The Effect of Early and Late Brain Tissue Reperfusion on Infarct Volume
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Objectives: To find out whether brain tissue reperfusion affects the volume of ischemic infarcts if observed within or after 8 hours of stroke onset. Methods: We performed 99mTc-Etich cyanistein dimer single-photon emission computed tomography (SPECT) in patients included in a single site of the ECASS II before treatment with recombinant tissue plasminogen activator (rt-PA, 0.9 mg/kg IV) (n=5), placebo (N=26), 6.8 hours after treatment, and after 7.1 days to determine the degree and extent of brain ischemia. Following a prospective protocol, the SPECT scans were analyzed blinded to treatment allocation using a graded scale for quantification. We defined “reperfusion” as a decrease in the graded scale by >25% comparing the follow-up scans with the baseline scan. The infarct volume were measured using the formula for irregular volumes, blinded to clinical information and the SPECT results. Results: SPECT detected reperfusion in 18 patients within 8 hours and in additional 10 patients at 7 days of stroke onset. Treatment did not affect the frequency of reperfusion. Twenty-four patients did not show reperfusion. These 3 groups did not differ at baseline with regard to gender, age, the NIH Stroke Score, the SPECT graded scale, and the extent of ischemic lesions on CT. One patient with early reperfusion died at day 15 from a non-neurological cause. Eight patients without reperfusion died until day 90. 5 of them from large parenchymal hematoma within 6 days of stroke onset. The mean infarct volume at day 1 was 137 ±141 ml without reperfusion, 37 ± 30 ml with late reperfusion (p=0.05, vs. no reperfusion), and 21.2 ± 26 ml with early reperfusion (p=0.0005, vs. no reperfusion). The mean infarct volume at day 7 was 115 ± 139 ml without reperfusion, 56 ± 42 ml with late reperfusion, and 26.7 ± 33 ml with early reperfusion (p=0.0007 vs. no reperfusion). Patients with early and late reperfusion had a better clinical outcome at 90 days than patients without reperfusion. Conclusion: Spontaneous reperfusion even if delayed 8 hours after stroke onset was associated with smaller infarctions and better clinical outcome.

The Validity and Reliability of a Novel Quantitative CT Score in Predicting Outcome Prior to Thrombolytic Treatment
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Background The significance of early ischemic change in the context of hyperacute stroke is unclear. Concern exists over the ability of clinicians to correctly recognize and interpret these changes. Improved methods of recognising and quantifying early CT changes are needed to influence patient selection for thrombolytic therapy. Methods: Consecutive patients with anterior circulation ischemic stroke were treated with intravenous t-PA according to NIHSDS guidelines. All pretreatment CT scans were prospectively evaluated. TIBI class was given to all the studies. The studies were interpreted by 2 radiologists blind to clinical information. Results: TIBI class assessed by the radiologist was compared with the ASPECTS score. Conclusion: Radiologist was able to correctly determine the TIBI class from the ASPECTS score.

Acute Cerebral Blood Flow as a Predictive Physiologic Marker for Symptomatic Hemorrhagic Conversion and Clinical Hemorrhage After Thrombolytic Therapy
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Background and Purpose: We looked at the ability of quantitative cerebral blood flow (qCBF) to act as a physiologic marker for the identification of patients (pts) at high risk for symptomatic hemorrhagic conversion (SHC) and/or clinical hemiation (CH). Methods: We reviewed 32 pts with acute cerebral infarction and who had qCBF measurements prior to or concomitant with thrombolytic therapy. Therapy was administered as follows: intravenous (iv) t-PA in accordance with FDA approved clinical guidelines (N=14), intra-arterial (ia) urokinase (UK) (N=7), iv and UK angioplasty (N=4), combined iv-ia t-PA (0.6 mg/kg) and ia t-PA (0.3 mg/kg) including one with concomitant angioplasty (N=5), iv t-PA and ia UK (N=1) and ia-PA (N=1). All pts. receiving iv-t-PA , iv/ia t-PA or iv t-PA and ia UK were treated within 3 hours and pts. treated with ia UK or ia-t-PA were treated within 6 hours of stroke onset. qCBF measurements were performed using xenon enhanced computerized tomography (XeCT). The mean qCBF in the symptomatic vascular territory was calculated by averaging standard regions of interest (ROI) in 3-4 hemispheric brain levels. Focal qCBF was defined as defined as two adjacent ROI within the symptomatic vascular territory with the lowest qCBF averaged over 3-4 hemispheric levels. Non-contrast CT scans were performed prior to and 24-72 hours after treatment. Results: The mean qCBF in pts. with SHC and/or CH after thrombolysis (N=9) was 14.3 ml/100g/min. In pts. without SHC or CH after thrombolysis (N=23) the mean qCBF was 28.8 ml/100g/min. P=0.0002. The focal qCBF in pts. with SHC and/or CH after thrombolysis was 8.6 ml/100g/min. In pts. without SHC or CH after thrombolysis the focal qCBF was 29.3 ml/100g/min. P=0.0007. Conclusions: XeCT qCBF can be combined with CT equipment, providing qCBF information for review within 15 minutes. It is ideally suited as a diagnostic study in pts. with acute stroke. qCBF may be an effective physiologic marker for the identification of patients at high risk for SHC and/or CH after thrombolytic therapy. By improving patient selection the utilization of thrombolytic therapy may be increased.

Thrombolysis in Brain Ischemia (TIBI) Flow Grades Predict Likelihood of Recanalization and Recovery in Intravenous TPA Treated Patients
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Background: Residual flow surrounding occlusion is an important predictor for success with coronary thrombolysis. Thrombolysis in Myocardial Ischemia (TIMI) grading system is an angiographic classification to measure residual flow and recanalization. We developed a Thrombolysis in Brain Ischemia (TIBI) classification using transcranial Doppler (TCD) to noninvasively monitor residual flow signals. In this study we examine the relationship between stroke severity and outcome in intravenous TPA patients evaluated by TCD emergently using this new TIBI classification. Methods: Previously established TCD occlusion criteria were followed to determine site of arterial occlusion. Residual flow waveforms were identified by TCD at depth just distal to presumed occlusion site, before, during and after intravenous (IV) TPA treatment. TIBI Grade I consisted of absent and minimal waveforms; Grade II: blunted and dampened; Grade III: stenotic and normal. NHSS scores were obtained at baseline and discharge. Results: 62 IV TPA treated patients were studied prospectively (age 66.5±16 years, pre-TPA NHSS 16.4±6.2, TPA bolus at 139±58 mmHg, 7 patients were excluded from the analysis (5 no temporal windows, 2 missing data). Pre-TPA NHSS scores were 19.5±6.0 for Grade I, n=30; 13.5±4.6 for Grade II, n=15; and 12.2±5.9 for Grade III, n=10 (p<0.05, vs. 1 and II). TIBI flow improvement to Grade III occurred in 30% (9/30) of initial Grade I and 46% (7/15) of Initial Grade II patients. Patients with final Grade III had better follow-up NHSS 6.2±2.9 (n=17), final Grade II 12.7±5.7 (n=13), and final Grade I 21.1±11 (n=11), (p=0.03 vs. II and III). In-hospital mortality was 35% (1/30) in patients with pre-TPA Grade I flow, and 12% (3/25) in pre-TPA Grades II-III, (p=0.43 p<0.037). Conclusions: No or minimal residual flow (TIBI Grade I) correlates with severe preocclusion neurologic deficit, poor clinical recovery and higher mortality in IV TPA treated patients. The presence of residual flow (Grades II and III) before thrombolysis is a prognostically favorable sign. The degree of TIBI flow grade improvement correlates with short-term recovery.

4

Oral Presentations
Thursday-Morning
OBJECTIVE: To identify variables predictive of intracerebral hemorrhage in patients treated with intravenous t-PA for acute ischemic stroke in routine clinical practice. Data were collected as part of the Standard Treatment with Actrease to Reverse Stroke (STARS) project which was a prospective, monitored, multi-center study evaluating the post-appearance evaluation of 480 patients within 6 hours of symptom onset who received t-PA at 59 centers were enrolled in this study. Data regarding baseline characteristics, medications, medical history, and CT-scan results were collected. Data on symptomatic and asymptomatic intracerebral hemorrhage were collected during the initial hospitalization and at 30 days. Using multivariable regression, the relationship of the baseline variables with symptomatic and asymptomatic hemorrhage during the first 72 hours was assessed.

RESULTS: A total of 11% of patients experienced an ICH during the first 72 hours of following treatment. Thirteen (3%) of the patients experienced a symptomatic hemorrhage and 28 (7%) experienced an asymptomatic hemorrhage. Of the 81 patients with evidence of stroke on the baseline CT scan, five (6%) experienced a symptomatic ICH compared to 8/308 (2.5%) following treatment. Thirteen (3%) of the patients experienced a symptomatic hemorrhage and 28 (7%) experienced an asymptomatic hemorrhage. Of the 81 patients with evidence of stroke on the baseline CT scan, five (6%) experienced a symptomatic ICH compared to 8/308 (2.5%) following treatment.

Our data suggest that the presence of early CT findings in patients with AIS is not predictive of unfavorable outcome following IV thrombolysis with t-PA.
Some Potentially Harmful Side Effects of Anti-ICAM-1 Antibody Administration in Preclinical Animal Studies of Stroke

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A clinical trial of murine anti-human ICAM-1 antibody (Elimolumab) therapy of acute stroke produced a higher incidence of clinical deterioration than treated in control patients. Even though the monoclonal anti-ICAM-1 antibody (1A29) was administered prior to and/or P-selectin on brain microvessels has been reported. We report additional evidence of the harmful side effects of 1A29 in preclinical animal models of stroke. Wistar rats and SHR were subjected to permanent middle cerebral artery occlusion (MCAO) with 24 h reperfusion. The infarct volume was assessed at 48 h after MCAO. 1A29 treatment did not cause a statistically significant decrease of the infarct size in either strain compared to PBS and IgG1-treated controls. 1A29 (2 mg/kg), PBS or isotype-matched immunoglobulin (IgG1) were administered intravenously just after reperfusion of the CCAO and 24 h after MCAO. The infarct size in PBS-treated controls was 287.6 ± 6.3 mm³ (Wistar) and 167.5 ± 2.5 mm³ (SHR) respectively, most ependymal cells and scattered choroid cells have the power of differentiation. Choroidal cells are modified ependymal cells. To identify the mechanisms of clinical deterioration that occurred in the Enlimomab trial.

Adaptive Transfer of MAb-Tolerized Splenocytes Decreases Infarct Size Following Transient Focal Cerebral Ischemia

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Background: We previously showed that animals tolerated to myelin basic protein (MBP) through oral administration of the antigen had significantly smaller infarcts following transient middle cerebral artery occlusion (MCAO) than rats tolerized to an irrelevant antigen. The neuroprotection in this model is presumably immunologically mediated and should therefore be conferred to naïve patients through adaptive transfer of lymphocytes. Methods: Male Lewis rats (250-350 grams) were tolerized to bovine MBP (n=12) or ovalbumin (OVA, n=15) through nasal instillation of antigen (200 μg) on 5 separate occasions over a period of 2 weeks. Animals were sacrificed after 3 hours of MCAO and 21 hours of reperfusion and infarct size determined using 2-(3-nitro-7-nitro-2,1,3-benzoxadiazol-4-yl)imidazole (CCTC) staining. Another group of animals similarly tolerated to MBP (n=12) or OVA (n=15) were sacrificed and single cell suspensions prepared from their spleens. The splenocytes were cultured in concanavalin A for 4 hours at 37°C, 10% CO₂ and the percentage of cells expressing HLA-DR and CD8 was determined.

Entry Criteria and Baseline Characteristics Predict Outcome in Acute Stroke Trials

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Introduction: Few phase III acute stroke trials have shown a treatment-related benefit. One reason for this may be the clearly different course of patients in the placebo group. Trials in which the placebo group has an excellent outcome may have difficulty demonstrating a drug-related benefit. In order to identify factors predicting a good outcome in the placebo group, a meta-analysis of acute stroke trials was performed. Methods: Review of the literature identified 43 randomized, placebo-controlled, late phase therapeutic trials in acute ischemic stroke. Entry criteria, baseline neurological characteristics, and outcome were extracted for the placebo group in each trial. Correlation coefficients (r) were calculated. Results: Entry criteria predicted outcome. The maximum interval from stroke onset to study enrollment (r = 0.59; p < 0.005) and total treatment (r = 0.50; p < 0.001) were significantly correlated with initial NIH stroke scale score (r = 0.72). The age cut-off for study entry directly correlated with the time of treatment (r = −0.72). The age cutoff for study entry directly correlated with increased mortality (r = −0.50), and frequency of atrial fibrillation (r = −0.98), mean age (r = 0.98), and frequency of atrial fibrillation (r = −0.64) predicted 3 month mortality. The age mean of enrollees was inversely related to the % patients with Barthel score = 95% (r = −0.81). Conclusions: These correlations provide insight into how entry criteria influence placebo group characteristics in acute stroke trials. In particular, enrollment of younger patients is associated with a lower rate of placebo group mortality and less disability at 3 months. Patients enrolled many more 3-month mortality onset have less severe deficits at time of enrollment and better survival. Entry criteria in stroke trials affect outcome of the placebo group, and thus may influence the likelihood of demonstrating therapeutic efficacy.
ECCO 2000 Study of Citicoline for Treatment of Acute Ischemic Stroke: Final Results

Background. Several studies in animal models of ischemic stroke treated with citicoline alone or in combination with neuroprotectants or thrombolytics and two clinical investigations suggest that citicoline may result in smaller infarcts compared to the control-treatment. Previous double-blind placebo-controlled studies involving patients with ischemic stroke have suggested that citicoline-treated patients experienced better neurologic recovery than placebo-treated patients. Hypothesis. We hypothesized that treatment with citicoline 1000 mg b.i.d. would result in increased neurologic recovery as measured by the NIHSS and limit infarct volume at week 12 as measured by MRI. Methods. Approximately 900 patients with a clinical diagnosis of ischemic stroke referred to the MCA distribution within 3 hr of symptom onset, a baseline NIHSS ≧3, pre-stroke Rankin ≦2, and free of other limiting or medically significant disease were randomized (1:1) at 125 investigator centers to 6 weeks of citicoline 1000 mg b.i.d. or matching placebo with the final assessment at week 12 post-stroke. NIHSS, Barthel Index, Rankin Scale, Health Utility Index, medical resource usage, week 12 T2 MRIs, and safety assessments were collected. At designated sub-study centers baseline DW-MRIs were also collected. The pre-specified, primary outcome was the comparison of the percentage of patients treated with citicoline or placebo that achieved at least a 7-point improvement from baseline on the NIHSS at endpoint using the ITT LOCF data set. Secondary outcomes were week 12 infarct volume, lesion growth from baseline (DW-MRI), improvements from baseline on the NIHSS at endpoint using the ITT LOCF data set. Results. Data were available in 793 patients. PHs occurred in 48 (11.8%) r-PA group patients (33 of those were type PH 2) and 12 (3.3%) placebo group patients (3 of those were type PH 2). Treatment differences were significant (P<0.01). Most PHs (60%) were symptomatic (i.e. responsible for clinical deterioration). In a stepwise logistic regression analysis, significant risk factors for PH were treatment with r-PA (P<0.03), atrial fibrillation (P<0.002), systolic blood pressure (P<0.001) and prior hypertension (P=0.04). Regarding PH2, significant risk factors were r-PA treatment (P<0.01), NIHSS at baseline (P<0.01) and extent of hypodensity (P<0.01). HIs occurred in 142 (34.9%) r-PA group patients and 141 (36.5%) placebo group patients. Treatment differences were not significant. Only 5% of HIs were symptomatic. In a stepwise logistic regression analysis, significant risk factors for HIs were NIHSS at baseline (P<0.01), extent of hypodensity on baseline CT (P<0.01) and infarct volume at day 1 (P<0.01). Regarding symptomatic hemorrhages treatments in r-PA group, significant risk factors were NIHSS at baseline (P<0.002), age (P=0.03), midline shift (P<0.001) and congestive heart failure (P=0.007). Conclusion. The findings in ECASS 2 confirm the importance of CT variables in addition to well known clinical variables as risk factors for severe hemorrhagic transformation in stroke patients. The findings are in line with what has been observed in ECASS 1. The contribution of those and other risk factors should be evaluated more accurately through an overview of all r-PA trials.

Combination Therapy Stroke Trial: r-PA +/- Lubeluzole
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Background. A neuroprotective drug may be safe and effective if given very early and in combination with r-PA to acute stroke patients. No clinical trial has yet tested this hypothesis. Objective: To assess the safety and efficacy of simultaneously combining the neuroprotective drug Lubeluzole with r-PA. Methods. Patients who qualified for and received r-PA (Activase® within 3 hours of symptom onset were randomized 1:1 to Lubeluzole (7.5 mg IV over 1 hr then continuous 5-day infusion of 10 mg/d) or placebo. Infusion of study medication was started before the end of the 1 hr r-PA infusion. Inclusion criteria were the same as FDA approved guidelines for r-PA, plus NIHSS ≦6 and absence of serious ventricular arrhythmia, AV block, or QT > 450 msec. EKG was continuously monitored until 48 hr post treatment. The primary outcomes were adverse events, especially hemorrhage and severe arrhythmia, and functionality as determined by the Barthel index divided into ≦75, 0.70, and dead. Results. 89 patients were randomized at 34 centers between 1/1997 and 6/1998. Mean (± s.d.) age was 71 ± 12.6 yrs, and mean NIHSS 15.9 ± 6.1. Mean time from symptom onset to r-PA was 147 ± 40 min and to randomization was 191 ± 41 min. The study was terminated by the company before the planned enrollment of 200 patients when a concurrent phase III trial of Lubeluzole vs placebo up to 8 hrs post stroke was found to be negative. At the time the study was terminated, no safety concerns had been identified and enrollment was procured on schedule. Overall, mortality was 26%. Complete results of the comparison of baseline characteristics and outcome between the r-PA + Lubeluzole vs r-PA + placebo groups will be presented. Conclusion. Combining neuroprotective drugs such as Lubeluzole simultaneously with r-PA is feasible, safe, and may result in increased efficacy over r-PA alone in acute stroke patients.

Thursday-Afternoon

Plasma Concentration of C-Reactive Protein and Risk of Ischemic Stroke: The Framingham Study
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Background. C-reactive protein (CRP) has been identified as a novel plasma marker of atherothrombotic disease. Previous studies have mostly related CRP to CHD in men, were often restricted to a case-control design, and lacked other pertinent risk factors to evaluate the joint and net effect of CRP on the outcome. Very few large-scale prospective epidemiologic studies of stroke were reported to date. Methods: We related plasma CRP to incidence of ischemic stroke and TIA in 591 men and 871 women of the Framingham Study original cohort, who were free of all CVD at their 1980-1982 examination. CRP concentrations were measured by an ultr insensitive assay (Hemagen Diagnostics). Analyses were done using sex-specific CRP quartiles (Q1=0-1.1, Q2=1.1-3.2, Q3=3.3-7.7, Q4=7.7-77 mg/mL), with Q1 as the referent group for the risk ratios (RR). Adjustments were made for age, smoking, total/HDL cholesterol, systolic BP, and diabetes. Participants were followed for 12 years for first ischemic stroke and TIA. Results: After adjustment for age, Q2 and Q4 were related to incidence of ischemic stroke and TIA in both men and women. Multivariate adjustment attenuated the response (see table). Conclusion: Elevated CRP (≧3.3 mg/mL) levels were related to increased risk of ischemic stroke and TIA in both sexes, suggesting a significant inflammatory component to cerebrovascular risk. Therapies to reduce the levels of CRP and potentially decrease risk of stroke and TIA warrant investigation.


Background: Long-term first-ever stroke rates are available from few population-based studies. Incidence rates for all strokes, including recurrences have not been previously reported from a defined population but would provide a better estimate of the overall occurrence of stroke from a public health perspective. A unique situation in Rochester, MN allows the ascertainment of virtually all cases of stroke in community residents, dating from 1955.

Methods: Comprehensive medical records of all residents of Rochester, Minnesota with a potential diagnosis of stroke during the 5 year period from 1/1/90 to 12/31/94 were reviewed. In addition to first- and stroke events during the period, all other strokes occurring among Rochester residents were also recorded. Incidence rates for first-ever stroke and major stroke subtypes were calculated, and compared to those dating from 1955. All-stroke incidence rates, and the incidence rates for any first stroke during the period occurring in a Rochester resident were also determined. Rates were adjusted to 1990 US white population.

Results: The incidence rate of first-ever stroke during 1990-1994 was 183 per 100,000 per year (age- and sex-adjusted), and for major stroke subtypes was 160 for first cerebral infarction, 24 for first intracerebral hemorrhage, and 6 for first subarachnoid hemorrhage. Stroke incidence was similar to that noted in 1985-1989 and 1980-1984. The total incidence of all stroke types including first, second, and all subsequent strokes occurring in Rochester residents during the 5 year period was 256 per 100,000 per year. For first stroke in the period, the incidence rate was 220 per 100,000 per year. The incidence rate for first-ever stroke was 71% of the all-stroke event incidence rate.

Conclusion: The incidence of stroke in Rochester is no longer declining, and has not changed over the last 15 years. This study provides unique, previously unavailable data concerning total-stroke incidence in a defined population. Considering first-ever stroke incidence rates alone underestimates the overall occurrence of stroke by 29% when compared to all-stroke incidence rates.
Background: Intima-media thickness (IMT) of the common carotid artery, bifurcation and internal carotid artery is associated differently with subtypes of cerebral infarction. Methods: All patients older than 55 years of age were consecutively recruited from May 18, 1993 to June 30, 1994. Ischemic strokes, confirmed by CT were classified as lacunar (LAC), anterior (AT) or posterior circulation infarct (POCI). For each case, we randomly selected controls. Relative risks per standard deviation increase of IMT with 95% confidence intervals were calculated with Cox’ proportional hazards regression, adjusting for age and gender. Results: During follow up 130 ischemic strokes occurred whereas among 32 LACI’s, 39 PACI’s, 22 TACI’s and 25 POCI’s. IMT of the bifurcation, internal carotid artery as well as the weighted average-IMT over the locations was associated with increased risk of LACI, PACI and TACI but not with POCI. The relative risks for LACI, PACI, TACI and POCI related to BIF-IMT were 1.7(1.3-2.3), 1.51(1.1-1.9), 1.71(2.2-4.4) and 1.40(2.9-2.0), respectively. For ICA-IMT corresponding relative risks were 1.8(1.3-2.5), 1.61(2.2-2.5), 2.71(1.4-0.0) and 1.0(0.6-1.6) and for the combined-IMT relative risks were 3.2(2.8-3.0), 2.2(1.7-2.9), 3.42(2.5-4.7) and 1.50(2.7-2.9), respectively. Conclusion: Increased IMT of the common carotid artery is significantly associated with increased risk of all subtypes of cerebral infarct. IMT of the bifurcation, internal carotid artery and combined-IMT is associated with lacunar and anterior circulation infarctions, but not with posterior circulation infarcts.

Baseline Frequencies, Isotopes, and Tilters of Antiphospholipid Antibodies in the Warfarin Aspirin Recurrent Stroke Study/Antiphospholipid Antibody Stroke Study (WARSS/APASS)/Collaboration; Preliminary Results
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Background: Antiphospholipid antibodies (aPL) are associated with an increased risk of first ischemic stroke, but their contribution to recurrent stroke risk is controversial. Objective: To determine the baseline frequency and characteristics of aPL in a cohort of ischemic stroke patients involved in a randomized, double-blind stroke prevention trial comparing warfarin and aspirin. Methods: Baseline tests for two types of aPL (lupus anticoagulant [LA] and anticardiolipin antibody [aCL]) were performed in 1,834 of 1,961 (93.5%) APASS-eligible WARSS patients. aCL assays were performed by ELISA using a polyclonal serum with subsequent isotyping and quantitation. Positive aCL was considered $\geq$23 GPL $\geq$15 MPL, and $\geq$2 APL units. LA assays included aPTT, and dilute Russell Viper Venom Time mixing studies and StuClot LA. Patients were classified as aPL+ if they were LA+ or aCL+. Preliminary Results: 743 (40.5%) patients were aPL+; 511 (27.9%) were aCL+, 357 (19.5%) were LA+ and 125 (16.8%) were positive for both. aCL isotype distribution was 350 (68.5%) IgG (303 low+; 38 moderate+ and 9 high+), 93 (18.2%) IgM (63 low+; 22 moderate+; 5 high+), 183 (35.8%) IgA (114 low+; 46 moderate+; 24 high+). aCL status was not significantly associated with age, race, education level, physical activity level, hypertension, diabetes mellitus, cigarette smoking, remote history of cerebral ischemia or other thrombotic event or index stroke subtype, but was significantly associated with gender. 43% of men vs. 37% of women were aPL+ (odds ratio 1.28, p=0.01). Conclusions: These results confirm that aPL are common, although predominantly in low titers, when several tests are used to evaluate for their presence in a large cohort of ischemic stroke patients. aPL appear to be independent of several important stroke risk factors. The number of patients who were positive for either aCL or LA but not both emphasizes the need to evaluate patients with a panel of aPL tests.
Invoking the modulation of parallel cellular pathways, the G-protein metabotropic glutamate receptors (mGluRs) and nitric oxide (NO) have been shown to require a host of cellular pathways to modulate neuronal programmed cell death (PCD). Since the cytosine proteases caspase-1 (ICE) and caspase-3 (CPP32) are mediators of neuronal PCD, we investigated whether these proteases negatively affect neuronal death when employed in experiments with OGD. Neurotoxicity in the presence of glutamate antagonists continued to inhibit neuronal death for 1 h, but became ineffective for 2 h. Following exposure to NO, cytosine protease activity progressively increased from a baseline of 2.1 ± 0.7 µmol/min/µg (ICE) and 3.3 ± 0.7 µmol/min/µg (CPP32) within the initial 6 h. Increase in cytosine protease activity was intimately associated with the induction of PCD, since application of either the ICE inhibitor YVAD-CHO or the CPP32 inhibitor DEVD-CHO significantly decreased the expression of PCD from approx. 73% (NO only) to approx. 23% (YVAD/NO or DEVD/NO). Activation of each of the mGluR subgroups (Group I (DHPG), II (LCCG-I), and III (L-AP4)) increased neuronal survival and prevented the induction of PCD during NO exposure. Yet, only the Group I agonist DHPG (750 µM) selectively decreased ICE and CPP32 activity from 7.9 ± 0.5 µmol/min/µg (NO only) in 2.3 ± 0.4 µmol/min/µg (DHPG/VD/NO) and 1.2 ± 0.4 µmol/min/µg (DHPG/DEVD/NO). Activation of mGluR subgroups I and III as well as mGluR antagonism with AIDA did not alter ICE or CPP32 activity. We demonstrate that NO induced neuronal PCD involves activation of the cytosine proteases ICE and CPP32, but that is the selective and unique modulation of cytosine protease activity by the Group I mGluR system that appears to offer a potential cellular target for the mGluR system to prevent ischemic neuronal injury.

**Oral Presentations**

**Group I Metabotropic Glutamate Receptors Selectively and Specifically Inhibit Cysteine Protease Activity During Ischemic Nitric Oxide Exposure**

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**Ischemic White Matter Injury in Brain Slices: A Functional and Structural Study**

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**Introduction.** Stroke causes irreversible damage to CNS white matter that may be initiated by reperfusion of volution.-gated Na+ channels in axons and AMPA receptors in oligodendrocytes. We developed a brain slice model to examine the pharmacology of ischemic glial and axonal injury in cerebral white matter. Methods. Coronal brain slices (400 µm thickness) including the corpus callosum were prepared from adult Swiss-Webster mice and exposed to oxygen-glucose deprivation (OGD) or normoxia for 15-60 min, followed by normoxic reperfusion for 9 hr. Resulting injury was assessed by immunolabeling with APC for oligodendrocytes, anti-GFAP for astrocytes and SM-E11 for axonal neurofilaments (NF). Dead cells were identified by Hoechst staining. Alterations in axonal integrity were imaged in slices labeled with DIO. Axonal conduction was monitored by extracellular recording of compound actions potentials across the corpus callosum. Results. Thirty min OGD resulted in a significant reduction in white matter APC (+)-oligodendrocytes (normoxia 67% vs OGD 8%), but not in GFAP (+) astrocytes (24 vs 26 %), accompanied by an increase in dead cell nuclei (control 5 vs OGD 44 %). Axonal NFL labeling was initially discontinuous and axonal retraction tails were observed. NF staining was fully lost at the end of 9 hr reperfusion. Compound action potentials disappeared well before the end of 30 min OGD and showed a poor initial recovery that vanished within 3-5 hr. Blockade of AMPA receptors with NBQX (but not NMDA receptor blockade with MK-801), prevented the loss of oligodendrocytes (control 8% vs NBQX 64%) and axonal NF staining. Keeping slices in Ca2+-free media during OGD considerably decreased oligodendrocyte loss (control 44% vs Ca2+-free 4%) and axonal injury. Blocking Na+ channels with TTX only partially prevented axonal NF staining but did not reduce loss of oligodendrocytes. Conclusions. OGD causes AMPA receptor and Ca2+-dependent oligodendrocyte death in brain white matter. Axonal damage involves Na+ and Ca2+ influx as well as AMPA receptor activation. This protection of oligodendrocytes may be an essential step in preventing axonal damage during white matter injury.
Conclusions: Activation of p38 Mitogen Activated Protein Kinase in Thrombin-Induced Brain Tolerance

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Background: Our recent studies have shown that prior intracerebral injection of thrombin or SIN-1 (a limited thrombolytic) attenuates the brain edema formation that results from either an intracerebral hemorrhage or an intracerebral injection of a large dose of thrombin. The aim of this study is to investigate whether such an early brain tolerance (thrombin precondioning) is involved in the activation of p44/42 mitogen activated protein (MAP) kinases. Methods: This study contained two parts. In the first part, rats received intracerebral infusions of either saline, one unit thrombin or one unit thrombin plus 1.3 µg PD 098059. After seven days, rats received a second intracerebral infusion of five units thrombin and brain water and ion contents were measured 24 hours later. Results: Western blot demonstrated that thrombin precondioning significantly reduced thrombin-induced brain edema. 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Clinical Outcomes are Similar when Stroke Neurologists and Emergency Room Physicians Prescribe Intravenous Tissue Plasminogen Activator for Acute Ischemic Stroke


A prospective study was conducted to monitor the safety and efficacy of intravenous t-PA treatment for acute ischemic stroke within a community network of 5 affiliated hospitals. Methods: Mercy Healthcare Sacramento established a stroke registry with prospectively collected data following FDA approval of t-PA for acute ischemic stroke. Results: Safety and efficacy data were collected on 43 patients. Stroke neurologists evaluated and treated 20 patients, and emergency medicine physicians evaluated and treated 23 patients after phone consultation with a neurologist and review of CT by radiology. Combined clinical results were directly comparable to the reported results of the NINDS trial (see figure). Median NIHSS score was 14, and 27% of patients had NIHSS > 20. Symptomatic intracerebral bleeding developed in 3 patients (7%). Two hemorrhages occurred (see figure). Median NIHSS score was 14, and 27% of patients had NIHSS evaluated and treated 20 patients, and emergency medicine physicians evaluated and treated 43 patients. Stroke neurologists of t-PA for acute ischemic with prospectively collected infrastuctures which can reduce the consequences of stroke. In patients with NIHSS > 20, and one occurred in an 87 y woman. Door-to-CT time was 44 in patients with NIHSS

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Background: It remains unclear whether intravenous (IV) or intra-arterial (IA) thrombolytic delivery is superior in acute ischemic stroke treatment. IV therapy is faster and more convenient, while IA therapy allows for mechanical disruption and higher drug concentration at the clot site. A protocol was developed combining both forms of delivery. Methods: Severe stroke patients (NIHSS≥15) with little or no CT changes were initially treated with IV TPA. IA thrombolysis was performed if there was a lack of clinical improvement and persistent occlusion identified on transcranial Doppler. Results: Combined therapy was performed on 10 occasions (9 pts; 4M, 5F; mean age 50.7 yrs, range 31-78); 1 patient had separate opposite hemisphere events and underwent combined IV/IA therapy twice. Mean baseline NIHSS was 24 (range 16-34). IA TPA (57.5±14 mg) was initiated 22±8 h after CT. CT-to-needle time was shorter between neurologists and ED physicians (48±10 vs 68±12) due to elimination of time waiting for radiology interpretation. Protocol violations (e.g.-dosing errors, heparin infusion, BP management, and diagnostic errors) were more frequently committed by ED physicians (33%) than by stroke neurologists (5%). Protocol violations ceased following an education program. During the acute hospital stay, 46% of patients were discharged directly home. 15% to acute inpatient rehabilitation, 21% to skilled nursing facilities, 10% to other hospitals for insurance reasons, and 8% died. Conclusions: The clinical results of the NINDS iv-t-PA stroke trial can be reproduced in the community. Outcomes were comparable whether the prescribing physician was a stroke neurologist or emergency medicine physician. Ongoing monitoring and education of emergency department staff is critical to achieve close adherence to t-PA treatment guidelines.

Effects of Aggressive Blood Pressure Reduction on Cerebral Blood Flow in Patients with Acute Intracerebral Hemorrhage

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Background: Aggressive pharmacologic blood pressure reduction (APBPR) in patients with severe hypertension and intracerebral hemorrhage (ICH) remains controversial. Theoretically, APBPR could reduce intracranial ICH and reduce adverse cardiovascular effects of hypertension, however, it could also decrease cerebral blood flow (CBF). We present 5 patients with acute ICH prospectively treated by our institution’s APBPR protocol using Xenon CT (XeCT) to assess resultant CBF changes. Methods: We identified all patients (10) with ICH undergoing 2 level, 2 blood pressure XeCT at our institution this past year. We excluded those imaged ≥24 hours post-ICH onset (4) or with hemorhagically transformed cerebral infarct (1). Systolic blood pressure (SBP) was first acutely reduced to 160-170mmHg, then to 130-140mmHg. A XeCT was obtained immediately after each reduction. Intrahematomal CBF, perihematomal edema (rim) CBF, regional cortical CBF, and global CBF were compared, respectively, at each SBP using proprietary software. A 20% change in CBF, or increase in the number of perithematomal cortical regions of interest below the ischemic threshold of 20 cc/100g/min was considered significant. Results: Median time from ICH onset to first XeCT was 5.5 hours. Mean ABC/2 ICH volume was 23cc. Mean (standard deviation) highest SBP prior to APBPR was 209 (12) mmHg. Three of 5 patients had a significant paradoxical increase in regional cortical CBF and 2 had no significant change. Two patients, however, had significant decreases in intra/perithematomal and/or global CBF. No patient neurologically deteriorated during treatment and no patient rebled in 24 hour followup CT. Conclusions: Defining the complex effect of APBPR on regional and local CBF in individual patients with acute ICH using XeCT is feasible and deserving of further investigation. Although all of our patients had improved or unchanged regional cortical CBF, two had significant declines in other CBF categories. Therefore, the indiscriminate use of APBPR without immediately available, patient-specific CBF data cannot currently be recommended.

ECCO 2000 Study of Citicoline for Treatment of Acute Ischemic Stroke: Effects on Infarct Volumes Measured by MRI

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Background: Several studies in animal models of ischemic stroke treated with citicoline alone or in combination with neuroprotectors or thrombolytics and two clinical investigations suggest that citicoline may result in smaller infarcts compared to the control-treatment. Previous double-blind placebo-controlled studies involving patients with ischemic stroke have suggested that citicoline-treated patients experienced better neurologic recovery than placebo-treated patients. Hypothesis: We hypothesized that treatment with citicoline 1000 mg b.i.d would limit infarct volume at week 12 as measured by MRI. Methods: Approximately 900 patients with a clinical diagnosis of ischemic stroke referable to the MCA distribution within 6 h. of symptom onset of stroke during an 8 week, baseline NIHSS ≥ 8, pro-stroke Rankin ≤ 2, other limiting or medically significant disease were randomized (1:1) at 125 investigator centers to 6 weeks of citicoline 1000 mg b.i.d or matching placebo with the final assessment at week 12 post-stroke. NIHSS, Barthel Index, Rankin Scale, National Institutes of Health Stroke Scale resource usage, week 12 T2 MRIs at week 12. At designated sub-study centers baseline diffusion weighted (DW) MRIs were also collected in approximately 175 patients. Secondary outcomes were week 12 infarct volume and lesion growth from baseline (DW-MRI study only). Results and Conclusions. Patient recruitment was completed in August, 1999. Final data collection, and verification are ongoing. The DW-MRI substudy on the effects of citicoline treatment on lesion growth from baseline, the MRI evaluation of the effect of citicoline on final infarct volume, and the relationship of these MRI findings to changes on the NIHSS will be presented and discussed in light of earlier data.

The Incidence and Occurrence of Total (First-Ever and Recurrent) Stroke

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Background and Purpose: It has recently been hypothesized that the figure of approximately half a million strokes substantially underestimates the actual annual stroke burden for the United States. The majority of previously reported studies on the epidemiology of stroke used relatively small and homogeneous population-based stroke registries. This study was designed to estimate the occurrence, incidence and characteristics of total (first-ever and recurrent) stroke using a large electronic administrative claims database representative of all 1995 US inpatient discharges. Methods: We used the Nationwide Inpatient Sample of the Healthcare Cost and Utilization Project, release 4, which contains approximately 20 percent of all 1995 US inpatient discharges. Since the accuracy of ICD-9-CM coding is sub-optimal, we performed a literature review of ICD-9-CM 430-438 validation studies. The pooled results from the literature review were used to make appropriate adjustments in the analysis to correct for some of the inaccuracies of the diagnostic codes. Results: There were 682,000 hospitalized strokes (0% CI, 666,000 to 704,000) and an estimated 68,000 non-hospitalized strokes. The overall incidence rate for total stroke (first-ever and recurrent) was 259 per 100,000. Conclusion: We conservatively estimate that there were at least 750,000 firstever or recurrent strokes in 1995. New findings during follow-up of these patients highlight the importance of preventive measures for a disease that has identifiable and modifiable risk factors and for the development of new and improved treatment strategies along with infrastructures which can reduce the consequences of stroke.
Moderate Induced Hypothermia Following Cardiac Arrest - a Safety and Feasibility Trial

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Background: No treatment exists for ischemic brain injury following cardiac arrest (CA). Anecdotal reports suggest that prolonged CA can be survived following accidental immersion in near freezing water. Moderate Induced Hypothermia (MIH) is especially neuroprotective in animal models of global ischemia. Methods: A safety and feasibility trial was designed to evaluate MIH following CA. Inclusion criteria included: return of spontaneous circulation within 60 minutes of ACLS, hypothermia initiated within 90 minutes, persistent coma, and lack of acute myocardial infarction or unstable dysrhythmias. Hypothermia was induced with cooling blankets, ice water gastric lavage, and ice packs. 33°C was maintained for 24 hours, followed by passive rewarming of 1°C per 4 hours. Results: Seven patients were prospectively enrolled from July 97-July 99. Mean time to restoration of spontaneous circulation was 28 minutes (range 9-39); initiation of hypothermia was 92 minutes (range 65-120) after achieving 33°C. Three patients (75%) survived for 24 hours, followed by passive rewarming of 1°C per 4 hours. Seven patients were enrolled. Results: Five patients died following withdrawal of care after showing no neurological improvement upon rewarming. Conclusion: MIH following CA is feasible and appears to be safe, but may be associated with an increased incidence of status epilepticus. Although our conclusions are limited by lack of a control group, historical reports suggest that our profoundly affected cohort would have a grave prognosis. The dramatic recovery of 2 of our 7 patients warrants further evaluation of MIH following CA.

Dramatic Improvement During Intravenous TPA Infusion Combined with TCD Monitoring is Associated With Complete Recovery

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Background: Clot dissolution with tissue plasminogen activator (TPA) can lead to early clinical recovery. Transcranial Doppler (TCD) can determine arterial occlusion and monitor recanalization during thrombolysis. Methods: Patients receiving intravenous TPA were monitored during infusion using portable TCD (Multigon 500M, DWL). Residual flow signals were obtained from clot location identified by TCD. NIHSS scores were obtained before and after TPA infusion. Results: 31 patients were studied (age 68±17 years, baseline NIHSS 18±5.6, TPA bolus at 134±60 min from symptom onset). TCD monitoring started at 125±57 min and continued for the duration of infusion. MCA was occluded in 24 patients, ICA-7, basilar-2, multiple occlusions-5, 3 patients had no windows. Recanalization on TCD was found in 18/31 patients at 50±19 min after bolus. Complete recanalization in 8 (26%) and partial in 10 (32%) patients. Dramatic improvement during TPA infusion (NIHSS < 3) occurred in 7 patients (23%); all had complete recanalization (baseline NIHSS range 7-22). Lack of improvement or worsening was associated with no recanalization, late recanalization, or re-occlusion (Table, p<0.01). Angiographic verification was obtained in 61% of patients. Conclusions: Dramatic improvement during TPA therapy occurred in 23% of all patients. Recovery is associated with recanalization while no early improvement indicates persisting occlusion or re-occlusion. Ultrasonic energy transmission by TCD monitoring may improve more clot surface to TPA and facilitate thrombolysis.

Rebleeding Leads to Poor Outcome in Ultra Early Cricotomi for Intracerebral Hemorrhage

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Background/Objective: We previously reported the results of a single-center randomized clinical trial comparing best medical therapy with surgical hematoma evacuation within 12 hours of symptom onset for intracerebral hemorrhage (ICH). At six months this pilot study demonstrated a modest, non-significant benefit for surgery compared with medical treatment in mortality (19 vs. 24%), and 10 point improvement in median Barthel score in survivors (65 vs. 55). We report here the new surgery arm of the study undertaken to determine if this benefit could be increased if surgery were performed within 4 hours of symptom onset. Methods: Adult patients were prospectively enrolled with spontaneous supratentorial ICH > 20 ml. Glasgow Coma Scale 3-5, and informed consent signed by patient or family. Exclusion criteria were: aneurysm or AVM, coagulopathy, intraventricular blood > 1/2 of the lateral ventricles, and a severe coexisting condition. Cranostomy and clot evacuation were commenced within 4 hours of symptom onset in all cases. Follow-up imaging was performed within 24 hours and mortality and functional outcome were measured at 6 months. Results: The study was stopped after a planned interim analysis of 11 enrolled subjects. There were 7 women and 4 men; median age was 57; median time from symptom onset to ER arrival was 47 minutes (15-132); median time to surgery was 180 minutes (95-240); median hematoma volume was 40 cc (23-84); median NIHSS and GCS was 18 (14-30); 6 and (6-15); respectively. 10 hematomas were parietal and 10 lobar. 6 month mortality was 36% and median Barthel was 25 (range 0-80) in survivors. Post-op rebleeding occurred in three patients all of whom died. A relationship between post-op rebleeding and mortality was apparent (p<0.03). Only two patients had completely successful hematoma evacuations (<5 cc residual). These two patients were the only ones to have 6 month Bartheles's > 75. Conclusion: Surgical clot evacuation within 4 hours had a high incidence of rebleeding indicating difficulty with surgical hemostasis. Patients in the 4 hour surgery arm had worse outcomes than those operated on within 12 hours or those treated with best medical therapy.

Differences in the Time Course of Risk of Ischaemic Stroke DistoI to Symptomatic and Asymptomatic Carotid Stenoses: The Asymptomatic Carotid Stenosis Study

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Background: The Asymptomatic Carotid Stenosis Study (ACSS) is a collaborative database of detailed individual patient data from clinical trials and cohort studies of patients with an asymptomatic carotid stenosis. Data on nearly 10,000 patients will be collated. The study aims to document the detailed natural history of asymptomatic carotid stenosis and determine prognostic factors for the risk of ipsilateral ischaemic stroke (IIS). Methods: This analysis is confined to 6269 patients with imaging of an asymptomatic carotid artery in whom there was a recently symptomatic stenosis of the contralateral carotid artery. The absolute risk of IIS distal to the stenosis and the rate of change of risk with time are compared for asymptomatic and symptomatic stenoses. Results: 1786 (29%) patients had >50% asymptomatic carotid stenosis. Of these, 316 had 80-99% stenosis and 247 had asymptomatic carotid occlusion. The time course of occurrence of IIS on follow-up distal to the asymptomatic stenosis was linear, whereas the time course of stroke distal to symptomatic stenosis was highly non-linear and decreased with time. The three year risk of IIS distal to an 80-99% symptomatic stenosis was considerably higher than that distal to an 80-99% asymptomatic stenosis - 21% (95% CI = 17 - 25) vs 8% (5 - 11), whereas the 8 year risk were comparable 25% (21-29) vs 9% (6 - 14 - 26). Conclusions: The risk of IIS distal to a recently symptomatic stenosis is high during the first three years but then levels off. The risk of IIS distal to the contralateral asymptomatic stenosis increases linearly with time and is comparable to that distal to the symptomatic stenosis after eight years. Further work is required to determine whether the long term risk distal to a truly asymptomatic stenosis is equally high.

Risk Factors for Lacunar Stroke: A Case-Control Transesophageal Echocardiographic Study

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Recently aortic atheroma has been shown to be an independent risk factor for ischemic stroke. However, little is known about the relationship between lacunar stroke and aortic atheroma. We studied 62 consecutive patients with first-ever lacunar stroke and 202 normal controls using transesophageal echocardiography and duplex ultrasonography in a case-control study to reassess the independent risk factors for lacunar stroke. In addition to vascular risk factors, we considered the role of extracranial carotid artery stenosis, aortic atheroma and cardioembolism. Hypertension (73% vs. 34%; P<0.001), smoking (75% vs. 4%; P<0.001), diastolic hypertension (75% vs. 4%; P<0.001), proximal and parietal aortic atheroma (plaque ≥ 5mm) (20% vs. 4%; P<0.001) were significantly more frequent in patients with lacunar stroke. These four variables and two further variables of clinical importance (carotid stenosis, and cardiac embolic source) were inserted into a multivariate analysis. Hypertension (P<0.001), smoking (P=0.001), and aortic arch atheroma (P=0.006) significantly increased the risk of lacunar stroke. In addition to the established risk factors of hypertension and smoking, aortic atheroma may be independently to the occurrence of lacunar stroke. Whether this is by the association of atheroma in large and small vessels, or directly caused by the aorta acting as a source of embolism, is uncertain.
Familial History of Stroke is a Risk Factor for Stroke. The Rotterdam Study
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Objectives: Although family history is perceived to be an independent risk factor for stroke, little information is available on this association. We investigated the relationship between family history and stroke outcome in the study area. This analysis concerns 7603 subjects, who were free from stroke at baseline and had a complete follow-up.

Methods: This study was conducted in the framework of the Rotterdam Study, an ongoing prospective population-based cohort study for which all inhabitants aged 55 years or over, living in a suburb of Rotterdam, The Netherlands, were invited. Baseline data collection was performed between 1990 and 1993. Once subjects enter the study they are continuously monitored and followed through linkage with automated medical records of the general practitioners working in the study area. This analysis concerns 7603 subjects, who were free from stroke at baseline and had a complete follow-up. Results: The mean follow-up time was 4.5 years and 533 first stroke occurred during the follow-up. History of stroke in any first degree relatives increased the risk of stroke statistically significantly, relative risk after adjustment for age, gender, hypertension, smoking habit, total cholesterol, hypertension, diabetes mellitus, coronary heart disease was 1.3 (95% confidence interval 1.0, 1.64). The relative risk in subjects who had more than one relative with history of stroke was 1.5 (95% confidence interval 1.0, 2.4).

