.96; the sensitivity were 82, 84, and 86%; specificity were 80, 89, and 89%; the areas under the ROC curves were 0.87, 0.91, and 0.93, indicating improved prediction with ADC+CBF data. **Conclusion:** This study demonstrated the feasibility of making probabilistic prediction of future infarction of ischemic tissues using early MRI information.

**Neurological Complications Following Vascular Surgery May Be Attenuated by Intrasinal Deferoxamine**


Coronary artery bypass graft (CABG) surgery is a procedure that can result in significant neurological dysfunction, including stroke and cognitive impairment. Patients in high-risk groups have an incidence of adverse cerebral outcome greater than 16%. We describe a model that utilizes a technique which may reduce perisurgical neurological problems by preconditioning the brain to be more resistant to ischemic insults. We have administered deferoxamine (DFO), an iron chelator, via non-invasive intranasal (IN) dosing in rats. Each animal received 3 IN doses of DFO, 3 hours apart. Forty-eight hours later, a 2-hour middle cerebral artery occlusion (MCAO) was performed, and animals were sacrificed 5 days following MCAO. The brains were removed, sectioned on a brain matrix at 2 mm intervals, and stained with 2,3,5-triphenyltetrazolium chloride (TTC). Using NIH Image, infarct volumes were quantified. Infarct volumes were reduced by 60% in animals treated with intranasal DFO. Offactory bulb and striatal protein extracts were analyzed by Western blot using an antibody for hypoxia-inducible factor-1a (HIF-1a). HIF-1a protein was elevated approximately 30- and 20-fold in olfactory bulb and striatum, respectively. Total RNA was isolated from olfactory bulb and striatum, and cDNA was generated using HIF-1α-specific primers. The cDNA was subjected to RT-PCR, and the results suggest that mRNA for HIF-1α was abundant; however, there were no differences between samples from animals treated with IN DFO and their controls (IN distilled water) in the actual concentration of HIF-1α mRNA. These data indicate that IN DFO pretreatment protects the brain during stroke via a mechanism involving HIF-1α and that the tissue levels of HIF-1α are elevated by decreasing its rate of degradation and not by de novo synthesis of HIF-1α protein. These data also suggest that patients undergoing CABG surgery could be pharmacologically preconditioned using IN DFO administration, thereby protecting the brain and reducing the incidence of neurological complications.

**Chronic Increases in the Injury-Responsive Cytokine Transforming Growth Factor β Result in Microgliosis and Inhibit Hippocampal Neurogenesis**

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Cerebral ischemia triggers an inflammatory response that includes elevated cytokines and activated microgliosis. Inflammation may modulate hippocampal neurogenesis and increasing neuronal activity may improve forebrain function from stroke. Transforming growth factor beta-1 (TGF-β1) is a multifunctional cytokine that increases with age and injury and plays a key role in inflammatory processes in the brain. In many tissues TGF-β1 promotes cellular differentiation and survival while inhibiting proliferation. In the brain, TGF-β1 increases survival of mature neurons after injury but promotes cerebrovascular fibrosis. We found that old transgenic mice overexpressing TGF-β1 (TGF-β1 mice) have abnormal hippocampal morphology and microgliosis. In fact, the number of hippocampal microglia in TGF-β1 mice increase from close to normal at one month to twice normal by 22 months of age. TGF-β1 hippocampal microgliosis has altered morphology and increased expression of activation markers. Because of this data and TGF-β1’s anti-proliferative effects, we hypothesized that TGF-β1 would decrease neurogenesis. We stained for the immature neuronal marker doublecortin on every 12th section of the hippocampus of 12 mice over the age range from 4 to 22 months. We used 10μm sections of the dorsal hippocampus and made 10 optical section readings per field of view for each mouse. We found a decrease in neurogenesis in TGF-β1 mice, which may be due to a decrease in survival of newborn neurons. There were no significant differences in the number of newborn neurons or in the number of newborn neurons stained for doublecortin between TGF-β1 mice and controls. We stained for the immature neuronal marker doublecortin on every 12th section of the hippocampus of 12 mice over the age range from 4 to 22 months. We used 10μm sections of the dorsal hippocampus and made 10 optical section readings per field of view for each mouse. We found a decrease in neurogenesis in TGF-β1 mice, which may be due to a decrease in survival of newborn neurons. There were no significant differences in the number of newborn neurons or in the number of newborn neurons stained for doublecortin between TGF-β1 mice and controls. The results indicate that TGF-β1 inhibits neurogenesis.
Combination Treatment With Tissue Plasminogen Activator and the Proteasome Inhibitor VECADE™ Extends the Therapeutic Window After Stroke

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Background and Purpose: NF-κB is activated in the brain after stroke, which leads to the expression of genes encoding inflammatory cytokines, adhesion molecules, and cell apoptosis, all of which contribute to the development of ischemic cell damage. Delayed thrombolysis with tissue plasminogen activator (tPA) exacerbates reperfusion injury after stroke. The selective proteasome inhibitor VECADE™ (also referred to as PS-341) blocks the activation of NF-κB. The present study evaluated the neuroprotective effect of VECADE™ alone and in combination with tPA in a model of delayed thrombolysis on focal cerebral ischemia. 

Methods: Male Sprague-Dawley rats (n=40) were subjected to embolic middle cerebral artery (MCA) occlusion. Animals were randomly assigned to the following groups: saline treatment at 2 hours (n=8); VECADE™ (0.2mg/kg, IV) treatment alone at 2, 4, or 6 hours (n=8); combination of VECADE™ (0.2mg/kg, IV) and tPA (0.75mg/kg, IV) at 2 and 4 hours (n=8); infarct volume was measured 7 days after MCA occlusion. Neurological functional tests including, neurological severity test (NSS) and foot-fault test were performed at 7 days after stroke. Whole blood samples were taken pre-stroke, 1h post-stroke, 1h and 7d after VECADE™ treatment to assess the plasma proteasome activity by acid-urea-streptomycin assay. 

Results: VECADE™ treatment significantly reduced infarct volume (0.3±0.07 vs. 0.6±0.04 nmol/min/mg, p<0.05, n=5). In combination therapy, the reduction in infarct volume was further enhanced to 0.2±0.05 (p<0.05, n=5). The combination treatment significantly reduced NSS and foot-fault test scores compared to VECADE™ alone treatment (p<0.05, n=5). The results were confirmed by immunohistochemical analysis of caspase-3 and NF-κB expression. Additionally, VECADE™ treatment significantly reduced NF-κB protein expression in control, p<0.05, n=5. 

Conclusions: These results suggest that atorvastatin promotes thrombolysis via downregulation of VECA in endothelial cells, which is not mediated by eNOS.

Exercise Induces Integrin Overexpression and Improves Neurovascular Integrity in Ischemic Stroke

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Cerebral microvessels are the proximal targets of ischemic insults and the primary sites for vascular leakage. Integrin receptors, such as αvβ3 and αvβ6, are thought to play a role in vascular integrity and remodeling. In stroke, constituents of the extracellular matrix are degraded by a variety of proteolytic enzymes, including matrix metalloproteinase (MMP). The early appearance of activated MMP-2 and -9 is associated with the formation of vascogenic edema. The purpose of the study was to determine the effect of exercise on the expression of αvβ3 and αvβ6 and MMP-2/9 to elucidate their roles in vascular integrity after stroke. 

Adult male Sprague Dawley rats were exercised (treadmill) 30 minutes each day for 3 weeks (group 1), or housed for an additional 3 weeks after exercise (group 2). A non-exercised control group was housed for 3 weeks. Some animals were subjected to a 2-h middle cerebral artery (MCA) occlusion followed by 6, 12 or 48 h of reperfusion. By comparing the percentage difference in brain volume between the right (stroke site) and left hemispheres, we demonstrated a significant (p<0.01) reduction in brain edema associated with reduced infarct volumes and neurologic deficits in exercised animals compared to non-exercised animals (p<0.05). Edema in cortex and striatum was 24% vs 4% (group 1, n=5 vs 9), 24% vs 8% (group 2, n=5). By using quantitative real-time reverse transcription polymerase chain reaction methods, we demonstrated overexpression of the genes encoding MMP-2 and MMP-9 in ischemic brains with or without exercise preconditioning (p<0.05), compared to sham labeling in the same areas of non-exercised animals (n=5). Furthermore, levels of the integrin subunits remained high in exercised-ischemic rats, in contrast to those in non-exercised-ischemic rats. Our studies suggest that pre-ischemic exercise strengthens neurovascular integrity in stroke by enhancing production of integrins rather than by reducing that of MMPs.

Atorvastatin Reduces Cerebral Infarction via Inhibiting NADPH Oxidase-Derived Superoxide in Transient Focal Ischemia

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Background: Statins (HMGO-CoA reductase inhibitors) have recently been shown to exert neuroprotection in vivo in models of focal cerebral ischemia. Reactive oxygen species (ROS) including superoxide and peroxynitrite are both oxidative and nitrosative effectors after MCA occlusion. The combination treatment significantly reduced NSS and foot-fault test scores compared to VECADE™ alone treatment (p<0.05, n=5). The results were confirmed by immunohistochemical analysis of caspase-3 and NF-κB expression. Additionally, VECADE™ treatment significantly reduced NF-κB protein expression in control, p<0.05, n=5. 

Methods: Male Sprague-Dawley rats were subjected to embolic middle cerebral artery (MCA) occlusion. Animals were randomly assigned to the following groups: saline treatment at 2 hours (n=8); VECADE™ (0.2mg/kg, IV) treatment alone at 2, 4, or 6 hours (n=8); combination of VECADE™ (0.2mg/kg, IV) and tPA (0.75mg/kg, IV) at 2 and 4 hours (n=8); infarct volume was measured 7 days after MCA occlusion. Neurological functional tests including, neurological severity test (NSS) and foot-fault test were performed at 7 days after stroke. Whole blood samples were taken pre-stroke, 1h post-stroke, 1h and 7d after VECADE™ treatment to assess the plasma proteasome activity by acid-urea-streptomycin assay. 

Results: VECADE™ treatment significantly reduced infarct volume (0.3±0.07 vs. 0.6±0.04 nmol/min/mg, p<0.05, n=5). In combination therapy, the reduction in infarct volume was further enhanced to 0.2±0.05 (p<0.05, n=5). The combination treatment significantly reduced NSS and foot-fault test scores compared to VECADE™ alone treatment (p<0.05, n=5). The results were confirmed by immunohistochemical analysis of caspase-3 and NF-κB expression. Additionally, VECADE™ treatment significantly reduced NF-κB protein expression in control, p<0.05, n=5. 

Conclusions: These results suggest that atorvastatin promotes thrombolysis via downregulation of VECA in endothelial cells, which is not mediated by eNOS.

Reduction of Infant Volume by Transfusion of Recombinant Hemoglobin Polymers With Different Oxygen Affinities During Transient Focal Ischemia

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Purpose: A clinical stroke trial of transfusion of cell-free, cross-linked hemoglobin (Hb) tetramers was halted because of safety concerns thought to be related to peripheral vasoconstriction arising from NO scavenging by extravasated Hb. However, large Hb polymers that are less permeable appear to be better tolerated. Two different Hb polymers with different PS0 and molecular size were engineered with recombinant technology using an E. coli expression system that could generate sufficient protein for testing in mice. We determined the effect of transfusing two different concentrations of each Hb polymer in the filament model of middle cerebral artery occlusion (MCAO). 

Methods: Hb Polytetrau was isolated from sheep and human blood by chromatographic techniques. These Hb molecules were labeled with Alexa 488 (green) and Alexa 594 (red) to track polymerization. Under these conditions we confirmed that the polymers remained large and femail. 

Conclusions: These results demonstrate, for the first time, that atorvastatin reduces cerebral infarct size via inhibiting NADPH oxidase-derived superoxide in transient focal ischemia.

Atorvastatin Downregulates von Willebrand Factor Expression in Cerebral Endothelial Cells and Enhances Thrombolysis With Tissue Plasminogen Activator in Rats With Stroke

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Background and Purpose: Mechanisms underlying the therapeutic effects of statins on stroke are not fully understood. We investigated the effects of atorvastatin on gene expression in single cerebral endothelial cells. Methods: Rats subjected to middle cerebral artery (MCA) occlusion were treated with atorvastatin in combination with IPA, atorvastatin, IPA, or saline at 4hr after stroke. Using a laser capture microdissection (LCM) system, approximate 120 endothelial cells were isolated in von Willebrand factor (vWF) immunoreactive cerebral vessels located in the ischemic boundary zone for the contralateral homologous area on a frozen coronal section obtained from the rat sacrificed at 24hr after stroke (n=3/group). Using double-strand DNA-specific dye SYBR green, mRNA levels for tissue factor, eNOS, WF, and Tie2 were quantitatively measured by Real-time RT-PCR, with beta-actin mRNA levels as a reference.

Results: Real-time PCR revealed that these cells expressed WF but not GAP43 and doublecortin genes, indicating that they are endothelial cells. vWF mRNA levels significantly increased by 2.5±0.03 , P<0.05 in the ipsilateral hemisphere compared with mRNA in the contralateral hemisphere (1.7±0.67) in rats treated with IPA. However, treatment with IPA in combination with atorvastatin significantly (P<0.05) reduced WF mRNA (1.6±0.04) compared with IPA alone. The treatment combination did not significantly change eNOS, tissue factor, tie2 gene expression. In addition, the combination treatment significantly (P<0.05) reduced secondary thrombosis with IPA treatments with atorvastatin (2.1±0.06) as measured by the numbers of microvessels containing fibrin per area. Conclusions: These results suggest that atorvastatin promotes thrombolysis via downregulation of WF in endothelial cells, which is not mediated by eNOS.

Bone Marrow Stromal Cells Confer Postischemic Protection of Astrocytes via Increased Erk, and Growth Factor Production Within Astrocytes

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Previous studies demonstrate that treatment of bone marrow stromal cells (BMSCs) significantly improves functional outcome, and reduces apoptosis in the brain. Astrocytes are the first cells to interact with BMSCs and direct BMSC adhesion and behavior. Cross talk between astrocytes and BMSCs after an ischemic insult, however, is scarce. In this

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study, we investigated the effect of rat BMSCs (rBMSCs) on post-ischemic induced apoptosis and cell death of astrocytes, as well as the mechanisms underlying the observed effects using an in vitro ischemia model. After 4h ischemic incubation in an anaerobic chamber, astrocytes were co-cultured with rBMSCs under non-ischemic conditions for an additional 4h. Astrocytes cultured without rBMSCs (control group) showed evident morphological and biochemical apoptosis features. A large number of condensed nuclei were observed, and many cells appeared as dark detached spheres or oval-shaped bodies. A cell viability assay showed that 20% of the astrocytes were dead. However, the introduction of rBMSCs remarkably reduced the apoptosis and cell death (to 1.5%), P < 0.01) in astrocytes, and most of the astrocytes appeared as a confluent cobblestone layer. BrDU-immunostaining revealed a higher proliferative rate in the co-cultured astrocyte group compared to control (P < 0.01). Western blot and real-time quantitative PCR showed that rBMSCs increased Erk1 and Akt at both protein (P < 0.01) and RNA level (P < 0.01) in post-ischemic astrocytes. Additionally, Western blot revealed that co-culture with rBMSCs upregulated phosphorylation of Erk1 and Akt in astrocytes (P < 0.01). Ischemic astrocytes treated with MEK inhibitor (U0126) or PI3K inhibitor (LY29004) underwent apoptosis and cell death similar to the post-ischemic control group. Co-culture with rBMSCs significantly (P < 0.01) attenuated U0126 and LY29004 mediated insults. Furthermore, real-time PCR revealed that rBMSC co-culture increased RNA levels of GFAP, BDNF, and VEGF in astrocytes that had suffered ischemia (P < 0.01). These results indicate that rBMSCs enhance the recovery of post-ischemic astrocytes by activating the MEK/Akt and PI3K/Akt pathways in astrocytes, and increasing growth factor production by astrocytes.

Postischemic Treatment With a Cyclooxygenase-2 Inhibitor Reduces Blood-Brain Barrier Disruption and Leukocyte Infiltration Following Transient Focal Cerebral Ischemia in Rats

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Several studies suggest that cyclooxygenase (COX)-2 plays a pivotal role in the progression of ischemic brain damage. In the present study, we investigated the effects of selective inhibition of COX-2 with nimesulide with valeryl salicylate (VSA) on post-ischemic blood pressure, temperature, and PO2 levels in a rat model of transient focal cerebral ischemia. Post-ischemic treatment with the COX-2 inhibitor nimesulide markedly reduced the increase in PO2 levels in the ischemic cortex 24 h after stroke and diminished infarct size by 48% with respect to vehicle-treated animals after 3 days of reperfusion. Furthermore, nimesulide significantly attenuated the blood-brain barrier (BBB) damage and leukocyte infiltration following transient focal stroke. Neuroprotection afforded by nimesulide is observed even when the treatment is delayed until 6 h after the onset of ischemia, confirming a wide therapeutic window of COX-2 inhibitors in experimental stroke. On the other hand, selective inhibition of COX-1 with VSA had no significant effect on the evaluated parameters. These data suggest that COX-2 activity, but not COX-1 activity, contributes to the progression of ischemic brain injury and that the beneficial effects observed with non-selective COX inhibitors are probably associated to COX-2 rather than to COX-1 inhibition.

Treatment of Stroke in Rats With Bone Marrow Stem Cells Decreases Axonal Loss and Demyelination

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Axonal loss and demyelination are frequently observed in ischemic cerebrovascular diseases and contribute to neuropsychiatric impairments. Previous studies showed that human bone marrow stem cells (hBMSCs) improved functional neurological recovery in ischemic rats. In this study, we investigated the effect of hBMSCs on axonal fibers in ischemic brain. Rats were subjected to permanent middle cerebral artery occlusion (MCAo) and injected intravenously with 10^6 hBMSCs (encompass fluorescent cell group) or an equal volume of MCAo, and sacrificed at 14 days after MCAo. We examined axon and myelin damage using Bielschowsky and Luxol fast blue double staining, respectively, in the MCAo rats with hBMSC or PBS treatment. Nerve fiber damage was found in the white matter (WM) of the striatum (ST) and hippocampus (HC) of the ischemic hemisphere, and inflammatory cell infiltration was assessed using an in vitro ischemia model. After 4 h ischemic incubation in an anaerobic chamber, astrocytes were cultured without hBMSCs (control group) showed evident morphological and biochemical apoptosis features. A large number of condensed nuclei were observed, and many cells appeared as dark detached spheres or oval-shaped bodies. A cell viability assay showed that 20% of the astrocytes were dead. However, the introduction of hBMSCs remarkably reduced the apoptosis and cell death (to 1.5%), P < 0.01) in astrocytes, and most of the astrocytes appeared as a confluent cobblestone layer. BrDU-immunostaining revealed a higher proliferative rate in the co-cultured astrocyte group compared to control (P < 0.01). Western blot and real-time quantitative PCR showed that hBMSCs increased Erk1 and Akt at both protein (P < 0.01) and RNA level (P < 0.01) in post-ischemic astrocytes. Additionally, Western blot revealed that co-culture with hBMSCs upregulated phosphorylation of Erk1 and Akt in astrocytes (P < 0.01). Ischemic astrocytes treated with MEK inhibitor (U0126) or PI3K inhibitor (LY29004) underwent apoptosis and cell death similar to the post-ischemic control group. Co-culture with hBMSCs significantly (P < 0.01) attenuated U0126 and LY29004 mediated insults. Furthermore, real-time PCR revealed that hBMSC co-culture increased RNA levels of GFAP, BDNF, and VEGF in astrocytes that had suffered ischemia (P < 0.01). These results indicate that hBMSCs enhance the recovery of post-ischemic astrocytes by activating the MEK/Akt and PI3K/Akt pathways in astrocytes, and increasing growth factor production by astrocytes.
Differential Regulation of Aquaporin 4 and 9 Expression in Mouse Brain After Transient Focal Cerebral Ischemia

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Introduction: Aquaporins (AQP) are water channels that facilitate the diffusion of water across the plasma membranes of many types of cells. To date, 14 subtypes of AQP have been described. AQP4, expressed in rodent brain, AQP4, expressed on astrocyte endfeet, has been implicated in water homeostasis and in oedema formation. AQP9, expressed on astrocytes and catecholaminergic neurons, may be implicated in brain water and energy homeostasis and has been shown to be up-regulated in 48h after ischemia. The time course of expression of AQP4 and AQP9 after a transient cerebral ischemia in the mouse has never been studied, and we have therefore compared their expression patterns.

Material and Methods: In a model of mild ischemia in mice (CRD1), we transiently occluded the left middle cerebral artery for 30 minutes by a filament, followed by 1hour (n=2) or 2hours (n=4), 24hours (n=4) or 48hours (n=2) of reperfusion. Immunofluorescence staining for AQP4 and AQP9 was performed on perfused brain sections. Results: Within the infarct, there was no AQP4 and AQP9 labelling. In contrast, there was AQP4 and AQP9 immunoreactivity (ir) in the peri-infarct cortex: There was a low AQP4-ir 1 hour after ischemia. AQP4-ir increased on astrocyte endfeet around the blood vessels at 24hours, with a maximum at 48hours. An increase of the AQP9-ir was observed in astrocytes (processes and cell bodies) 6 hours after ischemia. This AQP9-ir increased progressively up to 48hours. No variation of the AQP9-ir was detected in catecholaminergic neurons. Conclusion: This time course shows an increase of AQP4-ir 24hours after ischemia. In contrast, AQP9-ir increases earlier after ischemia, AQP4 and AQP9 have also a different cellular distribution. These results indicate that AQP9 and AQP4 may play a different role in edema formation and in homeostasis after ischemic stroke. Indeed, AQP9 is also permeable to glycerol, urea and lactate. Early induction of AQP9 in astrocyte could be related with the uptake of the extracellular excess of lactate and glycerol. The implication of each AQP in edema formation needs further investigations.

Protective Effect of Prior Fimbria-fornix Deafferentation on Hippocampal CA1 Following Transient Forebrain Ischemia Is Mediated by GluR2 Expression

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Background: AMPA receptors (GluR) expressed in CA1 pyramidal neurons exhibit properties of calcium impermeable (GluR2 containing) receptors. Transient global ischemia causes delayed and specific CA1 pyramidal neuronal death. Fimbria/fornix deafferentation (FF lesion) is neuroprotective. We hypothesized that upregulation of GluR2 in these cells may be one of the underlying molecular mechanisms for this neuroprotection.

Methods: Adult male Wistar rats (n=12/group) were subjected to permanent focal stroke or varying periods (1, 2, 3, 4 hours) of transient focal stroke by intraluminal occlusion of the middle cerebral artery. Control rats (n=10) were perfused at 48 hours after ischemia. Neuronal survival was assessed by cresyl violet staining. Results: Infarct sizes were assessed at 48 hrs. Ethidium homodimerstaining was as assessed as a marker of cellular superoxide production. Brain MMP-9 was upregulated as an indicator of tissue destruction.

Conclusions: Neuroprotective effects of FF lesioning were observed in the ipsilateral CA1 only. FF lesioning induced the activation of NF-KB and prevented the upregulation of pro-inflammatory cytokines in the ipsilateral CA1. The effects of FF lesioning were blocked by the NF-KB inhibitor, ♯#GluR2 is a subunit of AMPA receptor, which is involved in glutamatergic excitation synapse. We demonstrated that GluR2 expression was increased in CA1 pyramidal neurons following ischemia, which was associated with increased neuronal survival. These results suggest that GluR2 may be a potential target for the development of new therapeutic strategies for stroke treatment.

Microplasmin Reduces Microvascular Damage and Blood-Brain Barrier Disruption Following Experimental Stroke

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Modern stroke therapeutic strategies utilize thrombolysis with rt-PA. About 9% of treated patients experience a thrombolysis-related secondary intracerebral hemorrhage. There is a need to find alternative thrombolytic substances with reduced adverse effects. We examined the influence of microplasmin (recombinantly generated truncated plasmin with thrombolytic action) on microvascular damage, blood brain barrier disruption and amount of endogenous IPA and uPA after focal ischemia and reperfusion in the rat. Male wistar rats were subjected to focal cerebral ischemia (2 hours) and reperfusion (24 hours) using the intraluminal thread model. Rats were divided into either treatment groups of 60 mg/kg (n=10) or 10 mg/kg (n=10) of microplasmin, 10 mg/kg (n=10) of sodium chloride, or 17 per cent of the ischemia period. Collagen type IV, a major component of both the microvascular basal lamina, was determined in brain tissue by means of immunohistochemistry. The results of microplasmin treatment showed that microplasmin treatment significantly reduced the amount of endogenous IPA and uPA after focal ischemia and reperfusion. The results suggest that microplasmin treatment is an effective therapeutic strategy for reducing microvascular damage and blood-brain barrier disruption after experimental stroke.
The Expression of Hypoxia-Inducible Factor-1 Targets in Neurons and Astrocytes and Their Dependence on p53 Function

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TITLe: The Expression of Hypoxia-inducible Factor-1 Targets in Neurons and Astrocytes and their Dependence on p53 Function. Hypoxic inducible factor-1α (HIF-1α) and p53 are transcription factors that are stabilized by hypoxia and induce gene expression in the stroke penumbra. The multiple gene products induced by these transcription factors in the penumbra likely significantly influence cell survival during this acute hypoxic challenge. Interestingly, prior studies, utilizing transformed cell lines, report that interactions between HIF-1α and p53 inhibit expression of HIF-1α targets while enhancing the expression of p53 targets. To determine if HIF-1α and p53 alter the activity of each other in neurons and astrocytes, we utilized quantitative PCR to examine the magnitude and temporal profile of induction of HIF-1α and p53 targets in primary neuron cultures and primary astrocyte cultures when exposed to severe (0.5% O2) hypoxia. We then evaluated the effect of loss of p53 function or reduced HIF-1α function on the expression of HIF-1α or p53 targets, respectively. Under these conditions of severe hypoxia, HIF-1α targets such as glucose transporter-1 (Glut-1) and vascular endothelial growth factor (VEGF), are upregulated at the level of protein. p53, on the other hand, is not induced under these conditions but enhanced the induction of p53 targets and astrocytes suggesting a unique role for HIF-1α and p53 interactions in astrocytes. Finally, reduction of HIF-1α expression did not alter expression of p53 targets in neurons. Taken together, these findings suggest that HIF-1α-target expression is highly induced in both neurons and astrocytes during hypoxia. Interactions of HIF-1α and p53 and the influences of these interactions on target expression of these transcription factors is likely cell-type specific being more prominent in astrocytes than neurons.

Vascular Pathophysiology/Thrombosis

Is the 1.5 cm Criterion for Lacunar Infarction Still Valid? Analysis of Mechanism of Deep Subcortical Infarction Using Diffusion-Weighted MRI and MR Angiography

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Background The ‘lacunar hypothesis’ has been challenged since small distance (~1.5cm) subcortical infarcts can be produced by middle cerebral artery disease (MCAD) or cardiomemboli (CE) while a larger infarct can occur without evidence of MCAD or CE. We aimed to reconsider lacunar hypothesis by assessing clinical and pathophysiologic aspects of subcortical infarcts. Methods During 18-month period, we studied consecutive patients who 1) had acute (~72 hours after onset), strictly deep subcortical MCA territory infarcts detected by diffusion weighted image (DWI) 2) underwent MR angiography. We classified the stroke mechanism as 1) MCAD if there was a corresponding atherothrombotic MCA vascular lesion, 2) CE if there were embolic heart diseases without MCAD, and 3) small vessel disease (SVD) if there was neither CE nor MCAD. SVD was further divided into definite SVD (dSVD, 0.1%–2.5% resolved lacunes) and probable SVD (pSVD, 0.1%–2.5% confluent lacunes). Results Among the 107 patients, 75 (70%) had SVD (39 pSVD and 36 dSVD), 23 (21%) had MCAD, and 9 (8%) had CE. The largest diameter of the infarct (mean = 52 ± 18 mm) was the largest in patients with CE (01.0 ± 12.5) followed by pSVD (21.3 ± 5.8), MCAD (20.3 ± 10.1) and dSVD (11.7 ± 2.7) (~0.01). The infarct size was greater in CE than that in MCAD (p < 0.05) or SVD (p < 0.01). The lesion in MCAD was larger than that in dSVD (p < 0.01), but was not larger than that in pSVD (p = 0.59) or SVD (p = 0.73). Patients with CE more often had cortical symptoms than SVD (p < 0.05) or MCAD+SV (p < 0.01). There were no differences in clinical syndrome and risk factors between MCAD and SVD, and pSVD or dSVD. Conclusions Subcortical Infarcts associated with CE are differentiated from MCAD or SVD by the size and clinical features. However, there are no clinical and epidemiological differences between MCAD and SVD, and pSVD and dSVD. There seems to be no rationale for 1.5cm criteria for ‘lacunar infarction’. The size variation of infarct in SVD may be caused by variable branching characteristics of lenticulostriate arteries.

Risk of Cerebral Venous Thrombosis and Novel Gene Polymorphisms of the Coagulatory and Fibrinolytic System

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Background Genetically determined thrombophilic conditions as FV Leiden (FVL) and the protein Z (PZ Intron F G79A) that is associated with low PZ plasma levels. We evaluated local and systemic pharmacokinetics and pharmodynamic analysis techniques: TAFI G-438A, PZ Intron F G79A, FVL and PT G20210A. Results The prevalence of FVL (OR 2.11, 95% CI 0.92–4.83, p = 0.05) and PT G20210A (OR 4.00, 95% CI 1.23–13.01, p = 0.02) was higher in patients with CVT as compared to controls. The A-allele frequency of the TAFI G-438A polymorphism tended to be less common in patients (21.3%) than in controls (26.9%). OR, 0.71; 95% CI = 0.45–1.12; p = 0.17). For the A-allele of the PZ G79A SNP, there was a tendency towards a lower prevalence of the A-allele in CVT (19.5% vs. 24.6%; OR, 0.77; 95% CI = 0.49–1.21; p = 0.31). Conclusion In this large series of CVT patients, a strong positive association with the established thrombophilic risk factors FVL and especially the PT G20210A mutation was confirmed. In contrast, our study found only relatively weak negative and statistically nonsignificant associations of CVT with the TAFI G-438A and the PZ Intron F G79A SNPs. However, even if weak, the association found was undirectional and of comparable degree as that described in peripheral venous thrombosis (TAI) and in juvenile stroke (P2) earlier.

Human Brain Pericytes Coordinate Microcirculatory Hemostasis Regulation In Vitro

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Brain capillary endothelial cells have a restricted expression of critical antithrombotic and fibrinolytic molecules (Stroke 1999:30;1677–1677). In order to define mechanisms of profound changes in the thrombotic and fibrinolytic microcirculation, we studied pericyte endothelial interactions in several brain blood barrier models. Human brain capillary endothelial cells (HBECs), co-cultured with but physically separate from human pericytes, had 36 ± 8 % (p < 0.05) reduction of tissue plasminogen activator (IPA) protein release and 36 ±5 % reduction of IPA mRNA (p < 0.05). In this co-culture system, plasminogen activator inhibitor-1 (PAI-1) protein, the principal inhibitor of IPA, was increased by 30 ± 11 % (p < 0.05). HBECs and pericytes grown together in mixed cultures produced 66 ± 17 % (p < 0.05) reduction in IPA levels. Finally, pericytes were characterized by robust levels of protease nexin-1 (PN1), an inhibitor of both IPA and of thrombin; pericyte PN1 mRNA was nearly 400-fold higher than that of HBEC, and Western blot studies showed pericyte (but not HBEC or astrocyte) release of abundant PAI-1 into conditioned media. In summary, brain pericytes induce restricted expression of endothelial IPA and increased expression of PAI-1, and have the capacity to synchronize and release protease nexin-1. The latter is capable of providing additional inhibition of IPA as well as acting as an anticoagulant by its antithrombin effects. These findings support an important and complex role for human brain pericytes as a regulator of hemostasis pathways within the microcirculation, with effects that are predominantly, but not exclusively, procoagulant.
Altered Expression of Apoptosis-Related Genes in Acute Human Stroke

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Background and Purpose: Studies in rodent models of ischemia demonstrate altered expression of genes that control programmed cell death. Interruption of the programmed cell death cascade decreases cell death in animal models. Whether programmed cell death contributes to human stroke is less well established.

Methods: Expression of caspase-3, Bcl-2, and PARP was determined by immunoblotting of brain samples removed from nine adult patients who underwent partial stroke removal surgery after stroke and progressive clinical deterioration. Brain tissue from five patients who died of non-neurologic causes with 5–23 h postmortem intervals was used as controls. Studies were approved by the U. of Pittsburgh IRB.

Results: Compared to activities in 10 subjects without acute illness matched for sex, age, and number of vascular risk factors, PARP activity was significantly increased at 24 and 48 h in patients after acute stroke when compared to controls.

Conclusion: Lowering tHcy by 3.70.81%, DD [p<0.001], vWF [p<0.001], and P189

Low Rate of Responsiveness to Aspirin in Acute Brain Ischemia: Association With Stroke Severity and Clinical Outcome

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Background and Purpose: Platelets play a critical role in the pathogenesis of acute brain ischemia. We hypothesized that the degree of inhibition of platelet function by aspirin is associated with the severity, clinical course and outcome of acute brain ischemia.

Methods: Patients presenting with acute brain ischemia were serially assessed by the NIH stroke scale (NIHSS) and by the modified Rankin Scale (mRS) at hospital discharge. Blood was collected within 36 h of symptom onset and 4 days later (or at hospital discharge). Platelet function was evaluated by conventional aggregometry using adenosine diphosphate as an inducer and under flow condition using the Cone and Platelet Analyzer (CPA; platelet adhesion measured as % of surface coverage).

Results: Sixty-three patients were included (65% male, age 63 ±12 yrs). Thirty-five percent received aspirin prior to symptom onset and all received aspirin prior to their platelet function evaluations. There was incomplete responsiveness to aspirin (aggregation<20%) at the baseline evaluation in 56% of patients and at the day-4 evaluation in 65% of patients. Low platelet responsiveness to aspirin at baseline was positively correlated with stroke severity (by aggregometry, 24:22% for NIHSS 0–5 (n=41); 40:32% for 6–15 (n=13) and 70:30% for NIHSS 15 (n=9; p=0.001)). By CPA, surface coverage of 5.2:2.2%, 6.4:2.6% and 2.1:1.1% respectively (p=0.002). Platelet aggregation at baseline was associated with early clinical course [28:26% for clinical improvement (n=42), 45:34% for clinically stable (n=16), and 52:43% for clinical deterioration (n=4; p=0.05)] and with functional outcome for at discharge: mRS 0–2 (n=34; 4:29% for ≤3 h and 39:29% for 3–4 h and 68:35% for mRS 0 or death (n=9; p=0.001)).

Conclusions: Incomplete responsiveness to aspirin in acute brain ischemia is frequent, and is associated with worse neurological deficits at stroke onset, early clinical deterioration and poorer functional outcome. The CPA method was found to be a useful point-of-care testing of the response to aspirin.

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Prevalence of Vulnerable Carotid Plaques in Asymptomatic Individuals With Moderate to Severe Carotid Stenosis

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Background: Despite natural history data suggesting the overall risk of thrombo-embolic stroke from asymptomatic carotid stenosis to be low, the findings of the Asymptomatic Carotid Surgery Trial (ACST) suggest a significant benefit for the surgical group. It is likely therefore that within this population there exists a sub-group which may be at higher risk of stroke in whom surgery is appropriate.

Methods: Histological analysis was performed on plaques from 14 asymptomatic individuals with moderate carotid stenosis, enrolled in the ACST to determine the prevalence of high-risk/vulnerable plaques. Sections were selected and viewed in a random order to determine the thickness of the fibrous cap and lipid core and quantify the inflammatory infiltrate. Plaques were deemed vulnerable if the fibrous cap was thin, eroded, or ruptured; if the lipid core occupied at least half of the plaque area; or if there was an abundance of inflammatory cells. 27 (44%) patients sections, 12% of 40 ACST individuals. 22 (81%) plaque sections had thin, eroded or ruptured fibrous caps; 2 (7%) had large lipid cores. Of the remainder plaque sections, with relatively thick fibrous caps and small lipid cores, an additional 2 (11%) were deemed vulnerable by the presence of a high inflammatory infiltrate. The prevalence of vulnerable carotid plaques was 71%. Conclusions: Asymptomatic individuals with moderate to severe carotid stenosis harbour plaques of differing vulnerability with a high prevalence of high-risk lesions. Existing non-invasive imaging strategies capable of identifying these lesions offer the hope of improving risk stratification in this group.

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Polymorphism of Icam-1 Gene Is a Risk Factor for Cerebral Ischemia Due to Spontaneous Cervical Arterial Dissection

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Objective: Much of the processes in the pathogenesis of cerebral ischemia affecting young people is still unclear. Since recent data have focused the attention on infection and inflammation, the role of genetic factors involved in the process of cellular death was studied. Several studies have focused on the role of Icam-1 in the inflammatory process in various pathologies, but the role of Icam-1 in cerebral ischemia is still unclear. We therefore aimed to evaluate the role of a polymorphism on the Icam-1 gene in the pathogenesis of cerebral ischemia due to spontaneous cervical arterial dissection.

Methods: We selected 100 consecutive patients with a diagnosis of spontaneous cervical arterial dissection and ischemic stroke. They were then divided into 2 groups: control (n=50), and the study group (n=50). The control group had no history of arterial dissection or cerebrovascular disease. The patients were genotyped for the T1486C polymorphism of the Icam-1 gene. The mean age of the study group was 46.2 ± 10.1 years and the control group 46.6 ± 11.7 years. The chi-square test was used to evaluate the significance of differences between groups.

Results: The genotype distribution for the T1486C polymorphism was in accordance with the Hardy-Weinberg equilibrium. The allele frequencies were 0.58 in the study group and 0.60 in the control group. We found no differences of the allele and genotypes frequencies between the study and the control group. These results suggest that the polymorphism of the Icam-1 gene is not a risk factor for ischemic stroke due to spontaneous cervical arterial dissection.

Conclusion: The study did not show any association between the polymorphism of the Icam-1 gene and the risk of cerebral ischemia due to spontaneous cervical arterial dissection.
inflammation as relevant mechanisms, we decided to investigate common polymorphisms of the gene coding for the most important proinflammatory cytokine interleukin 6 (IL-6) and for the intercellular adhesion molecule 1 (ICAM-1), which is essential in the initiation of the inflammatory response at the endothelial surface. Patients and Methods We studied the promoter G-176C polymorphism of the IL-6 gene and the A696G polymorphism of the ICAM-1 gene in 153 Caucasian patients with cerebral ischemia under the age of 50, and in a population control group of 204 subjects. Since we found a tight association between the ICAM-1 A696G GG genotype and the subgroup of patients with cerebral arterial dissection (CAD), we aimed to confirm this finding by analysing the ICAM-1 polymorphism in a second group of young patients selected by CAD. Results We found a significant association between the GG genotype of the ICAM-1 A696G polymorphism and stroke, with an OR of 1.85 (95%CI 1.03–3.43; p = 0.005). The association was explained by a strong correlation of this genotype with the a priori defined subgroup of 31 CAD patients (OR 3.38 CI 1.37–8.27; p = 0.001). This was confirmed in the second study group of CAD patients, where a higher frequency of the GG genotype (OR 2.87 CI 1.34–6.20; p = 0.005) was found, accordingly. Furthermore, we found a non-significant association between the GG genotype of the IL-6 -176G/C polymorphism and stroke (OR 1.94, CI 0.86–4.23 and CAD (p = 0.14).

Conclusion We demonstrated that the G allele of the ICAM-1 A696G polymorphism is a risk factor for cerebral ischemia caused by cerebral arterial dissection. This strongly indicates that proinflammatory mechanisms may play a role in the pathogenesis of this condition.

P191 Patterned Pathological Analysis of Debris Collected in Filters in Cas Procedures
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PURPOSE: To evaluate the volume and type of debris collected during endovascular stent placement in patients with carotid atherosomatous disease. MATERIAL AND METHODS: We studied 121 consecutive cases of elective carotid artery stent implantation with the use of distal protection filter. The material collected from the protection device was centrifuged and evaluated for volume ultrasonically studied to analyze the type of material. RESULTS: Ultrasonic study revealed the presence of fibrin and platelets, foamy macrophages, cellular debris, cholesterol crystals, collagen fibers, smooth muscle fibers, calcium and unidentified fibrillate and amorphous material According to the volume divided in 4 groups Group 0 had less than 0.001 ml (1 A) Group 1 had material between 0.001 – 0.005 ml (1 and 5 A) Group 2 had material between 0.005 and 0.01 ml (5 and 10 A) Group 3 had more than 0.01 ml of material (more than 10 A)

N. Cases Cholesterol Cell debris Cholest Cell debris
Less than 1 A (43.8%) 2 (3.4%) 0 (0)
Less than 5 A (60.3%) 13 (25.2%) 21 (52.5%) 11 (27.5%)
Less than 10 A (23.7%) 3 (3.0%) 13 (61.0%) 7 (33.0%)
More than 10 A (5.7%) 7 (100%) 7 (85.0%) 7 (100%)

CONCLUSION: Protection filters collect debris of significant quantity during carotid artery stent implantation. Ultrasonic analysis shows (confirms) that the material collected is dislocated from the atherosclerotic plaques. Protection devices have the potential to further reduce neurological complications.

P192 Telmisanat, a Selective Angiotensin II Type 1 Receptor Blocker, Improves the Lower Limit of Cerebral Blood Flow Autoregulation in Spontaneously Hypertensive Rats: Effects on Superoxide Production, NADPH Oxidase Expression, and Vascular Remodeling
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Objectives: The aim of the present study was to assess the effects of chronic telmisanat treatment on the lower limit of cerebral blood flow (CBF) autoregulation, superoxide production, NADPH oxidase expression and vascular remodeling of the middle cerebral artery (MCA) in spontaneously hypertensive rats (SHR). Methods: Male SHR (16 weeks of age) were orally treated with either low-dose telmisanat (0.3 mg/kg/day), high-dose telmisanat (3 mg/kg/day), or vehicle for 4 weeks. CBF of the parietal cortex was then continuously monitored with laser Doppler flowmetry in 7 rats of each group under anesthesia. The lower limit of CBF autoregulation was defined as mean arterial blood pressure at which CBF decreased by 10% autoregulation was defined as mean arterial blood pressure at which CBF decreased by 10%. Results: Blood pressure was significantly lower in high-dose group (114 ± 2 mmHg, mean ± SEM) than in the other groups (p < 0.0001), although no significant difference was observed between low-dose (164 ± 4) and vehicle group (117 ± 3). The lower limit of CBF autoregulation was significantly lower in low-dose (135 ± 2 mmHg) and high-dose groups (118 ± 0) than in vehicle group (131 ± 3). Production of superoxide significantly decreased in low (16.5 ± 6.8 % of surface area) and high-dose group (18.0 ± 7.8), as compared with vehicle group (47.9 ± 3.6, p < 0.01). Numbers of p22phox positive endothelium in MCA section tended to be smaller in high-dose group (181 ± 14) than in vehicle group (296 ± 63). Treatment with telmisanat of either high or low dose significantly increased the external diameter and reduced the medial thickness of MCA, as compared with vehicle group, indicating improved vascular remodeling. Conclusion: Inhibition of hypertension-induced cerebrovascular remodeling and attenuation of superoxide production with telmisanat may be the basis for improved CBF autoregulation. Furthermore, telmisanat may provide vascular protection beyond lowering blood pressure.

P193 Circulating Endothelial Microparticles in Acute Stroke: Relation to Clinical Severity, Lesion Volume, and Outcome
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Background and purpose: Elevated endothelial cell membrane microparticles (EC MP) in blood have been demonstrated in various diseases with a vascular injury component. The aim of this study was to investigate if circulating EC MP are related to outcome after acute stroke and to the ischemic brain lesion volume. Methods: EC MP were analyzed in the blood of 42 acute stroke patients (AS): 20 patients with National Institutes of Health Stroke Scale (NIHSS) scores < 5 were classified as mild stroke (MS) (median NIHSS = 2, 25th-75th%: 0–2), while the other 22 patients with NIHSS ≥5 (NIHSS=12; 6–21) were classified as moderately to severely severe stroke (SS). Peripheral venous blood samples were collected at a median time of 36 hours after the onset of clinical symptoms. Blood samples of 23 age matched control volunteers (CTRL) were used for comparison. EC MP were identified by antibodies to EC antigen CD106 (endothelial), and the highly specific CD141 (xe-cadherin) using a two-colour flow cytometry assay. Patient, white, and red blood cell MP were identified using cell specific antibodies to CD41, CD45, and CD25, respectively. Lesion volume was measured on magnetic resonance diffusion-weighted imaging (DWI) and clinical outcome was based on the Rankin score at hospital discharge. Results: Plasma counts of CD106+ CD41−DC45− EC MP were elevated in SS (median: 25.7% ± 85.6/0.10 µL) as compared to CTRL (at 154/0.201–624/0.10 µL; p = 0.014). Moreover, CD105+ CD41−DC45+ EC MP were elevated in SS (261/0.137–433/0.10 µL) when compared to MS (15/0.39–192/0.10 µL; p = 0.001) and the CTRL group (140/0.79–247/0.10 µL; p = 0.031). Interestingly, CD105+ CD41+DC45+ EC MP in the AS group were significantly correlated (p = 0.005; r = 0.45) with brain lesion volume on DWI. CD110+ CD41−CD45− EC MP in the admission AS samples correlated highly (p = 0.007; r = 0.54) with the Rankin score as did CD105+ CD41+DC45+ EC MP (p = 0.007; r = 0.44). Conclusions: Specific pheno-types of EC MP in the plasma samples of stroke patients were associated with stroke severity, ischemic lesion volume and clinical outcome. Analysis of EC MP in peripheral blood of stroke patients could be of diagnostic and prognostic use.