Discussion: Our findings suggest that genetic susceptibility does play a role in the etiology of stroke.

The Impact of Disseminated Atherosclerosis on Survival Following Acute Stroke
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A thorough understanding of the survival following an acute stroke and of its determinants is essential not only for physicians but also for cost-effectiveness analyses that gauge the value of new treatments. Method: Survival following an ischemic stroke (IS) was evaluated using the health care records of 18,704 residents of Saskatchewan, Canada who suffered a stroke between 1990-1995. Data on patient characteristics and medical history were available retrospectively to January, 1980 and follow-up was complete to March, 1998. Kaplan-Meier survival curves were estimated and Cox proportional hazards analyses were conducted to examine the effect of diffuse atherosclerosis and other potential risk factors. Results: More than half (52%) of the patients were female and most (68%) were over 70 years of age at the time of stroke. Within 30 days, 100% of patients had died. At 90 days, 14.3% were dead, followed by 22.2%, 36.3% and 47.7% at 1, 3, and 5 years. Both 30 day mortality and post-30 day mortality was 1.54 times higher among patients with coronary or peripheral arterial involvement. The risk of dying was 44% higher in this population in Cox proportional hazards analyses controlling for age >65 years, sex, history of diabetes and prior stroke.

Conclusions: Patients with disseminated atherosclerosis are at considerably higher risk of dying following stroke. Thus, involvement of multiple vascular beds must be considered in determining the overall value of newer therapies.

MR Signatures of Infection vs. Salvageable Penumbra in Acute Human Stroke: A Preliminary Model
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Background: There is a recognized need for objective imaging methods to identify the best candidates for thrombolytic treatment. We have previously reported reversal of diffusion-weighted MRI (DWI) abnormalities in humans with intra-arterial thrombolytic therapy, suggesting that early DWI alteration alone is not an indicator of irreversible injury. We therefore sought to employ both diffusion and perfusion data to identify MR signatures of irreversible vs. reversible brain ischemia. Methods: Pretreatment and 7 day post-treatment T2/diffusion/perfusion MRIs were obtained in patients with large vessel anterior circulation occlusions successfully recanalized with intra-arterial thrombolysis. An automated image registration technique was employed to coregister pretreatment and 7 day images to allow a voxel-by-voxel analysis of MR data. Final infarct volume was outlined on day 7 T2-weighted and DWI sequences. A stepwise discriminant analysis was performed on 4 patients using baseline ADC, MTT, CBV, and CBF values to identify tissue that evolved to infarction vs. salvageable ischemic penumbra.

Results: Discriminant models incorporating pretreatment diffusion and perfusion variables correctly classified tissue fate (infarct vs. noninfarct) in 78% of voxels (range 68-88%). Both pretreatment diffusion and perfusion variables contributed independently to the models, with a greater contribution from the perfusion data. Within the initial perfusion deficit, voxels with an ADC value less than 500 mm²/sec had a 75% likelihood of proceeding to infarction, and voxels with an ADC value less than 620 mm²/sec had a 67% likelihood.

Conclusions: Models incorporating pretreatment MR perfusion and ADC variables can distinguish irreversibly injured from still salvageable tissue in patients undergoing intra-arterial thrombolytic therapy. This type of model may become a useful tool to identify the best candidates for thrombolytic therapy in the future.
Impact of Diffusion Weighted MRI (DWI) on Patient Management: Is It of Practical Value?

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Background: Although DWI provides unique information in stroke patients, the practical value of this test is disputed. Few data are available regarding the actual impact of DWI on patient management, particularly beyond the hyperacute (<24h) time period. This information is of critical importance in evaluating the true usefulness of this new technology. Methods: Patients admitted to the Stanford Stroke Service with stroke-like signs and symptoms were prospectively evaluated using traditional diagnostic techniques including history and physical examination, CT scan, and conventional MRI. The treating stroke neurologist then identified the clinical impression based upon these initial diagnostic tests, and subsequently after the DWI was completed. Changes in diagnostic impression, subsequent evaluation and treatment due to the DWI findings were then recorded. Results: 39 patients were evaluated. DWI was performed a mean of 28h (range 5-96h) after symptom onset. The diagnostic impression was altered in 41% (16/39) patients. The most common diagnostic change was from a non-embolic to an embolic cause (8/16; 50%). In 33% (13/39) DWI findings resulted in a major change in final treatment. DWI influenced changes in treatment were evident up to 96h after symptom onset. In addition, clinical confidence in the diagnosis was improved in 13/39 (33%). Of these patients, treatment was subsequently changed in 5/13 (38%). The most common change in treatment was from an antplatelet agent to warfarin (4/13 or 31%). The influence of DWI on diagnosis and treatment was not significantly different based upon initial stroke subtype classification (cortical, subcortical, posterior circulation), initial stroke syndrome classification (stroke, TIA or no-stroke), time to MRI (>24 vs <24h), or duration of ischemic symptoms. Conclusions: DWI findings influence not only the initial clinical impression, but also the subsequent management of many patients with stroke-like symptoms. It can be useful beyond 24h and potentially up to 96h after symptom onset.

Progression of Human Infarct by DW- and Perfusion-MRI and the Time Window for Acute Stroke Intervention

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Background: Many posit that the time window for treatment of ischemic stroke is 3 h or less based on animal models and the results of the four recent clinical studies of tPA. PROACT-II findings suggest that selected patients treated at longer times can benefit. Few direct data are available to systematically evaluate the evolution of human ischemic infarct as related to time from symptom onset. Methods, Diffusion Weighted MRI (DWI), Perfusion MRI, and MRA data were collected using common procedures. Patients had clinical signs of an MCA ischemic stroke within 24 h of onset, an NIHSS ≥ 5, a DW lesion ≥ 1 cm and without medical or MRI contraindications. Of 100 cases entered 81 patients had baseline and week 12 data; 19 patients had missing follow-up scans due to death (13), or other reasons. Baseline hyperperfusion volume, DW lesion volume, “penumbra” (Hyperperfusion-DWI lesion volume), MRA occlusion (none, partial, total), and final (i.e., week 12) in-stent volume, volume of DW lesion or penumbra converted to infarct, were extracted from the MRI data. Patients were classified according to time from symptom onset in 3 hr. intervals (i.e., 0-3, 3-6, etc. to 21-24h) and the percent of patients in each time-cohort with a penumbra, etc. as well as the lesion volumes were compared against time from stroke. Results, Among the baseline variables examined only the percent of patients with a penumbra (r=−0.6, p<0.05) exhibited a significant inverse correlation with time post stroke; penumbra volume tended (r=−0.5; p<0.1) to decrease with time. Approximately 82% of patients presenting in 0-3 h had a penumbra decreasing to 43% of patients at 21-24 h. A total occlusion by MRA was strongly (r=−0.7; p<0.02) associated with existence of a penumbra and penumbra volume (r=−0.7; p<0.05). Conclusions, We acknowledge the limitations of small samples and interpretation of these MRI measures. These findings suggest that selected patients presenting ≥ 3 to 24 h may potentially benefit from thrombolytic or neuroprotective therapy. A brief MRI evaluation could identify such patients for clinical trials, or ultimately treatment, expanding the utility of these therapies.

Magnetic Resonance Perfusion Imaging in Acute Ischemic Stroke Using Continuous Arterial Spin Labeling

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Background: The rationale behind thrombolytic therapy in ischemic stroke is penumbral salvage by rapid reperfusion. We used magnetic resonance perfusion (PI) and diffusion-weighted imaging (DWI) to examine the hypothesis that spontaneous reperfusion limits infarct expansion and improves stroke outcome. Methods: Twenty-eight patients with MCA territory stroke were studied with PI and DWI within 12 hours of stroke onset (19 patients within 6 hours). None received thrombolytic therapy. MRI studies were repeated at day 4, with T2-weighted imaging (T2-WI) at day 90. Clinical scores (Canadian neurological scale, Barthel Index and Rankin scale) were performed in conjunction with the imaging studies and were compared with the MRI lesion volumes. Results: Eighty-one MR studies were obtained. Major spontaneous reperfusion (>90% reduction in PI lesion by subacute study) occurred in 45% of patients and was associated with better clinical outcome and smaller final infarct size (p<0.05). Patients with major reperfusion had a 67% attenuation of subacute DWI lesion expansion and 50% attenuation of total (acute DWI - outcome T2-WI) infarct expansion (p<0.05). Tissue salvage of greater than 25%, calculated as (acute PI - outcome T2-WI)/acute PI X 100, occurred in 26% patients and was associated with reduced infarct expansion and improved stroke outcome (p<0.05). Conclusions: In acute ischemic stroke, major spontaneous reperfusion and salvage of ≥25% of hypoperfused tissue at risk of infarction improve stroke outcome and should be used as surrogate endpoints in clinical trials.

Reperfusion Attenuates Infarct Growth and Improves Stroke Outcome: A Combined PI/DWI Study

Peter Alan Barber, David G Darby, Qing Yang, Mark W Parsons, Patricia M Desmond, Richard P Gertzey, Ting Li, Brian M Tress, Stephen M Davis, Royal Melbourne Hosp, Parkville, VIC Australia

Background: The rationale behind thrombolytic therapy in ischemic stroke is penumbral salvage by rapid reperfusion. We used magnetic resonance perfusion (PI) and diffusion-weighted imaging (DWI) to examine the hypothesis that spontaneous reperfusion limits infarct expansion and improves stroke outcome. Methods: Twenty-eight patients with MCA territory stroke were studied with PI and DWI within 12 hours of stroke onset (19 patients within 6 hours). None received thrombolytic therapy. MRI studies were repeated at day 4, with T2-weighted imaging (T2-WI) at day 90. Clinical scores (Canadian neurological scale, Barthel Index and Rankin scale) were performed in conjunction with the imaging studies and were compared with the MRI lesion volumes. Results: Eighty-one MR studies were obtained. Major spontaneous reperfusion (>90% reduction in PI lesion by subacute study) occurred in 45% of patients and was associated with better clinical outcome and smaller final infarct size (p<0.05). Patients with major reperfusion had a 67% attenuation of subacute DWI lesion expansion and 50% attenuation of total (acute DWI - outcome T2-WI) infarct expansion (p<0.05). Tissue salvage of greater than 25%, calculated as (acute PI - outcome T2-WI)/acute PI X 100, occurred in 26% patients and was associated with reduced infarct expansion and improved stroke outcome (p<0.05). Conclusions: In acute ischemic stroke, major spontaneous reperfusion and salvage of ≥25% of hypoperfused tissue at risk of infarction improve stroke outcome and should be used as surrogate endpoints in clinical trials.

Friday-Afternoon

Prognostic Value of Diffusion-Weighted Imaging in Acute Stroke

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The early prediction of outcome after stroke may be valuable for decisions concerning acute stroke therapy, entry into drug trials and discharge planning. A number of clinical outcome predictors have been identified but much variation in outcome among patients with initially similar deficits may occur. We wished to determine if the ischemic lesion volume on magnetic resonance (MR) diffusion-weighted imaging (DWI) added independent prognostic information after adjustment for established clinical outcome predictors was made. Sixty-seven patients had undergone DWI within 48 hours of stroke onset. Logistic regression analyses were performed, the outcome variable being the presence of a good outcome (Barthel score ≥90) at 1-6 months or not. The predictors that were evaluated were age, sex, time of MR study after the onset of symptoms, history of hypertension, history of heart disease, NIH stroke scale score, entry into a drug trial and DWI lesion volume. In univariate analyses, DWI lesion volume (p<0.0007), NIH scale (p=0.0007) and time of MR study after the onset of symptoms (p=0.008) correlated significantly with outcome. In multiple logistic regression analysis the significant predictors were NIH score (p=0.001), time of MR study (p=0.02) and DWI lesion volume (p=0.04). After adjustment for age, NIH score and time of MR study, a DWI lesion volume ≤25ml was associated with a significantly greater likelihood of a good outcome (odds ratio ≥5.8, 95% CI = 1.1, 25.5). The predictive rule developed from the model identified patients with a good outcome with 78% sensitivity, 87% specificity and a positive predictive value of 89%. The ability of the model to give independent prognostic information during the first 48 hours of stroke should find applications in acute stroke management.

Withdrawn

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Cyclooxygenase-2 Contributes to Functional Hyperemia in Somatosensory Cortex Costantino Iadecola, Kiyoshi Niwa, Eiichi Arachi, Univ of Minnesota, Minneapolis, MN; Scott Sheng, Myriad Genetics Inc, Salt Lake City, UT; Elizabeth Ross, Univ of Minnesota, Minneapolis, MN

The prostaglandin-synthesizing enzyme cyclooxygenase-2 (COX-2) is expressed in a selected population of neocortical neurons, wherein it is localized in dendritic spines (PNAS 93:2317, 1996). Evidence suggests that COX-2 is involved in synaptic signaling and activity-dependent gene expression. In this study, we tested the hypothesis that COX-2 participates in the mechanisms coupling synaptic activity to blood flow in brain. Mice were anesthetized with urethane-chloralose and artificially ventilated. Arterial blood pressure and blood gases were controlled. The right vibrissae were mechanically stimulated and cerebral blood flow (CBF) was recorded in the contralateral whisker barrel cortex by laser-Doppler flowmetry. Cerebral blood glucose utilization (CGU) was assessed by the 2-deoxyglucose method with autoradiography. In C57BL/6 mice (n=12), vibriral stimulation increased CBF in the somatosensory cortex by 25% (mean±SE; p<0.01). Superfusion of the somatosensory cortex with the selective COX-2 inhibitor NS-398 (n=5) attenuated the increase in CBF dose-dependently (r=48.5% after 100 μM; p<0.01). However, NS-398 did not affect resting CBF or the CBF increase produced by hypercapnia (r=50.60 mM; n=6) and by cortical application of acetylcholine (ACH; 10 μM; n=6) or bradykinin (BK, 50 μM, n=6; p<0.05 from Ringer). The increase in CBF evoked by vibriral stimulation was 37.2% smaller (p<0.01) in mice with deletion of the COX-2 gene (COX-2 -/-) vs A/B wildtype mice (COX-2 +/+) mice. The increases in CBF produced by hypercapnia, ACh or BK were, however, not affected in COX-2 -/- mice (n=6/group). Resting CGU and the increase in CGU produced by vibriral stimulation in the somatosensory cortex did not differ in COX-2 +/+ (n=6) and COX-2 -/- mice (n=6; p>0.05). Suggesting that the impaired flow response was not a consequence of reduced neural activity in the null mice. We conclude that COX-2 is required for the full expression of the cerebral hemodynamic response evoked by vibriral stimulation. The expression of COX-2 in selected neurons might be a critical link between synaptic activity and cerebral perfusion in the central nervous system.
**Oral Presentations**

**Vascular Effects of Serotonin: Role of Gender and Effects of eNOS Deficiency**

Frank M Faraci, Kathryn G Lamping, Univ of Iowa, Iowa City, IA

Serotonin has been implicated in several pathophysiological conditions involving vasospasm and ischemia. Although constrictor responses of carotid and cerebral arteries to serotonin are increased in disease states including inhomogeneous and hyperreactive plaques, the account for this increase are not clear. We examined the hypothesis that contraction of the carotid artery to serotonin is normally inhibited by endothelial NO-synthese (eNOS) and thus enhanced by eNOS deficiency. 

**Results**: No substantial increase in eNOS expression was noted in men after temporary ischemia. 

**Conclusion**: Constrictor responses of the carotid artery to serotonin increased by 38% in male eNOS -/- mice, and more than doubled in female eNOS -/- mice (P<0.001). In contrast, maximal vasodilator responses to serotonin in eNOS -/- mice, and increased 5.4-fold in male eNOS -/- mice compared to wild-type (P<0.001). In contrast, maximal vasodilator responses to serotonin in eNOS -/- mice, and increased 5.4-fold in male eNOS -/- mice compared to wild-type (P<0.001). In contrast, maximal vasodilator responses to serotonin in eNOS -/- mice, and increased 5.4-fold in male eNOS -/- mice compared to wild-type (P<0.001). In contrast, maximal vasodilator responses to serotonin in eNOS -/- mice, and increased 5.4-fold in male eNOS -/- mice compared to wild-type (P<0.001). In contrast, maximal vasodilator responses to serotonin in eNOS -/- mice, and increased 5.4-fold in male eNOS -/- mice compared to wild-type (P<0.001). 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**Conclusions**: These findings suggest that constrictor responses of the carotid artery to serotonin are influenced by gender, eNOS deficiency is associated with increased vasodilator vasoconstrictor responses to serotonin, particularly in female mice, providing direct evidence that eNOS is a major determinant of vascular effects of serotonin. The results with eNOS +/- mice suggests that a 'gene-dosing' effect is present for vascular responses to serotonin.
Use of Antithrombotic Therapy Prior to a Stroke Admission
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Objective. The use of antithrombotic therapies plays a central role in stroke prevention therapy. Data from myocardial infarction suggest that antithrombotic therapy is underutilized, however, relatively little data exists for utilization patterns for stroke therapies. We examined medications prior to admission as a measure of stroke prevention practices in the community, especially among groups at known high risk for stroke. Methods. Data were collected (chart review) for up to 30 consecutive cases of acute ischemic stroke at each of 36 institutions beginning January 1, 1996 as part of the University HealthSystem Consortium Ischemic Stroke Benchmarking Project. Abstracted data included prior medical history and medication prior to admission. Results. 961 cases were abstracted and included in the study dataset (52% male, 40% aged <65 years, 25% aged 65-74 years, and 35% aged 75+ years, 66% Caucasian). Overall, 29.7% (285) were on aspirin, 5% (29) ticlopidine, 2.3% (22) dipyridamole, 8.8% (85) warfarin, and 1% (10) heparin. There were 59.2% (569) who were on none of these therapies. There were 34% (323) with a documented prior stroke or TIA. Of these, 41.2% (133) were on aspirin, 6.8% (22) ticlopidine, 2.5% (8) dipyridamole; 15.5% (50) warfarin; and 1.9% (6) heparin. There were 38.4% (124) who were on none of these therapies. For those with prior MIA/angiography, atrial fibrillation, or peripheral vascular disease, the rate of no therapy were similar with 40% (58/146), 38% (42/111), and 42% (21/50), respectively.

Among examined patient characteristics: age 65 or greater, 60% (576/961), (RR = 1.3; 95% CI: 1.1-1.5); Caucasian, 66% (630/961), (RR = 1.3; 95% CI: 1.1-1.6); and the presence of at least one significant comorbid disease, 52% (496/961) (RR = 2.7; 95% CI: 2.3 3.3), all were associated with higher rates of antithrombotic therapy. Conclusion. The low rate of antithrombotic therapy prior to admission, even among those with documented previous stroke/TIA, myocardial infarction/angiography, atrial fibrillation, or PVD strongly suggest that secondary prevention therapies are underutilized. The increased use of antithrombotic therapies represents an excellent opportunity to promote stroke prevention.

Background/Purpose: Several previous studies have reported on the benefits of carotid endarterectomy (CEA) contralateral to carotid occlusion with mixed results. None of these were randomized studies except for the NASCET study. The purpose of this study is to analyze the perioperative and late stroke rates of these patients from a randomized trial.

Methods and Patients: In the NASCET (153 patients) trial that randomized patients with ischemic stroke secondary to carotid stenosis to medical therapy or CEA contralateral to a symptomatic stenosis, the late results were reported. The study included 387 patients with a symptomatic ipsilateral carotid stenosis ≥60% (55% disease ≤80%). All patients underwent a carotid Doppler ultrasound and angiographic evaluation. The average age of the patients was 70 years (±10.3 years). After randomization, 387 patients were included in the analysis, 193 in the medical therapy group and 194 in the CEA group. The patients were followed up to 5 years. The incidence of late stroke and death rate was compared using the log rank test.

Results: The cumulative incidence of ipsilateral stroke at 5 years was 9% (16.6% in the medical therapy group vs 4.2% in the CEA group, p = 0.001). The cumulative incidence of ipsilateral death at 5 years was 11% (20.9% in the medical therapy group vs 6.7% in the CEA group, p = 0.006). The stroke-free survival rates at 5 years were 86.1% vs 92.8% (p = 0.008). The late cumulative incidence of ipsilateral death and stroke at 5 years was 14.2% (25.3% in the medical therapy group vs 9.3% in the CEA group, p = 0.001). The late cumulative incidence of stroke and all events at 5 years was 17.1% (29.5% in the medical therapy group vs 11.5% in the CEA group, p = 0.008).

Conclusion: The use of CEA for the contralateral carotid artery is associated with a lower risk of ipsilateral stroke and improved stroke-free survival at 5 years in symptomatic patients with contralateral carotid stenosis compared to medical therapy. These results support the use of CEA for contralateral carotid stenosis.
**Telemedicine Is a Feasible Way of Assessing and Managing Patients with Acute Stroke and Transient Ischemic Attacks**

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We are evaluating telemedicine as a means of improving the care of patients with neurological problems admitted to hospitals which do not have a neurologist on site. This study describes the outcomes of patients with stroke and transient ischemic attacks (TIAs) in a larger study of all adult patients with stroke. An interactive videoconferencing link, transmitting at 384 kbit/s, was set up between a neurological centre and a small rural hospital 80 miles away. All patients who presented to the rural hospital with neurological symptoms were eligible for inclusion to have a videocouction with a neurologist at the neurological centre. In the 4-month period 120 patients were studied of whom 25 had a diagnosis of stroke (21%) and 6 of TIA (5%). None of these patients had videocouction within 3 hours of onset of symptoms. The mean hospital to ER arrival time was 15 days for those with stroke and 4 days for TIA. For the 4 month period before the study, the respective hospital stays were 33 and 4 days. Follow-up of the study patients by face-to-face consultation at 3 months did not result in any change to the original diagnosis. We conclude that patients with stroke and TIA can be assessed accurately in the acute period by neurologists using telemedicine. For hospitals without neurological cover this may result in more efficient use of inpatient resources and provide greater access to therapies for acute stroke.

**Who Are the Appropriate Targets to Increase FDA Approved Acute Stroke Therapy?**

The TLL Temple Foundation Stroke Project

Lewis B Morgenstern, Univ of Texas, Houston, Houston, TX; Theodore H Wein, Arada Kunyosying, Lara Staub, L K Bartholomew, Susan Hickenbottom, Janet Groff, Lewis B Morgenstern, Univ of Texas, Houston, Houston, TX; Theodore H Wein, Lara Staub, Robert A Felberg, Theodore H Wein, Arada Kunyosying, Lara Staub, L K Bartholomew, Susan Hickenbottom, Janet Groff, Lewis B Morgenstern, Univ of Texas, Houston, Houston, TX

**Background/Objective:** The TLL Temple Foundation is a prospective, community-based surveillance and active intervention program for acute stroke treatment in non-urban East Texas. We report here surveillance of acute stroke treatment for the baseline period January-October, 1998 to delineate the most important targets for community intervention programs to increase acute stroke therapy. **Methods:** Subjects were prospectively identified through active and passive screening of the 5 hospitals in Angelina, Nacogdoches and Shelby counties. These counties were chosen since they are representative of the demographic and socioeconomic characteristics of non-urban Texas. The total population of the three counties was 151,207 (73.9% non Hispanic white, 17% African American, 10% Hispanic). Medical records were reviewed and patients and families interviewed. Cases were validated by fellowship-trained stroke neurologists based on TOAST criteria. **Results:** 2117 patients were screened with potential inclusion to the ER with symptoms suggestive of acute stroke. Of these, 225 were identified as stroke. 57% were women. 3 patients received IV-pa in (1.9%). All were appropriate candidates. 8 patients were eligible, but were not treated (3.6%). The most common reasons for not receiving IV-pa was time >/= 3 hours to hospital arrival (n=85, 37%) (delay time was considered a reason for exclusion only if no other exclusion applied) and rapidly improving symptoms (n=73, 32%). In hospital delay to treatment was found to prevent treatment in 12 (5.3%). Median delay time to hospital arrival was 3.5 hours (Q3-Q1 23 hours). **Conclusions:** Two years after approval of IV-pa for acute ischemic stroke only 1% of stroke patients received this therapy in a representative non-urban community. Rotational delay in hospital arrival rather than delay in hospital triage and treatment appears most valuable in this community. Educational intervention programs aimed at increasing FDA approved stroke treatment may also wish to target emergency physicians to expand treatment of eligible patients.
Predictors of 6-Month Functional Outcome After Stroke: The Northern Manhattan Stroke Study
Laura Lennihan, Bernadette M Boden-Albala, Tanja Rundek, I-Feng Lin, Myunghee Paik, Ralph L. Sacco, Columbia Univ, NY, NY

Objective: To determine predictors of 6-month poststroke functional status in a population-based, prospectively acquired cohort of patients with first stroke. Background: Identification of predictors of functional outcome after stroke is needed to elucidate mechanisms of and to assess interventions to enhance neurological recovery after stroke. Reported predictors of stroke outcome include age, stroke severity, previous stroke, urinary incontinence, and social support. Methods: From July, 1993 through June, 1997, 725 patients >39yrs living in Northern Manhattan with first stroke, infarct (INF) or intracerebral hemorrhage (ICH), were followed prospectively. Six-month functional outcome, based on Barthel Activities of Daily Living (ADLs) was categorized as dependent (DEP) (0-55), moderately dependent (MOD) (60-90), and independent (IND) (95-100). Polynomial logistic regression was used to calculate odds ratios (OR, 95%CI). Results: ICH had significantly higher 30-day mortality than INF (20% vs 6%, p=0.001), but did not have different 6-month ADL, ICH (OR 21%, MOD 40%; INF: DEP 17%, MOD 34%). In univariate analysis of 544 6-month survivors with ADL scores, PCS (INF: 492, ICH 52), worse functional outcome was predicted by age >65, female sex, white race, diabetes (DM), prestroke alcohol abstinence (ETOH), disabled prestroke (DIS), urinary incontinence 7-10 days poststroke (UI), and worse initial NIH stroke score (NIBSS) (all p<0.05), but not by recurrent stroke or social support. In multivariate analysis, DEP (v IND) was predicted by age >65 (1.4, 2.3-16.1), DIS (3, 1.4-6.5), no ETOH (3.4, 1.4-8.6), UI (12.1, 4.1-35.7) and worse NIBSS (1.3, 1.2-4.1); MOD (v IND) was predicted by female sex (1.7, 1.1-2.8), DM (1.9, 1.2-3.3), UI (4.7, 1.6-11.1), and worse NIBSS (1.1, 1.06-1.2). Conclusions: These findings confirm that older age, urinary incontinence, and greater stroke severity contribute adversely to 6-month ADL, in survivors of ICH. The factor of ICH: DEP (21%), MOD 40%; INF: DEP 17%, MOD 34%). These findings confirm that older age, urinary incontinence, and greater stroke severity contribute adversely to 6-month ADL, in survivors of ICH. The factor of ICH: DEP (21%), MOD 40%; INF: DEP 17%, MOD 34%).

Sensitivity to Change of SF-36 Summary Scores
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Background: Summary scores for health status measures are desirable for clinical trials and rehabilitation outcomes research. However, there may be a trade off between the simplicity of fewer statistical comparisons with summary scores and greater sensitivity to change of particular health domain scores. Objective: The purpose of this study was to compare the sensitivity to change of the SF-36 physical (PCS) and mental (MCS) component summary scores to the individual physical function domain scale (PFI) and the individual mental health domain (MH). Methods: Four-hundred and fifty-nine individuals from the Kansas City Stroke Study (mean age 70.5 ± 6.5 years, 71% white, 30% female, 50% moderate and 11% underweight or obese) completed a SF-36 at 1 month, 3 months and 6 months post-stroke. For the purpose of this study we have analyzed only 1 month and 3 month results. Sensitivity to change was examined by t-statistics from mixed models and the results were stratified by stroke severity measured by the Orpington Prognostic Scale. Results: The calculated t-statistics that compared changes from 1 to 3 months after stroke were: Minor strokes PCS (3.52**) MCS (2.49*) PFI (4.87**) MH (1.39). Moderate strokes PCS (4.55**) MCS (2.87**) PFI (9.00**) MH (1.66). Major strokes PCS (195) MCS (2.15*) PFI (1.86) MH (2.14*). **p<0.05, *p<0.01, ***p<0.001. The physical summary scores were less sensitive to change than the particular physical functioning domain; however, the summary mental health score is more sensitive to change than the individual mental health domain. Stroke severity affects sensitivity to change for all scores. Conclusion: The SF-36 MCS score appears to be sufficiently sensitive across all levels of stroke severity to measure mental health changes. The individual physical domain score is better than the PCS to measure physical health changes in minor and moderate strokes. Neither the PCS nor PFI pick up changes in major stroke due to a floor effect.

The Effect of Motor Impairment on Disability Following Stroke
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OBJECTIVE: To assess the relationship between change in motor impairment and change in disability during stroke rehabilitation. BACKGROUND: This relationship may provide insights into whether post-stroke rehabilitation alters disability by teaching compensatory strategies, by altering impairment, or both. METHODS: We analyzed the change in motor impairment assessed by the Fugl-Meyer motor scale (FM) and disability as assessed by the Functional Independence Measure (FIM) for 172 sequential patients admitted for inpatient rehabilitation within 90 days of an initial, single, unilateral, hemispheric, ischemic stroke, who had been previously independent in the community. Linear regression analysis and correlation coefficients tested the relationships between change in FM (total score; upper limb and lower limb subscores) and FIM (total score; self-care and mobility subscores). Clinical and demographic co-variables were also assessed. RESULTS: The correlation observed between change in total FM and change in total FIM score was 0.44, p < 0.0001. Change in both upper- and lower-limb FM motor subscores correlated with the change in self-care and mobility FIM subscores (r = 0.23, p = 0.003 and r = 0.18, p = 0.017, respectively). Other significant correlations were between discharge upper-limb FM and discharge self-care FIM subscores (r = 0.61, p < 0.0001), discharge lower-limb FM and discharge mobility FIM subscores (r = 0.74, p < 0.0001), and discharge total FM and discharge total FIM scores (r = 0.63, p < 0.0001). Age, sex, side of stroke, location of stroke, handness, presence of sensory deficit or visual field defect, total admission FM and FIM scores, time from stroke to rehabilitation, and length of stay in the rehabilitation unit did not significantly influence the correlation between impairment and disability. Linear regression analysis showed that for every ten-point increase in FM score, there was a 24-point increase in FIM. CONCLUSION: Impairment reduction following stroke rehabilitation contributes significantly to functional outcome. Our data allow quantitative estimation of the change in FIM score as a function of the change in motor impairment.
Objectives: We investigated theoretical magnetic resonance spectroscopy (MRS) changes in the motor cortex and subcortices of patients with hematomas located in the basal ganglia to examine the correlation between the loss of N-acetyl aspartate (NAA) and the degree of the motor deficit or clinical outcome. Methods: Thirty patients with stroke, 9 with putaminal hemorrhage and 4 with thalamic hemorrhage, were examined. T1-weighted imaging of the brain and proton MRS (multi-voxel method, 1 voxel: 1x1x2cm, area: 6x6x2cm) of the white matter of bilateral frontal lobes were performed with a 1.5 tesla MR system (Magnetom Vision, Siemens), and NAA/Cr and the ratio of the motor deficit scores and the Barthel indexes for disability. NAA, creatine (Cr), and the NAA/Cr ratio were measured serially: within 48 hours, two weeks, and one and two months later after the onset. Results: The mean NAA/Cr ratio within 48 hours after onset was slightly lower in the frontal lobe on the affected side than in the control and unaffected side, and it was significantly lower two weeks later (p=0.03). Reduction in frontal lobe NAA/Cr ratio on the side of the lesion worsened in the patients who showed no extension of the hematoma into the voxels. In the patients who showed good recovery of motor deficits, NAA/Cr ratio had remained constant or increased one month later. Patients in a persistent vegetative state showed loss of NAA in the frontal lobe on the unaffected side. There was a correlation between the motor deficit score and the magnitude of NAA loss in the frontal lobe on the affected side two weeks and one month after stroke (p=0.05). The degree of NAA loss showed the tendency to correlate with Barthel index. Conclusion: The degree of damage to the frontal lobe on the affected side, as shown by the magnitude of NAA loss, correlates with the motor deficit and may contribute to the clinical outcome after hemorrhage in the basal ganglia.

Objectives: We sought to evaluate the extent of bias due to ethnicity and language influences on cognitive tests. We investigated whether ethnicity and language influences on cognitive testing after a subarachnoid hemorrhage (SAH).Methods: We invited 700 patients in the Institutional Brain and Blood Vessels, Iseoka Japan; Sadao Suga, Keio Univ Sch of Medicine, Tokyo Japan; Ban Mihara, Institute of Brain and Blood Vessels, Iseoka Japan.

Objectives: We investigated theoretical magnetic resonance spectroscopy (MRS) changes in the motor cortex and subcortices of patients with hematomas located in the basal ganglia to examine the correlation between the loss of N-acetyl aspartate (NAA) and the degree of the motor deficit or clinical outcome. Methods: Thirty patients with stroke, 9 with putaminal hemorrhage and 4 with thalamic hemorrhage, were examined. T1-weighted imaging of the brain and proton MRS (multi-voxel method, 1 voxel: 1x1x2cm, area: 6x6x2cm) of the white matter of bilateral frontal lobes were performed with a 1.5 tesla MR system (Magnetom Vision, Siemens), and NAA/Cr and the ratio of the motor deficit scores and the Barthel indexes for disability. NAA, creatine (Cr), and the NAA/Cr ratio were measured serially: within 48 hours, two weeks, and one and two months later after the onset. Results: The mean NAA/Cr ratio within 48 hours after onset was slightly lower in the frontal lobe on the affected side than in the control and unaffected side, and it was significantly lower two weeks later (p=0.03). Reduction in frontal lobe NAA/Cr ratio on the side of the lesion worsened in the patients who showed no extension of the hematoma into the voxels. In the patients who showed good recovery of motor deficits, NAA/Cr ratio had remained constant or increased one month later. Patients in a persistent vegetative state showed loss of NAA in the frontal lobe on the unaffected side. There was a correlation between the motor deficit score and the magnitude of NAA loss in the frontal lobe on the affected side two weeks and one month after stroke (p=0.05). The degree of NAA loss showed the tendency to correlate with Barthel index. Conclusion: The degree of damage to the frontal lobe on the affected side, as shown by the magnitude of NAA loss, correlates with the motor deficit and may contribute to the clinical outcome after hemorrhage in the basal ganglia.

The Degree of Damage to the Frontal Lobe on the Affected Side, as Shown by the Magnitude of NAA Loss, Correlates with the Motor Deficit and May Contribute to the Clinical Outcome After Hemorrhage in the Basal Ganglia.
Oral Presentations

93

Stroke Knowledge, Prevention Practices, and Preferred Approaches to Stroke Education: Towards Developing a New Ethnically-Specific, Culturally-Sensitive Survey Tool
Susan Billings-Gagliardi, Nancy M Fontneau, Merrill K Wolf, MaryBeth Regan, Susan sprint: teaching first-year medical students about stroke prevention.

Introduction: The Health Belief Model and Self-Efficacy (an individual’s self-confidence to change behavior). We used the Henry Ford Health System database, a stratified, systematic random sample with race, age 50+ , and group assignments (Medicare, Medicaid, no insurance [NI] or stroke clinic patients [SC]) as stratification parameters to identify AAs (N=50) who participated in one of six FGs lasting 1.5 hours. We audiotaped, transcribed, and generated themes (summarized). Results: 79% were 60-70 yrs. old, 66% females; 79% had 12th grade education or lower, 32% had Medicare; 30% NI, 22% Medicaid; 16% SC. Themes from the sessions included poor knowledge about the nature of stroke (where or how it occurs and stroke risk factors). Most associated paralysis (60%), impaired speech (50%) and fear (42%) with stroke. The 3 most important perceived stroke prevention practices were: controlling hypertension (81%), hypercholesterolemia (58%), and obesity (31%). Barriers to stroke prevention included: lack of will power (20%), stressful environments (15%), being unable to control eating/exercise habits (14%), 57% preferred group approaches to stroke education vs. self-study (11%) or 1-on-1 (9%). Doctors (74%), stroke support groups (35%), TV (35%), and hospitals (31%) were their preferred sources of stroke information. The most desired stroke information included: warning signs/symptoms (65%), causes of stroke (55%), stroke management (55%), stroke prevention practices (43%), and stroke victim testimonials (33%). Conclusions: Our data identified barriers and preferences that may influence effective stroke education in AA communities and should help develop a more culturally-sensitive survey tool.

Background: Most stroke surveys have generally not been designed to be culturally sensitive to non-whites. Objectives/Methods: African Americans (AAs), 50+ yrs. old participated in focus groups (FGs) to gather information to design a culturally sensitive tool, explore stroke prevention practices, barriers, and preferred approaches to stroke education. We employed the Knowledge Gap Theory, the Health Belief Model and Self-Efficacy (an individual’s self-confidence to change behavior). We used the Henry Ford Health System database, a stratified, systematic random sample with race, age 50+, and group assignments (Medicare, Medicaid, no insurance [NI] or stroke clinic patients [SC]) as stratification parameters to identify AAs (N=50) who participated in one of six FGs lasting 1.5 hours. We audiotaped, transcribed, and generated themes (summarized). Results: 79% were 60-70 yrs. old, 66% females; 79% had 12th grade education or lower, 32% had Medicare; 30% NI, 22% Medicaid; 16% SC. Themes from the sessions included poor knowledge about the nature of stroke (where or how it occurs and stroke risk factors). Most associated paralysis (60%), impaired speech (50%) and fear (42%) with stroke. The 3 most important perceived stroke prevention practices were: controlling hypertension (81%), hypercholesterolemia (58%), and obesity (31%). Barriers to stroke prevention included: lack of will power (20%), stressful environments (15%), being unable to control eating/exercise habits (14%), 57% preferred group approaches to stroke education vs. self-study (11%) or 1-on-1 (9%). Doctors (74%), stroke support groups (35%), TV (35%), and hospitals (31%) were their preferred sources of stroke information. The most desired stroke information included: warning signs/symptoms (65%), causes of stroke (55%), stroke management (55%), stroke prevention practices (43%), and stroke victim testimonials (33%). Conclusions: Our data identified barriers and preferences that may influence effective stroke education in AA communities and should help develop a more culturally-sensitive survey tool.

94

Sprint: Teaching First-Year Medical Students About Stroke Prevention
Susan Billings-Gagliardi, Nancy M Fontneau, Merrill K Wolf, MaryBeth Regan, Susan Barrett, Jeannet D Keller, Thomas W Smith, Steven L Wertheim, Lyn Rea, Krista Johansen, Univ of MA Med Sch, Worcester, MA

Introduction: SPRINT is an innovative curriculum on Stroke Prevention, Recognition, Intervention, and Treatment that is presented within the first-year neuroscience course at the University of Massachusetts Medical School. Students learn essential neuroanatomy in the context of TIA’s or early stroke in progress. By taking this approach, prevention, early intervention, and counseling of patients on self-recognition of stroke can be emphasized. These relevant clinical materials are delivered in multiple short packets replacing or supplementing appropriate neuroscience sessions. Methods: Students’ knowledge, skills and attitudes about stroke were assessed pre-, immediately post-, and 8-months post- SPRINT. The testing instrument included short-answer, multiple choice, and self-assessment components. Data from two successive classes that completed SPRINT were examined using paired t-tests (n=64; n=57). Results: Significant improvements in students’ mean scores on all measures were found immediately post-SPRINT, and were maintained 8 months later (p<.001). More than 95% of students who completed SPRINT viewed stroke as preventable and treatable. Their examination scores in the neuroscience course were slightly higher than previous classes. Conclusions: SPRINT promotes the acquisition and retention of clinically important information about stroke and stroke prevention by first-year students without sacrificing basic neuroscience learning. SPRINT students understand the value of aggressive strategies against stroke. Modules of the SPRINT curriculum and an interactive multimedia web-site supporting them will be developed for nationwide distribution.

95

Perceived Emergency Nature of Stroke Symptoms as Reported by Medicare Beneficiaries in the Stroke Belt
Cynthia D Coventron, David S Nilavesa, David A Nicewander, Emily J Townsend, Health Care Financing Admin - Dallas Region, Dallas, TX

OBJECTIVES: To assess Medicare beneficiaries perceived emergency nature of stroke symptoms. This report is a part of the Making Advances in the Prevention of Stroke (MAPS) project. METHOD: A random sample of Medicare beneficiaries with a primary or secondary hospital discharge diagnosis of atrial fibrillation was selected from 11 southeastern states including the “stroke belt.” Computer-assisted telephone interviewing (CATI) was used to administer a telephone survey to these beneficiaries between July 1997 and March 1998. The survey contained questions asking respondents to rate how likely they would be to seek emergency treatment for various medical symptoms, including three stroke symptoms. We did an analysis to compare the beneficiaries’ perception of the emergency nature of each symptom as compared to their perception of the emergency nature of severe chest pains. RESULTS: Out of 32,756 Medicare survey respondents, 95.5% stated that they would be very or somewhat likely to seek emergency treatment if they experienced weakness, numbness, or hemiplegia. Among those surveyed, 91.1% stated that they would be somewhat or very likely to seek emergency treatment if they had trouble speaking or understanding speech. Also 87.3% of respondents stated that they would be somewhat or very likely to seek emergency treatment for severe headaches. For comparison, 95.7% of respondents reported that they would be somewhat or very likely to seek emergency treatment for severe chest pains. They perceived other symptoms (shortness of breath, running a high temperature, and nausea or vomiting) as having less of an emergency nature than severe headaches. CONCLUSIONS: High-risk Medicare beneficiaries in the “stroke belt” perceive stroke symptoms as requiring emergency treatment, similar to their perceptions about emergency treatment for severe chest pains. The pattern of responses for weakness, numbness, or hemiplegia were essentially the same as those for severe chest pains. We need more information in order to fully understand the factors which contribute to delayed presentation for medical treatment following the onset of a stroke.

96

Carotid Plaque Area as a Tool for Identifying Patients at High Coronary Risk

Treatment of vascular risk factors is more cost-effective in high-risk patients. We studied carotid plaque cross-sectional area measured in longitudinal views of the common, internal and external carotids by B-mode ultrasound as a way of identifying high-risk patients who would justify more aggressive therapy for risk reduction. 780 patients from an atherosclerosis and early stroke prevention clinic were followed annually for up to 6 years with measurement of carotid plaque and all known risk factors. Here we present results on the 599 patients with no stroke, including the “stroke belt.” Computer-assisted telephone interviewing (CATI) was used to administer a telephone survey to these beneficiaries between July 1997 and March 1998. We did an analysis to compare the beneficiaries’ perception of the emergency nature of each symptom as compared to their perception of the emergency nature of severe chest pains. RESULTS: Out of 32,756 Medicare survey respondents, 95.5% stated that they would be very or somewhat likely to seek emergency treatment if they experienced weakness, numbness, or hemiplegia. Among those surveyed, 91.1% stated that they would be somewhat or very likely to seek emergency treatment if they had trouble speaking or understanding speech. Also 87.3% of respondents stated that they would be somewhat or very likely to seek emergency treatment for severe headaches. For comparison, 95.7% of respondents reported that they would be somewhat or very likely to seek emergency treatment for severe chest pains. They perceived other symptoms (shortness of breath, running a high temperature, and nausea or vomiting) as having less of an emergency nature than severe headaches. CONCLUSIONS: High-risk Medicare beneficiaries in the “stroke belt” perceive stroke symptoms as requiring emergency treatment, similar to their perceptions about emergency treatment for severe chest pains. The pattern of responses for weakness, numbness, or hemiplegia were essentially the same as those for severe chest pains. We need more information in order to fully understand the factors which contribute to delayed presentation for medical treatment following the onset of a stroke.

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Development and Natural History of Leukoaraiosis in Patients with Ischemic Events and Carotid Artery Disease


Background: Leukoaraiosis (LA), a frequent finding on brain CT scan of elderly patients with cerebrovascular disease (CVD), is a risk factor for stroke and vascular death. The aim of this study was to examine the rate of development and natural history of LA in patients with CVD.

Methods: The extent of LA was assessed on the entry and follow-up CT scans from 337 patients enrolled in the Northern American Symptomatic Carotid Endarterectomy Trial (NASCET). The mean time period between CT scans was 7.8 years (4.4-9.6). Results: At entry, 296 patients had no LA, 31 (9.2%) had restricted LA and 10 (3.0%) had extensive LA. On the follow-up CT scan, the percentage of patients with restricted LA increased to 24.3% and with extensive LA to 11.3%. Among the 296 patients without LA at entry, 22.6% showed restricted LA and 4.1% extensive LA on the follow-up CT scan. Of the remaining 41 patients, 31 (75.6%) showed progression of their LA. New small deep brain infarcts (SDI) were twice as likely (61.5% vs 30.0%, p < 0.001) to occur in patients with SDI at entry in comparison to patients without SDI. Baseline characteristics, identified as risk factors for development or progression of LA, included age ≥ 65 years (p < 0.001), the presence of SDI (p = 0.02), and the presence of contralateral severe carotid stenosis or occlusion (p = 0.002). All other vascular risk factors, including history of hypertension, type of presenting ischemic event, degree of ipsilateral carotid stenosis, and treatment group (surgical or medical) were not statistically significant. Among the 110 patients who developed LA or showed progression, 43.6% had one or more strokes during follow-up in comparison to 30.8% in 227 patients who showed no change on CT (p = 0.02). Of the strokes that occurred, 29.2% presented with lacunar syndromes in the former group and 16.5% in the latter. Conclusion: LA develops quite commonly in patients with CVD. Its presence is associated with a higher occurrence of strokes, in particular of lacunar type.

CT Angiography of the Middle Cerebral Artery Elucidates the Association of Wernicke’s Aphasia with Cardiogenic Stroke

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Background: Wernicke’s aphasia, and posterior division MCA infarcts generally, occur disproportionately among patients with cardiac sources of emboli. The etiology of this association has not been previously explained. We hypothesized that several anatomic features of the MCA bifurcation could interact with the known larger average size of cardiac emboli to produce this association, and tested for the presence of these anatomic features using 3D space, adjusted for the horizontal plane and natural head posture.

Results: The mean age at 58 years (range 8-90), and 54% were female. Bifurcations were present in 84%, trifurcations in 9%, multiple branches in 6%. The 603 bifurcations from normal hemispheres were selected for detailed analysis. Posterior division lumen diameter was larger on average than anterior division, mean 2.13 mm (95% CI 2.08 to 2.18) vs 1.77 mm (CI 1.72 to 1.82), p<.0001. The angle between the MCA trunk and the anterior division was less severe than between the MCA trunk and the anterior division, mean 136° (CI 133° to 139°) vs 125° (CI 123° to 127°), p<.0001. The takeoff of the posterior division relative to gravity was downward relative to the takeoff of the anterior division, mean -70° (CI -51° to -89°) vs 24° (CI 19° to 29°), p<.0001. Age, gender, and laterality subgroup analyses were not significant. Inter-rater reliability ranged from .75 to .99. Conclusions: Anatomical features of the MCA bifurcation that favor larger emboli entering the posterior rather than anterior division include larger vessel diameter, more linear path, and disparate gravitational predilection. These anatomical features explain the well-documented association of Wernicke’s aphasia with cardioembolic stroke.