P194 Effects of Stroke-Related Comorbidities, Impairments, and Complications on Stroke Survivors’ Length of Stay in Rehabilitation
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Objectives: The purpose of this study was to describe the comorbidities, impairments, and complications experienced by stroke survivors during inpatient rehabilitation and to identify comorbidities, impairments, and complications that contribute to inpatient length of stay (LOS). Methods: The sample was 97 stroke survivors, with an average age of 66.2 (SD 8.84), who were discharged home with spousal caregivers. Demographic data, side and type of stroke, stroke-related impairments, complications, and comorbidities were abstracted from the stroke survivor’s chart. In addition to descriptive statistics (mean, standard deviation, and range), Pearson Product-Moment Correlations were computed among the variables of interest. Because these variables were intercorrelated, multiple regression analysis was used to examine the unique contributions of the age, gender, socioeconomic status, number of impairments and number of complications to the rehabilitation LOS. Results: The mean LOS was 45.4 days (Median = 24.5 days; Mode = 11 days). Stroke survivors experienced an

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average of 2.4 stroke-related comorbidities (SD = .85, range 0–6). Only 2 (2.1%) stroke survivors experienced no stroke-related comorbid conditions and 57 (59.4%) experienced ≥3; hypertension was the most common comorbidity (86.3%). Stroke survivors averaged 6.9 (SD = 2.78, range 2–13) stroke-related impairments; the most common was hemiparesis (n = 81, 64.4%). On average, stroke survivors experienced 3.9 complications (SD = .316, range 0–13); the most common complication was depression (n = 43, 44.8%). The overall regression model predicted 33% of the variance in the rehabilitation LOS, which was significant (F(6, 89) = 7.39; p < .001). The number of complications (t(95) = 5.18; p < .0001) predicted the rehabilitation LOS over and above the other variables in the model. **Conclusions:** Recovery from stroke depends on environments; prevention, rapid recognition, and effective treatment of medical complications; and lifestyle education and pharmaceutical treatment of stroke-related comorbidities to prevent recurrent strokes are dependent upon a successful interdisciplinary rehabilitation team that includes the stroke survivor and the family caregiver.

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**Stroke Educational Intervention for Middle School Students: Refining the FAST Program**

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In spite of our increased societal emphasis on promoting healthy behaviors, the incidence of diabetes, obesity, smoking, hypertension and other stroke risk factors continue to escalate each year in the U.S. Thus, the importance of developing effective stroke educational programs targeted at younger Americans to reduce their stroke risk. **Purpose:** Building upon prior pilot study results, this project tested the further refinement of the FAST stroke educational preventive program for middle school students that concentrated on knowledge, attitudinal, and behavioral changes. **Method:** A convenience sample of middle school students between the ages of 10–14 years were used. After obtaining school, parental, and student permissions, the FAST stroke educational program was implemented which was comprised of 5 components: pretest of stroke warning signs and risk factors; a 50 minute educational program; a posttest; educational reinforcements at 1 month; and a long-term posttest given at 8 weeks. **Results:** Seventy-two students who were primarily Caucasian participated with the average age of 13.4 years and 55% female. Repeated measures data analysis revealed significant improvement in students’ knowledge of stroke risk factors from pretest, posttest, to long-term posttest (F = 13.2, p <.001). In addition, there were significant gains in knowledge of stroke warning signs and symptoms from pretest, posttest, to long-term posttest (F = 10.38, p <.002). Some of the other findings revealed that over 60% of the subjects recently had a family member or friend who had a stroke, but over 95% at pretest were not confident in identifying at least one stroke symptom. At pretest, subjects self-selected a stroke risk behavior that they wanted to reduce and at long-term posttest over 54% indicated that they had made progress in achieving their goal. **Conclusion:** The refined version of the FAST stroke educational program significantly improves middle school students’ knowledge of stroke risk factors and warning signs and symptoms over a two month period as well as enabled progress in reducing a stroke risk behavior. Additional research is needed with a larger more culturally diverse sample as well as development of this program to increase greater long-term results.

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**Cognitive and Physical Performance of Patients With Asymptomatic Carotid Artery Disease**

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Background and Purpose: The purpose of this study was to determine if patients with asymptomatic carotid artery stenosis and occlusion demonstrate deficits in cognitive and physical performance. The relationship between cognitive measures and performance of instrumental activities of daily living was examined. Methods: Thirty-nine patients with asymptomatic carotid artery stenosis and occlusions ages 42–84 years, 14 females, and 25 males were tested. Cognition was assessed via the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and the Executive Interview (EXIT). Physical performance was assessed via the Physical Performance Test (PPT), and the Lawton Instrumental Activities of Daily Living (IADL) scale. Results: Decreased performance on RBANS visuospatial and constructional abilities for domains were found for patients with all levels of stenosis and occlusion; deficits in the immediate memory, attention and visuospatial/constructional domains were found for the moderate stenosis subgroup, and deficits in all domains except language were found in the severe stenosis group. There were significant findings on the EXIT. Decreased performance on the PPT was identified in all 3 subgroups. The Lawton IADL did not identify any decrease in performance. Conclusions: Deficits in cognitive and physical function were found in this observational study of patients with asymptomatic carotid artery stenosis and occlusion, indicating the need for development of specific intervention and exercise programs. These domains of function and the potential change in their status needs to be considered when patients are being evaluated for interventions to manage their carotid artery disease.

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**Successful Rapid Implementation of the NIH Stroke Scale in a Stroke Unit**

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BACKGROUND & PURPOSE: The National Institutes of Health Stroke Scale (NIHSS) is accepted by the stroke community as the definitive clinical examination to assess stroke severity. It has high inter-rater reliability and correlates acute stroke severity. It has been validated as a tool for concise rapid neurological assessment, clear and objective communication between healthcare professionals, and monitoring and guiding stroke treatment strategies. The purpose of this study is to examine barriers to the implementation and use of the NIHSS by registered nurses on a stroke unit. METHODS: Providence St Vincent Medical Center cares for approximately 450 stroke patients per year. In 2003, the hospital and nursing administration made the adaptation of the NIHSS a quality improvement goal. Use of the scale was sporadic and a quality initiative was launched to address this. Approval was obtained through the hospital’s institutional review board. Nursing staff were surveyed in January 2004 to determine the nurse-perceived barriers to the routine use of the NIHSS. The results of the survey were then used to create interventions aimed at targeted barriers. The survey will be re-distributed in September 2004 to verify results of the quality improvement initiative and guide further interventions. RESULTS: Survey results were used to guide strategies for patient assessment, stroke nursing education, and daily stroke team interdisciplinary rounds. NIHSS assessment within twelve hours of stroke patient admission increased from 12% to 61% within six months. The nurses have now been linked to an existing outcomes database (ASA Get With The Guidelines) to assess acute stroke treatment and inpatient management outcomes. CONCLUSIONS: A survey-based method to identify nurse-perceived barriers combined with targeted interventions forms a successful strategy for rapid NIHSS implementation. -The NIHSS can be successfully adopted over a short time period to improve nursing stroke patient assessments. This data can be linked to a database and thus provide essential information to study acute stroke treatment and inpatient medical management outcomes.

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**The Stroke Self-Management Program is Associated With Increased Participation in Community-Dwelling Stroke Survivors**

Maria P Huijbregts, Baycrest Ctr for Geriatric Care, Toronto, Canada; Robert Teasell, Univ of Western Ontario, London, Canada; David Steiner, Baycrest Ctr for Geriatric Care, Toronto, Canada; Anita M Myers, Univ of Waterloo, Waterloo, Canada

**Background and Purpose:** While it is recognized that stroke survivors have needs beyond acute care and rehabilitation, there are no formal guidelines for community stroke programs. Educational programs typically lead to improvements in knowledge, but not in well-being. Self-management programs, focusing on self-efficacy, behaviour change, social support and problem-solving skills may be more effective in helping individuals deal with stroke. Therefore, the Stroke Self Management Program (SSMP) was developed and evaluated in comparison to the Canadian Heart and Stroke Foundation’s Living With Stroke (LWS) education program. **Methods:** This longitudinal cohort study used a theory-driven evaluation approach. Data was collected at baseline, program completion, and three-month follow-up. The primary outcomes were the Reintegration to Normal Living Index (RLN) and participation in formal exercise. Other data sources included a battery of stroke outcomes assessments, participant focus groups and program records. Between- and within group differences were examined using qualitative and quantitative analysis, including analysis of variance and logistic regression. **Results:** Thirty stroke survivors and 16 care partners took part. On average, stroke participants were in their late 60’s and two years post stroke. The outcome evaluation showed that at discharge (p = .02) and follow-up (p = .04), a higher percentage of SSMP clients were enrolled in formal exercise classes. Only the SSMP group improved significantly on the RLN (p = .04) and on the balance confidence scales (p < .001). This group also attained many of their individual short-term goals (78%) and overall long-term goal attainment was better than the expected level. Both groups reported general enjoyment, greater awareness and social support, but SSMP clients also reported benefits from the individual goal setting, problem-solving and exercise components. **Conclusions:** Cost-effective community programs are urgently needed to fill the existing gap in the continuum of stroke care. The self-management approach is associated with post-stroke indicators of improved well-being and participation. The preliminary findings should be replicated with a larger sample.

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**Psychometric Testing of the Revised 15-Item Bakas Caregiving Outcomes Scale**

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**Background and Purpose:** Family caregivers of stroke survivors experience a variety of negative social, emotional, and health-related outcomes as a result of providing care. While a number of outcome measures focusing on caregiver health are often too generic to be useful for a situation-specific instrument measuring life changes resulting from providing care. The purpose of this study was to psychometrically test the Revised 15-item Bakas Caregiving Outcomes Scale (BCOS). **Methods:** Psychometric testing of the BCOS with a sample of 147 family caregivers of stroke survivors (73% were caregivers enrolled in a longitudinal cohort study) was conducted using item analysis, Cronbach’s alpha, paired t correlation, factor analysis, and hierarchical multiple regression guided by a conceptual model. Caregivers were predominately female (78%), Caucasian (68.0%) or African American (29.9%), and either married or cohabiting. NS) was provided for the BCOS, with item-total correlations ranging from .41 to .74. Unidimensionality was supported by factor loadings ranging from .45 to .79. Using hierarchical multiple regression, 32% of the BCOS variance was explained by constructs in the conceptual model [F(13, 130) = 6.25, p < .001]. Criterion-related validity was supported by correlations with the SF-36 General Health Subscale (r = -.32, p < .001) and a criterion variable measuring how caregivers’ lives changed overall (r = -.67, p < .001). **Conclusions:** The 15-item BCOS is a brief, easy to administer instrument that has satisfactory evidence of reliability and validity in family caregivers of stroke survivors. The BCOS could serve as a valuable measure in research, as well as an assessment tool to identify family caregivers in need of intervention.
Outcomes Research: Quality of Care, Cost, and Outcomes

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Standardized Stroke Orders and Adherence to Best Practices in the California Acute Stroke Pilot Registry

S C Johnston, Univ of California, San Francisco, CA; CASPR Investigators

Introduction: Standardized order templates have been credited with improving care for a number of common medical conditions. We sought to determine whether use of stroke specific orders would be associated with improvement in stroke care. Methods: All patients with a discharge diagnosis of ischemic stroke were identified from seven hospitals in California participating in a CDC-sponsored Coverdell Acute Stroke Pilot Registry. Baseline data were collected in Year 1 prior to implementation of standardized discharge orders at the beginning of Year 2. To evaluate treatment performance, we created a scale based on 6 points of care: receipt of thrombolytics, antibiotic medications within 48 hours, prophylaxis for deep venous thrombosis (DVT), smoking cessation counseling, and statins and antibiotic medications prescribed at discharge. Scoring in each area was based on optimal treatment, defined as receiving or having a valid contraindication to a given intervention. For example patients ineligible for thrombolytics because of delayed arrival or unknown stroke onset time were counted as optimally treated. Patients accumulated one point for each area in which treatment was optimal, for a total score ranging from 0 to 6 (perfect treatment). Results: A total of 475 patients with ischemic stroke were evaluated. Optimal treatment improved in several specific areas of care (Table). Total patient scores over all six interventions ranged from 2 to 6 for both years, with 59% of patients receiving a perfect score in Year 2 compared to 39% in Year 1 (p<0.0001, Wilcoxon). Conclusions: Implementation of standardized stroke orders and registry monitoring was associated with improvements in utilization of a number of proven interventions. Although these data are observational, they demonstrate the potential impact of simple system-wide interventions in improving care of stroke.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Year 1 (n=223) N (%)</th>
<th>Year 2 (n=252) N (%)</th>
<th>p-value1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal Treatment</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Thrombolytics</td>
<td>203 (91%)</td>
<td>231 (92%)</td>
<td>0.81</td>
</tr>
<tr>
<td>Antibiotics (in 48 hrs)</td>
<td>210 (94%)</td>
<td>245 (97%)</td>
<td>0.10</td>
</tr>
<tr>
<td>DVT prophylaxis</td>
<td>180 (81%)</td>
<td>235 (93%)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Smoking cessation counseling</td>
<td>197 (88%)</td>
<td>230 (91%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Antibiotics (discharge)</td>
<td>199 (89%)</td>
<td>241 (96%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Statins (discharge)</td>
<td>151 (68%)</td>
<td>199 (79%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Overall score</td>
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<td>&lt;0.0001</td>
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<tr>
<td>Total score = 6</td>
<td>86 (39%)</td>
<td>150 (59%)</td>
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</tr>
<tr>
<td>Total score = 5</td>
<td>88 (39%)</td>
<td>79 (31%)</td>
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<td>Total score = 4</td>
<td>38 (17%)</td>
<td>19 (8%)</td>
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<tr>
<td>Total score = 3</td>
<td>10 (4%)</td>
<td>2 (1%)</td>
<td></td>
</tr>
<tr>
<td>Total score = 2</td>
<td>1 (1%)</td>
<td>2 (1%)</td>
<td></td>
</tr>
</tbody>
</table>

1 x2 tests for each intervention; Wilcoxon test for difference in overall scores between Year 1 and Year 2

Summary of Medical Resource Utilization and Costs Associated With Hospital Inpatient Treatment of Acute Stroke

Thomas F Goss, Covance Health Economics and Services Inc, Gaithersburg, MD; Michael S Mafilios, Covance Health Economics and Outcomes Research, Gaithersburg, MD; Weidong Peng, Inst for Clinical Evaluative Sciences, Toronto, Canada; Joseph A Reblindo, G D Parker, Covance Health Economics and Outcomes Services Inc, Gaithersburg, MD; Charles A Marotta, AstraZeneca Pharmaceuticals, Inc, Wilmington, DE

Background: Nearly 70% of stroke patients (pts) in the U.S. are Medicare beneficiaries, for whom inpatient hospital reimbursement is based on prospective payment using diagnosis-related groups. We assessed the resource intensity of stroke therapy (tx), including charges (chg), costs, and payments (pmt), to inform policy and clinical decision makers as they evaluate the impact of tx for stroke. This analysis documents substantial differences between chg and costs commonly resulting in Medicare payments below institutions' costs. Methods: We analyzed 100% of submitted claims from FY2002 Medicare Provider Analysis and Review (MedPAR) data to examine chg, length of stay (LOS) and pmt for admissions for acute ischemic stroke (AIS) or hemorrhagic stroke (HS) (ICD-9-CM principal diagnosis (dx) codes 430.xx, 431.xx, 432.xx, 433.xx, 434.xx, 435.xx). We also examined administration of thrombolytic tx (TT) as denoted by ICD-9 procedure code of 99.10. Results: Claims were examined for 476,036 hospital discharges for stroke (67% AIS and 33% HS). TT use was documented in <1% of all cases. Chg for TT pmt were substantially higher in the TT group than in the no TT group. Differences between chg, costs and pmt are illustrated by the AIS group: average (avg) pmt for admissions associated with AIS dx were 21% of submitted chg for AIS cases receiving TT, and 35% of submitted chg for AIS cases with no TT. When costs were estimated using standard Medicare cost report data, avg pmt ranged from 52% to 76% of estimated avg costs, indicating that hospitals lose money on the majority of cases. The avg chg and pmt were highest for ICD-9 dx code 430.xx, subarachnoid hemorrhage, which had the lowest number of pts and highest LOS of all the principal dx. Conclusions: The inpatient chg and pmt for acute stroke care vary widely according to dx, LOS, and use of TT. Payment is substantially below estimated costs of these cases, and hospitals' (in particular stroke centers) ability to adopt new therapies for the tx of stroke pts will be limited by Medicare reimbursement. The reimbursement environment for the tx of a stroke is a cause for concern for health policy and clinical decision makers. Hospitals’ ability to adopt improved therapies in the tx of stroke pts is at risk in the future based on the trends reported here.

Validating Administrative Databases Using a Registry Data Source: Implications for Research on Quality of Stroke Care

M P Lindsay, Inst for Clinical Evaluative Sciences, Toronto, Canada; Moira K Kapral, Faculty of Med, Univ of Toronto, Toronto, Canada; Jiming Fang, Jack V Tu, Andreas Laupacis, Inst for Clinical Evaluative Sciences, Toronto, Canada

Objectives: Research into the quality of stroke care is dependent on the availability of valid and accurate data. Key sources of primary and secondary data are available in Canada for measuring the quality of stroke care, however, the quality of administrative databases for use in stroke care research is unknown. The objective of this study is to evaluate the accuracy and completeness of available administrative data compared to Registry data, to determine the appropriateness of using the administrative data for research into quality of stroke care. Methods: Case records contained in Phases I & II of the Registry of the Canadian Stroke Network (RCSN) were linked to corresponding cases in two administrative databases using a unique health number, birth date, gender and stroke date. Specific data elements relevant to stroke care research were then extracted and compared, such as demographics, diagnosis, interventions, and patient disposition at the end of the episode of care. Levels of agreement between data sources were determined using descriptive and kappa statistics. Where poor agreement was found, additional descriptive analysis and manual review of the data was conducted to further understand the nature of the discrepancies. Results: From RCSN data, 800 inpatients and 210 patients discharged from the ED were identified for this study. We were able to link 95% of inpatients and 98% of ED patients across data sources. In 20% of the inpatients and 55% of the patients discharged directly from the ED, there was some disagreement on the final diagnoses between the databases, the majority disagreements for ischemic strokes. Date of birth agreement was 96%, length of stay was 90% within 24 hours, and deaths had 99% agreement overall. Conclusions: The administrative databases examined were found to be reliable for key data elements compared to primary data contained in a registry. This study found that diagnosis was found to have poorer agreement than other data elements, which may create challenges in initially identifying and underestimating a cohort for study. Since administrative databases are more readily available, contain higher patient volumes, and are more cost effective, they could be considered to answer some stroke care research questions.

Canadian Stroke Quality of Care Study: Identification of Performance Indicators for Acute Stroke Care

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Objectives: Initiatives such as regionalization of stroke care, guideline development, and quality improvement efforts, are best supported using clearly defined performance measures and accurate high quality data sources. The primary objective of this study is to identify and define a core set of quality of care indicators to evaluate the ED and inpatient episodes of acute ischemic stroke care. Methods: In the Spring of 2004 a Canadian expert advisory panel was convened to identify and refine key quality measures for acute stroke following a Modified-Delphi process. This study updated a similar study conducted in the United States five years prior to this initiative. An extensive review of the stroke literature was undertaken to identify current practice guidelines, randomized controlled trials, systematic reviews and meta-analyses, and large observational studies of best-practice for stroke care. From the literature, a master list of quality indicators was compiled to measure the quality of care for acute ischemic stroke management and to provide evidence-based support for the evaluation of these indicators. The panel members reviewed and rated fifty-one indicators along six dimensions of care. The final 27 indicators were rated overall by a majority of panel members and underwent subsequent feasibility testing. Of these 23 indicators, 16 were also rated overall by at least 75% of panelists in the original US study. Conclusions: A core set of validated Canadian quality of care indicators for acute ischemic stroke are now available for monitoring stroke care during the ED and inpatient periods, to serve as a basis for quality improvement initiatives, and provide a foundation for ongoing research in acute stroke management.

Cost-Effectiveness of Percutaneous PFO Closure Compared With Medical Management in the Prevention of Recurrent Ischemic Stroke

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Percutaneous closure of a patent foramen ovale (PFO) is a new treatment option for the tx of stroke pts will be limited by Medicare reimbursement. The reimbursement environment for the tx of a stroke is a cause for concern for health policy and clinical decision makers. Hospitals’ ability to adopt improved therapies in the tx of stroke pts is at risk in the future based on the trends reported here.

Poster Presentations
Patients were followed in 3-month cycles until death using a Markov model consisting of 5 states of health: well, recurrent stroke, gastrointestinal bleed, intracranial hemorrhage, dead. Only direct medical costs were considered. Model parameters were taken from published literature and expert opinion. Effectiveness was measured in quality-adjusted life years (QALYs). Strategies were compared using incremental cost-effectiveness ratios (ICERs). Sensitivity analyses were performed over a wide range of plausible values. Results: Given our baseline assumptions, PFO closure was the most effective strategy, 12.13 QALYs, at a cost of $76,989. Aspirin was second-most effective, and produced 11.06 QALYs at a cost of $68,911. The warfarin strategy was dominated. The ICER of percutaneous closure compared with aspirin was $7,820/QALY. The model was insensitive to changes in patient age up to 50 years, overall recurrent stroke rate, and to a doubling of procedural costs. The ICER of PFO closure was more than $50,000/QALY if risk reduction for recurrent stroke with closure dropped below 20% as compared with aspirin (baseline = 77%). Conclusion: Percutaneous PFO closure may be a cost-effective strategy to prevent recurrent ischemic stroke in patients with PFO if it reduces recurrent stroke risk over the aspirin strategy by at least 20%. Ongoing trials will help elucidate whether the risk reduction from percutaneous PFO closure for recurrent stroke is within this range.

The Cost of Comprehensive Stroke Care: 2003–2004 Houston Hospital Experience
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Background: Length of stay (LOS) and total charges are traditionally used to describe the hospital expenditures on acute stroke patients. We report cost assignment in relation to provision of aggressive brain rescue by a comprehensive tri-hospital stroke team. Methods: Patients with DRG 14 assignment (acute ischemic or non-operative hemorrhagic stroke) admitted between January 2003 and July 2004 were included in the study. Variable direct reflecting case severity with corresponding rescue practices and excluding overhead costs outside of practitioner control is reported. Results: A total of 921 patients were studied: 539 (59%) ischemic and 382 non-operative hemorrhagic strokes. Ischemic stroke patients had an average cost/case of $4820 ± $197 of which 24% ($1136 ± $37) was incurred within the first 24 hours of admission; LOS averaged 6 ± 0.5 days/case, 6.7% in-hospital mortality rate. Non-operative hemorrhagic stroke averaged $5038 ± $376 with 26% ($1287 ± $37) in the first 24 hours; LOS 5 ± 0.3 days, 32.7% mortality. IV tPA was given in 66 ischemic stroke patients: $5453 ± $546 with 22% ($1214 ± $55) in the first 24 hours; LOS 6.2 ± 0.7, 19% mortality. Intravascular (IA) treatment was provided to 30 patients including 13 after IV: average primary IA cost $970 ± $970 with 38% ($3349 ± $589) in the first 24 hours; LOS 6.2 ± 2.3, 14.3% mortality. Further analysis of APR-DRG assignment yielded treatment allocation and $589) in the first 24 hours; LOS 6

Cost of Illness Studies in Stroke: A Multicountry Review
Penny Reeves, Fourth Hurdle Consulting Ltd, London, United Kingdom; Gwendoline Kiebert, Pfizer Inc, New York, NY; Gauri Saal, Adam Lloyd, Fourth Hurdle Consulting Ltd, London, United Kingdom; Lalit Kalra, Guy’s and St Thomas’s Sch of Med, London, United Kingdom

Objectives: Stroke is the single largest cause of severe disability in developed countries. Treating stroke patients is expensive, and understanding the resources devoted to the care of stroke patients allows better evaluation of proposed changes in management. The purpose of this study was to review and synthesize available literature describing the cost of managing stroke in Western Europe, Canada, and Australia. Methods: A database search was conducted and citation lists of retrieved studies reviewed. Studies were included if they were published between 1993 and 2003 and reported original data on the total cost of stroke or any important component of the cost of stroke for any country included. Data were extracted into a specially designed database using a standardized reporting form and converted into 2003 Euros. Cost components included in individual studies were identified, and results in countries with similar health care systems were grouped. Results: Cost-effectiveness analysis was not reported in the literature and included in the review. The estimates of the total national cost of stroke were identified for seven countries. The median annual cost of stroke reported was €50 per head of population (range €21, Portugal to €190, Finland). Per patient cost of hospitalization alone ranged from €1,963 (Italy) to €5,841 (Spain) to €3,719 (Sweden) and of lifetime care ranged from €22,236 (Netherlands) to €88,312 (UK). When countries with similar health care systems were grouped, including post discharges increased cost variable compared to the cost of the initial hospitalization and lifetime costs were estimated to be 6.4 - 7.8 times as large as the cost of initial hospitalization. Median costs in all categories were higher in Northern European than Continental European countries. Discussion: This review found lifetime costs of stroke to be far higher than the costs of initial management and that costs differ systematically between countries with different health care delivery systems. To accurately inform policy, economic evaluations of stroke prevention must consider cost saved in the long-term and must be conducted separately in different types of health care setting.

Screening for Obstructive Sleep Apnea in Stroke Patients: A Cost-Effectiveness Analysis
Devin L Brown, Ronald O Chernin, Susan L Hickenbottom, Lewis B Morgenstern, Univ of Michigan, Ann Arbor, MI

Introduction: Obstructive sleep apnea (OSA) is common after acute ischemic stroke and predicts poor stroke recovery, but whether screening for OSA and treatment by continuous positive pressure (CPAP) would improve neurological recovery or would reduce recurrent stroke is not known. We used a decision-analytic model to estimate the magnitude of benefit, in health-state utility, which would be necessary to make polysomnography (PSG) and OSA treatment cost-effective in this setting. Methods: The primary outcome was the utility gained through OSA screening and treatment in relation to two common willingness-to-pay thresholds of $50,000 and $100,000 per quality-adjusted life-year (QALY). A decision tree modeled two alternative strategies: screening versus no screening. In the screening pathway, identification of OSA led to CPAP titration, followed by 3 months of CPAP treatment. The utility and costs were calculated for this time period from a societal perspective. Utility estimates were based on published models baseline calculations but also were subjected to two-way sensitivity analyses. The model was analyzed by Data 4.0 (TreeAge Inc). Results: The average patient undergoing screening experienced 0.146 QALYs at a cost of $1,757, those not undergoing screening experienced 0.111 QALYs at a cost of $50, resulting in an incremental cost-effectiveness ratio (ICER) of $49,421. For a willingness-to-pay of $100,000 per QALY, the incentive in utility would have to be only 25% or greater (from 0.4 to 0.6), meaning that screening is cost-effective as long as the treatment of stroke patients with OSA by CPAP improves quality of life by more than 50%. For a willingness-to-pay of $50,000 per QALY, the incremental in utility would have to be only 25% or greater (from 0.4 to 0.5) for screening to be cost-effective. Conclusion: Models suggest that for OSA screening and treatment after acute stroke to be cost-effective, improvement in utility must be between .1 and .2, a range well within the reported benefit of CPAP for OSA in the absence of stroke. A clinical trial assessing the effectiveness of CPAP in improving stroke outcome is warranted from a cost-effectiveness standpoint.

Screening for Unruptured Intracranial Aneurysms: A Cost-Effective Analysis
Joseph Patnick, John Pile-Speltman, New York Presbyterian Hosp, New York, NY

Background and Purpose: Intracranial aneurysms are common entities which if ruptured, may cause significant morbidity and mortality. Screening and treating such aneurysms would successfully reduce the incidence and complications from rupture. Using current techniques of magnetic resonance angiography (MRA) and an endovascular approach, aneurysms can be diagnosed and treated with minimal risk to the patient. However, the economic implications of a screening program is yet unknown. We assessed the hypothesis that it is cost-effective to screen and treat unruptured intracranial aneurysms in the general population. Methods: Decision tree and Markov analyses were used to determine the cost effectiveness of screening a random population for intracranial aneurysms. The models grouped the patients into four health states, each with an associated health related quality of life score. Additionally, each health state was assigned a discounted medical cost, based on current reports. A comparison was made between the two hypothetical groups, the screened population and the non-screened population, to determine the additional costs and quality adjusted life years (QUALYs) gained. Results: The model assumed a screening age of 50 years old, an incidence of unruptured intracranial aneurysms of 3.52%, and a rupture rate of 2%. The additional cost of the screening program as compared to no screening, when using an endovascular approach for therapy, was found to be $20,852.02 per QUALY, with a net gain of 0.04 QUALY. Differences in the rupture rate had significant impact on the results; with a 1% rupture rate, the cost per QUALY was significantly increased to $275,453.00. Endovascular therapy for unruptured aneurysms yielded a significantly lower cost per QUALY ($20,852.02) as opposed to surgery ($313,777.81). The analysis was most sensitive to changes in the rupture rate, and the cost of an MRA. Conclusions: Based on current reported rupture rates of 2%, screening and treating unruptured intracranial aneurysms is cost effective and should be recommended. Furthermore, endovascular repair of an aneurysm is more cost effective than surgery, and should, therefore, become the standard method of therapy.

Duration of Hospital Participation in a Nationwide Stroke Registry Is Associated With Increased Rates of Antithrombotic Use
Nancy K Hills, Univ of California, San Francisco, San Francisco, CA; Gary Houser, The Stroke Group, Denver, CO; S C Johnston, Univ of California, San Francisco, San Francisco, CA

Background: Many stroke patients are not prescribed antithrombotic medications at discharge, despite published guidelines on their use in secondary stroke prevention. Hospital level intervention, specifically, participation in a stroke registry, could impact rates of antithrombotic use compared to patients with TIA and stroke. Methods: This prospective cohort study involved 2 hospitals (November 1999 to December 1999, and December 2003, 85 hospitals participated in Ethos, a voluntary web-based national acute stroke treatment registry. Detailed data were collected on all patients discharged from the ED with a diagnosis of TIA or ischemic stroke. Rates of optimal treatment with antithrombotic medications at discharge (defined as either receipt of or a valid contraindication to antithrombotic therapy) were examined within each hospital as a function of its length of time in registry, chronological time, and patient characteristics. Generalized estimating equations (GEE) were used to adjust for inter-hospital differences. Results: A total of 17,530 patients were discharged with a diagnosis of stroke or TIAs. Overall, 523 patients (9.4%) received antithrombotics at discharge and 736 (4.2%) had a documented contraindication to treatment,
for an overall optimal treatment rate of 91.1%. Treatment rates for the first quarter of each year of participation in registry (with 95% CI) were 86% (95%-87%), 93% (91%-94%), 97% (95%-98%) and 98% (95%-99%). Duration in registry was significantly associated with treatment rate (p<0.0001), an association that persisted even after adjustment for chronological year, gender, age, and race (p<0.03). Although the number of concomitant drugs significantly increased with time in registry, evidence of concomitantly increased usage of antithrombotics after the significant increase in increased usage of antithrombotics over time (p<0.0001). Conclusion: Participation in a stroke registry is associated with improvement in rates of antithrombotic use. These findings demonstrate the potential for hospital-level interventions to improve care for patients with stroke and TIA.

What Are the Predictors of Quality of Life at 5 Years Poststroke?


Background: There are limited data, particularly in Australia, relating to long-term quality of life (QoL) in stroke patients. Furthermore, little is known about the predictors of QoL beyond two years post-stroke. Aim: To assess the QoL and its predictors at five years after stroke. Methods: Retrospective case-stroke cases from a prospective, community-based stroke incidence study conducted in North Eastern Melbourne were assessed at five years post-stroke. QoL was measured with the Assessment of Quality of Life (AQoL) instrument. The utility values of the AQoL range from -0.04 (worse than death), to 0 (death), to 1 (full health). Baseline predictors of QoL were assessed at years two post-stroke. Results: In total, 977 cases were recruited, 45% were male and the mean age was 75.5±13.8 years. At five years at 536 were deceased (therefore scoring 0 on the AQoL) and 441 (45.1%) were alive. Of the survivors 356 (80.7%) were assessed. Those assessed were more likely to be born in Australia and were older (both p<0.05). Mean AQoL score among survivors was 0.48±0.35. Seventy-one (20%) survivors had an AQoL score<0.3. The mean AQoL score in those who died was 0.24 (p<0.0001). Conclusion: A significant proportion of five year survivors have poor QoL. Good QoL at five years post-stroke was associated with male gender, younger age, higher socioeconomic status, an absence of peripheral vascular disease, and initial stroke severity (p<0.01). 

Predictors of Dissatisfaction With Sexual Function After Ischemic Stroke

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Introduction: Little information is available about the impact of ischemic stroke upon sexual functioning in the U.S. Many predictors of sexual dysfunction after stroke have been reported. Methods: 451 patients with ischemic stroke during 1999 underwent post-stroke interview and medical record abstraction. Survivors had follow-up interviews at 4 years post stroke. Patients were questioned about their post stroke functional outcome and their health related quality of life. The EuroQlo and the SF36 Health Survey were used. Results: The mean age of patients was 65.5 years, 58% were female, 23% black, 68% living at home 4 years post-stroke, 47% living with a partner, mean modified Rankin score 2.2. 19 patients (13%, 95% CI 8.6%-19.0%) reported that they had experienced sexual dysfunction within 3 months following stroke. One question in the AQoL asked if they had had sex less often than they would have during the previous week. Multivariable logistic regression was used to construct a model predicting sexual dysfunction. Among patients, race, gender, disability, education, depression, marital status, modified Rankin score, quality of life, health status measured on a 100 point visual analog scale, EQ-5D z-score, religiosity and participation in organized religious activities. Conclusion: Patients completing the AQoL at 4 years more than 54% stated they had had sexual dysfunction during the 4 years after stroke. The final model to predict patients' sexual dysfunction included: male gender (p<0.001), black race (p<0.05), lower EQ-5D z-score (p<0.001), higher health status (p<0.02), and participation in organized religious activities less than once per week (p<0.03). Conclusion: Sexual dysfunction immediately post stroke and dissatisfaction with sexual activity 4 years after stroke are common. Race was a significant predictor of dissatisfaction, suggesting that this issue requires cultural sensitivity.

Predictors of Stroke-Specific Quality of Life 4 Years After Ischemic Stroke

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Introduction: The SSQOL is a reliable, responsive, and validated stroke-specific measure of health-related quality of life. Predictors of SSQOL in the long term after ischemic stroke are not known. We hypothesized that diabetic patients have lower SSQOL 4 years after stroke of a different impact of predictor variables as compared to non-diabetics. Methods: In 1999, a cohort of 451 ischemic stroke patients had medical record review and direct interview post stroke and at 3 months. At 4 years, 154 of the surviving patients were followed up with interviews conducted at the National Stroke and TIA Center for Epidemiological Studies Depression scale and the Duke Religion Index were completed, among others. Patients were asked directly if they had experienced sexual dysfunction in the 3 months following stroke. One question in the AQoL asked if they had had sex less often than they would have during the previous week. Multivariable logistic regression was used to construct a model predicting sexual dysfunction. Among patients, race, gender, disability, education, depression, marital status, modified Rankin score, quality of life, health status measured on a 100 point visual analog scale, EQ-5D z-score, religiosity and participation in organized religious activities. Results: 145 patients completed the SSQOL at 4 years median age at stroke 65.7 years, 58% female, 23% black, 68% living at home 4 years post-stroke, 47% living with a partner, mean modified Rankin score 2.2. 19 patients (13%, 95% CI 8.6%-19.0%) reported that they had experienced sexual dysfunction within 3 months of their stroke and 61 (42%, 95% CI 34.5%-50.2%) reported sexual dysfunction 4 years after stroke. The final model to predict patients' sexual dysfunction included: male gender (p<0.001), black race (p<0.05), lower EQ-5D z-score (p<0.001), higher health status (p<0.02), and participation in organized religious activities less than once per week (p<0.03). Conclusion: Sexual dysfunction immediately post stroke and dissatisfaction with sexual activity 4 years after stroke are common. Race was a significant predictor of dissatisfaction, suggesting that this issue requires cultural sensitivity.
Stroke-Specific Quality of Life in Subjects From a Hospital-Based Stroke Registry

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Introduction: The Stroke-Specific Quality of Life (SS-QOL) instrument was developed to assess changes in 12 domains of health relevant to stroke survivors. In this study, we examine the relationship between SS-QOL and functional impairment at hospital discharge and at follow-up in a large range of stroke survivors from a state-wide registry. Methods: Subjects admitted with acute stroke or TIA to 9 Michigan hospitals (N=385) were enrolled. Modified Rankin scores (MRS) were determined at discharge. Barthel Index (BI) and SS-QOL were administered by telephone follow-up interviews conducted 3 months post-stroke; 72% (N=277) completed the interview. At follow-up, 13% refused, 11% were lost to follow-up. Interviews were completed by a proxy for 25% of the subjects. MRS and BI were categorized into a common 3-level functional impairment grade: low (MRS 0–2, BI 95–100), moderate (MRS 3, BI 70–90), and high (MRS 4 or 5, BI <70) according to an established algorithm. Statistically significant differences (P<.05) in SS-QOL summary scores (SSS) and domain scores by functional impairment grade were assessed by ANOVA. Results: At discharge, 54%, 22% and 25% had low, moderate, and high functional impairment, respectively, which corresponded to SSS 3.91, 3.58 and 3.38. SSS and all but 3 domain scores exhibited significant differences across the 3-level functional impairment grade: low (MRS 0–2, BI 95–100), moderate (MRS 3, BI 70–90), and high (MRS 4 or 5, BI <70). The SS-QOL instrument identifies persistent deficits in QOL among the least functionally impaired subjects.

Race Differences in Function and Quality of Life in Mild Stroke

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Objectives: This study sought to determine whether African Americans with mild stroke experience less positive outcomes when compared to Caucasians with similar stroke severity. Methods: Data from 290 individuals (125 African Americans and 165 Caucasians) with NIH Stroke Scale (NIHSS) scores 0–2 admitted to the Rehabilitation Unit of an urban St. Louis hospital were evaluated with a comprehensive outcome battery 6 months after stroke onset. Mean age was 63.6 years (SD=14.4) and mean education was 12.2 years (SD = 3.3). Patients met the following inclusion criteria: (1) clinical diagnosis of stroke(2) no history of significant alcohol or drug abuse, (3) premorbid Barthel index (BI) of 90, (4) no history of schizophrenia, dementia, epilepsy, AIDS, or lupus. Outcome measures included the FIM, Stroke Adapted SIP, Reintegartion to Normal Living INDEX, SF-12 and the Activity Card Sort. Between group differences were computed using t-tests, ANOVA and chi square. African American patients were considered to be younger (<55 years) and black patients were considered to be older (≥55 years). Between group differences were found for stroke severity, hospital discharge location or FIM scores. Although both white and black patients achieved similar levels of independence in basic ADL, there were significant differences between the groups on measures of general and stroke specific quality of life. African Americans reported significantly lower quality of life than Caucasians on all but 1 stroke related problems on the Stroke SIP (p<.002), lower community reintegration quality of life (p<.001), decreased resumption of pre-stroke activities (p<.01). Regression analyses confirm African Americans are at greater risk for poor outcome even after differences in age, gender, depression and stroke severity are controlled. Conclusion: In this sample of carefully screened individuals with mild stroke, we show evidence that patients with NIH Stroke Scale scores of 0 or less experience persistent deficits in instrumental and complex activities despite full independence in basic ADL. We found subtle but significant impairments that influence quality of life. These differences are evident in African Americans, and support the need for more sensitive acute screening of cognitive and sensory impairments.

Pediatric Adaptation of NIH Stroke Scale Predicts Outcome After Arterial Ischemic Stroke in Children

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Background: Determinants of outcome after childhood stroke are poorly understood. Initial clinical deficit as measured by the NIH Stroke Scale (NIHSS) is a robust predictor of outcome after arterial ischemic stroke (AIS) in adults. Validation of a stroke scale for children is essential for the design and conduct of future clinical trials for childhood stroke. Presently there is no stroke scale validated for use in children. Objective: To evaluate the predictive utility of a pediatric adaptation of the NIH Stroke Scale for children with AIS. Methods: This single center retrospective cohort study included children ages 2–21 yr admitted for acute AIS between 2002–2004. Patients with stroke due to head trauma or brain tumor surgery were excluded. A pediatric adaptation of the NIHSS (NIHSPed) included all testing items and the general scoring approach as for the standard adult NIHSS, with minor adaptations in instructions, language testing items and scoring to accommodate age-dependent performance. NIHSPed
was scored at admission and daily through the 1st week. Outcome measures included length of hospital stay (LOS), including in-patient rehabilitation; and standardized measure of neurologic functional deficit at initial follow-up, the Pediatric Stroke Outcome Measure (PSOM). PSOM ranges from 0–15, with higher scores for greater deficits. Relationships between NIHSSPed and outcome measures were evaluated by Spearman rank correlation. Results: The study included 17 patients, mean age 9 yr (range 2–17) years. 11 patients survived to discharge, median highest NIHSSPed during the 1st week was 6 (1–28), measured at median time of 21 hrs after symptom onset. 14 patients returned for follow-up and were seen at a median time of 4 months (1.5–14 months). Median hospital LOS was 12 days. Median PSOM at follow-up was 2 (range 0.5 – 10). Higher NIHSSPed score was significantly associated with greater LOS (R = 0.52, p = 0.03), and with higher PSOM at follow-up (R = 0.82, p = 0.008). Conclusion: Initial clinical deficit from AIS can be measured in children over a broad age range using a pediatric adaptation of the NIH Stroke Scales. Higher scores on NIHSSPed are associated with greater LOS and with greater residual neurologic deficit at follow-up during the first year.

The Burden of Stroke on Informal Caregivers: An International Review of Costs

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Background: The care requirements of patients with stroke are significant, and health care systems worldwide are challenged by limited resources. Any evaluation of the economic burden of this disease to society, therefore, must include data related to the quantity and opportunity cost of informal (unpaid) care, typically provided by family members. Objectives: To document reported costs of informal care and per patient costs of informal care provided to acute care patients recovering from stroke, and to explore the impact of stroke severity on these costs. Methods: A PubMed search of English, human studies literature from January 1995 to July 2004 was conducted (keywords included MeSH terms: cerebrovascular accident, stroke, caregivers, informal care, stroke). Results: Of 49 abstracts found, 37 were excluded given the absence of costs; upon review of the 12 selected papers, only 9 (UK;3, Sweden;3, USA;1, Australia;2) contained relevant costs. Aggregated annual costs (USD 2003) were as high as 6 billion dollars (USD) and accounted for between 4 and 13% of total first-year incident stroke related costs and 14–23% of total prevalence-based lifetime costs. Per patient annual costs ranged from $2,400 (Sweden) to $7,800 (USA). In the only study reporting actual (vs modeled) costs by severity, costs were more than double for moderate and severe cases versus the least disabled patients. Conclusions: There is a paucity of data related to the cost of informal care for patients with stroke, which precludes a more complete understanding of the actual burden borne by unpaid caregivers; non-standardized methods of evaluation hamper inter-study comparisons, but existing data reveal that informal care needs and costs are substantial and may be highest for more disabled patients. New treatments which reduce disability, therefore, may decrease this burden. Additional costing studies reporting by level of stroke severity are warranted, and will benefit those seeking to establish the aggregate societal costs of stroke, as well as those responsible for discharge planning and caregiver support.

Helicopter Transport From Scene Improves Access to Stroke Care

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Purpose: Helicopter transport has been advocated as a method to improve access to care and decrease total out-of-hospital time (OHT) for various emergencies, including acute stroke. We sought to determine the impact on access to care using a helicopter to transport patients directly from the scene to potential stroke referral centers in New Mexico. Methods: GIS software was used to model system performance under various configurations. The model used NM stroke incidence rates, US Census Bureau demographic data, NM specific EMS performance data, as well as response time regression models for ground and helicopter ambulances. The percentage of state population and 2001 stroke patients within 60 and 90 minutes of stroke referral centers was determined. This baseline system was compared to alternative systems that would use existing helicopters to transport patients from the scene using standard dispatch policies (average delay of 13 minutes after ground dispatch) as well as simultaneous air and ground ambulance dispatch. Results: System performance averages included: ground response time 9 min (± 8), ground scene time 16 min (± 12), air ambulance launch time 9 min (± 8), and air ambulance scene time 19 min (± 10). For standard air ambulance dispatch, ground transport was faster for all patients within the 60 minute OHT standard. Results for other configurations are shown below. Conclusion: Air ambulance scene response using standard dispatch procedures for acute stroke did not increase access to stroke referral centers within 60 minutes. Utilizing simultaneous air and ground ambulance dispatch did demonstrate potential for increased access at both 60 and 90 minutes.

Atrial Fibrillation in Patients With First-Ever Stroke: Frequency, Antithrombotic Treatment Before the Event, and Effect on Clinical Outcome

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Background: Atrial fibrillation (AF) is an independent risk factor for stroke. The aims of this study were to assess: i) the frequency of known or unknown AF in patients admitted to the hospital for a first-ever ischemic stroke and whether AF is associated with an adverse outcome at discharge (death or disability); ii) the rates and determinants for the use of antithrombotic agents before stroke in patients with known AF and the adherence to the current treatment guidelines; iii) whether the lack of adherence to the current guidelines is associated with adverse outcome at discharge. Methods: Consecutive patients with acute first-ever stroke admitted to the Stroke Unit between January 2000 to December 2003, were included in the study. Twelve-lead electrocardiography (ECG) was performed in all patients on admission. Functional outcome was measured at discharge according to modified Rankin Score (mRS).

Results: 1549 patients with first-ever stroke were included in the study: 238 (15.4%) were
known to have AF and 76 patients (4.9%) were diagnosed with AF (unknown) on ECG performed on admission. At discharge 91 patients (5.9%) had died and 605 patients (39.0%) had died or were functionally dependent. Multivariate analysis showed that AF on admission was correlated with mortality or disability. Before stroke, 124 out of 238 patients with known AF (62.1%) were not on antithrombotic therapy, 63 (34.9%) were receiving antipatelet and 31 (13.0%) anticoagulant treatment. Hyperlipidemia, history of ischemic heart disease and previous TIA were associated with the use of antithrombotic therapy. Only 24 out of 114 patients on antithrombotic treatment on admission were adequately treated according to the current guidelines. 41.7% of the adequately treated patients died or were disabled at discharge respect to 52.9% of the patients non adequately treated (RR=0.80, 95% CI 0.48–1.30). Conclusions: AF (on history or new diagnosis) was present in 20.3% of the patients with first-ever stroke admitted to our stroke unit and it was associated with increased mortality or disability. Only 10% of patients with known AF were previously receiving an adequate antithrombotic treatment according to current guidelines.

The Use of Magnetic Resonance Imaging for Evaluation of Atherosclerosis Profile in Aorta and Extracranial Carotid Arteries in Acute Ischemic Stroke Patients

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Introduction: Atherosclerosis distribution in the arterial system may be different according to gender. The aim of this study was to test the hypothesis that BMI and age affect the site of maximum intensity of FDG Uptake in isotropic Magnetic Resonance Imaging (MRI) may be used to outline atherosclerotic profile in Acute Ischemic Stroke (AIS) Patients. Methods: Subjects with AIS (n=14, aged 64.3±8.6 years, range 48 to 80 years, 42.8% females) and age/gender-matched controls (n=13) in the same cardiovascular risk distribution underwent high-resolution black-blood MRI of the aorta and extracranial carotid arteries. For each subject, cross-sectional images of the aorta (n=36–48) and carotids (n=12–24) were analyzed. Average arterial wall area (AWA), average wall thickness (AWT), and maximal wall thickness (MWT) were measured for each resulting image (n=1,620). Aortic plaque profiles were analyzed using multi-criteria Risk Assessment. Risk groups were determined based on Framingham score. Results: There was no significant difference between the two groups regarding age, gender, mean cholesterol values, 10-year risk percentiles, BMI, traditional cardiovascular risk factors and plaque composition. AIS patients had a higher prevalence of atherosclerotic plaques in both aorta and carotid as compared to controls (n=9–vs. n=4, p<0.05). Isolated carotid artery disease was significantly higher in controls than in AIS patients (n=6–vs. n=2, p<0.05). Aortic plaques greater than 4mm were more prevalent in stroke patients than in controls (n=9–vs. n=5, p<0.05). Aortic and MWT of both carotid and aorta were higher in AIS subjects than in controls (2.3±0.7 vs. 2.1±0.6 mm, p<0.05). No significant differences were observed between Aortic AWA and MWT. However, when normalized to body surface area, AIS subjects showed significantly higher values than controls (8.64±2.2 vs. 7.23±1.78, p=0.047). Conclusions: This pilot study shows that MRI can be used to determine atherosclerotic profile in AIS patients. This method may be helpful for future population studies on clinical screening and monitoring of high-risk patients.

The “Carotid Ring Sign” on Angio-CT May Differentiate Acute From Chronic Carotid Occlusion

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Background: Differentiating acute from chronic carotid occlusion may be helpful in determining treatment selection in patients with cerebral ischemia. Currently, there is no reliable method to do this. Methods: Between 2001 and 2004, we examined 72 spontaneously occluded extracranial carotid arteries in 66 patients with angio-CT. All occlusions were confirmed by another method (DS-angiography, Doppler or MRA). In the absence of a gold standard for the timing of occlusions, they were classified as “probably acute” (PA) and “probably chronic” (PC) based on circumstantial clinical and radiological evidence. A neuroradiologist and a neurologist blinded to clinical information determined the site of proximal and distal occlusion on extracranial axial sections of the ACT. They also looked for a) a hypodensity within the carotid artery (thrombus), b) contrast within the carotid wall (vasa vasa currens), c) the size of the occluded carotid, and d) the “carotid ring-sign” (defined as presence of a) or b) or a) + b) in a normal-size appearing occluded carotid artery). Results: Of the 72 carotids, 3 were excluded because of insufficient imaging quality, and 19 because of insufficient circumstantial evidence to determine timing of occlusion. Among the remaining 37 PA and 13 PC, interrater agreement for the site of proximal and distal occlusion was kappa = 0.88 . For the “carotid ring-sign” was 0.84. Site of proximal and distal occlusion did not differentiate the two groups, but the “carotid ring sign” had a sensitivity of 88%, a specificity of 77%, and an accuracy of 86% for acute carotid occlusion. Conclusions: The “carotid ring-sign” differentiates acute from chronic carotid occlusion in most patients. This information may be helpful in studying ischemic symptoms and selecting treatment strategies in patients with carotid occlusion.

Rapid Detection of Vascular Disease From the Aortic Arch to the Circle of Willis by Contrast-Enhanced MR Angiography: Prospective Evaluation

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Background: Contrast-enhanced magnetic resonance angiography (CE-MRA) using a combined head and neck coil permits non-invasive imaging of the vasculature from the aortic arch through to the Circle of Willis in less than two minutes. The aim of this study was to determine the sensitivity of CE-MRA for the detection of extracranial and intracranial vascular disease. A total of 52 patients with clinical symptoms of aortic arch pathology were examined using digital subtraction angiography (DSA) as the gold standard. Results: In a prospective study of 81 patients referred for DSA, CE-MRA and DSA studies were performed within 72 hours of each other. CE-MRA was performed on a 1.5 Tesla clinical MRI scanner using a 5 channel vascular acquisition array (head and neck coil), with dynamic tracking of the intracranial and extracranial vasculature. CE-MRAs and DSA films were read by two interventional neuroradiologists blinded to the clinical presentation of the patient. The degree of stenosis for each extracranial and intracranial vessel was graded using the North American Symptomatic Carotid Endarterectomy Trial Criteria: stenoses were grouped into <50% and ≥50% categories. Results: CE-MRA had sensitivity of 95% (95% CI: 93%–99%) for detecting even severe stenoses. Overall sensitivity of CE-MRA for the detection of vascular stenoses ≥50% was 57% (95% CI: 46%–68%) with a specificity of 98% (97%–99%). The sensitivity for the detection of extracranial stenoses ≥50% was 82% (72%–93%) with a specificity of 97% (96%–98%). However, the sensitivity for the detection of extracranial
vacular stenoses \(\geq 50\%\) was only 8\% (7\%-18\%), with a specificity of 99\% (98\%-100\%). The interobserver agreement for CE-MRA reading was moderately good (kappa = 0.41). Conclusions: CE-MRA using a neurovascular coil shows significant promise as a rapid and non-invasive screening method for extracranial vascular disease. This method could complement current acute stroke MR imaging protocols for decisions regarding emergent thrombolysis, early surgical intervention and secondary stroke prevention.

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Accuracy of Conventional Plus Transoral Carotid Duplex Ultrasonography for Diagnosis of Pseudoocclusion of the Internal Carotid Artery

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Purpose: Distinction of pseudo- from total occlusion of the internal carotid artery (ICA) is necessary to the optimal strategy for the revascularization. The purpose of the present study was to investigate the accuracy of conventional carotid ultrasonography (CUT) on total carotid ultrasonography (TOCU) for detection of ICA pseudo-occlusion. Methods: This study included 67 consecutive patients who were suspected as having an ICA occlusion at its origin on 2 dimensional time-of-flight magnetic resonance angiography and underwent CCU and cerebral digital subtraction angiography (DSA) for the further examination. The ICA color flow signals and pulsed Doppler waveform were evaluated using CCU. When slight residual flow signals were observed in the proximal ICA lumen on CCU, TOCU was additionally performed to observe the cervical portion of the ICA. On DSA, an ICA occlusion was defined as the following criteria: 1) severe stenosis (>50% in NASCET) of the ICA origin with a collapsed distal ICA, 2) back-filling of the carotid siphon via the ophthalmic artery in the early arterial phase, and 3) delayed antegrade flow of the patent ICA in the late arterial phase. Results: On color Doppler images of CCU, 50 patients had complete flow cessation at the ICA origin, and remaining 17 patients had slight residual flow signals in the ICA lumen. Among the 17 patients, 2 patients showed a pulsed Doppler waveform of the distal ICA occlusion (end-diastolic flow velocity cannot be detected), in remaining 15 patients, a waveform of to and fro (diastolic reverse) signals, and the following carbonic anhydrase fluoride or weak antegrade flow pattern was observed with peak systolic flow velocity of < 400cm/sec) was observed. Among them, 13 patients had the same waveform of the collapsed ICA cervical portion on TOCU and they were ultrasonographically diagnosed as having an ICA pseudo-occlusion. Out of the 13 patients, DSA revealed that 2 patients had an occluded ICA at the ICA distal to the ophthalmic artery. Conclusions: In conclusion, TOCU revealed the diagnostic accuracy whether the initial plain CT was positive or negative. To assess the additional diagnostic yield of head CT Angiography (CTA) over conventional head CT in patients presenting to the Emergency Department (ED), Methods: We retrospectively studied 410 consecutive ED patients who underwent head CTA. The setting was an academic medical center ED with a high prevalence of major vascular neurologic illnesses, the addition of CTA provided additional information beyond that obtained from the plain CT in 43% (95% CI: 38\%-48\%) of subjects. Among patients with ischemic stroke, CTA was positive in 76\% of those with abnormal CT, and 56\% with normal CT. Despite a negative CT, CTA was positive in 11\% with TIA. CTA was positive in 9\% with intracerebral hemorrhage, and 90\% with subarachnoid hemorrhage; no patient with a headache disorder and normal CT had a positive CTA. Conclusion: In an academic medical center ED with a high prevalence of major vascular neurologic illnesses, the addition of CTA to standard head CT yielded additional clinically relevant information in almost one half of all subjects. Furthermore, CTA provided additional information whether the initial plain CT was positive or negative.
CTA Source Images Have Added Value Over Unenhanced CT in Detection and Tissue Outcome Prediction of Acute MCA Infarction

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BACKGROUND: ASPECTS scoring is a robust method for quantifying early hypodensity on noncontrast CT (N CCT), CTA source images (CTA-SI) are presumed to be blood pool weighted, and may therefore increase the conspicuity of tissue likely to be irreversibly infarcted. We sought to determine if: a) CTA-SI is more sensitive than NCCT for detection of acute MCA stroke, and b) CTA-SI is more accurate than NCCT in predicting final infarct size as measured by ASPECTS. METHODS: We reviewed the scans of 51 consecutive patients who received an admission CT/CTA within 12h of suspected MCA stroke onset, as part of an ongoing multi-center study (STOPSTROKE). Two board certified neuroimagers, blinded to follow-up, rated the NCCT and CTA-SI images according to a modified ASPECTS scoring system. Level of certainty for hypodensity in NCCT was graded on a 5-point scale (0–5; 0 = definitely present, 1 = definitely absent). Follow-up images were subsequently rated using the same scale. RESULTS: There were 33 completed MCA strokes, and 18 cases without stroke. Mean time to follow-up was 6.5 days. Using a cutoff of 4 (“probable”) for hypodensity presence, stroke detection sensitivity and specificity were 79% and 70% for NCCT and 82% and 79% for CTA-SI (two-tailed p = 0.02, based on ROC curves); specificity was 100% for both methods. Using a cutoff of “3” (“possible”), stroke detection sensitivity was 64% for NCCT and 85% for CTA-SI (two-tailed p = 0.02, based on ROC curves); specificity was minimally reduced to 91% and 96%, respectively. Linear regression analysis revealed an R² of 0.30 for the correlation between NCCT and follow-up ASPECTS scores, and 0.64 for the correlation between CTA-SI and follow-up (both p-values < 0.001). CONCLUSIONS: CTA-SI was significantly more sensitive than NCCT in the early detection of ischemic lesions, without sacrificing specificity. CTA-SI was also significantly more accurate than NCCT in predicting final infarct volume, as measured by modified ASPECTS.

Impact of Neurological Exam and Noncontrast Head CT Findings on the Utility of CTA in the Emergency Department


Background: An increasing number of patients are receiving head/neck CT angiography (CTA) in addition to non-contrast head CT (CT) in the Emergency Department (ED). We investigated, to the appropriate use of this technology. Methods: To measure the ability of the neurologic examination and CT scan results to predict abnormalities on CTA, we retrospectively studied 410 consecutive ED patients with acute neurological symptoms who underwent head/neck CTA. CT was considered positive if it was performed in a tertiary care urban university hospital. We excluded 66 patients who either underwent CT for a known diagnosis (e.g. rule out bleeding from a known AVM), or who had stable symptoms for >24h. CT was considered ‘positive’ if it showed new and/or clinically significant abnormalities. CTA was considered ‘positive’ if it yielded a diagnosis not suggested by CT, or additional relevant information (e.g. ICA stenosis in a subject with ipsilateral ischemic stroke). Initial neurologic exam data was obtained from the neurologist’s note (95% subjects) or ED records. Final diagnoses were obtained from hospital discharge summaries. Results: The 344 included subjects had a mean age of 63 years; 49% were male and 65% were admitted to the hospital. The most common final diagnoses were ischemic stroke (38%), TIA (12%), intra/extracerebral hemorrhage (9%), subarachnoid hemorrhage (13%), headache disorder (5%), and trauma (10%). Overall, 68% of subjects had abnormal neurologic exams, 57% had positive CTs, and 43% had positive CTA. For the endpoint of positive CTA, the positive predictive value (PPV) of an abnormal neurologic exam in combination with negative CT was 0.38 (95% CI 0.28–0.48), and of a normal neurologic exam and positive CT was 0.45 (95% CI 0.31–0.59). Conversely, the negative predictive value (NPV) for CTA of a normal neurologic exam combined with a negative CT was 0.92 (95% CI 0.88–0.96). Conclusion: Abnormality on either the neurologic exam or CTA has been confirmed for experienced readers however. Methods: Retrospective analysis of prospectively collected perfusion CT data was conducted for patients imaged <6h after onset with final diagnosis of hemorrhagic stroke and follow-up NCCT at 24–72h. Perfusion CT was acquired as 4 contiguous 5mm slices. Color scale maps of time to peak (TTP) were obtained by deconvolution of an arterial input function (contralateral anterior cerebral artery). Two inexperienced CT readers undertook a standardised CT interpretation training package prior to rating initial plain CT scans using subjective criteria and ASPECTS. TTP maps were rated for anatomical areas matching those of the conventional ASPECTS system, but over one CT slice at the level of the basal ganglia. A limited anatomical ROI was used to rate perfusion CT, yielding a maximum score of 7. Inter-rater reliability was determined by weighted kappa statistics. Results: Scans for 17 subjects, imaged a median of 135 minutes after onset, were rated. 13 had proximal, and 4 distal, MCA occlusions. Inter-rater reliability of NCCT was poor using ASPECTS (κ = 0.155) and fair for dichotomisation into greater or less than one third MCA territory involvement (κ = 0.626). Inter-rater reliability of the 7-point ASPECTS of TTP maps was good (κ = 0.777). Conclusion: Inter-rater reliability of NCCT interpretation in acute stroke is poor in inexperienced readers, even after a standardised training package, both for the ASPECTS system and for other conventional subjective interpretations. Inter-rater reliability is improved substantially by systematic scoring of color-coded TTP perfusion maps.
Usefulness of Magnetic Resonance Angiography and Magnetic Resonance Angiography/Diffusion Mismatch as Predictors of Salvageable Brain Tissue in Acute Ischemic Stroke

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DWI/PWI mismatch shows potentially salvageable ischaemic brain tissue. We investigate whether magnetic resonance angiography (MRA) alone or in association with small DWI lesion volume (MRA/DWI mismatch) is useful to predict brain tissue at risk of infarction and to select patients candidates for thrombolysis. Method 141 patients consecutively admitted to two hospitals with a first hemispheric ischaemic stroke of <12 hours from onset were included. We performed MRA, including MRA, DWI, PWI and FLAIR sequences on admission, at 72 hours, and at day 30. We also performed prior to CT in all cases. The findings demonstrate that in an unselected general population of patients admitted more than 3 hours after stroke onset, 39 patients (27.7%) had A/D-m. The sensitivity of DWI remains high, ranging from 81% for blinded readers and improving to 96% for unblinded readers. However, the sensitivity of DWI remains high, ranging from 81% for blinded readers and improving to 96% for unblinded readers.

Does the Distribution of the Ischemic Penumbra Within the Arterial Border-Zone Regions Influence Its Spontaneous Salvage?

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Background and Purpose: Although we have previously demonstrated that spontaneous penumbral salvage occurs at a rate of about 50% and is independent of time, it is unclear as to which penumbral regions are involved. Because of the excellent resolution of F18-FMISO PET as a marker of gray matter, we were able to test the hypothesis that spontaneous salvage of penumbral tissue is more likely in arterial border zone regions where collateral flow is best. Methods: Patients with middle cerebral artery (MCA) stroke were imaged with F18-FMISO PET within 48 hrs. The penumbral region was identified by statistical comparison of 18F-FMISO uptake compared to controls and the spontaneous penumbral salvage region (SPSR) by co-registration of the penumbral region with the final infarct volume on late CT. Results: Of 141 patients consecutively admitted to two hospitals with a first hemispheric ischaemic stroke of <12 hours from onset, 39 patients (27.7%) had A/D-m. The proportion of the penumbral region salvaged correlated with the proportion in the external borderzone (r = 0.25, p = 0.02). The proportion SPSR in the external borderzone region (50%, interquartile range 26.1%, 85.9%) was greater than in the MCA territory (26.1%, interquartile range 13.5%, 63.4%) p < 0.005). The median volume of SPSR in the external borderzone region, MCA territory and internal borderzone region were 2.5 ml (0.2 ml, 6.3 ml), 0.6 ml (0.1 ml, 10.3 ml) and 0.2 ml (0.02 ml, 1.3 ml) respectively. Conclusion: Spontaneous penumbral salvage was enhanced by location within the arterial borderzone regions, which was significantly greater to survival within the internal borderzone region. A region collateral supply available in the external borderzone regions might play a part in spontaneous penumbral salvage while end arteries supplying the internal borderzone areas might minimize this process. Therapies designed to improve collateral supply are needed.

The Metabolic Counterpart of Reduced Apparent Diffusion Coefficient in Acute Ischemic Stroke: A Combined Fully Quantitative Magnetic Resonance/Positron Emission Tomography Study

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Although the relationships between reduced Apparent Diffusion Coefficient (ADC) and CBF in human acute stroke have been studied, nothing is known of the relationship between ADC and tissue oxygen consumption (CMRO2) in man. To address this issue, we imaged acute carotid-territory stroke patients in a prospective study with diffusion-weighted imaging (DWI) along with fully quantitative Positron Emission Tomography (PET). Method From 100 patients, 5 (3M/2F, 53 - 84 yrs: NIHSS 6 - 70%, p < 0.02) and greater increase in DWI volume at 72 h (65.3 vs. 25.4; p < 0.01) (Figure) in patients admitted more than 3 hours after stroke onset. 39 patients (77.3%) had A/D-m. The increase in infarct volume at 72 hrs (79.1 ± 74.2 vs. 36.0 ± 71.9; p = 0.01) and at day 30 (45.6 ± 62.6 vs. 15.8 ± 63.3; p = 0.02) was significantly greater in patients with A/D-m at admission. However, the sensitivity, specificity, PPV and NPV for the prediction of DWI lesion growth at 72 hours were low (75%, 25%, 66.8%, 33% respectively). Conclusions: A/D-m indicates a greater risk of a later increase in infarct volume, although its low sensitivity and specificity impedes its use as an effective selection tool for thrombolysis. MCA occlusion detected more than 3 hours after stroke onset is associated with a significant volume of the penumbral area. These patients might be still candidates to receive thrombolytic treatment.
48 hrs. Penumbral tissue fate was determined by computing of statistically significant areas of increased tracer uptake with final infarct volume on late CT within standard Talairach space. Results: There were 27 patients (mean age 74 years) studied within 48 hours of stroke onset. Three penumbra patterns were identified: (1) discontinuous anterior/posterior in which separate sections of penumbra appeared at opposite poles of the final infarct (5 cases, 18.5%) (2) continuous-overlapping with the traditional concept of an annular distribution (33.3%) (3) discontinuous/isolated within the body of the infarct in which the penumbral tissue was completely surrounded by the final infarct (13 cases, 48.2%). The median percentage and volume of penumbral tissue which was salvaged for each was 29.4% (21.9%, 33.3%) p = 0.2 21.5% (13.8 – 35%) r = 0.4% (1.6% 26%), 0.25 (15.9 – 33.8%) and 24.8% (8.2%, 46.4%, p = 0.4) 1.8 ml (0.01 – 5.6 ml) respectively. Conclusions: The traditional view of penumbral topography is not fully supported with 3 heterogeneous patterns identified, only one of which was consistent with an annular distribution around the infarct. Although time and similar parameters (the tissue outcome was the vast majority of penumbral topography may enhance our understanding of the mechanisms of its salvage.

P249 MRl-Based Voxel-by-Voxel Prediction of Tissue Outcome in Acute Ischemic Stroke

Background: Predicting tissue outcome from early MRI scans is done visually (by assessing a visible diffusion-perfusion mismatch) or quantitatively. A number of quantitative models have been described, but to date these have been based on relatively small patient sample sizes (<20 patients). We sought to test a voxel-by-voxel predictive approach based on a generalised linear statistical model on a larger group of patients (n=74) to see if earlier reports of these approaches would still be valid in larger and presumably more diverse patient populations.

Methods: Consecutive patients enrolled in Brain Ischemia Study (BIS) within the first 12 hours of symptom onset and a follow-up imaging on day 7 or later in 74 patients with acute ischemic stroke. We used a supervised learning algorithm that predicted voxel-by-voxel tissue outcome. The model was trained using DWI, T2, apparent diffusion coefficient, mean transit time, cerebral blood flow, and cerebral blood volume as input parameters. The tissue outcome was modeled as a binary variable, either infarcted or non-infarcted. The region of interest for both training and application included voxels abnormal on mean transit time maps. We tested the ability of algorithm to predict tissue outcome using a leave-one-out approach (jackknifing) and computed the receiver operating characteristic (ROC) curve. Results: The area under ROC curve was 0.80. At the optimal operating point on the ROC curve, the algorithm predicted voxels that proceeded infarction with 63% sensitivity and 85% specificity. The correlation coefficient between the predicted volume of infarction and the actual volume on follow-up MRI was 0.90. Conclusion: The current algorithm that combines DWI and PWI is a valid and reliable method to assess the risk of infarction within ischemic brain regions.

P250 Conversion of Ischemic But Viable Tissue Into Infarction Increases With Age

Background: Brain regions normal on DWI but abnormal on mean transit time (MTT) maps represent tissue at risk of infarction, yet the fate of these regions is quite variable. The implied correlation between tissue outcome and initial imaging parameters is not surprising because each patient’s brain has different susceptibility to ischemic stroke. We hypothesize that individual patient characteristics such as age, gender, and stroke mechanism might be markers for tissue susceptibility to ischemia and thus play role in determining tissue outcome in human stroke.

Methods: Consecutive patients with acute ischemic stroke and DWI/MTT mismatch were included. All had MRI obtained within 12 hours of symptom onset and a follow-up imaging on day 7 or later in 74 patients with acute ischemic stroke. We used a supervised learning algorithm that predicted voxel-by-voxel tissue outcome. The model was first trained using DWI, T2, and ADC as input parameters. Tissue outcome was modeled as a binary variable (1 — infarction, 0 — no infarction). Multivariate analysis revealed that age and pretreatment PWI mismatch were independent predictors of pretreatment PWI mismatch 185% (range 13-1318). Age was positively correlated with pretreatment perfusion lesion volume (p = 0.49, p = 0.009) and with pretreatment diffusion lesion volumes (DWI, r = 0.35, p = 0.03, ADC, r = 0.41, p = 0.028). Age also correlated with pretreatment NIHSS (r = 0.38, p = 0.035). Age did not correlate with mismatch lesion volumes. Multivariate analysis revealed that age and pretreatment PWI volume were independent predictors of pretreatment ADC volume. Conclusions: Older age is associated with larger perfusion lesions in acute ischemic stroke, suggesting that older individuals may have impaired collateral flow producing perfusion failure. Age also predicts ADC lesion volume independently of perfusion lesion volume, suggesting greater neuronal vulnerability and accelerated progression to tissue infarction in the elderly.

P252 Evolution of Ischemia Over 14 Minutes Visualized by DWI in Hyperacute Stroke Patients
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Introduction: Over the scale of hours and days, following the onset of stroke has been characterized using diffusion weighted imaging (DWI) and the apparent diffusion coefficient (ADC) of water, respectively. It is not known whether there are systematic pathologic changes over longer periods in human stroke. We hypothesized that the volume of the lesion on DWI would change and the ADC value would also show a similar trend.

Methods: Within 6 hours of onset and prior to any therapy, 24 ischemic stroke patients were imaged twice, separated by 14 minutes, using CSF suppressed DWI. Lesions were segmented on each DWI (4000 SAX) each patient utilizing the automated algorithm described earlier. Results: Sub-regions were defined by the resulting overlap (“core”) and non-overlap (“progressing” and “reversing”) between the two time points. The lesion volume on DWI and the value of the lesions in the comparisons were computed using paired t-test. Values given are mean (SD). Results: Average time from onset to imaging was 2.6 (1.3) hours and median NIHSS was 13. Overall, lesion volume increased nominally from 14.3 (19.1) to 15.4 (18.9) ml, but this difference was not significant, p = 0.504. Lesion ADC values for all sub-regions, 0.60 x 10^ − 3 cm²/sec (0.050), were lower than that of homologous contralateral tissue, 0.80 cm²/sec (0.048), p = 0.001. In the “core”, the ADC decreased by 0.008 cm²/sec (0.034) but was not significant, p = 0.292. However, 6 patients had greater than 20% decrease while 9 had a greater than 20% increase in lesion volume. Similarly, significant differences were observed in the discordant sub-regions: the ADC in the “reversing”, increased by 0.053 (0.037), p < 0.001, and in the “progressing”, decreased by 0.034 (0.035), p < 0.001. Conclusions: We did not observe a significant increase in lesion volume or decrease in lesion ADC volume over a 14 minute period. However, individual patients both showed progression or reversal of lesion extent that was supported by a significant increase or decrease in the ADC of the corresponding sub-regions. In conclusion, early after stroke onset, ischemic injury as assessed by DWI, does not show significant progression or regression over a 14 minute period of observation.

P253 Apolipoprotein E Genotype Influences the Evolution of Ischemic Brain Injury
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Background: Apolipoprotein E (ApoE) genotype appears to have an effect on clinical outcome after ischemic stroke. Variations in ApoE genotype may also affect the rate of progression in tissue injury outcome following ischemic insult. We hypothesized that incorporating ApoE status into the analysis of tissue outcome as predicted from acute MRI may help identify a genetic component to salvagable brain tissue in ischemic stroke.

Methods: We studied 27 consecutive stroke patients in whom ApoE status information, acute MRI (<12 hours of symptom onset), and follow-up DWI were available (administered at 1 hour and 7 or later) in 28. We computed voxel- and lesion volume mapping (generalized linear model) that predicted voxel-by-voxel tissue outcome. The model was first trained using DWI, T2, and ADC as input parameters. Tissue outcome was modeled as a binary variable (1 — infarction, 0 — normal). We then developed another model for these same patients using only the input data of those patients with ApoE at 7 hours and input data of the form of 3 additional binary variables (ApoE2, ApoE3, ApoE4). We tested both models’ abilities to predict tissue outcome using a leave-one-out approach (jackknifing) and computed receiver operating characteristic (ROC) curves for each.

Results: The area under ROC curve rise from 0.656 prior to the incorporation of ApoE status to 0.714 after. This improvement in prediction indicates ApoE status impacts tissue outcome after infarction. Further work is needed to elucidate the precise mechanism by which ApoE exerts this influence. Conclusion: Combining genetic and imaging data into a single tissue signature model in acute human stroke appears feasible. When genetic data are incorporated with imaging data, genotype information appears to reduce the variability in predictions of tissue outcome in human stroke.
Background: Infarct volume in diffusion-weighted MRI (DWI) is increasingly used as an outcome measure in acute stroke. The gold standard in assessing DWI lesion volume is the traced area (planimetric) method. However, this method is slow and difficult to apply in the acute setting. In contrast, abc/2 is a much easier and faster method but it has yet to be validated. Here we aim to compare the level of concordance between the abc/2 method and the planimetric method in the measurement of infarct volume in DWI sequences. Methods: DWI sequences were obtained using a 1.5 T MRI. Abnormalities were analyzed in the trace image to avoid anisotropy. In order to measure DWI lesion volume by the manual segmentation method the perimeter of the area of abnormal signal intensity was traced on each DWI map and, subsequently, the volumetric software estimated the total volume using the thickness and the area measured on each slice. The abc/2 method consisted of dividing the product of the anteroposterior (a), transverse (b) and longitudinal (c) diameters of the lesion by 2. Each volume calculation was performed three times and the mean value was calculated and taken as definitive. Results: We studied 87 patients with acute infarction within the first 12 hours of onset. There was excellent correlation (Spearman’s rho = 0.97; P < 0.001) between the two methods. The average deviations were somewhat greater. There was a subgroup of 16 patients with all deviation of two measurements were calculated for each lesion and then averaged across all patients. CONCLUSIONS: Quantitative volumes by a single reader can provide highly reliable results of ischemic lesion volumes on DWI, MTT and FLAIR. In general, the error of the lesion volume measurement remained consistent from the acute to 3 and 24 Hour time points. The most consistent measurement was seen with FLAIR.

Table. Volume (cc) Statistics by Modality

<table>
<thead>
<tr>
<th>Modality</th>
<th>Time Point</th>
<th>Sample Size</th>
<th>Read One Average</th>
<th>Read Two Average</th>
<th>Pearson Correlation Coefficient</th>
<th>Absolute Volume Difference</th>
<th>Mean % Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>86</td>
<td>16.97</td>
<td>16.24</td>
<td>0.98</td>
<td>2.99 ± 5.08</td>
<td>29.59 ± 49.70</td>
<td>11.72</td>
</tr>
<tr>
<td>DWI</td>
<td>3 Hour</td>
<td>67</td>
<td>23.73</td>
<td>24.04</td>
<td>1.97 ± 0.60</td>
<td>21.98 ± 33.45</td>
<td>1.31</td>
</tr>
<tr>
<td></td>
<td>24 Hour</td>
<td>45</td>
<td>56.31</td>
<td>54.82</td>
<td>3.01 ± 5.94</td>
<td>26.44 ± 52.31</td>
<td>7.46</td>
</tr>
<tr>
<td>MTT</td>
<td>3 Hour</td>
<td>43</td>
<td>98.49</td>
<td>97.92</td>
<td>1.22 ± 24.11</td>
<td>16.82 ± 27.61</td>
<td>6.95</td>
</tr>
<tr>
<td></td>
<td>24 Hour</td>
<td>33</td>
<td>68.28</td>
<td>64.37</td>
<td>2.83 ± 1.34</td>
<td>31.94 ± 58.97</td>
<td>6.25</td>
</tr>
<tr>
<td>FLAIR</td>
<td>Day –108</td>
<td>103</td>
<td>30.88</td>
<td>30.19</td>
<td>1.85 ± 4.05</td>
<td>26.86 ± 53.45</td>
<td>6.16</td>
</tr>
</tbody>
</table>

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P254 Comparison of Planimetric and Abc Volumetric Methods to Measure Diffusion-Weighted Imaging Lesion Volume in Patients With Acute Ischemic Stroke
Salvador Pedraza, Carla Guerue, Jaume Asturias, Jose Meniz, Mar Castellanos, Maria Garcia, Victoria Medina, Joaquin Serena, Hoop Doctor Josep Trueta, Girona, Girona, Spain

Significant Artifact Reduction in Arterial Input Function Measurements for Quantitative Perfusion Imaging Using Dual-Echo Spiral-OUT-Spiral-IN Parallel MRI
Roland Bammer, Maarten A Lansberd, Stanford Univ, Stanford, CA; Michael E Moseley, Greg W Albers, Stanford Univ, Stanford, CA; Vincent Thijs, Univ of Leuven, Leuven, Belgium; Andrei V Alexandrov, Univ of Texas Med Sch, Houston, TX

Residual Arterial Flow Correlates With Apparent Diffusion Coefficient in Acute Middle Cerebral Artery Stroke
Alessandra Pavlovic, Inst of Neurology, Belgrade, Serbia and Montenegro; Clark W Sitton, Yosik Kim, Zsofia Garami, Andrei V Alexandrov, Univ of Texas Med Sch, Houston, TX

Transcranial Ultrasound Angiography: A New Contrast-Specific Imaging Mode
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Rationale and Objectives We present a new UCA imaging mode that offers an angi-like view of the intracranial vasculature and that may allow documentation of intracranial vascular anatomy with increased sensitivity and specificity. Methods Study design A Siemens Elegra and a Sonoline Antares were used for the studies in a total of 30 patients, after written informed consent. Imaged ultrasonic contrast agent was used, administered as bolus injections between 0.5–2.0ml. The main goal was to visualize the intracranial arteries, including the following vascular territories: middle cerebral artery (M1–M3), internal carotid artery (C1-C4), anterior cerebral artery (A1, A2), posterior cerebral artery (P1–P3). transcranial Ultrasound Angiography (tUSA) Using a B-mode phase inversion technique, the wideband harmonic frequencies are acquired and used for image generation. Different from other transcranial ultrasound techniques, tUSA is mainly characterized by lower output power (25–70%), lower mechanical index (MI 0.5–1), and higher fundamental frequency (1.3–2.0MHz). Results The sensitivity of tUSA to visualize the above mentioned vascular segments was as follows: Compared to other vascular imaging techniques, i.e. Color- or Power-Doppler, USPA provides improved spatial resolution and vascular delineation even of small vessels in the range of 1 millimeter. Figure: Circle of Willis Additional vessel segments could be visualized more consistently such other vascular imaging techniques, i.e. Color- or Power-Doppler, tUSA provides improved spatial resolution and vessel conspicuity. These improvements allow one to perform more reliable measurements of the AIF, while still being sufficiently sensitive to small T2*-changes in white matter.

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Intra-Rater Reliability of Quantitative Ischemic Lesion Volumes on Diffusion-Weighted, Mean Transit Time, and FLAIR MRI
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BACKGROUND AND PURPOSE: We investigated the hypothesis that volumetric measurements of ischemic lesion volumes provide high intra-rater reliability when assessed by different imaging modalities at various times from onset. Methods: Three phase analysis software was used for measurement of ischemic lesion volumes from diffusion weighted MRI (DWI), mean transit time (MTT) perfusion MRI, and FLAIR MRI at acute (< 3 hours from stroke onset), subacute (3 and 24 hours after the first scan), and chronic (> 3 days from admission) time points. A semi-automated technique for identification and manual editing of the lesions was used by a single reader, blinded to patient treatment and time point. The reader measured the volume of each lesion on two occasions separated by at least 1 week. Measurements from each modality were performed independently of those from the others. An average volume for the sample was calculated for each read. In order to measure the absolute volume of the difference and the percentage deviation of two measurements were calculated for each lesion and then averaged across all patients. RESULTS: The volume statistics for the two separate reads performed at least one week apart are listed in the Table. The test-retest correlations were 0.98 to 1.00. There was good agreement between the average of each read (≤ 5% for DWI and FLAIR; ≤ 10% for MTT). The average deviations were somewhat greater. There was a subgroup of 16 patients with all time points, and the volume statistics for this subset were consistent with those of the large group of patients. CONCLUSIONS: Quantitative volumes by a single reader can provide highly reliable results of ischemic lesion volumes on DWI, MTT and FLAIR. In general, the error of the lesion volume measurement remained consistent from the acute to 3 and 24 Hour time points. The most consistent measurement was seen with FLAIR.

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Transcranial Ultrasound Angiography: A New Contrast-Specific Imaging Mode
Thilo Hoelscher, Univ of California, San Diego, San Diego, CA; Wilko G Willikens, Ruhr-Univers, Bochum, Germany; Scott E Olson, Karen Alton, Lama Al-Khoury, Yu D Cheng, Patrick D Lyden, Robert F Mattrey, Univ of California, San Diego, San Diego, CA
Ultrasound Perfusion Imaging Differentiates Compensated Hyperperfusion From Infarcted Tissue in the Acute Phase of Stroke: Preliminary Results

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BACKGROUND: Transcranial ultrasound perfusion imaging (UPI) using echo-contrast agent microbubbles is a novel approach to assess normal and altered brain perfusion. Recent studies have already demonstrated its usefulness in acute ischemic stroke of the middle cerebral artery (MCA) territory. It is unclear, however, whether UPI also differentiates between different degrees of hemodynamic compromise.

METHODS: Using UPI, 19 patients were investigated within 12 hours after symptom onset. In 9 of these the large MCA stroke and 10 with signs of compensated hyperperfusion in the MCA territory due to unilateral high-grade stenosis or occlusion of the internal carotid artery (ICA). Multi-modal MRI including diffusion-weighted (DWI) and perfusion-weighted (PWI) imaging was promptly obtained in all patients and used as a reference method to classify hemodynamic compromise.

RESULTS: The standardized UPI procedure consisted of local measurements of acoustic intensities in regions of interests (ROIs) (1) before contrast agent injection (“tissue harmonic intensity”, THI), (2) of the “tissue to peak intensity” (TPI) in cerebral tissue after contrast agent bolus injection, and (3) of the parenchymal loss of microbubble-related signal intensity due to high acoustic energy during a contrast agent steady state (“microbubble destruction imaging”, MDI). RESULTS: In patients with compensated hyperperfusion acute DWI MCA territory (1), 0.85 ± 0.13, (24.4 ± 19.8, p < 0.05), and MDI showed reduced values (5.9 ± 9.6 dB, p < 0.05) compared to ROIs of contralateral normal tissue, whereas THIs were not different (9.1 ± 10.1 dB). In contrast, patients with large MCA infarction showed differences of both THI (6.4 ± 11.5 dB, p < 0.05) and MDI (4.9 ± 8.4 dB) in ROIs of ischemic compared to normal tissue (p < 0.05). CONCLUSION: This preliminary study suggests that UPI may differentiate areas of compensated hypoperfusion from infarcted tissue since THIs measured before contrast agent injection are diminished in early infarction but normal in compensated hypoperfusion.

MMP-9: Biomarker for Salvageable Tissue in Acute Stroke?

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Background: Matrix metalloproteinases (MMPs) have been linked to blood brain barrier integrity in stroke and thus have been investigated as candidate markers for stroke outcome. Previous studies comparing MMP-9 levels with lesion volume in humans have been conflicting. One study found a low correlation (r = 0.385, n = 39) between MMP-9 and infarct volume while another found no correlation (n = 24). Other investigators have found that the presence of hemorrhagic transformation was associated with both higher MMP-9 and higher final infarct volume (n = 38), implying that under some conditions, there may be a relationship between MMP-9 and outcome.

Methods: Surface enhanced laser desorption/ionization (SELDI) analysis of unfractionated was performed on citrated plasma from patients (n = 35) diagnosed with ischemic stroke (mean time following onset ~36 h) and compared with the protein expression profiles of age and sex matched controls (n = 32). Samples were run in duplicate on 3 different Proteins (imaging, CM10, Ni). To correct for differences between 2 populations, the datasets were analyzed with several multivariate algorithms: Logical Analysis of Data (LAD) and k-folding cross-validation, Support Vector Machines (SVM) and CART (Classification and Regression Tree).

Results: 15 distinct peaks with p-values of < 0.05 were identified. A peak at 11.1 kDa was significantly elevated in stroke patients (p-value = 0.00057) correlated with the severity of the stroke. However, this peptide alone was unable to segregate the 2 populations with high sensitivity or specificity. Using LAD as a panel of several markers (m/z: 28.122, 61, 56.202, 8755.8, and 8703.1) which reliably separated stroke patients from control samples (average sensitivity and specificity of 92.5% and 86.9%, respectively). These four markers were also found to be critical in separating the 2 populations using other multivariate algorithms, including SVM and CART.

Current work is aimed at identifying these 4 markers, as well as using high-throughput preselection steps to detect more low abundant proteins and improve on sensitivity and specificity measurements. Conclusions: Current work is aimed at identifying these 4 markers, as well as using high-throughput preselection steps to detect more low abundant proteins and improve on sensitivity and specificity measurements.

Protein Expression Profiling of Plasma Separates Stroke Patients From Age- and Sex-Matched Controls: Implications for Discovery of Novel Biomarkers for Stroke

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Background and purpose: Stroke is a leading cause of morbidity and mortality in the United States. An early diagnostic test would be beneficial in treating this disease and could aid in improvement of clinical outcomes. Our purpose was to see if a protein marker of acute ischemic stroke could be identified.

Methods: Surface enhanced laser desorption/ionization (SELDI) analysis of unfractionated was performed on citrated plasma from patients (n = 35) diagnosed with ischemic stroke (mean time following onset ~36 h) and compared with the protein expression profiles of age and sex matched controls (n = 32). Samples were run in duplicate on 3 different Proteins (imaging, CM10, Ni). To correct for differences between 2 populations, the datasets were analyzed with several multivariate algorithms: Logical Analysis of Data (LAD) and k-folding cross-validation, Support Vector Machines (SVM) and CART (Classification and Regression Tree).

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**Acute Management**

**Patients Taking Lipid-Lowering Agents at the Time of Acute Ischemic Stroke Have Lower Mortality and Less Severe Strokes**

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**Objective:** To determine if patients taking lipid lowering agents (LLA) at time of stroke have a better outcome than patients not taking LLA. **Background:** Hydroxymethylglutaryl-CoA reductase (HMG-CoA) activity inhibitors (“statins”) have neuroprotective effects in rodent models of ischemic stroke, especially when given prior to stroke onset. Little data is available on the effect of statins and other LLA on stroke severity in humans. **Methods:** The Northern Manhattan Stroke Study is a population-based study designed to determine stroke incidence and prognosis. Cases were eligible if they were: (1) diagnosed with first cerebral infarction (fatal or non-fatal); (2) age ≥40 at stroke onset; and (3) resident in northern Manhattan. Cases or proxies were interviewed regarding medications taken prior to stroke. The NIH Stroke Scale (NIHSS) was used to assess stroke severity, and severity was categorized as mild (NIHSS 0–5), moderate (6–14), or severe (≥14). Odds ratios and 95% confidence intervals (OR, 95% CI) for association between LLA use and stroke severity were calculated using logistic regression. **Results:** Data was assessed in 90-day windows. **Results:** Results: Mean age of patients was 71.6 ± 12.6 years, and 44.8% were men. Of 691 patients, 63 (9.1%) were taking LLA. Younger patients and those with history of hypertension, diabetes, hyperlipidemia or coronary artery disease were less likely to be taking LLA. Sex, smoking, and congestive heart failure were not associated with LLA use. The 90-day mortality rate was significantly lower in those taking LLA (1.6% vs 11.2%, p = 0.017). Of 649 patients with data available on stroke severity, patients on LLA at time of stroke showed a trend toward less severe stroke (8.8% versus 16.5% severe strokes; OR 0.55, 0.23–1.32). Age was strongly associated with severity: those age ≥70 had twice the risk of a severe stroke (OR 1.95, 1.25–3.02). After adjusting for age and sex, the association of LLA with reduced stroke severity was minimally changed (OR 0.62, 0.26–1.48). This effect was independent of other major stroke risk factors. **Conclusions:** Patients taking LLA at time of acute ischemic stroke have lower 90-day mortality and may have less severe strokes. Prospective studies of the neuroprotective effects of LLA, and statins in particular, are warranted.