Screening for Intracranial Stenosis- The Positive Predictive Value of Transcranial Doppler Velocity Thresholds

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Background: Patients with >50% intracranial arterial stenosis may require more intensive therapies for stroke prevention. Transcranial doppler (TCD) is a convenient noninvasive screen for intracranial stenosis. The accuracy of different mean flow velocity (MFV) thresholds for determining the degree of stenosis is uncertain. Methods: We prospectively compared the accuracy of TCD criteria and MFV thresholds to magnetic resonance or digital subtraction angiography in patients with symptoms of cerebral ischemia. Stenosis on angiography was measured as the percent ICA stenosis, and >50%. Results: Among 33 (24%) had distal internal carotid (ICA), middle (MCA), posterior cerebral or basilar artery stenosis on angiography. TCD showed 31 true positive, 9 false positive, 2 false negative, and 94 true negatives. For all vessels, TCD had sensitivity 93.9%, specificity 91.2%, positive predictive value (PPV) 77.5%, negative predictive value (NPV) 97.9%. The trade off in sensitivity and specificity for MCA MFV thresholds is shown below (table). Reasons for false positive findings include collateralization of flow in the presence of proximal ICA stenosis and pre-stenotic to stenotic MCA velocity ratios of 1<2. Conclusions: TCD is both sensitive and specific in identifying >50% intracranial arterial stenosis. A MFV threshold cutoff of >150cm/sec has an optimal sensitivity and specificity of 0.93 for >50% MCA stenosis. To avoid false positive results, a pre-stenotic to stenotic MCA velocity ratio of 1:2 should be used in addition to MFV threshold.

Reproducibility of Microembolus Detection in Patients with Asymptomatic Internal Carotid Artery Stenosis

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Background: There has been recent interest in the use of Transcranial Doppler microembolus detection to predict symptoms of cerebral ischemia in patients with symptomatic and asymptomatic internal carotid artery (ICA) stenosis. However, little is known about test-retest results of the technique. AIM: To test reproducibility of microembolus detection in patients with asymptomatic ICA stenosis. METHODS: 153 arteries with 60-99% ICA stenosis in the Asymptomatic Embolus Detection (ASED) Study had six monthly microembolus detection using transcranial Doppler. Of these patients, 80 had repeat microembolus detection the same day or up to 10 days apart from the scheduled study. The off-line six-decibel threshold microemboli positivity and negativity results for the 60 minute scheduled and repeat studies were compared. RESULTS: Of 91 repeat arterial studies performed the same day or within 2 weeks of the scheduled visit, 85 (93%) were the same with respect to microembolus detection. Of 13 studies performed 15 to 10 days from the scheduled visit, only 9 (69%) were the same. DISCUSSION: Shedding of microemboli appears to be a variable phenomenon in individual patients with asymptomatic ICA stenosis. Most of the variability in microembolus detection occurs if repeat studies are performed more than two weeks from examination.

Longterm Outcome in Symptomatic Intracranial Vertebrobasilar Occlusive Disease

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Background: The prognosis of intracranial vertebrobasilar (VBI) occlusive disease is thought to be poor. Endovascular therapies are emerging but bear inherent risks and need to be balanced against longterm prognosis of medical therapy. This study evaluates the longterm prognosis in patients with symptomatic VBI. METHODS: Symptomatic VBI patients with at least moderate stenosis of the intracranial posterior circulation who presented to the Cleveland Clinic Foundation between 1998-1994 were followed prospectively. Stroke risk factor lesion location and severity, type of therapy, stroke recurrence rate, and telephone Barthel Index (0-100) were determined. RESULTS: A total of 68 patients were prospectively followed. Patients were followed for a mean of 7.5 years to 10 years. Isolated BA stenosis was present in 26, ICA stenosis in 13, PCA stenosis in 4 and multilevel lesions in the remaining 15 patients. Initial treatment consisted of warfarin 27, ticlopidine 12, aspirin 11, and combination treatments in 3. RESULTS: At 10 years followup, the average Barthel score in survivors was 67.7±15.6% with independence. Ten patients (14.7%) were lost to followup. CONCLUSION: Long term morbidity and mortality are lower than previously reported. Stroke risk is significantly higher in patients with multilevel stenoses. Evaluation of any endovascular procedure needs to balance the relative low risk of longterm medical management.
Background: Hemicraniectomy is a new surgical treatment for massive ischemic brain swelling. Initial reports suggest drastic reduction in mortality and morbidity compared to standard medical therapy. Since these findings may be limited by a selection bias we performed a multicenter evaluation of the clinical practice of hemicraniectomy. Methods: Retrospective case-control study of patients (3 year period) with large MCA strokes admitted within 48 hours of onset including hemicraniectomy cases. Risk factors, lab data, and CT scans were abstracted with a standardized case report form. Mortality was divided into neurologic and nonneurologic death. Results: 251 patients with large MCA strokes were identified: 109 neurologic deaths, 16 nonneurologic deaths, and 126 survivors. Hemicraniectomy was performed in 50 patients. In bivariable analyses, hemicraniectomy was performed in younger patients (50.6±12.6 vs. 67.4±13.3 y) with less HTN, DM, AIB, CHF or prior stroke. Patients undergoing hemicraniectomy were more likely to have headache or nausea/vomiting (66% vs 24% in the first 24 hours. Hemicraniectomy cases had lower serum glucose, and more early ischemic CT changes. Multivariable analysis identified age (OR 0.92 (0.87-0.99), p=0.022) and N/V (OR=2.4 (1.2-4.9), p=0.039) as only independent predictors of hemicraniectomy. Only involvement of other territories on CT was independently predictive of death (OR 24.9, 95%CI (6.2-93.8), p=0.005). Adjusting for baseline differences of age and N/V, the one month mortality with hemicraniectomy was OR 0.48 (p=0.12) versus controls. Further adjustment for baseline NIHSS and CT findings revealed OR 0.25 (p=0.02) versus controls. Conclusion: In this multicenter study, clinicians selected younger patients with fewer risk factors for hemicraniectomy. Adjusting for baseline differences in the hemicraniectomy and medical therapy groups, hemicraniectomy was associated with a statistically significant reduction in one month mortality. However, infarction exceeding the MCA territory into other vascular territories tended to negate the benefits of hemicraniectomy.

Predictors of Fatal Brain Edema in Massive Hemispheric Ischemic Stroke

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Background: Early identification of stroke patients at risk for fatal brain edema may be useful in selecting patients for aggressive medical and surgical interventions. Prior studies suggested that early nausea/vomiting and major hypodensity on baseline CT were predictive of hemicraniectomy. Methods: Retrospective multicenter case-control study of all patients over a 3 year period with large MCA strokes admitted within 48 hours of symptom onset. Patients who were treated with hemicraniectomy were excluded from this analysis. Medical records, lab data, and CT scans were abstracted with a standardized case report form. Cases, defined as patients who died of massive brain swelling, were compared to all remaining patients as controls. Results: 201 patients with large MCA strokes were identified: 94 (47%) died of brain swelling, 12 (6%) died of non-neurological causes, and 95 (47%) survived at day 30. Multivariable analysis, adjusted for age and clustered by center, identified the following predictors of fatal brain edema: history of hypertension (OR 3.0, 95%CI 1.2-7.6, p=0.02), history of heart failure (OR 2.1, 95%CI 1.5-3.0, p=0.001), WBC count (OR 1.08 per 1000 WBC/ml, 95%CI 1.01-1.14, p=0.002), >50% MCA hypodensity (OR 6.3, 95%CI 3.5-11.6, p=0.001), and other territory (ACA, PCA, anterior choroidal artery) involvement (OR 3.3, 95%CI 1.2-9.4, p=0.02). Temporal lobe hypodensity was associated with lower risk of fatal edema (OR 0.4, 95%CI 0.2-0.8, p=0.001), but was usually occurred together with major MCA hypodensity. Initial level of consciousness, NIHSS, early nausea/vomiting, and serum glucose were significantly associated with neurological death in bivariable but not multivariable analyses. Conclusion: An increased risk of fatal brain edema is associated with history of hypertension or heart failure, increased baseline WBC count, and major early hypodensity involving more than 50% of the MCA territory and other vascular territories. These data confirm and expand upon prior research using a broad-based patient population. The presence of these risk factors identifies those stroke patients who may require aggressive therapeutic approaches.

Neurological Monitoring of Therapeutic Hypothermia After Hemispheric Stroke

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Background: Microdialysis was used for neurological monitoring of stroke patients treated with moderate hypothermia. Microdialysis is a method for monitoring excitatory amino acids or metabolic end products in the extracellular space that occur after an ischemic stroke. Methods: Patients (n=3) with MCA infarction of the left hemisphere were treated with hypothermia (33°C). Microdialysis probes (CMA 70, Sweden) and an ICP measuring device (Spiegelberg, Germany) were inserted into the infarcted and non-infarcted cortex. Online monitoring of microdialysis samples was performed every 1-3hr using the CMA 600 microdialysis analyzer. Concentrations of glutamate, glycine, lactate and pyruvate were measured. Results: Dialysate concentration of glutamate was up to 400μmol/l in the infarcted cortex compared to 0.5-μmol/l in the non-infarcted cortex. Glycerine levels were increased to 1000μmol/l in the infarcted cortex compared to 50-100μmol/l in the non-infarcted hemisphere. During passive rewarming the lactate-pyruvate ratio was 5x higher in the infarcted cortex. In patients 1 and 3, glutamate and glycine decreased by 40-50% during 72h of hypothermia and remained there during rewarming. The lactate-pyruvate ratio decreased to the same level as decreased in the non-infarcted tissue. In patient 2, glutamate, glycine and the lactate-pyruvate ratio of the non-infarcted cortex started to rise sharply 12hr before clinical sign of transtentorial herniation occurred and 34h before ICP increased up to 27mmHg and the patient died. Conclusion: Microdialysis is a useful monitoring tool for neurological alterations during hypothermic treatment after stroke. Hypothermic treatment of severe stroke appears to be associated with a continuous decrease of excitatory amino acids and glycine. The normalization of the lactate-pyruvate ratio could either reflect spontaneous reperfusion or sufficient energy for aerobic metabolism in hypothermia. Microdialysis seems to be more sensitive than evolved potentials and ICP in detecting fatal secondary neuronal injury.

One-Year Follow-up in Patients Treated with rt-PA in Clinical Routine

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Background: In a recent study (Kwiatkowski et al. NEJM 1999;340:1781-87) evidence of sustained benefit at one year from streptokinase in patients with acute stroke was provided. Objective: To study whether similar results may be attainable in everyday practice if current guidelines for treatment and management are followed closely Methods: 1121 patients with acute stroke were included at our stroke center between March 1996 and July 1998 strictly in accordance with the AHA guidelines. We have followed up those patients for 12 months after their treatment. Results: Base-line characteristics and complication rates were comparable to those of the NINDS study except for a somewhat younger average age (mean 63 years) and lower NIHSS (median: 11.4% of our patients showed minimal or no disability (Rankin 0 or 1) at 12 months (table). The recrrent stroke rate was 6.6%, the TIA rate 3.3%, 6 patients (4%) died after the first 3 months of them due to recrrent stroke. Five of them had already been severely disabled at 3 months. Conclusion: These observations further encourage the routine use of rt-PA for the treatment of acute ischemic stroke in strict accordance with the AHA guidelines.
Background and Purpose: Subarachnoid hemorrhage (SAH) patients are at risk for delayed brain injury due to vasospasm (VSP). This delayed injury is a potential cause of central fever.

Our primary hypothesis was that VSP might be associated with fever occurrence in a multivariate model. Methods: We prospectively studied patients admitted to a neurologic ICU with the diagnosis of non-traumatic SAH. Hunt-Hess and Fisher grades, Glasgow Coma Score, bacterial culture data (urine, sputum, spinal fluid and catheters), daily transcranial Doppler (TCD) maximum velocities and maximum temperature were recorded in each case. Patients were divided into two groups: febrile, as defined as temperature above 38.5°C for at least 2 consecutive days (Group 1); and afibrile (Group 2). VSP was considered present if verified by either TCD or angiographic criteria. Results: Ninety-three consecutive patients were studied in a 1-year period. Thirty-nine patients had fever for 2 or more consecutive days (Group 1). Thirty-one (80%) of Group 1 patients were found to have VSP; only 25 of 54 (46%) patients in Group 2 had VSP (p < 0.01). In the multivariate analysis, VSP remained a predictor of fever occurrence (p = 0.008), whereas Hunt-Hess and Fisher grades and Glasgow Coma Score did not. Conclusions: Fever in SAH is associated with VSP independently of severity of the presenting hemorrhage or presence of infection.

Saturday-Afternoon

Effect of Hyperventilation on Cerebral Hemodynamics and Oxygen Metabolism Following Acute Brain Injury

BACKGROUND: Acute hyperventilation causes cerebrovascular vasodilatation, reducing cerebral blood volume (CBV) and cerebral blood flow (CBF). Whether this reduction in CBF is sufficient to reduce cerebral oxygen delivery below cerebral oxygen metabolic demand and thus cause ischemia remains controversial, especially in patients with acute traumatic brain injury (TBI).

METHODS: Nine intubated mechanically ventilated patients were studied 11.2 ± 1.6 (range 8-14) hours after TBI. Glasgow Coma Score was 5.6 ± 1.8. CBV(ml/100g/min), CBF(ml/100g/min), oxygen extraction fraction (OEF) and CMRO2(ml/100g/min) were measured with PET at baseline and after 30 minutes of hyperventilation to a target pACO2 of 30 torr. RESULTS: Hyperventilation (HV) produced significant reductions in CBF and CBV but did not change CMRO2 (see Table below).

CONCLUSIONS: We found no evidence that hyperventilation to pACO2 of 30 torr in patients with acute traumatic brain injury produced reductions in CBF were sufficient to cause global cerebral ischemia.

The Predictive Value of NIH Stroke Scale on Discharge Disposition, Length of Stay and Direct Cost for Ischemic Stroke
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Background and Objectives: The NIHSS score was developed for assessing neurological deficits in the NIHSS TPA stroke trial. This scale continued to be widely used in stroke clinical trials because of its strong inter- and intra-rater reliability. The NIHSS score was recently shown to be a good predictor for early clinical progression during the first 48 hours after acute ischemic stroke and a correlation was found between admission NIHSS scores and direct costs. No studies have been done to determine the applicability of NIHSS in daily clinical practice. We present our data on the predictive value of NIHSS score on discharge disposition and length of stay (LOS). Methods: Data were obtained on 227 patients treated for acute ischemic stroke by the OSF Stroke Team between June 1, 1998 and May 31, 1999. NIHSS scores were collected at admission, day 2, and discharge. LOS, discharge disposition, direct cost, age, gender, ethnicity, and marital status were collected. Data were analyzed using SPSS® for Windows. Level of significance was determined by a p < 0.05. Results: Patients in this study had an average age of 69, 51% were male, and 94% were Caucasian. One-hundred twenty-one (53%; median admission NIHSS = 7) were discharged home, 63 (28%; median NIHSS = 8) went to inpatient rehabilitation, 32 (14%; median NIHSS = 14) to the skilled care or nursing home, and 11 (5%; median NIHSS = 18) died. The median LOS was significantly shorter for patients with NIHSS <= 6 on admission (4 days) as compared to those with a NIHSS > 25 (9 days). The direct costs were also significantly different between these groups ($3500 for patients with NIHSS <= 6 and $10474 for patients with NIHSS > 25). Conclusion: A strong correlation was observed between the admission NIHSS score and LOS, direct cost, and discharge disposition. Our data also support the NIHSS score as a predictor for patient discharge status and LOS. Neurologists should consider adopting the NIHSS as one standard of care assessment for all ischemic stroke patients. This acceptance may lead to a better understanding of the predictive value of such scales in the prognosis for patients with ischemic stroke.

Withdrawn
Carotid Endarterectomy in Patients with Severe Symptomatic Carotid Stenosis and a Reduced Distal Internal Carotid Artery Lumen Diameter: A Combined Analysis from ECST and NASCET


Background: Carotid endarterectomy (CEA) for 70-99% symptomatic stenosis reduced the risk of stroke in the European (ECST) and the North American (NASCET) trials. In both trials, the stroke risk on medical treatment increased with severity of stenosis, but then fell in patients with narrowing or collapse of the internal carotid artery (ICA) distal to the stenosis. Despite the paradoxically low risk of stroke on medical treatment, patients with this pre-occlusive syndrome are generally thought to require urgent CEA. We determined the efficacy of CEA in this subgroup in a combined analysis of individual patient data from ECST and NASCET.

Methods: We studied the 1247 patients in ECST and NASCET who had 70-99% symptomatic stenosis by the method of measurement used in NASCET. Abnormal post-stenotic narrowing of the ICA was defined on the pre-randomisation carotid angiogram, as published previously, as a ratio of the ICA:CCA (common carotid artery) lumen diameters of less than 0.42. Results: The 5 year risk of ipsilateral carotid territory disabling or fatal stroke on medical treatment was lower in the 199 (16%) patients with abnormal narrowing of the distal ICA than in those without: 3.9% vs 13.9% (P = 0.01). In the CEA group, the 5 year risks of ipsilateral disabling or fatal stroke or surgical stroke or death were 8.9% and 3.9% respectively (P = 0.18). Consequently, CEA reduced this risk in patients without narrowing of the distal ICA (HR = 0.26, 95% CI = 0.20, P < 0.0001), but there was no evidence of benefit in patients with narrowing (HR = 2.05, 95% CI = 0.66, 3.5, P = 0.5). This heterogeneity of treatment effect was statistically significant (X^2 = 8.7, P = 0.003). Conclusions: There was no evidence of benefit from CEA in patients with abnormal narrowing of the ICA distal to a 70-99% symptomatic carotid stenosis. This is a post-hoc subgroup analysis, and must be interpreted with caution, but it is reported because it is consistent across both trials.

Long-Term Prognosis of Patients with Unruptured Intracranial Aneurysms and Symptomatic Internal Carotid Artery Stenosis


Background and purpose: Carotid angiography performed as a prelude to carotid endarterectomy (CEA) in patients with symptomatic internal carotid artery (ICA) stenosis may reveal an unruptured intracranial aneurysm (UIA) in about one of every 40 patients. The best management strategy for these patients is uncertain. Methods: The prevalence of UIA was calculated in patients with symptomatic ICA stenosis who participated in NASCET. Patient characteristics were examined in relation to the presence of an UIA, and the 5-year risk of stroke ipsilateral to the ICA stenosis was computed using Kaplan-Meier event-free survival analysis. Results: Among 2885 patients, 35 women (4.0%) and 55 men (2.7%) had an UIA (96% of UIA < 10 mm). Fifty-one UIAs were on the side of the symptomatic ICA. The prevalence of UIA in Blacks was 9.9%, in Caucasians 2.9%, and in other races 3.6% (p = 0.04). UIAs were more common in patients presenting with a TIA (3.9%) than with a stroke (2.2%) (p = 0.07); in smokers (3.9%) compared to non-smokers (2.5%) (p = 0.03). Intracranial stenosis of the ICA or other major intracranial arteries was associated with an UIA (4.1% versus 2.6%, p = 0.04). The degree of ICA stenosis was not associated with UIAs. The 5-year ipsilateral stroke risk for CE patients was 10.0% in the presence and 14.8% in the absence of an unruptured UIA. For medically treated patients these risks were 22.7% and 22.5%, respectively. Conclusions: For symptomatic ICA stenosis in the presence of an UIA < 10 mm, CE can be considered without first repairing the UIA.
Complications of Carotid Stenting in High Surgical Risk Patients
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Introduction: The complication rate for carotid endarterectomy (CEA) in patients with symptomatic and asymptomatic carotid artery disease is known from data obtained in randomized clinical trials such as NASCET and ACAS. However, in high risk individuals due to either anatomic factors or medical comorbidity, the surgical complication rate is higher and may represent a reasonable alternative. Methods: The records of consecutive patients considered high risk for CEA undergoing carotid stenting were combined from three active stenting centers. The data collection was performed at each center based on local protocols. Patients were examined following the procedure by either the operator or local neurologist. The study Abbreviation: CEA

Conclusion: Although the complication rate is higher and may represent a reasonable alternative, CEA in high-risk patients should be performed with experienced and skilled operators and whether similar results would be achieved in general practice is uncertain. A randomized trial of carotid stenting v CEA might be particularly useful in this high surgical risk group.

Combination Aspirin-Clopidogrel Therapy in Patients with Ischemic Stroke
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Background: Combination aspirin-ticlopidine therapy has been shown to have enhanced effect on the prevention of platelet aggregation in patients resistant to aspirin therapy. No such data has been reported to date with combination aspirin-clopidogrel therapy. Methods: This study evaluated 56 patients receiving combination aspirin-clopidogrel for recurrent ischemic stroke prevention. Patients were evaluated for safety, efficacy, and outcome on platelet aggregation of aspirin-clopidogrel therapy. Patients with previous ischemic stroke cared for at the University of Illinois were prospectively placed on combination aspirin-clopidogrel. Indications for combination therapy include: aspirin resistance, partial inhibition of platelet aggregation on single aspirin therapy, on aspirin-clopidogrel therapy, and on aspirin-ticlopidine therapy, failure of treatment with aspirin, clopidogrel, or aspirin-ticlopidine combination therapy. Results: No major or fatal bleeding events were noted. No major stroke or death was documented during the follow-up period. Conclusions: The combination aspirin-clopidogrel is effective in enhancing inhibition of platelet aggregation in patients previously reported to be resistant or have incomplete response to aspirin single therapy, and may have a similar degree of platelet aggregation (slight improvement in some cases) was maintained in patients switched from aspirin to aspirin-clopidogrel therapy. The combination aspirin-clopidogrel regimen is safe and has the potential to be used as a rescue therapy in patients with aspirin resistant to aspirin therapy.
P11
Clopidogrel May Enhance the Clinical Efficacy of Carotid Artery Stent Implantation: The EMILY Registry
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Purpose: Clopidogrel, a new thienopyridine derivative, has been shown to possess experimental and clinical antplatelet activity that is superior to aspirin. Recent randomized trials have shown its effectiveness after coronary stent implantation. Recently, there has been increasing use of this agent after stent implantation in the carotid arteries. There is no data as to the effectiveness of this agent in this population. Methods: To determine the safety and efficacy of clopidogrel in patients undergoing carotid artery stenting we designed a multicenter registry involving 13 US centers that had performed more than 50 procedures and are using clopidogrel after stent implantation. All pts will undergo 30 days follow-up. Results: At this time, data has been obtained on 114 pts comprising 72 male and 42 female patients with a mean age of 64±9 yrs. Carotis artery disease and peripheral vascular disease were present in 72% and 30% of pts respectively. Culpit lesions were located in the left and right internal carotid arteries in 53% and 47% of pts respectively. Mean pre-procedure diameter stenosis was 82±11%. The self-expandable WallStent was implanted in 83% of pts achieving a mean post-procedure diameter stenosis of 2±6%. Angiographic procedural success was achieved in all pts. At 30 day follow-up, Transient ischemic attacks, minor strokes and major strokes occurred in 3.3% and 1.3% of pts respectively. There was no neurological death or intracranial hemorrhage. Conclusions: These preliminary data indicate that clopidogrel is safe and effective antplatelet agent in pts undergoing carotid artery stent implantation. Complete data on all registry pts will be available at the time of presentation.

P12
The Neuroanatomy of Post-Stroke Depression and Quality of Life
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Purpose: While neuroanatomical correlates of post-stroke depression (PSD) have been documented, their relationship to stroke-specific quality of life (QOL) is unknown. Specifically, PSD has been associated with left anterior lesions and the severity of PSD is known to relate to stroke depression scores. However, no association between PSD and stroke specific QOL has been previously described. We used a neuropsychological/neuroanatomical approach to search for neuroanatomical correlates of PSD, in a sample of ischemic stroke survivors.
Methods: Ischemic stroke survivors (n = 56) were recruited from the Neurorehabilitation program of a VA Medical Center. PTSD-QOL (Post-Stroke Quality of Life) was used to assess QOL. Depression Inventory or the Center for Epidemiologic Studies Depression Scale and the SSQOL were used to assess stroke-specific QOL. Lesions were classified stroke lesions as anterior, intermediate, or posterior, using standard techniques. T-tests, correlations and ANOVAs were used to assess relationships among lesion location and PSD and among lesion location and stroke-specific QOL. Results: PSD was identified as significant independent predictors of functional dependency or death (GOS 4 or5 ) (p = 0.01). However, in the logistic regression model, IVH, poor Hunt Hess grade, and advanced age were superimposed on T1 anatomical scans (acq. matrix-256*256; 124 slices; 1.2 mm thick; 50° flip angle). Activity was measured with PET scans, pre- and post-stroke, and also with PET scans following a 3 month washout period. Functional imaging results were compared to control subjects who were PET scanned under identical conditions. The study was approved by the institutional review board of each participating university.

P13
Intraventricular Hemorrhage Predicts Poor Outcome in Patients with Subarachnoid Hemorrhage
Background: Intraventricular hemorrhage (IVH) in patients with subarachnoid hemorrhage (SAH) is associated with a poor Hunt Hess score. SAH is known to cause neurological dysfunction, decrease post-stroke SA, more so in chronic than in subacute stages. Although the long-term functional outcomes and IVH are well documented, their relationship to stroke-specific QOL has never been examined. We prospectively examined 156 first-ever stroke patients twice: at 2-4 months and at 2 years after the stroke. Post-stroke depression was assessed using DSM-IV criteria. EI (excessive/inappropriate laughing/crying) and SA (sexual relationship, libido, sexual functions, erection, frequency, erectile function) were asked of the patients with the use of a standardized questionnaire. Results: Of the 156 patients, 80 who were sexually active prior to stroke were included. Of these, 7 were found to be depressed, and were excluded. Twenty-six patients (16% ) had EI, and 47 were emotionally stable (ES). SA including libido, sexual functions, and erectile functions were reported to have declined in 58%, 73% and 26% of the patients at 2-4 months, which recovered significantly (p<0.05) at 2 years and follow up. However, the recovery was less prominent in EI than in ES group patients (p<0.01). Multivariate analyses showed that low sexual frequency before stroke (LSFBS) was significantly (p<0.05) related to decreased post-stroke coital frequency while LSFS and the presence of EI were significantly (p<0.025) associated with decreased erectile function at post-stroke 2-4 months. At 2-year post-stroke, EI was found to be significantly related to decreased libido, coital frequency and erectile function(p<0.05). Age, gender, laterality of stroke, Barthel index, motor dysfunction and the presence of hypertension and diabetes mellitus were not independently related to SA at post-stroke 2-4 months and 2 years. Conclusion: EI is a factor significantly related to decreased post-stroke SA, more so in chronic than in subacute stages. Although the cause-effect relationship remains uncertain, post-stroke EI and SA changes may in part be attributed to an alteration of an identical neurotransmitter, serotonin.

P14
Longterm Follow-up in Patients with Cerebral Ischemia and Patent Foramen Ovale
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Background: Paradoxical embolism through a patent foramen ovale (PFO) is a potential cause of ischemic stroke, particularly in younger patients without other possible etiologies or risk factors for stroke. Longterm data concerning stroke recurrence in patients with PFO is scarce. Method: We evaluated stroke recurrence and bleeding complications on different treatments (aspirin, or no pharmacotherapy, aspirin or no treatment) in 102 patients with PFO and ischemic stroke diagnosed between 1991 and 1997, who came regularly to our vascular outpatient clinic. The mean follow-up was 17.2 months. In addition, a longterm follow-up of all 300 patients with PFO, diagnosed in association with cerebral ischemia in our department from 1991 to 1997, is currently performed for stroke recurrence rate and possible risk factors for recurrence. Results: Initial secondary prophylaxis in all patients after the first stroke was phenprocoumon. Sixteen patients were changed to aspirin or ticlopidine after 3 months to 3 years. The recurrence rate of cerebral ischemia was 3.3% per year, which is slightly above the rate of other studies. All events were transient ischemic attacks. No patient suffered from a new permanent stroke. The rate of bleeding complications on phenprocoumon (n=5) was 4% per year with one lethal complication (0.75% per year). The results of the longterm follow-up of all 300 patients in correlation to possible risk factors and treatment are going to be presented. Discussion: The pilot evaluation shows a low recurrence rate of cerebral ischemia in patients with PFO. Therefore, the need of a longterm anticoagulant therapy or an early interventional cardiovascular therapy seems to be uncertain up to now. The longterm data will provide more information about the recurrence rate of cerebral ischemia in patients with PFO and potential risk factors.

P15
Sexual Activities and Emotional Incontinence in Stroke Patients
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Background: Patients often develop depression or emotional incontinence (EI) after stroke. Although post-stroke depression has been shown to be related to decreased sexual activities (SA), the relationship between EI and SA has never been examined. Methods: We prospectively examined 156 first-ever stroke patients twice: at 2-4 months and at 2 years after the stroke. Post-stroke depression was assessed using DSM-IV criteria. EI (excessive/inappropriate laughing/crying) and SA (sexual relationship, libido, sexual functions, erection, frequency, erectile function) were asked of the patients with the use of a standardized questionnaire. Results: Of the 156 patients, 80 who were sexually active prior to stroke were included. Of these, 7 were found to be depressed, and were excluded. Twenty-six patients (16% ) had EI, and 47 were emotionally stable (ES). SA including libido, sexual functions and erectile functions were reported to have declined in 58%, 73% and 26% of the patients at 2-4 months, which recovered significantly (p<0.05) at 2 years and follow up. However, the recovery was less prominent in EI than in ES group patients (p<0.01). Multivariate analyses showed that low sexual frequency before stroke (LSFBS) was significantly (p<0.05) related to decreased post-stroke coital frequency while LSFS and the presence of EI were significantly (p<0.025) associated with decreased erectile function at post-stroke 2-4 months. At 2-year post-stroke, EI was found to be significantly related to decreased libido, coital frequency and erectile function(p<0.05). Age, gender, laterality of stroke, Barthel index, motor dysfunction and the presence of hypertension and diabetes mellitus were not independently related to SA at post-stroke 2-4 months and 2 years. Conclusion: EI is a factor significantly related to decreased post-stroke SA, more so in chronic than in subacute stages. Although the cause-effect relationship remains uncertain, post-stroke EI and SA changes may in part be attributed to an alteration of an identical neurotransmitter, serotonin.

P16
Bilateral Movement Enhances Cortical Activity Associated with the Paretic Hand in Acute Stroke: A Functional Magnetic Resonance Imaging (fMRI) Study
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Modern neuroimaging methods allow noninvasive study of brain plasticity mechanisms in patients recovering from stroke. Following recovery, patients performing unilateral motor tasks with the paretic hand demonstrate altered brain activity patterns. We report preliminary data from a longitudinal investigation of bilateral movement in patients recovering from stroke. Twenty-seven subjects having unilateral stroke (left hemispheric injury) were examined. All patients were recovering at least 4 months post-stroke. Seven patients (3 normal controls and 3 stroke patients (2 acute, 1 chronic)) performed tasks involving repetitive gripping with the left hand alone, right hand alone, and both hands simultaneously. All subjects performed a set of 37 tasks; 5 each for the left and right hands. Five tasks were performed without paretic hand involvement and 32 tasks included the paretic hand. Movement of the left hand alone, right hand alone, and both hands simultaneously activated the left hemisphere significantly more than right hemisphere when the left hand was not involved. When both hands were contralateral, movement with the left hand alone, right hand alone, and both hands simultaneously activated the left hemisphere significantly more than right hemisphere when the left hand was not involved. When both hands were ipsilateral, movement with right hand alone and right hand alone activated the right hemisphere significantly more than left hemisphere when the right hand was not involved.
Intracortical inhibition and excitation were measured using a paired-pulse paradigm of transcranial magnetic stimulation (TMS). Five patients with a right subcortical infarct and 4 controls were evaluated using a conditioning stimulus of 95% of motor threshold (MT) followed by a test stimulus of 120% of MT. Stroke patients were evaluated within 7 days and 1 month after onset. Interstimulus interval (ISI) varied between 3 and 10 msec. Responses were recorded in the 1st Response muscle. Amplitudes of conditioned responses were compared to unconditioned responses (test stimulus only). Results are summarized in figure 1. Observations in controls confirmed earlier reports of inhibition at short ISI and facilitation at longer ISI. In stroke patients, inhibition at short ISI was significantly lower than in controls (p < 0.03) for the unaffected hemisphere (UH), and showed a trend towards reduction in the stroke hemisphere (SH). At longer ISI, the intracortical facilitation in stroke patients was not different from controls and showed a trend to increase at 1 month. These results support a long-lasting disinhibition of the UH after stroke.

Figure 1: Comparison of Intracortical Inhibition and Facilitation Between Normal Subjects and Stroke Patients with Interstimulus Interval (ISI) of 10 ms after Stroke.

### P18

**Risk Factors for Continued Cigarette and Alcohol Use After Subarachnoid Hemorrhage**


**Background:** Cigarette and alcohol use are important lifestyle risk factors for aneurysmal subarachnoid hemorrhage (SAH). However, the frequencies and predictors of continued use of cigarettes, alcohol and cocaine after SAH have not been clearly defined. We examined changes in these three lifestyle factors in patients before and three months after SAH.

**Methods:** We prospectively studied 202 patients with aneurysmal SAH. Of the 166 patients discharged alive, we collected 3 month follow-up assessments on 140 patients (84%).

**Results:** Fifty-four percent (63/117) of patients smoked premorbidly; of those, 44% (26/59) had resumed smoking at three months. Of the 5 patients (<1%) who used cocaine premorbidly, both who followed-up had continued to use cocaine. Unmarried patients were more likely to continue smoking (64% vs. 32% married; p = 0.03), and younger patients (61% vs. 29% older; p = 0.02) were more likely to continue smoking. We found no other factors that were significantly associated with continued cigarette use. Likewise, we determined no factors that were significantly associated with continued alcohol use.

**Conclusion:** Three months after SAH, 44% of smokers continued using cigarettes despite its negative health consequences. The smokers who continued using cigarettes were more likely to be unmarried or of younger age. We identified no factors that were significantly associated with continued cigarette use. Likewise, we determined no factors that were significantly associated with continued alcohol use. Since cigarette use is the largest preventable risk factor for aneurysmal SAH, it is especially important to target smokers for aggressive intervention.

### P19

**Predictors of Return to Work After Subarachnoid Hemorrhage**


**Background:** Subarachnoid hemorrhage (SAH) continues to be an important cause of mortality and morbidity. Survivors are often unable to return to their premorbid activities. We sought to identify factors which were predictive of decreased work status in survivors of SAH at three months. Methods: A cohort of 166 consecutive patients with SAH who were alive at three months were included in the analysis. We included only those patients who were employed (full-time, part-time, or housewife) prior to admission (n = 101). We examined demographic factors, acute illness variables, and 3 month outcome measures such as emotional state and physical disability. A complete data set was available for 68% (69/101) of the patients. In a univariate analysis, we compared patients who were back to their baseline work status to those who had not returned to their premorbid level of work. Significant predictors of decreased work status after SAH were examined in a logistic regression.

**Results:** Sixty-one percent (101/166) of patients were employed prior to hospital admission. At 3 months 64% (62/97) of these patients had not returned to their previous level of employment. Forward stepwise logistic regression identified the following factors significantly related (p < 0.05) to a decreased work status: worst Hunt Hess during hospitalization (OR 17), At 3 months 64% (62/97) of these patients had not returned to their previous level of employment. Forward stepwise logistic regression identified the following factors significantly related (p < 0.05) to a decreased work status: worst Hunt Hess during hospitalization (OR 17).

### P20

**Functional Recovery in Brain Hemorrhage Versus Infarction: Distinct Trajectories of Cognitive and Motor Recovery During Inpatient Rehabilitation**

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Intracerebral hemorrhage and ischemic infarction can produce stroke syndromes with indistinguishable functional and neurologic deficits. The outcome may differ based on stroke mechanism. We studied whether these pathophysiologically distinct conditions are associated with specific trajectories of functional recovery. The medical records of all patients admitted to our hospital’s stroke rehabilitation program during 1997 and 1998 were reviewed. Functional recovery was assessed by changes in the Functional Independence Measure (FIM) scores, including the motor and cognitive subscores. Patients were included in the study if their primary reason for admission was a stroke syndrome with a corresponding lesion on CT or MRI and their complete FIM data were available. Of 541 stroke program admissions, 435 cases satisfied the inclusion criteria, including 363 infarcts (83.4%) and 72 hemorrhages (16.6%). Infarcts and hemorrhages were similar in terms of age, sex, stroke laterality and length of stay. Compared with the infarct group, the hemorrhage group included a higher proportion of patients with subarachnoid hemorrhage (p = 0.001) and cerebellar involvement (p < 0.05), and a lower proportion with hemorrhagic hipoponamic involvement (p = 0.001). The hemorrhage group had lower mean admission FIM scores (54.3 ± 24.5 versus 60.5 ± 25.0 for infarcts; p = 0.05). Increase in total FIM scores during inpatient rehabilitation did not differ between infarcts and hemorrhages (23.2 ± 16.7 for infarcts, 24.7 ± 16.5 for hemorrhages, p = 0.47). However, while the two groups had similar increments in the FIM motor subscores (20.3 ± 14.2 for infarcts, 20.6 ± 14.4 for hemorrhages, p = 0.81), they differed significantly in terms of increment in the FIM cognitive subscores (2.9 ± 4.5 for infarcts, 4.1 ± 5.2 for hemorrhages, p = 0.02). In a regression analysis, younger age (p < 0.001) and male sex (p = 0.01) were strongly associated with overall FIM increment but stroke location was not. We conclude that recovery of cognitive deficits in brain hemorrhage is accelerated compared with brain infarction, motor recovery in the two groups is not significantly different.
Poster Presentations

P22

Individual and Group Analysis of PET Activation Maps of a Simple Motor Task in Hemiparetic Patients and Age-Matched Controls
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Introduction: Most brain activation studies in motor recovery have concerned complex manual tasks in fully recovered pts, and most lacked individual statistical analysis and age-matched controls. We used 3D-PIPET and simple auditory cued thumb-to-index tapping (TIT, 1.26 Hz) of the affected hand. We compared each pt and the group to age-matched normals. Subjects and methods: 4 right-handed pts (60 ± 15 yrs) with partially recovered right-side pure motor hemiparesis due to first-ever striato-capsular stroke, were studied 1-4 mo after onset with H2O (ECAT HR TIT, 1.26 Hz). Task was replication 4 times each of i) rest with eyes closed, metronome on, ii) right TIT. Overactivations relative to healthy age-matched right-handed subjects (p<7, 60 ± 11 yrs) were assessed with SPM 96, and localization was based on MNI and Talairach’s templates. Stringent cutoffs (z>4.92 for individual and z>3.36 for group) were determined from permutation analysis on control group data. Results and comments: Group analysis: hyperactivations occurred in a distributed bilateral primary and secondary motor network including SM1 (hand area) and BA 40, similar to earlier reports, but & BI with some favoring the FIM and others the BI. Although difference in responsiveness is change on the MRS.

P23

Are the FIM Motor Scale and Barthel Index Responsive to Stroke Recovery?
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Objective: Two disability outcome measures frequently used to assess effects of interventions on recovery from stroke are the motor subscale of the Functional Independence Measure (FIM) and the Barthel Index (BI). The need to demonstrate the responsiveness of the FIM & BI to change is widely recognized, but no consensus has been reached on best methods of responsiveness. This study used multiple techniques to assess responsiveness to recovery over 3-6 months after stroke. Methods: Data on 1-3 month change in the FIM & BI were available for 401 of 459 participants in the Kansas City Stroke Study with 152 showing improvement on the modified Rankin Scale. Responsiveness to change was assessed with improved responsiveness to recovery over 3-6 months after stroke. Methods: Data on 1-3 month change in the FIM & BI were available for 401 of 459 participants in the Kansas City Stroke Study with 152 showing improvement on the modified Rankin Scale. Responsiveness to change was assessed with improved responsiveness to recovery over 3-6 months after stroke. Results: Individual analysis: overactivation of SM1 (hand area) occurred in the affected side in 3 pts and in the opposite side in 2 pts (both with mirror movements) and pattern of overactivation in secondary motor areas was highly variable among pts. Results and comments: Group analysis: hyperactivations occurred in a distributed bilateral primary and secondary motor network including SM1 (hand area) and BA 40, similar to earlier reports, but & BI with some favoring the FIM and others the BI. Although difference in responsiveness is change on the MRS.

Analysis of the ROC: sensitivity, specificity, and AUC, were calculated using the appropriate methods. AUCs were compared using the technique of 2D-PET and simple auditory cued thumb-to-index tapping (TIT, 1.26 Hz) of the affected hand. We compared each pt and the group to age-matched normals. Subjects and methods: 4 right-handed pts (60 ± 15 yrs) with partially recovered right-side pure motor hemiparesis due to first-ever striato-capsular stroke, were studied 1-4 mo after onset with H2O (ECAT HR TIT, 1.26 Hz). Task was replication 4 times each of i) rest with eyes closed, metronome on, ii) right TIT. Overactivations relative to healthy age-matched right-handed subjects (n=7, 60 ± 11 yrs) were assessed with SPM 96, and localization was based on MNI and Talairach’s templates. Stringent cutoffs (z>4.92 for individual and z>3.36 for group) were determined from permutation analysis on control group data. Results and comments: Group analysis: hyperactivations occurred in a distributed bilateral primary and secondary motor network including SM1 (hand area) and BA 40, similar to earlier reports, but & BI with some favoring the FIM and others the BI. Although difference in responsiveness is change on the MRS.

P24

Effects of Focal vs. Diffuse Pathology on Memory After SAH

Background: Cognitive dysfunction, particularly memory problems, are increasingly regarded as important and disabling sequelae of SAH. However, the precise cause of memory dysfunction after SAH remains unclear. We compared the relative impact of global and focal acute pathology on memory functioning 3 months after SAH. Methods: We prospectively recorded acute clinical and CT variables and performed a 3 month assessment of cognitive function in a multi-ethnic cohort of 96 consecutively admitted patients with SAH (mean age = 50, 63% female). Visual memory was measured with a composite score derived from the Rey Complex Figure and the Visual Reproduction subtest from the Wechsler Memory Scale-Revised. Verbal memory was measured with a composite score derived from the California Verbal Learning Test (CVLT). Factors representing diffuse injury were: Hunt Hess grade; SAH Sum Score, bicaudate index, and hydrocephalus. Variables selected as indices of acute focal pathology were: (for each hemisphere) lateralized SAH sum score, ventricular blood, temporal horn diameter, aneurysm location, infarction, and vasospasm in ACA/MCA territory. Acute predictors were correlated with the memory indices and variables with significant correlations were used as factors in 2 ANCOVA models. Results: Analysis of the differences in memory scores revealed no significant correlations with visual or verbal memory. Conclusion: Our study suggests that global and focal acute pathology may have a differential impact on memory function after SAH, depending on the chronicity of the diffuse injury that was related to memory functioning after SAH, including hydrocephalus.

P25

Proxy Ratings of Stroke-Specific Quality of Life (SS-QOL) Scores
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Background/Purpose: The SS-QOL is a newly developed and validated stroke-specific quality of life scale. Although proxy ratings of QOL are necessary for many stroke survivors due to stroke-related language or cognitive impairments, the relationship between patient (P) and proxy (Pr) SS-QOL scores is unknown. The purpose of this study was to evaluate the validity and accuracy of Pr SS-QOL ratings. Methods: Ischemic stroke survivors with no significant language or cognitive impairments were recruited as part of an ongoing study of the SS-QOL. Overall SS-QOL score and domain scores range from 1.0 (worst) to 5.0 (best). A trained interviewer independently administered the SS-QOL to patients and an identified proxy. All interviews were done between 1 and 6 months post-stroke and within 3 days of each other. Pearson product moment correlations were used to assess the relationship between P-Pr overall SS-QOL scores and individual domain scores. Paired t-tests were used to assess systematic differences between P and Pr QOL assessments. Results: The characteristics of the first 14 P-Pr pairs were: male-female; 53/47, 14/10 yrs. Most proxies were spouses (64%). Mean (sd) time from stroke to interview was 58 (50) days. Overall Pr SS-QOL scores were moderately correlated with P scores (r = .59, p = .03) and were not significantly biased (P<.03, P<.16). Physical domains such as mobility, self care and upper extremity function were highly correlated (r > .7) as were self-care. Psychological and social domains were less correlated (r < .5). For the SS-QOL, Pr systematically reported lower (worse) scores in the Personality (Pr-2.7, P-3.7, p = .03) and Family Roles (Pr-2.9, P-3.7, p = .03) domains. Conclusions: Overall proxy SS-QOL scores and physical domain scores are unbiased and significantly correlated with patient scores. Proxy responses on some psychosocial domains are less strongly correlated with patient responses, and proxies report significantly lower Personal and Family Roles scores. Ongoing field testing will evaluate whether overall proxy SS-QOL ratings can be reliably substituted for patient ratings.

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F26  Post-Stroke Depression and Emotional Incontinence: Correlation with Lesion Location

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Background: The role of the location of stroke on post-stroke depression (PSD) and emotional incontinence (PSEI) has not been well established. Method: We retrospectively studied 148 patients with single, unilateral stroke at 2-4 months after onset of stroke regarding the presence of PSD (using DSM-IV criteria and Beck Depression Inventory) and PSEI. Lesion location was assessed by CT/MRI. Results: There were 94 men and 54 women with the mean age of 62 years. Twenty seven patients (18%) had PSD and 50 (34%) had PSEI. The lesions included 120 cortex and 22 hemorrhage. The presence of PSD was not related to the location, laterality or the size of the lesion. The frequency of PSEI, but not of PSD, was higher in women than in men and in ischemic stroke than in hemorrhagic one (p<0.05, respectively). Although both PSD and PSEI were related to dysfunction and location (anterior vs. posterior cortex) of the lesion, the latter was a stronger determinant for PSD (p<0.05). The prevalences of PSD and PSEI were: 75% and 100% in the fronto-temporal stroke, 59.5% and 40% in predominantly frontal stroke of middle cerebral artery territory (n=18), 12.5% and none in occipital stroke (n=8), 19% and 45.2% in lenticulocapsular stroke (n=42), 10.5% and 15.8% in thalamic stroke (n=19), none and 33.3% in medullary stroke (n=3), 15.8% and 52.6% in pontine base stroke (n=19), 36.4% and 54.5% in medullary stroke (n=11) and none and 22.2% in cerebellar stroke (n=9), respectively. No patients with partial (n=10) or dorsolateral pontine (n=5) lesions had PSD or PSEI. The latter was more closely related to lenticulocapsular strokes.