**Survey of Emergency Physicians Regarding rtPA for Acute Ischemic Stroke**

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**Introduction.** Despite the results of the NINDS rt-PA Stroke Study and support from the neurological community, the use of rt-PA for acute ischemic stroke is controversial among Emergency Medicine (EM) residents. Skeptics believe that the symptom-onset to time of treatment (sICH) risk is too high and/or the benefit is too low. Currently, the upper limit of sICH risk which would be considered tolerable, and lower limit of associated benefit with lytic therapy for acute ischemic stroke are unknown. We surveyed EM physicians to determine these values. **Methods.** To determine if patients taking lipid lowering agents (LLA) had a lower extent of brain ischemia during the acute phase of ischemic stroke.

**Conclusions.** Of 649 patients, 63 (9.1%) were taking LLA. Younger patients and those with a small increase in the median [quartiles] DWI lesion volume was observed (2 cc [6–8]), whereas an important drop of the NIHSS score was found at 72 hours (0 points [0.14]). Patients with POM but not CDM had DWI lesion >25 ml (n = 14; 4.1 t-PA) or NIHSS score <8 (n = 14; 6-PA). In the first group the initial median DWI volume increased by 104cc [4.5, 202] at 72 hours, but the median NIHSS score (20 points) did not change. Similar results were observed in patients not treated with t-PA. The group with NIHSS >8 showed a mild reduction in the median NIHSS score (3 points [−9,7]) and increase in DWI lesion (4cc [−10,50]) at 72h. Conclusions: CDM identifies penumbra in most patients, although it fails to identify tissue at risk in patients with large initial DWI lesions. However, in this group, hyperperfused brain is likely irreversibly damaged.
Does “Get With The Guidelines—Stroke” Improve Adherence to NINDS Time Targets in Patients Hospitalized With Ischemic Stroke or TIA? 

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**Background:** Get With The Guidelines (GWTG)—Stroke is the American Stroke Association program to improve hospital care in patients admitted with acute ischemic stroke or TIA, including reducing time to treatment. **Methods:** We used inter-hospital collaborative meetings, best practice sharing and an Internet tool for data collection, reporting and decision support in 18,361 IS patients from 99 hospitals. Data collection comprised baseline (collected prior to 4/03) and four consecutive quarters (4/03 to 3/04). Patients from 3 CDC-funded Paul Coverdell acute stroke registry prototypes (MA, OH, GA) were included if the hospitals used the GWTG tool for data entry and GI during all 4 quarters after baseline. In those patients arriving <3 hr after onset, we measured compliance (%) with NINDS recommendations (CT<25 min) and (tPA<60 min), and mean Door to CT, Door to tPA, and Onset to tPA times. **Results:** A complete database was obtained when documented as the cause of inability. Compliance (%) was recorded at each quarter and compared to baseline; trends over time were assessed by Mantel-Haenszel chi-square test or simple linear regression. Door to CT was non-normal and was analyzed in the regression model as rank data. Results: CT times improved, but less than 25% of patients got a CT<25 min or tPA<60 min. While delays in patient arrival were common and remained static, exclusions due to delays in CT performance decreased dramatically. **Conclusions:** GWTG-Stroke implementation was associated with improved compliance with NINDS time targets for CT scan but not tPA. The proposed targets may not be widely achievable in the current environment. To accomplish this, an integrated stroke systems approach may be needed to get patients to dedicated stroke centers more rapidly and with early notification.

**Table: Predictors of 90 day Mortality**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate Analysis OR (95% CI)</th>
<th>Multivariate Analysis OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSS score</td>
<td>1.10 [1.07–1.14], &lt;0.0001</td>
<td>1.11 [1.07–1.15], &lt;0.0001</td>
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<tr>
<td>Age (yr)</td>
<td>1.03 [1.01–1.05], 0.0004</td>
<td>1.03 [1.01–1.05], 0.0017</td>
</tr>
<tr>
<td>Time to treatment (hr)</td>
<td>1.31 [1.15–1.49], &lt;0.0001</td>
<td>1.23 [1.05–1.43], 0.0086</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.94 [1.91–4.54], &lt;0.0001</td>
<td>2.94 [1.91–4.54], &lt;0.0001</td>
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<tr>
<td>Atrial fibrillation</td>
<td>2.29 [1.45–3.61], 0.0004</td>
<td>ns</td>
</tr>
<tr>
<td>Heart rate</td>
<td>1.01 [1.00–1.02], 0.03</td>
<td>ns</td>
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Comparison of MERCI Mortality With NINDS

**MERCI Study Investigators, Wade S Smith, Univ of California, San Francisco, San Francisco, CA**

**Background:** The Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial reported a 43% overall mortality compared with 19% in the NINDS intravenous t-PA trial. We address whether this difference in mortality can be explained by differences in baseline variables. **Methods:** Clinical data from MERCI (n=141 patients) and the NINDS placebo group (n=312) were combined and both univariate and multivariate analysis of mortality at 90 days was performed. Twenty-five variables were considered in the model including the variable “study” (1 for MERCI, 0 for NINDS). Using multivariate logistic regression, we examined the independent association between mortality at 90 days and study. **Results:** Variables predictive of 90-day mortality in univariate analysis (p<0.05) were baseline NIHSS score, age, time to treatment, study, atrial fibrillation, and heart rate (see table). Multivariate regression modeling revealed NIHSS, age and time to treatment, and not study, were significant. **Discussion:** The high mortality reported in the MERCI trial is likely due to stroke severity. The presence of a large vessel intracranial occlusion during stroke has negative prognostic significance.

Blood Glucose But Not Blood Pressure Course Predicts Spontaneous Hemorrhagic Transformation After Acute Ischemic Stroke

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**Background and Purpose:** Hemorrhagic transformation (HT) is a frequent complication of large strokes. Factors associated with this complication are not well known in populations not submitted to thrombolytic therapy. In the present study, we aim to evaluate the predictors of spontaneous HT after acute ischemic stroke. **Methods:** We studied consecutive patients not submitted to thrombolysis admitted within 24 hours of acute stroke onset. Patients underwent a structured clinical evaluation and diagnostic tests for stroke etiology investigation. Blood glucose and blood pressure (BP) were collected periodically for 48 hours. Neuroimaging data (CT or MRI) on presence of HT was sought, classified into hemorrhagic infarct (HI) or parenchymal hematoma (PH). We then analyzed possible variables associated with HT and PH. **Results:** We admitted 170 patients from January, 2001 to September, 2003. Mean age was 66±14 years, 39% females. Median NIHSS score was 5 (range 0 to 36), mean admission systolic BP was 158 mmHg (range 98 to 240 mmHg) and diastolic BP was 93 mmHg (range 42 to 170 mmHg). HI was present in 8.2% of patients, and PH in 2.9%. Predictors of HI in univariate analyses were (<p<0.05): hyperglycemia (<200 mg/dl) on admission, 24 and 48 hours; diabetes; atrial fibrillation; total anterior circulation infarct (TACI) on Oxfordshire classification; and non lacunar infarcts on TOAST classification. Predictors of PH were: blood glucose in the first 24 hours; NIHSS score; and TACI. In a multivariable analysis, remained predictors of HI: admission hyperglycemia (OR=1.18; 95% CI=1.06–1.30); TACI (OR=1.18; 95% CI=1.03–1.35) and atrial fibrillation (OR=1.25; 95% CI=1.09–1.45). Multivariable predictors of HP were: blood glucose (OR=1.01 for every 10 mg/dl increase; 95% CI=1.00–1.02) and NIHSS score (OR=1.01 for every 1 point increase; 95% CI=1.00–1.01). Blood pressure course in the first 48 hours (including spontaneous increases or decreases over 25% from baseline) did not affect the prevalence of either HI or HP. **Conclusions:** Hyperglycemia in the first 48 hours is a strong independent predictor of HI and PH in acute stroke patients. Even large BP fluctuations do not seem to affect the prevalence of HT in patients not submitted to thrombolysis.

Respiratory Muscle Weakness and Aspiration in Acute Stroke Patients

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**Background:** The consequences of aspiration in acute stroke patients depend not only on oro-pharyngeal incoordination but also on the integrity of mechanisms to clear airways. Weakness of respiratory muscles may result in ineffective airway clearing but has not been investigated. **Methods:** Respiratory muscle strength was assessed in 11 stroke patients within 1 week of onset and compared with 10 age-matched controls. A double balloon catheter was passed through the nose and oesophageal (P0.0), gastric (Pga) and transdiaphragmatic (Pdi) pressures measured during twitch stimulation of the phrenic nerves (TwPgas) for abdominal muscles strength (expiratory). Inspiratory and expiratory pressures at the mouth and cough flow were also measured. These tests were repeated after 6 weeks to assess recovery. **Results:** Stroke patients showed significantly lower cough flow rates and lower inspiratory and expiratory pressures on volitional manoeuvres compared with matched controls. However, there were no significant pressure differences between stroke patients and normal controls during phrenic nerve or T10–11 spinal root stimulation. Aspiring stroke patients had more severe impairment of muscle function compared with non-aspirators. Respiratory muscle function improved during recovery. **Conclusions:** Acute stroke patients have significant weakness of respiratory muscle function due to central mechanisms, which impair their ability to clear airways. Better understanding of mechanisms, consequences and management of this weakness may help to reduce the frequency of chest infections in stroke patients.
Telestroke Network Improves Stroke Care in Nonurban Areas: The Telemedic Project: Integrative Stroke Care in Eastern Bavaria


Background: Telemedicine in network of two stroke centers and 12 regional hospitals. The network was established in order to achieve specialized care for all stroke patients in eastern Bavaria.

Methods: All network hospital established specialized stroke ward where qualified teams manage acute stroke patients. Physicians in the local hospitals are able to contact the two stroke centers via videoconference system and digital transfer of DICOM-data. The service is available 24 hours per day and is staffed with experienced strokeologists. The data were collected prospectively. In 2003 4179 stroke patients were admitted to the network-hospitals. Between Feb. 1 2003 and Aug. 1 2004 a total of 3524 teleconsultations were performed. 141 patients received systemic thrombolysis with 11 patients. P273

Blood Glucose Control in Acute Stroke: Different Targets for Diabetic and Nondiabetic Patients?

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Background: We sought to determine if disparities in stroke treatment were present in a large sample of hospitalized stroke patients. Methods: Get With The Guidelines-Stroke used inter-hospital collaborative meetings, best practice sharing and an Internet tool for data collection, reporting and decision support in 21563 Sites and TIA patients from 99 hospitals. Data collection comprised baseline (collected prior to 4/30) and four follow-up quarters of data (from 4/01 to 3/04). Patients from 3 states (PA, OH, MI) had a survey of stroke registry prototypes (MA, OH, GA) were included if the hospitals used the GWTG tool for data entry and QI during all 4 quarters after baseline. A logistic regression model examined disparities in measures that were significant in univariate analysis (SAS). Variables included were age, race, gender, hospital size, presence of housestaff and time by quarter. Measures with disparity were: use of IV tPA or documention of ineligibility (why no tPA) in patients who arrived >2 hours (ED-2 h) and >3h (ED-3 h) after symptom onset; use of tPA>60 min, and antithrombinics within 48 hours when appropriate (Rx AT<48h). Results: Patients were 44% male and 80.7% Caucasian, 13.4% African American. Mean age was 72.3 years (0.5% ± 0.5 years). All 1 measure improved over time. No major disparities were seen. In women and Blacks, early and anti-arrhythmic use occurred less frequently. Larger hospital was associated with better performance in all tPA measures. Hospitals with the <100 IS discharges had less early anti-arrhythmic use, documented tPA inefficacy, and early CT scans. The absence of housestaff was associated with more frequent CT <25 min, tPA < 60 min and documented tPA inefficacy. Conclusion: Larger disparities exist in acute stroke delivery associated with both patient and hospital characteristics. Larger hospitals performed better on many measures, but interestingly the presence of house staff slowed down evaluation and treatment. Strategies to improve performance should be targeted.

Blood Glucose Control in Acute Stroke: Different Targets for Diabetic and Nondiabetic Patients?

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Aims To study the impact of blood glucose control on early stroke mortality in diabetic and non-diabetic stroke patients, and to identify the optimal blood glucose level for each patient category. Material and methods A representative sample of 84 diabetic and 383 non-diabetic stroke patients was studied. Logistic regression analyses were performed in order to estimate the impact of blood glucose control on admission and during hospital stay and other clinical parameters on 30-days case-fatality. Receiver operating characteristic (ROC) curves were used to predict case-fatality by blood glucose control. Results Blood glucose, body temperature and level of consciousness were independently related to early stroke mortality in both diabetic and nondiabetic patients (table 1). The blood glucose levels during the entire hospital stay had a greater impact on 30-days case-fatality than the blood glucose values on admission, particularly in diabetic patients. A blood glucose level above 10.3 mmol/l predicted 30-days case-fatality in diabetic patients (figure 1 A). The corresponding value was 6.3 mmol/l in non-diabetic patients (figure 1 B). Conclusion Improved blood glucose control may have a potential to reduce early stroke mortality. The therapeutic goal seems to be considerably lower in non-diabetic than in diabetic patients.
The Cost-Effectiveness of Acute Stroke Treatments: A Comparison of Using Prototypical Thrombolytic and Neuroprotectant Therapies

By David B Matchar, Gregory P Samsa, Duke Univ Med Ctr, Durham, NC

Background and Purpose: Emergency Department (ED) management of transient ischemic attack (TIA) is variable, yet the risk of stroke and death following this event is high. We examined temporal trends of ED practice patterns in managing TIA over a 5-year period, during which time stroke treatment changed and TIA management guidelines were published.

Methods: All TIA seen in EDs between 1993–94 and 1999–2000 were identified within an urban population of 1.3 million using retrospective chart review. Data on admission rate, CT rate in the ED, and time from ED arrival to CT scan were collected. Primary outcomes were rates of stroke, recurrent TIA, and death from all causes during the twelve months after the index ED visit. Life-table analysis methods were used to estimate the outcome rates.

Results: A total of 643/791 (81%) of TIA patients within the population during the study period from 1993–94 and 68% of patients admitted in1999 (p < 0.05). The rate of CT in ED evaluation of TIA increased from 50% of discharged patients in 1993–94 to 86% of discharged patients in 1999 and from 75% to 95% of admitted patients (p < 0.001 for both). Median time to CT in 1993–94 was 1.2 hours (interquartile range 0.8–1.9) and decreased to 1.0 hours (interquartile range 0.7–1.8; p < 0.005) in 1999. The risk for the combined outcome of death/stroke/recurrent TIA following initial TIA within this population did not change significantly over time, and for 1993–94 vs. 1999 was 5% vs. 3% at 7 days, 9% vs. 7% at 30 days, 14% vs. 13% at 90 days, and 18% in both study periods at 180 days (p > 0.04).

Conclusions: The rate of admission following a first TIA in this population-based study did not change over time. The rate of imaging in the ED increased significantly from 1993–94 to 1999, while the time to obtain imaging decreased significantly. The short- and long-term risk of death, stroke, or recurrent TIA remained high and is consistent between the time periods studied.

The Effectiveness of Lipid-Lowering Drugs on Stroke, Recurrent MI, and Mortality After the Acute Coronary Syndrome: A Meta-Analysis

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Background: Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) have been increasingly used for the treatment of hypercholesterolemia. The objective of this meta-analysis was to estimate the effectiveness of early statins (lipid lowering drugs) treatment on stroke, recurrent myocardial infarction, and mortality in the patients with acute coronary syndrome.

Methods: A comprehensive search was performed in MEDLINE, the Cochrane Library, and EMBASE databases. A manual search was also performed using reference lists. Inclusion criteria were: (1) patients who had confirmed myocardial infarction (MI) at admission; (2) stated one of three outcomes and treatment with statins or other lipid lowering drugs, (3) initiated lipid lowering treatment before discharge or at the time of discharge from the hospital, and (4) all-cause mortality, recurrent MI, and stroke were outcomes. A pooled proportional (1-odds ratio) and its corresponding 95% confidence interval (CI) in both fixed effects and random effects model were used. Results: A total of 62796 patients (case: 18075, control: 44721) were included in these studies. There was significant difference between stroke (1.66 statins vs. lipid lowering drugs) and placebo or usual care (OR: 0.54, 95% CI: 0.4 - 0.6) for the mortality from all causes. Patients who received statin (lipid lowering drugs) treatment had not significant benefit in terms of prevent recurrent MI (OR: 1.1, 95% CI: 0.7–1.5). Statin (lipid lowering drugs) treatment significantly prevented stroke after the coronary syndrome (OR: 0.53, 95% CI: 0.4 – 0.8). Conclusion: This meta-analysis suggests that treatment with statins or lipid-lowering drugs in acute coronary syndrome significantly reduced in mortality from all causes and prevented stroke, but not recurrent MI.

Molecular Markers of Neurotoxicity, Neuroinflammation, and Blood-Brain Barrier Disruption in PW/DWI and Clinical/DWI Mismatch

By Miguel Blanco, Hosp Clinico Univ, Santiago, Spain; Mar Castellanos, Joaquín Serena, Hosp Univ Josep Trueta, Girona, Spain; Manuel Rodríguez-Yáñez, Tomás Sobrino, Roger Leira, Hosp Clinico Univ, Santiago, Spain; José Vivancos, Hosp Univ La Princesa, Madrid, Spain; Ignacio Lizasoain, Univ Complutense, Madrid, Spain; Salvador Pedraza, Antonio Darro, Hosp Univ Josep Trueta, Girona, Spain; José Castillo, Hosp Clinico Univ, Santiago, Spain

Background and purpose: PWI/DWI (PDM) and clinical/DWI (CDM) mismatch are emergent concepts which identify ischemic brain at risk of infarction. Our aim was to determine whether PDM and CDM are associated with a similar profile of molecular signatures of neurotoxicity after ischemic stroke. Methods: We studied 208 patients within 12 hours from stroke onset. At baseline (median time from onset, 151 min) NIHSS score and multimodal MRI were evaluated. CDM was diagnosed when the NIHSS score >9 and DWI lesion volume >25 ml, and PDM (evaluated in 79 patients) when the ratio between the PWI and the DWI lesion volumes was >1.2. Glutamate, GABA, L-arginine, interleukin-6 (IL-6), tumour necrosis factor-alpha, matrix metalloproteinase-9 (MMP-9), and cellular fibronectine (cF) were determined in blood samples obtained within 24 hours of admission. Results: There was a significant difference of M0, M60 and CDM and PDM respectively. On admission and at 24 hours, glutamate, and IL-6 concentrations were significantly higher in patients with CDM and PDM than in those without mismatch, although the effect was stronger in patients with CDM. MMP-9 and cF concentrations were significantly higher in patients with CDM but not in those with PDM. In logistic regression models, glutamate (p = 0.002) and cF (p = 0.0001) levels at baseline were independently associated with CDM. No molecular marker was selected in the multivariate models for PDM. Conclusion: Patients with PDM and CDM show high plasma concentrations of molecular markers for neurotoxicity, inflammation, and blood-brain barrier disruption. These findings support the idea that CDM reflects ischemic tissue at risk of cytotoxic mediated infarction.
Hyperglycemia in Acute Stroke: To Be or Not to Be Diabetic—Therapeutic Implications
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Introduction: Several studies have found the deleterious role of hyperglycemia in acute stroke, and that this effect is higher in non-diabetic patients. However, a recent interim analysis of GLA study has pointed out that up to 82% of acute stroke patients with glucose levels higher than 150 mg/dl had a previous history of diabetes, whereas no non-diabetic patients had a glucose level higher than 150 mg/dl. Moreover, the previous history of diabetes in acute ischemic stroke was associated with significantly larger volume of mismatch in patients with posterior circulation strokes (15% of all ischemic strokes) compared to anterior circulation strokes. Therefore, the objective of this study was to evaluate the effect of initial hyperglycemia in acute ischemic stroke patients with and without a previous history of diabetes.

Methods: In this retrospective study, we evaluated the cases of acute ischemic stroke between January 2014 and December 2015 in the neurology department of Hospital Clinic (Barcelona, Spain). The inclusion criteria were: acute ischemic stroke defined by the diagnostic workup and symptoms lasting for ≥24 hours. The cases were divided into two groups: Group I included patients with a previous history of diabetes (n = 62), and Group II included patients without a previous history of diabetes (n = 91). Glucose levels were measured at admission, and the patients were divided into high (≥150 mg/dl) and normal (<150 mg/dl) hyperglycemia. The primary outcome was death or disability, defined as mRS >2. The secondary outcomes were: death or disability observed in all patients without significant interaction with HAS in the multivariate model (Wald χ² = 17.8, p = 0.0001; adjusted OR 0.4, 95%CI, 0.2–0.8), and at 1-year in 11% in the stroke unit vs. 30% in GMW (p = 0.0001; adjusted OR 0.6, 95%CI, 0.3–1.2). Death or disability defined as Barthel Index <80 was present at 1-month in 10% of the patients in the stroke unit vs. 65% in GMW (p = 0.0001; adjusted OR 0.4, 95%CI, 0.3–0.7), and at 1-year in 14% in the stroke unit vs. 41% in GMW (p = 0.0001; adjusted OR 0.4, 95%CI, 0.2–0.8). Similar trends were found in analyses by sub-groups. Conclusions: Patients with acute stroke treated in a dedicated short-term acute stroke unit achieved better outcomes at discharge and follow-up. The proven effectiveness of stroke units extends to a dedicated short-term acute stroke care setting.

Differential Effect of Vascular Location on the Volume of Diffusion-Perfusion Mismatch in Acute Stroke
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Background: Diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI) have been used increasingly in recent years to evaluate acute stroke in the emergency setting. The diffusion-perfusion mismatch (DPM) has been visualized both in anterior and posterior circulation stroke. Also, it has been demonstrated that stenosis in intracranial posterior circulation was associated with significantly larger volume of mismatch than intracranial anterior circulation and extracranial carotid artery. However, the relationship between DWI and PWI is not well understood. The aim was to investigate the relationship between DWI and PWI in acute stroke.

Methods: The study was conducted in a single center from 2012 to 2014. Patients with acute stroke were included in the study. The PWI parameters were: 10.0 s TE, 3.7 s TR, 15° flip angle, 15 ml saline bolus injection, and 5-minute scan duration. The DWI parameters were: b-value of 1000 s/mm², TE = 80 ms, TR = 4000 ms, and 4 mm 3D FIESTA sequence. The PWI and DWI were performed with a 3.0 T MRI scanner (Sonata, Siemens, Germany). The DWI and PWI were analyzed using in-house software. The volume of mismatch was calculated by subtracting the DWI volume from the PWI volume.

Results: A total of 50 patients with acute stroke were included in the study. The mean age of the patients was 58 years (range: 21–89). The median NIHSS score was 15 (range: 1–23). The mean time from symptom onset to imaging was 3.5 hours (range: 0–24). The mean volume of mismatch was 90 cm³ (range: 0–400). The mean difference in volumes between DWI and PWI was 50 cm³ (range: 0–180). The mean correlation coefficient for total score was 0.94 (95% CI 0.84, 1.00). Reliability scores were similar among specialists and centers and there were no differences between nurses and physicians. Kappa scores were higher among raters previously certified. These certification DVDs are reliable for NIHSS certification, and scoring sheets have been posted on a website for real-time, on-line certification.

Poster Presentations
**P287 Temporal Trends in Emergency Department Arrival Times for Acute Ischemic Stroke: A Population-Based Study**

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**Introduction:** While there are many medical contradictions that limit rt-PA use for acute ischemic stroke (IS), time from symptom onset to arrival has been shown to be the most important factor. We present data regarding temporal trends in arrival times for acute IS within a large, biracial population. **Methods:** All IS from 7/93–6/94 and 1/99–12/99 within our population of 1.3 million were identified by review of all primary and secondary hospital discharge diagnoses ICD-9 codes 430–438 in 7/93–6/94 and 430–436 in 1999 at all local hospitals and clinics, and a sampling of outpatient sites. Subtype, symptom onset time, and ED arrival times were collected from the medical record. **Results:** There were 2,308 IS in 1993/94, and 2,542 in 1999. There were no significant differences between the two study periods in the percentage of IS that presented to an ED (80%) or that had documented times of symptom onset and arrival (–30%). In 1999, 20% of all IS patients arrived within 3 h of symptom onset, compared to 18% in 1993/94 (p = 0.02), see Figure for percentages of arrivals within each time window. **Discussion:** Despite the approval of rt-PA by the FDA and numerous public awareness campaigns, there was only marginal improvement in arrival times for IS patients in 1999 compared to 1993/94. Further research is needed to assess the effectiveness of public awareness campaigns in changing knowledge and behavior of acute stroke patients. Only 8% of all IS patients arrive to an ED 3–8 h after symptom onset, a time window that is the focus of several ongoing acute IS treatment trials. Expansion of the treatable time window to 8 h may not dramatically affect the percent of IS patients treated with acute therapies.

**P288 Creatinine Level May Not Be Required Before Emergency CTA in Acute Stroke Assessment**

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**Background:** The wait for a creatinine result often delays CT angiography (CTA) when required for rapid triage of acute stroke patients. At our institution, we proceed with CTA without creatinine levels in emergent situations if there is no known history of renal disease. This study was performed to evaluate CTA appearance without a creatinine level is available (n = 82) the rate of RCN was actually higher, but not significantly in the group with known creatinine than the unknown group (relative risk = 1.0). None of the 185 patients developed acute renal failure needing dialysis. **Conclusion:** We present data regarding temporal trends in arrival times for acute IS within a large, biracial population. **Methods:** All IS from 7/93–6/94 and 1/99–12/99 within our population of 1.3 million were identified by review of all primary and secondary hospital discharge diagnoses ICD-9 codes 430–438 in 7/93–6/94 and 430–436 in 1999 at all local hospitals and clinics, and a sampling of outpatient sites. Subtype, symptom onset time, and ED arrival times were collected from the medical record. **Results:** There were 2,308 IS in 1993/94, and 2,542 in 1999. There were no significant differences between the two study periods in the percentage of IS that presented to an ED (80%) or that had documented times of symptom onset and arrival (–30%). In 1999, 20% of all IS patients arrived within 3 h of symptom onset, compared to 18% in 1993/94 (p = 0.02), see Figure for percentages of arrivals within each time window. **Discussion:** Despite the approval of rt-PA by the FDA and numerous public awareness campaigns, there was only marginal improvement in arrival times for IS patients in 1999 compared to 1993/94. Further research is needed to assess the effectiveness of public awareness campaigns in changing knowledge and behavior of acute stroke patients. Only 8% of all IS patients arrive to an ED 3–8 h after symptom onset, a time window that is the focus of several ongoing acute IS treatment trials. Expansion of the treatable time window to 8 h may not dramatically affect the percent of IS patients treated with acute therapies.

**P290 The “Stroke Team Remote Evaluation Using a Digital Observation Camera (STRoKe DOC)” Telemedicine System: Methods**

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**Objective:** To describe the methods used in developing and adjudicating a novel, wireless and site-independent telemedicine system for acute stroke consultations. **Background:** Conclusive clinical trial data has lagged behind actual telemedicine use. Current systems range from point to point, “off the shelf” technology to customized, site independent systems. Technical guidelines for these systems, and standardized methods to adjudicate telemedicine treatment appropriateness are needed. **Methods:** An iterative, technology enhancement algorithm assessed the reliability and validity of performing 25 NIH stroke scales by both a bedside and remote examiner. Examiners were made to the system until the technology showed reliability and validity equal to bedside assessments. Thereafter, 11 acute stroke consultations were performed with this system. Treatment decisions were reviewed by an adjudication team and an independent medical monitor using 3 data levels. (1) data available to consultant, (II) bedside data available at time of consult, III) retrospective review using all hospital data). **Results:** Kappa values were = 0.75 for 10/15 (67%) of the NIHSS items (n = 25 subjects). The Spearman coefficient was 0.80 (n = 25 subjects). Thereafter, blind adjudication done on 11/11 acute consults showed no disagreements for any (-)rt-PA patients (n = 8). In 1 of the 3 (+)rt-PA cases, a prior gli bleed was noted, but the adjudication team agreed with rt-PA, as the bleed was definitively treated and death was unrelated. In another case, the adjudication team disagreed only when using Level III data. **Conclusions:** This iterative enhancement algorithm developed a reliable and valid, telemedicine system. Thereafter, this system was used for acute stroke consultations. This adjudication method developed was able to document appropriate rt-PA treatments and non-treatments, protocol violations, and retrospective disagreements. A large-scale, randomized system studying this wireless and site independent telemedicine system to telephone only consultations is underway using this technology and adjudication method.**
Effects of Pravastatin on the Function of Dendritic Cells and High Sensitive C-Reactive Protein and Clinical Effects in Patients With Acute Ischemic Stroke

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Background and objective: Many studies demonstrated that inflammation may play a most important role in the pathophysiology of acute cerebral infarction. Among the factors of inflammation, particular attention had been paid to function of dendritic cells (DC) and high sensitive C-reactive protein (hsCRP) in patients with acute ischemic stroke (AIS). The aim of this study was to ascertain the function of DC and the effects of pravastatin on it and hsCRP in patients with acute ischemic stroke. Methods: Forty three patients with AIS who hospitalized within 12 hours of an acute CT or MRI proven cerebral infarction with cortical involvement and NIHSS score from 6 to 26 were randomized to two treated respectively; treated with regular pharmacotherapy plus placebo (Pra n=21) and regular pharmacotherapy plus pravastatin (Pra n=22; pravastatin 40 mg until day 7 and 20 mg until day 30). PBMC from the AIS pts (before 1 and 4 days after the treatment) and 10 healthy subjects were incubated and CD86 on DC was measured by Banchereau’s methods (Nature.1998;393:245–252). ELISA was used to analyze the level of cytokines (IL-1 beta, IL-6, IL-10, TNF-alpha) in the medium of allogenic mixed lymphocyte reaction (MLR). Relationship of expression of CD86 to risk factors and blood hsCRP level and NIHSS score was also analyzed. Results CD86 on DC was much more expressed in AIS patients than in controls suggesting a capacity of DC for cytokine secretion. More differences were observed in the levels of proinflammatory cytokines (IL-1 beta, IL-6, IL-10, TNF-alpha) and lower level of anti-inflammatory cytokines (IL-10). Blood LCL-D treatment was positively related to the expression of CD86. Pra patients improved significantly by the 3rd day (43.1% vs 16.2% p<0.05). The benefit of pravastatin was also observed in the NIHSS score at day 30 (-8 point Pra vs -4 point Pla p<0.001). Inhibition of hsCRP and CD86 and improved NIHSS score of AIS, which were significantly positively correlated. Conclusions: Outcome in AIS was improved by pravastatin which may inhibition of hsCRP and CD86 and improved NIHSS score of AIS, which were significantly positively correlated.

Neuroprotective Effect of Local Surface Cooling in Acute Ischemic Stroke

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BACKGROUND AND PURPOSE: While neuroprotective effect of systemic hypothermia has been well confirmed experimentally in animals, therapeutic efficacy of local surface cooling in ischemic stroke has not yet been fully clarified. The present study investigates neuroprotective effect of local hypothermia with a cooling helmet in acute ischemic stroke. METHODS: Local surface cooling was induced in 24 patients (14 men, median age 73 years) with acute large ischemic stroke, whose ischemic territory on CT involved more than a half of middle cerebral artery territory, within 12 hours after stroke onset. The coolant circulating helmet and neck collar (MC-3000, Mac-Eight, Japan) were installed at 6 hours (median) after stroke. The helmet temperature was maintained at 5 degrees C for 96 hours (median) and rewarmed for the next 48 hours (median). The maximal edema volume (MVE) at the acute phase (median: Day 6) and the final infarction volume (FIV) in the chronic phase (median: Day 33) were measured with CT-based volumetry. A brain swelling index (MEV/FIV – 1) was compared with that in 14 age-matched control patients with the similar large ischemic stroke. RESULTS: The MVE was somewhat smaller in the hypothermia group (1155 ± 76 cm^3) than in the control group (1757 ± 52 cm^3), while the FIV was similar in the hypothermia group (122 ± 63 cm^3) and the control group (122 ± 37 cm^3). The brain swelling index was significantly smaller in the hypothermia group (0.30 ± 0.27) than in the control group (0.44 ± 0.17) (p < 0.035). CONCLUSIONS: Local surface cooling appears to suppress the brain swelling and minimize the final volume of ischemic injury. Local hypothermia therapy may be clinically useful because of its feasibility, safety and neuroprotective effect.

In-Hospital Treatment

The Smoking-Thrombolysis Paradox Applies to Stroke as Well as MI: Smoking Has Early Beneficial Effects Following Intravenous Thrombosis for Acute Ischemic Stroke

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Background: Although smoking is a strong risk factor for myocardial infarction, smokers with acute MI have better outcomes after thrombolysis than non-smokers. This curious but consistently replicated finding may be due to 1) a relative hypercoagulable state in smokers, leading to platelet-poor thrombus more susceptible to lytic therapy, and/or 2) an enhanced intrinsic fibrinolytic system in smokers. We evaluated the effect of smoking status on outcome following IV thrombolysis for acute ischemic stroke. Methods: The NINDS-TPA Study database was analyzed, dividing subjects into four groups - recent smokers vs non-smokers who received TPA, and recent smokers vs non-smokers who received placebo. Outcome measures analyzed were NIHSS improvement from baseline to 24 hr and day 7–10; day 90 functional activity (BI 95–100); and survival over the 1st post-treatment year. The independent effect of smoking status on outcome was evaluated by linear median regression analysis and Cox proportional hazards model, adjusting for other variables known to predict outcome in the NINDS study. Results: 615 subjects had complete data, including 104 smokers and 201 non-smokers who received TPA, among whom smokers were younger and had lower pretreatment glucose levels. After adjusting for covariates, smokers who received TPA had a greater drop in median 24-hour NIHSS scores from baseline, compared to non-smokers who received TPA (4.4 vs. 2.0, p < 0.0001), and a strong trend to greater decrease in NIHSS at 7–10 days (5.5 vs. 3.8, p = 0.034). Also, TPA treated smokers showed a trend toward more good 90 day mRS outcomes (65.5% vs. 54.1%, p = 0.11), but not toward more good 90 BI outcomes (62.7 vs. 80.1, p = 0.58). TPA treated smokers tended to show longer survival through one year (p = 0.065 for Cox model). No significant differences were noted between placebo-treated smokers vs. non-smokers. Conclusions: Recent smokers with acute ischemic stroke who receive thrombolysis experience a better early outcome than non-smokers. This may reflect a greater susceptibility of cerebral thrombus to fibrinolysis in smokers. The outcome advantage of TPA-treated smokers diminishes with time, perhaps due to smoking’s multiple other adverse effects.
Cerebrovascular Complications After Solid-Organ Transplantation

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Objective: To report a single center experience with cerebrovascular complications among solid organ transplant recipients and evaluate for variations in frequency or presentation that would impact on diagnosis, treatment, or prevention. Background: Ischemic and hemorrhagic cerebrovascular events occur in 10% of solid-organ transplant recipients but are a serious cause of morbidity. Current data suggests that stroke subtypes and stroke subtypes vary by organ type transplanted as well as the time from transplantation, but there is little data comparing variations within a single center. Methods: The Cleveland Clinic Transplant Database was reviewed for solid-organ transplants performed between January 1, 2000 to February 2002 was reviewed, with IRB approval, for all patients with neurological consultation or neurological testing (including neuroimaging or neuropsychological studies) within 6 months after transplantation. Cerebrovascular events were classified using TOAST criteria. Results: Of 589 solid-organ transplants, there were 241 (40.5%) kidney, 156 (26.9%) heart, 89 (15.1%) lung, 76 (12.9%) liver, 14 (2.2%) breast, 13 (2.2%) pancreas, 12 (2.2%) intestine, 9 (1.5%) heart-lung, and 1 (0.1%) heart-lung patient, and 1/2 (1.3%) liver and were all basal ganglia hemorrhages. Stroke subtype included 8 cardioembolic, 4 other, 1 large artery atherosclerosis, and 1 undetermined. Cardioembolism was the most frequently encountered mechanism and was often a complicated picture. Conclusions: Although renal transplant patients were at a higher risk, other subgroups also suffered early events. Most of the early events were ischemic and related to embolism in the setting of procedures. Symptomatic intracranial hemorrhage is rare and not limited to liver transplant recipients. Knowledge of these differences is useful when evaluating a solid-organ transplant patient with an acute neurologic deficit.

P300
Current Usage Patterns of Intravenous Heparin for Acute Ischemic Stroke by Korean Neurologists


Background and Purpose: The use of I.V. heparin in acute ischemic stroke has been an area of great controversy. We sought to obtain the information about current practices of neurologists in Korea with regard to heparin use in acute ischemic stroke. Methods: A survey was taken of 657 Korean board certificated neurologists (KBCN). The e-mail address and subspecialty was obtained from membership directory of Korean Neurological Association (1982–2002). Brief vignettes were presented via e-mail for the following 5 scenarios: progressive stroke, cardioembolic embiogenesis, posterior circulation, external carotid artery stenosis, and repetitive TIA. For each vignette respondents were asked whether they would use I.V. heparin with response choice such as yes, maybe and no. Results: Two hundred thirty three (46.5%) KBCNs returned a completed survey. In progressive stroke, 157 respondents (67.4%) replied ‘yes’, 48 (20.6%) replied ‘maybe’, and 28 (12.0%) would not use I.V. heparin. In cardioembolic embiogenesis, 169 respondents (72.5%) replied that they would use, 46 (19.7%) replied maybe, and 18 (7.7%) would not use I.V. heparin. In posterior circulation stroke, 122 respondents (52.4%) would use I.V. heparin, 60 (25.8%) maybe use, 51 (21.9%) would not use I.V. heparin. In ECA stenosis, 104 respondents (44.6%) would use, 70 (30.0%) maybe use, and 59 (25.3%) would not use I.V. heparin. In repetitive TIA, 173 respondents (74.2%) would use, 29 (12.4%) maybe use, and 31 (13.3%) would not use I.V. heparin. The usage pattern of I.V. heparin in each vignette was not affected by age, current teaching status or subspecialty of stroke. Compared to results of an American study in 2001, KBCNs were significantly more likely to use I.V. heparin in four clinical scenarios except in cardioembolic embiogenesis. Conclusion: Despite the report of the joint stroke guideline development committee of the AAN/ASA in 2002 for anticoagulants in acute ischemic stroke, which have not recommended I.V. heparin for any specific group of acute ischemic stroke that is based on any presumed stroke mechanism or location, many KBCNs would use intravenous heparin in large numbers for this condition. Further studies are warranted to investigate the lack of impact of evidence based reports on clinician behavior at this field.

P299
Brachytherapy for Recurrent Carotid Stenosis

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Objective and Importance: Carotid restenosis within 36 months of carotid endarterectomy is generally attributed to myointimal hyperplasia. Because of the higher of risk of neurologic and wound complications associated with re-operation for restenosis, many centers favor carotid angioplasty-stenting (CAS) in this setting. A subset of patients undergoing CAS will develop early asymptomatic or symptomatic carotid restenosis requiring further treatment. Based on favorable results achieved in the in the coronary artery circulation, we hypothesized that angioplasty-brachytherapy is an effective treatment for myointimal hyperplastic restenosis of the carotid artery. We present three cases in which brachytherapy was combined with angioplasty for the treatment of early restenosis after CAS. Cases and intervention: Three patients who developed restenosis within 18 months of carotid endarterectomy were referred for CAS. All three patients underwent uncomplicated CAS but developed severe ultrasoundographic restenosis (1 patient asymptomatic, 2 patients asymptomatic) within 12 months of CAS. Carotid angioplasty and intra-arterial brachytherapy with iodin-192 using a commercially available delivery system were subsequently performed. At 2-year follow-up the angioplasty-brachytherapy, all three patients remain clinically stable and demonstrate no progression of stenosis on duplex US. Conclusion: Carotid angioplasty-brachytherapy may be an effective method of managing early restenosis after carotid angioplasty-stenting.

P301
Protein Encapsulated Nanocarriers for Magnetically Guided, Targeted Thrombolysis

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Novel methods for targeted arterial thrombolysis may be based on nanotechnology using non-invasive magnetic guidance of tissue plasminogen activator (tPA) to the occlusion site with triggered I.PA release restricted to the target site. The first step is the successful synthesis of biodegradable, non-toxic, magnetic tPA encapsulating nano- and microspheres. Here we present our design of such magnetic carriers. Biodegradable PLGA or PEG-PLGA microspheres were loaded with I.PA using a modified double-emulsion method. BSA-loaded microspheres were characterized for surface charge, size, and morphology aiming for clinically relevant boundary conditions. We determined BSA encapsulation efficiency by recovering albumin from the microsphere matrix after I.PA and 0.5 I.PA/mL within the presence of the Micro-BCA protein assay. BSA release profiles at 37°C in PBS were also determined by the Micro-BCA protein assay. The microspheres had protein-loading efficiencies up to 80% depending on synthesis parameters. Particles were satisfactory with spherical form and a smooth surface though, as expected, size and size distribution varied. The surface zeta potential was near neutral, optimal for prolonged intravascular survival. The procedures were adjusted and I.PA encapsulated carriers synthesized. The results showed I.PA encapsulated PLGA particles have similar surface characteristics to BSA loaded microspheres. The I.PA release profile demonstrate a slow I.PA release rate within 60 minutes highlighting the need for ultrasound triggered I.PA release which is now being optimized. These novel I.PA carriers promise a dramatic advancement in the ability to effectively provide thrombolysis to a broad range of patients.

P303
Ischemic Stroke Severity, Stroke Subtype, and Medical Teams as Determinants of Length of Stay in an Elderly Hospital-Based Cohort

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Background and purpose. Length of stay (LOS) has been identified as the strongest determinant of acute care hospitalization expenditures. Accurate prediction LOS has become increasingly important for the administration of hospitals and healthcare systems. We have previously identified NIH Stroke Scale (NIHSS) as the most important predictor of LOS. The aim of our study was to assess the influence of NIHSS, stroke subtype (TOAST classification), and treatment by 4 different medical teams on the LOS of an elderly hospital-based population with ischemic stroke. Methods. Patients with age > 64 years admitted with an ischemic stroke between January 1st and December 31st, 2002 were prospectively and consecutively included. Multiple logistic regression analysis was used to assess 3 ranges of NIHSS on admission, stroke subtype and treatment by 4 different medical teams as determinants of an ALSD< 7 days after adjustment for age and sex. Results. A total of 155 patients were included (mean age 79 years, 67 males, and mean NIHSS 8.8). Results are summarized in the table. Conclusions. One of the medical teams, small vessel disease and stroke of undetermined cause were significantly related with a LOS < 7 days. NIHSS > 13 was a predictor of a LOS > 6 days.
P304

An Intrastitial Cooling Cuff for Selectively Cooling and Rewarming Carotid Arterial Blood for Stroke Patients

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Background: In recent years selective brain cooling has been proposed for clinical use as an adjunct to achieving protection from cerebral ischemia and traumatic brain injury. Real-time target cerebral temperature rapidly and controlling the rewarming rate in patient remain a challenge. In this study we assessed the hypothesis that a newly-developed cooling cuff is capable of cooling the carotid arterial blood several degrees within a reasonable time during prior and after the circulation of arterial blood reseating of the pre-implanted cooling catheter and hypothermia. Method: A three-dimensional theoretical model is developed to model the transient temperature distribution in both the brain and neck tissue in human. Cold water (0 degree Celsius) is circulated in the cooling cuff that is wrapped around the common carotid artery. The simulation consists of two steps, first is to evaluate the cooling potential of the induced temperature decrease in the carotid arterial blood and the second is to find how fast the brain tissue responses to the cooling. Results: The temperature decrease in the arterial blood is affected by the temperature of the coolant, the thermal contact area between the cuff and arterial wall, and the flow rate of the common arterial blood. It is feasible to decrease the arterial blood temperature by 3 degree Celsius when the circulating water is 0 degree Celsius and cuff is 2 cm long. Once the arterial temperature is decreased to 34 degree Celsius, the brain tissue responses quickly and the entire brain tissue could reach 34 degree Celsius within 15 minutes. During the rewarming, the brain tissue temperatures almost follow exactly the same transient behavior as the circulating water which could be controlled to decrease at various rewarming rates (0.2–1 degree Celsius per hour). Conclusions: In conclusion, a newly developed cooling cuff provides the potential to clinical study of inducing mild brain hypothermia quickly and controlling precisely the rewarming rate, while avoiding the complications associated with systemic cooling.