F27 Depression After Subarachnoid Hemorrhage: Frequency, Predictors, and Impact on Quality of Life


Background: Depression is a well-established complication of stroke. However, the frequency, predictors, and impact of depression after subarachnoid hemorrhage (SAH) are less well defined. Methods: We prospectively investigated a multiethnic cohort of 202 patients with acute SAH (60% women, mean age 53 years). Risk factors studied included demographic factors, pre-existing psychiatric diagnoses, presence of SAH, type of aneurysm repair, and functional and cognitive discharge status. We assessed depression using the Center for Epidemiological Studies - Depression scale and quality of life (QOL) using the Sickness Impact Profile and Medical Outcome Study - Short Form 36 at three months (120 patients). Predictor variables were identified using multiple logistic regression after a univariate analysis to identify candidate variables. Results: Depression was diagnosed in 38% of patients at three-month follow-up. Univariate analysis identified the following risk factors: 1) demographics: less than 12 years of education, non-Caucasian, and non-English in English (P<0.001); 2) acute SAH stage: worst Hunt & Hess grade, cerebral infarction, and absence of intraventricular hemorrhage (P<0.003); 3) functional-cognitive status: low performance on telephone interview of cognitive status (TICS) and verbal attention test (VSAT) at discharge (P<0.002). However, only non-Caucasian (P=0.048), worst Hunt & Hess grade (P<0.001), and absence of intraventricular hemorrhage (P<0.001) were predictors of depression in logistic regression. Using the t-test for equality of means, all measurements of QOL were significantly (P<0.001) were predictors of depression in logistic regression. Using the t-test for equality of means, all measurements of QOL were significantly (P<0.001). Conclusions: The development of PSD and PSEI is strongly influenced by the lesion location, probably associated with the chemical neurotransmitter related to the fronto/temporal lobe-based ganglia-brainstem circuitry. Although the lesion distribution is similar between PSD and PSEI, the latter is more closely related to lenticulocapsular strokes.

P28 Functional Recovery Following Cerebellar Stroke

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Background: Functional recovery cerebellar stroke has not been well-defined to date. We studied patients admitted to a rehabilitation hospital following a new cerebellar stroke. Aims: (1) to quantify functional recovery at discharge from a cerebellar stroke. (2) to identify functional long-term functional recovery. (3) To identify variables in the acute phase which predict functional outcome. Methods: We retrospectively reviewed records of all patients admitted to a rehabilitation hospital in 1997 and 1998 following cerebellar infarct or hemorrhage. Clinical and neuroimaging data were recorded on all cases. Follow-up (FU) information was obtained by telephone interview. Disability at admission (A-FIM), discharge (D-FIM), and follow-up (FU-FIM) was quantified using the Functional Independence Measure (FIM), a time-adjusted 15-item scale of functional independence. Outcome measures were the change in FIM from admission to discharge and FU-FIM score. Feasible and multivariable analysis was performed to assess the effect of factors suspected to affect outcome. Results: 30 cases were identified, 23 male, 8 female, mean age 67.8 years. 23 cases had infarcts, (9 multiple infarcts, 7 had primary hemorrhages. 4 clinical syndromes were identified at presentation. Median A-FIM was 64.5, median D-FIM was 102.5 and median FU-FIM was 25. Coexisting cerebral infarcts were significantly associated with lower FU-FIM (p<0.04), with a trend for lower A-FIM in patients with multiple (brainstem or cerebral) infarcts (p=0.09). FU data was obtained for 23 (76.7%) cases. Stroke-MF interval was 18 months (9-31mo). There were 6 deaths (20%) and recurrent strokes, 5/0% at FU. FIM were obtained on 17 cases. Median FIM was 124. Comorbidities were significantly associated with lower FIM (p<0.05) with a trend towards lower FU-FIM in patients with initial stupor/coma (p=0.09). Age, hemorrhage or multiple infarcts did not predict F-FIM.

P29 Cardiovascular Stress Testing in Stroke Survivors

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Objective: The purpose of this study was to assess cardiovascular endurance in individuals with mild to moderate deficits after stroke. Methods: Thirty-four, ambulatory subjects comprised a cardiac stress test study. All subjects were examined by a cardiologist before testing and were considered at moderate risk for cardiovascular events before exercise was utilized. The exercise protocol included a 10 W/min. increase in workload and a consistent pedaling speed of 60 RPM. S Primary measures included percentage of maximum heart rate, peak VO2, peak METS, and duration of exercise. Results: Subjects (age = 71 ±11.1) scored a median of 2.4 on the Orpington Prognostic Stage (stroke severity), and had an average score of 23.8 on the Fugl-Meyer Lower Extremity Motor Score. The median time since stroke onset and completion of the stress test was 68 days. The percentage of maximum heart rate achieved was 77.5% with a median peak VO2 of 795 ml/min. The median duration of exercise was 4.7 min. and a median peak METS of 2.9. Conclusion: Individuals with mild to moderate deficits after stroke have extremely limited endurance. The peak METS reported in this study is equivalent to those required for basic activities of daily living. Therefore, it is important that the cardiovascular endurance in these individuals be assessed and addressed during rehabilitation.
Introduction The relationship between recovery of sensory functions after stroke and changes in SEFs has not been previously studied. Methods We recorded somatosensory evoked magnetic fields (SEF) to median nerve stimulation at one week and at three months in 14 patients with first ischemic MCA (middle cerebral artery) stroke presenting with somatosensory deficits. MRI was used for source localization. Two-point discrimination ability (2P) was measured at both times for all patients. SEFs were measured using a whole-head neuromagnetometer with 122 channels. Twenty-three age-matched healthy subjects served as controls. The neuronal generators of the first and the second cortical SEF deflection (N1m and P1m, respectively) at the primary somatosensory cortex were modelled with equivalent current dipoles. Results The amplitude of P1m increased significantly during follow-up at the affected hemisphere (p = 0.009, sign test), whereas the amplitude of N1m did not (p = 0.8). In five of the six patients with increased P1m, the severely impaired 2P also recovered. Conversely, 2P was improved in only one patient with no change in P1m. Four of the five patients with increased amplitude of P1m and recovered 2P had corticobulbar lesions; one had a posterior thalamic infarct. The increase in P1m correlated significantly with improved 2P (p = 0.01; V/square test). P1m and 2P were unchanged in the remaining seven patients. Conclusion In recovering stroke survivors, the recovery of sensory information can be detected using whole-head MEG. During follow-up, the increase of an early cortical SEF deflection originating in the primary sensory cortex paralleled the recovery of 2P. Thus, MEG may be useful for studying the recovery of sensory functions after MCA stroke.

P34

Attention and Learning Following Stroke
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The purpose of this study was to investigate systematically selected attention and motor learning abilities in older individuals with and without stroke. 36 stroke survivors and 30 typical adults over 60 years of age performed three laboratory tasks designed to assess different aspects of attention and learning. A divided attention task required participants to respond to the color of a series of alphabet characters as they were presented on a computer screen while at the same time monitoring the series of letters for a repeated letter. Dependent measures were response time and repeated letter report accuracy. A 2x2x2 attention task required participants to switch response criteria between different characteristics of a visual display (number of objects or shape of objects). The dependent measure was response time. A learning task involved a hand positioning device consisting of 4 instances of each of 4 types of switches. Participants manipulated the switches in sequences that were repeating or random. Motor learning was assessed by the decrease in response time in repeating versus random sequences. Results indicate that overall, stroke survivors were slower than typical older adults on each task. In the divided attention task, both groups were equally slowed by the requirement to perform two tasks at once. However, stroke survivors accomplished this at the expense of accuracy in reporting the repeated letter. The attention switching data showed a similar pattern - response time slowing with the requirement to switch attention for both groups, but stroke survivors were less accurate. Adults with and without stroke showed similar response time differences between the repeated and random sequences on the motor learning task, indicating equivalent levels of learning. This study suggests that attentional abilities are affected in chronic stroke-stroke survivors were able to match performance levels of typical older adults only by sacrificing accuracy levels. Learning ability as assessed in the present context appears to be preserved in stroke, indicating a complex pattern of preserved and affected cognitive abilities.

P35

Predictors of Anxiety Disorder After Subarachnoid Hemorrhage

Background: Anxiety disorder is a well-established complication of stroke. However, the frequency, predictors and impact of anxiety disorder after subarachnoid hemorrhage (SAH) is less well defined. Methods: We prospectively enrolled about 200 patients with acute SAH (60% women, mean age 53 years). Risk factors studied included: demographic variables, premorbid psychiatric medication or illness, acute physiologic parameters of SAH, type of aneurysm repair, and functional status. We assessed anxiety disorder using the State Trait Anxiety Inventory (STAI) and quality of life (QOL) using the Sickness Impact Profile and the Medical Outcome Study - Short Form 36 at 3 months (120 patients). Predictor variables were identified using multiple logistic regression after a univariate analysis to identify candidate variables. Results: The Anxiety inventory classified 27% of patients as having state and 35% as having trait anxiety at three months; 20% follow-up. Univariate analysis identified the following risk factors (P < 0.05): 1) demographic: non-Caucasian, non-fluency in English, history of alcohol use, history of depression, and premorbid unemployment; and 2) acute SAH stage: cerebral infarction and absence of intraventricular hemorrhage. However, only history of alcohol use, absence of intraventricular hemorrhage, and cerebral infarction (P < 0.02) were predictors of anxiety in logistic regression. Using the t-test for equality of means, all measurements of QOL were significantly (P < 0.01) worse in anxious individuals at three months: (P36

Gene Transfer of Calcitonin Gene-related Peptide Prevents Vasoconstriction after Experimental Subarachnoid Hemorrhage
Kazumori Toyoda, Frank M Faraci, Toshiharu Ueda, Shuichiro Ono, KU Med Ctr, Iowa City, IA

We have reconstituted adenoviruses (Ad5RSVprepro-CGRP) that expresses calcitonin gene-related peptide (CGRP), a potent vasodilator, and reported that gene transfer to neonatal rabbits in vivo expresses CGRP and attenuates contraction of the basilar artery in vitro. Peak expression of CGRP occurs 5 days after injection of the virus. In this study, we determined whether gene transfer of CGRP in vivo ameliorates cerebral vasoconstriction after experimental subarachnoid hemorrhage (SAH). Arterial blood was injected into the cervical magna of rabbits 5 days after injection of Ad5RSVprepro-CGRP (8 x 10^8 pfu), Adjalgal (control virus), or vehicule. Diameter of the basilar artery was measured using digital image angiography before (day 5) and 2 days after (day 7) SAH. CGRP levels in CSF from Ad5RSVprepro-CGRP-treated rabbits were 0.005±1.003 nM at baselines (day 0), 1.9±2.2 mU on day 5, and 2.0±3.5 mU on day 7. Thus, gene transfer with Ad5RSVprepro-CGRP produced a 400-fold increase in CGRP in CSF. In rabbits treated with Adjalgal, diameter on day 5 (1.00±0.25 mm) was 13% greater than in rabbits treated with vehicle or Adjalgal (984±13 mm, P=0.05), suggesting that gene transfer of CGRP increased resting diameter. In rabbits treated with vehicle or Adjalgal, diameter on day 7 (942±23 mm) was 23% smaller than day 5 (P<0.0005). In rabbits treated with Adjalgal, diameter on day 7 (906±10 mm) was not less than on day 5 (P=0.11), but was reduced by 19% (22±27 µm, P=0.001) after intracisternal injection of a CGRP receptor antagonist, CGRP (8.37±0.5 mmHg). Reactivity of the basilar artery in vivo was also determined 2 days after SAH (day 7). In rabbits after SAH, contraction of the basilar artery to serotonin was greater than after injection of artificial CSF instead of blood (P<0.01), maximal response (Rmax) 58±7 % vs. 42±11 %. The contraction was less after 2 days after SAH (Rmax 70±11 %) than after Adjalgal or vehicle (P=0.02). We conclude that gene transfer of CGRP in vivo to SAH rabbits attenuates contraction of the basilar artery, and prevents vasoconstriction in vivo in response to blood.

Poster Presentations

303
Adenoviral-Mediated Gene Transfer of Inducible No-Synthase Alters Vascular Function
Carol A Giannetti, Frank M Faraci, Yi Chu, Donald D Heistad, Univ of Iowa, Iowa City, IA

Expression of inducible NO-synthase (iNOS) occurs during inflammation and may have major effects on vascular tone, but it is difficult to isolate effects of iNOS per se from other effects of inflammation. We have constructed an adenoviral vector containing cDNA for iNOS (AdCMV-iNOS), to examine the hypothesis that gene transfer of iNOS to blood vessels impairs both vasocostriction and endothelium-dependent relaxation. The recombinant iNOS virus is very difficult to grow, and no previous studies have described vasomotor effects of gene transfer of iNOS. Function of carotid arteries from New Zealand White rabbits was examined in vitro 24 h after incubation with vehicle, AdNOS (10^9 pfu/mL) or a control virus (AdBglII, 10^9 pfu/mL). Contraction of carotid arteries in response to phenylephrine (PE) was impaired following iNOS gene transfer. For example, the force of contraction (in grams) produced by PE (1μM) in vessels treated with vehicle, AdBglII and AdiNOS, (n=11 or 12) was 4.5±0.3 (mean±SEM), 4.8±0.4 and 1.4±0.3 (P<0.01, AdiNOS vs. vehicle and AdBglII). Relaxation of carotid arteries to acetylcholine also was greatly impaired following iNOS gene-transfer. Maximum relaxation to acetylcholine (3μM) (expressed as percent relaxation following preconstriction with PE) was 70% ± 6%, 7.6% ± 1.7% in arteries incubated with vehicle, AdBglII and AdiNOS, respectively (n=8, P<0.01, AdiNOS vs vehicle and AdBglII). Responses to nitroprusside were normal in vessels following AdiNOS.

Aminoguanidine (AG, 300μM), or L-N-iminoisyln (L-NIL, 100 μM), which are relatively selective inhibitors of iNOS, improved both contractile function and endothelium-dependent relaxation in arteries transfected with iNOS. These data suggest that transgene expression of iNOS is a sufficient stimulus to produce impairment of contractation and endothelium-dependent relaxation in carotid arteries. Furthermore, this impairment occurs in the absence of systemic factors, such as activated leukocytes.

Acute Increases of Integrins αβ3 and αβ1β3 on Cerebral Microvessels in Ischemic Brain After Focal Embolic Cerebral Ischemia in Rats
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Integrins αβ3 and αβ1β3 are important in mediating thrombus formation. To determine whether these two integrins contribute to progressive impairment of cerebral microvascular perfusion after middle cerebral artery (MCA) occlusion, we investigated the temporal and spatial immunoreactivity of these two integrins in ischemic brains to correlate the patterns of expression to microvascular plasma perfusion and fibrin deposition. Rats (n=32) were subjected to 15 min to 4 h of embolic MCA occlusion. Monoclonal antibodies against rat αvβ3 murine αβ1β3 and murine or human integrins were used for immunohistochemistry. The number of vessels containing αβ3 or αβ1β3 immunoreactivity were measured using a MCID image analysis system. Cerebral plasma perfused vessels and fibrin deposition were measured in three dimensions by laser scanning confocal microscopy. αβ3 and αβ1β3 immunoreactivity was not detected in sham operated rats and in the contralateral hemisphere of animals. At 15 min of ischemia, αvβ3 immunoreactivity was detected on endothelial cells of a few vessels in the ischemic area (6.2%). At 1 h after embolic ischemia, αβ1β3 and αβ3 immunoreactivity microvessels significantly increased (876±305, p<0.01) throughout the ischemic area, at many of microvessels in the striatum were no longer αβ3 or αβ1β3 immunoreactive. One hour after embolic MCA occlusion, αβ1β3 immunoreactivity was initially detected, presumably on platelets and/or platelet derived microparticles, along the luminal surface of vessels in subcortex (23±7%. At 4 h of stroke, numbers of microvessels containing αβ1β3 or αβ3 immunoreactivity significantly (p<0.05) increased in the striatum (209±59) and the cortex (80±7). A significant reduction of microvascular plasma perfusion and an increase in fibrin deposition were detected in the subcortex at 1 h and extended to the cortex at 4 h of stroke. Our data suggest that acute increases in αβ3 or αβ1β3 on microvessels and deposition of platelet and/or platelet derived microparticles containing integrin αβ3 may contribute to progressive microvascular perfusion deficits after embolic MCA occlusion.
Threshold Duration of Ischemia for Cerebral Artery Myogenic Tone, Infarct Size and Neurologic Deficit

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This study investigated the time period of ischemia for which middle cerebral arteries (MCA) maintained myogenic activity and determined if this dysfunction correlated with infarct size and focal neurologic status. The MCA occlusion model in rats was used to induce variable periods of ischemia (15, 30, and 120 minutes), followed by 24 hours of reperfusion (confirmed by laser Doppler). Ischemic MCAs were then removed and studied in vitro in an arteriograph system that allowed control of transmural pressure (TMP) and measurement of lumen diameter. MCAs were equilibrated for 1 hour at TMP=75mmHg, after which diameter was recorded and the amount of myogenic tone determined. In these same animals, infarct volume was determined using TTC staining and focal neurologic status assessed using a 28 point scoring system. Sham-operated control arteries (n=6) developed 27±2% spontaneous myogenic tone at 75mmHg and had no area of infarction or neurologic deficit.

MCAs that were ischemic for 15 minutes (n=6) had similar tone as control arteries (%tone=25±5; p=0.05), however, longer periods of occlusion resulted in significantly diminished myogenic tone: %tone=11±2 for 30 minutes (n=8) and 8.5±2 for 120 minutes (n=9) of occlusion (p<0.01 vs. control for both). Infarct size also increased with increasing time of ischemia, as did neurologic deficit. The infarct size and neurologic score for animals with 15, 30 and 120 minutes of occlusion was: 5.4±2.2mm3 and 5.7±0.16; 9.3±2.1mm3 and 6.5±0.23; 38.7±7.7mm3 and 10.3±0.37 (p<0.01 vs. control for all). For individual animals, the amount of tone significantly correlated with both infarct size (% (p=0.025) and neurologic score (p<0.001) that the less the MCA possessed, the greater the infarction and the worse the neurologic deficit. These data demonstrate a significant effect of ischemia on the myogenic activity of MCAs, the threshold being between 15 and 30 minutes of occlusion. This dysfunction correlated with unfavorable stroke outcome, suggesting that MCA function may be an important determinant of ischemic brain damage by affecting cerebrovascular resistance during postischemic reperfusion.


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Introduction: Recent advances in magnetic resonance imaging (MRI) provide images or maps of relative cerebral blood flow (CBF) and mean transit time (MTT) of a tracer through the tissue. We compared relative CBF measurements by functional MRI with those of positron emission tomography (PET) to validate this technique in acute ischemic stroke. Methods: Permanent middle cerebral artery occlusion (MCAO) (n=10) and reperfusion after 2-hour ischemia (n=5) MCAO was induced transorally in pigs. CBF and cerebral blood volume (CBV) were measured before, 1 hour, and 6 hours after MCAO. Then, perfusion-weighted imaging (PWI) by dynamic gradient echo EPI with a bolus of magnetic susceptibility contrast agent ([15O]H2O) was performed. Results: MCAO induced a CBF decrease, which was demonstrated by both PET and PWI, in relation to the extent of collateral flow from the ACA to the MCA shown by DSA. After reperfusion, four pigs showed postischemic hyperperfusion correlated with the severity of previous ischemia, whereas one pig with mild ischemia failed to show hyperperfusion. Permanent MCAO increased CBV for regions with a CBF value greater than 60% of the contralateral value, whereas CBV was decreased for regions with a CBF value less than 60% of the contralateral value. In contrast, after reperfusion, CBV varied, i.e. increased or decreased, even for regions with a CBF value greater than 60% of the contralateral value. The measure of MTT (MTT = CBV/CBF) was extremely sensitive to mild ischemia of regions with CBF values above 60% of the contralateral value. CBF and CBV measurements by PWI were significantly correlated to those by PET (r²=97%); 77%, respectively). Conclusions: PWI assesses decreased CBF and CBV in acute stroke. As a valuable tool in clinical practice, PWI allows therapy to be tailored to the individual patient with acute stroke.

Diffusion Abnormality Predicts Derangement of Oxygen Delivery and Anaerobic Glycolysis/Cumulative PET/DWI Studies in Acute Stroke of Pigs

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Introduction: Pathophysiological imaging that distinguishes reversible from irreversible brain tissue allows therapy to be tailored to each patient during the first hours after onset of stroke. We investigated the correlation of the apparent diffusion coefficient (ADC) to physiological variables by PET when evaluating tissue viability. Methods: Permanent (n=10) or reperfusion (2-hour (n=5) MCAO was induced transorally in pigs. CBF, the partition volume of water (PVW: as an index of vasogenic edema), and CMRO2 were measured before and every hour for up to 6 hours after MCAO, at which time CMRGLC was measured. Then DWI and histology were performed. Results: Permanent MCAO induced a reduction of CMRO2 and CMRGLC related to the magnitude of residual flow as a function of time. The reperfusion was followed by postischemic hyperperfusion as well as by progressive declines of CMRO2 and CMRGLC that were correlated to the severity of the previous ischemia. DWI showed that the ADC decrease was significantly related to the reduction of CMRO2, and CMRGLC, both in permanent and reperfusion MCAO, whereas the ADC decrease failed to be related to the CBF decrease after reperfusion. The ADC decrease (< 80% of the contralateral value for permanent MCAO or < 70% for reperfusion) corresponded to the severely decreased CMRO2 (< 50% of the contralateral value) which led to infarction confirmed by histology. Moreover, the vasogenic edema estimated by PWV increased from 90% to 70% of the contralateral ADC value and thereafter decreased to 60% of the contralateral in permanent MCAO. However, after reperfusion the vasogenic edema remained normal above 75% of the contralateral ADC value and increased below 75-70% of the contralateral. Conclusions: A diffusion abnormality manifested by an ADC decrease is a good index of "tissue at risk" after stroke. An ADC decrease to less than 70% and/or to 70-75% of the contralateral indicates irreversible cellular injury and an endangered tissue due to anaerobic glycolysis, even within 2 hours of the MCAO. Thus, the regions with an ADC decrease of more than 80% of the contralateral after stroke can be fully rescued.

Aggregation Profiles Differentially Affect Stroke Outcome in Mice


In stroke, microvascular thrombus accrues distal to the primary occlusion. We compared the ability of 2 GPIIb/IIIa antagonists (GP Ib/IIa to platelet (plt) deposition and improve stroke outcome in mice. In vivo, XV454 inhibits both plt macro- and microaggregation, while YZ202 inhibits only the former. Mice were subjected to 45 min intraluminal middle cerebral arterial occlusion, then reperfused. At 23 hrs, we measured laser doppler cerebral blood flow (CBF), arterial occlusion, then reperfused. At 23 hrs, we measured laser doppler cerebral blood flow (CBF) of the ischemic hemisphere (% contralateral flow); infarct volumes (15NetVol) on serial cerebral sections; intracerebral hemorrhage (ICH) as maximal ICH diameter (mm) on coronal slices; and platelet/confluent platelet deposition of 111In-labeled plt. Four groups were studied in blinded fashion: XV454 (2 mg/kg IV, n=7), XV454-vehicle controls (n=6), YZ202 (2 mg/kg IV, n=7), YZ202-vehicle controls (n=7). At these doses, comparable levels of plt macroaggregation were observed for XV454- and YZ202-treated mice. Data (Table) show that despite similar inhibitory potencies of 2 GP Ib/IIa for plt macroaggregation, only the agent which inhibits both macro- and microaggregation plt accumulation. CBF and 15NetVol in stroke. Although increased ICH was noted with XV454, there was no mortality with either agent. GP Ib/IIa antagonists represent a new treatment approach for ischemic stroke, but the relative effect of a given agent on plt macro- versus microaggregation may be important in defining both efficacy and risk profile.

<table>
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<th>Condition</th>
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<td>63±2.4</td>
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*P<0.05 vs. control; **P<0.001 vs. control.
Cerebral arteriovenous malformations (AVMs) are vascular dysmorphogenesis forming a tangle of thin walled vessels which lack peri-endothelial support structure. Tie2 and VEGF receptors are endothelial cell-specific tyrosine kinases which appear to play a critical role in angiogenesis. During angiogenesis, endothelial cells differ to be regulated by VEGF and its receptors; Tie2, a receptor for angiopoietins, organizes peri-endothelial cell recruitment to form mature vessels. We hypothesized that the vascular phenotype of AVMs is a result of an imbalance between VEGF and Tie2 signaling and investigated protein expression of Tie2, VEGF receptor-1 (VEGFR-1) and VEGF receptor-2 (VEGFR-2) in AVM tissue. Methods: After biopsy, we obtained brain-frozen surgical samples from 5 AVM patients (n=5) and, as controls, cerebral cortex from 5 patients undergoing temporal lobectomy for seizure disorder. After homogenization, equal amounts of protein from each sample were subjected to immunoblot analysis using antibodies specific for Tie2, VEGFR-1, VEGFR-2 and the endothelial-specific cell marker, CD31. Results: CD31 was expressed in all samples to a similar degree. Tie2 was undetectable in all AVMs, whereas normal brain samples expressed abundant Tie2. VEGFR-1 was detectable in 4 out of 5 AVMs and VEGFR-2 was undetectable in all AVMs. In contrast, normal brain had weak expression of both VEGFR-1 and VEGFR-2. Discussion: The principal finding of this study is the absence of Tie2 receptor protein in AVMs, the lack of which may be responsible for a failure in the recruitment of peri-endothelial support cells in AVM vessels. Although VEGF receptors are normally down-regulated post-natal, an imbalance between Tie2 and VEGF signaling may contribute to the pathological angiarchitectue observed in AVMs.

Does Vasodilator-Stimulated Phosphoprotein Contribute to Risk for Intracranial Aneurysm? Rola N Al-Aouar, Helena Kuivaniemi, CMMG, Wayne State Univ, Detroit, MI; Antti Ronkainen, Univ of Kuopio, Kuopio Finland; Juha Hernesniemi, Univ of Helsinki, Helsinki Finland; Adnan Al-Raddadi, David Evans, CMMG, Michigan State Univ, East Lansing, MI; Anna-Maija Mylläri, Univ of Oulu, Oulu Finland; Gerard Tromp, CMMG, Wayne State Univ, Detroit, MI

Introduction: Intracranial aneurysm (IA) is a lethal disease involving dilatation, weakening, and subsequent rupture of blood vessels supplying the brain. Epidemiological studies suggest that IA is familial. The use of microstatelet markers in a genotype-wide scan suggested a susceptibility locus in the chromosomal region 19q13.2. We identified a number of genes in this region whose biological functions qualify them as candidate genes underlying IA pathogenesis, or development, or both. Our hypothesis is: there is at least one gene, with one or more alleles, that predisposes people to IA. One of the genes in the interval is the vasodilator-stimulated phosphoprotein (VASP). VASP is stimulated by a vasodilator, is phosphorylated, plays a role in signal transduction and cell-cell adhesion, and is a component of the actin-based stress-filaments; therefore, it is probable that VASP plays a role in local blood pressure regulation. Consequently, we considered VASP to be highly relevant to IA, and we chose it for positional-candidate gene analysis. Methods: We used the polymerase chain reaction (PCR) to amplify short regions encompassing the exons of the VASP gene. We sequenced the PCR products to identify one or more variants that could be used to construct a specific DNA test. Results: A sequence variant was identified at the nucleotide 1211 of the fourth intron in the VASP gene. Due to its location, the nt 1211 variant is unlikely to be the causative change that predisposes people to IA; however, it was used as a tool in a specific DNA test for association studies. Our specific DNA test was carried out on 114 Finnish IA patients and 145 Finnish controls. The genotype frequencies (P=0.047), and the allele frequencies (P=0.049), were significantly different between the patients and the controls. Conclusion: These results suggest that one or more alleles of the VASP gene, or a near-by mutation, contribute to increased risk for IA. Further experiments will require detailed analysis of the VASP and its neighboring genes to identify the causative mutations.

Mechanism of Endothelin-1 Induced Contraction of Rabbit Basilar Artery Alexander Y Zubkov, Shadon Rollins, Andrew D Parent, John Zhang, Univ of MS Med Ctr, Jackson, MS

Background: Endothelin-1 (ET-1) is a causative agent for cerebral vasospasm, a prolonged contraction of major cerebral arteries after subarachnoid hemorrhage. This study is undertaken to investigate the signal transduction of ET-1-induced contraction in rabbit basilar arteries. Methods: ET-1-induced contractions were recorded in isometric tension. MAP kinase inhibitors PD-98059 and UO126, JAK2 inhibitor AG-490, P13K inhibitor Wortmannin, Src inhibitor Damaclanthacin, tyrosine kinase inhibitors Genistein and PKC inhibitors Calphostin C and Staurosporine were used. Results: 1) ET-1 produced concentration-dependent contraction and MAPK activation in the rabbit basilar artery by activation of ERK (extracellular signal-regulated kinase)2. MAPK inhibitors PD-98059 and UO126 produced dose-dependent inhibition of ET-1-induced contraction. 2) Src tyrosine kinase inhibitor Damaclanthacin, PI 3K inhibitor wortmannin and JAK2 inhibitor AG-490 abolished ET-1-induced contraction. 3) PKC inhibitor staurosporine but not calphostin C abolished, and PTK inhibitor genistatin reduced partially, ET-1 induced contraction. 5) In arteries pre-contracted by ET-1, PD-98059, UO126, wortmannin, AG-490, genistatin and staurosporine, ET-1 induced hypertension was not observed. Conclusions: 1) Induced a biphasic and time-dependent activation of MAPK (Western blot). The response was observed at 5-30 mm, the level of MAPK was decayed at 60 mm and re-elevated at 2-4 hrs. 2) PD-98059, UO126, wortmannin, AG-490 and genistatin, but not staurosporine or wortmannin abolished the effect of ET-1 on MAPK immunoreactivity. Conclusion: This study demonstrated that PKT, MAPK and PKC all contribute to ET-1-induced contraction of rabbit basilar artery. MAPK is downstream on PKT, Src and JAK pathways, but not on PKC or PI3K pathways. Inhibition of these pathways may offer alternative treatment for ET-1 induced contraction and cerebral vasospasm.

Can We Safely Reverse Anticoagulation in High-Risk Patients with Cerebral Hemorrhage? Management Perspective in 142 Patients Thanh G Phan, Eelco F. M. Wijdicks, Mayo Clin, Rochester, MN

Background and Aim: Limited data is available to guide the management of anticoagulation in patients with cerebral hemorrhage (ICH) at high thromboembolic risk. Method: Review the outcome of anticoagulation discontinuation in 142 patients presenting with ICH and who have high risk of ischemic stroke. All the patients in this cohort had warfarin discontinued on admission. Results: The median follow-up was 74 years (range 23-98 years). The indications for anticoagulation were: mechanical heart valve (52 patients; group 1), atrial fibrillation and cardioembolic stroke (53 patients; group 2), and recurrent TIA/stroke (37 patients; group 3). The median prothrombin time on admission was 21.3 seconds (range 10.5-110 seconds). Prus stroke occurred in 27% and 43 % of group 1 and group 2 respectively. Death occurred in 42.6% of the 142 patients. The median time off warfarin in this cohort was 10 days (range 0-5840 days). The median time to ischemic stroke onset following warfarin discontinuation in 9 patients was 75 days (range 1-540 days). Only 3 patients who started the first week. In the 35 patients who had warfarin restarted, five had recurrence of ICH. The median time to ICH recurrence was 570 days (range 15-3345 days). Conclusion: Discontinuation of warfarin for 1-2 weeks has a low probability of embolic events.

Bradykinin Mediates the Effect of an ACE Inhibitor on the Lower Limit of Cerebral Autoregulation in Rats Junichi Takada, Tetsuko Nagao, Satooru Buyasai, Hisako Oboshi, Takahari Kitazono, Masatoshi Fujishima, Kyushu Univ, Fukuoka Japan

Background and purpose: In stroke patients with hypertension, the autoregulation curve of cerebral blood flow (CBF) shifts towards higher blood pressure levels. Angiotensin converting enzyme inhibitors (ACEIs) revert the change in autoregulation. Thereby, ACEIs prevent cerebral ischemia during antihypertensive treatments. It is believed that such effects of ACEIs on CBF autoregulation are achieved by the attenuation of large arterial constriction induced by angiotensin II (ATII). However, ACEIs also inhibit kininase II, which inactivates the breakdown of bradykinin (BK), and previous studies demonstrated that the inhibition of endogenous BK degradation participated in the acute antihypertensive effect of ACEI. Therefore we investigated whether the acute effect of an ACEI on the lower limit of CBF autoregulation is also mediated by the potentiation of BK-mediated vasodilatation. Methods: In 28 male Sprague-Dawley rats, CBF was measured by laser-Doppler flowmetry during stepwise controlled hypertension by exanguination. The lower limit of CBF autoregulation was defined as the mean arterial pressure at which CBF decreased by 20% of the baseline value. The rats were pretreated with an ACEI (captopril) in group A, a BK B2 receptor antagonist ( Hoe 140) in group B, and both captopril and Hoe 140 in group AB. Rats in group C were served as control. The lower limits of CBF autoregulation were compared among the 4 groups. Results: In group A, the lower limit of CBF autoregulation was 43±3.5mmHg (mean±SE), which was significantly lower than 57±5mmHg in group C. There were no statistical differences among groups B (69±3.5mmHg), (64±4.5mmHg) and C in the lower limit of CBF autoregulation. Conclusions: Inhibition of BK B2 receptor reverted the effect of captopril on the lower limit of CBF autoregulation. This result suggests that lowering of the lower limit of CBF autoregulation by captopril is mediated by the potentiated BK-mediated cerebral vasodilatation.
Detection of Specific Antibodies in Patients with Allergic Reactions to Alteplase

Martin Grund, Univ fuer Neurologie, Kiel Germany; Thomas Knoll, Roman L. Huber, Staudtisches Krankenhaus Hohenacch; Munich Germany; John Rudolf, Wolf-Dieter Heiss, Univ fuer Neurologie, Kiel Germany

Serious allergic reactions have rarely been reported with administration of alteplase. In two institutions 290 patients with acute ischemic stroke were treated with iv alteplase. We observed 4 cases with allergic reactions during alteplase infusion. One patient developed orolingual angioedema 45 min. after initiating the infusion. Three patients exhibited an anaphylactoid-type reactions 15, 30 and 50 min. respectively, after initiating the infusion. In all patients, symptoms resolved on iv and anti-allergy treatment and iv alteplase administration was administered. Previous exposure to alteplase could be excluded in all patients. Blood samples were drawn from all patients. They were analyzed with ELISA for antibodies to alteplase. In two of the patients with non-imaging human protein, it should not be immunogenic in humans. In a series of more than 1600 patients treated with alteplase for AMI, antibodies against alteplase could be detected in only 0.18 % of patients several days or weeks after treatment, none of them suffered from allergic reactions (Reed et al., Thromb Haemost 1990;64:276-80). Our results suggest that our patients had pre-existing antibodies which were cross-reactive with one or more components of alteplase and therefore precipitated the allergic reactions. The incidence of allergic reactions of >1% in our population underlines the importance of intensive care monitoring during thrombolysis with t-PA for acute ischemic stroke.

Using Prognostic Models to Select Intracranial Hemorrhage Patients for Acute Intervention

J. Claude Hemphill III, David C Bonovich, Geoffrey T Manley, S. Claiborne Johnston, Univ of CA, San Francisco, San Francisco, CA

Background: The use of prediction models to accurately and reliably distinguish patients at the time of intracerebral hemorrhage (ICH) presentation with regard to short-term mortality could improve patient selection for early intervention. Methods: Medical records and head scans of all 116 patients presenting with supratentorial ICH to the University of California and San Francisco General Hospital during 1997 and 1998 were reviewed. Complete information was available in 107 patients, and this was entered into two different prediction models of 30-day mortality after ICH. Model 1 (Tihochuk et al., Ann Neurol 1991;29:658-663) consisted of four variables: pulse pressure, Glasgow Coma Scale (GCS) score, presence of intraventricular hemorrhage (IVH) and ICH volume. Model 2 (Broderick et al., Stroke 1993;24:987-993) consisted of two variables: GCS score and ICH volume. For patients in whom 30 day outcome was not known, status at time last seen was used. Results. Overall mortality was 43% (46/107). Using 50% risk of death as a cut-point, model 1 had a sensitivity of 90% but a specificity of only 74%. Model 2 had a sensitivity of 93% and a specificity of 89%. Conclusions: Both models could be applied to our population with reasonable accuracy. Further validation in an independent cohort would be needed before applying either model to a patient presentation.

Intraarterial Laser Thrombolysis Therapy for Clinical Stroke: A Feasibility Study


OBJECTIVE AND BACKGROUND: Approved TPA thrombolysis is limited to three hours of stroke onset and is associated with a significant risk of hemorrhage. Intraarterial (IA) thrombolysis appears to extend the time window to six hours but takes up to two hours and is associated with a 10% risk of symptomatic ICH. By avoiding the use of thrombolytic drugs, IA laser thrombolysis has the potential to dissolve the clot within minutes with fewer hemorrhagic complications. We designed a phase II trial to confirm that our techniques work and to encourage us to expand the model to a phase III trial. METHODS: The laser system used consists of a Thulium laser (30Watt) and a YAG laser (15Watt). The laser light is directed through an optical fiber bundle and is focused on the clot using a pulsed dye laser emitting 577nm light that is selectively absorbed by the clot and not vessel wall. Clinical criteria include ischemic stroke with a NIHSS > 5 who can be treated within 8 hours (anterior) or 24 hours (posterior). Angiographic criteria include complete occlusion (TIMI 0) of a cerebral vessel with a diameter of 2-5 mm. Successful angiographic recanalization is defined as a TIMI 2 or greater and a residual luminal diameter of > 50%. Maintenance of patency and stroke injury is assessed by MRA/MRI at 24 hours and 30 days. Functional and neurologic outcomes and occurrence of AEs are assessed up to 90 days. Maintenance of patency and stroke injury is assessed by MRA/MRI at 24 hours and 30 days. Functional and neurologic outcomes and occurrence of AEs are assessed up to 90 days. Conclusions: Clinical experience with IA laser thrombolysis in stroke patients is the expected to be completed this fall and final results will be presented.

The ATLANTIS T-PA Acute Stroke Trial: Results for Patients Treated Within Three Hours of Stroke Onset

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Objective: To evaluate clinical outcomes in the subgroup of patients treated within 3 hours of stroke symptom onset in the ATLANTIS Thrombolysis for Acute Noninterventional therapy in Ischemic Stroke (ATLANTIS) study. Methods: Sixty-one of the 761 patients enrolled in the ATLANTIS study were treated within 3 hours of symptom onset (38 randomized to placebo, 23 received t-PA). The 90-day outcomes were evaluated with the NIHSS, modified Rankin, Barthel, and Glasgow scales. The 30- and 90-day mortality rates and the symptomatic ICH rates through day 10 were compared. Results: Baseline characteristics of the t-PA and placebo patient populations were well matched. Mean age ≥ 66 years and mean baseline NIHSS ≥ 12 for both groups; the median baseline NIHSS was non-significantly lower among the t-PA patients (9 ± 12, p = 0.4). The rates of highly favorable outcome (0.1) on the NIHSS were significantly increased in the t-PA group: 63% in the t-PA group, 26% in the placebo group at 90 days, p = 0.001. Non-significant trends in favor of t-PA were detected on the Rankin, Barthel and Glasgow scales. The rate of symptomatic ICH within 10 days of treatment was higher in the t-PA group (13% vs. 0%, p = 0.02). Mortality was non-significantly increased in the t-PA group (17% vs. 5%, p = 0.12) at both 30 and 90 days. Conclusion: Data from the subgroup of patients treated within 3 hours of symptom onset in the ATLANTIS trial support both the beneficial effects of t-PA and the increased risk of symptomatic ICH documented in the NINDS study.

Underlying Structure of the NIH Stroke Scale: Results of a Factor Analysis

Patrick J. Lyden, Univ of CA San Diego, MA; Daniel C. Broderick, Food & Wine Health System, Detroit, MI; Charles M Jackson, Univ of CA San Diego, La Jolla, CA; John Murler, NINDS, Bethesda, MD; Rashmi Kothari, Univ of Cincinnati Med Ctr, Cincinnati, OH; Thomas Brott, Mayo Clin, Jacksonville, FL; Justin A Zivin, Univ of CA San Diego, La Jolla, CA

Background and Purpose: No stroke scale has been validated as an outcome measure using data from a clinical trial demonstrating a positive therapeutic effect. Therefore, we proposed to use data from the NINDS t-PA Stroke Trial to determine whether the NIHSS was valid in patients treated with t-PA, and to explore the underlying clinimetric structure of the NIHSS. Methods: We performed an exploratory factor analysis of NIHSS data from Part 1 (n = 291) of the NINDS t-PA Stroke Trial to derive an hypothesized underlying factor structure. We then performed a confirmatory factor analysis of this structure using NIHSS data from Part 2 of the same trial (n = 335). We then tested whether this final factor structure could be found in t-PA and placebo treated patients serially over time after stroke treatment. Using 3-month outcome data, we tested for an association between the NIHSS and other measures of stroke outcome. Results: The exploratory analysis suggested that there were 2 factors underlying the NIHSS, representing left and right brain function, confirming the content validity of the scale. An alternative structure comprised of 4 factors could be derived, with a better goodness-of-fit: the first 2 factors could represent left brain cortical and motor function, respectively, and the second 2 factors could represent right brain cortical and motor function respectively. The same factor structures were then found in t-PA and placebo patient groups studied serially over time, confirming the exploratory analysis. All 3-month clinical outcomes were associated with each other at subsequent time points, confirming predictive validity. Conclusions: This is the first study of the validity of a stroke scale in patients treated with effective stroke therapy. The NIHSS appeared to be valid in patients with acute stroke, and for finding treatment-related differences. The scale was valid when used serially over time following stroke, up to 3 months, and showed good agreement with other measures of outcome. These data will be used to generate a modified NIHSS.

Intraarterial TPA in Acute Ischemic Stroke Related to Internal Carotid Artery Dissection

Laurent Derex, Hosp Neurologique, Service de Neurologie B, Lyon France; J.-P. Oury, Centre Hospitalier Universitaire, Lyon France; E. Pouine, Service de Neurologie, Lyon France; S. Galanaud, Service de Neurologie, Lyon France

Intravenous TPA in Acute Ischemic Stroke Related to Internal Carotid Artery Dissection

Wayne M Clark, Oregon Health Sci Ctr, Portland, OR; Brian W. Buckelew, Oregon Med Laser Ctr, Portland, OR

Little is known about the safety and efficacy of intravenous (IV) tissue plasminogen activator (t-PA) in acute ischemic stroke (AIS) related to internal carotid artery (ICA) dissection. Accordingly, we aimed to describe the outcome of 11 patients who suffered from AIS related to ICA dissection and were treated with IV t-PA (0.8 mg/kg, onset of symptoms within 7 hours before the initiation of therapy). By June 1999, 128 consecutive AIS patients referred to our stroke unit were treated with IV t-PA. Out of these, 11 patients (8.6%) had ICA territory AIS related to ICA dissection (2 women and 9 men). Mean age was 49 years (± 12.3). Mean day 90 modified Rankin Scale score was 2.4 (± 1.6). No death was observed and one intracerebral hemorrhage with clinical deterioration occurred. No local compressive sign, nor cranial nerve palsy were noted. Only 4 patients out of 11 made an excellent recovery (mRS 0–1) – and cerebral angiography performed in all cases confirmed the presence of persistent occlusion of the symptomatic ICA and/or middle cerebral artery in 9 out of 11 cases. Thrombolytic treatment with IV t-PA in AIS related to ICA dissection does not seem to carry an additional risk as compared to the currently admitted risk of IV t-PA in AIS.
Intravenous Tissue Plasminogen Activator for Internal Carotid Artery Occlusion— Outcome and Mechanisms of Recovery

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Background: It has been suggested that IV Tissue Plasminogen Activator (tPA) would not be able to thrombolise the large clot associated with Internal Carotid Artery (ICA) occlusion and therefore, would be ineffective in this setting. Vascular imaging, safety, and outcome of tPA therapy for ICA occlusion is not well described. Methods: We prospectively studied patients with ICA occlusion treated with IV tPA. All patients received bedside Transcranial Doppler and either Digital Subtraction or Magnetic Resonance Angiography acutely and in follow up. Occlusion and recanalization was assessed by: proximal ICA (PHCA), terminal ICA (TICA), and Middle Cerebral Artery (MCA). Baseline NIHSS and long term follow up Rankin scores were obtained. Results: We collected 20 consecutive patients; Age 63±9.8, Sex Male/Female 10/10. Acute resumption of flow in the PHCA or TICA (n=18) was complete 100%, partial 16%, and none 74%; in the MCA acute flow resumption (n=18) was complete 35%, partial 24%, and none 41%. Follow up outcome; Rankin 0-1 was 44%(n=8), Rankin 2-3 was 17%(n=3), Rankin 4-5 was 17%(n=3), Rankin 6(Death) was 22%(n=4). There was 1 TPA related intracerebral hemorrhage. Outcome was closely related to resumption of MCA flow (table). Conclusion: IV TPA therapy for ICA occlusion appears safe and may improve outcome. Most patients did not recanalize their ICA. Resumption of MCA flow, either by clot dissolution or collaterals was strongly associated with good outcome.

Resumption of Articular Flow and Outcome

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Multivariable Analysis of Predictive Factors Related to Outcome at Six Months After Intracranial Artery (IA) Thrombolysis for Acute Ischemic Stroke

Toshio Ueda, Saburo Sakaki, Shinshu Ohta, Shoro Ohue, Ehime Univ Sch of Medicine, Ehime Japan, William T C. Yuh, The Univ of Iowa, Iowa City, IA.

Background Recent reports have suggested that a rapid assessment of pretreatment residual cerebral blood flow (CBF) could be utilized to optimize selection criteria for thrombolysis in acute ischemic stroke patients to improve clinical outcome. We investigated retrospectively residual CBF and other clinical factors related to outcome at 6 months after IA thrombolysis using multivariable analysis. Methods Seventy-six patients received IA thrombolysis within 6 hours of symptom onset. Multiple regression method was used to analyze associations between the modified Rankin scale (MRS) at 6 months after treatment and clinical factors including age, infarction type, duration of ischemia, dose of urokinase, degree of recanalization, hemorrhage, National Institutes of Health Stroke Scale score (NIHSS), and residual CBF evaluated by pretreatment single-photon emission-computed tomography (SPECT). SPECT values were assessed using the regional-to-cerebella ratio (R/CE) ratio of ischemic region to cerebellum and asymmetry index. Results MRS at 6 months was good (0–3) in 65% and poor (4–6) in 35%. Factors significantly related to MRS at 6 months were: R/CE ratio (P < 0.0001), NIHSS at baseline and follow-up day (P < 0.0001), cardiogenic infarction (P = 0.0014), age (P = 0.0074), and recanalization grade (P = 0.0007). NIHSS of >20 (OR=6.17, CI: 2.57-14.48), R/CE ratio <0.35 (OR=3.61, CI: 1.23-7.26), cardiogenic infarction (OR=3.61, CI: 1.31-9.86), incomplete recanalization (grade <3) (OR=2.87, CI: 1.58-5.21), and older age (>75 years) (OR=2.81, CI: 1.57-5.02) were determined to be significant independent predictors of poor outcome. Conclusions The residual CBF, neurologic score at baseline and following day, age, and recanalization grade correlated significantly with the residual CBF. The pretreatment NIHSS may be key predictors of long-term clinical outcome after intra-arterial thrombolysis in acute ischemic stroke patients.

Immediate Anticoagulant Therapy for Acute Ischaemic Stroke: A Systematic Review of Seven Randomized Controlled Trials Directly Comparing Different Doses of the Same Anticoagulant

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Background: A recent published systematic review showed that in direct comparisons with control, anticoagulants used in the treatment of acute ischemic stroke provided no net short or long-term benefit, and resulted in a significant increase in intracranial hemorrhage. We have subsequently aimed to determine whether, for a given anticoagulant agent, a higher or lower dose regimen has a more favorable balance of risk and benefit in the treatment of acute ischemic stroke. Methods and Results: A systematic review of all randomized controlled trials (RCTs) directly comparing different doses of anticoagulant in patients with acute ischemic stroke was performed using the search strategy of the Cochrane Collaboration Stroke Review Group. Seven RCTs were identified which directly compared high and low doses of: unfractionated heparin (two trials), low molecular weight heparin (two trials), heparinoid (two trials) and specific thrombin inhibitors (one trial). The two heparinoid trials (345 patients) were confidential and unpublished; data were not available for inclusion in this review. One small trial of unfractionated heparin (11 patients) did not provide data on clinically relevant outcomes; data were available for the four remaining trials, and included a total of 10,543 patients. When compared to lower doses, higher doses of anticoagulant significantly increased the odds of symptomatic intracranial hemorrhage (odds ratio [OR] 2.21, 95% Confidence Interval [CI] 1.59-3.06) but did not reduce the risk of recurrent stroke (OR = 1.21, 95% CI 0.96-1.53), death from all causes (OR = 1.04, 95% CI 0.95-1.14), or death or dependency at final follow-up (OR < 0.98, 95% CI 0.91-1.06). This pattern was the same for all types of anticoagulant evaluated. Conclusion: Compared to low doses, higher doses of anticoagulant increase the risk of intracranial hemorrhage, but do not improve the overall short or long-term outcome in patients with acute ischemic stroke. If anticoagulants are to be used at all for treating acute ischemic stroke, the dose should be kept as low as possible.

Cerebral Angioplasty and Stenting for Intracranial Atherosclerotic Occlusive Diseases


Background and purpose: To safely perform percutaneous transluminal cerebral angioplasty (PTCA) for intracranial arteriographic lesions, complications and restenosis following PTCA must be prevented and reduced. Our purpose was to assess the effect, safety and short-term arteriographic or clinical outcomes following cerebral angioplasty and stenting (CAS) for intracranial atherosclerotic occlusive lesions. Methods: Between February 1997 and March 2017, 16 patients (15 men and 1 woman) with 18 intracranial atherosclerotic occlusive lesions underwent CAS using balloon-expandable coronary stents. Age ranged between 43 (±10) and 66 (±11) years. Thirteen patients were treated in the chronic stroke stage, 2 patients in the acute stroke stage and one patient suffering crescendo ischemic attacks. Results: Sixteen lesions in 14 patients were sufficiently dilated without any complications. AE stents were implanted in 12 lesions, Multilink stents in 2 lesions, a NIR stent in one lesion and GR2 stent in one lesion. In 4 lesions, restenosis was observed at the stent sites during follow-up (6-18 months). Arteriographic restenosis occurred in one patient 6 months after CAS with GR2. Conclusion: Cerebral angioplasty and stenting may be a safe and effective means to resolve an intracranial atherosclerotic occlusive disease and yield a favorable arteriographic and clinical outcome.
Stroke Treatment Economic Model (STEM): Predicting Long-Term Costs from Functional Status

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Background and Purpose: As new therapies for acute ischemic stroke are forthcoming, there is an increasing need to understand the long-term economic implications of acute stroke treatment. Yet their elucidation in the context of drug development is problematic given the time and design constraints. An economic disease model was created to fill this information gap.

Methods: The model is divided into three modules: (i) an acute one incorporating short-term clinical trial (or other) data, (ii) a long-term one—composed of several Markov submodels—predicts transitions over time among locations based on two population studies, and (iii) a bridge component groups the survivors at the end of the acute module according to functional status and location. Functional groups are defined based on the Barthel Index or Rankin score. An example of the analyses that can be conducted with STEM is provided using data collected in two international clinical trials of a neuroprotectant drug (1,341 patients).

Results: Using the trial data in the acute module, the mean cost of managing a stroke patient acutely is approximately $16,490 (Euro 15,690). Hospital stay was the major cost driver accounting for more than 70% of this cost. By the end of the trials, there was a pronounced difference in the distribution of patient locations between the two functional groups: 81% of the survivors with a minor stroke were at home compared to 39% of those with a major stroke. It is predicted in the long-term module that the mean subsequent cost over 15 years amounts to $65,605 USD (Euro 61,210) per patient. 124,566 USD (Euro 116,221) for a major stroke versus 45,894 USD (Euro 42,820) for a minor stroke.

Conclusions: Linking functional recovery observed at the end of acute stroke treatment with patients’ treatment and residential locations allows STEM to estimate the long-term economic impact of interventions for acute ischemic stroke. Since medium to long term data on patient location are available, the quantification of the long-term stroke impact is data driven and thus enhances the confidence in the predicted results.

Does Exact Indication Prevent Hemorrhagic Complications Using Streptokinase in Acute Ischemic Stroke?

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Background: The improvement of rapid and accurate stroke identification by prehospital personnel (ambulance service) could significantly increase the number of patients admitted to the hospital in the therapeutic window period and could expedite the administration of therapy. Objective: The aim of our study was to estimate the accuracy of stroke diagnosis by paramedics in the prehospital period. Methods: This prospective study included all consecutive stroke patients diagnosed by a stroke unit team between March and August, 1999. Prehospital diagnostic errors (false positive or false negative) were estimated by comparison between the ambulance unit and stroke unit records. The sensitivity and specificity of diagnostic methods in the prehospital period with negative and positive predictive values were analyzed. Results: Of 267 stroke patients identified by the stroke unit team, 171 patients were hospitalized by ambulance units with the diagnosis of stroke. Of those, stroke was not confirmed by the stroke team (false positive error) in 46 patients (27%). Additionally, of 931 patients diagnosed by paramedics as having non-vascular neurological disorders, 27 patients were identified as having stroke by the stroke team (3% false negative error). Prehospital diagnosis of stroke had a 82% sensitivity and a 95% specificity; it had a 73% positive predictive value and a 97% negative predictive value. Conclusion: The accuracy of acute stroke diagnosis by prehospital personnel must be increased by special training.

Center

Medical Effectiveness and Medical and Economic Efficiency of a Stroke Treatment Center

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Introduction: We determined the medical effectiveness and medical and economic efficiency of a stroke treatment center (STC), a comprehensive multidisciplinary program for stroke. We compared stroke outcomes at our University Hospital (UH) before and after the initiation of the STC.

Methods: Our UH has provided stroke unit care through the department of neurology since 1970. In August 1996 we launched a STC having a broader and integrated emphasis on stroke treatment from the prehospital evaluation through the rehabilitation phase of care. Our STC has 24 hr/day acute treatment capability with stroke neurologists, neurologic and vascular surgeons, and interventional neuroradiologists. Using Hospital Service Cost Review Commission data for diagnostic codes 434 and 435 we computed the total yearly admissions (TYA), and compared by Mann-Whitney test the following stroke outcomes for the year prior to and for two consecutive years after STC initiation: hospital mortality (HM), length of stay (LOS), and hospitalization cost (HC).

We determined the percentage of patients receiving IV t-PA among all patients and of those with ischemic stroke diagnosis arriving at our UH within three hours of symptom onset. We calculated mean time to treatment (MTT), and compared by Pearson Chi Square test three month outcomes of our stroke patients receiving IV t-PA therapy with those of the t-PA treated group in the NINDS IV t-PA study. Results: For diagnostic codes 434 and 435 TYA increased; LOS and HC decreased; HM did not change. 27% of all patients, and 44% of patients diagnosed with ischemic stroke arriving within three hours of symptom onset received IV t-PA. MTT for t-PA patients transported by 911 was 125 mins. Three month outcome for t-PA treated patients compared favorably with those in the NINDS study. Conclusion: Development of an STC provides medically effective and efficient care for stroke patients and is cost efficient over standard stroke unit care. (Supported in part by USPHS training grant HL07612-14.)
Background and purpose: Tissue plasminogen activator (tPA) has been recently approved in Canada (Feb. 1999) for treatment of acute ischemic stroke based on the NINDS tPA trial. In contrast to the growing post approval experience in the United States, there is limited data to address safety and efficacy of IV tPA in routine clinical practice in Canada. The purpose of this study was to assess our center’s experience with IV tPA for acute stroke by reviewing 1) safety, 2) treatment time, and 3) outcome.

Methods: Retrospective chart review of all patients (n=311) receiving IV tPA for acute ischemic stroke at the University of British Columbia (Vancouver Site) from May 96 to March 99. Follow-up data was obtained by telephone interview. Results: Symptomatic intracerebral hemorrhage occurred during the first 36 hours in 1 (3.6%) patient. One patient (3%) had a systemic hemorrhage which required transfusion. The median time from onset of stroke to treatment was 170 minutes (range 124-190 minutes). The median “door to needle” time was 84 minutes (range 19-140 minutes). There was an inverse relationship between the time from stroke onset to hospital arrival and the “door to needle” time. For each 10 minute delay in time from stroke onset to hospital arrival, there was a 7 minute decrease in the door to needle time (p<0.001). During the three years examined, there was an improvement in the median “door to needle” time of 20 minutes. At time of follow up 39% of patients had a favorable outcome on the mRS (0-1) and 45% had a favorable outcome on the BI (95-100). Conclusions: Our safety and patient outcome compare favorably to NINDS and Phase IV data. The median “door to needle” time lengthened as more treatment time was available and the “door to needle” time was beyond recommended standards. However, treatment times improved with added experience. This review has enabled us to streamline our therapy. Sites should periodically audit their data to ensure safety and improve efficiency.

Risk of Early Anticoagulation After Thrombolysis

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Introduction: Early use of heparin after iv thrombolysis in acute stroke is still controversial.

Objective: To compare incidence of hemorrhage in two matched-pair samples that received different heparin regimens immediately after thrombolysis. Methods: Beginning in March 1996, we offered iv r-PA to more than 200 stroke patients in a prospective open study with inclusion criteria similar to those of the NINDS trial. The first 100 patients received 24000 IU heparin/4 (high dose, adjusted to 1.5-2 times APTT) immediately after thrombolysis, the following received low dose intravenous heparin (10000 IU). Two groups of patients with different heparin regimens were matched for baseline NIHSS and age. All patients underwent CCT at baseline, after 24 h and at day 5-2 NIHSS was assessed on admission, at 24 h and at 3 months. Hemorrhagic transformation was classified as hemorrhagic infarction or parenchymal hematoma (Pessin et al. Clin Neuropathol.13(271-289). Parenchymal hematoma was subdivided into symptomatic and asymptomatic. Results: 45 pairs of patients were analyzed. Median baseline NIHSS was 11.5 pts (range 2-22 pts). Incidence of parenchymal hematoma was higher in the high dose heparin group (p=0.039)(table). All symptomatic hematoma in the high dose heparin group were fatal (vs. 1 in the low dose group). NIHSS scores after 24 h and 3 months were not significantly different in both groups.

Conclusion: High dose heparin immediately after thrombolysis increases the risk of parenchymal hematoma. Whether this risk can be outweighed by a potential benefit needs further elucidation.

Determinants of Emergency Medical Services Use for Patients Presenting to the Emergency Department with Stroke Symptoms

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The use of emergency medical services (EMS) has been associated with shorter delays from the onset of stroke symptoms to hospital arrival and treatment; however, the determinants of EMS use among stroke patients have been evaluated in only a few studies. The Second Delay in Accessing Stroke Healthcare (DASH-II) study prospectively evaluated 617 patients presenting with stroke-like symptoms to emergency departments (ED) in three states. Among the 610 patients with information on EMS use, 46% were male, 48% were over 70 years of age, 69% were white, and 46% arrived by EMS. Use of EMS did not differ by gender, but increased with age, such that 57% of those older than 70 years of age used EMS but only 35% of those 70 years or younger. After adjusting for age and gender, there were differences in EMS use by study center. After adjusting for age, gender, and study center, patients that lived alone were less likely to use EMS (OR=0.65, 95% confidence interval (CI)=0.43-0.97). When patients were asked about possible reasons for delay, concern for cost was not associated with EMS use (OR=0.95, CI=0.50-1.75). EMS use was also not associated with a prior history of stroke (OR=0.95, CI=0.65-1.40), knowledge of stroke symptoms (OR=0.71, CI=0.46-1.08), or self-report of having been told that they were at high risk for stroke (OR=0.91, CI=0.61-1.33). Surprisingly, patients who reported having received information about the symptoms of stroke any time in the past were less likely to use EMS (OR=0.64, CI=0.42-0.96). In contrast, patients who reported a high sense of urgency (10 on a 10 point scale) to seek medical care for their symptoms were more likely to use EMS than those that expressed less urgency (1 to 9 on a 10 point scale) (OR=1.62, CI=1.06-2.47). In this population, conveying information about stroke symptoms in a way that emphasizes their urgency may be an effective intervention strategy to increase EMS use and thereby reduce delay time.
Misdiagnosis of Subarachnoid Hemorrhage: Frequency, Risk Factors, and Clinical Impact

Background: Misdiagnosis of subarachnoid hemorrhage (SAH) can have severe consequences. We sought to determine the frequency and risk factors of misdiagnosed SAH, and evaluate its clinical impact. Methods: Between July 1996 and December 1998 a multiethnic cohort of 202 consecutively enrolled patients (men, age 53) with acute SAH was prospectively studied. We recorded the type of contact (ER, MD office, Clinic or Hospital Admission), tests performed (CT or LP), and preliminary diagnosis of all medical contacts prior to admission to Columbia Presbyterian’s Neuro-ICU. Demographic and clinical factors were compared in patients who were correctly diagnosed or misdiagnosed, and the impact of deterioration for misdiagnosed individuals was analyzed. Results: Twenty-seven of 202 (13%) patients with SAH were misdiagnosed. The majority of misdiagnosed patients were initially evaluated in an ER (56%, 15/27) or an MD office (26%, 7/27). Migraine or tension headache was the most common misdiagnosis (52%, 13/25). The most frequent diagnostic mistake was failure to obtain a CT scan (74%, 20/27). An additional 15% (4/27) were misdiagnosed due to misinterpretation of CT scan results. Patients who were misdiagnosed were more likely to have a Hunt Hess grade of 2 (84%) than those correctly diagnosed (39%) (p=0.001). Demographic factors were not significantly different for the two groups. Thirteen of 27 misdiagnosed patients (48%) subsequently deteriorated before they were correctly diagnosed, including 7 with a decrease in Hunt Hess grade and 4 from rebleeding. Conclusion: Nearly 15% of all patients hospitalized for SAH are initially misdiagnosed, and good grade patients are at the highest risk. Emergency room clinicians need to have the highest index of suspicion for SAH, especially in mildly symptomatic patients.

Low Molecular Weight Heparins and Heparinoids in Acute Ischemic Stroke: A Systematic Review
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Low molecular weight heparins and heparinoids (LMWH) appear to be superior to unfractionated heparin with respect to safety and efficacy in venous thromboembolic disease and acute coronary syndromes. However, their role in ischaemic stroke remains unclear although they are frequently used. We have systematically reviewed randomised trials of LMWH in acute ischaemic stroke to determine their safety and efficacy. Trials were identified from the Cochrane Library (v. 2, 1999) and previous systematic reviews, and included if they were randomised, placebo or open controlled, non-confounded, initiation treatment within 7 days of stroke onset, had CT to exclude primary haemorrhage, reported by the end of 1998, and recorded outcome. Eleven completed RCTs involving 3048 patients were identified; data were available from ten of these. Four trials explicitly excluded patients with presumed cardioembolic stroke. Treatment with LMWH was associated with trends to increased end-of-treatment (OR 1.22, 95% CI 0.87 to 1.71) and end-of-trial (OR 1.04, 95% CI 0.85 to 1.29) case fatality; the combination end-point of death and disability was non-significantly reduced (OR 0.83, 95% CI 0.70 to 1.05). Whilst LMWH significantly reduced the incidence of postoperatively identified deep vein thrombosis (DVT, OR 0.36, 95% CI 0.21 to 0.61) and symptomatic pulmonary embolism (PE, OR 0.28, 95% CI 0.14 to 0.59), they increased the risk of symptomatic intracranial haemorrhage (OR 1.83, 95% CI 1.04 to 3.24) and major extracranial haemorrhage (OR 2.16, 95% CI 1.26 to 3.70). Although LMWH reduce venous thromboembolic events in patients with acute ischaemic stroke, they increase the risk of intracranial and extracranial bleeding, and do not appear to improve survival and disability after stroke. LMWH should not be used in the routine management of patients with ischaemic stroke. However, their ability to reduce DVT and PE means they may be beneficial in stroke patients at particular high risk of venous thromboembolic events, e.g. those with morbid obesity or inherited coagulopathies. Ongoing studies may further define the role of LMWH in acute ischaemic stroke.

Non-Hospitalized TIA and Stroke: Management by Primary Care Physicians
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Background: Patients with TIA or stroke frequently first contact their primary care physician (PCP) rather than seeking care at a hospital emergency room. There are little data available indicating how PCPs manage these patients. Methods: We carried out a systematic audit of the medical records of 176 patients with no prior history of cerebrovascular disease, who presented with a new TIA (n=95) or stroke (n=81) to one of 27 general internal and family medicine practices located in 2 cities. Results: Seventy-nine percent of those with TIA vs. 88% with stroke were evaluated on the day their symptoms occurred (p=0.12). Only 6% were admitted to a hospital for evaluation and treatment on the day of the index visit (2% TIA; 10% stroke, p=0.03); only an additional 3% were admitted over the subsequent 30 days. Seventy percent were consulted for 45% of patients. A brain imaging study (CT/MRI) was ordered by the PCP at the index visit in 27% (21% TIA, 35% stroke; p=0.44), regardless of whether the patient was also referred to a specialist. Carotid ultrasonic studies were obtained in 25% (36% TIA, 12% stroke; p=0.003), EKGs in 19% (18% TIA, 21% stroke; p=0.60), and echocardiograms in 16% (19% TIA, 14% stroke; p=0.34). Specialists obtained brain CT or MRI in an additional 3% and carotid ultrasounds in an additional 10% at the first visit. Of the non-hospitalized patients who did not have any diagnostic procedures at the time of the index visit (36% of patients), 8% were hospitalized and 3% had additional tests over the next 30 days. Twenty-two percent of patients (31% TIA, 33% stroke; p=0.70) were not hospitalized and had no evaluations performed over the first month after presenting to a PCP with a first TIA or stroke. Conclusion: These data show that only a very small proportion of patients evaluated in a PCP’s office for a first TIA or stroke are hospitalized and that the majority are managed without specialist consultation. Only a minority had either brain or cerebrovascular imaging studies, or additional cardiac tests. Nearly 1/3 of all TIA and stroke visits were not evaluated. Further PCP education regarding the importance of promptly and fully evaluating patients with TIA or stroke may be warranted.
Decline in Blood Pressure During Transesophageal Echocardiography (TEE)

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Methods: The use of TEE was investigated using commercially available, comprehensive data tracking software specifically designed for use in stroke populations. All TEE data were collected from consecutive ischemic stroke and TIA patients from August 1,1997 to July 30, 1998. The data included all heart rate (HR), systolic (SBP), diastolic (DBP) and mean blood pressures (MBP), time and dose of narcotics used for conscious sedation, and time of probe insertion and removal. Results: The population consisted of the 192 ischemic stroke and TIA patients admitted to a university affiliated urban hospital. Of those, 152 had echocardiography as part of their diagnostic work-up, 79/52% had TEE. Of the 79 TEE patients, 51/64% had complete vital sign, drug and probe insertion times. Though not typically the highest BP recorded during the procedure, the first blood pressure recorded prior to the start of the procedure was used as baseline and compared to the lowest pressure recorded during the procedure. Analysis of the data showed that during the procedure the mean drop in SBP, DBP, and MBP was 25%, 24%, and 25%, respectively. Over half of all patients experiencing at least a 25% decline in pressure. Blood pressure decline consistently began with administration of conscious sedation and continued throughout the procedure. The decline of BP did not coincide with insertion of the imaging probe, nor was there a concomitant decrease in heart rate, indicative of vagal response. Discussion: The data show a clinically significant decline in BP relative to administration of narcotic medications for conscious sedation. The data do not suggest that the vagal response is responsible for the drop in BP. The mean drop in BP is outside the hypothesized compensatory range for the cerebral autoregulatory mechanisms. Conclusion: Decline in BP may be a frequent and serious complication of conscious sedation during TEE. Interventions may include optimal hydration, holding antihypertensive medications prior to the procedure, and evaluation of medications used during conscious sedation.

Combined Intra-arterial and Intravenous Thrombolysis Therapy for Acute Ischemic Stroke

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Objective: To determine the feasibility of combined intravenous (IV) and intra-arterial (IA) thrombolytic therapy and evaluate its associated risks. Background: The early administration of thrombolytic agents improves outcome in patients with acute ischemic stroke. Prompt reperfusion appears important in assuring good recovery. Several reports have commented on IV or IA routes of treatment. IV treatment with smaller than recommended doses followed by IA infusion near the site of vessel occlusion may increase the rate of recanalization and lead to better clinical results with reduced frequency of intracranial hemorrhage (ICH). Methods: Our Brain Attack Team evaluated patients presenting within 3 hours of symptom onset. Those patients who did not appear to be improving and who had no evidence of ICH by head CT scanning were treated with IV rTPA (0.6 mg/kg). Subsequently they underwent emergent MRIs of the head. T2-t-Grase, and echo planar diffusion and perfusion-weighted images were generated. Patients with evidence of imaging abnormalities indicative of acute cortical infarct underwent cerebral angiography. Once vessel occlusion was determined, IA urokinase was given to achieve recanalization up to a maximum of 1.5 million units. All patients received IV heparin after treatment. Results: We treated 13 patients with this protocol. Their mean age was 67±13 years and 54% of them were men. The median NIHSS at presentation was 15 and there was a significant improvement 24 (NIHSS=4) and 120 (NIHSS=4) hours after treatment (p=0.005, Wilcoxon signed rank sum test). Four patients developed hemorrhagic transformation of the ischemic area after treatment but only one became symptomatic and died. Six patients were discharged to home, and six to rehabilitation facilities. All patients that survived had a Barthel Index >95 three months after treatments. Conclusion: Our data suggests that combined IV and IA thrombolysis for acute ischemic stroke is feasible and is associated with decreased stroke severity and improved clinical outcome. Further studies are necessary to corroborate these findings.

Intra-Arterial Thrombolysis in the Setting of Acute Cervical Arterial Dissection

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Background: The theoretical risk of provoking recurrence or extension of dissecting hemorrhage has limited the use of intravenous thrombolysis for thromboembolic complications of acute cervical arterial dissection. We present a case series that demonstrates the feasibility and safety of intra-arterial thrombolysis in the setting of acute dissection. Methods: Case series of four patients treated with intra-arterial urokinase for acute cervical arterial dissection and acute cerebral ischemia. Results: Mean patient age was 31 years, range 18-41. Two patients were male, two female. Pretreatment NIHSS averaged 20.3. Cervical carotid dissections were present in three cases (bilateral in one), producing cervical carotid occlusion in two, distal MCA emboli in one, and clot propagation through the length of the internal carotid to the MCA in two. One patient had cervical vertebral dissection producing occlusion, with distal basilar embolism. Minor precipitating trauma was present in three cases, absent in one. No patient had an evident underlying arteriopathy. Time from ischemia onset to initiation of urokinase averaged 4-7 hours in the anterior circulation cases. In the posterior circulation case, treatment was initiated 36 hours after initial ischemic symptoms, 3 hours after severe worsening. Microcatheters were advanced through the affected cervical vessels and positioned supselectively within the distal clot. An average dose of 605,000 units of urokinase achieved recanalization of intracranial vessels in all (TIMI grade 2 flow in three, TIMI grade 3 in one). Proximal occlusion of the dissected cervical vessel with GDC coils was performed to prevent further thromboembolism in two. Post-thrombolysis treatment employed antiplatelet therapy without the use of anticoagulation. Hemorrhagic transformation without deficit worsening occurred in one case. Long-term outcome was excellent, with Barthel scores of 100 and GOS of 1 in all. Conclusions: In patients with cervical arterial dissection and resulting intracranial thrombus, intra-arterial thrombolysis delivered beyond the dissection site can produce early reperfusion and excellent functional outcome.

Intra-Arterial Thrombolytic Therapy in Central Retinal Artery Occlusion


Purpose: To evaluate the safety and efficacy of intra-arterial thrombolytic therapy with urokinase for treatment of central retinal artery occlusion. Methods: Retrospective review of medical records of nine patients with central retinal artery occlusions who received urokinase by direct infusion via the ophthalmic artery between 10/95 and 6/98 was carried out. Results: Mean time from onset of visual symptoms to the initiation of urokinase infusion was 10 hours and 17 minutes with a range of 3 hours 15 minutes to 23 hours. Doses of urokinase ranged from 750,000 to 1,100,000 units. All patients received unfractionated heparin IV for 24 hours after the procedure. Patients ranged in age from 22 to 78 yrs. Four patients regained normal vision with times to treatment being 3hrs 15min, 4hrs, 24 hrs and 24 hrs. Three patients had partial return of vision with times to treatment being 4hrs 35min, 4hrs 50min, and 23hrs. Two patients had no return of vision with times being 6hrs and 11hrs 35min. One patient who was treated at 22hrs and had partial return of vision suffered an intracranial hemorrhage 6 hours after completion of the procedure and subsequently died of complications of the hemorrhage. The other 8 patients had no complications. Conclusions: Retinal artery occlusion can be successfully treated with intra-arterial thrombolytic therapy. The outcome is not correlated with the time of retinal ischemia up to 24 hrs. The procedure has inherent significant risk.
Restricting use of iPA to specialized “Stroke Centers” would limit patient access to treatment and result in delays, limiting efficacy. Methods: The Stroke Treatment in the Community (STIC) study has collected data detailing the treatment situation, outcomes, and hemorrhagic complications of iPA treated patients in MN from 1996-99 and here present comparison data for academic (Group A), and non-academic metropolitan (Group B) and rural (Group C) hospitals in order to assess the validity of concerns regarding hospital/physician expertise. Results: Deviation from the NINDS protocol and treatment late in the recommended time window occur with similar frequency in each group. Early infant change (EIC) on CT scan is recognized with greater frequency at academic and metropolitan hospitals (p<0.015). The higher % treated patients with severe stroke at academic and rural hospitals may account for trends toward higher mortality and lower % good outcome when compared to metropolitan hospitals. There were no measurable differences in rate of symptomatic ICH between the three groups (p=0.79) or on the basis of physician type (neurologist vs non-neurologist, p=0.74). Conclusions: Given the absence of major differences in treatment approach and outcome, there is no justification for restriction of this therapy on the basis of hospital/physician type or academic affiliation.

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**Background & Aims:** Baseline neurological deficit was the most important early prognostic predictor of 90d-mortality and good long-term outcome in 615 randomized acute stroke patients of ECASS (iPA versus placebo within 6 hrs). However, the lack of unequivocal threshold levels in ECASS raises doubts on the prognostic relevance of early neurological scoring. We reviewed other clinical trials and compared neurological with functional thresholds. Methods: We use data from n=1693 patients randomized to placebo in 4 trials with nimodipine. Functional capacity was scored at medication (-48h from stroke onset) as a Barthel index. Neurological deficit was scored concurrently, but on varying scales (e.g. Toronto, Mathew, Orgogozo). Prognostic significance was assessed by (profile) likelihood methods in context of logistic and Cox’s regression models for 90d to 108d mortality, adjusting for age, and also gender effects if any, and stratifying according to trial. Results: All data consistently show an optimal cutoff of 20 on the Barthel functional scale below which mortality is 4 times higher (OR=4.25, 95%ci. 3.3-5.5). Similarity, there are optimal prognostic thresholds for age of 70 years (OR=2.7, 95%ci 2.1-3.5, n=1690), though there are actually two trial populations. It is seen by likelihood plots that it is impossible to establish similarly optimal prognostic thresholds for differential mortality on the neurological scales. Throughout, the functional score explains mortality better while the neurological scores do not add (P<0.05). Linear regression between functional and neurological scores within the first 48 hrs is much weaker than after 90d and explains less than 25% of variability. Conclusions: The lack of prognostic threshold levels on the neurological scales is confirmed in another 1650 placebo-treated patients from controlled acute-stroke clinical trials. Functional capacity, as measured on the Barthel index scale, at baseline seems to be a more important predictor of survival outcome than neurological deficit. This may lead to include Barthel index among the early assessments for prognostic purposes.
Evaluation of Patients with Transient Ischemic Attack in an Emergency Observation Center Reduces Hospital Admissions and Decreases Cost of Evaluation

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Beginning in July, 1998, selected patients with suspected TIA presenting to a community teaching hospital emergency department (ED) were evaluated in an emergency observation unit (EOC). All patients had neurology consultation, and carotid Doppler, MRA, cerebral angiography or CT scan as indicated. Objectives: To compare admission and cost of evaluation of patients with suspected TIA before and after EOC evaluation began in an EOC. Methods: Consecutive patients with suspected TIA were identified from the ED log for 2 periods: a control period from August 1, 1997 through May 31, 1998, and the study period from August 1, 1998 through May 31, 1999. Data on ED patients were collected prospectively, and by chart review on all other patients. Cost (not charge) data obtained from a hospital database included direct and indirect costs but not physician professional fees. Controls were inflated by 3% for comparisons. Results: Demographic characteristics of the two groups were similar except for current use of antipiloseptic medications (44.7% control vs. 35.4% study) and prior TIA (24.9% vs. 16.1% study). A total of 70 patients were evaluated in the EOC during the study period, with 21 (30%) subsequently admitted to the hospital. There was a significant decrease in admissions from the ED (p < 0.001, Chi-square, see Table). For patients with final diagnosis of TIA or possible TIA and early discharge (length of stay less than 3 days or EOC discharge) cost per patient was $218±1010 (median $209±76) for control patients (n = 53) vs. $179±906 (median $144±0) for study patients (n = 65). P = 0.016, Wilcoxon Rank Sum). Conclusion: EOC evaluation is feasible and results in a reduction in admission evaluations and cost of evaluation for selected patients with suspected TIA.

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<th>ED Discharge</th>
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<tr>
<td>Control (n=216)</td>
<td>50 (23.6%)</td>
<td>50 (25.7%)</td>
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<tr>
<td>Study (n=243)</td>
<td>62 (26.2%)</td>
<td>157 (65.2%)</td>
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</table>

Effects of Aspirin or Heparin Inadvertently Given to Patients with Hemorrhagic Stroke

Sarah L. Keir, Steff L. Marmar, John A. Wulfert, Peter A. Sandrock, Kristen G. Grey, Edinburgh United Kingdom; Zheng-Ming Chen, On behalf of IST and CAST collaborative groups, Oxford United Kingdom

Aim To determine whether a few doses of aspirin or heparin inadvertently given to patients with acute hemorrhagic stroke were harmful. Methods The International Stroke Trial was an open randomised trial of aspirin, subcutaneous heparin, both or no treatment within 48 hours of ischemic stroke. The Chinese Acute Stroke Trial compared aspirin with placebo. Patients could not be randomised before CT if the clinical suspicion of intracerebral hemorrhage was low and CT was likely to be delayed. Thus a few patients with ‘hemorrhagic stroke’ (either a primary intracerebral hemorrhage or hemorrhagic infarct) were inadvertently randomised. Results A total of 4051 patients were randomised. 773 of 7758 first scanned after randomisation had a hemorrhagic stroke of whom 398 patients had been allocated to aspirin and 375 to control, and 310 were allocated to heparin and 289 to control. The trial treatment was stopped after 76 in 1997. In these patients with hemorrhagic stroke, aspirin was associated with a non-significant reduction of 18 non-fatal strokes or deaths per 1000 patients treated (95% CI 0 to 35) and no significant increase in any of the specified primary adverse events. Conclusion These data suggest that in a large randomized trial, aspirin was not harmful in patients with hemorrhagic stroke. There are no significant trends for an improved outcome with aspirin and a poorer outcome with heparin but the confidence intervals indicate that either treatment could result in benefit or hazard.
Usefulness of Triphasic Perfusion CT for Intravenous Thrombolysis with Tissue Plasminogen Activator in Acute Ischemic Stroke

Yongboom Kim, Kwang-Ho Lee, Chin-Sang Chang, Soo-Jin Cho, In-Seon Jin, Dept of Neurology, Samsung Med Ctr, Seoul South Korea; Dong-Yu Na, Dept of Radiology, Samsung Med Ctr, Seoul South Korea; Hye-Seung Lee, Dept of Neurology, Samsung Med Ctr, Seoul South Korea; Hong-Sik Byun, Dept of Radiology, Samsung Med Ctr, Seoul South Korea

Background: Intravenous (i.v.) thrombolysis for acute ischemic stroke has been investigated in several clinical trials without enough information of collateral flow and perfusion deficit in the ischemic areas. The therapeutic time window may vary from patient to patient depending on these information. Triphasic perfusion CT (TPCT) can provide this information as reliably as conventional angiography. Objective: To assess the safety and efficacy of thrombolysis within 7 hours of stroke onset according to the extent of perfusion deficit on TPCT. Methods: The precontrast CT (PCT) was taken and then TPCT was performed after power injector-controlled i.v. administration of contrast media in patients with acute middle cerebral artery (MCA) stroke. Sequential scans of early, middle, and late phases were obtained. The whole procedure took 5 minutes. Depending on collateral blood flow, perfusion deficit was graded as severe perfusion deficit (SPD) or moderate perfusion deficit (MPD). Twelve patients (57.1%) improved by 4 or more points from baseline NIHSS score within a day. The patients with MPD 50% or more of the MCA territory had a higher chance of early improvement than those with MPD less than 50% (4/4 vs. 8/8 respectively). No fatal hemorrhage developed. Only one patient with 50% symptomatic small basal ganglia hemorrhage after thrombolysis. Conclusion: Thrombolysis may be safely done within 7 hours in patients with severe SPD on TPCT. The large extent of MPD on TPCT may predict early improvement after thrombolysis.

The Canadian Activase for Stroke Effectiveness Study (CASES)
Mark D. Hill, Phillip A. Barber, Alastair M Buchan, Cases Study Group, Univ of Calgary, Calgary Canada

Background: Therapy for acute stroke using rtPA was approved in Canada in February 1999. The Canadian Activase for Stroke Effectiveness Study Group was formed to study the use of rtPA in Canada in a year 2 year post-marketing study. Purpose: To prospectively examine whether the efficacy of rtPA for acute stroke, demonstrated in the NINDS trial, can be translated into effectiveness in routine clinical practice across Canada. Methods: The CASES group is a collaboration among the Canadian Stroke Consortium (CSC), the Heart & Stroke Foundation of Canada and Roche Canada. Centres across the country were registered and recruitment is ongoing. Patient information is being collected prospectively and evaluated in a blinded fashion. The study protocol has been approved by the ethics board at each centre. Demographics, stroke risk factors, blood pressure, biochemistry, hematology, and CT scans are being collected. NIHSS and mRS scores are being collected. Outcomes will be monitored at discharge and at 3 months. Results: In the first five months, 54 centres are registered. 116 patients have been treated with 3 symptomatic intracerebral hemorrhages. Complete information is available on 59 patients(Table). Conclusions: CASES is an ongoing prospective evaluation of the effectiveness of rtPA in acute stroke. The symptomatic hemorrhage rate is 2.6%. To date, no safety concerns have been identified.

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The Effect of Vasodilators on Blood Pressure in Acute Stroke, a Systematic Review of Individual Patient Data from Randomised Controlled Trials

Fiona J Bath, Robert Iddenden, Philip M Bath, Univ of Nottingham, Nottingham UK

Hypertension is associated with a poor outcome in acute stroke and yet lowering blood pressure (BP) may be hazardous according to some studies. Relevant trials were identified from searches of the Cochrane Library and Cochrane Stroke Group database of RCTs in acute stroke; searches suggested that there were >80 relevant trials. Trialists and pharmaceutical companies were invited to join BASC and share their individual patient data (IPD). Analysis (summary statistics, multivariate analysis) of data from 3,399 patients from 23 acute stroke trials was performed. Multivariate analysis suggests that functional outcome (combined death & disability) is related to age, treatment delay, early systolic BP (change in BP in first 24 hours), previous hypertension and study (all with p<0.1). Treatment allocation was unimportant in all models. Angiotensin converting enzyme inhibitors, beta blockers, calcium channel blockers and glyceryl trinitrate (nitric oxide donor) each lowered BP acutely. Magnesium and naftidrofuryl did not alter BP. These analyses are provisional since data are available on only a proportion of relevant trials, as such, they do not help in informing how BP should be managed in acute stroke although analysis of a near complete data set is likely to help. We invite trialists of relevant studies to join BASC and share their IPD by contacting us: Fiona.bath@nottingham.ac.uk, telephone/fax +44 115 840 4795 or website http://www.nottingham.ac.uk/stroke-medicine/basc.

Vasoactive drugs on early BP in acute stroke

<table>
<thead>
<tr>
<th>Drug group</th>
<th>Subjects</th>
<th>BP Δ mmHg</th>
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<tbody>
<tr>
<td>ACE-i</td>
<td>15</td>
<td>-1.4/4.8</td>
</tr>
<tr>
<td>β-blockers</td>
<td>234</td>
<td>-6.9/2.1</td>
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<tr>
<td>CBP</td>
<td>260</td>
<td>-4.0/3.6</td>
</tr>
<tr>
<td>CCB</td>
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<td>-1.1/1.3</td>
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</table>

Familial Aggregation of Stroke and Intracerebral Hemorrhage

Daniel Woo, Univ of Cincinnati, Cincinnati, OH; Laura Suerbeck, Univ of Cincinnati, Dept of Neurology, Cincinnati, OH; Janne Kheury, Univ of Cincinnati, Department of Environmental Health, Cincinnati, OH; Janice Carrozella, Univ of Cincinnati, Dept of Neurology, Cincinnati, OH; Charles Moomaw, Univ of Cincinnati, Institute for Policy and Res, Cincinnati, OH; Brett Kissela, Joseph Broderick, Univ of Cincinnati, Dept of Neurology, Cincinnati, OH

Introduction: Familial aggregation (FA) of stroke may be secondary to genetic risk factors or familial aggregation of environmental risk factors. Identifying familial aggregations of stroke is necessary for segregation and linkage analysis to identify genetic risk factors for stroke. We undertook a study of the risk of FA of stroke among cases of intracerebral hemorrhage (ICH) compared to age, race and gender matched controls. Methods: All patients diagnosed with ICH within a 50 mile radius of Cincinnati, OH were identified. Each case enrolled into the study was matched to two controls by age, race and gender. Cases and controls participated in an extensive interview which included family history of stroke and genetic sampling. FA of stroke was defined as having two or more first-degree relatives with an ischemic or hemorrhagic stroke. Logistic regression analysis was used to compare the risk of FA of stroke in cases compared to controls. Secondary analysis was done for cases less than 70 years of age to exclude most cases of ICH due to amyloid angiopathy and to control for the effect of age as a risk factor. Results: Between 6/1/97 and 5/31/99, 139 cases of ICH and 251 age, race and gender matched controls without a history of stroke were enrolled into the study. The relative risk of FA of stroke for a case with ICH is 2.16 (95% confidence interval (CI): 1.00, 4.70). In secondary analysis, 79 (57%) cases were less than 70 years and age were matched to 144 controls. Of the cases less than 70 years, 20 (25%) had one first-degree relative with stroke and 8 (10%) had a FA of stroke. Of the 144 matched controls, 30 (21%) had one first-degree relative with stroke but only 4 (3%) had a FA of stroke. The relative risk of FA for ICH <70 years of age was 4.0 (95% CI 1.20, 13.28). Conclusions: Familial aggregation of stroke is significantly more common among cases of ICH who were less than 70 years of age compared to matched controls without a history of stroke. Further investigation of these families is needed to determine whether the aggregation of stroke is due to familial aggregation of known risk factors such as hypertension, or due to unidentified genetic risk factors for stroke.
Prevalence of Silent Brain Infarcts in the Elderly: The Rotterdam Scan Study
Sarah E Vermeer, Erasmus Univ Med Sch, Rotterdam Netherlands; Matthijs Oudkerk, Daniel den Hoed Cancer Ctr, Dept of Radiology, Rotterdam Netherlands; Jan Ceci de Grooth, Leiden Univ Med Ctr, Dept of Neurology, Leiden Netherlands; Frank-Erik de Leeuw, Univ Hosp Utrecht, Dept of Neurology, Utrecht Netherlands; Albert Hofman, Erasmus Univ Med Sch, Dept of Epidemiology, Rotterdam Netherlands; Peter J Koudstaal, Univ Hosp Rotterdam, Dept of Neurology, Rotterdam Netherlands; Monique Ms Breteler, Erasmus Univ Med Sch, Dept of Epidemiology, Rotterdam Netherlands

Objective To study the prevalence of silent brain infarcts among the elderly. Background In first stroke patients prior brain infarctions on MRI are common. With the increasing use of cerebral imaging techniques, asymptomatic or silent infarcts are detected more often in healthy elderly as well. Only two large population-based studies thus far reported the prevalence of silent brain infarcts in the general population: the Cardiovascular Health Study found a prevalence of 31%, whereas Kobayashi et al showed a prevalence of 11%. Methods This study forms part of the Rotterdam Scan Study, a prospective population-based cohort study among 1077 subjects aged 60 years or older. Self-reported history of stroke and TIA was obtained before scanning. All 1077 participants underwent MRI scanning of the brain. Infarcts were defined as lesions with focal hyperintensity on proton-density and T2-weighted MRI scans with corresponding hypointensity on T1-weighted images, sized 3 mm or larger. The study included a total of the history of stroke and TIA. In all subjects with infarcts on MRI medical records were checked for history of stroke or TIA. MRI scans were reviewed by a neurologist to see if clinically overt stroke and TIA were related to the infarctions on MRI. Results Infarcts on MRI were detected in 136 of 1077 subjects (13%). In 85 subjects their scan showed only one infarct (62%) and in the remaining 51 subjects two or more infarcts were seen. Preliminary findings show that at 84% of the subjects the infarcts on MRI were silent. In 9% the infarcts were due to symptomatic stroke or TIA and in 7% both symptomatic and silent infarcts were seen. Infarcts on MRI increased significantly with increasing age and were found in men more often than in women. Conclusion Silent brain infarcts are common in the elderly population. The difference in prevalence of silent infarcts in our population (11%) and in the Cardiovascular Health Study (31%) needs further clarification.

Diabetes Is Independently Related to Subcortical Infarcts
Gabriel R De Frestas, Gerald Devysv, Laura Boretta, CHUV, Lausanne Switzerland; Guy van Meurs, Institute of Social Medicine, Lausanne Switzerland; Julien Bogossiavisky, CHUV, Lausanne Switzerland

Background and Objective: Although diabetes is an established risk factor for stroke, it is unclear whether strokes may be different in diabetic patients. The aim of this study was to investigate stroke subtype and outcome in diabetics and to assess the association between diabetes and subcortical infarcts. With the study method, which included risk factors, etiology, lesion topography, clinical findings and outcome in 3,362 first stroke patients admitted to a primary care center, patients were defined as diabetics if they had a known history of diabetes before stroke (at least two fasting plasma glucose levels > 6 mmol/L). To assess the relation between diabetes and subcortical infarcts patients were divided into four groups: hypertensive diabetic (H-D+), hyperensive non-diabetic (H-D), non-hypertensive diabetic (H-D+) and non-hypertensive non-diabetics (H-D-). Results: There were 472 patients with diabetes. Diabetics were 5.3 years older than non-dietics and had a two times lower incidence of intracranial hemorrhage (P = 0.002). Small vessel disease and ≤ 50% atherosomatic large-artery stenosis were more common in diabetic patients than in non-diabetic (123 [28%] vs. 424[17%] and 92[21%] vs. 304[12%], respectively). Non-ischemic cardiopathy, artery dissection and undetermined causes were less frequently in diabetics (2085% vs. 304[12%], 205% vs. 100[4%] and 225% vs. 346[14%], respectively). Diabetes had a lower incidence of superficial infarcts (153[36%] vs. 1085[44%](P = 0.001). In contrast, subcortical infarcts were more common in these patients (136[31%]) vs. 594[24%]((P = 0.001). Stroke severity, clinical outcome and mortality were comparable between diabetics and non-diabetics. Subcortical infarcts were found in 97 (32%), 33(31%), 39 (27%), 26[18%] of H-D+, H-D, H-D+ and H-D- patients, respectively (P = 0.001). OR 39 non-hypertensive diabetics with subcortical infarcts, 20 had no other risk factors for diabetes. Conclusions: Diabetes influenced stroke etiology, topology and, but not functional outcome. Our findings suggest that diabetes is independently associated to subcortical infarcts.

Rate of Stroke Recurrence in Patients with Primary Intracerebral Hemorrhage
Michael D Hill, Univ of Calgary, Calgary, AB Canada; Frank L Silver, Toronto Western Hosp, Toronto, ON Canada; Austin C Peter, Jack V Tu, Ices, Toronto, ON Canada

Background: Primary intracerebral hemorrhage (PICH) is a devastating illness with high early mortality. Hypertension is a major risk factor for both ischemic cerebrovascular disease (ICD-9-CM code 433) and PICH. Rates of PICH are available at the Toronto Hospital, Toronto, Canada. Methods: Computerized hospital records from 1986-1996 were searched retrospectively for patients with a discharge diagnosis of intracerebral hemorrhage (ICD-9-CM code 431) to identify index cases. Charts were abstracted for demographic and clinical characteristics. CT, MRI scans or radiologist reports were reviewed. To determine recurrence, the database was linked to the Ontario Government Vital Statistics Registry and to the Canadian Institute for Health Information (CIHI) database of hospital discharge abstracts. Logistic regression analysis was used to identify factors predicting mortality after PICH. A Cox proportional hazards model was fitted to identify predictive factors for recurrent ICH or stroke. Results: A total of 746 charts were identified by computer search. After abstraction, 423 index patients with PICH were identified. Of these, 27.4% died in the first 30 days of their admission. Predictors of death were age > 70 years, intraventricular rupture, and hemispheric hemorrhage. The recurrence rate for PICH was 2.4% per year while the recurrence rate for ischemic cerebrovascular disease was 3.0% per year. The only significant predictor of readmission for ICH was lobar location of the index hemorrhage with a relative hazard of 3.8 (95% CI 1.2 to 12.0). Conclusions: This large series showed that PICH has a high 30-day mortality rate. Patients with lobar hemorrhage have a 3.8 fold increased risk of recurrent ICH. Survival from the initial insult portends a moderate risk of recurrence of 2.4% per year for ICH and 3.0% per year for cerebrovascular disease. Thus, PICH may be a risk factor for ischemic stroke.
Prospective Study of Return to Work After Ischemic Stroke

Marcella A Wozniak, Steven J Kittner, Thomas R Price, Univ of Maryland Sch of Medicine, Baltimore, MD

Prospective studies of return to work after ischemic stroke are few. To define factors influencing return to work after ischemic stroke, 174 patients less than age 65 at time of stroke were recruited from Baltimore-Washington regional hospitals from 8/96 to 12/96. All reported paid employment outside the home >35 hours/week and were discharged home or to acute rehabilitation. Physical disability (Barthel Index), depression screen (CES-D) and job characteristics (Job Content Questionnaire) were obtained at 6 weeks. A follow up questionnaire determining recurrent medical events, work and disability (Barthel) status and health related quality of life (MOS SF-36) was administered at 6 and 12 months. Interim analysis are reported for 174 patients, 150 with 12 month follow up and 24 with only 6 month follow up. The study sample was 35% women and 45% African-American. At six weeks, 69% were independent in all their activities of daily living. By six months, one patient had died, and 101(58%) had returned to work. In patients working, 87% had returned to the same job and >81% worked full time. By 12 months, three patients had died, 7 who had resumed work were not working, and 11 not working at six months were working. LIFetable analysis revealed physical disability at 6 weeks (Barthel Index) was strongly predictive of subsequent time to return to work (p<0.01 by log rank). Age, ethnicity, gender and depression screen score at 6 weeks were not significantly related to time to return to work. We conclude that a substantial proportion (~%) of this relatively young stroke population, with no to moderate physical disability at 6 weeks, did not return to work by one year. Physical disability at 6 weeks was the strongest predictor of return to work, which usually occurred by 6 months.