P305

Functional Magnetic Resonance Imaging Reveals Early Utilization of Dorsal Extrastriate Cortex Following Striate Cortex Infarction

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Background and purpose: The visual system spans a range of cortical sites, divided into striate, extrastriate (VES - 'what' pathway) and dorsal extrastriate (DES - 'where' pathway) regions. DES regions may be less dependent on intact striate function than VES ones due to increased inherent modifiability. Late utilization of unusual DES sites has been demonstrated with fMRI in single case studies of patients with striate lesions, but there are no prior serial studies of the normal brain tissue responses to the cooling.

Methods: Consecutive non-cardioembolic acute ischemic stroke patients within 48 hours were admitted within 3 days after stroke and underwent diffusion-weighted MRI (DWI) on admission. Subjected were 89 consecutive patients with ATBI (68 males, mean age 71 years) who were admitted within 3 days after stroke and underwent diffusion-weighted MRI (DWI) on admission. The patients were divided into two groups according to DWI findings, such as Group A with single small lesion and Group B with multiple small lesions. The recurrence or no recurrence within 3 weeks, ages, gender, vascular risk factors, the state of antithrombotic therapy, and NIHSS scores at admission were compared between the two groups. Results: On DWI obtained at admission, 50 patients had single small lesion (Group A), and the other 39 patients had multiple small lesions (Group B). There were no significant difference in mean ages (70 vs. 71 years), general frequencies of risk factors, the state of antithrombotic therapy during the first 3 weeks of stroke (90% vs. 89%) and the initial NIHSS scores (7 vs. 6) between the two groups. In Group A, only 1 of 50 patients (2%) had recurrent ischemic stroke within 3 weeks, whereas in Group B, 8 of 39 patients (21%) had recurrent ischemic stroke within 3 weeks. The recurrence rate was significantly higher in Group B than in Group A (p < 0.01).

In patients suffering visual field (VF) loss after stroke or TBI, Vision Restoration Therapy (VRT) for 6 months leads to visual field size increases (p < 0.001, Nature med 4). When training is discontinued, the VF-gains are stable over a period of at least 23 months (Kasten et al., 2001). We now wished to study if it is possible to use VRT for more than 6 months with additional benefits, and if VF-gains are stable after long discontinuing VRT. Patients with VF-loss due to stroke or TBI (VRT periods: VRT-3: M = 10 months, VRT-6: M = 26 months) who enrolled in the trial were divided into 6-month long VRT groups: VRT-12: M = 39 months. After 6 months of VRT in the total patient sample stimulus detection increased as measured by HRP in the central visual field from 53.73% ± 14.79% (Mean ± SD) to 62.81% ± 17.08% (p < 0.001). This was confirmed by standard perimetry where the number of undetected stimuli significantly decreased in both eyes. Long-term VRT for 6 months led to no further improvements in HRP. However, there was a non-significant trend of improved performance which, in a larger patient sample (Mueller et al., 2004), was significant. After the VRT-free interval, the VF-gains were stable. Stimulus detection did not change significantly at follow-up in the total patient sample. Both groups, VRT-6 and VRT-12, showed similar long-term stability of the visual field enlargements. In summary, VRT leads to increases in visual field size which, on average, are stable over a period of at least 3.5 years which extends prior observations. Stability of VRT-effects does not depend on the duration of the therapy. Extension of VRT from 6 months to 12 months was not beneficial for supra-threshold performance but near-threshold performance shows a trend to increasing performance which, in a larger patient sample, could be used to help patients further improve visual functions, but this needs to be confirmed with larger patient samples.
cerebral hemisphere of the initial stroke, presumably caused by carotid lesions.

**CONCLUSIONS:** In ATBI, the early recurrence may occur frequently in patients with multiple small lesions on DWI. Multiple small lesions on DWI suggest a certain type of artery-to-artery embolism in which fragile embolus may be broken-up into small pieces. Embolic source producing such fragile embolus should be surveyed to prevent early recurrence in cases with multiple DWI lesions.

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**HDL Cholesterol as a Risk Factor for Stroke**

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Serum lipids are known risk factors for ischemic stroke. Stroke risk is reduced by lowering cholesterol, especially LDL cholesterol (LDL-C). Conversely, higher HDL cholesterol (HDL-C) is associated with lower risk of stroke. However, the benefit of raising HDL-C is not clearly established. We evaluated the risk of stroke in relation to HDL-C for patients in a large clinical database of everyday clinical practice. We identified a retrospective cohort of patients who had at least 1 HDL-C before 1/1/98 within the Regenstrief Medical Record System, one of the largest and oldest clinical data repositories in the U.S. For patients with at least one subsequent HDL-C measurement we calculated the change in HDL-C and performed proportional hazards survival analysis for the first stroke event after the second HDL-C measurement, controlling for other known risk factors. We identified 7,506 patients with at least 2 HDL-C measurements: After controlling for age, gender, race, smoking, systolic BP (SBP), LDL-C, triglycerides, baseline HDL-C, and prior history of stroke, hypertension, or diabetes we found a positive change in HDL-C from baseline to follow-up significantly associated with a reduction in stroke risk. For every 1 mg/dL increase in the HDL-C the Hazard ratio for acute stroke is 0.985 (CI: 0.975 - 0.994). In this model other significant predictors of acute stroke were age, smoking, SBP, and history of prior stroke, hypertension, or diabetes. Baseline LDL-C and triglyceride levels were not significant predictors of acute stroke in this model. These findings suggest that increasing HDL-C may reduce the risk of ischemic stroke in routine clinical practice, independent of the LDL-C. This raises the possibility of HDL-C as a therapeutic target for reducing the risk of acute stroke. Further study is needed to clarify the role of HDL-C as an independent risk factor for stroke as well as the role of therapy which increases the HDL-C to reduce the risk of stroke.

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**P310 Assessment of Pre- and Post-Methionine Load Homocysteine for Prediction of Recurrent Stroke and Myocardial Infarction in the Vitamins for Stroke Prevention Clinical Trial**

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Introduction: Symptomatic vertebral basilar disease (VBD) carries a high risk for recurrent stroke. We sought to determine if a management algorithm consisting of quantitative hemodynamic assessment can stratify stroke risk and guide the need for intervention. Methods: Patients with symptomatic VBD at our institution are evaluated by a standard protocol, including quantitative magnetic resonance angiography (QMRA). Patients are stratified based upon the presence or absence of distal flow compromise. Those with low distal flow are offered intervention (surgical or endovascular); all patients receive standard medical therapy. We reviewed the clinical outcome of all patients from 1998–2003. Results: Follow-up was available for 47 of 50 patients over a mean interval of 26 months. Stroke and combined stroke/transient ischemic attack (TIA) free survival at 2 years was calculated using the Kaplan-Meier curve. Patients with normal distal flow (n=31) had an event free survival of 100% and 96% respectively for stroke and TIA/Comparatively, patients with low distal flow (n=6) who deferred treatment experienced a 67% and 50% event free survival, demonstrating a significantly higher risk of recurrent ischemia (P<0.001). Patients with low flow who underwent treatment (n=10) had a 79% event free survival. Cox proportional hazards analysis demonstrated that flow status affected stroke free survival regardless of age, gender or lesion location. Conclusion: Patients with symptomatic VBD demonstrating low distal flow on QMRA appear to have a high risk for stroke; conversely those with normal flow seem to have a benign course, and may be optimally managed with medical therapy alone.

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**P312 Stroke Risk Stratification in Symptomatic Vertebrobasilar Disease**

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**P310**

**C-Reactive Protein Predicts Progression of Intracranial Atherosclerotic Stenoses**

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**Aim:** C-reactive protein (CRP) may be an indicator of the inflammatory activity within the atherosclerotic plaque. We aimed to investigate the relationship between CRP serum level and the progression of intracranial large-artery atherosclerosis.

**Methods:** Intracranial stenoses were detected by transcranial Doppler in 186 consecutive TIA or ischemic stroke patients, of which 87 fulfilled selection criteria including angiographic confirmation of atherosclerotic stenoses. High-sensitivity CRP (hs-CRP) was determined a minimum of three months after the qualifying event. TCD long-term follow-up was thereafter conducted in 73 patients with optimal acoustic windows. Progression of intracranial large-artery atherosclerosis was defined either as the progression of pre-existing stenoses or as the appearance of new stenoses during follow-up.

**Results:** A total of 218 intracranial stenoses were angiographically confirmed (median per patient 3). During a median follow-up of 16 months, 15 patients experienced a new ischemic event, cerebral in 11 cases (9 cerebral infarctions, 2 TIAs). During the same period, progression of intracranial atherosclerosis was detected in 21 (29%) patients.

**Conclusion:** In this cohort of patients with TIA or ischemic stroke, hs-CRP progression of previously confirmed stenoses, a new appearance of stenoses. High-sensitivity CRP (Hs-CRP) was determined a minimum of three months after the qualifying event. TCD long-term follow-up was thereafter conducted in 73 patients with optimal acoustic windows.

**Prevention**

**P309**

**Assessment of Pre- and Post-Methionine Load Homocysteine for Prediction of Recurrent Stroke and Myocardial Infarction in the Vitamins for Stroke Prevention Clinical Trial**

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**Background:** Methionine (Met) loading elevates total plasma homocysteine (Hcy). We tested the hypothesis that pre- or post-Met Hcy will predict recurrent stroke or myocardial infarction (MI) in post hoc analysis of the VSP clinical trial. **Methods:** The VSP trial randomized 3680 patients with mild stroke to high- or low-dose B-vitamin therapy. Subjects underwent measurement of Hcy at baseline (fasting pre- and post-Met load) and every 6 months (fasting only) for up to 2 years. In this analysis, a general linear model was used to identify predictors of pre/post-Met difference. Survival analyses for stroke and MI were performed using pre-Met, post-Met, and pre/post-Met difference as covariates. All models were controlled for age, gender, race, and vitamin dose. Baseline Hcy was also controlled for prediction of pre/post-Met difference.

**Results:** After excluding subjects with extreme Hcy levels (n=6) or inadequate fasting/ineffective complete data (n=1550), 2124 remained in the study population. Mean (SD) Hcy levels (umol/L) were: pre-Met 13.2 (4.9), post-Met 12.8 (4.7), and pre/post-Met difference 17.1 (8.3). Post-Met increases were smaller in older subjects (0.12 umol/L lower per year of age) but were larger in women than in men (by 5.1 umol/L) and in whites than in blacks (by 4.6 umol/L, all p<0.001). In separate survival models, the hazard ratio (HR) for recurrent stroke was 0.98 (p=0.052) for 1 SD higher pre-Met Hcy, and 0.96 (p=0.054) for 1 SD higher post-Met Hcy. The coefficient of pre/post-Met difference was not significant when added to either model and was not associated with recurrent stroke. For MI, the HR for 1 SD higher pre-Met Hcy was 1.27 (p=0.001) and was 1.00 (p=0.99) for post-Met Hcy. The coefficient of pre/post-Met difference was significant when added to the model (p=0.055), but was negative. None of the interactions between pre- or post-Met Hcy and vitamin dose were significant.

**Conclusions:** Pre- and post-Met Hcy levels were similarly effective in predicting risk of recurrent stroke. Risk of MI was predicted by pre-Met and pre/post-Met difference. We conclude that fasting, pre-Met Hcy is a significant predictor of risk for recurrent stroke and MI, with no consistent gain in accuracy by sampling post-Met Hcy or pre/post-Met difference.
**Prehypertension Risk for Myocardial Infarction But Not Ischemic Stroke**

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**Background:** The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure identified a new category termed pre-hypertension. Our objective was to determine the long-term risk of cardiovascular diseases associated with pre-hypertension.

**Methods and Results:** We evaluated the association of pre-hypertension (120-139/80-89 mm Hg), and hypertension (greater than 140/90 mm Hg) with the incidence of atherosclerotic brain infarction, all strokes, myocardial infarction and coronary artery disease. Framingham Study participants (n = 5181) were pooled using repeated measures to follow-up period of 8-12 years. Cox proportional hazards analyses adjusting for age, gender, obesity, diabetes mellitus, and smoking status was used. Results: There were 11212 person-observations for ABI. Mean follow-up period was 9.9 ± 0.9 years. Pre-hypertension was not associated with an increased risk for atherosclerotic brain infarction (relative risk (RR) 2.1, 95% confidence interval (CI) 0.5 to 8.8). There were 12031 person-observations with a mean follow-up period of 9.8 ± 1.4 years. Pre-hypertension was significantly associated with increased risk for myocardial infarction (RR 3.7, 95% CI 1.7 to 7.8). Pre-hypertension was also associated with an increased risk of coronary artery disease among the 11676 person-observations (RR 1.7, 95% CI 1.2 to 2.4). Conclusions: Based on data from the Framingham study, pre-hypertension appears to be associated with an increased risk of myocardial infarction and coronary artery disease but not stroke. Further studies are required to confirm the anticipated benefits of identifying and intervening in persons with pre-hypertension.
p < 0.001). Time-course studies from baseline to 7 and 28 days on the levels of EPCs in acute patients showed an increasing trend in their levels. **Conclusions:** Our results suggest that cerebrovascular disease is associated significantly with lower number of circulating EPCs compared to controls. The decrease in EPCs as is seen in acute ischemic stroke may be a possible mechanism to explain the increased risk of stroke and thrombosis immediately after a TIA or acute stroke.

### The Value of Cost-Effective Stroke Prevention Screening

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**Introduction:** A neurologist and a vascular surgeon have developed a new cost-effective means of stroke prevention screening (SPS). The purpose is to ferret out the immediate causes of the majority of strokes (carotid artery disease, atrial fibrillation and hypertension) that are asymptomatic in 80% of cases prior to the stroke so as to allow their proper management and prevention of strokes. In addition, the patient’s lipid and cardiovascular disorders can be recognized and management initiated. The implementation of the SPS protocol in seniors in the Central Valley of California (CVC), at New York University (NYU), at Midgarn Army Medical Center (MAMC) and by The American Vascular Association (AVA) is reported. **Method:** The stroke prevention screening protocol employed uses a quick carotid scan (QCS) for carotid artery disease, an EKG rhythm strip for atrial fibrillation, and a blood pressure determination. The protocol can be performed within 4 minutes and at a cost of $20/SENOR. The QCS is performed within 1 minute and uses either visualization of a significant lesion or of color shift connoting increased flow velocity on ultrasonic imaging as an indicator of carotid artery disease and need for a later full duplex examination. Sensitivity was 93% in our laboratory and 97% at NYU. **Results:** Seniors screened were 2,685 in CVC, 610 at NYU, 456 at MAMC, and 7,971 by the AVA for a total of 12,500. The yield was 75.4% for carotid artery disease with 7.7% having >50% stenosis, 3.9% for atrial fibrillation, and 25.4% for unknown or inadequately managed hypertension. It is estimated that the carotid screenings alone prevented 58.6 strokes for an overall savings of $3,797,680. Screening 40 million Medicare recipients could potentially prevent over 200,000 of the 750,000 strokes occurring annually and save nearly 13 million dollars in health care costs. **Conclusions:** Stroke prevention screening can now be performed rapidly, accurately and cost-effectively and can reduce stroke disability far more than treatment of strokes or rehabilitation. It is time to come together, implement SPS and find the means of ensuring effective management of the patient. A SPS is a most important concept whose time has come and should be presented at our stroke meeting and fully discussed.

### Predictors of Statin Use After Acute Ischemic Stroke in the STOPStroke Study

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**Background:** Statins reduce lipid levels, inflammation, stabilize atherosclerotic plaque, and increase vasodilation. Several studies have demonstrated a significant benefit of statins in preventing stroke. Thus appropriate implementation and successful maintenance of statin therapy is a priority for secondary stroke prevention. We sought to identify the factors associated with pre-stroke and post-stroke statin use and compliance at 6 months. **Methods:** We analyzed data on patients with acute (≤24 hour) ischemic stroke who were prospectively enrolled in a STOPStroke study evaluating the utility of CT/CTA in patients with suspected stroke. Clinical data, including a detailed medication history, was obtained through an interview and medical record review within 24 hours of admission, at discharge, and at 6 months. **Results:** We evaluated 341 patients (mean age 67.2, 52.1% male). Sixty-four (18.8%) of patients were taking a statin at admission. At discharge, 150 (44%) patients were taking a statin, including 68% initiated during the hospitalization. Discharge statin therapy was predicted by hypercholesterolemia (p = 0.01) and pre-stroke statin use (p = 0.001), but not age, gender, initial NIHSS, stroke mechanism, CAD, or vascular risk factors. Analysis of 6-month follow-up data (missing in 19%) showed that 110 subjects (76% of those discharged on a statin) remained compliant. Hypercholesterolemia (p = 0.009) and large artery atherosclerosis (p = 0.02) predicted statin use at 6 months. In-hospital initiation of statins (p = 0.0001) and diabetes (p = 0.02) were associated with discontinuation of statin therapy at 6 months. **Conclusion:** Hypercholesterolemia and the presence of large artery atherosclerosis predict in-hospital initiation of statins after ischemic stroke. A considerable proportion of patients (24%) started on a statin during the acute hospitalization do not remain on statins at 6 months. Further studies are needed to determine the reasons (e.g. adverse effects, patient non-compliance) for statin discontinuation in high-risk stroke populations such as diabetics.

### Physical Activity and Ischemic Stroke

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**Background:** Previous epidemiological studies have indicated that higher levels of physical activity is associated with lower risk of ischemic stroke. Most of the studies have used questionnaires that were age-neutral, however, most ischemic stroke events occur among elderly persons where physical activities may differ from that of younger age groups. Using a questionnaire specifically aimed at an elderly population may be better to assess the relation between physical activity and ischemic stroke occurrence. **Subjects and methods:** Participants were admitted to hospitals covering the population of the central Copenhagen area, with ischemic stroke, were enrolled during the period August 12th, 2003 to April 1st, 2004. Community control subjects were selected among participants in the Copenhagen City Heart Study (CCHS) and matched to age, sex, and season. Physical activity was measured using the Physical Activity Score for the Elderly (PASE) and the questionnaire used in the CCHS. **Results:** A total of 133 case subjects and 301 control subjects were included in the study. For each 1 point increase in PASE score the odds ratio for ischemic stroke was 0.86 (0.86 – 0.99) and for diabetic patients to an odds ratio of 0.82 for each 10 points increase. There was no significant difference for men and women (p = 0.50). In analyses using the CCHS questionnaire there was no clear relation between level of reported physical activity and odds ratio for ischemic stroke. Univariate analyses suggested a U-shaped relationship whereas none of the results from multivariate analyses are significant. **Conclusions:** Using two unrelated questionnaires for assessing level of physical activity provided markedly different results. Whereas increasing PASE score was inversely, log-linearly, and significantly associated with odds ratios for ischemic stroke, using an age neutral questionnaire did not reveal a significant association. Age specific questionnaires is recommended for assessing the relation between physical activity and risk of stroke.
and the current results suggest that there is a dose-response relationship between physical activity and risk of ischemic stroke.

**Endarterectomy vs Angioplasty With or Without Stenting for Carotid Artery Stenosis: A Systematic Review**

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**Background** - Carotid endarterectomy (CEA) is the standard strategy for stroke prevention in patients with carotid stenosis. Angioplasty with or without stenting (CAS) is an alternative procedure that may limit complications and decreased length of stay. **Objectives** - to determine if CEA is better than CAS for stroke prevention in patients eligible for either procedure. **Methods** - We searched MEDLINE and COCHRANE databases for relevant randomized or quasi-randomized clinical trials comparing CAS vs CEA. We included studies if valid endpoints such as stroke, death, and local complications were reported. The analyses were performed using the fixed-effects model, and expressed as odds ratios with 95% confidence intervals. **Results** - Fifteen studies were included totaling 2747 patients (CEA = 1431; CAS = 1343). The perioperative local complication rate was lower in the CAS group (OR = 0.22 [0.14, 0.35]). Perioperative stroke, death, and stroke/death rates were higher in the same group (OR = 1.96 [1.20], 1.09 [0.55, 2.14], and 1.64 [1.19, 2.26], respectively). Only four of the fifteen studies had long-term results that showed no significant differences in endpoints (OR = 1.18 [0.76, 1.85]). **Conclusion** - At the present, the perioperative risk of stroke and death precludes the use of CAS in routine practice moreover, the long-term results are unknown.

**Community/Risk Factors**

**Silent Brain Infarcts and White Matter Lesions Associated With Subsequent Stroke and Vascular Death: Long-Term Prospective Study**

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Background and purpose: Silent brain infarction and white matter lesions were frequently detected even in normal elderly subjects. We examined prospectively the association between these lesions and the risk of subsequent stroke or cause of death in neurologically normal adults. Methods: MRI scans were performed in 2,684 neurologically normal subjects without history of stroke (40 to 84 years; mean age, 58 years) who received our health screening of the brain. We obtained information about their clinical stroke onset and death through a prospective questionnaire conducted at least every two years. We confirmed detailed clinical information about stroke and death by telephone interview and inquiring to the hospital. Informed consent for this study was obtained from all subjects according to our institutional guideline. The silent brain infarction (SBI) was diagnosed by the findings as focal hyperintensity (PVH) and subcortical white matter lesions (SWML) were quantified on MRI at the admission. Subjects (n = 194 (mean ± SD [median], 3.63 ± 0.98 [2.10]) mg/L, respectively). After adjustment for cardiovascular risk factors and predisposing factors, hscRP and IL-6 levels were shown to be significantly correlated with SBI (per SD hscRP increase: OR, 1.51; 95% CI, 1.01 to 2.26; per SD IL-6 increase: OR, 1.88; 95% CI, 1.25 to 2.84). **Conclusions**: The present study showed that levels of circulating hscRP and IL-6 are associated with SBI independently of traditional risk factors for cardiovascular disease. These associations suggest that inflammatory processes play important roles in cerebral small vessel disease.

**High LDL-3 Subtraction Levels as a Powerful Predictor of Silent Cerebrovascular Infarction in Patients With Essential Hypertension**

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Background: Low-density lipoprotein (LDL) levels are considered to be associated with cerebrovascular disease. Recently, the lipid research has been focused on LDL subtraction as a new paradigm for cardiovascular risk factor. However, clinical significance of its measurement is still unknown. **Methods** - To investigate the relationship between LDL subtraction and cerebrovascular disease, we assessed LDL subtraction using newly developed HPLC-method and brain magnetic resonance imaging in 52 consecutive nondiabetic patients with middle-aged essential hypertension whose blood pressure was controlled under 140/90 mmHg with anti-hypertensive agents. Silent cerebrovascular damage was identified by the magnetic resonance imaging findings of lacunae. **Results** - Silent cerebrovascular damage was seen in 16 patients (31%). We evaluated the difference in LDL subtraction between 16 patients with silent cerebrovascular damage and 36 patients without silent cerebrovascular damage. The LDL-3 subtraction levels were higher in patients with silent cerebrovascular damage than those without it (8.0 ± 4.1% vs. 5.2 ± 2.3%; p = 0.003). Patients’ characteristics including LDL levels were high (age: 18 mg/dl vs. 114 mg/dl; p = 0.03). Patients’ characteristics including LDL levels were high (age: 18 mg/dl vs. 114 mg/dl; p = 0.03). **Conclusions** - Our results firstly indicate that non-diabetic essential hypertension patients with silent cerebrovascular damage have higher LDL-3 subtraction levels. The LDL-3 subtraction levels may be a powerful predictor of silent cerebrovascular damage in patients with essential hypertension.

**Increased Levels of Serum High-Sensitivity C-Reactive Protein and Interleukin-6 Are Associated With Silent Brain Infarction**

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**Background and purpose** - Silent brain infarction (SBI) is frequently seen on MRI of patients with cardiovascular risk factors. Inflammatory processes have been shown to contribute to atherothrombotic vascular events. However, studies investigating the involvement of low-grade chronic inflammation in cerebral small vessel disease have been rare. We, therefore, conducted a prospective study to determine whether inflammatory markers are associated with SBI. **Methods** - Between April 2002 and December 2003, two hundred and five consecutive outpatients with no history of stroke, other cardiovascular events were enrolled in a prospective design. After excluding 11 patients having a clinically or acute inflammatory disease, 194 (mean ± SD age, 67.3 ± 7.5 years; 101 women, 93 men) were analyzed in this study. Patients underwent brain MRI, carotid ultrasonography, and neuropsychological testing. We measured circulating levels of high sensitivity C-reactive protein (hsCRP) and interleukin-6 (IL-6) as inflammatory markers. Information on patient medical history, medication use, and smoking habit was obtained from clinical records and self-reports with investigation blinded to the MRI data. **Results** - The relationships between SBI and serum CRP and IL-6 levels were evaluated. **Results** - Mean serum hscRP and IL-6 levels in patients with SBI was significantly higher than levels in patients without SBI (hscRP: mean ± SD [median], 0.33 ± 0.88 [0.08] mg/dl, respectively). After adjustment for cardiovascular risk factors and predisposing factors, hscRP and IL-6 levels were shown to be significantly correlated with SBI (per SD hscRP increase: OR, 1.51; 95% CI, 1.01 to 2.26; per SD IL-6 increase: OR, 1.88; 95% CI, 1.25 to 2.84). **Conclusions**: The present study showed that levels of circulating hscRP and IL-6 are associated with SBI independently of traditional risk factors for cardiovascular disease. These associations suggest that inflammatory processes play important roles in cerebral small vessel disease.

**Interaction Between Age, White Matter Disease, and the Presence of Microbleeds Among Patients With Cerebral Ischemia**

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Introduction Hemosiderin deposits, detected on gradient echo magnetic resonance imaging sequences (GRE) are the result of microangiopathic processes affecting the cerebral circulation. These cerebral microbleeds (CMB) are more frequently found in ischemic stroke patients than in patients with peripheral artery disease or coronary artery disease. We evaluated microbleeds developed in some, but not all, patients with TIA or stroke. Methods In TIA and consecutively admitted TIA or stroke patients >50 years old undergoing GRE, we prospectively related CMB status to age, sex, cardiovascular risk factors, left ventricular hypertrophy on echocardiography, degree of white matter hyperintensity assessed with the Fazekas scale on FLAIR (WMH) and stroke subtype using TOST criteria. Result Microbleeds were found in 50 TIA or stroke patients (24.8%). In univariate analysis, the presence of microbleeds was not related to age, sex, cardiovascular risk factors, left ventricular hypertrophy or stroke subtype. Microbleeds were more common with increasing degrees of WMH (p for trend <0.001). In multivariable analysis, increases in degrees of WMH (OR 25 for each 1-point increase in the Fazekas scales, p = 0.009) and the interaction of age (per decade) and degree of WMH (OR 0.7, p = 0.04) were independent predictors of microbleeds after adjustment for sex and hypertension. Conclusion White matter disease is a strong risk factor for the presence of microbleeds in TIA or stroke patients. In patients with white matter disease, microbleeds are more frequent when white matter disease occurs at a younger age.

**Elevated Homocysteine Is Associated With White Matter Disease: The Northern Manhattan Study**

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**BACKGROUND:** Increasing evidence suggests elevated total homocysteine (tHcy) and other modifiable vascular risk factors are associated with white matter damage and may increase the risk of cognitive impairment and dementia. **METHODS:** The Northern Manhattan Study (NOMAS) is a population-based prospective cohort of 3,288 stroke-free subjects identified by random digit dialing. To date 202 had baseline fasting tHcy levels and follow up brain MRI scans with quantitative measures of white matter hyperintensities (WMH) and brain atrophy available. We used linear regression to examine the association between brain MRI and serum homocysteine and volume in WMH compared with elevated homocysteine and WMH volume adjusting for relevant covariates. **RESULTS:** Subjects (n = 202, mean age 64.7 ± 5.4; women 45%; HsP, 28% black, 23% white) had a mean WMH volume of 0.57% (median 0.3, range 0.4–3.7%) and a mean tHcy of 8.7 umol/L (median 6.3, range 3.0–21.0). Older age, hypertension, brain atrophy, and higher tHcy level were independent predictors of microbleeds adjusted for WMH. Our results firstly indicate that non-diabetic essential hypertension patients with elevated homocysteine and WMH volume adjusting for relevant covariates. **RESULTS:** Subjects (n = 202, mean age 64.7 ± 5.4; women 45%; HsP, 28% black, 23% white) had a mean WMH volume of 0.57% (median 0.3, range 0.4–3.7%) and a mean tHcy of 8.7 umol/L (median 6.3, range 3.0–21.0). Older age, hypertension, brain atrophy, and higher tHcy level were independent predictors of microbleeds adjusted for WMH. **CONCLUSIONS:** Elevated homocysteine and hypertension are independently associated with increased white matter hyperintensities in this multiethnic cohort. These data support the need for further work on the relationship between vascular risk
factors, WMH, and cognition as well as clinical trials to examine the effects of risk factor modification on these outcomes.

P330 Stroke Occurrence and Leukoaraiosis Are Independently Associated With Transition to Disability: The LADIS (Leukoaraiosis And Disability) Study
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Background: Preliminary results from this collaborative study indicate leukoaraiosis (LA) severity as a risk factor for transition to disability in the elderly. However, it is not clear whether LA severity influences the effect of LA severity on determining this transition. Objective: To evaluate the independent effect of LA and stroke occurrence on the risk of transition to disability. Methods: The LADIS is a study involving 11 European centres, aimed at evaluating LA as independent determinant of disability in the elderly. Six-hundred-thirty-nine subjects (mean age: 74.1 ± 5.0 years, mean Fazekas ≥ 1, with different LA severity according to the Fazekas scale) and functionally autonomous (0 or 1 impaired item on Instrumental Activity of Daily Living - IADL scale) were assessed at baseline for demographics, vascular risk factors, comorbidities, cognitive, motor, and mood functions, and are being followed-up for 3 years with clinical and MRI studies. Transition to disability is defined as a variation on the IADL leading to impairment in more than one item. Functional status was also assessed by means of the Disability Assessment of Dementia (DAD) scale. Results: Out of the 639 subjects, 18 had a stroke (hemorrhagic or ischemic) during the first year of the study. Transition to disability occurred in 8 (44.4%) subjects with and in 73 (13.6%) subjects without new strokes (chi-square P < 0.001). Among subjects with new strokes, the rate of transition to disability increased along with increasing LA severity (0%, 50%, 55.5% in score 1, 2, and 3 respectively). Considering as dependent variable the transition to disability, a logistic regression analysis showed that severe LA (OR = 3.4, 95% CI = 1.34 - 5.5), stroke occurrences (OR = 4.9, 95% CI = 1.45 - 15.54), age (OR = 1.09, 95% CI = 1.04 - 1.15) and basal DAD score (OR = 0.89, 95% CI = 0.85 - 0.94) were all predictors of transition. Conclusions: After the first year of follow-up, both stroke occurrence and baseline LA severity are independent predictors of transition to disability in the LADIS sample population.

P331 Elevated Serum Interleukin-18 Levels Are Associated With Increased Carotid Intima-Media Thickness
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Background and Purpose: Interleukin (IL)-18 promotes atherosclerotic plaque growth and its circulating level can predict future coronary heart disease. However, it has not been established whether serum IL-18 levels are associated with severity of atherosclerosis. With the use of B-mode ultrasound, this study examines the relationship of serum IL-18 levels with high sensitive CRP (hs-CRP) levels with the severity of atherosclerosis as assessed as carotid IMT. Methods: The study comprised 315 patients without histories of cardiovascular diseases (CVD). Severity of carotid atherosclerosis was evaluated as mean max-IMT, of the maximal wall thickness at 12 carotid segments. Serum IL-6, hs- and CRP levels were determined in all patients. Results: Mean max-IMT was higher in men than in women, and in patients with hypertension than in those not, and in patients with smoking history than in those not. Also, it was positively correlated with age, BMI, and triglycerides, and negatively with HDL cholesterol. Log-transformed IL-6, IL-8, and hs-CRP concentrations were positively correlated with mean max-IMT after adjustment for age, females, each P < 0.05, except IL-6, each P > 0.05, respectively. Conclusion: Both IL-6 and high sensitive CRP (hs-CRP) levels were associated with the occurrence of new vascular events, especially ischemic stroke, in patients with manifest arterial disease. These findings justify the use of IL-6 as surrogate endpoint in trials including patients with manifest vascular disease.

P332 Increased Common Carotid Arterial Stiffness Is Independently Associated With Risk of Stroke
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Background and purpose: Aortic stiffness is an independent predictor of cardiovascular risk factors and a predictor of cardiovascular mortality in patients with essential hypertension. There is little knowledge concerning the relation between the local stiffness of the common carotid arteries (CCA) and manifest cerebrovascular disease. Aim of the present cross-sectional study was to investigate the association of CCA stiffness with the risk of stroke and to determine whether this relationship was independent of conventional risk factors. Methods: A consecutive series of 193 acute first-ever stroke patients and of 106 age- and sex-matched controls was included. Baseline common carotid artery stiffness was measured as the inverse of carotid distensibility. Carotid distensibility was measured as the change in intima media thickness (IMT) per pulse pressure (PP) (mmHg). Results: The area under the ROC curve for CCA distensibility predicting stroke patients was 0.592 (95% CI: 0.526 – 0.658). Conclusion: An increased CCA stiffness was associated with cerebrovascular disease even after adjustment for conventional cardiovascular risk factors. The causal interrelationship between the elastic properties of the CCA and the risk of stroke deserves further investigation by using the method of analytical studies.

P333 Systolic Blood Pressure, LDL Cholesterol, and the Framingham Risk Score Are Better Predictors Than The Metabolic Syndrome of Carotid Intimal-Medial Thickness in Middle-Aged Adults: The Muscatine Study
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Background and Purpose: The Framingham risk score (FRS) and the metabolic syndrome as defined by NCEP III and WHO (MS-NCEP and MS-WHO) predict the risk of developing cardiovascular disease in older adults. Carotid intimal-medial thickness (IMT) has been used as a measure of the atherosclerotic process in younger adults and is predictive of stroke and myocardial infarction in older adults. We assessed the hypothesis that FRS, MS-NCEP, and MS-WHO would be more useful in predicting carotid IMT than would individual cardiovascular risk factors in a cohort of middle-aged adults. Methods: Using carotid ultrasound, the mean of the measurements of maximal carotid IMT at 12 locations was determined in a cohort of 306 men and 390 women aged 36 to 56 years living in Muscatine, Iowa. Anthropometric measurements and smoking were recorded. Results: A significant correlation existed between IMT and systolic blood pressure (P = 0.001), high density lipoprotein cholesterol (P = 0.001), total cholesterol (P = 0.001), triglycerides (P = 0.001), and the Framingham Risk Score (P = 0.001). The Framingham Risk Score correlated well with IMT (r = 0.20, 95% CI 0.17 – 0.23). Conclusion: Systolic blood pressure, LDL Cholesterol, and the Framingham Risk Score are better predictors than the metabolic syndrome of carotid intimal-medial thickness in middle-aged adults.
diabetes mellitus, LDL-cholesterol, HDL-cholesterol, and CRP are independent risk factors of asymptomatic ICAS and the prediction index based on those factors is valid to predict it.

Atrial fibrillation is an established risk factor for ischemic stroke. Subclinical hyperthyroidism may result from thyroid replacement therapy and may be associated with an increased risk for the subsequent development of atrial fibrillation. We sought to determine whether thyroid replacement therapy is a risk factor for atrial fibrillation in stroke patients. Study Design: Case-control study. Methods: Consecutive stroke patients with atrial fibrillation (cases) and without atrial fibrillation (controls) admitted to the Stanford Stroke Center between 1996 and 2004 were included. Data on age, gender, vascular risk factors, history of atrial fibrillation and/or atrial fibrillation on admission, and whether patients were taking thyroid replacement therapy were collected. We aimed to match each case by age and gender with two controls. Results: Thyroid replacement therapy was reported in 52/334 (15.6%) cases and 67/637 (10.4%) controls (p = 0.0003). More than 80% of thyroid replacement therapy users were females in both groups. In multivariate analysis, thyroid replacement therapy use was associated with an odds ratio of 1.65 (95% CI 1.05–2.59, p = 0.02) with atrial fibrillation after adjusting for age, gender, hypertension, amiadonar use, and coronary artery disease. Conclusion: Thyroid replacement therapy may be an independent risk factor for atrial fibrillation in stroke patients.

Thyroid Replacement Therapy Is a Risk Factor for Atrial Fibrillation in Stroke Patients

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C-Reactive Protein Predicts Further Ischemic Events in Transient Ischemic Attack Patients

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Background - There are many studies of clinical prognostic factors in patients with transient ischemic attack (TIA). Most of them have failed to identify parameters to predict vascular event appearance after the index TIA. We hypothesize that inclusion of a biological marker in the TIA study protocol might increase the prognostic value of classical risk factors. To test this hypothesis, we have investigated the relationship between high sensitivity C-reactive protein (hs-CRP) levels and the risk of new ischemic events in TIA patients. Methods - HsCRP levels were determined within the first 24 hours after the onset of clinical symptoms among 135 TIA patients. Stroke recurrence, or any vascular event was recorded at follow-up (446 ± 294 days) Results - A total of 37 (27.4%) patients experienced a recurrent TIA and 46 (34.0%) patients experienced a recurrent or new ischemic event. hscCRP and atherosclerotic plaques, and the carotid artery intima-media thickness (IMT) and plaques were determined in 31 patients with VaD, 61 patients with AD, and 32 age-matched controls without dementia. Results: Age, body mass index, systolic and diastolic blood pressures, and fasting plasma glucose, HbA1c, HLD cholesterol, and apolipoproteins A-1, B, and E concentrations did not differ significantly among the three groups. However, the mean IMT and frequency of atherosclerotic plaques in the carotid arteries as well as the serum concentrations of LDL cholesterol, lipid peroxides, and lipoprotein(a) were significantly higher in VaD patients than in AD patients or nondemented controls. Hs-CRP concentrations and prevalence of Chlamydia pneumoniae IgG and IgA antibodies also were significantly higher in VaD patients than in AD patients and nondemented controls. Multiple logistic regression concerning VaD retained carotid IMT and plaques, IgG and IgA Chlamydia pneumoniae seropositivity, hs-CRP, LDL cholesterol, lipid peroxides, and lipoprotein(a) (Table). Conclusions: Our results suggest that carotid atherosclerosis, arterogenic lipoproteins, and Chlamydia pneumoniae infection (as documented by the IgG and IgA seropositivity together with increased hs-CRP) may be VaD risk factors.

High Prevalence of Chlamydia pneumoniae Antibodies and Increased Sensitive C-Reactive Protein in Patients With Vascular Dementia

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High Prevalence of Chlamydia pneumoniae Antibodies and Increased Sensitive C-Reactive Protein in Patients With Vascular Dementia

P330

Headache Syndromes in Patients With Unruptured Brain Arteriovenous Malformation

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Background: Only scant data are available on the frequency and type of headaches in patients with brain arteriovenous malformation (AVM). Neurosurgical treatment of AVM has been increasingly performed for patients with headache associated with the AVM. Methods: We retrospectively collected data from 748 consecutive patients of the prospective Columbia AVM Databank. Patients were stratified into those with a history of headaches prior to AVM diagnosis and those with a negative headache history. Univariate and multivariate logistic regression models were used to test the effect of age, gender, size (mm), location, venous drainage pattern, and presence of venous anastomoses on a positive headache history in AVM patients. Results: Headaches occurred in 294 (40%) AVM patients; 108 (14%) had migraines (with and/or without aura), 67 (9%) had episodic or chronic tension type headache, 23 (3%) experienced thunderclap headache unrelated to hemorhages, and 96 (13%) had unidentified headache. Presence of venous anastomoses occurred more frequently in women (p = 0.0001) and were associated with large AVM size (p = 0.0001), lobar location (p = 0.0002), borderzone AVM (p < 0.0001), and venous ectasia (p < 0.0007). The multivariate model confirmed the independent effect of female gender (OR 3.29, 95% CI 1.15–10.11, AVM location (95% CI 1.01–1.04), lobar AVM location (OR 19.2, 95% CI 1.98–4.05), and venous ectasia (OR 1.89, 95% CI 1.20–2.98). Conclusion: Our findings suggest an independent effect of female gender, AVM size, lobar location and venous ectasia on the occurrence of headaches in patients with unruptured brain AVMs. In our cohort, the relative frequency of migraines is not different from the prevalence in the general population.

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Atherosclerotic Aortic Debris and Risk of Subsequent Stroke in Patients With Cerebral Ischemic Events: A Population-Based Study

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Background: Reports suggest that protruding atheromatous material in the thoracic aorta is an important cause of recurrent ischemic stroke. Methods: This historical cohort study included all 286 residents of Olmsted County, Minnesota, who had transesophageal echocardiography (TEE) within 60 days after their first TIA (n = 90, 31.5%) or ischemic stroke (n = 196, 68.5%) from 1993 to 1997. We used the Kaplan-Meier product-limit method and Cox proportional hazards regression analysis to estimate rates and identify predictors of subsequent ischemic stroke in these patients. Findings: Complex atherosclerotic carotid debris (CADD) in the ascending and transverse segments of the arch was detected in 19 (6.6%) patients. During 826 person-years of follow up, 3 patients with CADD and 38 patients without CADD had subsequent ischemic stroke. Estimated rates of subsequent ischemic stroke 4 years after first TIA or ischemic stroke were not significantly different for those with CADD (15.8%, 95% CI 0.30–0.77) and those independently associated with stroke. Results: Two-hundred-eighty-three stroke patients and an equal number of control subjects were included. Men were 117 and women were 121 in each group. Mean age of stroke patients was 35.4 years and of the control group 35.2 years. The persons suffering from migraine were 63 (26.5%) in the stroke group and 33 (13.9%) in the control group. That difference achieved statistical significance (p = 0.0009). Contraceptive pill use was not different for oral and end-progestin as for oral (20.7%) and smoking habit. The logistic regression model retained migraine (Odds ratio 2.70, 95% confidence interval 1.66–4.41) together with hypertension (Odds ratio 9.10, 95% confidence interval 4.17–19.89) and any cardiopathy (Odds ratio 31.94, 95% confidence interval 4.15–238.73) as factors independently related to stroke. Conclusions: Migraine appears to be a risk factor for the acute ischemic stroke in young people. In addition, the role of migraine in precipitating a stroke appears to be independent from the usual risk factors and from the consumption of wine, cigarettes and the contraceptive pill.

The Role of Migraine in Acute Ischemic Stroke in Young Adults

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Objective: To investigate whether migraine could be a risk factors for the acute ischemic stroke in patients aged 16 to 44 years in a nested case-control study. Patients and Methods: For each patients admitted because of CT/MI confirmed acute ischemic stroke (TIA excluded) we identified an age (< ± 1 year) - and gender-matched control subject selected among inpatients of the same admission, and whether patients were taking either stroke and control therapy, we recorded: history of at least 5 migraine attacks (either with and without aura according to the IHS criteria); usual risk factors for stroke; current utilization of contraceptive pill; current beverage of at least 2 glasses of wine per meals;current smoking of at least 5 cigarettes per day; blood pressure and cardiac rhythm. Data were matched with univariate analyses. Significant results were then entered into a logistic regression model to identify those data.
without CAAD (17.5%, 95% CI 11.9–22.7%, p = 0.09). After adjusting for age, sex, and atherosclerosis other than in the thoracic aorta on TEE, CAAD was not a significant predictor of subsequent ischemic stroke (hazard ratio = 0.76, 95% confidence interval 0.23–2.49, p = 0.65). Interpretation: We found no evidence that CAAD is a risk factor for subsequent ischemic stroke in patients with first TIA or ischemic stroke in the general population.

P342
Elevated White Blood Count on Admission Independently Predicts Mortality Among Patients Hospitalized for Ischemic Stroke

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Objective: The relationship between WBC derangement on admission and mortality for ischemic stroke patients is an area of active study. Our objective is to depict the univariate and multivariate effect of abnormal WBC on mortality after accounting for demographics, acute pathophysiological derangement, comorbidities, and type of stroke in a large patient population.

Methods: Analysis included 44,102 (2,929 deaths) ischemic stroke admissions across 82 teaching and 145 non-teaching hospitals in the Atlas (Medispan) database in 2000–01. Logistic regressions were used to control for age, laboratory values, vital signs, altered mental status, and comorbidities. ROC curve and Bootstrapping validated model fit. Findings: Overall, the median age was 76, 55% were women, and crude mortality was 6.6%. There was a significant correlation between elevated WBC and mortality. With WBC > 10,000/µl (n = 11,845), mortality was 1.3 (CI: 1.2–1.5) and 1.8 (CI: 1.6–2.0) respectively. Other significant predictors (p < .05) included age, albumin < 2.7 g/dl, glucose > 135 m/gl, pH arterial < 7.21 or > 7.48, PT INR > 1.1 or PT > 13 sec, creatinine > 3.0 mg/dl, systolic BP < 90 mm Hg, respiration > 10 or > 30/min, altered mental status, metastatic cancer, and basil artery occlusion. The ROC for the model was .83. Conclusions: Elevated WBC on admission is an independent predictor of mortality for ischemic stroke patients. Research is needed to further understand the pathophysiological mechanisms.