Background: Volume of first cerebral infarct has been studied in clinical trials, and has ranged from 26-34 cm³. The first phase of the Greater Cincinnati/Northern Kentucky Stroke Study collected data on stroke volume and location in blacks in the greater Cincinnati population from 1/93-6/93. Methods: The available baseline or subsequent CT and MR scans of all 257 black patients with a cerebral infarct between 1/93-6/93 were evaluated by a study neurologist. Volumetric measurements were performed by the modified ellipsoid method from available films. Results: Of the 257 black stroke patients, 179 had a first clinical stroke. Of these, 149 had films available for review and 81 had an infarct on imaging that was definitely or possibly related to the clinical symptoms. Others had multiple infarcts, one infarct not related to clinical symptoms, or no infarct. In the 81 patients, the median stroke volume was 2.75 cm³. Infarct volume was significantly related to stroke location with subcortical < cortical < combined subcortical/cortical (p = 0.0001). There was a trend towards larger infarcts in patients ≥ the median age of 71 years (p = 0.099).

Conclusions: In a community-based study, the median volume of first infarct in blacks was significantly smaller than infarct volumes reported previously. The large proportion of small, mild strokes may be one explanation for the low percentage of stroke patients who meet the inclusion criteria for treatment with t-PA.
Predictors of Compliance with Antihypertensive Medications in Patients with Intracerebral Hemorrhage


Introduction: Non-compliance with medical therapy is thought to be a common cause of hypertensive ICH, but this has not been studied systematically. This study was done to determine the frequency of compliance with antihypertensive medications and predictors of non-compliance in a cohort of patients with hypertensive ICH. Methods: A retrospective chart review was done to identify patients with hypertensive ICHs. They were classified into compliant, non-compliant, undiagnosed, and untreated based on whether they were diagnosed with hypertension and were treated with antihypertensive medications. Demographic factors, insurance status, and outcomes were also analyzed. Comparisons were made using ANOVA, Pearson’s Chi-square, and logistic regression analysis. Results: The cohort consisted of 139 patients; 71 male; 68 female; 72 Caucasian, 66 African-American, and 1 Asian. African-Americans had a mean age of 55.7 ± years compared to 65.0 ± years in Caucasians. Only 65 patients (47%) were compliant, 37 (27%) were non-compliant, 32 (23%) were untreated and 5 (4%) were undiagnosed. Compliance was strongly associated with age, as older patients were more compliant than younger patients (p = 0.001 by ANOVA). Females were more compliant than males (58% vs. 38%, p = 0.02 by Chi square). Insurance status was associated with compliance, as 65% of Medicare patients were compliant vs. 37% of Medicaid and 32% of private insurance patients (p = 0.02 by Chi square). Adjusting for age, race, gender, and insurance in a logistic regression model, age was strongly associated with compliance (p < 0.001), while gender was weakly associated with compliance (p = 0.05). Outcome was most associated with age (p < 0.001), with older patients having worse outcomes. This persisted after controlling for other factors. Conclusion: A majority of patients with hypertensive ICH are either non-compliant or untreated with antihypertensive medications. Older patients are more compliant, yet have a worse outcome. Educational efforts aimed at improving the compliance of younger patients and re-emphasizing the treatment of hypertension may be useful for preventing ICH.

Incidence and Outcome of Stroke in the Young in a Population Study

Carmine Marini, Leonardo Triggiani, Federica De Santis, Nicola Cimini, Antonio Carolei, Univ of L’Aquila, L’Aquila Italy

Objective: To evaluate stroke incidence and outcome in subjects under 45 years of age. Methods: All first-ever strokes occurred in the L’Aquila district, central Italy (L’Aquila Province with population 297,838 inhabitants, 58.7% under 45 years of age at the 1991 census) were traced by active monitoring of in and outpatient health services. Outcome in survivors was evaluated at discharge using the modified Rankin scale. Between January 1994 and December 1998, out of 4535 patients who had a first-ever stroke, 89 (2%) were under 45 years of age (35 men and 34 women). Mean age was 36.1 ± 8.1 years (35.7 ± 8.5 in men and 36.9 ± 7.5 in women). Clinical diagnoses were confirmed by brain CT and/or MR in all patients. Fifty-one patients (57%) had a cerebral infarction, 18 (20%) an intracerebral hemorrhage, and 20 (23%) a subarachnoid hemorrhage. Intracranial aneurysms (n = 12) or arterio-venous malformations (n = 6) were detected in 18 out of 38 patients (47%) suffering from either intracerebral (n = 5) or subarachnoid (n = 15) hemorrhage. The crude annual incidence rate was 61.0/100,000 (95% CI 59.0-63.5). The annual incidence rate was 61.0/100,000 (95% CI 59.0-63.5) than in women (41/100,000, 95% CI 2.9). The incidence rate was 4,000/100,000 when standardized to the 1996 European population. The 30-day case fatality rate was 11.2% (95% CI 6.2-19.4). No fatal initial events and only one stroke recurrence occurred within one year. The proportion of individuals who died was higher among patients with intracerebral hemorrhage (39%) followed by the lower proportion (16.7%) of individuals with severe disability (mRS = 3). The proportion of individuals with severe disability (mRS = 3) was higher (47.1%) than among patients with cerebral ischaemia paralleled by the absence of fatal events. The proportion of individuals with favorable outcome (mRS = 0) was higher (90%) among patients with subarachnoid hemorrhage paralleled by a lower mortality rate (15%). Conclusions: We found a low incidence of first-ever stroke of any type in subjects under 45 and a different event distribution when compared to the overall stroke population indicating that early detection of aneurysms and arterio-venous malformations is necessary in the young.

Risk Factors for Mild Cognitive Decline and Dementia of the Vascular and Alzheimer’s Type

John S Meyer, Gaiinea M Rauch, Ronald A Austrow, Anvarul Haque, Baylor Coll of Medicine, Houston, TX

Risk factors accelerating cerebral atrophy-degenerative changes and cognitive decline were correlated with repeated measures of cerebral atrophy. CT densities, perfusions and cognitive test performances among aging normative subjects. Two hundred twenty four cognitively and neurologically normal volunteers were studied longitudinally. Mean age at entry was 59.5 ± 15.8 years. Mean follow-up is now 4.3 ± 3.1 years. 41 developed cognitive decline: mild in 22 cases (Group M), 19 became demented (Group D), 8 with Vascular Dementia (VAD), 11 with Alzheimer’s Dementia (DAT). 183 remained cognitively unchanged (Group U). Accelerating perfusional declines, cerebral atrophy, polio- and leuko-araiosis were: TIAs, hypertension, hyperlipidemia, diabetes mellitus, and heart disease. After age 60, cerebral atrophy (p < 0.05), ventricular enlargement (p < 0.05), polio- and leuko-araiosis (p < 0.05) geometrically increased as cerebral perfusions declined (p < 0.05). Risk factors accelerating perfusional declines, cerebral atrophy, polio- and leuko-araiosis were: TIAs, hypertension, smoking, hyperlipidemia, male gender. Leuko-araiosis increased as white matter perfusion decreased before cognitive decline appeared (p < 0.05). TIAs (p < 0.05), hypertension (p < 0.05), hyperlipidemia (p < 0.05) were associated with VAD, and family history of neurodegenerative disease (p < 0.05) - with DAT. TIAs, hypertension, hyperlipidemia, smoking and male gender are associated with accelerated cerebral atrophy-degenerative changes that predispose to mild cognitive decline and dementia. Control of vascular risk factors is useful for preventing ICH. Interaction Between Stroke, Dementia and Gender in a Cohort of Elderly Community Residents Aged 65 Years and Older

Francois Rosanet, Univ Hosp Pellengrin, Bordeaux France; Sylviane Lafont, Jean-Francois Dartigues, Unite INSERM 330, Univ Victor Segalen, Bordeaux France; Jean-Marc Orgogozo, Univ Hosp Pellengrin

Objectives: To examine stroke and dementia incidence and to evaluate the risk of dementia after stroke in elderly community residents. Method: A community based cohort of elderly people, aged 65 years and older (PAQUID project), was studied longitudinally for 8 years. Among the 3675 non-demented subjects initially included in the cohort, 75.8% participated in the follow-up. Risk ratios of dementia and stroke were estimated using a Cox model with delayed entry in which the time scale is the age of the subjects. Results: At baseline the observed prevalence of stroke was 6.9%. During the 8 year follow up the adjusted incidence of stroke was 1.59/100 person-years (1.95 in men and 1.35 in women). The risk ratio of stroke in women compared with men was estimated by the model to be 0.59 (p < 0.0002). At follow up the cumulative mortality rates were 59.6% in the prevalent stroke group, 32% in the incident stroke group and 35.6% in the non stroke group. The risk ratio of death after stroke was estimated to be 4.5 (p < 0.0001) for the incident stroke group and 2.6 (p < 0.0001) for all patients in the cohort. The risk ratio for incidence of dementia after stroke to 0.0297 to 0.0013%. Conclusion: The incidence of stroke in this population-based study is in accordance with data previously reported in France. Stroke increases more than 2-fold the risk of dementia but the interaction between sex and age for the risk of dementia is not explained by stroke.

Validation an Epidemiology Based Stroke Incidence Prediction Model

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Background: From an individual hospital perspective, acute stroke risk education and outreach programs intended to reach the public, EMS and potential referral physicians are often poorly targeted. This is due to limited information concerning where, on a local level, stroke incidence is likely to be greatest. Using published epidemiology information, a predictive model was built to project, at a zip code population level, the expected annual stroke incidence. Objective: To assess the true predictive ability of the model by comparing the predicted incidence with a recorded incidence in metropolitan areas and zip codes. Methods: Yale New Haven Hospital (YNNH) provided the total annual actual acute stroke number (AASN) reported to the State of Connecticut. All zip codes within a 20 mile radius of YNHH were included in the analysis (n=52). The age, gender, and race demographic traits for each zip code in 1997 were secured from the U.S. Census Bureau and run through the model to generate a predicted annual acute stroke number (PAASN). This predicted number was then compared to the State’s recorded actual AASN. Results: The model predicted a PAASN of 1557 versus 1750 actual reported strokes in the 52 zip codes studied by population. The mean/median (n=108) and (std dev) of stroke events per zip code were .1430%/ .1399%, the age, gender and race demographic traits for each zip code in 1997 were secured from the U.S. Census Bureau and run through the model to generate a predicted annual acute stroke number (PAASN). This predicted number was then compared to the State’s recorded actual AASN. Results: The model predicted a PAASN of 1557 versus 1750 actual reported strokes in the 52 zip codes studied by population. The mean/median (n=108) and (std dev) of stroke events per zip code were .1430%/ .1399%, the mean of the predicted versus actual was not statistically significant, p-value 0.072, 95% confidence interval of the difference -0.0297 to 0.0013%. Conclusions: The model predictions for PAASN and AASN are highly correlated. The probability of stroke incidence per person between the two models is not statistically different. Based on the above findings one can apply the model with a high level of predictive confidence. The epidemiology based stroke incidence prediction model, when applied to a local market situation, will provide very valuable information for education and outreach priority decisions.

Poster Presentations 319

P110

P111

P113

P114
A Model for a State-Based Multidisciplinary Approach to Improve Stroke Awareness and Care: The Michigan Stroke Initiative (MSI)

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Background: In Michigan, the long term decline in stroke mortality ended in 1992. In 1996, stroke was responsible for 6.9% (n=5,718) of all deaths and 3.2% (n=36,718) of all hospitalizations in Michigan. Objectives: To collect population-based data on current stroke care in Michigan and develop strategies for improvement. Methods: The Michigan Department of Community Health, Greater Detroit Area Health Council, American Heart Association, Michigan Peer Review Organization, Michigan Health & Hospital Association, Michigan State Medical Society, managed care and hospital administrators, physicians, nurses, and pharmaceutical representatives convened in 1997. We obtained data from state Medicare hospital discharges (DRGs 14 and 15) and structured surveys of acute and preventive stroke care/resources/attitudes of all Michigan hospitals (n=175) and all physicians registered with state medical societies(n=5,521). Results: From 10/1/97 to 9/30/98, 19,675 Medicare-insured cerebrovascular events occurred: average age 77 years, 7.4% hospital mortality, and $197,556,265 in hospital costs. Surveys were returned from 97(55%) hospitals: 46% had a clinical pathway for stroke, 21% did not have tPA use in their clinical pathway, and 49% were interested in help with a tPA protocol. Physicians returned 836 (15%) surveys: 29% ER physicians, 9% neurologists, 27% intensivists, 37% family practitioners, and 4% other tPA had been given by 22% of physicians (40% ER physicians, 51% neurologists, 10% primary care other). Half were unaware of the cost-savings of tPA and most expressed concern over adopting tPA as a standard of care. Stroke risk factors were not routinely screened by 24% of physicians. Conclusion: A large, multi-disciplinary, sustained effort towards enhanced state-based stroke care is feasible and may be a model for other state-based stroke initiatives. Our data suggest several areas for improving physician and hospital awareness of current, optimal stroke-related practices. Subcommittees have been formed to develop action plans for correction of these deficiencies.

The Stroke Belt Consortium: A Model for Regional Stroke Educational Programs and Policy Development

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The Stroke Belt Consortium was formed in 1994 to enhance and coordinate educational activities among diverse groups within the Stroke Belt region. These programs deal with all aspects of stroke care, including acute diagnosis and treatment, preventive efforts, and stroke education. The Consortium has expanded to include more than 350 members and 35 different organizations. Groups that participate in the Consortium include health care providers, academics, state legislators, NINDS, pharmaceutical companies, non-profit organizations, managed care, minority groups, and pharmacists. By bringing together representatives from diverse groups, the Consortium can empower and coordinate organizations and activities that typically do not interact. Examples include legislators working with physicians, pharmaceutical companies cooperating among each other, and managed care groups working with health care providers. The Consortium’s annual meeting serves as a focal point for the presentation of new research data, the exchange of ideas for unique educational programs, and the development and implementation of new policies. This is accomplished through lectures, workshops, and breakout sessions. The activities of the Consortium have led to the formation of a number of state-based legislative efforts, such as the North Carolina Heart Health and Stroke Prevention Task Force and the Florida Stroke Partnership Council. Each one has been successful in receiving substantial funding for stroke educational programs. Other successful programs sponsored by the Consortium include a survey of stroke awareness, development of materials on Stroke Awareness, and the development of guidelines for Stroke Centers as well as a “Bill of Rights” for stroke patients. The Stroke Belt Consortium offers one model for the successful integration of diverse organizations and professionals on a regional basis. This model may be useful in other regions of the country with distinct or specific needs for developing stroke programs dealing with education, legislation, and other policy issues.
We elucidated the clinical features of patients with two subtypes of chronic atrial fibrillation (AF), i.e., paroxysmal or persistent AF, and compared the incidence of cerebral thromboembolism between each group. The study included 301 consecutively admitted patients with chronic AF (123 paroxysmal AF (group A) and 180 persistent AF (group B) patients), 188 men and 113 women from 34 to 97 years of age. The mean (± SD) age of patients in group B (73 ± 11 yrs) was significantly greater (p = 0.029) than that in group A (70 ± 12 yrs). Echocardiographic diameter of the left atrium in group B (45 ± 10 mm) was significantly larger (p = 0.0004) than that in group A (37 ± 7 mm). Left ventricular ejection fraction in group B (61 ± 14%) was significantly smaller (p = 0.016) than that in group A (67 ± 11%). The incidence of congestive heart failure was significantly greater (p < 0.001) in group B (51%) than in group A (21%), and mortality in group B (13%) was significantly higher (p = 0.045) than in group A (6%). However, the risk of cerebral thromboembolism in group B (26% or 8.0%/year) was not significantly larger (p = 0.136) than that in group A (17% or 5.2%/year). Cerebral thromboembolism occurred in 81% and 94% of the patients 60 years or older in groups A and B, respectively. The incidence of cerebral thromboembolism in patients without underlying disorders in group A was only 7% (p < 0.01). We concluded that the risk of cerebral thromboembolism in patients with paroxysmal AF was essentially equal to that with persistent AF. Antithrombotic therapy was recommended for those patients 60 years or older in both groups, and for patients with paroxysmal AF with underlying disorders.

We elucidated the clinical features of patients with two subtypes of chronic atrial fibrillation (AF), i.e., paroxysmal or persistent AF, and compared the incidence of cerebral thromboembolism between each group. The study included 301 consecutively admitted patients with chronic AF (123 paroxysmal AF (group A) and 180 persistent AF (group B) patients), 188 men and 113 women from 34 to 97 years of age. The mean (± SD) age of patients in group B (73 ± 11 yrs) was significantly greater (p = 0.029) than that in group A (70 ± 12 yrs). Echocardiographic diameter of the left atrium in group B (45 ± 10 mm) was significantly larger (p = 0.0004) than that in group A (37 ± 7 mm). Left ventricular ejection fraction in group B (61 ± 14%) was significantly smaller (p = 0.016) than that in group A (67 ± 11%). The incidence of congestive heart failure was significantly greater (p < 0.001) in group B (51%) than in group A (21%), and mortality in group B (13%) was significantly higher (p = 0.045) than in group A (6%). However, the risk of cerebral thromboembolism in group B (26% or 8.0%/year) was not significantly larger (p = 0.136) than that in group A (17% or 5.2%/year). Cerebral thromboembolism occurred in 81% and 94% of the patients 60 years or older in groups A and B, respectively. The incidence of cerebral thromboembolism in patients without underlying disorders in group A was only 7% (p < 0.01). We concluded that the risk of cerebral thromboembolism in patients with paroxysmal AF was essentially equal to that with persistent AF. Antithrombotic therapy was recommended for those patients 60 years or older in both groups, and for patients with paroxysmal AF with underlying disorders.

Rostro-Caudal Gradient for Risk of Incident Hemorrhage in Patients with Brain Arteriovenous Malformation (AVM)

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Objective: To investigate the effect of brain AVM location on the risk of intracranial hemorrhage at initial presentation. Methods: A total of 398 consecutive patients from the New York Brain AVM Database were evaluated. Univariate and multivariate analyses were applied to compare the frequencies of incident intracranial (parenchymatous/intraventricular/subarachnoid) hemorrhage with different AVM locations. Results: In 45 (15%) cases, the AVM was located intracranially. Of the 353 patients with supratentorial AVM location, 327 patients had a lobar (coritico-subcortical) AVM. In 120 patients, a frontal lobe AVM location - either frontal lobe alone (n=72) or frontal/parietal/fronto-temporal location (n=48) - was found. The rates of hemorrhage differed significantly by AVM location. Of the infratentorial AVMs, 31 (69%) presented with hemorrhage as compared to 169 (48%) of the supratentorial AVMs (p<0.008). Of the patients with frontal AVMs, 37% presented with hemorrhage as compared to 103 (50%) with other lobar AVM locations (p<0.03). The effect was also strong when comparing frontal AVM with the total group of brain AVM including those located in the basal ganglia and infratentorially (p<0.001). The groups did not differ by age, gender, AVM size, venous drainage pattern and associated (extra/intramidal) aneurysms. Conclusion: These findings suggest a rostro-caudal gradient of increasing hemorrhage risk depending on AVM location. Frontal AVM location may be a determinant for lower risk and infratentorial AVM location for higher risk of intracranial hemorrhage at initial presentation.

Recurrent Cerebral and Retinal Vascular Events After Retinal Ischemia or Embolism

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Purpose: To determine the characteristics of recurrent cerebral and retinal vascular events in patients who present with retinal ischemia or embolism. Methods: Consecutive patients with a diagnosis of transient monocular blindness, retinal or optic nerve infarction, and asymptomatic retinal embolism, and referred to the Neurology or Ophthalmology Departments of the Boston Medical Center and the Boston VA Medical Center were prospectively enrolled. The study duration was 21 months. Each patient underwent a standard battery of tests that included neurologic scales than disability indexes. Retrospective assessment of these 5 scales can be done reliably from a community hospital medical record.

Poster Presentations

Incidence of Cerebral Thromboembolic Infarction Associated with Paroxysmal or Persistent Atrial Fibrillation

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Perception of Stroke Among Children

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Background: Stroke is a preventable and acute treatable disease. It has been well documented that lack of knowledge regarding stroke and stroke risk factors exists amongst the general population. Children are the pillars of our society. The purpose of this study was to determine childrens baseline knowledge of stroke and stroke risk factors. Methods: A questionnaire was administered to school-aged children at a private lower/upper school on Long Island, NY. The population was divided into lower school which consisted of grades 3, 4 and 5, age range 8-11, median age 10 and upper school which consisted of grades 7, 9 and 10, age range 12-16 years, median age 15. Results: Of 110 respondents, 62 were from the lower school (L.S.) and 48 were from the upper school (U.S.) 1.8% of L.S. and 56% of U.S. children could identify what a stroke was. 8% of L.S. and 52% of U.S. children could identify how the brain was injured during stroke. 45% of L.S. and 77% of U.S. children knew to seek help during stroke. L.S. children identified chest pain (45%), pain (42%), dizziness (37%) and headache (34%) and U.S. children identified dizziness (75%), blurred vision (58%), pain (58%) and headache (56%) as symptoms of stroke. Finally, L.S. children identified hypertension (44%), heart disease (37%), alcohol use (34%) and smoking (34%) and U.S. children identified hypertension (92%), stress (69%), heart disease (58%) and obesity (52%) as risk factors of stroke. Conclusion: There is limited knowledge amongst school-aged children regarding stroke. The children associated stroke symptoms and descriptions to heart attack, which demonstrates the great education effort regarding heart disease. Education of school-aged children may reduce stroke risk factors in adulthood.

Perspective Assessment of Five Stroke Scales and Disability Indexes in the Community Setting

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Background: Retrospective stroke outcomes studies are hampered by the inability to accurately measure initial severity of impairment. Objectives: To evaluate the validity and reliability of retrospective assessments of the National Institutes of Health(NIHSS), Canadian Neurological(CNS), Scandinavian Stroke(StSS) Scales and Barthel & Rankin Disability Indexes in a community setting. Methods: Scales were prospectively measured in 34 acute stroke patients admitted to a community hospital by a stroke neurologist uninvolved in their care. Retrospective scoring using predefined algorithms was performed by 3 neurologists from medical and record documentation in the 1st 24h of admission. Agreement between prospective and retrospective scores(validity) and inter-rater reliability were determined using intraclass correlation coefficients(ICC)and calculation of the maximum difference among ratings(MDR). Results: see Table Conclusions: Agreement between prospective and retrospective scoring and inter-rater reliability was good for all scales. Reliability and validity were better for neurologic scales than disability indexes. Retrospective assessment of these 5 scales can be done reliably from a community hospital medical record.
The Feasibility of an Internet Web-Based, International Study on Brain Arteriovenous Malformations (the AVM World Study)  

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Objective: To evaluate the feasibility of an internet web-based, world wide study on brain arteriovenous malformations (AVM) Methods: A pilot study website has been created and offered to a limited number of possible international participants who were invited to register for a validity study (http://cuaa.js.columbia.edu/avm=validity). Displaying jpeg-formatted magnetic resonance (MR) and angiographic images on the website, the study evaluated inter-observer agreement on AVM size (measured in number of brain gyri), venous drainage pattern (deep and/or superficial), and presence of aneurysms (intratral, feeding artery, or unrelated to shunt flow). Intraclass correlation coefficient (ICC) and Conger’s multiple rater kappa (w) statistics were applied to determine chance corrected inter-observer agreement among the respondents. Results: As of August 12th, 1999, 17 participants (17 neurologists, 2 neuroradiologists) from 11 different countries registered for the study. 12 (65%) responded to all questions requested. Web browser incompatibility rendered 2 (11%) and 1 (6%) unable to open the entire set of study pages on the website. In the remaining 4 (21%), the response was incomplete, or the volume of response was unexpected (<0.29) was post. Conclusion: Our findings suggest that an internet web-based study is technically feasible provided a common standard of local computer software at the participating sites. The agreement on basic morphological AVM features, however, was lower than expected and justifies plans for a larger validation study.

Urinary Tract Infections in Stroke Rehabilitation: Association with Indwelling Urinary Catheter Placement During Acute Hospitalization  

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Urinary tract infection (UTI) and urosepsis, is the most common medical complications during stroke rehabilitation, can delay functional recovery and increase cost of medical care. The purpose of this study was to evaluate clinical factors that predict the occurrence of UTI in a prospective cohort of 1026 consecutive patients admitted to a stroke rehabilitation program. After excluding 15 patients with anuria or due to read failure of 1016 were analyzed by logistic regression analysis. The incidence of UTI was 31% within the cohort. With univariate logistic analysis, the strongest predictor of UTI during rehabilitation was indwelling urinary catheter (IUC) placed during acute stroke care (OR=4.73, 95%CI (3.49 to 6.41)). After controlling for admission NIHSS, the odds ratio for IUC was only slightly attenuated (OR=3.41, 95%CI 2.46 to 4.89). Conclusion: The association was robust and not associated with IUC. Occurrence of UTI was independently associated with increased length of rehabilitation stay and daily cost of care. These findings indicate that placement of IUC during acute care following stroke is a risk factor for later UTI and is associated with higher cost and morbidity. Given that most stroke patients have uninhibited neurogenic bladder, IUC should be reserved only for those with bladder outlet obstruction or who require precise fluid input and output monitoring.

Changes in Cerebral Perfusion After Carotid Angioplasty and Stenting. Angiographic Evaluation and Predictor  

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OBJECTIVE: Using digital angiography, changes in ipsilateral cerebral blood flow velocity before and after carotid angioplasty and stenting were investigated. A grading system was developed to evaluate angiographic perfusion changes. METHODS: Clinical data of 87 patients (age 69±9 years) who received unilateral angioplasty and stenting for symptomatic or asymptomatic internal carotid stenosis (mean degree 68±13%) were retrospectively analysed. On angiograms, lesion characteristics were measured using NIH-Image software. Pre- and post-stent images were matched for each patient by consensus. RESULTS: Improvement in flow was defined on the basis of spatial or temporal distribution of contrast, i.e., either filling of blood vessels previously not visualised spatiotemporally or increase in transit time of contrast. Perfusion ratings were performed independently by two raters in a blinded fashion (1 = less vessels on post-stent image; 0 = no change; 1 = more branches; 2 = capillary blush; 3 = capillary blush and small veins; 4 = large veins or sinuses). RESULTS: For the grading scale, an interclass correlation coefficient of 95.9% (Kappa 0.72) was obtained. Perfusion change was observed in 77% of patients. Perfusion was improved in 75%. Grade 1 was attributed in 33%, grade 4 in 4-6% of patients. The distribution of grades was normal (median of 1). In 18.4% of all cases with ipsilateral anterior cerebral artery filling from the contralateral side, a normal filling pattern was restored after stenting. Improved perfusion was associated with a high degree of ipsilateral stenosis (P<0.05), right- sided lesion (P<0.05), and a high ratio of pre- to post-stent diameter of the lesion (P<0.02). Restoration of the normal ACA filling pattern was associated with little or no contralateral stenosis (P<0.001). CONCLUSION: The grading system described can be used to reliably assess perfusion changes after PTAS and may be applicable for other revascularization techniques and pathologies. Increased perfusion is seen in most cases of carotid angioplasty and stenting and depends on the degree of hemodynamic inflow obstruction that can be relieved by stenting.

Distal Embolic Stroke is an Important Perioperative Complication of Carotid Stenting, Which is Performed for Carotid Artery Stenosis. Our purpose is to elucidate whether distal embolic stroke during carotid stenting can be predicted by ultrasonographic evaluation of carotid plaque character. Methods: Twenty-two patients underwent carotid stenting for 24 narrowed carotid arteries. Prior to surgery, plaque character of 24 arteries was evaluated with B-mode and color Doppler ultrasonography and was classified into 3 types, such as echolucent (n=11), echogenic (n=8) and calcified (n=5). The echoluency of plaque was further evaluated quantitatively from the echogenicities of plaque and vascular lumen, which were calculated from gray scales on digitized B-mode images ranging from 0 (absolutely black) to 255 (absolutely white). The echoluency of plaques was obtained from plaque echogenicity subtracted by vascular lumen echogenicity. Following carotid stenting, diffusion weighted MRI was performed in all patients, and the relationship of plaque character with distal lesions was studied. Results: Following the stenting, neither distal lesion nor ischemic symptom was found in 4 arterial territories (Group A), new distal lesions without symptom were developed in 7 arterial territories (Group B), and new lesions with symptoms were developed in 6 arterial territories (Group C). Echolucent plaque was found more frequently in Group C (66%) than in Groups A (31%) and B (27%) (p < 0.05). Kruskal-Wallis rank test. The calculated echoluency of plaque was significantly lower in Group C (12.0±6.1) than in Groups A (25.8±15.6) and B (31.5±16.3) (p < 0.05. Fisher’s LSD), while no difference was found between Groups A and B. Conclusions: Carotid stenting may be complicated by symptomatic or asymptomatic distal embolism. Of these two types of embolism, symptomatic one appears to be closely connected with the existence of echolucent carotid plaque. The quantitative analysis of carotid plaque echolucency may make it possible to predict the occurrence of symptomatic distal embolism during carotid stenting.
P130
The Decision to Withdraw Medical Support in Intracerebral Hemorrhage May Lead to Self-Fulfilling Prophecies

Background: Models for predicting outcome in intracerebral hemorrhage (ICH) are based upon patient populations in which medical support may be withdrawn at the advice of the treating physician or at the request of the family. Personal biases about the futility of therapy may influence these models since support may be withdrawn in patients perceived to have little chance of meaningful survival. Methods: We retrospectively reviewed the medical records and radiographic studies of 113 consecutive patients with spontaneous ICH. The clinical and radiographic characteristics of patients undergoing aggressive medical care and those in whom support was withdrawn were compared. Clinical outcome in patients with ICH volume >70 cm^3 and GCS ≤8 was assessed, because these findings have been associated with adverse chance of survival (1). Statistical analyses were performed using the two-tailed t-test for continuous variables and χ^2 for dichotomous variables. Multiple logistic regression was performed to identify independent predictors of outcome. Significance was set at p<0.05.

Results: Overall mortality was 38.1% (43/113). Medical support was withdrawn in 76.7% (33/43) of dying patients. Withdrawal of support led to death in all cases. Hematoma size was larger (73.2 cm^3 vs 46.3 cm^3, p<0.009). GCS lower (5.5 vs 9.2, p<0.001), and IVH more common (64.8% vs 66.2%; p=0.046) among patients in whom support was withdrawn. There were 29 patients with ICH >60 cm^3 and GCS ≤8; support was withdrawn in 41.4% (12/29) and 65.5% (19/29) died. Within this subgroup, there were no significant differences in the age, hematoma volume, GCS, or frequency of IVH in patients who lived and died. Of the survivors, 6/10 (60%) were discharged to rehabilitation or better, an outcome associated with surgical intervention (OR = 23.8, 95%CI = 2.15, 260; p<0.01). Patients who were withdrawn in any patient underwent surgery.

Conclusions: Decision to withdraw medical support in patients with ICH should be made with caution, as patients in poor prognosis categories can have a reasonable outcome with aggressive therapy. References: (1) Broderick JP et al. Stroke 1993;24:987-993.

P131
The Low Normothermia Concept: Maintaining a Body CORE Temperature Between 36.0 and 37.0°C in Non-Ventilated Acute Stroke Patients - a Feasibility Study
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Objective: Elevated body temperature increases mortality and worsens outcome in acute stroke patients. In experimental animal models, even a minor reduction in core temperature was neuroprotective. Pharmacological treatment (paracetamol, metamizol) usually fails to lower body temperature below 37.5°C. We present a concept with continuous body surface cooling towards core temperatures between 36.0 and 37.0°C in acute stroke unit patients without mechanical ventilation or muscle relaxation. Methods: Acute non-comatose stroke patients are kept on a water-perfused cooling mattress for 24 hours. Shivering and peripheral vasoconstriction are avoided by infusion of pethidine and dihydroergotoxine. Vital parameters are registered online, relevant laboratory tests are performed every 12 hours. Findings: We treated 14 patients so far. The mean baseline NIHSS score was 16.1 ± 5.2. All patients had baseline temperatures > 37.0°C, two patients > 38.0°C (mean 37.6 ± 0.3). A core temperature between 36.0 and 37.0°C could be achieved in all patients between 1 and 12 hours (mean 4.0 hours) and was maintained for at least 24 hours. We did not observe a decline in the level of consciousness, respiratory dysfunction, electrolyte disturbances, coagulation disorders, renal dysfunction or major skin irritations. Compared to baseline, five patients had an increase of their CRP level beyond 5 mg/l (mean CRP after cooling 5.0 ± 4.8 mg/dl), seven patients received antibiotic treatment during cooling or within three days after. The first two patients received a dihydroergotoxine bolus and experienced a drop in mean blood pressure of > 20%. MABP was stable in the other patients. All patients tolerated the procedure without major discomfort. Conclusions: Core body temperatures between 36.0 and 37.0°C can be rapidly achieved and maintained in acute stroke patients without ventilation or muscle relaxation. Dihydroergotoxine bolus administrations result in blood pressure drops and have to be avoided. Adverse events were mild and temporary. To assess the potential benefit, a controlled trial is ongoing.

P132
Tec Evaluation of Antiplatelet Therapy for Postoperative Thromboembolism in Carotid Endarterectomy (CEA)
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Objective: Demonstration that perioperative microembolization is associated with increased risk of perioperative stroke, and that use of transcranial Doppler monitoring enables assessment of efficacy of antithrombotic medication. Methods: Transcranial Doppler monitoring of the middle cerebral artery for detection of embolization in 79 monitored carotid endarterectomies was assessed. Dextran therapy was used routinely. In six cases where transcranial Doppler monitoring showed high microembolization rate, a Dextran receptor antagonist was used. Results: There were two strokes in the aggregate series. Both of these were associated with high rates of embolization (>150 embolus/hour). When Dextran failed, a platelet receptor antagonist routinely eliminated embolization (zero embolus/hour). In the six instances where this procedure was followed, no patient suffered a perioperative stroke. Conclusion: High rates of microembolization after CEA are associated with perioperative stroke. Administration of antiplatelet therapy is effective in reducing or abolishing such embolization. In cases where Dextran is not effective, use of a GPIIb/IIIa receptor antagonist was successful in abolishing all embolization. No patient in whom embolization was abolished suffered a perioperative stroke.

P133
Induced Hypertension in Acute Ischemic Stroke Management
Guy Rorrod, Alain Z. Segal, Mustapha Ezeddinide, Colin T. McDonald, Jamila Oliveira-Filho, Walter J. Kossohiet, Lee H. Schwamm, Ferdinando Buonanno, MA Gen Hosp, Boston, MA

Background: The aim of our study was to determine whether the use of induced hypertension in the management of acute stroke is feasible and safe, and to characterize which patients with acute stroke are more likely to respond to this therapy. Methods: All acute stroke patients seen in the emergency room within 12 hours from onset of symptoms and with an NIHSS of at least 4 were considered for induced hypertension. Phenylephrine was used to raise the initial systolic blood pressure to at least 160 mmHg or by 20% over the initial SBP up to 200 mmHg. Patients considered for thrombolysis, patients with recent history of myocardial infarction, unstable angina, or midline shift on the head CT scan were excluded. Patients were considered responders if after 30 minutes of increased blood pressure the NIHSS improved 2 points or more and if the exam worsened after having the blood pressure return to baseline. If they responded, patients were then maintained on induced hypertension therapy. Results: From December 1998 and July 1999, 11 patients were treated with induced hypertension between 7 and 10 hours from symptom onset. In 6 patients, the neurological exam improved between 2 and 6 points following the increase in blood pressure, while in 5 it did not. In the responder group there were 3 embolic strokes to the MCA stem, 2 low flow strokes due to carotid stenosis and one lacunar stroke. All non responding patients had embolic strokes. The symptoms that improved with increased blood pressure were motor weakness in all patients, disorientation and aphasia in one patient each. No patients developed neurological, cardiac, renal or other complications while on phenylephrine or for 3 days following the discontinuation of induced hypertension. Patients treated with induced hypertension improved daily, with daily weak attempts. Conclusions: We found that induced hypertension is feasible and safe in patients with acute ischemic strokes. Despite the small number of patients studied, a sizable proportion respond to this therapy. All different subtypes of stroke can be improved by this therapy. It is not clear yet if induced hypertension will change long term outcomes. Induced hypertension shows promise in the management of acute strokes.
**Poster Presentations**

**P135**

**Temporal Patterns of Response to Hypervolemic and Hypertensive Therapy in Patients with Symptomatic Vasospasm Following Subarachnoid Hemorrhage**

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**Background and purpose:** Angioplasty and intra-arterial papaverine are used for patients with symptomatic vasospasm following subarachnoid hemorrhage (SAH) who do not respond to hypervolemic and hypertensive therapy (HHT). There is no consensus regarding time period for observation of response to HHT. We performed this study to determine the time course of response to HHT. **Methods:** We reviewed the medical records of 67 patients treated with HHT following onset of symptomatic vasospasm. Clinical information including timing of initiation of HHT and response, requirement for intervention techniques, infarct on CT scan, Glasgow Outcome Scale (GOS) score at three months was collected. Clinical response to HHT was defined by improvement in Glasgow Coma Scale (GCS) score at 1 hour. **Results:** The three patterns of temporal responses were observed after initiation of HHT: early improvement (n=22), late improvement between 3-24 hours (n=21), and no response (n=19). Among responders, men were more likely to show early response compared to women (p<0.0002). The GCS at initiation of HHT was similar in early (10.9±3.7), late (11.2±3.1), and non-responders (10.3±3.2). The GCS was significantly lower in non-responders (9±3.5) compared with early (12.4±2.7) and late responders (11.8±2.9) after 24 hours of HHT (p<0.01). The frequency of cerebral infarctions on follow-up CT scan was similar between early and late responders. The new formulation of GCS was better in detecting interventional approaches that should be considered if early response is not observed. The present study suggests that delayed response to HHT can be observed in some patients. In the absence of progressive deterioration, a longer trial of HHT is probably justified prior to endovascular treatment.

**Conclusion:**

Conclusions: In contrast to popular belief that interventional approaches should be considered if early response is not observed, the present study suggests that delayed response to HHT can be observed in some patients. In the absence of progressive deterioration, a longer trial of HHT is probably justified prior to endovascular treatment.

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**P136**

**The Importance of Additional Events in Estimating the Costs of Stroke**

Judith A O'Brien, Danielle Pierce, J J Caro, Careo Res, Concord, MA

**Objective:** To assess the importance of health care costs associated with subsequent ischemic strokes. **Methods:** Using unique ID numbers and appropriate IC92 codes, a population of patients with ischemic stroke was identified from Massachusetts (MA) 1996/1997 patient-level discharge databases. The first 1996 admission for ischemic stroke for each patient was considered the index stroke. Subsequent admissions for another ischemic stroke within 12 months were assessed in terms of hospital costs, length of stay, discharge disposition pattern and post-acute care costs. Costs were adjusted for medical inflation and cost-to-charge ratios, and were averaged using a log transformation to address highly skewed distributions. The discharge database was supplemented by fee schedules, other agency and survey data, and the literature to establish first-year post-acute care costs. All costs are reported in 1996 US dollars. **Results:** An index stroke population of 7,691 patients was identified. Of the 68% who were discharged alive, 8.4% were readmitted for a subsequent stroke within the following year. Of the 615 patients readmitted, 95% survived the new hospital stay. The mean hospital cost for the index event was $7,275 compared to $7,672 for a subsequent admission. Although the overall cost of hospitalization was slightly lower for the subsequent stroke compared to a longer mean length of stay of 2 days, the mean per diem cost during the stay was $112,716 vs. $112,216. At second event discharge, 68% received further sub-acute inpatient or home health care compared to 63% after the index event, resulting in higher post-acute care costs in the first year for the secondary event ($40,127 vs. $35,710). **Conclusions:** To properly estimate the cost of stroke, additional hospital costs for secondary events need to be considered. This analysis shows that the increased economic burden resulting from these secondary events goes beyond just the additional cost of another hospitalization.

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**P137**

**Development of a Stroke Severity System: Knoll Ischemic Stroke Score (KISS)**

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**Background and Purpose:** There has been substantial interest in identifying predictors of survival for stroke patients. Current instruments used for measuring stroke severity are confined to either diagnostic, neurologic, functional or disability measures. The purpose of this study is to develop a stroke severity system that combines instruments from different domains to better predict long-term survival. **Methods:** We took advantage of a particularly broad array of clinical and physiological variables collected during a randomized clinical trial of ischemic stroke patients (Stroke Treatment With Ancrod Trial). 455 patients completed a battery of instruments seven days post stroke and then they were followed for one year. **Results:** Out of the 453 patients, 53% of the patients were male, 77% were 65 or older, 89% were White and 75% had hypertension. 155 (31%) patients died during the study period. Age was a highly significant predictor (P<0.001) of mortality, but there were no statistically significant differences in 12-month survival by gender, race, educational level, smoking status or handlessness. The best model of survival was the Knoll Ischemic Stroke Score. This model included the Scandinavian Stroke Scale (excluding gait), Rapid Disability Rating Scale, prior stroke history and age. This model had substantially greater predictive power (R²=30, c statistic=.86) than the Scandinavian Stroke Scale alone (R²=.20, c statistic=.78). **Conclusion:** This study demonstrates that combining day 7 post-stroke information from multiple domains substantially improves the ability to predict 12-month survival of ischemic stroke patients compared to data from a single domain.

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**P138**

**Patients Who Received Thrombolysis for Acute Stroke and Required Mechanical Ventilation: Outcome and Analysis**

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**Background:** Historical reports suggest that patients with acute ischemic stroke who require mechanical ventilation (MV) have poor outcomes. Whether treatment with thrombolysis modifies outcome is underdetermined. **Methods:** We reviewed all acute ischemic stroke patients, admitted through the Emergency Department, who received IV and/or Intralial (IA) thrombolysis and required MV from 2/96-7/99. Outcome Rankin was determined through last available records, clinic follow up, or telephone interview. **Results:** 30 patients received thrombolysis and required MV (Age: 63±14 years, NIHSS 21±9, Glasgow Coma Score (GCS) 11±4, time to thrombolysis 150±42 minutes, time of follow up 8.9±9.9 months). Reasons for intubation were: Airway protection 17, Oropharyngeal angioedema from TPA 2, Cardiac 2, Pulmonary 2, and Procedure 7 (hemorrhagic stroke, 3/AIV/ thrombolysis 5, hypothermia 2; some patients had multiple procedures). Outcomes were Rankin of 0-2 (n=14), 3-4 (n=8), and 5-6 (n=8). Outcome was not associated with age, initial NIHSS, initial gcs to intubation, time to thrombolysis, or length of ventilation. 2/7 patients intubated for TPA related intracerebral hemorrhage(ICH) died. Outcome and reason for MV were examined (table). **Conclusions:** A significant portion (40%) of patients who received thrombolysis and required MV had an outcome Rankin score 5/4. Presenting clinical indicators did not predict outcome. Patients who required MV for reversible reasons fared better than patients for airway protection due to worsening neurological condition. No patients intubated for TPA related ICH survived.

**P139**

**The Treatment of Giant Intracranial Arteriovenous Malformations Using Multimodality Therapy**

Steven D Chang, Jaime R Lopez, Stanford Univ, Stanford, CA; Richard P Levy, Loma Linda Med Ctr, Loma Linda, CA; Michael P Marks, Gary K Steinberg, Stanford Univ, Stanford, CA

**Objective:** Giant AVMs (>6 cm) represent a difficult group of AVMs, often carrying higher treatment morbidity and mortality than smaller AVMs. The purpose of this study was to review our series of patients with giant AVMs treated since 1987. Methods: Twenty-eight patients with giant AVMs were treated, including 12 males (43%), and 16 females (53%). Presenting symptoms included hemorrhage (13; 46%), headache (7; 25%), seizures (5; 18%) and progressive neurologic deficits (2; 7%). Spetzler-Martin grade was: III (1), IV (5), and V (22). Mean AVM size was 6.7 cm (range, 6.15 cm). Venous drainage was superficial (5), deep (11), or both (12). AVM location was eloquent in 26 patients, and non-eloquent in 2 patients. At presentation, 15 patients (54%) were graded excellent, 9 good (32%), and 4 poor (14%). Patients were treated with surgery (n=16; 57%), embolization (n=26; 93%), and radiosurgery (n=25; 89%). Most patients received multimodality treatment including embolization and surgery (n=3), embolization and radiosurgery (n=10), or embolization, radiosurgery, and surgery (n=13). Two patients received radiosurgery alone. For those patients treated with radiosurgery, the mean dose was 19 Gy (range, 11.5 to 25 Gy). Of the 26 patients treated with embolization, 2 received 2 or more embolization stages. Of the 16 patients undergoing surgery, 10 required one operation, 5 required 2 operations, and 1 required 3 operations. Mean follow-up: 52 months. Twenty patients (71%) were angiographically cured of their AVMs. Eight patients (29%) had residual AVM on their most recent angiogram, but 3 of these 8 patients were < 3 years post radiosurgery. Two patients (7%) died during follow-up; one from residual AVM hemorrhage, and one from complications from sinus thrombosis. Other complications included carotid dissection during embolization (n=1), increased seizures after radiosurgery (n=1), and radiation necrosis (n=1). Clinical results at 52 months mean follow-up were: 21 excellent (75%), 5 good (18%), and 2 dead (7%). **Conclusion:** Many patients with giant AVMs can be successfully treated. Multimodality treatment is usually necessary to achieve AVM obliteration.
Safety and Efficacy of Low Molecular Weight Heparin (LMWH) Instead of Unfractionated Heparin (UH) in Cerebrovascular Patients Requiring Anticoagulation

David C Tong, Shahweil Ashawi, Stanford Stroke Ctr, Palo Alto, CA; Melissa Choy, Stanford Univ, Stanford, CA

Background: SQ LMWH is equivalent or superior to IV UH while being converted to warfarin therapy. Our review experienced complications with the LMWH Lovenox in a study of 124 patients treated with full dose SQ LMWH or IV UH while being converted to warfarin therapy. Data were gathered on the frequency of recent stroke and bleeding complications that occurred two weeks of treatment. Results: 96 patients were identified, 57 UH and 39 LMWH treated patients (Table). Of these patients 72/5 (12.4%) heparin treated patients developed complications versus 1/39 (2.6%) LMWH treated patients (p=0.13). Bleeding was the complication in 6/57 (10.5%) of the UH and 1/39 (2.6%) of the LMWH cases. Recurrent neurological complications occurred in 5/57 (7.0%) and 1/39 (2.6%) of the LMWH treated patients (p=0.65). Conclusions: LMWH appears to be similar (or possibly superior) to UH in cerebrovascular patients requiring short term therapeutic anticoagulation. SQ LMWH may be an attractive alternative to IV UH in this situation.

Clinical Characteristics of Heparin and LMWH Treated Patients

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</tr>
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</tr>
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P144

Symptomatic Middle Cerebral Artery Stenosis: Should Angioplasty Be Attempted?