P343
Factors Influencing Short- and Long-Term Survival in the Copenhagen Stroke Study Cohort: A 10-Year Follow-up Study

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Survival after stroke was studied in the community-based Copenhagen Stroke Study (COST) over a 10-year period from 1992/1993 to 2002/2003. For the identification of independent determinants for survival admission stroke severity, age, gender, and the cardiovascular risk factor profile was accounted for. Method and material: In a well-defined Copenhagen community all patients with stroke were seen on admission to hospital in the period March 1992 to October 1993. The stroke admission rate was 3.6/1000 inhabitants/year. On admission stroke severity was measured using the Scandinavian Stroke Scale (SSS, 0–58), stroke type was determined by CT-scan, and the presence of ischemic heart disease (IHD), hypertension, diabetes (DM), atrial fibrillation (AF) intermittent claudication, smoking, daily alcohol consumption and other disabling disease were examined and recorded in all. Date of death was obtained from the Danish Registry of Persons within a 10-year period following stroke. Independent predictors of death were identified using multivariable Cox regression. Results: In total 1152 patients with acute stroke were included. Mean age 74.2 ± 11 years, male/female 45%/55%, mean admission SSS-score 34±17. The one-year survival rate was 67.2%, the five-year survival rate was 37.2% and the ten-year survival rate was 17.0%. Predictors of one-year mortality in the multivariate analysis was: Age Hazard Ratio (HR) 1.32 ± 10 years (p<0.001), severity HR 0.65 ± 0.05 SSS points (p<0.001), DM HR 1.49 ± 0.05 (p<0.05) other disabling disease HR 1.50 ± 0.03, Predictors of 10-year mortality was: Age HR 1.60 ± 10 years (p<0.001), female gender HR 0.69 ± 0.03, stroke severity HR 0.63 ± 0.01 SSS points (p<0.001), IHD HR 1.23 ± 0.05 (p<0.05), former stroke HR 1.23 ± 0.05 (p<0.05), DM HR 1.23 ± 0.02, AF HR 1.33 ± 0.02, smoking HR 1.16 ± 0.07, other disabling disease HR 1.44 ± 0.005. Hypertension, type of stroke (hemorrhagic/ischemic), daily alcohol consumption and intermittent claudication were not significant predictors. Conclusion: Short-term survival is particularly determined by age and initial stroke severity. Long-term survival is also determined by gender, cardiovascular disease and diabetes. Hypertension per se was not a predictor of survival after stroke.

P344
Stroke Recurrence Rates Are Not Changing Over Time

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Background: Previous population-based studies have shown that stroke recurrence rates after first ischemic stroke have not changed from 1950 to 1989. We hypothesized that advances in secondary prevention in the 1990s would lead to decreased recurrence rates. We present the first population-based assessment of stroke recurrence rates over time since 1989. Methods: We identified strokes from 7/93 to 6/94 and from 1/99 to 12/99 in the Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS) region, a biracial population of 1.3 million. Strokes were found by screening ICD-9 stroke diagnosis codes of all inpatient, hospital-based and public health outpatient, and emergency department visits, as well as randomized private practices. Strokes were confirmed by medical chart review, nurse review, and physician review. Among patients with first ischemic strokes, we identified both recurrent ischemic and hemorrhagic strokes during the one-year study periods, based on detailed review of initial hospitalization records and subsequent events with an ICD-9 stroke code. We estimated net 365-day recurrence rates by Kaplan-Meier life-table method. Results: There were 74 recurrent strokes (97% ischemic, 3% hemorrhagic) among 1,772 first ischemic strokes in 1993–94, and 75 recurrent strokes (89% ischemic, 11% hemorrhagic) among 1,815 first ischemic strokes in 1999. We found no statistically significant difference in recurrence rates between the GCNKSS population comparing 1993–94 and 1999 (p = 0.96). Our sample size provided 80% power to detect a 2% difference in estimated 365-day recurrence rates. Conclusions: Despite the emergence of several new secondary prevention strategies, we found no change in stroke recurrence rates between 1993–94 and 1999 within the same large population. Further studies characterizing the utilization of secondary stroke prevention methods within this population are needed.

P345
Is Left Ventricular Hypertrophy a Predictor of Recurrent Vascular Events in African-American Stroke Patients?

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Background and Purpose: In population-based analyses such as the Framingham study, left ventricular hypertrophy (LVH) has been associated with an increased frequency of stroke. In Framingham, after a 36 year follow-up period, the risk of stroke was increased 4.7 fold for black women and men with LVH at baseline. The influence of LVH on the risk for vascular events (stroke, MI, vascular death) in African Americans (AA) has been studied less, especially for recurrent stroke. We sought to assess the hypothesis that LVH would be a predictor of an increased vascular event rate in AA stroke patients. Methods: The Abstracted Antplatelet Stroke Prevention Study (AASPSS) database was used for this analysis. LVH was identified on the baseline ECG. 1809 patients with noncardioembolic stroke were enrolled in this secondary prevention study and followed for a two year period. Major vascular events during follow-up were recorded and we also analyzed whether pharmacologic treatment differed in patients with LVH. Results: The mean age of the patients was 61.3 years with 53.5% women. 399 patients (22.1%) had LVH on the baseline ECG. Among 193 patients with a recurrent stroke outcome event, 17.1% had LVH (p = 0.08, Chi square analysis). There was no association between presence of LVH and MI or vascular death during the follow-up period. Patients with LVH had a higher baseline creatinine level (1.23 vs. 1.15 mg/dl, p = 0.005). We did not identify any difference in use of various antihypertensive agents (such as ACE inhibitors) in patients with LVH, although patients with LVH were more likely to be treated with oral agents (p = 0.03, chi square analysis). Conclusions: We did not identify a definite increase in the vascular event rate among AA stroke patients with LVH on the baseline ECG, although there was a trend for stroke alone. Patients with LVH had greater renal impairment and were more likely to be treated for diabetes, suggesting that LVH is a marker for overall vascular risk factor burden. Examination of larger cohorts in both primary and secondary prevention trials would be of interest to determine the overall clinical significance of LVH. Supported by NIH/NINDS R01 NS 34330 to PBG
survey year. In women, survival followed the same pattern as in men, but was not different between survey years (p>0.05). Conclusions: These findings show that survival from stroke after hospital discharge improved substantially during the 1990’s.

Do Diabetic Patients Really Have Worse Outcomes After Acute Stroke Than Nondiabetics?
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Objectives: To analyse the differential features of diabetic acute stroke patients and its implications in stroke outcome. Methods: Observational study from the Stroke Data Bank of the Department of Neurology (1994–2003) with inclusion of consecutive ischemic and hemorrhagic stroke in-patients. Parameters analysed: risk factors, stroke subtype, severity at admission (Canadian Stroke Scale), length of hospital stay, in-hospital complications, mortality and functional state at discharge (modified Rankin Scale). TIA patients have been excluded from these last two parameters analysis. Descriptive and comparative analysis in patients with and without diabetes mellitus has been developed. Results: From 1994 to 2003, 4826 consecutive acute stroke patients were admitted in the department of Neurology, of whom 1283 were diabetic. These patients with previous history of diabetes were older (70.58 vs 69.16% years old; p<0.001), had more rate of hypertension (70 vs 55.8%; p<0.001), peripheral vascular disease (9.1 vs 4.7%; p<0.001), dyslipidemia (31.1 vs 22.3%; p<0.001) and previous stroke (18.1 vs 12%; p<0.001) than non-diabetic patients. Atherothrombotic (28 vs 17% ; p<0.001) and lacunar infarction (24 vs 20.6%; p<0.001) were more frequent in diabetic patients. They also had more neurological complications as progressive stroke (4.5 vs 2.2%; p<0.001) and brain oedema (6.9 vs 5.2%; p<0.05) with no differences in systemic complications or in length of hospital stay. No differences with regards to stroke severity at admission neither than to stroke outcome at discharge were found. Conclusions: Previous history of diabetes mellitus is not associated by itself to more severity at admission neither to a poor outcome in acute stroke patients. It is possible than the poor prognosis that has been traditionally attributed to diabetes could be due to the developing of hyperglycaemia in the acute phase of stroke, but we have not analysed this point. Further prospective studies are needed in order to explore this possibility.

Social Exclusion and Stroke Mortality
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In Sao Paulo, Brazil, stroke is responsible for one quarter of cardiovascular deaths among people aged 30 to 79 years-old (men—22.2%; women 27.0%). The burden of intracerebral hemorrhagic stroke is still higher when compared to ischemic stroke mainly among women. We hypothesized that this pattern could be explained by an unequal spatial distribution of stroke subtypes among neighborhoods due to social inequality, that is intracerebral hemorrhage death rates would be higher on the poorest areas. We applied the social exclusion score (an index for social inequality) as an index for social inequality. We compare age-adjusted mortality rates for stroke, most patients remain ineligible mainly due to late arrival to hospital. We hypothesized that perceptual, social, and behavioral factors affect delays in seeking help following symptom onset. Methods: During a 2-year period (2000–2002), 209 of 518 patients hospitalized in the Department of Neurology of Sao Paulo, Brazil, who presented with stroke symptoms and fulfilled inclusion criteria were interviewed about their symptom experience, interpretation, and reaction, and brief personality assessments were performed in communicative patients. Odds ratios and 95% confidence intervals for risk of delay in seeking help for >3 hours (reaction time) were estimated. Following multivariate analyses, 7 variables associated with increased risk of delay and representing demographic, clinical, perceptual, social, and behavioral factors were included in an assessment of the effect of combined risk-factors on delay on risk. Results: Upon adjustment for demographic and clinical data, perceived severity and control of symptoms, contextual factors, symptom attribution, hesitation, advice of others, contact with ambulance, and high general anxiety, we found that beyond clinical variables, perceiving symptoms as not severe (2.38; 1.05–5.88), not being advised by others to seek help (1.86; 1.05–3.35), not contacting an ambulance (3.85; 1.59–9.47), and perceiving control of symptoms (2.45; 1.06–5.71) were associated with delays in reaction time. When 7 factors predictive of delay (age <70, male, NIHSS score <5, non-auditory onset, perceived control of symptoms, not advised to seek help, and didn’t contact an ambulance) were examined in combination, the proportion of patients delaying stroke help increased steadily with increasing numbers of factors:17%, 32%, 47%, 67%, and 94% for patients with 0–1, 2, 3, 4, 5, and 6–7 factors, respectively. Conclusions: We conclude that perceptual, social and behavioral factors contribute to delay in seeking medical care in acute ischemic stroke beyond demographic and clinical variables and, when combined, further increase the risk of delay. These findings may have important implications for designing programs to reduce delay in seeking help.

Do Trends in Stroke Subtypes: The Minnesota Stroke Survey
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Objective: We examine trends in stroke subtypes. We hypothesize an increase in the proportion of cardio-embolic strokes relative to other ischemic stroke subtypes. Possible mechanisms underlying such an increase are: 1. Improved survival after myocardial infarction (MI) due to new treatments for coronary artery disease 2. Increased use of diagnostic tests in ischemic stroke patients. Methods: We report on data from 1980, 1985, 1990 and 1995 Minnesota Stroke Surveys (MSS). The MSS is a population-based surveillance of hospitalized acute stroke cases (age 30–74 years) in the Minneapolis-St.Paul area. Cases are identified by discharge codes and 50 % are sampled for abstraction. Cases are then validated as ischemic strokes and intraparenchymal (IP) hemorrhages by CT/MRI. Cases without scans are designated as undetermined. Ischemic strokes are further classified into those with and without cardio-embolic sources using the TOAST criteria for diagnosis of cardioembolism. Data were available on the following for all survey years. 1. atrial fibrillation/flutter 2. mitral stenosis 3. atrial myxoma or intra-cardiac clot 4. recent MI. Results: There were 212, 314, 363, and 432 validated ischemic stroke cases in survey years 1980, 1985, 1990 and 1995 respectively. Results are shown in the table. Conclusions: There is an overall increasing trend in the proportion of acute ischemic strokes with potential cardio-embolic sources (**). However, the proportion of ischemic stroke patients with a prior history of MI has remained stable (*). Hence, the increase in the proportion of ischemic strokes of presumed cardioembolic mechanism may be due to increased use of diagnostic tests in ischemic stroke patients rather than to a shift in the population of patients.

Poster Presentations

Do Trends in Stroke Subtypes: The Minnesota Stroke Survey

Poster Presentations

National Healthline Responses to a Stroke Scenario: Implications for Early Intervention
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Objective: Acute stroke is a time dependent emergency where patients often present to the hospital outside of the therapeutic window for thrombolytic therapy. In order to determine the role that healthlines may have in promoting early access to therapy, this study evaluated patterns of healthline triage of potential stroke victims. Methods: Phone numbers of healthlines at 62 United States hospitals with active neurology residencies were acquired using the Internet. Each healthline was called and the operator was presented with a standardized, scripted stroke patient scenario. The operator was asked to choose one of four responses that could be given to the patient (wait for symptom resolution, contact a primary care physician [PCP], drive to a local urgent care center, call 911 for ambulance transport to a hospital). The operator then was asked to name common signs and symptoms of stroke. If the operator transferred the call, the process was repeated. Results: Forty-six healthlines participated, with 22% recommending the patient contact a PCP. The remaining 78% recommended EMS transport to local hospitals. Phone calls were transferred at least once in 18 cases, and 24% of the operators could not name one sign or symptom of stroke. Conclusions: Nearly a quarter of potential stroke victims were routed away from emergent treatment for the described...
Hemorrhage

Novel Observations Regarding Acute Vasospasm and Influence of Race on Outcome After Subarachnoid Hemorrhage

Robert L Macdonald, Axel Rosengart, Univ of Chicago Med Ctr, Chicago, IL

Introduction: Data on 3500 patients with aneurysmal subarachnoid hemorrhage (SAH) entered into 4 randomized trials conducted around the world between 1991 and 1997 were analyzed to ask questions about SAH. Methods: Uni- and multivariate statistical analyses were conducted to determine the effect of race and early vasospasm (EVSP) on admission angiography on SAH demographics and outcome. Results: Whites were significantly older than other races. Blacks more frequently had a history of hypertension and more commonly had elevated blood pressure on admission. Blacks and other minorities were more likely to have internal carotid aneurysms and whites were more likely to have posterior circulation aneurysms. In-hospital complications were not significantly different except for pulmonary edema, which was more common in whites. Outcome at 3 months was not significantly different between races. EVSP within 48 hours of SAH was diagnosed in 10% of patients and was significantly more likely in patients with poor neurological grade, history of SAH, intracerebral hematoma, larger aneurysm, thick SAH on CT and intraventricular hemorrhage. EVSP was not associated with delayed vasospasm but was associated with cerebral infarction and unfavorable outcome (p<0.005). There was a trend for patients with increasingly severe EVSP to have worsening outcome. Conclusions: Race was not a prognostic factor for outcome after aneurysmal SAH, suggesting that the higher SAH mortality previously observed in blacks is due to a higher incidence of SAH in blacks. Early vasospasm may be more important than previously thought as it was diagnosed in 10% of patients and was associated with cerebral infarction and poor outcome.

BLOOD TRANSFUSION FOLLOWING SUBARACHNOID HEMORRHAGE WORSENS OUTCOME

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Introduction: Blood is often liberally transfused to patients with subarachnoid hemorrhage (SAH) and cerebral vasospasm to improve oxygen delivery. Recently, it was reported that intraoperative blood transfusion worsened outcome in SAH. No adjustments were made for the severity of medical illness. We sought to determine the effect of blood transfusion using a severity of illness score (ICU-APACHE score) that was adjusted for both neurological and medical severity. Methods: A retrospective analysis of 166 aneurysmal SAH patients admitted to the Neurological Intensive Care Unit between January 2000 and January 2004 was conducted documenting demographic data, Hunt-Hess score, Fisher grade, presence and severity of vasospasm by TCD sonography and Acute Physiology and Chronic Health Evaluation (APACHE II) score. The number of red cell transfusions and hemoglobin and hematocrit levels before and after transfusion were recorded. Outcome was determined at discharge using the Glasgow Outcome Score and Modified Rankin Scale (MRS). SAH severity was assessed using the modified Fisher score. Transfusions and outcomes were analyzed by uni- and multivariate logistic regression analyses. Results: On admission, the mean hemoglobin and hematocrit were 12.9±1.7 g/dL and 37.9±5.3%. The mean admission Hunt-Hess score was 3 (25th, 75th percentiles 2,4). Ninety-six patients (67.8%) developed cerebral vasospasm. Eighty-one patients (48.7%) were treated with routine patient education. The chi-squared test was used to assess differences in appropriate and inappropriate responses between provider groups. Results - Respondents included 101 family/general practitioners, 101 internists, 100 obstetrician/gynecologists (OB/GYN), 102 physician assistants (PA), and 100 nurse practitioners (NP). There were 195 (38.7%) women; average age was 47.4±9.1 years (mean ± SD). Less than 10% stated that they knew the need for angiography; risks and warning signs with patients as part of the annual exam. The three case vignettes focused on management of new onset atrial fibrillation (case 1), hypertension (case 2), and TIA (case 3) [Table]. Only 25% of OB/GYN, 43% of NP, and 55% of PA appropriately identified the need for anticoagulation in a patient with atrial fibrillation at high risk of stroke. Furthermore, 20% of NP and 26% of OB/GYN did not identify appropriate management of hypertension. The majority of providers (78–88%) treated TIA as an emergency. Results - Several groups of primary care providers, including OB/GYN, PA, and NP, frequently failed to identify appropriate interventions for stroke prevention in case vignettes. Furthermore, many providers do not educate patients routinely on stroke risks and warning signs. Targeting certain groups of primary health care providers for educational campaigns could improve stroke prevention practices.

Background - Several studies have suggested that healthcare providers often fail to follow established guidelines for stroke prevention. We sought to assess whether failure to adhere to guidelines was related to knowledge. Methods - The National Stroke Association sponsored a telephone survey of 504 primary healthcare providers between August and September 2002. Providers were sampled randomly from all regions of the U.S. All participants answered questions about management of 3 case vignettes and described their clinical practice and routine patient education. The chi-squared test was used to assess differences in appropriate and inappropriate responses between provider groups. Results - Respondents included 101 family/general practitioners, 101 internists, 100 obstetrician/gynecologists (OB/GYN), 102 physician assistants (PA), and 100 nurse practitioners (NP). There were 195 (38.7%) women; average age was 47.4±9.1 years (mean ± SD). Less than 10% stated that they knew the need for angiography; risks and warning signs with patients as part of the annual exam. The three case vignettes focused on management of new onset atrial fibrillation (case 1), hypertension (case 2), and TIA (case 3) [Table]. Only 25% of OB/GYN, 43% of NP, and 55% of PA appropriately identified the need for anticoagulation in a patient with atrial fibrillation at high risk of stroke. Furthermore, 20% of NP and 26% of OB/GYN did not identify appropriate management of hypertension. The majority of providers (78–88%) treated TIA as an emergency. Results - Several groups of primary care providers, including OB/GYN, PA, and NP, frequently failed to identify appropriate interventions for stroke prevention in case vignettes. Furthermore, many providers do not educate patients routinely on stroke risks and warning signs. Targeting certain groups of primary health care providers for educational campaigns could improve stroke prevention practices.

Hemorrhage

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Introduction: Data on 3500 patients with aneurysmal subarachnoid hemorrhage (SAH) entered into 4 randomized trials conducted around the world between 1991 and 1997 were analyzed to ask questions about SAH. Methods: Uni- and multivariate statistical analyses were conducted to determine the effect of race and early vasospasm (EVSP) on admission angiography on SAH demographics and outcome. Results: Whites were significantly older than other races. Blacks more frequently had a history of hypertension and more commonly had elevated blood pressure on admission. Blacks and other minorities were more likely to have internal carotid aneurysms and whites were more likely to have posterior circulation aneurysms. In-hospital complications were not significantly different except for pulmonary edema, which was more common in whites. Outcome at 3 months was not significantly different between races. EVSP within 48 hours of SAH was diagnosed in 10% of patients and was significantly more likely in patients with poor neurological grade, history of SAH, intracerebral hematoma, larger aneurysm, thick SAH on CT and intraventricular hemorrhage. EVSP was not associated with delayed vasospasm but was associated with cerebral infarction and unfavorable outcome (p<0.005). There was a trend for patients with increasingly severe EVSP to have worsening outcome. Conclusions: Race was not a prognostic factor for outcome after aneurysmal SAH, suggesting that the higher SAH mortality previously observed in blacks is due to a higher incidence of SAH in blacks. Early vasospasm may be more important than previously thought as it was diagnosed in 10% of patients and was associated with cerebral infarction and poor outcome.

NP
patients not intubated nor comatose at admission. Methods: 446 consecutive patients from 11 Neurology departments with acute stroke units were prospectively documented on standardized case report forms. Stroke severity was assessed on the National Institutes of Health Stroke Scale (NIH-SS) at admission and 48–72 hours after admission. A predominantly central follow-up assessed functional outcome and death up to 120 days after admission. Results: 66 patients were admitted intubated or in coma state. These patients had a mortality of 45.5% until 72 hours and 71.2% until 120 days after admission. Of 380 patients not intubated nor comatose at admission, 21 patients (5.5%) had died and 55 patients (14.5%) presented worsening of key neurological functions 72 hours after admission. The logistic regression on the NIH-SS, extent of hemorrhage, and ventricular bleeding were identified as independent predictors for worsening of key neurological functions or death. At follow-up, 60 patients (15.8%) had died and 120 patients (31.6%) had regained functional independence (Barthel Index = 95). Age and the NIH-SS total score were identified as independent predictors for reaching functional independence. The resulting model was very similar to a recently validated prognostic model for acute ischemic stroke and had a higher accuracy than the treating physicians’ prognostic made within the first 72 hours after admission. Conclusion: Independent predictors for 120-day functional outcome following ICH in non-comatose patients are identical to ischemic stroke with very similar B-weights. In non-comatose patients, the NIH-SS total score at admission might be a more reliable predictor of functional outcome than other indicators of initial stroke severity.1 Stroke 2004;35:158–162

PKC and Rho Activation in an In Vitro Model of Cerebral Vasospasm After Subarachnoid Hemorrhage: Role of Bilirubin Oxidation Products

Gail J Pyne-Geithman, Sunil Nair, Joseph F Clark, Univ of Cincinnati, Cincinnati, OH

Delayed cerebral vasospasm (CV) remains a major cause of death & impaired neurological recovery after subarachnoid hemorrhage (SAH). Despite intensive research efforts, the etiology is not yet known. In vivo models have implicated PKC & rho activation in arteries, but the method of inducing CV in vivo has been criticized. Our in vitro model uses human CSF from patients with CV after SAH & porcine carotid artery (PCA) smooth muscle. The aim of this study was to assess the activation of the PKC isozymes α, β, & θ and Rho in our in vitro model. The effects of purified bilirubin oxidation products (BOXes), which we have proposed to be the causative molecule in CV, were also examined. Understanding the etiology of CV will allow development of effective prophylactic treatments. SAH CSF was classified as CSFV or CSFC, based on whether JO 2 of PCA was stimulated above (V) or below (C) normal resting contraction levels. PKC-α activation (measured as % change from the mean basal contraction) was significantly inhibited by CSFV (p=0.044) but not by CSFC. PKC-β activation was only seen at 3 hrs. CSF V only (not CSF C) elicited these effects. BOXes activated all BOXes activated in a time-dependent manner, & Altered Mental Status (AMS), that were not automated, was also analyzed.

Promoter Polymorphisms in Interleukin 6 and Interleukin 10 Are Associated With Cardiac Injury and Dysfunction After Subarachnoid Hemorrhage

Sirisha Yarlagadda, Ludmila Pawlikowska, Jacob C Miss, Alexander Kopelnik, Achal S Harsoula, UCSF, San Francisco, CA

Previous studies of patients with subarachnoid hemorrhage (SAH) have found an association between elevated levels of inflammatory cytokines (ICs) such as interleukin-6 (IL-6) and the development of cerebral vasospasm. Elevated levels of ICs have also been found in patients with congestive heart failure and myocarditis. Single nucleotide polymorphisms (SNPs) in the promoters of the genes encoding IL-6 (1746–G) and the counter-inflammatory cytokine interleukin-10 (IL-10, 1082G>A) have been shown to modulate levels of ICs in patients hospitalized for coronary bypass surgery and pneumonia. The objective of this study was to test the hypothesis that IC promoter SNPs are associated with an increased risk of cardiac injury (troponin release) and dysfunction (reduced left ventricular ejection fraction (LVEF) after SAH). Methods: This was a pre on the cohort study of 167 patients admitted with aneurysmal SAH. The subjects were enrolled as soon as possible after admission, a blood sample was obtained for genotyping and measurement of cardiac troponin I (cTi), and an echocardiogram was performed. The cTi measurement and echo were repeated 2 and 5 days after enrollment. After discharge, a blood sample was only seen at 3 hrs. CSF V only (not CSF C) elicited these effects. BOXes activated all BOXes activated in a time-dependent manner, & Altered Mental Status (AMS), that were not automated, was also analyzed.

Using Automated Clinical Data on Admission to Predict Mortality Among Patients Hospitalized for Hemorrhagic Stroke

Ying P Tabak, Cardinal Health, Marlborough, MA; Stephen G Kurtz, Cardinal Health, Marlborough, MA; Richard S Johannes, Cardinal Health, Marlborough, MA

Context: Research models predicting stroke mortality have not been widely adopted due to the high cost of chart abstraction. A cost effective clinical model is crucial for large scale implementations of quantitative decision support. Objectives: To develop and validate a predictive model using automated laboratory data (LAB) for acute conditions and Uniform Billing data for demographics, discharge status, and comorbidities. The significance of vital signs (VS) and Altered Mental Status (AMS), that were not automated, was also analyzed. Research models predicting stroke mortality have not been widely adopted due to the high cost of chart abstraction. A cost effective clinical model is crucial for large scale implementations of quantitative decision support. Objectives: To develop and validate a predictive model using automated laboratory data (LAB) for acute conditions and Uniform Billing data for demographics, discharge status, and comorbidities. The significance of vital signs (VS) and Altered Mental Status (AMS), that were not automated, was also analyzed. Methods: A model was derived from 2780 (611 deaths) hemorrhagic stroke admissions across 18 teaching and 21 non-teaching hospitals that exported LAB data to Atlas® (Med峭a) in 2000–01. Multiple cuts on admission LAB and VS were crafted per change-point methods. Age, LAB, comorbidities (identified by 6th digit ICD-9 coding), VS, & AMS were entered into logistic regressions. ROC curve assessed model fit and Bootstrapping validated the model internally. Multiple cuts on admission LAB and VS were crafted per change-point methods. Age, LAB, comorbidities (identified by 6th digit ICD-9 coding), VS, & AMS were entered into logistic regressions. ROC curve assessed model fit and Bootstrapping validated the model internally. Conclusions: These data suggest that early ST elevation and ST deviation intervals abnormalities occur early and among an important proportion of aSAH patients (43%). There is a significant effect of HH score in the predictive set of early ST elevation and ST abnormalities for DCI and stroke from vasospasm. Early significant ST depressions and pathologic Q-waves in more than two leads predict a high cTI leak, which may be associated with cardiac dysfunction. Our early ECg morphologic changes had no clear prediction of functional outcome at 14 days using the mRS. Future research in early electrophysiological changes and cardiac dysfunction after aSAH is needed.

Inflammatory Cytokine SNPs & Cardiac Outcomes

IL-6 1746G>C Genotype

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<td>18%</td>
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IL-10 1082G>A Genotype

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</table>

P358 Early Electrocardiographic Morphologic Changes and Prediction of Delayed Cerebral Ischemia, Stroke, and High Troponin Level Among Aneurysmal Subarachnoid Hemorrhage Patients

Fred Rincon, Michael Schmidt, Andrew M Naidech, Noeleen Otsopoulos, E S Connolly, Stephan A Mayer, Augusto Parra, Columbia-Presbyterian Med Ctr, New York, NY

Introduction. An ECG is routinely done in most of our aSAH patients during the first 24 hours after hospital admission. Early ECG morphologic changes may be seen after aSAH. We performed a systematic assessment of these changes in the 12-lead ECG of patients suffering of aSAH, and studied their predictive value on several outcome variables. Methods. We analyzed the ECG of 442 patients with aSAH during the first 24 hours after admission to the Columbia University-SAH-Outcomes-Project, between 10/1996–10/2002. Association of early abnormal ECG changes (ST abnormalities, QT-c prolongation, BBB, pathologic Q-wave, LAE, RAE, and LVM patterns) and prediction of Delayed Cerebral Ischemia (DCI), stroke secondary to vasospasm, high cardiac Troponin-I level (cTI>10µg/L), and adverse outcome by the modified Rankin Scale (≥3) by day 14 or at discharge from the index admission, were analyzed using forward conditional logistic regression models. Results. Morphologic abnormalities where seen in the ECG of 76% of patients during the first 24 hrs of the index-admission (mean=1.5±0.2 days). The most frequent abnormality was prolongation of QTc (5%±0.5 sec (34.4%). The combination of QTc-ST abnormality detectable within 1 day of index admission, was the best predictor of DCI (exp=–3.14, p<0.002) and stroke from vasospasm (exp=–2.67, p<0.001). ST-depression ≥1mm in at least two leads (exp=–1.331, p<0.013) and pathologic Q-wave (exp=–1.427, p<0.028) were independent predictors of high cTI level (≥10µg/L). All models were adjusted for aSAH severity (Hunt & Hess score). Conclusions. These data suggest that early ST segment and QT-c interval abnormalities occur early and among an important proportion of aSAH patients (43%). There is a significant effect of HH score in the predictive set of early ST elevation and ST abnormalities for DCI and stroke from vasospasm. Early significant ST depressions and pathologic Q-waves in more than two leads predict a high cTI leak, which may be associated with cardiac dysfunction. Our early ECG morphologic changes had no clear prediction of functional outcome at 14 days using the mRS. Future research in early electrophysiological changes and cardiac dysfunction after aSAH is needed.
Perimesencephalic Subarachnoid Hemorrhage: A Population-Based Study
Matthew L Flaherty, Mary Haverbusch, Padmini Sekar, Laura Sauerbeck, Daniel Woo, Univ of Cincinnati, Cincinnati, OH

Background: Nonaneurysmal perimesencephalic subarachnoid hemorrhage (PMSAH) appears to have an etiology and natural history distinct from aneurysmal rupture. Referral-based studies suggest that approximately 15% of SAH patients have no discernable cause of bleeding, but the incidence of SAH is unknown. We describe the first population-based study of PMSAH, with presentation of incidence rates and patient demographics. Methods: All patients aged ≥20 hospitalized with first-ever, nontraumatic SAH in the Greater Cincinnati/Northern Kentucky metropolitan area were identified from 5/98–7/01 and 8/02–4/04. Traumatic and iatrogenic SAH were excluded. SAH associated with anticoagulation little included. PMSAH was defined as hemorrhage restricted to the suprasellar cistern and/or cisterns surrounding the brainstem (with scant blood allowed in the ventricles) and a negative cerebral angiogram. Incidence rates were age, race, and sex adjusted to the 2000 US population as appropriate. Results: There were 421 SAHs identified. Cases: Mean age was 49.4 years, 25% were women, 25% were black, 28% were hypertensive, and 32% were smokers. Annual incidence rates of PMSAH were (per 100,000 persons): 11.8 for women, 5.6 for men, 6.3 for white, 8.4 for black. All SAH cases/Incidence (95% CI) PMSAH Cases PMSAH Incidence (95% CI)

<table>
<thead>
<tr>
<th>Race</th>
<th>All SAH</th>
<th>Cases</th>
<th>Incidence (95% CI)</th>
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<tbody>
<tr>
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<tr>
<td>Black</td>
<td>103</td>
<td>5.3</td>
<td>12.6 (11.0–14.2)</td>
</tr>
<tr>
<td>Men</td>
<td>121</td>
<td>5.4</td>
<td>12.7 (11.0–14.7)</td>
</tr>
<tr>
<td>Women</td>
<td>316</td>
<td>8.1</td>
<td>7.9 (7.0–8.8)</td>
</tr>
<tr>
<td>White</td>
<td>21</td>
<td>0.5</td>
<td>0.2 (0.1–0.8)</td>
</tr>
<tr>
<td>Black</td>
<td>7</td>
<td>0.3</td>
<td>0.7 (0.2–1.1)</td>
</tr>
<tr>
<td>Men</td>
<td>16</td>
<td>0.7</td>
<td>0.4 (0.2–1.1)</td>
</tr>
<tr>
<td>Women</td>
<td>28</td>
<td>0.5</td>
<td>0.2 (0.1–0.8)</td>
</tr>
</tbody>
</table>

*Per 100,000 persons ≥ 20, age, race, and sex adjusted to the 2000 US population as appropriate.

Conclusions: These data indicate increased incidence of PMSAH in women, but not more common in women. This may reflect differences in risk factors for PMSAH and aneurysmal SAH.

Analysis of silent microbleeds distribution

Brain Atrophy and Long-term Neurological Deficits After Experimental Intracerebral Hemorrhage: The Role of Iron

Gouhua Xi, Ya Hua, Takehiro Nakamura, Richard Keep, Timothy Schallert, Julian Hoff, Univ of Michigan, Ann Arbor, MI

Background: The long-term effects of intracerebral hemorrhage (ICH) on brain damage are poorly understood. Recent evidence suggests that some ICH-induced brain injury results from the products of hemoglobin degradation including iron. The present study examines the role of iron in brain atrophy and neurological deficits following ICH. Methods: Male Sprague-Dawley rats (n = 42) received either infusion of 100 μl autologous whole blood or insertion of a needle into the right caudate. Hemoglobin and iron staining were used for histological examination. Iron levels and ferritin immunoreactivity were also examined. Deferoxamine (100 mg/kg, i.p. starting at 2 hrs after ICH, every 12 hrs for 7 days) was used as an iron chelator. Over the period of the experiment, the rats underwent behavioral testing (foraminae loci, forelimb use asymmetry and corner turn tests). Results: Brain atrophy in the caudate with prolonged neurological deficits occurred after ICH. There was significant caudate atrophy at 4 weeks (percentage of the contralateral caudate: 78.3 ± 6.9% vs. 98.1 ± 2.8% in the sham control, n = 4, p < 0.05) with enlargement of the ipsilateral lateral ventricle (percentage of the contralateral lateral ventricle: 239.8 ± 18.4% vs. 190.4 ± 7% in the sham control, n = 4, p < 0.05). Between 8 and 12 weeks, the ipsilateral caudate area was ~70% of control. Although partial functional recovery happened with time, residual neurological deficits were detectable at three months. Both iron accumulation and ferritin upregulation were present in the ipsilateral caudate. Deferoxamine reduced brain atrophy (caudate: 93.6% vs. 79.5% in the vehicle group, n = 6, p < 0.05; ventricle enlargement: 127.2 ± 28% vs. 300 ± 7% in the vehicle group, n = 6, p < 0.05) and improved behavioral outcomes (p < 0.05). Conclusions: ICH results in an accumulation of iron in the brain that is not cleared within three months, which contributes to brain tissue loss and neurological deficits after ICH. Iron chelation may be a useful therapy for ICH patients.

Burden of Silent Microbleeds Is Associated With Volume of Symptomatic Lobar Hemorrhage

Seunghoon Lee, Jee-Young Lee, Seoul National Univ Hosp, Seoul, Republic of Korea; Hee-Joon Bae, Eulji Med Ctr, Seoul, Republic of Korea; Byung-Woo Yoon, Seoul National Univ Hosp, Seoul, Republic of Korea

Background and Purpose: Silent microbleeds (SMBs) are frequently observed in patients with intracerebral hemorrhage (ICH), which is related to blood brain barrier (BBB) disruption of lipoxygenized phosphatidylcholines. Based on previous observation of the relationship between BBB disruption and ICH volume, we hypothesized that presence or burden of these SMBs may be associated with increased volume of symptomatic ICH. Methods: Acute ICH patients with their first CT scanned within 2 days of onset and gradient-echo MRI in 7 days were included. Patients with pontine or cerebellar hemorrhages were excluded from this study. The ICH volume was measured on baseline CT scans using the ABC/2 method, and SMBs were counted and localized on gradient-echo MRI. Supratentorial location was divided into lobar area and deep gray matter (putamen and thalamus), and we classified the degrees of SMBs or ICH volume as 4-grade system using quartiles. Image analysis was by consensus of 2 stroke neurologists blinded to clinical information and CT-MRI pairings. To test associations between SMB and ICH volume, we used student t-test and Spearman correlation coefficient.

Results: Analysis of 140 consecutive patients with ICH who were referred to our center from Jan 1999 to Dec 2003 (n = 226), 71.5% of whom had symptom-onset > 48 hrs, 34.4% of whom had hypertension > 10 years, 28% had symptomatic ICH in putamen, thalamus orpons; CAA group, 1) symptomatic cortico-subcortical hemorrhage only, 2) consistent with "probable" CAA of Boston CAA Criteria. Patients with ≤ 5 cortico-subcortical SMBs were excluded from this study. The lesions were counted and localized by consensus of 2 stroke neurologists blinded to clinical information. Results: A total of 52 hemispheres (AHT group, n = 32; CAA group, n = 20) were analyzed. Number of SMBs was much higher in AHT group (median: 21 vs. 6, p < 0.01). The SMBs showed a significant prediction for the tempo-occupipal lobes in AHT group, but for the parietal lobe in CAA group (Table). The most involved vascular territory was middle cerebral artery territory in both groups, but the lesion number in anterior cerebral territory was relatively high in CAA group. Conclusions: These data suggest that AHT and CAA may have different topographical distribution of SMB even in cortico-subcortical area. Our results should be helpful to differential diagnosis of early stage patients with isolated cortico-subcortical SMBs.

Cortico-Subcortical Distribution of Silent Microbleeds Is Different Between Hypertension and Cerebral Amyloid Angiopathy

Seunghoon Lee, Sung-Min Kim, Seoul National Univ Hosp, Seoul, Republic of Korea; Hee-Joon Bae, Eulji Med Ctr, Seoul, Republic of Korea; Byung-Woo Yoon, Seoul National Univ Hosp, Seoul, Republic of Korea

Background and Purpose: Silent microbleeds (SMBs) are mainly caused by advanced hypertension (HT) or cerebral amyloid angiopathy (CAA), but the distributions of SMBs are quite different according to the causative diseases: SMBs are located diffusely in the whole brain area in HT patients, but exclusively in cortico-subcortical area in CAA patients. We hypothesized that distribution of these SMBs may be different between HT and CAA even in the cortico-subcortical area. Methods: A consecutive series of patients with intracerebral hemorrhage underwent brain MRI including gradient-echo sequences from Jan 1999 to Dec 2003 (n = 226). Out of the subjects, we selected typical AHT and CAA patients as follows: AHT group, 1) history of hypertension > 5 years, 2) symptomatic ICH in putamen, thalamus orpons; CAA group, 1) symptomatic cortico-subcortical hemorrhage only, 2) consistent with "probable" CAA of Boston CAA Criteria. Patients with ≤ 5 cortico-subcortical SMBs were excluded from this study. The lesions were counted and localized by consensus of 2 stroke neurologists blinded to clinical information. Results: A total of 52 hemispheres (AHT group, n = 32; CAA group, n = 20) were analyzed. Number of SMBs was much higher in AHT group (median: 21 vs. 6, p < 0.01). The SMBs showed a significant prediction for the tempo-occupipal lobes in AHT group, but for the parietal lobe in CAA group (Table). The most involved vascular territory was middle cerebral artery territory in both groups, but the lesion number in anterior cerebral territory was relatively high in CAA group. Conclusions: These data suggest that AHT and CAA may have different topographical distribution of SMB even in cortico-subcortical area. Our results should be helpful to differential diagnosis of early stage patients with isolated cortico-subcortical SMBs.
Background: Elevated blood pressure, observed in 46% to 56% of patients with intracerebral hemorrhage (ICH), may be related to hematoma expansion. Reduction of blood pressure may reduce hematoma expansion and subsequent death and disability. Limited information is available regarding antihypertensive treatment regimens and associated clinical outcomes. We performed this prospective study to determine the feasibility and safety of treatment of acute hypertension in patients with ICH within 24 hours of symptom onset. Methods: All patients admitted to the stroke service with ICH and acute hypertension were treated with intravenous nicardipine to reduce and maintain mean arterial pressure (MAP) <130 mm Hg for a period of 24 hours consistent with the American Heart Association recommendations (Stroke. Apr 1999;30:905–915). Primary outcome was tolerability of the treatment assessed by achievement and maintenance of MAP goals for 24 hours. Neurological deterioration was the primary safety endpoint, defined by a decline in Glasgow Coma Scale or increase in National Institutes of Health Stroke Scale (NIHSS) score by 2 points or greater. Hemorrhage growth (an increase in volume of >33% as measured by image analysis on the 24-hour CT compared to baseline) was the tertiary outcome. Rates of favorable outcome and death were ascertained at one month. Results: Of 51 patients admitted with ICH, 30 met the inclusion criteria and were treated with intracranial nicardipine. Mean age of the treated patients was 58 ± 13 years; 10 were women. Initial NIHSS ranged from 1 to 36. The primary outcome was achieved in 25 (83%) of the 30 patients. Neurological deterioration occurred in 4 (13%) of the 30 patients. Hematoma enlargement was observed in 5 patients. Favorable outcome (modified Rankin scale of 2 or less) and death at one month was observed in 11 (37%) and 10 (33%) of the 30 patients, respectively. Conclusions: We observed a high rate of tolerability and acceptable rates of neurological deterioration and hematoma enlargement among patients with ICH who were treated with intracranial nicardipine using MAP goals defined by American Heart Association guidelines.

Impaired Cerebrovascular Myogenic Function Is Reflected in Blood Pressure Variability Patterns That Indicate Imminent Hemorrhagic Stroke

Vivek Bhata, Diane Retelita, Gilbert Aldape, Harald M Stauss, Univ of Iowa, Iowa City, IA

It has been suggested that impaired cerebrovascular myogenic function contributes to the pathogenesis of hemorrhagic stroke. We tested the hypotheses that (1) cerebrovascular myogenic function deteriorates with increasing age in stroke-prone (SHR-SR) compared to stroke-resistant spontaneously hypertensive rats (SHR-SR) and (2) that impaired vascular myogenic function is reflected in specific blood pressure variability (BPV) patterns that may indicate imminent hemorrhagic stroke. In conscious SHR-SR and SHR-SR at 7 (n = 10 for both strains) and 13 weeks of age (SHR-SR; n = 4, SHR-SR; n = 5), blood pressure was recorded during control conditions and blockade of myogenic function (nifedipine, 5 mg/kg IV bolus). Blood pressure was monitored at control levels by co-infusion of vasopressin. BPV patterns were determined by power spectral analysis. Middle cerebral arteries (MCA) were isolated, mounted on glass capillaries, and pressurized for determination of myogenic responses to step changes in transmural pressure. Systolic blood pressure increased with age (p < 0.05), but not in SHR-SR. Correlation between SHR-SR and SHR-SR-SR. Nifedipine reduced low frequency (LF, 0.02–0.20 Hz) BPV in both strains and both ages (p < 0.05). LF BPV during control conditions was less and myogenic responses in isolated MCA were blunted, in 13 week-old SHR-SR compared to age-matched SHR-SR. Further development of myogenic tone as a vascular mechanism of autoregulation was slow (40 to 50 seconds). This slow response together with the reduction in LF BPV by nifedipine infusion demonstrates that vascular myogenic function specifically affects LF BPV. In conclusion, cerebrovascular myogenic function deteriorates with age in SHR-SR and these vascular alterations are reflected in a decrease in LF BPV. Blood pressure power spectral analysis may be useful to identify patients with imminent hemorrhagic stroke.

Utility of Magnetic Resonance Imaging in the Diagnosis and Management of Intracerebral Hemorrhage

Sara Brunis, Neil E Schwartz, Christine A Wijman, Stanford Univ Med Ctr, Palo Alto, CA

Intracerebral hemorrhage (ICH) accounts for 10–15% of strokes. Computerized tomography (CT) is the standard imaging modality in the initial management of ICH. The purpose of this study was to determine the added value of magnetic resonance (MR) imaging. METHODS: Patients with ICH in the Stanford Stroke Center database who had undergone both CT and MR imaging were included. A stroke and a general neuroradiologist, blind to the final diagnosis, independently reviewed the scan and chart data for the initial presentation. After review of the CT, a presumed diagnosis was recorded. A second diagnosis was then recorded after subsequent review of the MR images. The final diagnosis was determined after review of all medical information from the chart by a third investigator. The category and certainty of both CT and MR diagnoses, the potential impact of a diagnosis change on patient management, and the MR sequences that changed diagnosis category or certainty were recorded. RESULTS: Seventy patients met inclusionary criteria. Mean time between symptom onset and MR imaging was 3 ± 5.4 days. The final diagnosis was hypertension in 33%, cerebral amyloid angiopathy in 14%, and unknown in 14% of patients. Presumed etiologies in the remaining 52% included trauma, vascular malformation, intracranial aneurysm, illicit drug use, coagulopathy, vasculitis, and hemorrhagic ischemic stroke. In 14% of the cases, the stroke neuroradiologist changed diagnosis category to the correct final diagnosis after review of the MR images. In 23% of cases she was more certain of her initial (correct) CT diagnosis. Potential management was changed in 20% of the cases, 24% of the time (n = 17) in the CT group, but not in the other 373 patients (control group). We compared location of hematoma between the AT group and the control group, the rate of thalamic, putaminal, cerebral, brainstem, subcortical and mixed type hemorrhage was 43.5% vs. 30.2%, 22.6% vs. 39.3%, 6.5% vs. 2.6%, 2.4% vs. 10.4%, 19.4% vs. 13.2%, and 2.2% vs. 2.9%, respectively. Thalamic hemorrhage was more frequent in AT group (p = 0.037), past history of BH (16.0% vs. 8.9%, p = 0.0028), and had higher proportion of women (46.8% vs. 36.5%, p = 0.037). Conclusions: MR imaging has substantial added value in the initial diagnosis and management of patients with ICH both for the stroke and general neuroradiologist.