Background: Scant data exist on defining patients suitable for angioplasty of intracranial artery stenosis. We sought to evaluate the safety and feasibility of balloon angioplasty in patients with symptomatic high-grade M1 stenosis. Methods: Four consecutive patients (2 male, aged 65 and 67 years; 2 female, aged 54 and 73 years) presented to our Stroke Unit with symptomatic high-grade M1 stenosis of the middle cerebral artery (MCA). All had recurrent TIA and/or minor stroke despite therapeutic anticoagulation. Based on clinical angiographic and hemodynamic criteria, we proposed a treatment algorithm for balloon angioplasty of high-grade M1 stenosis. Results: In two patients, transcranial Doppler (TCD), single photon emission computerized tomography (SPECT) and MR perfusion (MRP) studies suggested hemodynamic compromise of the ipsilateral distal MCA territory and elective percutaneous transluminal angioplasty was attempted. In patient #1, angioplasty led to the luminal narrowing from 90% to 30%. Two days after treatment, TCD demonstrated asymptomatic recurrence of high flow-velocities at the angioplasty site, but distal MCA waveforms beyond the stenosis remained normal as did the patient in case #2, attempted angioplasty led to MCA occlusion and infarction in the territory of the lateral lenticonuclare arteries. He underwent extra-to-intracranial bypass surgery 2.5 weeks later and improved steadily over the following month. The remaining 2 patients did not show flow-dysregulation distal to the stenosis. Both became asymptomatic after one week of iv-heparin or antipatelet therapy. All 4 patients remained asymptomatic on oral anticoagulation (mean follow-up 3 months). Conclusion: Our preliminary findings suggest that angioplasty is feasible in patients with symptomatic high-grade MCA stenosis. The development of a testable algorithm for treatment decision should be based on evidence of poststenotic flow-dysregulation as defined by TCD, SPECT and MRP. Because MCA occlusion and recurrent stenosis constitute major treatment risks we propose conservative treatment in those patients without documented poststenotic flow-dysregulation.
Effect of Aortic Atherosclerosis on Hemostatic Markers in Patients with Ischemic Stroke
Ryoichi Otao, Takashi Morishita, Masahito Yasaka, Kazuyuki Nagatoku, Kazuo Minematsu, Takenori Yamaguchi, National CV Ctr, Suita

[Background and Purpose] Complicated lesions in the aortic arch are recently recognized as a potential source of emboli. Because hypercoagulable state is often observed in patients with severe atherosclerotic diseases, aortic atherosclerosis itself may also enhance the coagulability and result in promoting embolic events derived from other diseases such as nonvalvular atrial fibrillation. We evaluated relationships between hemostatic markers and atherosclerosis in the thoracic aorta. [Methods] We studied 78 consecutive patients who were examined by transoesophageal echocardiography (TEE) because of suspected ischemic stroke. We measured plasma levels of prothrombin fragment 1+2 (F1+2), activated factor VII, thrombin-antithrombin III complex (TAT), antithrombin III activity (ATIII), protein C activity (PC), α2 plasmin inhibitor (α2PI) and D-dimer. Using TEE, we evaluated whether complicated atheromas (thickness ≥3.0 mm, marked irregular surface and/or broad acoustic shadow) were present or not in the thoracic aorta. Ultrasonographic findings were compared with hemostatic markers. We also performed stepwise multiple regression analysis to evaluate the independent influence of aortic atherosclerosis, age, sex and other atherosclerotic diseases on F1+2, the direct indicator of thrombin generation. [Results] The patients with complicated lesions (n=47) had significantly higher levels of F1+2 (1.28±0.71 vs 0.82±0.33 nmol/l), TAT (6.5±5.88 vs 3.1±3.0 μg/ml), D-dimer (1.59±2.54 vs 0.45±0.54 μg/ml), and lower levels of ATIII (92.9±11.5 vs 99.2±10.8%), PC (100.6±16.3 vs 109.4±15.9%), α2PI (95.9±12.2 vs 104.0±12.5%) than those without such lesions (n=31, p<0.05 in each parameter). After the stepwise multiple regression analysis, the complicated lesions remained significantly associated with F1+2 (p=0.0007). In 17 patients who presented abnormally high levels of F1+2 (>1.4 nmol/l), 16 (94%) had complicated lesions in the aorta. [Conclusions] Atherosclerotic lesions in the aorta were closely related with hypercoagulable state, and may play an important role in the development and pathophysiology of thromboembolism.

Early Diagnosis of Hemorrhagic Transformation a Diffusion / Perfusion Weighted Magnetic Resonance Imaging Versus Computed Tomography Study
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New magnetic resonance imaging (MRI) techniques such as diffusion weighted imaging (DWI) might detect hemorrhagic transformation (HT) earlier than CT. Nine patients who experienced an acute carotid territory ischemic stroke either treated with t-PA (4) or antiocoagulant (5) were included. Patients underwent the following radiological protocol twenty four hours after stroke onset: A) a second CT scan B) MRI including and axial isotropic (DWI) SE EPI sequence, time of flight MR angiography (T.O.F MRA), and PWI with an axial T2*-W gradient echo-EPI sequence using 20 ml gadolinium contrast agent (Gd-DTPA). C) a third CT scan performed within one week after stroke in all patients who had a suspicion of HT on DWI. DWI showed an heterogeneous area of signal loss consistent with acute bleeding in six patients, in five of them the second CT scan failed to show an HT. An aditional CT scan performed one week after stroke confirmed HT previously suspected by DWI. The hypintense core was more prominent after PWI-T2*-W gradient echo-EPI sequence. On T.O.F MRA, an arterial occlusion was found in patients who had HT. These new MRI techniques may allow an earlier detection of HT, thus improving the management of stroke.

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<th>Week 4</th>
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P145

P144

P148
Poster Presentations

P149
Laminin Levels in Acute Stroke Patients May Serve as a New Marker for Therapeutic Decisions
Simone Wagner, Pamela Kath, Egon Werfe, Univ of Heidelberg, Heidelberg Germany; Ambra Puzzi, Humphrey A Gardner, Scripps Res Institute, La Jolla, CA; Werner Hacke, Univ of Heidelberg, Heidelberg Germany

Introduction: Postischemic degradation of the vascular basal lamina results in cerebral oedema and possible parenchymal haemorrhage. Basal lamina degradation is due to proteolytic cleavage of extracellular matrix molecules for example laminin by metalloproteinases. Thrombolytic therapy increases the risk of cerebral haemorrhage by its intrinsic proteolytic activity and via activation of MMPs. The aim of this study was to determine the possible usefulness of different thrombolytic strategies on the time course of the appearance of laminin in the peripheral blood of stroke patients and to examine whether pre-treatment laminin levels can contribute to the decision for or against thrombolysis.

Methods: Peripheral venous blood was collected on day 1, 2, 4, 8 from stroke patients (thrombolysis n=10, iv. heparin n=12, hypothermia n=6) with an infarction in the middle cerebral artery territory and from 25 age matched healthy control persons. ELISAs and additional Western-Blot analysis using antibodies against different chains of the heterotrimeric molecule of laminin were performed. Results were correlated with infant size on the CT and with the NIH score.

Results: The levels of plasma laminin measured by ELISA dropped in a characteristic pattern about 50% of that control on day one. It declined slowly from day 2 to day 4. Western blots suggested an increase in the expression of parts of the alpha and beta chain of laminin, whereas the gamma chain, where the ELISA-antibody epitope is located, decreased on western blot as well. 3 patients displaying almost unmeasurable levels of laminin measured by ELISA suffered secondary asymptomatic hemorrhages and 1 had a borderline MCA/PCa infarct. Further studies are needed to determine possible cut levels for or against thrombolysis.

P150
Cerebral Blood Flow as a Predictor of Clinical Outcome After Thrombolytic Therapy for Acute Ischemic Stroke
Steven Goldstein, Howard Yonas, James M Gebel, Aksam Kassam, Charles A Rumberger, Guven Uzen, Carol A Batch, Lori Massaro, Andrew D Filtik, Giorgio Rubin, Lawrence R Wechsler, Univ of Pennsylvania Med Ctr Stroke Institute, Pittsburgh, PA

Background and Purpose: We compared the relationship of quantitative cerebral blood flow (qCBF) and admission NIH Stroke Scale (A-NIHSS) to clinical outcome after thrombolytic therapy for acute ischemic stroke. Methods: We reviewed 32 patients (pts.) with acute cerebral infarction and who had qCBF measurements prior to or concomitant with thrombolytic therapy. Treatment was administered as follows: intravenous (iv) t-PA in accordance with FDA approved clinical guidelines (N=14), intra-arterial (ia) t-PA (UK) (N=7), iv and ia t-PA combined (N=4), combined iv t-PA (0.6 mg/kg) and IA t-PA (0.3 mg/kg) including one with concomitant angiology (N=5), iv t-PA and US (N=1) and iv t-PA alone (N=1). All pts. receiving iv t-PA, iv/la t-PA and iv/la t-PA and 1 ia UK were treated within 3 hours and pts. treated with ia UK or ia/la t-PA were treated within 6 hours of stroke onset. qCBF measurements were assessed using computerized tomography perfusion (CTP) imaging in 26 pts. and CISS in 6 pts. CTP was prospectively included in a database. In pts. receiving UK, the A-NIHSS and MRD was calculated retrospectively by chart review. Results: There was a highly significant correlation, by regression analysis, of qCBF in the symptomatic vascular territory with MR-D (P<0.001, R=0.77; 95% CI 4.2-4.7), with a cut-off of 0.25 ml/min/100 g, which was 100% specific and 60% sensitive. A-NIHSS and MRD were correlated (r=0.75, P<0.001). Conclusion: qCBF can be used as a physiologic marker to predict clinical outcome at discharge after thrombolytic therapy. As such, it appears to be superior to a clinical scale, the NIHSS. By improving patient selection it is hoped that the utilization of thrombolytic therapy will increase.

P151
Carotid Endarterectomy Decision-Making: Noninvasive Testing vs. Angiography
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Purpose: Carotid endarterectomy (CEA) is often performed based on the results of noninvasive vascular imaging (NIVI). We determined how often angiography (ANGIO) would alter a decision to proceed with CEA compared to angiography as the sole testing strategy. Methods: We reviewed all CEA performed at our academic center from 1996 to 2001. Patients with >50% common carotid artery stenosis were considered indications for CEA. Patients with >90% stenosis of ICA/MCA stem lesions. Half of all patients demonstrated easily recognized ischemic penumbras. The average volumes of the ischemic penumbra, delineated by disease state, were: ICA/MCA stem - 134 ml, branch vessel - 50 ml, lacune - 3 ml, and small vessel - 23 ml. Penumbra maps reveal measureable ischemic penumbras nearly 50% of the time. This consecutive series including one with concomitant angioplasty (N=1) and ia t-PA (N=4), combined iv t-PA (0.6 mg/kg) and ia t-PA (0.3 mg/kg) (N=7), ia UK and angioplasty (N=6) with an infarction in the middle cerebral artery territory and from 25 age matched healthy control persons. ELISAs and additional Western-Blot analysis using antibodies against different chains of the heterotrimeric molecule of laminin were performed. Results were correlated with infant size on the CT and with the NIH score.

Results: The levels of plasma laminin measured by ELISA dropped in a characteristic pattern about 50% of that control on day one. It declined slowly from day 2 to day 4. Western blots suggested an increase in the expression of parts of the alpha and beta chain of laminin, whereas the gamma chain, where the ELISA-antibody epitope is located, decreased on western blot as well. 3 patients displaying almost unmeasurable levels of laminin measured by ELISA suffered secondary asymptomatic hemorrhages and 1 had a borderline MCA/PCa infarct. Further studies are needed to determine possible cut levels for or against thrombolysis.

P152
Diffusion Weighted Magnetic Resonance Imaging in Posterior Circulation Stroke
Rafael H Linhas, Gottfried Schlaut, Claudia Chavez, Irima Starostokhaya, Harvard Med Sch, Boston, MA; Steven J Warach, Ninds/Nih, Bethesda, MD; Louis R Caplan, Ilah Lufinante, Harvard Med Sch, Boston, MA

Background: Diffusion Weighted Imaging (DWI) is sensitive in the evaluation of acute stroke patients. However, no studies have specifically assessed the capability of DWI in detecting posterior circulation ischemia. The small size of brainstem lacunes and the poor visualization of posterior fossa pathology make CT even less useful in such strokes. In addition, the utility of stroke scales and their relation to lesion volumes has not been studied for posterior circulation strokes. Methods: In 115 patients (18%) had symptoms related to posterior circulation ischemia by imaging and clinical criteria. Among those 115, we included in the study all patients (40) who had DWI within 24 hours from symptom onset (mean 7.7±1.1 hours). Seventy-five were excluded. In 45 patients imaging was obtained later than 24 hours, in 12 patients DWI was not performed, in 11 patients the symptoms resolved within 24 hours, 6 patients had hemorrhages and 1 had a borderline MCA/PCa infarct. Results: A DWI lesion corresponding to the patient's symptoms was detected by 2 investigators blinded to the clinical presentation and by the neuroradiologist in all 40 patients. Regarding lesion site, seven were medullary, two cerebellar, 10 pontine 1 midbrain, 7 thalamic, 5 in the occipital, 2 in the temporal cortex and 5 were multiple. Simultaneous acquisition of T2WI showed the lesion in 16 of 40 (40%). In 19 patients DWI was able to differentiate new strokes from old infarcts. DWI acute lesion volume did not correlate with NIHSS score (r=0.3; p=0.17; Spearman-Rank) even when the DWI lesion volumes were divided into cortical (r=0.4; p=0.04) and subcortical (r=0.3; p=0.2). Conclusions: Although prior studies reported few acute DWI-negative small brainstem strokes, in this series of patients DWI was able to detect the brain lesion responsible for the symptoms in all patients with posterior circulation disease imaged. DWI lesion volume does not correlate with NIHSS score, suggesting that NIHSS is more weighted towards anterior circulation stroke symptoms. DWI is very useful in the evaluation of patients with posterior circulation disease.

P153
Value of Diffusion and Perfusion MRI in 118 Unselected Stroke Patients
Erank Kahya, Candice J Perkins, Robert Peyster, S U N Y Stony Brook, Stony Brook, NY; George P Newman, SUNY at Stony Brook, Stony Brook, NY

INTRODUCTION: Diffusion and perfusion MRI are useful in the diagnosis of acute stroke but their overall value, sensitivity and dependence on stroke location and etiology remain unknown. To address this issue, we reviewed the imaging and determined lesion volumes of 118 consecutive, unselected patients who presented for evaluation of acute ischemic stroke and underwent echo-planar MRI. METHODS: FLAIR, trace diffusion images (DI) and mean transit time maps (MTT) were analyzed for all patients presenting between 9/98 and 7/99.

Each sequence was scored for acuteness, neuroanatomy and vascular territory. Lesion volumes were determined by image analysis. Perfusion was calculated as the difference between MTT and DI lesion volumes. Each case was categorized as ICA/MCA stem, Branch Vessel, Lacunar, Small Vessel, or Basilar Artery disease. RESULTS: There were 140 MRR’s in 118 patients, including 79 acute strokes, 29 cases with only old strokes and 10 normal studies. In 37 of the acute stroke patients (47%), DI was able to detect an acute lesion that FLAIR did not. DI was most valuable in identifying acute lacunar infarcts. FLAIR failed to identify 62% of lacunar infarcts recognized with DI, 43% of small vessel, 38% of branch vessel and 38% of ICA/MCA sten lesions. Half of all patients demonstrated easily recognized ischemic penumbras. The average volumes of the ischemic penumbra, delineated by disease state, were: ICA/MCA stem - 134 ml, branch vessel - 50 ml, lacunae - 3 ml, and small vessel - 23 ml. Maximum penumbra volumes were nearly 400 ml. For patients with branch vessel disease, we confirmed a modest correlation (r=0.49) between DI and MTT lesion volumes for branch occlusions but not ICA or stem lesions (Neuro 52:1125,1999). In 7 cases (9% of acute stroke lesions), FLAIR suggested small vessel disease but DI or MTT revealed carotid or branch occlusion. CONCLUSIONS: Diffusion imaging nearly doubles the likelihood of detecting lesions in patients with acute ischemic stroke and can improve diagnostic accuracy. MTT maps reveal measurable ischemic penumbras nearly 50% of the time. This consecutive series demonstrates the general utility of advanced MRI in the diagnosis and management of acute stroke.
Evaluation of Cerebral Perfusion by Dynamic MRI Bolus Tracking in CASASIL
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Background: CASASIL is a small artery disease due to Notch3 mutations. This disease leads to subcortical ischemic strokes and dementia associated with MRI T2 white-matter signal abnormalities. The severe ultrastructural arterial wall changes might affect cerebral perfusion and vasoactivity. Aim: To detect cerebral blood flow (CBF), blood volume (CBV) and mean transit time (MTT) alterations in CASASIL. Methods: We performed dynamic MRI studies in 15 symptomatic CASASIL patients (7 and 8 w/o dementia, mean age = 58 ± 7 y) and 10 age-matched controls. Asymmetric spin echo EPI (7 slices, 5 mm thick, intermediate 5 mm, TR = 1600ms, TE = 80 ms, asymmetry delay = 20 msc) was performed during a bolus injection of 0.1ml of gadoteric acid before and 20 min after acetazolamide (ACZ) administration (17 mg/kg iv). Absolute values of CBF, CBV and MTT were calculated using the singular value decomposition technique. Circular regions of interest were positioned along the cortical mantle and within the centrum semi-ovale. ANOVA (repeated factors) was done to compare perfusion parameters between groups. Results: A significant reduction in CBF (17.3 ± 11.4 vs 21.9 ± 7.9 ml/min/100ml; p = 0.05) and CBV (0.78 ± 0.39 vs 1.20 ± 0.34 ml/100ml; p = 0.001) was observed within the white matter. ACZ significantly increased CBF and CBV in all regions without significant difference between patients and controls. White-matter CBF and CBV remained lower in patients than in controls after ACZ administration (respectively 23.35 ± 12.09 vs 34.97 ± 13.82, 1.02 ± 0.63 vs 1.72 ± 0.65; p<0.05). MTT did not differ from that measured in controls. Conclusion: This shows a reduction in white-matter blood volume and flow in CASASIL. Despite vasodilation by ACZ challenge, the white-matter blood volume remains lower than that of controls, which suggests a permanent reduction of vessel capacitance. Additional investigations are necessary to determine if the reduction in the number and/or the diameter of microvessels is responsible for this decreased white-matter blood volume. Furthermore, our data suggest that the deficient cerebral perfusion in CASASIL might be improved by pharmacological vasodilation.

"Breaking up is Hard to Do": A Novel Method for Deconstructing Hyperintensities on MRI in Vascular Dementia
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Background: The significance of hyperintense lesions (HL) on magnetic resonance imaging (MRI) is unclear in dementia. The problem with current tissue classification techniques is that HLs lie between grey and CSF intensities and that brain surface voxels often are misclassified as lesion. Furthermore, global lesion volumes do not distinguish between anatomically, and possibly functionally, distinct lesion categories. Objective: To develop a valid method of quantifying HL volumes in different locations. Methods: Twenty dementia subjects with varying amounts of HLs had MRI and cognitive assessments. A 7-step semi-automated protocol was devised to couple segmentation with manual, anatomically-defined classification protocols and a novel computer connectivity algorithm. Mean volumes were derived for deep white, periventricular, thalamic, basal ganglia, and external capsule HLs, with very high intra/inter-rater reliabilities (thalamus k=0.75, all others k>0.9). Results: After accounting for age, education and head size, regression models showed that total brain paranoia and thalamic lesions significantly predicted cognitive impairment on the Mattis Dementia Rating Scale (DRS) (R²=0.753, p<0.0001). Brain paranoia and thalamic HLs also predicted lower attention and concentration scores (R²=0.69, 0.79, both p<0.0005). Paraphrenia and basal ganglia HLs predicted poorer scores on memory (R²=0.60, p<0.0001) and construction subtests (R²=0.47, p<0.0004). Total lesion, which included misclassified brain surface voxels, significantly predicted DRS score (p<0.0001) but this disappeared when the misclassified voxels were excluded; i.e., failure to exclude this artifact yielded spurious correlations, while failure to sub-classify lesions masked important relationships. Conclusions: Thalamic and other key lesions interacted with global brain volume to account for significant variance in measures of cognitive impairments. With this protocol, anatomically distinct HLs can be examined separately for functional significance. These methods will be useful for studying the role of cerebrovascular disease in dementia.

Spontaneous Improvement of Hemodynamic Failure in Occlusive Disease of Major Cerebral Arteries: Importance of Contralateral Vascular Lesion
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Introduction: Recently, several studies demonstrated that impaired cerebral hemodynamics in patients with occlusive lesions of major cerebral arteries may improve without surgical revascularization. To investigate a relation between this spontaneous improvement and changes of vascular lesions, we conducted a long-term follow-up study using PCT. Methods: Twenty-two patients with atherosclerotic occlusion or severe stenosis (≥75%) of the ICA or MCA trunk were studied. Eighteen patients had unilateral occlusive lesions, and the other 4 patients had bilateral occlusive lesions at entry. PET measurements were repeated during a mean follow-up period of 3.3 years. Repeated evaluations of vascular lesions were made by cerebral angiography or MRA. PET measurement were made in each MCA territory, and the cerebral hemodynamics was classified into three stages: Stage 0 (normal hemodynamics). Stage I (reduced CBF/CBV ratio without OEF elevation), and Stage II (reduced CBF/CBV ratio with OEF elevation). Results: Hemodynamic stage changed in 10 patients. Six patients, whose contralateral vascular lesions remained insignificant, exhibited spontaneous improvement of hemodynamic stage (Stage II→I. 4: Stage II→0: 1: Stage I→0: 1). In the other 4 patients, hemodynamic stage worsened (Stage I→II). Two patients had bilateral occlusive lesions at entry. One patient showed significant progression of stenosis in the contralateral ICA. The remaining one patients with unilateral MCA lesion (with moyamoya vessels) demonstrated no additional vascular changes. Significant differences were observed in changes in CBF/CBV ratio and OEF between patients with and without contralateral occlusive lesions (p<0.05 vs p<0.005, and p<0.05 vs p<0.026, p<0.05, respectively). A correlation between OEF change and the observation period was not significant. Conclusions: Spontaneous improvement of hemodynamic failure is not a rare phenomenon in patients with unilateral occlusive lesions. However, it might not be expected in patients with bilateral occlusive lesions.

Parenchymal Hypodensity on CT Scan Predicts Hemorrhage After Intraparenchmal TPA in Acute Stroke
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Purpose Parenchymal hypodensity has been proposed as a risk factor for hemorrhage after recombinant tissue plasminogen activator ( tPA ) thrombolysis Methods At Millard Fillmore hospital in Buffalo and at Hermann hospital in Houston , we reviewed 70 patients ( 42 men , 28 women ) who were treated with intravenous TPA for acute MCA stroke: Age range was 44-93 ( Mean 71 years ) > Initial Head CT scans were analyzed by two neuroimager observers blinded to clinical outcome . Basal ganglia hypodensity was measured in Hounsfied units (HU ) using a GE 9800 Work Station . Contralateral to ipsilateral difference in density was calculated using the non affected side as control Results - The time between icus and tPA infusion averaged 2.9 hours . Eight patients had intraperinchemmal hemorrhage ( 2 fatal and 6 non fatal ) . The hemorrhage group had significantly more severe relative basal ganglia hypodensity ipsilateral to the stroke symptoms ( mean 6.6 ± 0.7 HU , RANGE 4-10 HU ) than the non hemorrhage group ( mean 2.8 ± 0.7 HU ; range 0-9 HU ) ( p = 0.0001; unpaired t test ) . All patients in the hemorrhage group had basal ganglia hypodensity of > 5 HU except one patient with hypodensity of 4 HU . All patients in the non hemorrhage group had basal ganglia hypodensity of <4 HU , except one patient with hypodensity of 9 HU . Age , gender and time between icus and TPA Infusion did not significantly differ between the two groups Results we hypothesize that relative basal ganglia hypodensity ( 5 HU or greater ) formally measured by CT may be a useful method of risk stratification to select acute stroke patients for thrombolysis therapy

Serial Evolution of MRS Parameters and Their Comparison with Diffusion and Perfusion MR in Acute Stroke
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Background: In acute ischemic stroke, proton magnetic resonance spectroscopy (MRS) enables loss of neuronal integrity to be detected with reduced N-acetylaspartate (NAA), and anaerobic glycolysis with the presence of lactate. The combination of MRS with MR perfusion (PI) and diffusion-weighted imaging (DWI) has not been studied in a serial systematic manner. Methods: We therefore studied 16 patients with DWI, PI and single voxel MRS in the DWI core, within 24 hours of stroke onset (5 patients < 6 hours). This protocol was repeated at days 3 and 90, with outcome infarct size determined by T2-MRI. Clinical scores (Canadian Neurological Scale, Barthel Index and Rankin Scale) were performed in conjunction with the MR studies. NAA and lactate peak areas were calculated using a computed analysis package. Results: Elevated lactate was present in all patients acutely and remained elevated at day 3. Acute and subacute lactate levels in DWI and T2-MRI correlated with major clinical outcomes (r=0.64-0.78, p<0.04). No decrease in NAA levels was observed until day 3. At this stage NAA correlated with subacute clinical score, DWI and PI lesion volumes (r=0.75-0.80, p<0.001). Subacute NAA and lactate predicted both eventual infarct size (r=0.71, p<0.001) and clinical outcome scores (r=0.65-0.71, p<0.002). At day 90, lactate levels were reduced, but the persistent presence of lactate correlated more strongly with clinical outcome (r=0.79, p<0.0002). NAA levels remained unchanged. Conclusions: In ischemic stroke, lactate is the earliest MRS abnormality, with reduced NAA not detected until day 3. Serial changes in lactate and NAA mirror stroke evolution as measured by clinical scores, DWI and PI, and provide valuable prognostic information.

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Accuracy of Color Doppler Versus Angiography in the Quantification of Proximal Vertebral Artery Stenoses

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Purpose: Obstructive lesions of proximal vertebral arteries probably represent about 30% of stroke patients. Our aim was to assess the validity of color Doppler sonography versus selective intra-arterial angiography in the quantification of proximal vertebral artery stenoses.

Material and Methods: A prospective blind study of 316 vertebral arteries was undertaken between 1996 and 1998 for the first time. One hundred fifty-eight patients with cerebro-vascular disorders without cerebral hemorrhage were studied consecutively by frequency and amplitude modulated color Doppler flow imaging and then intra arterial angiography. The stenoses were quantified by morphological and hemodynamic criteria and classified in 6 groups: 0%–20%; 21%–39% arteries; 40%–49%; 50%-69% arteries; 70%–99% and ≥100% stenosis. Statistical tests: Sensitivity, specificity, prevalence and accuracy of ultrasonic methods were defined in reference to angiographic data.

Results: Intraarterial correlation coefficients and likelihood ratios were determined. Results: Ten of the 12 occlusions were identified, the two false negatives were due to 2 revascularized vessels. Stenoses greater than 70% were detected in 71% of the cases with a specificity of 99%: the kappa value was 0.80, positive and negative predictive values (therapeutically relevant) were 96% and 96% Moderate stenoses (<50%) giving only morphological criteria were differentiated from tight stenoses (>50%) in 2/3 of the cases. The major part of false negative stenoses (38) in the different groups was related to inthracraniatic or very deep origin of the artery,tortuous vessel or anechoic stenosis. Conclusion: Duplex sonography should be proposed first in vertebral-basilar attacks or stroke to detect and quantify proximal vertebral artery stenoses for surgery or angioplasty.

Background: Vertebr-basilar strokes appear to have the same causes as carotid strokes. Acute Multiple Infarcts on Diffusion-Weighted MRI

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Objectives: To determine the frequency, topographical patterns and stroke mechanisms of acute multiple infarcts (AMIs) detected on diffusion-weighted MRI (DWI). Background: A few studies have addressed the issue of acute multiple cerebral infarcts, but they were based on CT or conventional MRI. DWI is superior to conventional MRI in earlier detection of acute small ischemic lesions and discrimination of acute lesions from chronic infarcts or white matter high signal intensities. Methods: We studied 328 consecutive ischemic stroke patients who underwent DWI and conventional MRI/MRA within 4 days of symptom onset. AMIs were defined as non-contiguous high signal intensities on DWI as more than one vascular territory. Stroke mechanism was determined by TOAST criteria. Results: We found acute multiple lesions on DWI in 88 (26.8%) of total patients. AMIs in anterior circulation (AC) were found in 62 cases; unilateral hemisphere in 42, and bilateral hemisphere in 20. Seventeen had AMIs in posterior circulation (PC), and 9 in both anterior and posterior circulations (APC). The stroke mechanisms were large artery atherosclerosis (LAA) in 54 cases (42 in AC, 10 in PC, 2 in APC), cardioembolic (CE) in 22 cases (10 in AC, 6 in PC, 6 in APC), small artery occlusion (SAO) in 5 (all in bilateral hemisphere in AC, and other or undetermined in 7 cases (5 in AC, 1 in PC, 1 in APC). The most common cause of stroke was LAA in AMIs in AC and PC, and CE in AMIs in APC. Hemorrhological abnormalities (n=14) or malignancy (n=4) were associated with AMIs in bilateral hemisphere in AC, and SAO was the main presumed cause of stroke in bilateral smaller deep infarcts. Conclusions: Acute multiple infarcts in different vascular territories occur in about a quarter of patients with ischemic stroke. LAA and CE were the main causes of stroke, and hemorrhological abnormality may be a contributing factor in the pathogenesis of bilateral acute cerebral infarcts. These results suggest that different topographical patterns are associated with different vascular pathology and stroke mechanism.

Ultrasound Criteria for Intracranial Recanalization: An Angiographic Correlation

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Background: Transcranial Doppler(TCD) can demonstrate arterial occlusion and subsequent recanalization in acute ischemic stroke patients treated with intravenous tissue plasminogen activator (tPA). Limited data exist to assess the accuracy of recanalization by TCD criteria.

Methods: In patients with acute middle cerebral artery (MCA) occlusion treated with IV TPA, we compared post-treatment TCD to angiography (digital subtraction or magnetic resonance). On TCD, recanalization was defined as partial occlusion by blunted or damped signals, and recanalization by normal or static signals. Results: 27 patients were studied (age 62±18, 17.9 M F). TCD was performed at 14±5 hours and angiography at 73±156 hours after stroke onset. Recanalization on TCD had the following accuracy characteristics compared to angiography: sensitivity 91%, specificity 95%, positive predictive value 91%, and negative predictive value 93%. The defined flow grades correlated with patency of vessels at angiography (r2=0.63, p<0.001). Table: A TCD finding of MCA recanalization accurately predicts vessel patency on angiography. Partial signal improvement on TCD should be interpreted as persistent occlusion on angiography.

TCD and Angiographic Findings

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TCD Pulsatiluty Measures as an Index of Diffuse Small Vessel Disease

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Objective: To correlate elevation in TCD pulsatility indices (PIs) with MRI evidence of small vessel disease and vascular risk factors. Background: Elevation in pulsatility indices as measured by transcranial doppler have been postulated to reflect downstream increased vascular resistance caused by small vessel ischemic disease. However, no prior studies have been performed to correlate imaging findings of small vessel disease with TCD PIs.

Methods: We identified consecutive patients who underwent TCD studies and brain MRI within 6 months of each other during a 2 year period. Three independent raters, blind to clinical and TCD data, graded MRIs for lacunar disease, pereverticular and deep white matter hypetensities (PWI & DWMI), and pontine leukoariosis employing a standardized rating scale. Patients with cervical or intracranial stenoses, large hemisphere infarcts, and absent transtemporal windows were excluded. Results: 55 patients (25 F, 30 M, mean age 62 years) met inclusion criteria. Correlations between TCD MCA PIs and MRI manifestations of small vessel disease were: PWI 0.52 (p<0.0001), DWMI 0.53 (p<0.0001), lacunar disease 0.4 (p<0.0025), and combined PWI&DWMI/lacunes 0.56 (p<0.001). Correlation between pontine ischemia and vertebrobasilar PIs was 0.41 (p=0.007). Univariable analysis showed age, hypertension, sex, and combinations of disease correlated with white matter disease measures. After adjusting for these factors in a multivariate Poisson regression analysis, pulsatility index remained an independent predictor of white matter disease. Receiver operator curve analyses identified PI cutoffs that allowed discrimination of PWI with 99% sensitivity and 86% specificity and discrimination of DWMI with 70% sensitivity and 73% specificity.

Conclusions: Elevation in pulsatility indices as measured by TCD shows strong correlation with MRI evidence of small vessel disease. TCD may be a useful diagnostic test in the identification of diffuse small vessel disease.

Time-Related Changes in Cerebral Blood Volume in Patients with Increased Oxygen Extraction Fraction

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Background and Purpose: In the analysis of a longitudinal study of cerebral hemodynamics and stroke risk in patients with symptomatic carotid occlusion, we frequently observed patients with increased oxygen extraction fraction (OEF) and paradoxically normal or reduced cerebral blood volume (CBV). The purpose of this analysis is to investigate the relationship between CBV and other clinical and hemodynamic factors in patients with increased OEF.

Methods: The results of a prospective study of cerebral hemodynamics and stroke risk were reviewed for patients with symptomatic carotid occlusion and increased OEF. Measurements of CBV, OBF, CBF and CMRO2 were made on study enrollment. Patients were divided into two groups based on comparison of left to right hemispheric ratio of CBV to normal controls: (1) normal or reduced ipsilateral CBV, and (2) elevated ipsilateral CBV. The two groups were compared in regards to stroke risk, hemodynamic and metabolic measurements, and clinical risk factors for stroke. Results: Of 30 patients with increased OEF, ipsilateral CBV was normal or reduced in 24 patients and elevated in 6. No differences in CBF, CMRO2, or OEF were found between the two groups. Clinical risk factors were similar between the two groups, with the exception of the time elapsed between the last ischemic symptom and study enrollment. Patients with elevated CBV had more recent symptoms than group 1 patients (p = 0.006). A linear relationship between the time from last symptom and the CBV ratio was found (p = 0.03). Seven ipsilateral strokes occurred during the follow up period (mean 3.1 months). The occurrence of subsequent ipsilateral stroke was strongly associated with increased CBV (5 of the 7 strokes, p = 0.006, log rank statistic).

Conclusion: Contrary to experimental data from many studies of acute reductions in perfusion pressure, we frequently found increased OEF and normal or reduced CBV distal to an occluded carotid artery. This phenomenon was time-related and associated with a reduced risk of stroke. A reduction in CBV may be a compensatory mechanism to regain vasodilatory capacity, occurring prior to any improvement in OEF.
NIH Stroke Scale Unreliable in Untrained Hands

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Abstract Objectives: The NIH Stroke Scale helps to define candidates for thrombolytic treatment and supports other important clinical decisions. We evaluated it by testing last-year medical school students who had not been formally trained in its use. Methods: The scale (principles, utilisation, methods for scoring, main pitfalls) was presented to last-year medical students between two stroke lectures. Following a 30-minute study period, a case from the NIH training videotape (case 1, tape II: total score 4) was presented and the 11 items scored by 42 volunteers. The analyses focused possible errors of potential clinical relevance. Results: Only 15 students (36%) scored all items correctly. Twenty (48%) gave results at least two points apart from the correct total score, and 14 students (33%) found scores ≥ 6, which could lead to the inappropriate use of rt-PA. At least 10% of the students made mistakes in at least (8 out of 11) items of the scale. Conclusions: Graduating medical students are not apt to use the NIH Stroke Scale without specific training. The magnitude of the mistakes found in the present study is enough to inappropriately include or exclude patients from rt-PA treatment. Training programs should be considered a sine qua non for qualification for rt-PA use in daily clinical practice.

P164

Characterizing Brain Tissue at Risk for Infarction

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Objective: To define and characterize cerebral tissue at risk for stroke progression. Background: Some studies have suggested that the mismatch between a larger perfusion and a smaller diffusion lesion indicates tissue at risk for infarction. However, a quantitative characterization of this tissue at risk is not available yet. This would provide a way to evaluate newer stroke therapies with regard to the amount of ischemic tissue salvaged. Methods: We operationally defined a subregion within the mismatch zone that went on to become part of the infarcted region (seen on follow-up MR scans). We retrospectively selected 34 patients with an acute onset of a hemispheric stroke from our database who had undergone a combination of two MR diffusion-weighted imaging (DWI) studies, a perfusion weighted imaging (PWI) MR study, and a T2 weighted study in the chronic phase. We applied a logistic regression model using maps of the relative mean transit time (rMTT), relative cerebral blood flow (rCBF) and three different maps of the relative cerebral blood volume (rCBV) to predict tissue at risk for infarction. Three different maps of the CBV were calculated by integrating the area under the tissue concentration time curve up to three different end points (initial-CBV, up to the peak of a contralateral control region (CCR), peak-CBV, up to the peak of each region, total-CBV, up to the point where the tissue concentration time curve reaches in local minimum again): Results: Maps of the rCBF and initial-CBV were significant predictors (p<0.001) for identifying tissue at risk. Total-CBV was a significant predictor (p<0.001) as well although it was not as good as the initial-CBV. Tissue that subsequently progressed to infarction was characterized by a reduction in the initial-CBV (46% of contralateral control region (CCR)), an increase (131% of CCR) in the total-CBV, and a reduction (29% of CCR) in the rCBF, while the operationally defined ischemic core showed a more severe reduction in the rCBF (11% of CCR) and in the initial-CBV (22% of CCR). Conclusion: Establishing these MR indices will aid our understanding of factors that lead to infarct progression and will help in deciding on therapeutic interventions in the acute phase.

P165

Preoperative Diagnostic Imaging of Carotid Stenosis

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Background: Carotid Stenosis (CS) is a major risk factor for stroke. Since carotid endarterectomy (CEA) has been proven to be beneficial for both symptomatic and asymptomatic patients with significant CS, accurate preoperative assessment of carotid stenosis is essential. Although carotid duplex is often used a screening test, most patients being evaluated for CEA undergo additional imaging with magnetic imaging angiography (MRA) or contrast angiography (CA). Due to the expense and risk associated with invasive CA, and refinements in MR imaging non-invasive MRA is increasingly used in the evaluation of patients with CS. Objective: To retrospectively compare invasive and non invasive evaluations in assessing carotid stenosis and to assess the safety of performing CEA using only non invasive studies. Methods: The medical records of 395 patients who underwent CEA between 1993 and April 1999 were reviewed. Risk factors for CS and major postoperative complications were abstracted. Preoperative imaging studies were assessed. Angiographic complications were also noted. Results: Of the 395 patients in the study, 575 (22%) were male while 320 (55%) were female. The mean age was 71 (range 50-88). Overall, non invasive studies alone were used in 61%(241) patients and CA was used in 31%(155). Since 1994, the use of MRA had steadily increased (from 25% to 75%) with a proportionate decrease in the number of arteriograms performed. Postoperatively, stroke occurred in three (1.4%)patients in the MRA group and four patients (3.4%) in the CA group (p=0.3; n.s.). Angiography resulted in two strokes(1.3%). Conclusion: Based on this large experience, we conclude that most patients can undergo successful CEA without invasive studies. Although CA remains the most accurate test for assessing CS; MRA may eventually supplant CA in the preoperative assessment of the majority of patients with CS.

P166

Stroke Etiology in Patients Presenting Within 6 Hours

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Background: Most studies investigating stroke etiology are limited because of incomplete patient evaluations. Methods: We determined stroke etiology using TOAST criteria in 78 patients seen within 6 hours of stroke symptom onset from November 1994 to July 1999 who had cerebral angiography screening prior to intra-arterial thrombolysis. Transesophageal echocardiography (TEE) was done on 48 patients in whom a clear etiology was not established by history, physical, or angiography. Results: Of the 78 patients evaluated, 42 were male and the mean age was 62 years (range 15-89). Sixty-five patients were Caucasian. 12 were African American and 1 was Asian. Nine patients (11.5%) had large artery atherosclerosis, 7 involving the extracranial carotid, and 2 with proximal middle cerebral artery stenosis. Small vessel occlusion was seen in 4 (5%). Thirty-four patients (43.5%) had cardioembolic stroke (18 with high risk sources and 16 with medium risk sources). Cerebral angiography was normal in 9 of these 34 patients. The remainder had large vessel intracranial occlusion. Other etiologies were found in 11 patients (14%) including 6 occurring after elective cerebral or coronary angiography, 2 venereal dissection, 2 with conversion disorder, and one due to presumed Epstein Barr encephalitis. While 20 patients (26%) had a stroke of undetermined etiology, 15 of these had two or more potential causes, with cardioembolism being a possible source in all 15 cases. The remaining 5 patients (6%) had no clear etiology. These 5 patients were less than 60 years old and had large vessel intracranial occlusions, suggesting an embolic source, although TEE was normal. Conclusion: An etiology can be identified in the majority of stroke patients undergoing emergent cerebral angiography and selective use of TEE. In only 6% of patients was at least one potential etiology not found. In this series, cardioembolic stroke was the most common cause accounting for 43.5% of all strokes and was a possible source in all patients with multiple etiologies.
Sex and Age-Related Regional Differences in Cerebral Hemodynamics

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Background: Anatomical, functional, and ischemic tolerance differences exist between carotid and vertebrobasilar systems. Knowledge about influence of sex and age on regional hemodynamics changes regarding both systems is limited. Objective: To determine the role of sex and aging on vasodilatory response as measured by means of simultaneous assessment of vasomotor reactivity (VMR) between anterior and posterior circulation.

Methods: We prospectively evaluated 76 healthy volunteers (38 males /38 females) between 20 and 80 years without history of cardiovascular, respiratory or neurological disease. To exclude large-vessel stenosis on cerebral circulation all cases underwent a carotid and vertebral ultrasound and transcranial Doppler (TCD). TCD-VMR was determined by simultaneous monitoring of the right middle cerebral artery (MCA) and the left posterior cerebral artery (PCA) using the transtemporal approach, calculating the percentage increase in mean flow velocity during apnea (breath holding index). End-tidal CO2, blood pressure (BP) and heart rate (HR) were continuously monitored. The relationship between MCA-VMR and PCA-VMR was estimated for each subject by an interregional index (IRI = MCA-VMR/PCA-VMR).

Results: No changes in BP and HR were recorded during the breath holding test. There was a negative correlation between age and both MCA-VMR (r = 0.3, p < 0.009) and PCA-VMR (r = 0.62, p < 0.001). Moreover, a positive correlation was found between IRI and age (r = 0.41, p < 0.04). This was related to a greater reduction in PCA-VMR with increase of age. On the other hand, both MCA-VMR and PCA-VMR were significantly (p < 0.002) higher in women and conversely, IRI was significantly (p < 0.006) lower in women. In addition, we found that women with the IRI was significantly (r = 0.008) higher in the post-menopausal than in the pre-menopausal ones. Conclusion: There is an age-related reduction of VMR in both anterior and posterior circulation, being greater in the vertebrobasilar system. These data suggest that arteriolosclerosis related to aging mainly affect the posterior circulation. On the other hand, estrogen may play an important role in determining the regional differences in VMR.

Predictive Value of Transcranial Doppler Screening for Severe Carotid Stenosis

Revisard Ioannis Christou, Robert A Felberg, Neeraj Dubey, James C Grotta, W Scott Burgin, Marc D Malkoff, Andrei V Alexandrov, Univ of Texas, Houston Med Sch, Houston, TX

Background: Rapid identification of significant carotid disease has important implications for patient management. Transcranial Doppler (TCD) has been shown to have good sensitivity, but only a fair specificity in identification of extracranial severe carotid stenosis. Our aim was to establish screening accuracy parameters for TCD in extracranial and intracranial carotid disease. Methods: We prospectively screened consecutive stroke patients referred for TCD. TCD was performed for the diagnosis of intracranial and extracranial carotid disease. Results: 720 patients had TCD of whom 517 had angiography and/or CDTI within 60 days (0.9 days ± 5.8) (Age 63 ± 15.7, Gender: M256; F264). For 70-99% carotid stenosis or occlusion, TCD had sensitivity 79.4%, specificity 86.2%, Positive Predictive Value (PPV) 57.0%, Negative Predictive Value (NPV) 94.8%, and accuracy 87.4%. For 50-99% carotid stenosis or occlusion, TCD had sensitivity 67.5%, specificity 83.9%, PPV 54.9%, NPV 90.0% and accuracy 81.6%. TCD detected intracranial lesions with 84.9% accuracy and extracranial lesions with 84.1% accuracy (table). Conclusions: In this cohort, TCD is an accurate and convenient bedside screening test for detecting hemodynamically significant carotid artery disease. It is sensitive and specific for ≥70% carotid stenosis or occlusion in both extracranial and intracranial carotid disease.

Accurate Parameters of TCD Screening for ≥70% Carotid Stenosis by Site

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<tr>
<th>Site</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
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<tr>
<td>Extracranial</td>
<td>75%</td>
<td>86%</td>
<td>54%</td>
<td>59%</td>
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<tr>
<td>Intracranial</td>
<td>78%</td>
<td>89%</td>
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The Acute Phase Response After Ischemic Stroke

Florian Buggle, Armin J Grau, Matei Spigel, Werner Hacke, Univ of Heidelberg, Heidelberg, Germany

Background: The acute phase response (APR) is a local and systemic reaction to acute tissue injury. It is insufficiently known whether ischemic stroke is associated by an APR independent from acute infection which often complicates the acute stage after stroke. Methods: We studied the course of leucocytosis, C-reactive protein and fibrinogen in consecutive patients with ischemic stroke who remained free from infection during the first week after acute stroke (n = 54) or developed sepsis within two days after ischemic stroke (n = 17). Exposure criteria were a history of infection within the week before stroke and trauma within the preceding month. Standardized daily investigations were performed to identify any new infection after stroke. Results: In patients without infection, leucocytosis on admission was higher (8.8 ± 2.5/6, mean±SD) than on day 4 (7.5 ± 2.2, p < 0.001), day 7 (7.7 ± 2.4, p < 0.001) and follow up (±3 months) examination (7.5 ± 2.0, p < 0.01). Fibrinogen (admission: 3.15 ± 0.84 g/l, day 4: 3.28 ± 0.82, day 7: 3.1 ± 0.92, follow up: 3.27 ± 1.21) and CRP (admission: 6.4 ± 2.86 mg/l, day 4: 5.3 ± 7.3, day 7: 4.5 ± 5.3, follow up: 4.8 ± 5.9) did not change significantly. APR-parameters neither correlated with NIH-score values on admission nor on follow up examination. Patients with early infection after stroke had longer lasting leucocytosis (admission: 11.0 ± 2.7/6, day 4: 11.2 ± 2.8, day 7: 9.3 ± 2.2, follow up: 7.5 ± 1.5, p < 0.01). Fibrinogen rise from admission (3.18 ± 2.13 g/l) to day 4 (4.81 ± 2.14, p < 0.01) and day 7 (5.15 ± 1.88, p < 0.01) and decreased towards follow up (4.02 ± 1.48). CRP levels increased from admission (2.4 ± 5.39 mg/l) to day 4 (9.06 ± 10.9, p < 0.05) and day 7 (9.02 ± 7.3). Patients with a worse NIH-score on admission (mean: 13, 25-27% quartiles 6-24, patients without infections; 3, 1-4, p < 0.001) and on follow up (with infection: 2, 0.5-6.5, without infection: 0, 0-0.5, p < 0.05). Conclusion: Independent from infection, ischemic stroke is associated with a short (≤3 days) - lasting leucocytosis but not with increased fibrinogen or CRP levels. For clinical practice, it is important that a longer lasting leucocytosis or a rise of fibrinogen or CRP require the search for acute infection.