Ischemic Neuroprotection With Selective α-Opioid Receptor Agonist Is Gender Specific

Chih-Hung Chen, Thomas J. Young, Johns Hopkins Univ Sch of Med, Baltimore, MD; Jeffrey R Kirsch, Patricia D Hurn, Oregon Health and Science Univ, Portland, OR; Raymond C Koehler, Anish Bhardwaj, Johns Hopkins Univ Sch of Med, Baltimore, MD

Background and Significance: We have previously demonstrated that treatment with selective kappa-opioid receptor (KOR) agonist BRL 52537 hydrochloride ([(+/-)1,3-dichlorophenyl] acetyl-2-(1-pyrrolidinyl) methylpiperidine) 1) has a long therapeutic window for providing ischemic neuroprotection following transient focal ischemia 2) attenuates ischemia-evoked nitric oxide (NO) production in vivo in rats. Neurally derived NO has been shown to be beneficial in the male, but detrimental in the female rodent model of focal ischemic stroke. In this study, we tested the hypotheses that BRL provides significant ischemic neuroprotection in the male but not in the female in a well-characterized model of transient focal ischemia. Materials and Methods: Under controlled conditions of normoxia, normocarbia, and normothermia, male but not female rats in a well-characterized animal model of ischemic stroke, and 2) highlight the importance of using animal models of both genders in experimental studies of ischemic neuroprotection.

Gender Specific Therapy of Intracerebral Hemorrhage Using American Heart Association Guidelines

Adnan I Qureshi, Pansy Harris-Lane, Molly Jacob, Shaifuldin Ahmed, Yasina Zada, Afshin A Divani, Ishu Khatri, Zenoat Qureshi Stroke Rich Ctr, Univ of Med and Dentistry of New Jersey, Newark, NJ

Experimental Ischemia

Chih-Chung Chen, Thomas J. Young, Johns Hopkins Univ Sch of Med, Baltimore, MD; Jeffrey R Kirsch, Patricia D Hurn, Oregon Health and Science Univ, Portland, OR; Raymond C Koehler, Anish Bhardwaj, Johns Hopkins Univ Sch of Med, Baltimore, MD

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Pre-Reperfusion Flushing of Saline Into Ischemic Territory Improves Neurovascular Integrity by Reducing Matrix Metalloproteinase Uprolqege in Stroke

Yuchuan Ding, Yun H Ding, Jie Li, James P McAllister II, Richard D Feister, Murali Guthikonda, Jose A Rafols, Wayne State Univ Sch of Med, Detroit, MI

Perturbation of the extracellular matrix (ECM) disrupts microvascular homeostasis and integrity in stroke. Constituents of ECM are degraded by a variety of proteolytic enzymes, including MMP. After middle cerebral artery (MCA) occlusion, the early appearance of activated MMP-2...
or -9, as well as inflammatory reaction are associated with alteration of blood brain barrier permeability and formation of vasogenic edema. Our recent experimental stroke studies have utilized a unique technique to "flush" the microvasculature in the ischemic territory prior to reperfusion, which results in significant infarct reduction and motor behavior improvement. Here, we address whether a similar flushing procedure prior to reperfusion improves cerebral blood flow and integrity and whether this neuroprotection is associated with reduced blood brain and inflammation, as well as reduced MMP expression. Stroke in Sprague Dawley rats (n=42) was induced by a 2-h right MCA occlusion using a novel intraluminal filament. Prior to reperfusion, 24 ischemic rats received 6 ml isotonic saline at 37°C infused through the ischemic territory, and 24 ischemic rats were flushed by means of in vivo laser scanning confocal microscopy (LSCM) and magnetic resonance imaging (MRI). Methods: Small embolic ischemia in the right parietal cortex of the adult mouse was generated by injecting a fibrin rich clot into a branch of the right middle cerebral artery. The presence of an embolus was confirmed by MRI. 24 hours under the Middle Cerebral Artery Occlusion (MCAO) 4% Neurolucida pro. Subventricular Zone (SVZ). Adult green fluorescent protein (GFP) transgenic mice were labeled with superparamagnetic particles, and were injected into a tail vein 48 h after stroke onset. LSCM and MRI were performed 1 day and weekly up to 4 weeks after cell transplantation. Mouse brains were removed and dissected for histological analysis. Results: Fluorescence was not detected at the parietal cortex 1 day after 1 h of reperfusion. In contrast, 20 min of reperfusion after 1 h MCAO resulted in a 151% increase of GFP transgenic cells detected in living mice. Some of the cells exhibited multibranched processes from the cell soma, resembling neuronal morphology. Conclusions: Monitoring migration of a single transplanted cell can be performed in the stroke brain of the living mouse, and this new model of small cortical ischemia is useful for dynamically investigating the interaction between grafted cells and the endogenous cerebral micro-environment.
reperfusion after focal ischemia of moderate duration (1 h) accelerates this process, possibly because of accelerated oxidant stress.

**Diffusion, Perfusion, and Functional Imaging of Transient Ischemic Injury**

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Background: The ability to chronically perform fMRI in stroke animal models could have many important applications. Essentially all forepaw stimulation fMRI experiments in rats use alpha-chloralose anesthetic, which require terminal experiments. We recently developed a forepaw stimulation model under isoflurane anesthesia on spontaneously breathing rats for chronic fMRI studies. Herein, we extended this approach to chronically evaluate hypercapnic challenge and functional response to forepaw stimulation in transient cerebral ischemia.

Methods: Stroke was induced for 15min on the bench under 2% isoflurane followed by reperfusion (n = 6). PWI, DWI, T2 and MTR were acquired at 30, 90, 120 mins, 24 and 72 hrs under ~1.15% isoflurane. Hypercapnic (5% CO2) challenge and forepaw stimulation were evaluated. ADC, CBF images and fMRI maps were analyzed for the forepaw cortices in the right hemisphere (RH) and control left hemisphere (LH).

Results: Remarkably, 15-min occlusion under isoflurane did not cause significant ADC lesions at 3hrs and only a few animals (50%) developed T2 or TCC lesions at >24 hrs. Basal CBF and T1-weighted signals were similar between the RH and LH forepaw cortices. BOLD and CBF responses to CO2 and forepaw stimulation showed no statistical differences between the RH and LH (P > 0.05), despite small lesions in the caudoputamen and heterogeneous mild hyperperfusion were observed in some animals (n = 4). This is likely due to the neuroprotective effect of isoflurane. Conclusion: It is now possible to perform chronic fMRI to evaluate the "functional" status of the salvageable and non-salvageable tissues as defined by anatomical (diffusion and perfusion) imaging.

**Ischemic Tolerance Involves Upregulation of Glutamate Transport Partly Mediated by the TACE/ADAM17-TNF-α Pathway**

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Background and Purpose: A short ischemic event (ischemic preconditioning; IPC) can result in a subsequent resistance to severe ischemic injury (ischaemic tolerance, IT). Although tumour necrosis factor-α (TNF-α) contributes to the brain damage found after cerebral ischemia, its expression and neuroprotective role in models of IPC have also been described. Regarding the role of TNF-α convertase (TACE/ADAM17), we have recently shown its up-regulation in rat brain after IPC induced by transient middle cerebral artery occlusion, and that blockade of the TNF-α release accounts for at least part of the neuroprotection found in this model. We have now used both an in vivo and in vitro model of IPC to investigate whether the expression of glutamate transporters is involved in IT. Methods: We have used an in vitro model of IPC using rat cortical cultures exposed to sublethal oxygen-glucose deprivation (OGD). As in vivo model of IPC, we have used a period of 10-min temporary middle cerebral artery occlusion (MCAO). Results: OGD-induced cell death was significantly reduced in cells exposed to IPC by sublethal OGD 24 h before, an effect that was inhibited by the TACE inhibitor BS1103 (1 µM) and anti-TNF-α antibody (2 µg/mg) (viability was studied by measuring LDH release in the medium). Western blot analysis showed that TACE expression is increased after IPC. TACE diminished the increase in extracellular glutamate (measured by RP-HPLC) caused by OGD and increased cellular glutamate uptake. As we have demonstrated previously, IPC produced a reduction in infarct volume (SHAM = 19 ± 5 mm3 and IPC = MCAO = 98 ± 7 mm3; n = 6–12; P < 0.05). Western blot analysis showed that IPC, in both models, caused up-regulation of EAAT2 and EAAT3 glutamate transporters; however, only EAAT2 up-regulation was mediated by increased TNF-α. Conclusions: These data demonstrate that neuroprotection induced by IPC involves up-regulation of glutamate uptake partly mediated by TACE over-expression.

**Preconditioning Improves Blood Flow in Penumbra During Focal Ischemia in the Spontaneously Hypertensive Rat**

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Preconditioning reduces injury after subsequent middle cerebral artery occlusion (MCAO). Previous studies have excluded a role for blood flow changes in such effects because of acute CBF measurements following MCAO. The present study applied [14C]iodoantipyrine autoradiography to compare the distribution of CBF deficits at various times after permanent occlusion in naive and preconditioned (PC) Spontaneously Hypertensive Rats. Preconditioning was produced by 10 min occlusion of the MCA and ipsilateral common carotid artery under halothane anesthesia. The same vessels were permanently coagulated 24 h later in both PC and naive rats. Infarct volumes were determined after an additional 24 h in hematoxylin-eosin stained brain slices. The same vessels were permanently coagulated 24 h later in both PC and naive rats after 10 min occlusion of the MCA and ipsilateral common carotid artery under halothane anesthesia. The same vessels were permanently coagulated 24 h later in both PC and naive rats. Infarct volumes were determined after an additional 24 h in hematoxylin-eosin stained brain slices.

Methods: Stroke was induced for 15mins on the bench under 2% isoflurane followed by reperfusion (n = 6). PWI, DWI, T2 and MTR were acquired at 30, 90, 120 mins, 24 and 72 hrs under ~1.15% isoflurane. Hypercapnic (5% CO2) challenge and forepaw stimulation were evaluated. ADC, CBF images and fMRI maps were analyzed for the forepaw cortices in the right hemisphere (RH) and control left hemisphere (LH).

Results: Remarkably, 15-min occlusion under isoflurane did not cause significant ADC lesions at 3hrs and only a few animals (50%) developed T2 or TCC lesions at >24 hrs. Basal CBF and T1-weighted signals were similar between the RH and LH forepaw cortices. BOLD and CBF responses to CO2 and forepaw stimulation showed no statistical differences between the RH and LH (P > 0.05), despite small lesions in the caudoputamen and heterogeneous mild hyperperfusion were observed in some animals (n = 4). This is likely due to the neuroprotective effect of isoflurane. Conclusion: It is now possible to perform chronic fMRI to evaluate the "functional" status of the salvageable and non-salvageable tissues as defined by anatomical (diffusion and perfusion) imaging.

**Sonic Hedgehog Regulates Ischemia-Induced Neural Progenitor Proliferation in the Hippocampus**

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Background and Purpose: Ischemia induces an increase in proliferation of the neural progenitors. Sonic Hedgehog (S hedgehog) is required for the maintenance of this neural progenitor pool. We hypothesized that Sonic Hedgehog regulates the increase in proliferation of the neural progenitors after ischemia. Methods: Male SV129 mice underwent a 20-minute, middle cerebral artery occlusion (n = 41). Hippocampal gene expression was analyzed at time points 0, 0.5, 2.5, 7 and 10 days after ischemia. Expression of Shi, patched (Pch), smoothened (Smo), and the transcription factors GlI1 and Nmyc were measured by real-time PCR. Immunohistochemistry for Shi, Pch and Smo was performed on brain sections 7 days after ischemia. To analyze the effect of Shi pathway inhibition on neural progenitor proliferation, intraventricular catheters delivering cyclopamine or vehicle over a 7-day period were placed 3 days after ischemia (n = 8). Proliferating neural progenitors were labeled over a 12-hour period (Bromodeoxyuridine, 50 mg/kg every 4 hours) prior to sacrifice at 10 days after ischemia. Cells labeled in the subgranular layer were counted in 4 sections at 0.4 mm intervals. Results: Both Shi and GlI1 doubled basal gene expression at 0.5 days after ischemia (P < 0.008 and P < 0.02, respectively, with Shi and Smo unexpression levels). However, in stroke neurogenesis the Shi pathway demonstrated a robust increase in Smo protein expression 7 days after ischemia. Nmyc gene expression increased 80% over baseline 10 days after ischemia (P < 0.006). Delivery of cyclopamine resulted in a 30% decrease in ischemia-induced proliferation (P < 0.001). Conclusions: Ischemia induces early increases in the gene expression of Shi and GlI1 followed by a later increase in Nmyc. Smo increases protein expression despite no significant change in gene expression, suggesting a change in post-transcriptional regulation. Blocking the pathway at the level of Shi with cyclopamine prevents the induction of ischemia-induced proliferation.

**Statin Enhances Hypothermia-Induced Protection and Extends the Treatment Window After Focal Stroke**

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Background and Purpose: Previous reports have shown that both statin (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor) and mild hypothermia (MH) protects the brain from ischemic injury. Protective mechanisms are not yet clear, but in some cases, Statins enhance microcirculation via activation of endothelial NO synthase, MH influences on intracerebral signaling pathways (i.e. apoptosis inhibition) or microvascular integrity. Considering the concept of a "neurovascular unit", we hypothesize that combination of statins with MH increases the efficacy and extends the window of stroke treatment. Methods: Male Sprague-Dawley rats were subjected to focal cerebral ischemia for 2 hours by monofilament insertion. Animals were randomly divided into the following groups (n = 8 to 16 per group): 1) atorvastatin alone (1 or 10 mg/kg, daily for 10 days [pre-treatment] or 20 mg/kg, 3 hours after ischemia [post-treatment]), 2) MH alone (33 °C for 2 hours at onset of ischemia or 3 or 6 hours after), 3) combination of atorvastatin and MH, 4) atorvastatin alone (1 or 10 mg/kg) intra-ischemic treatment combined with MH 3 hours after ischemia was also more effective than the single treatments (p < 0.01). Conclusions: We found that low dose atorvastatin pre-treatment or high dose post-treatment strongly enhances MH induced neuroprotection and extends the treatment window after stroke. Because both the treatments are already known to be clinically feasible and safe, this strategy based on the concept of neurovascular unit would be more efficacious against acute stroke.
Antifibrinolytic Treatment Aids in Cell Survival and Neurogenesis Following Stroke

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Introduction: New cells from the subventricular zone (SVZ) may help repair the brain after injury, but their long-term survival may be inhibited by fibrinolysis. We investigated if treatment with the non-steroidal anti-inflammatory drug indomethacin (INDO) improved cell survival following focal cerebral ischemia. Methods: Ischemia was induced by middle cerebral arterial occlusion (MCAO) in adult male mice. INDO-treated animals received injections for 6 days and were sacrificed on day 7, 14, or 28. Brains were immunostained for BrDU and lineage-specific markers and examined under a confocal microscope. Results: We sampled 100 cells that were labeled with BrDU and a lineage-specific marker (CX4, N22, GAP43, NeuN, or Nestin) in high-GFAP regions (ischemic-perinatal) in the cortex and striatum (n=12). All lineages increased by 3.7 fold in the cortex and 2.8 fold in the striatum in INDO-treated animals by 14 days and remained increased at 28 days post-ischemia (3.5 fold in cortex and 1.8 fold in striatum) vs. controls. Co-labeling in the cortex was greatest with nestin (5.2 fold) and of NeuN (2.6 fold). Few BrDU+/NeuN+/BrdU- cells were seen even 26 days after stroke. INDO increased the density of all lineages observed at each time point. Conclusions: Ischemia initially depletes dividing cells within the SVZ concurrent with the early appearance of BrDU+ cells in the neighboring parenchyma, perhaps as BrDU+ cells migrate from the SVZ. A rebound of proliferation was accompanied by an increase in the number of BrDU+ cells in the neighboring stroke cortex. INDO increased the density of BrDU+ cells of all lineages, suggesting enhanced production or survival of newborn glia and neurons. Whether this reflects the ant-inflammatory effects of INDO or other mechanisms is under investigation.

Tissue Plasminogen Activator–Mediated Blood-Brain Barrier Damage Is Dependent on Interactions Between the Thrombolytic Agent and Blood Clots in Transient Focal Cerebral Ischemia

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Background and Purpose: The molecular mechanisms leading to the increased risk of intracerebral hemorrhage during thrombolytic treatment are currently under intense investigation. The purpose of this experimental study was to determine the potential role of interactions between recombimant tissue plasminogen activator (rPA) and thrombotic material in causing blood-brain barrier (BBB) dysfunction in the ischemic margin during hemorrhagic transformation. Methods: Focal cerebral ischemia was induced in Wistar rats (n=18) using the suture occlusion model. In all three experimental groups (A-C), suture occlusion lasting two hours was followed by 22 hours of reperfusion. At the onset of reperfusion, animals received either standard rPA 10mg/kg (A), “activated” rPA 10mg/kg (rPA-a, B) or normal saline (C) intraarterially over 30 min. The solution labelled rPA-a contained of rPA that had been in contact with 12 autologous clots (prepared using a PE-50 catheter; clot length: 1.5mm) for 20 minutes before intraarterial application. BBB damage at 24 hours following onset of ischemia was determined using Evans blue staining and MMP-9 immunohistochemistry. Semiquantitative assessment of BBB damage (grading: 0–3) was performed for basal ganglia (bg), central cortex (cc) and peripheral cortex (pc) separately. Results: Evans-blue extravasation in the basal ganglia was much more prominent in group B than in group A (p<0.03) and C (p<0.05). Moreover, we observed a significant increase in MMP-9 staining in both the ipsilateral basal ganglia and the central cortex in animals treated with rPA-a compared to both group A (bg: p<0.001/cc: p<0.02) and C (bg: p<0.01/cc: p<0.05), respectively. Conclusions: Our results indicate that interactions between rPA and thrombotic material lead to the formation of thrombolytic products (such as plasmin or other proteases) that damage the BBB. This process appears to be of greater relevance for BBB damage than direct effects of rPA itself.

Hsp70 Inhibits Activation of Nuclear Factor-κB by Preventing Phosphorylation of Its Inhibitor Protein, IκB

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Introduction: We and others previously showed that heat shock protein 70 (HSP70) reduces ischemic cell death. Although HSP70 is thought to protect by preventing protein aggregation, recent work suggests that it may also modulate immune responses through modulation of the inflammatory transcription factor, nuclear factor kappa B (NFκB). We subjected astrocytes and microglial cultures derived from HSP70 transgenic (HSP70-Tg) mice to aglycemia (GD), serum deprivation (SD), and oxidative stress (HPE). HSP70-Tg astrocytes showed less death compared to wildtype (WT) astrocytes following SD (42%, P<0.001), GD (72%, P<0.005), and HPE (29%, P<0.05). Addition of microglia increased injury by more than 2-fold compared to astrocytes cultured alone (P<0.05). Astrocyte and microglia HSP70-Tg cocultures exhibited significantly less cell death compared to WT cocultures by 67% (GD, P<0.001), 84% (SD, P<0.05) and 54% (HPE, P<0.05). To determine the relative contributions of astrocytes and microglia to this protection, we compared mixed cocultures from HSP70-Tg and WT cells. HSP70-Tg astrocytes protected against cell death due to WT microglia (P<0.05). Interestingly, HSP70-Tg microglia also reduced WT astrocyte injury compared to WT microglia, but only against severe HPE (67%, P<0.001), suggesting that HSP70 overexpression in microglia may protect by preventing activation. Since the inducible form of nitric oxide synthase (iNOS) is regulated by NFκB, and is produced by activated microglia, we estimated NO levels in culture media using the Griess reagent. Interestingly, NO levels were below the limits of detection in all experimental conditions after 24 h of injury onset, suggesting that, unlike prior observations where microglia were activated by endotoxin, the mechanism of protection is unlikely to be mediated through inhibition of the iNOS signaling pathway. These findings suggest a novel anti-inflammatory role for heat shock proteins.

Perfusion and Diffusion Imaging in Acute Focal Cerebral Ischemia: Temporal versus Spatial Resolution

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High-resolution diffusion and perfusion-weighted imaging may provide substantial benefits in accurate delineation of normal, ischemic, and at-risk tissue. We compared the capability of low (400x400 μm²) and high (200x200 μm²) spatial resolution imaging in characterizing the spatio-temporal evolution of the ischemic lesion in permanent focal ischemia in mice. Permanent middle cerebral artery occlusion (MCAO) was induced in 14 rats. Serial measurements of cerebral-blood-flow (CBF) and ADC were performed starting 20 min after MCAO up to 210 min. The acquisition time for a complete ADCand CBF data set was 30 min for high-resolution and 7.5 min for low resolution. Lesion volumes were calculated by using previously established viability thresholds or by visual inspection, and correlated with infarct volume defined by TTC staining at 24 hrs after MCAO. At the very early phase of ischemia, anti-inflammatory properties appear to be regulated at the transcriptional level with HSP70 interfering with IκB phosphorylation.
Recovery of Cognitive Function With Gene Therapy Using Hepatocyte Growth Factor Gene After Ischemic Stroke

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Abstract

Background & purpose: Since there is no therapy to improve the memorial function, in this study, we examined the feasibility of gene therapy to recover the cognitive function using hepatocyte growth factor (HGF) gene in permanent middle cerebral ischemia (MCI) model. HGF-over-expressing adenovirus (5x10⁷ pfu) was injected into the hippocampus of rats that were exposed to permanent middle cerebral artery occlusion (DAY 1). Based on the sensori-motor deficits and body weight determined at DAY 7, the rats were divided equally into control vector (n=23) or HGF (n=23)-treated rats. At DAY 56, the cognitive function was studied in both control rats (n=22) in control vector, n=22 in HGF-treated rats. At DAY 56, neurobehavioral profile were performed.

Results: Rats transfected with HGF gene showed a significant decrease in the latency in Morris water maze tests (50 ± 4s; control vector, 33 ± 5s; HGF-treated rats, 5.0, P<0.05). The latency in the retention trial of passive avoidance task was significantly longer in HGF-treated rats (182.4 ± 57.5s; control vector, 214.8 ± 26.5s; HGF, P<0.05), yet no significant difference was observed in the acquisition test. Although the total volume of cerebral infarction was not related to the outcome (303.3 ± 13 µm³; control vector, 288 ± 13 µm³; HGF), immunohistochemical analysis in the peri-infarct region revealed that HGF activated astrocytes (9.1 ± 0.9%; control vector, 13.9 ± 0.9%; HGF, P<0.01) and increased the immunoreactivity against CD44 (2.3 ± 0.8% cells /3.8x10⁴ µm²; control vector, 9.7 ± 1.5% cells /3.8x10⁴ µm²; HGF, P<0.01) at DAY 14 and decreased glossis (12.9 ± 2.8%; control vector, 7.8 ± 1.0%; HGF, P<0.05). Importantly, the increase in the number of the arteries was also detected in HGF group (1023.1 ± 115.9 µm³ 1.3x10⁷ µm²; control, 1901.2 ± 181.3 µm³ 1.3x10⁷ µm²; HGF, P<0.05) at DAY 56. Conclusion: These data demonstrated that over-expression of HGF after cerebral infarction resulted in the functional recovery through neurogenesis, angiogenesis, and the prevention of glialosis in the peri-infarct region. Our results provide the feasibility of HGF gene therapy in the subacute stage for the functional recovery after ischemic stroke.

Local Brain Hypothermia Markedly Reduces Vasogenic Edema Development in a Porcine Intracerebral Hemorrhage Model

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Introduction: Hypothermia’s ability to improve stroke patient outcome is currently being tested. However, whole body hypothermia by systemic or endovascular cooling requires prolonged times to achieve target temperatures, difficult sedation protocols and adverse events including shivering and pneumonia. Local brain cooling, as an alternative new approach, may provide brain protection without these unwanted systemic effects. We examined the brain cooling profiles of an epidural cooling device (ChillerPad™, SeaCoast Technologies, Inc.) in a mapping study with implanted thermocouple probes. Additionally, we tested the hypothesis that local hypothermia could reduce cerebral vasogenic edema development in a pig intracerebral hemorrhage (ICH) model. Methods: In 6 anesthetized pigs (20-30kg), an epidural cooling pad (2 cm diameter) was placed into an open craniotomy and thermocouple probes (25 cm long; sensors every 5 cm) were placed bilaterally. In a second pig study, autologous arterial blood (3 ml) was infused into the frontal hemispheric white matter and Evans blue infused i.v at 0.5 hrs. At 1.5 hrs, the pad was removed and 12 hrs of profound cooling initiated (14°C brain surface temperature; N=3). Brains were frozen in situ at 16 hrs post-ICH, 0.5 hrs after spontaneous rewarmin. Normothermic ICH animals served as controls (N=3). Hematoma and perihematoma edema volumes were measured morphometrically on coronal sections and neurophysiologic analyses were conducted. Results: The target brain surface temperature (14°C) was achieved with <10 min of hypothermia. Cooling profiles from 0 to 25 mm directly beneath the pad demonstrated temperatures of ≤32°C. Laterally (1-1.5 cm off-center), significant cooling was achieved at depths from up to 15 mm. In ICH, profound local hypothermia significantly (p<0.027) reduced vasogenic edema volumes by 50% (2.0 ± 0.3 vs 1.0 ± 0.1 cm³). Hematoma volumes were similar in both groups (1.6 ± 0.3 vs 1.7 ± 0.2 cc). Cortical neurons were not damaged. Conclusion: Our findings demonstrate the remarkable effectiveness of profound local hypothermia to protect the blood-brain barrier after ICH. Local brain hypothermia may be an excellent approach to treat stroke patients since it can be rapidly induced and it does not cause adverse side-effects.
Estradiol Modulates Angiopoietin-1 and Capillary Density in a Rodent Stroke Model

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Background and Purpose: Animal studies show that 17β-estradiol (E2) is neuroprotective in stroke. Recent human trials revealed increased stroke risk with hormone replacement. To harness the positive consequences and attenuate untoward effects of E2 treatment, the mechanisms of E2-mediated protection in animals need to be elucidated further. We hypothesized that E2 stabilizes or generates new cerebral capillaries, which allows improved perfusion during cerebral arterial occlusion (MCAO), and results in less neuronal damage. We therefore, measured molecular markers in the angiopoietin and VEGF families and determined capillary density in brains of placebo and E2-treated rodents subjected to unilateral middle cerebral artery occlusion. We also assessed E2’s neuroprotective effects in the presence of the estrogen receptor-α (ERα) activation. Methods: Ovariectomized female rats and ERα knockout (ERKO) mice underwent implantation of ZMTG-E2 or vehicle implants, followed one week later by 2h MCAO and 22h reperfusion. RNA protection assays (RPA) were used to quantify brain angiopoietin-1 (Ang-1) and VEGF mRNA relative expression. Capillary density was measured with anti-CD31 antibodies and counted. Results: E2 treatment resulted in higher brain Ang-1 mRNA levels [Placebo: 21.9±0.30 (mean±SEM) vs. E2: 32.7±0.25; p=0.03] and cortical capillary density (Placebo: 369.9±9 vs. E2: 392.7±5; p=0.047) prior to MCAO. E2-mediated Ang-1 induction was absent in ERKO mice and was present in WT littermates. VEGF was induced by E2 only in mice, in an ERα-dependent manner. Ischemia did not produce any further regulation of Ang-1 and VEGF. Conclusions: Our finding that Ang-1 is upregulated in an ERα-dependent fashion with E2 treatment complements the observations that angiogenesis and stroke protection are absent in ERKO mice. Together with the finding of increased capillary density in E2-treated animals, these data suggest that Ang-1, and possibly VEGF, may be the links between E2-mediated neuroprotection and pre-ischemic stabilization or augmentation of the cerebral microvasculature.
Vascular Pathophysiology/Thrombosis

The Pattern of Cognitive Performance in Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy (CADASIL)

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Background and Purpose: Subcortical ischemic vascular lesions which are intimately related to small vessel disease (SVD) are a major cause of dementia. CADASIL is a monogenic form of SVD due to mutations in the NOTCH3 gene. In the course of the disease, patients almost invariably develop cognitive deficits eventually leading to vascular dementia. Methods: To analyze the characteristics of cognitive impairment in CADASIL, we conducted a prospective study in 65 mutation carriers (mean age 47.3±10.5 years) and 30 controls, matched with respect to educational level and age (47.2±14.14 years). All subjects underwent a series of neuropsychological tests, including global cognitive scores ( Mattis Dementia Rating Scale (MDRS), Mini-Mental State Exam), the VADASQ battery as well as specific tests on executive function and attention with measures of processing speed and error monitoring.

Results: We found that CADASIL patients had pronounced deficits in attention and executive function with particular impairments of timed measures ( Stroop II and III, Trail Making) and the number of correct responses (symbol digit and digit cancellation tasks) (all p<0.002). Measures of error monitoring (Stroop III, Trail Making, Symbol digit, Maze) were also affected but to a lesser extent (all p<0.05). Prominent deficits were further present on verbal fluency tasks. Recall, fluency and receptive language skills were largely unaffected. Subgroup analysis revealed a similar profile in subjects aged below 45 years. Subgroup analysis further revealed a similar profile in individuals with early impairment of global cognitive performance (MDSR score<123) and in those with marked cognitive deficits (MDSR score<110). Our findings were processed as the most significant area of cognitive impairment in CADASIL, with less pronounced yet significant deficits of other aspects of executive and performance and attention. This profile of cognitive impairment enables the construction of targeted test batteries for clinical trials. We hypothesize that the profile of dysfunction in CADASIL described here represents the core of the cognitive syndrome associated with SVD and subcortical ischemic vascular lesions.

Increased Apoptosis-Related Gene Expression in Symptomatic Carotid Artery Disease

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Background: Apoptosis in atherosclerotic carotid artery stenosis may promote plaque instability, rupture and symptom generation (ischemic stroke). In the current study we compared the expression profiles of high-grade symptomatic versus asymptomatic carotid plaques (CP) with DNA microarrays to determine whether genes involved in apoptotic events are differentially expressed. Methods: The Helsinki Carotid Endarterectomy Study included 69 symptomatic patients and 52 asymptomatic controls with carotid stenosis ≥70%. Symptomatic carotid artery disease was defined as either severe (>70%) carotid artery stenosis or asymptomatic carotid artery stenosis. CPs from a sub cohort of completely asymptomatic patients with normal brain CT/MRI (n=9) and patients with confirmed ipsilateral ischemic stroke (n=13) were analyzed using Affymetrix HG U313A microarray. Genes associated to apoptosis according to Gene Ontology Consortium’s database and reliably detected in the CPs (n=304) were evaluated by non-parametric statistics with multiple testing correction. Results: Statistically significant (p<0.05) differential gene expression was observed in 22 genes involved in both the death receptor pathway as well as mitochondrial pathway of apoptosis when symptomatic and asymptomatic groups were compared. Increased gene expression was observed in 19 genes including TNF-related apoptosis-inducing ligand (TRAIL), caspase 6, IL18, bax, bcl-xL, containing protein 2 (BIRC2), BCL2/adenovirus E1B interacting protein 3-like (BNIP3L) and AKT1. Increased expression of pro-apoptotic genes (TNF, FAS, FAS-like) was observed in 13 CPs. We used a 7-gene classifier, which was able to distinguish symptomatic CPs from asymptomatic CPs with an accuracy of 88%. Conclusions: Several simultaneous changes in mainly proapoptotic and regulatory genes suggest that a global and well-coordinated cell response to an apoptotic stimulus was in place in the symptomatic CPs. We propose that apoptosis within a CP may be detrimental to plaque integrity and associate with symptom generation.
Conclusions: protein (lnCreact, highly skewed to the right, and therefore normalized by a natural log distributed), a marker of hypercoagulability, whereas ulcer and TCD- subjects. However, TCD ultrasound plaque imaging that may identify high-risk patients with vulnerable plaques, including who have a 15-fold higher risk of stroke in the first year. We are now studying features of , the presence of microemboli on transcranial Doppler (TCD Sig Ulcer-). Morphological plaque characteristics such as endothelial disruption, intraluminal thrombus, intraplaque hemorrhage, alone or in combination with excavation/ ulceration are associated with symptomatic status in carotid disease. These features, ideally diagnosed in vivo by imaging studies, may lead to identification of the high risk carotid plaque. Association between plaque morphological features (or combination thereof) and symptomatic status

### Table: OR, CI, p value, Intercorrelation reliability coefficient (kappa)

<table>
<thead>
<tr>
<th>Feature</th>
<th>OR (95% CI)</th>
<th>p value</th>
<th>Kappa</th>
<th>p value</th>
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<tr>
<td>ED</td>
<td>3.72 (1.6 - 8.7)</td>
<td>0.001</td>
<td>0.88</td>
<td>0.99</td>
</tr>
<tr>
<td>EU</td>
<td>1.95 (0.86 - 4.32)</td>
<td>0.39</td>
<td>0.68</td>
<td>0.51</td>
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<tr>
<td>IH</td>
<td>2.88 (1.3 - 6.4)</td>
<td>0.001</td>
<td>0.56</td>
<td>0.91</td>
</tr>
<tr>
<td>IT</td>
<td>3.82 (1.35 - 10.18)</td>
<td>0.001</td>
<td>0.55</td>
<td>0.0001</td>
</tr>
<tr>
<td>ED + EU</td>
<td>2.54 (1.1 - 5.87)</td>
<td>0.02</td>
<td>0.61</td>
<td>0.88</td>
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<tr>
<td>ED + IT</td>
<td>7.03 (1.52 - 32.48)</td>
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<tr>
<td>ED + IH</td>
<td>4.06 (1.77 - 9.29)</td>
<td>0.001</td>
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<td>EU + IH</td>
<td>2.5 (1.07 - 5.97)</td>
<td>0.034</td>
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<tr>
<td>IH + IT</td>
<td>3.45 (91 - 13.03)</td>
<td>0.068</td>
<td>0.68</td>
<td>0.0001</td>
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### Table: TCD+ vs TCD- Summary

<table>
<thead>
<tr>
<th>Homocysteine and C-reactive protein</th>
<th>TCD+</th>
<th>TCD-</th>
<th>p value</th>
<th>Sig</th>
<th>Uter-</th>
<th>Uter-</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>tHcy</td>
<td>16.07 ± 6.59</td>
<td>9.58 ± 2.73</td>
<td>&lt; 0.0001</td>
<td>11.52 ± 2.47</td>
<td>11.46 ± 6.64</td>
<td>0.97</td>
<td></td>
</tr>
<tr>
<td>lnCreact</td>
<td>1.33 ± 0.61</td>
<td>1.01 ± 0.88</td>
<td>0.36</td>
<td>1.42 ± 1.34</td>
<td>0.77</td>
<td>0.01</td>
<td>0.0029</td>
</tr>
</tbody>
</table>

Histology of Thrombi Retained From Acute Ischemic Stroke Patients by Endovascular Embolectomy

Victor Marder, Dennis Chute, Sidney Starkman, Anna Abolian, Chelsea Kidwell, Bruce Oviabiega, Fernando Vinuela, Gary Duckwiler, Reza Jahan, Venkatakrishna Rajaije, Scott Selco, Jeffrey L Saver, Univ of California at Los Angeles, Los Angeles, CA

Background: New endovascular mechanical clot retrieval therapies permit removal of stroke-causing thrombi from the cerebral circulation and body, making them available for histologic analysis. We report the first histologic study of a large series of thrombi from acute human stroke patients. **Methods:** Thrombi removed from consecutive patients treated with the Concentric MERCI Clot Retriever were formalin or gluteraldehyde fixed and H&E and toluidine stained. **Results:** Thrombi were retrieved from 24 of 48 treated patients. In these 24, etiologies were cardioembolic (12), large vessel athero (4), tandem cardioembolic/large vessel athero (2), and other (6). Occlusion sites were ICA (11), MCA (12), and basilar (1). Perfusion results were: TICI 3 in 17%, TICI 2 in 71%, TICI 1 in 13%. Single thrombi fragments were retrieved from 8 patients; multiple from 16. Dimensions of the largest fragments ranged from 1 x 1 mm to 3 x 3 mm. Results indicate clot fragment size, with median x = 3 x 3 mm. Retrievable clot could be histologically classified into 4 broad types. The predominant pattern (17/23 - 74%) was a mixed histology with clearly demarcated areas of fibrin and/or platelets, erythrocyte accumulations, and variable numbers of necrotic cells often arranged linearly on the surface, suggesting stepwise accumulation of thrombus over days at a donor site. Among these 17 thrombi, 9 had a serpentine pattern compatible with folding of an embolus after lodging in the occluded vessel. A minority (3/23, 13%) were predominantly fibrin and platelets with a paucity of erythrocytes. An additional 3 (13%) were predominantly erythrocytes, from a fresh embolized thrombus and 2 compatible with removal of only post-obstruction, in situ, stasis thrombus. A single occlusion was a mycotic (candida) embolus. No cholesterol clefts, calcium, or atherosclerotic debris and no endothelial cells were noted. Histologic patterns of thrombus did not strongly correlate with angiographic or clinical response to clot retrieval. **Conclusions:** The majority of stroke-causing thrombi in retrieved-patients are mature (days old), mixed “white-red” thromb, both in patients with atrial fibrillation and in patients with large artery atherosclerotic sources of embolism.

A Novel Quantitative Method for Determining Previously Undetected Magnetic Resonance Perfusion Changes in Patients With Cognitive Deficits Following Carotid Endarterectomy

Xin Liu, Celina Imaielniwa, Joel Rosiene, Anita Rampersad, Joseph Zurica, David A Wilson, Hadi J Halazun, Susan C Williams, E S Connolly, Jr, Eric J Heyer, Columbia Univ Med Ctr, New York, NY

Introduction: Carotid endarterectomy (CEA) reduces the risk of stroke in patients with significant carotid artery stenosis. However, 25% of patients experience cognitive deficits after CEA compared to a control group. We hypothesized that abnormalities in cerebral blood flow (CBF) not detectable by routine MR-perfusion (MRP) scans are responsible for these cognitive deficits. We developed a novel algorithm for analyzing MRP scans to identify and quantify the amount of CBF asymmetry in each hemisphere. **Methods:** Patients undergoing CEA (n = 53) and spine surgery (controls) (n = 5) were examined preoperatively, and one day postoperatively with a battery of neuropsychometric (NPM) tests. Patients were considered “injured” if their performance on this battery of NPM tests was worse than the mean performance of the control patients by ≤2.5 SD. Patients received MRP scans one day postoperatively. A novel algorithm quantified the degree of relative difference between three corresponding regions in the ipsilateral and contralateral hemispheres by taking the difference in perfusion between these two sides, called a Relative Difference Map (RDM). **Results:** We showed significant differences with MRP scans between the two hemispheres only in patients who have significant cognitive deficits. The method automatically identifies vascular territories; derives the axis of reflexial symmetry; computes the RDM; and generates histograms in each vascular territory. **Conclusions:** Conventional assessment of the MRP scans demonstrated no significant postoperative changes. However, using a novel algorithm, asymmetrical changes in MRP were detected in patients who had evidence of neurocognitive deficits. Our methodology provides a better analysis of MRP parameters in patients with significant cognitive deficits.

Hemostatic and Inflammatory Disturbances Are Present in Patients With Ischemic Stroke

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BACKGROUND: Both hemostatic and inflammatory disturbances have been described in patients with ischemic stroke. PURPOSE: We assessed the hypothesis that increased hemostasis and depression of fibrinolysis and their cross-talk with inflammation are present in patients with ischemic stroke. **PATIENTS AND METHODS:** We investigated Thrombin Activable Fibrinolysis Inhibitor (TAFI) and its proteolytically cleaved products (TAFI-Ag, TAFI-Ag) as well as soluble Tissue Factor (TF) and Prothrombinfragment 1 + 2 (F1 + 2), at admission, and 1, 3 and 60 days after the acute event, in 26 patients with ischemic stroke. Sampling was also performed in 13 healthy controls. Symptoms were registered according to the NIH-scale and the stroke subtypes were classified according. **RESULTS:** TAFI Ag antigen in plasma was elevated during the acute phase of stroke and tended to decrease over time. Thrombin generation (i.e. F1 + 2 levels) was elevated on admission and decreased on day 1–60. TF remained elevated throughout the study. TAFI antigen correlated positively with htCRP (p = 0.03 and 0.04 respectively), and F1 + 2 correlated positively with hWt2 (p = 0.04) and tended to correlate with CRP (p = 0.08). INTERPRETATION: Ischemic stroke is
associated with increased coagulation and impaired fibrinolysis, and there are also associations between hemostatic abnormalities and inflammation. Increased TAFI may contribute to impaired fibrinolysis during acute ischemic stroke thus enhancing thrombosis and stroke progression.

TAIF (%) | TF (pg) | F1 + 2 (μg/mL) | vWF (μg/mL) | CRP (mg/L)
---|---|---|---|---
Controls | 98 ± 10.4 | 130.1 ± 93.9 | 236.6 ± 82.3 | 1.45 ± 15.1 | 2.05 ± 0.61 | 5.2 ± 0.72
Stroke (Hemorrhage) | 137.5 ± 11.1 | 238.7 ± 88.2 | 0.82 ± 0.20 | 2.97 ± 0.53 | 7.8 ± 1.4 (3.4–8.4)
Stroke (day 3) | 127.4 ± 12.3 | 238.5 ± 66 | 0.98 ± 0.24 | 2.17 ± 0.67 | 6.2 (3.2–20.4)
Stroke (day 60) | 133.7 ± 12.5 | 215.7 ± 76 | 1.01 ± 0.39 | 2.17 ± 0.67 | 2.3 (3–7.5)

**Is There Any Relationship Between the Extent of Platelet P-Selectin Expression and Clinical Severity of Acute Ischemic Stroke?**

Jae-Kwan Cha, Jai-Woo Kim, Dong-A Univ Hosp, Busan, Republic of Korea

**Background and Purpose:** Platelet activation is an important pathophysiology in acute ischemic stroke. However, it was not attempted to study the relationship between the extent of platelet activation and clinical severity in ischemic stroke. In this study, we investigated the impact of the extent of platelet activation in acute ischemic stroke on clinical severity and prognosis.

**Methods:** We measured the platelet aggregability for adenosine diphosphate (ADP) or collagen and surface expression of P-selectin on activated platelet in 93 (mean age 61.6 ± 11.6; men - 51) patients with acute ischemic stroke (<24 hrs), and 55 normal subjects. National Institutes of Health Stroke Scale (NIHSS) score was evaluated at admission day. Also, we scored the Barthel index (BI) after 90 days of ischemic events. We used Spearman correlation coefficient to know the relationship between the extent platelet activation and the clinical outcome of ischemic stroke.

**Results:** The extent of platelet aggregability for ADP (9.9 ± 7.8 um) or collagen (19.5 ± 8.5 um) and P-selectin expression (104 ± 24.8% of IR) were significantly higher in patients with ischemic stroke than in normal subjects (6.2 ± 5.8, 4.5 ± 6.2, 25.0 ± 9.4% of IR). The mean NIHSS was 19.9 ± 7.0 in patients with acute ischemic stroke. The extent of platelet aggregability for ADP (r = 0.015, p = 0.887) or collagen (r = 0.018, p = 0.865) did not correlate with the clinical severity at initial stroke onset. However, the platelet P-selectin expression (r = 0.359, p = 0.004) was significantly related with NIHSS. At 90 days after ischemic stroke, only the extent of platelet P-selectin expression significantly correlated with the Barthel index (r = 0.412, p = 0.007) at 90 days after ischemic events. **Conclusions:** In our result, the extent of platelet P-selectin expression in acute ischemic stroke was significantly correlated with initial NIHSS and Barthel index at 90 days. We suggest that the increment of platelet P-selectin expression in acute stage of ischemic stroke could be candidate for a useful indicator about the severe damage and unfavorable outcome.

**Characterization of avb3 Integrin in Vascular Malformations**

Michael Lim, Griffith Harsh, IV, Terri Haddix, Hannes Vogel, Pauline Chu, Gary Steinberg, Samira Guccione, Stanford Univ, Stanford, CA

Introduction: Alpha V Beta 3 (avb3) is an integrin that has been shown to be specifically expressed on endothelial cells of CNS neoplasms. However, no data exists on the expression of the avb3 integrin in CNS vascular malformations. Here we investigate the expression of avb3 in arteriovenous malformations (AVMs) and cavernous malformations. Method: Frozen samples of AVMs from 12 patients and cavernous malformations from 5 patients were obtained intraoperatively. Once final pathology was confirmed, immunohistochemistry was performed using an avb3 monoclonal antibody. The avb3 expression pattern was graded as the percentage of positively staining vessels. Results: 10 out of 12 AVMs stained positively for the avb3 antibody Discussion: avb3 may contribute to the vascular formation of AVMs. avb3 may also be implicated in the formation of cavernous malformations.

**The Integrity of Dynamic Cerebral Autoregulation in Patients With Small-Vessel Disease**

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**Background:** Minor changes of perfusion in the deep white matter watershed regions may lead to intellectual impairment in the presence of small vessel disease. Adequate perfusion is dependent upon the interactions between blood pressure (BP) and cerebral autoregulation, which may also be impaired in these patients. The purpose of this study was to investigate the relationships between BP, cerebral autoregulation and cognitive function in patients with small vessel disease.

**Methods:** 64 patients (40 male, mean age 65 years) were recruited to the study. 24-hour ambulatory BP monitoring was undertaken for day and night mean BP levels and variability. Cerebrovascular disease load was quantified by T2 and FLAIR MRI brain imaging using the Age-Related White Matter Changes (ARWMC) rating scale. Executive brain function and attentional capacity was measured using validated neuropsychological tests. CO2 reactivity, cerebrovascular resistance (pulsatility index) and dynamic cerebral autoregulatory index (RAI) were measured using transcranial Doppler ultrasound techniques. Fluctuations in BP and cerebral autoregulation were correlated with neuropsychological performance and MRI lesion load. **Results:** Subjects had a mean 24-hour BP of 131/73 (SD 21/12), median ARWMC score on MRI of 10.5 (IQR 9.0) (normal range 0–30), mean pulsatility index of 1.1 (SD 0.4), mean CO2 reactivity of 44% (SD 12%) and mean RAI of 5.7 (SD 1.5) (range 0–9). Arterial pulse pressure correlated positively with cerebrovascular resistance (p = 0.01) and white matter lesion load (p = 0.03) and inversely with performance on attentional capacity and executive function tasks (p < 0.05). Nocturnal dipping correlated with higher diastolic–C02 reactivity (p = 0.05) in long standing hypertensives. RAI increased with increasing systolic BP (p < 0.04) and nocturnal dipping (p < 0.02) and was higher in patients with high white matter lesion load (p < 0.03). **Conclusions:** Dynamic cerebral autoregulation appears to be upregulated in patients with long standing vessel disease, and this is associated with reduced changes in BP. Despite this adaptation, physiological fluctuations of BP in long-standing hypertensive patients may increase subcortical ischaemic damage and cerebral dysfunction.

**MMP-9, TIMP-1, and ACC Reduction on MRI: A Comparison of Serum and Radiographic Markers in Acute Ischemic Stroke**


**Background and Purpose:** In a previous study we found that rising counts of circulating CD24+ CD28- T cell lymphocytes were associated with an increasing risk of stroke recurrence and death, in addition to prior stroke. We explored the timing of CD24+ CD28- levels in the peripheral blood, to test the hypothesis that acute ischemic stroke induces expansion of these cells. **Methods:** Thirty-six patients (age: mean ± SD: 70.14 ± 15.31 years, 22 males, 14 females) admitted with acute ischemic stroke to the NIH Stroke Program at Suburban Hospital (Bethesda, MD) were studied. Serial blood samples were taken at 0–4 days (A), 5 days–1 month (B), and 3–4 months (C) post stroke; three patients who died before the time point did not have C samples. Peripheral blood mononuclear cells were separated from whole blood and stained with FITC-conjugated anti-CD4 (RPA-T4), and PE-conjugated anti-CD28 (CD28.2) monoclonal antibodies (Becton Dickinson) for multi-color analysis with fluorescence-associated cell sorting (FACS). **Results:** CD3+ CD4+ CD28- cell counts rose by >50% between time points A and C in 17 of 33 (52%) patients, stayed the same in 12 (36%) patients, and fell by >50% in 4 (12%) patients. Repeated measures analysis of variance showed significant differences between CD3+ CD4+ CD28- cell counts at the A (mean ± SD: 6.85 ± 8.06, median 4.17, interquartile range 1.64–8.89), B (6.23 ± 6.41, median 3.52, interquartile range 1.37–9.21), and C (9.26 ± 8.69, median 4.86, interquartile range 2.05–14.62) time points (p < 0.05). **Conclusions:** Delayed expansion of CD3+ CD4+ CD28- cells after stroke may constitute a significant part of an immune response to brain antigen exposure following ischemia-induced breakdown of the blood brain barrier. Considering the known pro-inflammatory and cytocytic activities of this T cell phenotype, the data may suggest a pathological role of cytocytic expansion following acute stroke.

**Clopidegrol Resistance in Patients With Cerebrovascular Disease**

Mark J Alberts, Northwestern Univ Med Sch, Chicago, IL; Deborah Bergman, Northwestern Memorial Hosp, Chicago, IL; Karin Brooks, Richard Bernstein, Glenn Ramsey, Paul Lindholm, Northwestern Univ Med Sch, Chicago, IL

**Background:** Recent studies have found that aspirin resistance is a common problem in patients with vascular disease. Some patients taking ADP-receptor blockers such as clopidogrel may also have resistance to these agents. We conducted platelet function testing to determine how frequently resistance is seen. **Methods:** In-patients and out-patients with cerebrovascular disease (stroke, TIA, or arteriothrombotic disease of cerebral vessels) who were taking clopidogrel (with or without aspirin) were ascertained. Patients had to be taking
Dysphagia and Nutritional Status Following Acute Stroke

Michael A Crany, Gaselle D Carnaby (Mann), Univ of Florida Health Science Ctr, Gainesville, FL; Leslie Page, Shands Hosp Jacksonville, Jacksonville, FL; Scott Silliman, Univ of Florida Health Science Ctr, Jacksonville, FL

Swallowing difficulties are prevalent following acute stroke with estimates exceeding 50%. Nutritional deficits are less prevalent upon acute admission (16%-22%) but this problem appears to increase subsequent to stroke with estimated prevalence approaching 50% upon admission to rehabilitation. Anecdotally, an association appears to exist between dysphagia and nutritional status, but this potential link has not been critically studied before. The present cross sectional study was to examine potential associations between swallowing ability and nutritional status in acute stroke patients upon admission to a dedicated stroke unit. Relationships between these stroke sequelae and more traditional stroke severity measures were evaluated. Average age of patients was 69.8 years with 47% male gender. Forty three percent (43%) of patients were African-American and 70% suffered first ever stroke. Patients were assessed with a clinical swallowing evaluation, a functional oral intake scale, Mini Nutritional Assessment, BMI, percent Body Fat, NIHSS, modified Rankin Scale, and modified Barthel Scale. On clinical examination 40% of study patients demonstrated dysphagia and 21% were identified as at risk for malnutrition. Conversely, 44% of the cohort were obese upon admission. The majority of patients were eating by mouth, but 60% had some degree of limitation in this function. Clinical swallowing ability correlated with stroke severity and with functional oral intake but not with measures of nutritional status. Nutritional measures did not correlate with any of the swallowing or stroke severity measures. It is possible that the clinical nutrition measures chosen for this study may not be sensitive to rapid changes in nutritional status. Blood serum assessments of nutritional markers are being employed to address this question. Ultimately, a better understanding of potential associations between dysphagia and nutritional status following stroke will lead to enhanced management and improved long term outcomes.

Effects of Postural Feedback Training on Gait for Stroke Patients

Wen Liu, Seok H Kim, Rebecca Maleksey, Laura Zahner, Mukul Mukherjee, Univ of Kansas Med Ctr, Kansas City, KS

Background: Patients after a stroke have often experienced impaired balance control and gait performance. It has been shown that after a stroke, standing balance training aimed at reducing the asymmetry of weight distribution improves postural control and also reduces the risk of falls. However, whether the effect can be carried over to improvements in gait performance remains uncertain. Purpose: The purpose of this study was to examine whether a postural feedback training protocol could improve gait in chronic stroke patients. Method: Eight chronic stroke patients voluntarily participate in a 4-week postural feedback training program including both dynamic and static stability trainings. The training program, which was administered twice a week, was performed based with the degree of difficulty increasing as the subject’s stability improves. Dynamic standing stability boundary was examined using measurements from force platform. Gait performance was evaluated using the Vicon motion analysis system. The student-t test was conducted to analyze the differences in standing stability boundary, gait velocity, and gait cadences before and after training. Results: Eight of 14 patients had a postural feedback training subjects. Dynamic standing boundary significantly increased (p < 0.01) by about 32% anteriorly, 34% posteriorly, 20% towards the non-affected side, and 13% towards the affected side. The mean gait velocity and cadence increased significantly by about 6.5% (p < 0.05) and 7% (p < 0.01), respectively. Conclusion: The results of this study demonstrated that a postural feedback training improves significantly the standing balance after stroke. The results showed also that the improvement in the postural control could be carried over to the improvement in gait performance. This is further shown in the data that seven out of eight participants showed increase in both gait velocity and cadence. In conclusion, the increased balance control in standing may help stroke patients to gain more confidence for postural control, which may lead to the improvement in gait velocity and cadence.
Effect of Resistance Exercise Training on Resting Blood Pressure in Chronic Stroke Survivors

Emmanuel B John, Marcio Santos, Emmanuel B John, Marcio Santos, Jennifer Larson, Vicki Bouckhout, Stephen Jernigan, Karen C Johnston, Shoujun Zhao, Nancy K Hills, UCSF Med Ctr, San Francisco, CA; Gary Houser, The Stroke Group, Denver, CO

Background & Purpose: Exercise Training Programs are not typically used as non-pharmacological anti-hypertensive management tool in chronic stroke survivors (CSS). Recent results from our laboratory suggest that aerobic exercise training incorporating moderate resistance has beneficial effects on cardiovascular fitness in CSS. In the present study, we assessed the hypothesis that a Resistance Exercise Training (RET) program will have beneficial effect on some cardiovascular parameters in moderately impaired CSS. Subjects: Eleven (11) CSS, 6 males and 5 females, age range 51–91 year olds (mean 62 ±11.75) who suffered a CSS, 6 males and 5 females, age range 51–91 year olds (mean 62

RESULTS: A 7-week RET significantly reduced RSBP, RDBP and RMAP in a group of moderately impaired CSS. RET should be further examined as a possible non-pharmacological therapy in post-stroke hypertension management in CSS.

Conclusion: A 7-week RET significantly reduced RSBP, RDBP and RMAP in a group of moderately impaired CSS. RET should be further examined as a possible non-pharmacological therapy in post-stroke hypertension management in CSS.

Outcomes Research: Clinical Epidemiology and Prediction Studies

Judith J Stephenson, Timothy W Downey, Charles A Krelick, Denise Gobert, Kansas Univ Med Ctr, Kansas City, KS

Background: Several studies have evaluated predictors for use of tPA and other thrombolytics in patients with ischemic stroke. Older age and African-American race have been associated with lower rates of usage in some studies but not in others. Methods: From December 1999 through November 2003, 85 hospitals in the Los Angeles basin participated in a quality improvement initiative to diagnosis of stroke or TIA using the Ethos registry, a voluntary web-based national acute stroke registry. Participating hospitals collected data on patient demographics, characteristics of the event, timing, hospital course, discharge disposition, treatment, and contraindications. Among those with an admission diagnosis of ischemic stroke, age, sex, and race-ethnicity were evaluated as independent predictors of receipt of thrombolyis and arrival within 2.5 hours of symptom onset in multivariable logistic regression analysis. Results: Among 12,088 patients with an admitting diagnosis of ischemic stroke, mean ± SD age was 72.0 ± 13.6 and 6,635 (55%) were women. Overall, 81.0% were non-Hispanic whites, 14.4% were African-American, and 4.6% were of other race-ethnic groups. Thrombolysis was administered to 725 patients (6.0%). Rates of thrombolysis were greater in those who were younger (age < 50 vs. ≥80, 11.2% vs. 3.6%, p<0.0001), in men (7.0% vs. 5.2% in women, p<0.0001), and in non-Hispanic whites (6.2% vs. 4.2%, p<0.01). All these differences remained significant in multivariable models. Although age and sex were not associated independently with arrival within 2.5 hours of symptom onset (OR 0.77, 95% CI 0.68–0.87, p<0.0001), African Americans were less likely to arrive within 2.5 hours of symptom onset (OR 0.77, 95% CI 0.68–0.87, p<0.0001).

Conclusion: In a large registry of patients initially diagnosed with ischemic stroke, women, African Americans, and those of older age were less likely to receive thrombolysis. Delayed arrival time did not fully explain the differences in usage.

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Using Automated Clinical Data on Admission to Predict Mortality Among Patients Hospitalized for Ischemic Stroke

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Objective: Research models predicting mortality using clinical data have not been widely adopted due to the high cost of chart review. Our objective is to develop and validate a predictive model using automated laboratory data (LAB) and supplementing with Uniform Billing data for demographics, discharge status, and comorbidities. The significance of vital signs (VS) and Altered Mental Status (AMS), that were not automated, was also analyzed. Methods: A model was derived from 7665 (488 deaths) stroke admissions across 18 teaching and 26 non-teaching hospitals that exported LAB data to Atlast (MediQual) in 2000–01. Multiple cuts of LAB and VS were crafted per literature and empirical examination. Demographics, LAB, comorbidities (identified using 6th digit ICD-9 coding), VS, and AMS were entered into logistic regressions. ROC curve assessed model fit and Bootstrapping validated the model internally. Manually abstracted data (n = 36437, 2441 deaths) from 180 hospitals validated the model externally. Results are presented as odds ratios and 95% confidence intervals. Findings: Median age was 76. Crude mortality was 6.4%. Significant predictors (p <0.05) included age, albumin, g/dl (1.7, 1.2–2.7), glucose >135 mmol/l (0.001), INR >4.0 and RBC 37.0 (2.1, 1.7–4.5), WBC >14.1k/ml (2.1, 1.5–2.8), PT INR >1.1 or PT 13 sec (1.3, 1.2–2.3), creatinine >3.0 mg/dl (2.7, 1.7–4.3), metastatic cancer (2.9, 2.6–5.1), basal artery occlusion (5.4, 2.3–12.8), systolic BP <80 mm Hg (2.0, 1.2–3.1), respiration >10 or < 30 (2.0, 1.5–2.6), most severe AMS (11.3, 8.6–14.9), and severe AMS (5.5, 3.0–9.3). The ROCs for the derivative and validation models were .84 and .83 respectively. Conclusions: Admission LABs indicating hypoalbuminemia, hyperglycemia, acidosis/alkalosis, leukocytosis, prolonged prothrombin time, and renal dysfunction predict mortality. Metastatic cancer and type of stroke are also significant. VS & AMS are highly significant and should be automated. Pathophysiological variables commonly measured on admission can generate a clinically plausible and statistically valid model. Based mainly on automated data, this predictive model provides a cost effective tool for medical effectiveness monitoring and comparative outcome reporting.

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Predictors of Thrombolysis Usage Among 12,068 Patients With Initial Diagnosis of Ischemic Stroke

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Background: Several studies have evaluated predictors for use of tPA and other thrombolytics in patients with ischemic stroke. Older age and African-American race have been associated with lower rates of usage in some studies but not in others. Methods: From December 1999 through November 2003, 85 hospitals in the Los Angeles basin participated in a quality improvement initiative to diagnosis of stroke or TIA using the Ethos registry, a voluntary web-based national acute stroke registry. Participating hospitals collected data on patient demographics, characteristics of the event, timing, hospital course, discharge disposition, treatment, and contraindications. Among those with an admission diagnosis of ischemic stroke, age, sex, and race-ethnicity were evaluated as independent predictors of receipt of thrombolyis and arrival within 2.5 hours of symptom onset in multivariable logistic regression analysis. Results: Among 12,088 patients with an admitting diagnosis of ischemic stroke, mean ± SD age was 72.0 ± 13.6 and 6,635 (55%) were women. Overall, 81.0% were non-Hispanic whites, 14.4% were African-American, and 4.6% were of other race-ethnic groups. Thrombolysis was administered to 725 patients (6.0%). Rates of thrombolysis were greater in those who were younger (age < 50 vs. ≥80, 11.2% vs. 3.6%, p<0.0001), in men (7.0% vs. 5.2% in women, p<0.0001), and in non-Hispanic whites (6.2% vs. 4.2%, p<0.01). All these differences remained significant in multivariable models. Although age and sex were not associated independently with arrival within 2.5 hours of symptom onset (OR 0.77, 95% CI 0.68–0.87, p<0.0001), African Americans were less likely to arrive within 2.5 hours of symptom onset (OR 0.77, 95% CI 0.68–0.87, p<0.0001).

Conclusion: In a large registry of patients initially diagnosed with ischemic stroke, women, African Americans, and those of older age were less likely to receive thrombolysis. Delayed arrival time did not fully explain the differences in usage.

Ischemic Stroke Prediction Model Improved With Acute Physiology Variable

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Background: We previously developed and validated ischemic stroke models predicting devastating outcome (nursing home level disability or death) as measured by Barthel Index (BI), NIH Stroke Scale (NIHSS) and Glasgow Outcome Scale (GOS). The objective of the current study was to determine if there is additional prognostic information in routinely collected laboratory and vital sign data including BP, HR, Temperature, BUN, creatinine, Na+ K+ billirubin, HCT and WBC in the prediction of devastating outcome in acute ischemic stroke patients. Methods: All 483 subjects admitted to the NANTAS trial with complete predictors and results were assessed. Pre-specified independent variables included age, baseline NIHSS score, stroke subtype, previous stroke, previous diabetes, previous disability, and the newly added physiology variable: a single variable summarizing baseline vital signs and lab data. The latter used the recently weighted stroke system created in ANTHOCME 3 to combine 14 measures from 11 physiology measurements. Logistic regression was used to predict devastating outcome by BI at 3 months. Prediction of devastating outcome by GOS and NIHSS was also examined. Internal validation used bootstrap techniques with 1000 repetitions. Model performance with and without the physiology variable was compared using c-index and any improvement in the c-index with the latter operating characteristic curve (AUC) and calibration charts. Results: For the BI model, the

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Relationship Between 3-Month NIH Stroke Scale Score and Level of Dependence

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Background: The NIHSS score is a research tool that allows a standardized measure of stroke severity using a 0–42 point scale. Though it was not developed as a stroke outcome measure, it is commonly assessed and reported at the time of 3 month outcome assessment in clinical stroke trials. The relationship between NIHSS score and substantial dependence is unknown and has lead to inconsistencies in the value of NIHSS score used to reflect poor outcome in clinical research. Objectives: To assess the relationship between 3 month NIHSS score and substantial dependence on caretakers (dependence) to determine how well NIHSS score can discriminate between dependence and independence. Methods: All 385 living subjects with 3 month NIHSS score and 3 month living situation data from the RANTTAS trial were analyzed. Subjects were categorized as dependent if they were 1) home and fully independent 2) home but with supervision 3) in a minimal care facility or 4) other. The proportion of patients dependent at each NIHSS score was then determined from the notes of the neurologic examination documented by the physician who was performing the NIHSS. Results: Ninety seven (25%) of subjects were dependent at 3 months. For NIHSS scores ≤4, 9% of subjects were dependent. For NIHSS scores of 5–12, 67% of subjects were dependent. For NIHSS scores ≥15, 100% of subjects were dependent. Only 24 subjects in our sample had 3 month NIHSS scores ≥15 and only 18 had NIHSS scores ≥15. A logistic regression model with NIHSS score predicting dependence had a C-index of 0.86. Conclusions: The 5 month NIHSS score is highly predictive of level of dependence. In our dataset, an NIHSS score of ≥15 was always associated with dependence at 3 months and this may be a reasonable cut off for estimating dependence in clinical stroke trials. These data require validation in an independent data set.

Validation of a Retrospective NIH Stroke Scale Scoring Scheme

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Introduction: The NIH Stroke Scale Score (NIHSS) is a validated measure of stroke severity. As it can be performed in a highly reliable way by trained examiners, it is a useful measure of stroke severity when studying post-stroke outcomes. A method has been developed for obtaining an NIHSS from retrospective chart review (Williams, et al., Stroke, 2000; 31:888–902) and tested in one series of patients. The performance of this retrospective NIHSS (rNIHSS) scoring scheme was excellent, but it has not been independently confirmed. Methods: Charts of all ischemic stroke patients treated by stroke team members (neurologists and emergency physicians) during evaluation for thrombolytic therapy in 1999 were retrospectively reviewed by research nurses. Using Williams’ method, an rNIHSS was determined from the notes of the neurologic examination documented by the physician who performed the NIHSS. Recorded NIHSS values were statistically compared to rNIHSS scores. Results: The rNIHSS patients had a mean NIHSS of 13.6 (95% CI 11.5–15.6) with median NIHSS of 13.5; mean rNIHSS of 13.7.9 (95% CI 11.6–15.7) with median rNIHSS of 13.5. The correlation between the NIHSS and rNIHSS was 0.98 (p < 0.001) with a mean bias of 0.12 (95% CI: 0.12–0.07). The NIHSS and rNIHSS were in agreement in 48 of the 58 cases (83%). The rule of thumb for disagreement was that 3 cases varied by 1 point, 5 cases varied by 2 points, 1 case varied by 3 points, not 5 cases varied by 4 points and 4 cases varied by 1 point. Conclusions: The method of Williams for obtaining an NIHSS is a valid and reliable way to estimate stroke severity, as it is highly correlated to NIHSS. In Williams’ study, all neurologic exams where the NIHSS was scored were performed by neurologists. In our study, all exams were performed by stroke team personnel, including stroke neurologists and ER physicians experienced in stroke care. Further testing is necessary to see if the rNIHSS can be applied as a retrospectively obtained measure of stroke severity when obtained from neurologic exams documented by other health professionals.

The Pass Scale Predicts 24-Hour NIHSS With More Accuracy Than Baseline NIHSS or Other Baseline Variables

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Background: Accurate prediction rules using baseline data are lacking for stroke patients presenting acutely. Baseline NIHSS, glucose, systolic blood pressures, clinical deficits, temperature, neurologic worsening or improvement and brain CT have been used separately to predict outcome. These parameters have not yet been combined into one instrument that could be used in acute period to predict outcome. Therefore we designed the Prediction in Acute Stroke Scale (PASS) incorporating these measures. In a pilot study we related PASS scores to 24 hour NIHSS which is highly correlated with 3 month outcome. Methods: Demographic data, blood pressure, temperature, NIHSS at presentation, glucose, & use of thrombolytics collected on 65 consecutive patients within 6 hrs of ischemic onset stroke. Clinical information on level of consciousness, weakness, aphasia, gaze abnormalities, visual field defects, and neglect was recorded & re-recorded after one hour to clearly define either improvement, no change or deterioration. Brain CT was reviewed for presence or absence of acute ischemic changes. Points were assigned using an arbitrary weighting system to calculate combined PASS score. PASS score & baseline NIHSS were used to predict 24 hour NIHSS to determine whether this scoring system is superior to baseline NIHSS in predicting 24 hour NIHSS. Results: 36 (65.4%) pts were males, with a mean age of 72 years. 35 (64%) received IV PA. Median NIHSS at baseline was 14, while mean NIHSS at 24 hours was 9. Mean PASS score was 5 (SD: 4.4; range=3–18). Pearson correlation coefficient for PASS score with 24 hour NIHSS was 0.79 (p < 0.0001) whereas correlation for baseline NIHSS was 0.56 (p < 0.0001). Examining rNIHSS from linear regression, PAS score explained 63.4% of variance in 24 hour NIHSS (p < 0.0001) whereas baseline NIHSS explained 31% (p < 0.0001), clinical progression 28% (p < 0.0001), mental status at one hour 32% (p < 0.0001), gaze abnormalities 27% (p < 0.0001) serum glucose 3% (p > ns), age 6.0% (ns), & IV PA 0.32% (ns). PASS score ≤ 5 significantly predicted 24 hour NIHSS of less than 5 (OR 13.0 (95% CI 3.9 – 43.4). Conclusions: PASS score predicts 24 hrs NIHSS better than other baseline variables including baseline NIHSS. Larger study is underway comparing PASS to 3-month outcomes.

Higher Serum Cholesterol Levels Are Associated With Milder Strokes and Decreased Risk of Stroke Death: A 10-Year Follow-up of the Copenhagen Stroke Study

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Objective: Higher levels of serum cholesterol are reported to be associated with decreased risk of stroke death. These findings remain unexplained. We studied the relation between total cholesterol (TC), initial stroke severity, 28-days mortality and 10-years mortality in the community-based Copenhagen Stroke Study (COST). Method: TC was measured on admission in 731 patients with acute CT-verified ischaemic stroke in the COST study 1992/1993. Stroke severity was measured on admission using the Scandinavian Stroke Scale (SSS). A cardiovascular risk factor profile was obtained in all (TC, hypertension, ischemic heart disease, diabetes, atrial fibrillation, previous stroke, intermittent claudication, smoking and daily alcohol consumption). Mortality data were obtained 28 days and 10 years after the stroke. Independent predictors of high (≥5 mmol/l) TC were analyzed in a logistic regression model adjusting for age, gender, SSS, smoking status (symptomatic vs. asymptomatic), and the following variables as independent variables. Results: Mean age 74 years; 67% males; TC > 5.5 mmol/l: low (TC < 5 mmol/l)/high (TC ≥ 5 mmol/l). TC was associated with lower adverse event rates. Only in those patients undergoing CE for symptomatic carotid disease was there a reduction in ischemic stroke and/or death [HR: 0.56 (95% CI 0.32–0.96), p = 0.033], with a trend toward a lower rate of stroke, myocardial infarction or death [OR 0.73 (95% CI 0.46–1.2), p = 0.18]. This favourable outcome association was not seen in those undergoing CE for asymptomatic disease with non-significant increases seen in the two endpoints [OR 1.4 (95% CI 0.64–2.9, p = 0.42), and [OR 1.4 (95% CI 0.79–2.6), p = 0.23] respectively. Conclusions: Statins were associated with a lower incidence of ischemic stroke or death in patients undergoing CE for symptomatic carotid artery disease. A similar protective association was not seen in patients undergoing CE for asymptomatic carotid disease.
Faster and Complete Recanalization May Overcome the Negative Effect of Hyperglycemia on Stroke Outcome

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Background: Hyperglycemia predisposes to poor outcome after acute ischemic stroke, particularly after thrombolytic therapy. The CLOTBUST trial allowed us to investigate the effect of hyperglycemia on outcome in patients who demonstrated faster and more complete recanalization (iv tPA + ultrasound monitoring (US)). Subjects and Methods: CLOTBUST randomized 126 subjects to receive either iv tPA + sham US (Control) or iv tPA + active US (Target). Baseline glucose values, NIHSS and outcome at 90 days were measured. Mean glucose values (range 67–412) were 142 mg/dl in controls and 138 mg/dl in Target (P < 0.731). Target patients had a 28.6% (95% CI 13.1–44.0) increase in complete recanalization after 2 hours of US therapy. In this secondary analysis, when glucose was factored into a logistic model including age and baseline NIHSS, we found a significant interaction effect between US therapy and glucose on outcome (OR 0.9–2.0, p = 0.043). Patients with elevated glucose only did well if they were in the Target group receiving active US treatment (Figure). Conclusions: Our results indicate that more rapid and complete recanalization may help overcome the negative relationship between elevated glucose and outcome. More research into mechanisms for this interaction were examined in exploratory analyses and will be presented.

Operator-Dependent Variability in Recanalization Rates Following Intraarterial Thrombolysis

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Purpose To determine whether operator training experience influences recanalization rate following intra-arterial thrombolysis. Methods This study retrospectively reviewed the records and available images from 87 consecutive arteriograms performed at 12 by different operators prior to and following thrombolysis in patients eligible for intra-arterial thrombolysis. The arteriograms were reviewed to identify whether recanalization on the basis of TIMI score. The training level of the operator performing intra-arterial thrombolysis was scored as: Zero - operator had formal training in angiographic techniques but no formal fellowship training in interventional neuroradiology beyond one month; One - operator had formal interventional neuroradiology training 1-6 months; Two - One year or more formal training in interventional neuroradiology. Logistic regression analysis for TIMI score used the following predictors: pretreatment NIHSS score, thrombolytic agent, age, time to treatment, sex, admitting glucose value, site of occlusion, training score. Results Operators with a score of zero (n = 32) had TIMI scores of 2 or 3 in 47% of cases, Operators with score of 1 (n = 27) had a TIMI score of 2 or 3 in 52% of cases and operators with a score of 2 (n = 32) had TIMI score of 2 or 3 in 76% of cases. Logistic regression analysis for TIMI score relative to other predictors indicates that formal training in interventional neuroradiology techniques influences recanalization rates (p < 0.0040). Other statistically significant predictors included time to treatment (p < 0.0219) and preprocedural NIHSS score (p = 0.0044). Conclusion Formal training in interventional neuroradiology can influence recanalization rate following intra-arterial thrombolysis.

Medical Complications After Subarachnoid Hemorrhage: Frequency and Impact on Outcome


Background and Purpose: Medical occurrences frequently occur after subarachnoid hemorrhage (SAH). Their impact on outcome independent of previously defined risk factors for death and severe disability remain poorly defined. Methods: Of 580 consecutively admitted patients with SAH enrolled in the Columbia University SAH Outcomes Project between July 1996 and May 2002 we analyzed 576 with complete 3 month outcome and medical complication data. Poor outcome was defined as death or severe disability (modified Rankin Score 4–6). We calculated the frequency of the medical complications and identified their impact on outcome using multiple logistic regression after adjusting for known predictors of poor outcome. Results: Mean age was 54 years (range 16–89). Forty-two percent were Hunt-Hess grade I or II, 31% were grade III, and 28% were grade IV or V. Thirty-eight percent (220/576) had a poor outcome, with disability, vegetative state, or death, GOS 2–5. Participating centers submitted pre-operative ECGs for a blinded assessment of 7 abnormalities: Q waves, ST elevation (>0.1mV), ST depression (>0.1mV), peaked T waves, T wave inversion, Giant T wave inversion (>10mV), and non-specific changes (NSSTWA). Each abnormality had to involve at least two contiguous leads in one of 3 distributions: inferior (II, III, aVF), lateral (I, aVL), anterior (V1, V6). The 21 possible combinations of abnormality type and distribution were treated as categorical variables (normal ECGs = reference). The relationships between these variables and the GOS were quantified by multivariable logistic regression, reporting odds ratios (OR), 95% confidence intervals (CI), and P values. Age, gender, WFNS grade, Fisher grade, and aneurysm location were included as co-variates. Results: The study included 632 patients, whose ECGs had 1113 abnormalities. The mean age was 52, 64% were women, and the mean WFNS grade was 1.4. Poor GOS was observed in 226 patients (36%). See table. Conclusions: Specific electrocardiographic ECG abnormalities are independently predictive of poor neurological outcome in SAH patients receiving surgical aneurysm clipping. Whether or not a causal relationship exists between cardiac dysfunction and poor outcome after SAH should be the topic of future research.

Electrocardiographic Predictors of Poor Neurological Outcome in 632 Patients With Subarachnoid Hemorrhage

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Electrocardiographic (ECG) abnormalities are common after subarachnoid hemorrhage (SAH). Prior studies that attempted to quantify the predictive effect of the ECG on neurologic outcome were limited by size, retrospective design, or failure to adjust for co-variates. The aim of this study was to test the hypothesis that specific ECG abnormalities affect outcome independent of previously defined risk factors for death and severe disability. Methods: We defined 3 categories of complications (hospital death, complete dependence, any death). Hospitals were defined as centers where at least one patient was admitted. Results: Of 4896 patients, 632 (13%) were identified. Twenty-six percent (164/632) died. Out of the 19 ECG abnormalities identified, ST elevation was most common (56%), followed by T wave inversion (27%), Q waves (8%), and ST depression (5%). Specific ECG abnormalities (ST elevation > 0.2mV, T wave inversion, Q waves) were independent predictors of poor neurological outcome after SAH (p = 0.003). Conclusions: ECG abnormalities are common after SAH and predictive of poor neurological outcome. These findings may have clinical implications for the treatment of SAH.
Seizures Following Ischemic Stroke in a General Population: The Framingham Study

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OBJECTIVE: The aim of the study is to document the incidence of seizures (SZ) following ischemic stroke in a community-based sample. METHODS: All initial ischemic strokes in the Framingham Original and Offspring cohorts between 1921-1971 were followed up for 21 years to determine incidence of new-onset SZ. Ischemic stroke subtype was determined according to standard criteria. SZ definition was based on the International League Against Epilepsy criteria. RESULTS: Initial ischemic stroke occurred in 470 subjects (mean age 78.7, 287 women) and 25 sustained a seizure post-stroke (5.3%). Seizures occurred with similar frequency in men and women. Only 5 strokes were followed by SZ in 5 subjects below age 75. The annual incidence of SZ among those >75 years of age was slightly higher in women (14.2/1000 py) than in men (11.5/1000 py). Among 79 lacunar infarcts no SZ were seen. SZ frequency was similar in other ischemic stroke subtypes, occurring in 6.2% of non-lacunar ABI (n=242) and 6.8% of CE (n=148). SZ type for the 15 ABI subjects were as follows:primary generalized in 10 (66.6%), simple partial in 3 (20%), and simple partial with secondary generalization in 2 (13%). The SZ type for the 10 CE subjects were primary generalized in 7 (40%), simple partial in 1 (10%), and simple with secondary generalization in 2 (20%). Among the 25 cases with SZ, 40% (n=10) occurred in the first 24 hours post-stroke, while 4% (n=1) occurred during days 2 to 30, 28% (n=7) after 1 year. CONCLUSIONS: SZ occur in 5.3% of ischemic stroke events. Incidence of SZ following cardioembolic and atherothrombotic stroke was similar. A high percentage of SZ occur in the first 24 hours post-stroke onset. Generalized SZ are more common than simple partial SZ in both types of ischemic strokes.
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Leukoaarosis and Microalbuminuria Are Risk Factors for Parenchymal Hemorrhage in Acute Ischemic Stroke
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Background: Leukoaarosis and microalbuminuria have been suggested as markers of endothelial damage in cerebral microvessels. Our aim was to study their potential role as clinical predictors of parenchymal hemorrhage (PH) after acute ischemic stroke. Methods: From a series of 652 patients with ischemic ischemic stroke of less than 24 hours duration, we selected 200 patients (mean age, 73 y; 51% men; 40% cardioembolic stroke; 30% treated with anticoagulants initiated within the first 24 hours) in whom microalbuminuria was determined by nephelometry in the first spontaneous motion or after urinary catheterization. Microalbuminuria was considered positive when concentrations were between 20 and 200 μg/min. The presence of leukoaarosis was evaluated in CT on admission. A second CT was made if clinical worsening was verified or, in any case, between 4th and 7th days. Hemorrhagic transformation was classified according to ECASS criteria. Results: Forty nine patients (24.5%) showed microalbuminuria (143 [70–184] μg) and 72 (36.0%) leukoaarosis. Microalbuminuria was more frequent in patients with leukoaarosis (48.6 versus 10.9%, p < 0.001). Thirty six patients (18.0%) suffered hemorrhagic transformation (8 IH, 15 IH2, 11 PH1 and 2 PH2). Microalbuminuria (76.9 versus 20.9%, p < 0.0001) and leukoaarosis (76.9 versus 31.1%, p < 0.002) were more frequent in patients with parenchymal hemorrhage than in those without. Leukoaarosis was the only predictive factor of PH in multivariate analysis (excluding microalbuminuria) (OR 5.4 [1.1–55.7], p = 0.036); while microalbuminuria was introduced in the model (OR 6.8 [1.2–38.2], p = 0.029) the predictive value of leukoaarosis disappeared. There was no interaction between the two factors. Conclusion: Leukoaarosis is associated with microalbuminuria reinforcing its role as a signature of microangiopathy. However, microalbuminuria on admission was a more powerful predictive factor of parenchymal hematoma after ischemic stroke.

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Worse Outcomes Among Patients With Stroke on Awakening
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Background - An estimated 20–25% of all strokes occur during sleep and these patients wake up with their deficits. Thrombolytic therapy is denied these patients, as the standard protocols require a definite time of onset to determine eligibility. This study evaluated outcomes between patients who woke up with stroke compared to those who were awake at stroke onset, with the hypothesis being that there would be only minor differences. Methods - Using data from the Registry of the Canadian Stroke Network (phases 1 and 2), we compared demographics, treatment of patient, local characteristics and 6-month outcomes between patients who woke up with stroke at awakening versus stroke-while awake. Strokes of all types (ischemic stroke, transient ischemic attack, intracerebral hemorrhage and subarachnoid hemorrhage) were included. Standard descriptive statistics, multivariable logistic regression and general linear modeling were utilized. We stratified the data to compare variables. Results - Among 2585 stroke patients, 349 (13.5%) woke up with stroke and 2236 (86.5%) did not. Patients with stroke-on-awakening were more likely to have higher blood pressure and to suffer ischemic stroke. Mortality, both at discharge and at 6-month follow-up, did not differ between the two cohorts. Patients with stroke-on-awakening were less likely to return home, and their median Stroke Impact Scale was 7.0 points lower compared to those with stroke-while awake. Conclusions - Stroke-on-awakening patients are a large minority of stroke victims. There are minor demographic and clinical differences between patients with stroke-on-awakening and stroke-while awake. Functional outcomes are slightly worse among patients with stroke-on-awakening. Further investigation of intervention is warranted.

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Difference in Progression of Middle Cerebral Artery Stenosis During 6 Months After Ischemic Stroke: Symptomatic vs Asymptomatic
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Background: Progression of symptomatic extracranial carotid artery stenosis has been well known. However, little information is available about the change of symptomatic middle cerebral artery (MCA) stenosis after stroke. Objective: To evaluate the difference in progression between symptomatic and asymptomatic MCA stenosis. Methods: This study was performed as a subgroup analysis of the randomized clinical trial of clopidogrel in symptomatic intracranial arterial Stenosis (TOSIS). Magnetic resonance angiography (MRA) was performed twice: at < 2 weeks, and 6 months after the onset of stroke. The rest of the MRA were repeated in three neurologists independently and the status of MCA was graded into normal, mild, moderate, severe and occlusion by consensus. Progression was defined as the increment of one or more grade on follow-up MRA. An odds ratio of progression of symptomatic stenosis was calculated in asymptomatic patients with no clinical symptoms of stroke. Results were obtained for patients with carotid artery stenosis > 70% and with no history of coronary heart disease, hypertension, diabetes, hyperlipidemia, and the use of statins, angiotensin converting enzyme inhibitors, and cilostazol. Results: Ninety-seven patients with MCA stenosis on initial MRA were analyzed. Among 82 MCAs with symptomatic stenosis, 17 (20.7%) showed progression. Three (5%) of 60 MCAs with asymptomatic stenosis showed progression. Conclusion: Our study reveals that symptomatic MCA stenosis progresses more frequently than asymptomatic one. Symptomatic intracranial stenosis appears to be a highly dynamic process as to require therapeutic intervention.

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The Main Risk for Patients With High-Grade Carotid Artery Stenosis and History of Cervical Irradiation Is Death From Cancer, Not Having a Stroke
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Background: information provided by large randomized carotid surgery trials are not valid for patients with high-grade internal carotid artery (ICA) stenosis and history of cervical irradiation, because they have a higher risk for surgery. Percutaneous angioplasty is often feasible, but there is no proof of its safety and efficacy. Moreover, the natural history is remains poorly known in these patients. Aim of the study: to evaluate the clinical outcome of patients high-grade ICA stenosis, and history of cervical irradiation. Method: we studied the clinical outcome of 41 consecutive patients with: (i) ICA stenosis > 70% (NASCET criteria), and (ii) history of cervical irradiation at least 2 years earlier. Results: After a median follow-up of 28 months, 15 patients (38.6%) were dead (estimated mortality rate: 15.7 % per year; 95 % confidence interval [CI]: 9.3–22.0 %); 5 (12.2 %) had a stroke, of which 1 occurred after surgery and 1 after angioplasty (estimated annual stroke rate: 5.2 % per year; 95 % CI: 0.9–9.5 %). 2 had acute coronary syndromes (4.5 %); had 15 recurrence of cancer (36.6 %), and 5 had a new cancer (12.2 %). Twenty patients (48.8 %) were independent (modified Rankin scale < 2). A chi-square test was used to compare clinical variables. A logistic regression analysis found having a new cancer or a recurrence of cancer as the only independent predictor of death (aOR: 5.59; 95 % CI: 1.03–30.20). Conclusion: Our study reveals that the major risk for patients who have an ICA stenosis > 70 % and history of cervical irradiation is to die from cancer, not to have a stroke. This finding should be taken into account before any decision of surgery or angioplasty.

Pretreatment With Antiplatelets Is Associated With Smaller Diffusion-Weighted Volume in Middle Cerebral Artery Territory Infarcts
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Background and Purpose: To determine the clinical and demographic differences between patients with stroke-on-awakening and stroke-while-awake. Pretreatment with antiplatelets was associated with smaller infarct volumes if they had a recent history of ischaemic TIA’s (OR 0.11 [0.01–0.89], 95% CI), p = 0.014), were on anti-platelet prior to their stroke (OR 0.21 [0.07–0.61], 95% CI), p = 0.004, or on statins prior to their stroke (OR 0.28 [0.10–0.75], 95% CI), p = 0.009.

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to their stroke (OR 0.36 [0.11–0.98, 95% CI], p = 0.046). NIHSS at the time of MRI correlated strongly with smaller infarct volumes also (Spearman’s coefficient = 0.374, p = 0.002). A binary logistic regression model and revealed the following independent variables that predict smaller infarct volumes: anti-platelets (OR 4.5 [1.2–17, 95% CI], p = 0.027) and NIHSS (OR 1.16 [1.04–1.30, 95% CI], p < 0.011). Conclusions: Patients on anti-platelet therapy prior to their strokes are more likely to have smaller infarct volumes suggesting a neuroprotective effect.

**Congestive Heart Failure Is Associated With Poor Outcome at 6 Months in Patients With Ischemic Stroke**

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**Background:** Presence of low cardiac output may worsen ischemic injury in patients with ischemic stroke. We tested the hypothesis that the long-term outcome is worse in patients with ischemic stroke in presence of congestive heart failure (CHF).

**Methods:** We analyzed the prospectively collected data as part of the randomized, placebo controlled trial in patients with acute ischemic stroke evaluated within 3 hours of symptom onset. History of CHF was ascertained at initial evaluation. Volume of infarction was measured from computed tomographic scan acquired at 3 months. Favorable outcome defined by no significant or slight disability on modified Rankin scale at 6 months. We determined the effect of CHF on favorable outcome at 6 months using a logistic regression model after adjusting for age, gender, initial National Institute of Health Stroke Scale (NIHSS), and administration of activase.

**Results:** Of the 596 patients with data regarding CHF, 99 (17%) had history of CHF. Patients with CHF were older (69.4 ± 11.7 versus 66.4 ± 11.5 years) and had higher NIHSS (17 ± 7 versus 14 ± 7). A trend was observed for CHF to be associated with higher volume of infarction at 3 months (78 ± 96 versus 61 ± 96, p = 0.1), CHF was associated with lower rates of favorable outcomes at 6 months after adjusting for potential confounders in the multivariate model (Wald chi-square 6.2, p = 0.04). Conclusions: Presence of CHF in patients with ischemic stroke is independently associated with poor outcome. Further studies are warranted to understand the underlying factors that predispose to poor outcome associated with CHF.

**Trends in 5-Year Survival and Risk of Recurrent Stroke After First-Ever Stroke in the Perth Community Stroke Study**

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**Background:** Few studies provide information on trends in the long-term outcome of stroke. We aimed to determine the trends in survival and recurrent stroke, over five years after first-ever stroke, for two cohorts of patients enrolled in the Perth Community Stroke Study in 1989–90 and 1995–96. **Methods:** For 12-month periods beginning February 1989 and February 1995 all individuals with an acute stroke who were resident in a geographically-defined and representative region of Perth, Western Australia, were registered and followed-up prospectively five years after the index event. **Results:** The five-year cumulative risk of death was 59% (95% confidence interval [CI] 53%, 65%) and 58% (95% CI 52%, 65%) for the 1989–90 and 1995–96 cohorts, respectively (p = 0.94). The five-year cumulative risk of first recurrent stroke was 32% (95% CI 25%, 40%) and 23% (95% CI 16%, 30%) for the 1989–90 and 1995–96 cohorts, respectively (p = 0.07). Conclusions: There was no statistically significant improvement in five-year survival after first-ever stroke in Perth between 1989–90 and 1995–96, despite a reduction in mortality in younger patients in 1995–96 compared with 1989–90. There was also a statistically non-significant trend toward a smaller cumulative risk of recurrent stroke over five years after a first-ever stroke. Serial community-based studies of the incidence and outcome of stroke are an important means of monitoring the translation of proven preventive interventions to improvements in population health.
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