Applied Criteria for Echocardiography in Stroke and TIA

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Methods: Use of echocardiography was investigated using commercial software designed for stroke research. The sample consisted of admissions for ischemic stroke or TIA to the stroke unit of an urban, teaching hospital. There were no statistically significant differences in the age, race, stroke type, or co-morbidity between the pre and post intervention samples. The pre-intervention sample consists of consecutive patients, prospectively collected between November 7, 1995 and November 7, 1998. The intervention consisted of implementing the following order criteria for TTE vs. TEE, based on current research and analysis of the first data set. Criteria were given to residents and attending physicians. The post-intervention data were prospectively collected from consecutive patients from August 1, 1997 to July 30, 1998. Results: Of 377 patients with ischemic stroke or TIA, admitted during the pre-intervention period, 232(62) had complete data. Of those, 141(60) had echocardiographic diagnosis during the work-up. TEE was performed on 134(95) patients, TEE in 7(5) patients. Diagnostic findings included hypo or akinesia of the LV wall in 22(51%) patients, and a total of 12(8.5) patients with PFO, aortic atherosclerotic disease, and atrial or ventricular mass or thrombus and yield was 35 pathologic findings in 30(21) of 141 patients. After implementing new echo criteria, data collection was continued. Of 392 patients admitted to the post-intervention sample (233, 62%) had complete data. Of 125(52) who had echocardiography, TEE was performed in 73(48), TEE in 79(52). Diagnostic findings included hypo or akinesia of the LV wall in 25(18) patients, LA thrombus in 13(17%), ascending/anomalous aortic lesions 20(14%), LV thrombus or aneurysm (n = 1), PFO 128, atrial aneurysm 3(1), and 211 patients with SEC Total yield was 73 (vs. 35) pathologic findings in 39(27) of 152 patients. Of the specific cardiac etiologies of PFO, aortic atherosclerotic disease, and atrial or ventricular mass or thrombus, 49(31) (vs. 12(8.5) in first sample) were discovered in the second sample analysis. Conclusions: Applied criteria for the use of echocardiography increases diagnostic yield in the stroke and TIA population.
Solute Interleukin-1 Levels in Individuals with Asymptomatic Carotid Disease

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Objective: To determine whether soluble interleukin-1 molecule-1 (sICAM) levels differ amongst individuals with varying degrees of carotid stenosis and as well when compared to control subjects. Methods: sICAM levels were determined in patients referred for the assessment of asymptomatic carotid bruits as well as in control subjects either with or without vascular risk factors (VRF). Demographic information was collected and all individuals underwent complete neurological examinations, routine hematologic and biochemical blood tests, baseline electrocardiograms and cervical ultrasonography. Subjects were categorized into one of four groups; Group 1-carotid stenosis ≤50%. Group 2-carotid stenosis ≥ 50%. Group 3-control subjects with VRF and Group 4-control subjects without VRF. sICAM levels were correlated with the degree of carotid stenosis and were also compared between different patient groups using analysis of variation (ANOVA) and unpaired t tests. Results: sICAM levels were measured in 112 patients. The mean age was 69 years and 57% were females. Follow-up ranged from 8-44 months. Mean sICAM levels were highest in those with carotid stenosis ≤ 50% (322.7 ng/mL) and in control subjects with VRF (339.0 ng/mL) and lowest in those with carotid stenosis ≥ 50% (286.0 ng/mL) and control subjects without VRF (259.9 ng/mL). Mean sICAM levels were significantly higher in those with ≥ 50% stenosis group but this did not quite reach statistical significance (p=0.0759). There was a positive trend in favor of increasing sICAM levels being associated with increasing degrees of carotid stenosis, though this did not reach statistical significance (p=0.102). Conclusions: Mean sICAM levels are significantly higher in individuals with vascular risk factors and in those with higher grade documented asymptomatic carotid stenosis when compared to control subjects without vascular risk factors.

Use of Coagulation Tests in the Evaluation of Acute Ischemic Stroke
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Background and purpose: Coagulation abnormalities may be an important cause of ischemic stroke, particularly in young patients with few traditional risk factors. Specialized coagulation tests such as functional Protein C, Protein S, antithrombin III (ATIII), lupus anticoagulant (LA), antithrombin (ACL) antibodies, and activated protein C resistance (APCR) are being used to evaluate IS patients for underlying coagulopathies. Each specialized coagulation battery costs about $1000. The aim of this study was to evaluate the use and appropriateness of coagulation tests in patients with acute IS. Methods: Medical records of consecutive IS patients admitted to an academic medical center over 1 year (n=219) were reviewed. Patient demographics, stroke risk factors, history of DVT or miscarriage, family history of stroke, and coagulation test results (PT, PTT, platelet count, protein C, S, ATIII, LA, ACL antibodies, and APCR) were recorded. Stroke subtype was assigned using TOAST criteria. Inappropriate testing was defined as testing performed in patients with other reasons for or contraindications to anticoagulation, protein C/S in warfarin-treated patients, or APTT/INR in patients on heparin. Results: Sixty-two (27%) patients had specialized coagulation testing. Race, sex, history of miscarriage or DVT, family history of stroke, contraindications to, or other reasons for anticoagulation did not differ significantly between tested and untested patients. Testing was negative correlated with patient age (Spearman r=-0.51, p<0.0001; mean age of tested vs. untested patients was 55 vs. 71 years, respectively, p<0.0001). Testing also differed based on stroke subtype with the highest proportion of tested patients in the “undetermined” category (p<0.0001). However, overall 34% of patients were tested inappropriately. Conclusions: Age and undetermined stroke subtype were the only variables significantly associated with specialized coagulopathy testing. However, over 1/3 of patients were tested inappropriately. If these findings are generalizable to other settings, more judicious use of these tests would lead to considerable cost savings.

Vascular Imaging Predicts Early Clinical Fluctuation in Patients with Resolving Deficit
Robert A Felberg, Andrew M Demchuk, Ioannis Christou, W Scott Burgin, Marc D Malkoff, Anne W Weijer, Andrei V Alexandrov, Univ of Texas, Houston Med Sch, Houston, TX

Background: Fluctuating acute stroke is a difficult clinical problem. Resolution of neurological deficits is related to spontaneous recanalization or restoration of collateral flow. Vascular imaging of early fluctuation has not been well characterized. Methods: We prospectively monitored patients who presented with a focal neurological deficit resolving within six hours of symptom onset. Patients were evaluated using bedside Transcranial Doppler (TCD) examination and/or Computed Tomography (CTA), Digital Subtraction (DSA) or Magnetic Resonance(MRA) angiography when feasible. Fluctuation was determined as a change in focal neurological deficits is related to spontaneous recanalization or restoration of collateral flow. Neuroradiological abnormalities may be an important cause of ischemic stroke, particularly in young patients with few traditional risk factors. Specialized coagulation tests such as functional Protein C, Protein S, antithrombin III (ATIII), lupus anticoagulant (LA), antithrombin (ACL) antibodies, and activated protein C resistance (APCR) are being used to evaluate IS patients for underlying coagulopathies. Each specialized coagulation battery costs about $1000. The aim of this study was to evaluate the use and appropriateness of coagulation tests in patients with acute IS. Methods: Medical records of consecutive IS patients admitted to an academic medical center over 1 year (n=219) were reviewed. Patient demographics, stroke risk factors, history of DVT or miscarriage, family history of stroke, and coagulation test results (PT, PTT, platelet count, protein C, S, ATIII, LA, ACL antibodies, and APCR) were recorded. Stroke subtype was assigned using TOAST criteria. Inappropriate testing was defined as testing performed in patients with other reasons for or contraindications to anticoagulation, protein C/S in warfarin-treated patients, or APTT/INR in patients on heparin. Results: Sixty-two (27%) patients had specialized coagulation testing. Race, sex, history of miscarriage or DVT, family history of stroke, contraindications to, or other reasons for anticoagulation did not differ significantly between tested and untested patients. Testing was negative correlated with patient age (Spearman r=-0.51, p<0.0001; mean age of tested vs. untested patients was 55 vs. 71 years, respectively, p<0.0001). Testing also differed based on stroke subtype with the highest proportion of tested patients in the “undetermined” category (p<0.0001). However, overall 34% of patients were tested inappropriately. Conclusions: Age and undetermined stroke subtype were the only variables significantly associated with specialized coagulopathy testing. However, over 1/3 of patients were tested inappropriately. If these findings are generalizable to other settings, more judicious use of these tests would lead to considerable cost savings.

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We studied 50 consecutive patients; Age 61±14, Male 50%; time examined from symptom onset 165±96 minutes. All patients had TCD and 68% had angiographic examinations(CTA 4%, DSA 10%, MRA 44%). 6 patients were excluded due to absent temporal windows. Large vessel occlusion was found in 16(32%) of patients. Stenosis 18%(n=9); and 54%(n=27) had normal studies. Fluctuation occurred in 16%(n=8) patients. Fluctuation was more common in the occlusion and stenosis groups than in the normal group (p<0.0001; χ²=12.05; p<0.0001). Conclusions: Early clinical fluctuation is strongly associated with the presence of large vessel occlusion or stenosis. Normal vascular studies were associated with a stable resolution without subsequent fluctuation. Urgent vascular evaluation is warranted for patients with resolving deficits. The potential role of thrombolysis for fluctuating patients with proven vascular lesions needs to be established.
Background: The clinical significance of the length and number of transient ischemic attacks (TIAs) remains controversial. Studies have analyzed the temporal aspects of TIAs in general and of carotid territory TIAs, but no reports have compared these features between anterior and posterior circulation TIAs. Objective: To compare the duration of anterior and posterior circulation TIAs. Methods: We retrospectively analyzed 120 patients (68 men: 52% women, median age: 65 years, range: 27-98) from the New England Medical Center and the Beth Israel Deaconess Medical Center Stroke Registries, 60 with anterior and 60 with posterior circulation TIAs, regarding the duration and number of spells. TIs were classified into anterior or posterior circulation according to clinical symptoms and neuroradiological findings (MRI, MRA, carotid ultrasound or TCD). Patients who had strokes were excluded. Duration of TIAs was divided into <15 min, 15-60 min, >1 hr. Number of spells was divided into 1, 2-5, 6-9, ≥10. Results: Among patients with anterior circulation TIAs, 20 (33.3%) had spells that lasted <15 min, 17 (28.3%) lasted between 15 min-1 hr, and 23 (38.3%) >1 hr. In the posterior circulation TIA group, 38 (63.3%) of the patients had spells lasting <15 min, which was significantly increased, OR of 3.5 (P=0.002, 95% CI: 1.5 to 7.88). Regarding the number of TIAs, among patients of the anterior circulation group, 29 (48.3%) presented with only one spell, 18 (30%) with 2-5 spells, 3 (5%) with 6-9 spells, and 7 (11.6%) with ≥10. Patients presenting with ≥10 spells had significantly more number of TIAs compared to patients presenting with <10 spells. (P<0.001). We previously reported the finding that anterior circulation TIAs were longer lasting and less frequent when compared to posterior circulation TIAs. These findings support the hypothesis that anterior and posterior TIAs often have different pathophysiologic mechanisms.

Validation and Reliability of Retrospective Scoring of the NIH Stroke Scale
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Background/Purpose: Since administrative datasets do not include stroke-specific data, retrospective assessment of stroke severity is necessary for optimal risk adjustment of outcomes data. Prior assessment of NIH Stroke Scale (NIHSS) retrospective scoring only included patients in clinical trials, a setting in which the level of chart documentation is likely higher than in usual practice. The purpose of this study was to assess the validity and reliability of retrospective NIHSS scoring in a consecutive series of ischemic stroke patients in a usual clinical setting. Methods: An algorithm for retrospective NIHSS scoring was developed and tested using written admission history and physical (H&P) examinations. NIHSS items not present in the H&P were coded normal. One investigator prospectively scored the admission NIHSS in consecutive ischemic stroke patients (n=30). Two independent raters certified in administering the NIHSS used the algorithm to retrospectively score the same cases from photocopies of H&P. Linear regression was used to examine the relationship between retrospective (NIH-R) and prospective (NIH-P) scoring and to assess interrater reliability. Pairwise t-tests were used to compare the NIH-P and NIH-R. Weighted kappa statistics were calculated to determine the level of agreement of NIH-R and NIH-P individual items. Results: Mean (sd) age of the subjects was 63 (14) years, mean (range) NIHSS NIH-P was 5.4 (2.6) and NIH-R was 5.3 (0) for the 30 patients included. Only 1 NIH-P had complete data for all NIHSS items, 9 were complete except for ‘extinction’. Other frequently absent items (n=1) were ‘dysarthria’ and ‘commands’ (5). Agreement was high for both NIH-R and NIH-P (r=0.9, F1=0.95, p<0.001) and between raters (r=.99, F1=0.98, p<0.001). Weighted kappa for NIH-R and NIH-P individual items was excellent, ranging from 0.44 for ‘questions’ to 0.95 for ‘gait’. Consistency results are high for both NIH-R and NIH-P. Agreement in usual clinical settings. Agreement on individual items is higher for motor than for higher cortical function items. Assuming that missing items are normal appears valid for NIHSS scoring in this setting.

Utility of Testing Young Patients with Ischemic Strokes for Inherited Coagulation Inhibitor Deficiencies
James W Schmitz, Magid Amari, Univ of Arkansas, Little Rock, AR; Louis M Funk, Sarkis M Nazarian, McClellan VA Med Ctr, Little Rock, AR

The role of inherited deficiencies of Proteins S (PS), and C (PC), and antithrombin III (AT-III) is well established for intracranial venous thrombosis. How often these inherited coagulation inhibitor deficiencies (ICID) cause arterial cerebral ischemia is less clear. Testing for ICID is often routinely recommended as part of the ‘young stroke’ work-up. Yet, the literature documenting how often they are found in young CI patients is contradictory. In view of this, we tested the following hypothesis: in patients under age 50, with a first, arterial, cerebral infarct, whose family history (FH) and medical history do not suggest an ICID, the yield of a laboratory search for such disorders will be low. Study population - 55 patients under age 50, with arterial stroke. Diagnosis was made on clinical grounds, supplemented by imaging studies. PC and PS levels were measured by clotting-based assays, all done in the same laboratory. Among the 55 patients, none had clinical features, medical history, or FH suggesting a prothrombotic state. Results - PC and AT-III levels were normal in every patient. Four patients had low PS levels. In 2, repeat testing in 4-6 months was normal. The other 2 could not be contacted for repeat testing, but both had at least one potential cause of acquired PS deficiency. Conclusion - our data suggest that patients under 50 with a first, arterial CI, and no FH or personal history to suggest thrombophilia, are very unlikely to have ICID, and that the yield of a laboratory search for such deficiencies will be extremely low. The literature suggests that low levels of PS, PC and AT-III found in the above setting are more often acquired than inherited. When low levels are discovered, it is important that testing be repeated, and acquired causes be excluded. Patients with ICIDs causing arterial strokes almost always have a positive FH or features of a thrombophilic state. The 55 patients we studied were the largest unselected cohort of young CI patients from the U. S. examined for ICID. We believe they are representative of young patients with CI residing in the Stroke Belt. Our findings may not apply to other young stroke populations.
Absence of Selective White Matter Ischemia in Chronic Carotid Stroke

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Background and Purpose: The deep white matter may be the location of an arterial borderzone, vulnerable to ischemic injury through hemodynamic mechanisms. The purpose of this study was to determine the frequency of chronic selective ischemia of the deep white matter in patients with carotid occlusion. Methods: Thirty-six patients with carotid stenosis and structurally normal deep white matter were studied with position emission tomography (PET). Measurements of oxygen extraction fraction (OEF) were made in superficial (cortical and sub-cortical) regions in the middle cerebral artery territory and in deep white matter (internal borderzone) regions. The presence of selective ischemia of the deep white matter was assessed by the ratio of deep white matter to superficial OEF. Ipsilateral hemispheric ratios in patients were compared to a group of contralateral hemispheric and 15 normal controls. Results: Deep white matter to superficial OEF ratios (+ 95% confidence limits) were 0.59 (+ 0.047), 1.01 (+ 0.06), and 1.02 (+ 0.08) for ipsilateral, contralateral, and normal hemispheres, respectively. No statistically significant difference between ipsilateral and contralateral (p = 0.001) or normal hemispheres (p = 0.6) was found; nor when the analysis was limited to patients with increased superficial OEF (n = 9). Individual deep white matter to superficial ratios were within the normal range for all patients. Conclusions: The deep white matter was not subject to a greater degree of ischemia than the overlying cortex in our sample of 36 patients with carotid occlusion. Deep white matter infarctions seen in patients with carotid occlusion should not be ascribed to chronic selective hemodynamic compromise occurring at an internal arterial borderzone.

Interspecialty Measurement of Carotid Stenosis: Are We Speaking the Same Language?

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Background: Methods of angiographic carotid stenosis measurement have not been standardized. Objective: To determine the interspecialist agreement regarding carotid stenosis measurement and clinical decisions among physicians from different specialties. Methods: 30 angiograms with varying degrees of carotid stenosis were reviewed by a stroke neurologist (SN), general neurologist (GN), neurosurgeon (NS), neuroradiologist (NR), and vascular surgeon (VS). A numerical percentage stenosis was measured, categories were assigned (70-99%, 50-69%, <50%), presence of ulceration was recorded, and a recommendation regarding carotid endarterectomy (CEA) was made based on a hypothetical patient. All physicians used the NASCET method of stenosis measurement. Results: Using the SN as the gold standard, other specialists recorded the carotid stenosis within 10% of the SN fairly infrequently (GN 50%, NS 50%, NR 50%, VS 27%). The concordance correlation coefficient was 0.63, 0.63, and 0.67 for the GN, NS, and NR (fair to moderate agreement) and 0.46 for the VS (poor to fair agreement). Agreement with the SN for assigning stenosis categories was moderate for the NR (weighted kappa 0.46) and fair for the GN, NS, and VS (weighted kappa 0.35, 0.41, and 0.32, respectively). Agreement regarding the presence of ulceration was moderate for the NS (kappa 0.41), fair for the GN and VS (kappa 0.27 and 0.25, respectively) and poor for the NR (kappa 0.15). Agreement with the SN regarding performing CEA in a hypothetical 70 year old woman with recent reinital transient ischemic attacks was fair for the VS (kappa 0.35) and poor for the GN, NS, and NR (kappa 0.12, 0.19, and 0.17, respectively). Conclusions: Physicians from different specialties viewing the same angiographic images can have substantial rates of disagreement with regard to stenosis evaluation, category assignment (severe, moderate, or mild), and detection of ulceration. These disagreements can be reflected in the choice of therapy (medical vs. surgical options). The variability in angiographic assessment among physicians from different specialties may lead to nonuniform application of clinical trial results to individual patients.
Recanalization Rates in Cervical Carotid and Vertebral Dissection
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Objective: To determine rates of recanalization or normalization of previously noted stenosis or occlusion in carotid and vertebral arterial dissection. Methods: A retrospective analysis of 134 cases of cervical carotid or vertebral dissection encountered at our stroke centers from 1995 to 1999 was performed. Of these patients, 46 had follow-up imaging by either MRA/CTA or cerebral angiography at various time points. Patients were separated into those presenting with complete vessel occlusion and those presenting with high grade stenosis. Follow-up imaging studies were reviewed to determine the rates of recanalization in occlusive dissection, and the rates of stenosis resolution in cases of high grade stenosis. Results: Of the 46 cases identified, 29 had high-grade stenosis at presentation. Of these patients, 19 (68%) had complete resolution of the vessel abnormalities, while 6 (21%) had no change in the degree of stenosis. Two patients had partial improvement in the degree of stenosis, and two went on to permanent vessel occlusion. Although patients were not reimaged at routine intervals, those who demonstrated resolution of stenosis typically did so within six months, with four months being the mean time to vessel normalization in those reimaged within six months from presentation. There were 17 cases of patients who presented with vessel occlusion. Of these patients, 10 went on to completely recanalize the vessel. The remaining seven had complete recanalization on follow-up imaging. Among patients who did recanalize or have resolution of stenosis, vessel dissections were often associated with neck trauma (12 of 29 patients) such as chiropractic maneuvers. Conclusions: In cases of cervical arterial dissection, a high percentage of patients recanalize the occluded blood vessel within six months (at least 40% in our study). Patients who present with a high-grade stenosis have a higher rate of resolution of vessel abnormalities than those with complete occlusion. Reimaging 3-6 months following presentation will usually clarify if recanalization has occurred.

Reproducibility of Measurements of Cerebral Infarct Volume
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Background and purpose - Infarct volume is increasingly used as an outcome measure in clinical trials of therapies for acute ischemic stroke. We tested which of four different methods to measure infarct size or volume on CT scans has the highest reproducibility. Methods - Infarct volume and total intracranial volume were measured with Leica Q500MC image analysis software on 45 CT scans of patients who underwent stroke rate stroke trial. The scans were performed 8 days (±2 days) after the onset of symptoms. The methods tested were based on a semi-automated pixel thresholding, b. manual tracing of the perimeter, c. a stereological counting grid, and d. measurement of the largest diameter. The measurements were performed independently by two observers; the first observer performed all measurements twice. Results - Seven scans were excluded for technical reasons. Measurement of the largest diameter was not accurate for the smallest and largest infarcts. Of the other methods, manual tracing of the perimeter of the infarct had the lowest intra- and inter-observer variability: coefficients of variation, 12.2% and 19.9%, respectively. None of the methods tested was reliable for measurement of lacunar infarcts. For total intracranial volume, manual tracing also provided the highest reproducibility: intra- and inter-observer coefficient of variation. Conclusion - Manual tracing of the perimeter is the most reproducible method for measurements of the volumes of the infarct and the total intracranial space in multi-center trials of therapies for acute ischemic stroke.

Matrix Metalloproteinases in Jugular Venous Blood in Patients with Complete Middle Cerebral Artery Territory Infarction
Markus Hon, Rainer Apfel, Olho-Winfried Ulrich, Wolfgang Jakob, Ludger Rosin, Univ of Regensburg, Regensburg Germany

Background: In complete middle cerebral artery (MCA) occlusion the acute clinical course usually is determined by space-occupying hemispheric edema resulting in a 80% mortality rate due to uncontrollable intracranial pressure (ICP) elevation. Recent experimental and clinicopathologic studies raised the importance for a role of matrix metalloproteinases as mediators of blood-brain barrier disruption and tissue destruction in focal brain ischemia. Methods: In 10 consecutive patients (6 males, 4 females; mean age 43.5 years) admitted to our ICU immediately after hemispheric stroke and showing early CCT signs of complete MCA territory infarction, serial blood samples were drawn from a catheter placed in the jugular venous bulb at the side of the MCA occlusion. Beside routine measurement of jugular bulb oxygen saturation, lactate concentration, and serum levels of neuron-related proteins, MMP protein expression was visualized gelatin zymography over a time course ranging from 12 hours to 7 days after the stroke symptoms and signs. Results: Evolution of ischemic brain edema was monitored by continuous ICP measurement and follow-up CCT scans. Results: All patients developed infarction of the entire MCA territory, and 2/10 showed additional infarction of the ipsilateral ACA territory. In all patients, the marked increase of MMP-9 (92 kDa) compared to control was detectable at 12 hours post stroke, while at 24 hours MMP-9 (72 kDa) enzymatic activities had returned to baseline. Incoincidently, a second even slight increase of MMP-9 activity was found at day 4. On the other hand, zymogram analysis of MMP-2 activity showed unequivocal results. Conclusions: By describing early upregulation of MMPs also in humans, the present data confirm findings in rats (Romanczuk et al. 1998) and non-human primates (Hes et al., 1999). Since inhibition of MMP-9 has been shown to reduce infarct size in rodents, the appearance of this protease in the cerebral venous blood in patients with acute MCA occlusion is of particular interest in suggesting MMP-9 as a new therapeutic target in focal brain ischemia.

Cerebral Microembolism in Aortic Arch Atherosclerosis
Alain Viguier, Anne Pouy le Traon, Pierre Massabain, Luc-Vahon, Vincent Larrue, Univ de Toulouse, Toulouse France

Objective: To find out the frequency of microembolic signals (MES) in patients with acute cerebral ischemia and aortic arch atherosclerosis. Methods: We studied 40 consecutive patients with ischemic stroke (n=27) or TIA (n=13) in the anterior circulation, aged 45 or more and who could have a transcranial Doppler (TCD) scanning and a transosophageal echocardiography within 7 days of onset of symptoms. Patients with carotid stenosis ≥50% and those with a cardiac source of embolism were excluded. Patients underwent TCD monitorings of both middle cerebral arteries for 1 h. MES were diagnosed off-line by an investigator blind to other data. Results: Forty patients had an aortic arch plaque≥4mm in thickness;16 patients had an aortic arch plaque<4mm;10 patients had no aortic arch plaque. We found MES in 2 patients. Both had an aortic plaque≥4mm. Conclusion:In this prospective study, MES were only found in patients with severe aortic arch atherosclerosis. However the frequency of MES was low. A multicentre study is needed to assess the clinical significance of MES in this population.

Diagnostic and Prognostic Value of Serum Fibrinogen Levels in Patients with Asymptomatic Carotid Disease
Lucy Viera, Jeffrey Minuk, Christina Wolfsion, Liam Durcan, McGill Univ, Montreal, PQ Canada, Ariane Mackey, Hosp de l’Enfant Jesus, Quebec, PQ Canada; Robert Cote, McGill Univ, Montreal, PQ Canada

Objective: To determine whether levels of serum fibrinogen in neurologically asymptomatic individuals presenting with carotid stenosis ≥50% can be related to the degree of carotid stenosis and the occurrence of ischemic events. Methods: Serum fibrinogen levels were measured in consecutive patients referred for the assessment of asymptomatic carotid brunts (ACB). Demographic data, including vascular risk factors were collected. All patients underwent carotid ultrasoundography, routine hematologic and biochemical blood work and electrocardiograms. Patients were scheduled for regular neurological examinations and were followed for the occurrence of ischemic vascular events which included transient ischemic attack, ischemic stroke, myocardial infarction and vascular death. Serum fibrinogen levels were correlated with the degree of carotid stenosis and the occurrence of ischemic events. Results: Fibrinogen levels were measured in 215 patients with ACB. Mean follow-up was 18.7 months (range 1-71 months). The mean age was 69.2 years and 63% were females. Fibrinogen levels did not correlate with the degree of carotid stenosis. Mean fibrinogen levels were 3.1 g/l in those with stenosis ≥50%, which was similar to those with stenosis ≤50% (NS). Twenty ischemic events were recorded in 14 patients during the follow-up period. Ischemic events were more frequent in patients with carotid stenosis ≥50% (18 events) vs. those with a stenosis ≤50% (4 events). Mean fibrinogen levels were 3.37 g/l in those with ischemic events and 3.13 g/l in those without (p=0.151). Conclusion: In our cohort of neurologically asymptomatic individuals, serum fibrinogen levels did not correlate with the degree of carotid stenosis as measured by ultrasonography or with the occurrence of ischemic vascular events. The relatively small sample size and short duration of follow-up may have partially contributed to these results, however both recruitment and follow-up of this cohort is ongoing.

Contrast Enhanced Transcranial Color Coded Duplexsonography for Evaluation of Collateral Pathways in Patients with Critical Symptomatic Carotid Disease and Limited Acoustic Windows
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Background and Purpose: To assess the diagnostic efficacy of contrast-enhanced transcranial color coded duplexsonography (CE-TCCD) for noninvasive evaluation of collateral pathways through the Circle of Willis in patients with limited acoustic windows and critical symptomatic carotid disease. Methods: We prospectively evaluated 24 consecutive patients (5 females, 19 males, mean age 63.3 ± 13.3) with CE-TCCD (contrast agent: Levovist®; Schering, Germany) and correlative transfemoral digital substraction angiography (DSA). We only included patients with critical symptomatic carotid stenosis (≥90% lumen diameter reduction) or carotid occlusion and no detectable colorflow signals of the Circle of Willis by unenhanced TCCD due to limited acoustic windows. 22 patients had unilateral disease (13 stenoses, 9 occlusions), 2 patients had bilateral disease (1 bilateral occlusion, 1 occlusion on one side and stenosis on the other). Results: In all patients CE-TCCD enabled full visualization of the Circle of Willis bilaterally. In 15/24 patients DSA demonstrated collateral flow through the anterior communicating artery (Acom), which was visualized by CE-TCCD in 14 (93.3% sensitivity). CE-TCCD was correct in 89 patients in whom by DSA there was no collateral flow through the Acom (88.9% specificity). CE-TCCD identified 8 out of 11 patients with angiographically proven collateral flow through the posterior communicating artery (Pcom)(72.7% sensitivity). In 13 patients DSA did not show collateral flow through the Pcom, which was suggested by CE-TCCD in 12 (92.3% specificity). We evaluated 4 patients within 24 hours after onset of stroke, of whom one underwent emergency carotid endarterectomy because of insufficient collateral flow. Conclusion: In patients with symptomatic critical carotid disease and limited acoustic windows, CE-TCCD can markedly increase the sensitivity and specificity of TCCD for detection of intracranial collateral pathways. Evaluation of flow through the Pcom, however, appears to be less reliable than through the Acom.
The Predictive Value of Triphasic Perfusion CT for the Development of Severe Brain Edema in Acute Ischemic Stroke

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Background: Cerebral blood flow measurement and NIH stroke scale score (NIHSSS) within 6 hours of stroke onset may be used for predicting fatal brain edema in acute ischemic stroke. Triphasic perfusion CT (TPCT) can provide the information of collateral blood flow and perfusion deficit (PD) in the ischemic areas as reliably as conventional angiography in patients with acute ischemic stroke. Objective: To determine whether the extent of PD on TPCT within 6 hours of stroke onset could predict the subsequent development of severe brain edema. Methods: We reviewed 14 patients with acute middle cerebral artery (MCA) stroke, who had a minimum baseline NIHSSS of 20 in left hemisphere lesions or a minimum baseline NIHSSS of 15 in right hemisphere lesions within 6 hours after symptom onset. TPCT was performed with power injector-controlled, intravenous administration of contrast media. Sequential scans of early, middle and late phase were performed. The whole procedure took 5 minutes. Depending on the collateral flow, PD was graded as severe perfusion deficit (SPD)/moderate perfusion deficit (MPD). To assess the severity of hemispheric brain edema, horizontal displacement of pineal gland and septum pellucidum was measured on follow-up CT and/or MRI. The significant midline shift (SMS) was defined as more than 5mm contralateral shift of both pineal gland and septum pellucidum. Results: SMS was seen only in 7 of all 14 patients. The mean NIHSSS of 7 patients with SMS was not higher than that of the remaining 7 patients without SMS (left MCA stroke: 20.2 vs. 20.6; right MCA stroke: 15.5 vs. 16.5). All six patients with SPD more than 67% of presumed MCA territory showed SMS. SMS was not seen in 6 patients with SPD less than 60%. Of the remaining 2 patients with SPD around 50% of the presumed MCA territory, only one showed SMS. Conclusion: Within 6 hours of MCA stroke onset, TPCT may be used to predict the subsequent development of severe edema and to warrant more aggressive medical or neurosurgical interventions.

Primary Angiitis of the Central Nervous System in Children

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Primary angitis of the central nervous system (PACNS) was first described in 1959 by Cavuto and Feigen. While classically a disorder of middle age there have been a few reports in children. The frequency, course, and management of PACNS in children, however, remains very poorly defined. We describe 5 children who meet criteria for the diagnosis of PACNS including: unexplained neurological deficits, angiographic abnormalities typical of vasculitis, and exclusion of other etiologies. Four patients had an acute presentation, three with ischemic infarcts and one with hemorrhage. One presented with headache and vomiting. All five patients had abnormal MRIs associated with features of stroke. Only one patient had a cerebrospinal fluid pleocytosis and/or elevated protein. Most notably, three patients had progressive radiographic changes during the initial period of clinical and diagnostic evaluation and 45% patients had progressive changes prior to initiation of cyclophosphamide therapy. These radiographic changes were associated with distinct clinical progression in at least two patients. Upon diagnosis, four patients were treated with a combination of corticosteroids and cyclophosphamide. One patient received only corticosteroids. This case series also suggests that CNS vasculitis may occur more frequently in the pediatric population than previously appreciated and should be carefully considered in the differential diagnosis of frequent or severe headaches and/or strokes. Together, these observations suggest that PACNS diagnosis may be affected in this disorder, that a normal CSF analysis does not predict a benign course, and that management with cyclophosphamide may be critical for control and limitation of disease progression.

The Accuracy of Intracranial Large Artery Occlusive Disease Assessment Using Transcranial Colour Coded Duplex Sonography

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We performed a retrospective review of 712 scans performed between December 2002 and May 2005. The scan population comprised of patients with normal or mildly abnormal CSF, as proposed by some investigators, is unlikely to exist in children. This series also suggests that CNS vasculitis may occur more frequently in the pediatric population than previously appreciated and should be carefully considered in the differential diagnosis of frequent or severe headaches and/or strokes. Together, these observations suggest that PACNS diagnosis may be affected in this disorder, that a normal CSF analysis does not predict a benign course, and that management with cyclophosphamide may be critical for control and limitation of disease progression.

Ultrasonographic Findings to Predict Patients’ Outcome in Hyperacute Ischemic Stroke

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Purpose: We examined whether ultrasonographic (US) findings in hyperacute ischemic stroke were useful to predict patient’s outcome. Methods: Out of 329 consecutive patients with acute ischemic stroke or TIA, 77 patients (56 men and 21 women; mean age, 70.8 years) with carotid stroke or TIA were entered into the present study. They were examined by both CT and Doppler carotid ultrasonography within 6 hours after symptom onset. Early CT findings (PCP, PD) were defined as obstruction of the lentiform nucleus, loss of the insular ribbon and/or cortical effacement. US findings were considered positive, when ICA stenosis ≥70% or the side-to-side ratio of the end-diastolic flow velocity in the common carotid artery > 1.4, indicating ICA or MCA trunk occlusion based on our data, were observed. NIHSS on admission and modified Rankin scale on day 30 were evaluated. We classified patients into 4 group: Group 1 (n = 35), with negative CT and negative US; Group 2 (n = 18), with negative CT and positive US; Group 3 (n = 6), with early CT findings and negative US; Group 4 (n = 38), with early CT findings and positive US findings. Results: NIHSS score was high in order of Group 4 > Group 3 > Group 2 > Group 1 (p < 0.0001, Kruskal-Wallis test) and was more strongly related to CT findings than US findings. However, modified Rankin scale was high in order of Group 4 > Group 3 > Group 2 > Group 1 (p < 0.0001, Kruskal-Wallis test) and was more strongly related to US findings than CT findings. By multiple regression analysis, positive US findings (p = 0.002, Odds ratio = 13.2) were the best predictor of poor outcome as compared to NIHSS on admission (p = 0.034, Odds ratio = 11.6) and early CT findings (P = 0.37). Conclusion: US findings of hyperacute ischemic stroke may be valuable to predict patients’ outcome and superior to early CT findings and NIHSS on admission.

Comparison of Apparent Diffusion Coefficient Between Reversible MRI Lesions During Status Epilepticus and Ischemic Lesions in Stroke

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Background and Purpose: Magnetic resonance imaging (MRI) demonstrates transient change of foci of signal during or following status epilepticus (SE). Pathophysiological mechanisms of such reversible signal changes during SE have not yet been fully elucidated. We compared apparent diffusion coefficient (ADC) of reversible lesions in epileptic patients with that of ischemic lesions in stroke patients. Methods: MRI using echo-planar imaging (EPI) with 1.5 T Siemens system was performed in four patients with SE during ictal state and nine patients with cerebral infarction at 3-120 hours after stroke. ADC maps were obtained using T2-weighted EPI (b value of 0 s/mm^2) and three-directional isotropic diffusion weighted EPI (b value of 1,000 s/mm^2). ADC values were measured in high signal lesions on diffusion weighted imaging (DWI) and the homologous contralateral normal regions. ADC ratio of lesion to contralateral region (LC/ratio) was also calculated. Results: MRI in the four patients demonstrated 13 focal lesions with high signal changes on DWI during SE. The lesions were located ipsilateral to the epileptic focus and disappeared on MRI following the discontinuation of SE. ADC values in these lesions were significantly lower than those in the contralateral regions (781.9 ± 295 vs. 866.7 ± 99 µm^2, p = 0.005) showing LC/ratio 0.90 ± 0.07. MRI in stroke patients displayed high signal lesions with features of acute infarcts were observed. Two of four corresponding areas on the follow up CT. ADC values in these ischemic lesions were 432.3 ± 19 µm^2 at 3-24 hours and 640.6 ± 25 µm^2 at 24-120 hours after stroke. LC/ratio was 0.5 ± 0.4 and 0.3-24 hours and 0.4 ± 0.3-24 hours after stroke, respectively. ADC values and LC/ratio in SE were significantly higher than those in ischemic lesions (p < 0.0005). Conclusions: The reversible lesions on MRI observed during SE, where ADC is reduced to a significant degree, compared with that in ischemic lesions, may be manifested due to mechanisms different from those in cerebral infarction. The enhancement of membrane permeability may be participated with the manifestation of reversible lesions.
Spread of Negative Symptoms to Contiguous Body Areas: A Clinical Marker of Amyloid Angiopathy?

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Background: Cerebral amyloid angiopathy (CAA) usually presents with lobar hemorrhage or dementia. CAA has been reported to present with TIA-like spread of negative symptoms to contiguous body areas. It has been suggested that such a presentation may be diagnostic of CAA. The objective of this study is to assess (1) if spread of negative symptoms is an uncommon presentation of ischemic stroke and (2) if patients presenting with this symptom complex frequently have CAA.

Methods: 70 consecutive patients presenting with stroke-like symptoms were prospectively evaluated for symptoms at onset, presence of hemorrhage on MRI, risk factors for stroke, and final diagnosis. Results: 20 patients awake with maximum symptoms making it impossible to establish presence or absence of spread of symptoms at onset. Of the 50 awake at onset of symptoms, 14 (28%) described a spread of symptoms to contiguous body parts: 9 patients had multiple symmetrical spells. None had history of migraine. The mean age was 63.4 years (44 - 78). The underlying etiology was ischemic TIA or stroke in all. None had clinical course or imaging features typical of CAA. Ischemic symptoms were due to arterio-occlusive (10), anticoagulant (4), and undetermined (2). All had MRI scans, none had evidence of hemorrhage. All 7 echo MRI scans were negative for hemorrhage (including both with undetermined cause). 11 were treated with anticoagulation. None suffered hemorrhage. No differences were found between those with and without spread of symptoms.

Discussion: To our knowledge, this represents the first time of the hypothesis that spreading negative symptoms is a marker for CAA. Our data indicate that spread of negative symptoms to contiguous body parts is common at the onset of ischemic TIA/stroke. In our series, none had evidence of underlying CAA. The frequency of CAA in the elderly is reported to be 25% - 57%. The coexistence of CAA and ischemic symptoms presenting with spread may represent coexistence of common illines in an at-risk population.

Conclusion: The spread of negative symptoms is a common symptom at the onset of cerebral ischemia. It is neither specific for nor indicative of CAA.

Human Albumin Therapy, at Moderate Doses, Is Highly Neuroprotective in Experimental Focal Ischemia

Ludmila Belayer, Wei Zhao, Raul Busti, Myron D Ginsberg, Univ of Miami, Miami, FL

We have previously shown that high-dose human serum albumin (HSA, 2.5g/kg body weight), reduces focal ischemic injury when given 2h after middle cerebral artery occlusion (MCAo). The purpose of this study was to assess whether lower, potentially clinically applicable doses would also neuroprotect. We subjected halothane-anesthetized male Sprague-Dawley rats (n=15, 280-340g) to a highly reproducible model of 2-hour MCAo by insertion of a poly-L-lysine-coated intraluminal nylon suture. Human serum albumin in doses of either 0.68 or 1.25 g/kg body weight (or saline control) was administered i.v. immediately after removal. Neurobehavioral examination at 240-min MCAo confirmed an initial high-grade deficit (score 11 out of possible 12) in all rats. Saline-treated rats continued to show high-grade neurological deficits (mean score, 9-10) during the 3-day survival, while albumin-treated rats showed marked neurological recovery (with HSA1 2.5g/kg, score±3±2±0.5 SEM, p<0.001). Three days after MCAo, brains were perfusion-fixed, and histogram volumes and brain edema were quantitated. HSA therapy markedly reduced the volume of cortical infarction, by 66±3% (0.68 g/kg dose group) and 96±4% (1.25 g/kg dose group) (p<0.05). Subcortical infarct was also significantly diminished (by 52-58%) by HSA in each dose-group. Brain edema was reduced by 74±8% by 1.25 g/kg HSA and was eliminated by both HSA doses in the albumin group. These results strongly support a high beneficial effect of moderate-dose human albumin therapy in acute focal ischemia and suggest the possible clinical utility of this agent to treat patients with acute ischemic stroke.
Enriched Environmental Stimulation Increases Cell Proliferation and Neurogenesis in the Dentate Gyrus and Improves Neurological Function in the Adult Ischemic Rats

Li Zhang, Ru Li Zhang, Zheng Gang Zhang, Cecylia Powers, Michael Chopp, Henry Ford Hosp, Detroit, MI

An enriched environment enhances improvement of neurological function after focal cerebral ischemia in rats. However, it is unknown whether this functional improvement is related to brain plasticity. We therefore, measured the effects of an enriched environment on brain plasticity in ischemic rats. Male Wistar rats were subjected to middle cerebral artery (MCA) occlusion by a fibrin rich clot. Ischemic rats were maintained for 6 weeks in an enriched environment after stroke (n=4) or were placed in standard cages (n=4) as a control group. Motor and somato-sensory functions were measured once a week for 6 weeks after stroke. To determine whether the proliferation of cells in the dentate gyrus is affected by environment, bromodeoxyuridine (BrdU), the thymidine analog used as mitotic labeling, was injected daily(y.p) after ischemia for 14 days. All rats were sacrificed at 42 days after 42 days after stroke. BrdU immunoreactive nuclei were counted on eight coronal sections which encompass the entire dentate gyrus. There were no significant differences in infarct volume between the enriched (38.2±5.8%) and control (41.9±5.0%) groups. Numbers of BrdU immunoreactive cells in the granule cell layer were 31.9±2.6/mm2 in the ipsilateral (control), 28.9±3.6/mm2 in the contralateral (control), 51.1±2.8/mm2 in the ipsilateral (p<0.05 vs. control) and 50.7±4.2/mm2 in the contralateral (enriched, p<0.05 vs. control). More than 80% of BrdU immunoreactive cells had morphological characteristics of granule cells, suggesting neurogenesis. Rats housed in an enriched environment exhibited significant improvements in recovery of motor and somatosensory functions compared with rats housed in standard cages. Our data indicate that an enriched environment increases cell proliferation in the adult ischemic brain and that increases in neurogenesis may related to functional improvement after stroke.

Different Dynamics of Metabolic Recovery After Thrombolyis of Clot Embolism and Reversible Thread Occlusion in Mice

Takayuki Hata, Guenther Mies, Ryuji Hata, Konstantin-Alexander Hossmann, Max-Planck-Institute for Neurological Res, Cologne Germany

Reversible thread occlusion models are widely used to study molecular mechanisms of delayed neuronal injury after spontaneous or thrombolysis-induced reperfusion. However, the reperfusion profile after clot lysis differs markedly from that after thread occlusion, and may profoundly alter the postischemic recovery process. We, therefore, compared the dynamics of metabolic recovery in these two models of transient focal ischemia. In mice the left MCA was occluded either by intraluminal thread insertion (n=21) or by intracarotid injection of fibrin-rich blood clots (n=23). One hour later, reperfusion was initiated by thread withdrawal or by clot lysis using an intra-arterial infusion of 10 mg/kg rtPA. Regional energy metabolism and protein synthesis (PS) were measured in cryostat sections by bioluminescence and H3-leucine incorporation techniques, respectively. Before reperfusion, ATP depletion and PS inhibition areas were similar in the two models. PS inhibition exceeding the ATP depletion area by up to 30%. Within 1 h after thread withdrawal, ATP but not PS recovered, followed by progressing secondary energy failure. Thrombolyis led to a much later recovery which, however, included PS and was permanent. The data demonstrate that secondary energy failure is unique to transient thread occlusion. This raises concerns about the relevance of this model for the study of reperfusion injury.

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<tr>
<td>Thread</td>
<td>ATP</td>
<td>40 ± 5</td>
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<td>56 ± 6</td>
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Values are mean values (% of contralateral hemisphere, mean ± SD). * p<0.05.

Cysteine Protease Activity in Focal Cerebral Ischemia

Chakezie C Amadi, Univ of Kentucky, Lexington, KY; Mary L Holtz, Dept of Veterans Affairs Med Ctr, Lexington, KY; Susan D Caddock, James W Geddes, Luther C Pettigrew, Univ of Kentucky, Lexington, KY

Background: Cysteine proteases are calcium-activated enzymes that cleave cellular protein substrates. Two families of cysteine proteases, calpains and caspases, attack spectrin and other microtubular elements and may promote neuronal apoptosis during ischemia. We tested the hypothesis that calpain and caspase-mediated proteolysis occurs independently in brain during post-ischemic reperfusion. Methods: Male spontaneously hypotensive rats underwent middle cerebral artery occlusion for two hrs, followed by 15 min or 1, 6, or 24 hrs of reperfusion (n=6 per group). Ischemic cortex was removed, snap-frozen, and homogenized for western blot analysis. Spectrin fragments at 145/150 kDa, produced by calpain, and 120 kDa, derived by caspase, were quantified by laser densitometry. Results: Both spectrin fragments increased in quantity as proteolysis continued during post-ischemic reperfusion. The mean quantity of the 145/150 kDa fragment significantly at 6 and 24 hrs of reperfusion, compared to the two earlier time points. (See table.) Comment: Our results show that calpain and caspase were increasingly active during post-ischemic reperfusion. The robust elevation of the 145/150 kDa fragment after 6 hrs suggests the ubiquity of calpain in tissue or acceleration of the enzyme reaction in the presence of a co-factor or the loss of an inhibitor. We conclude that both cysteine proteases become more active during post-ischemic reperfusion. Although they appear to function independently, our data do not exclude the possibility of interaction between calpain and caspase through secondary mediators.

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<tr>
<td>145/150 kDa</td>
<td>31 ± 1.3</td>
<td>11.1 ± 4.6</td>
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<td>120 kDa</td>
<td>53 ± 1.8</td>
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mean ± SEM normalized to uninfarcted cortex.

P205

NGF-I A and NGF-I B mRNA Expression Correlates with Improved Functional Recovery Induced by Environmental Enrichment After Middle Cerebral Artery Occlusion in Rats

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Background Environmental enrichment improves functional outcome after ischemic stroke in rats, without altering infarct volume. Neuronal plasticity-related processes in brain regions outside the lesion may be of importance for improved recovery. Inducible transcription factors (ITFs), including NGFI-A and NGFI-B are related to neuronal plasticity processes and may be mediators of neuronal recovery after stroke. Stress, with high levels of glucocorticoids acting on the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR) in the brain, after ischemia may increase brain damage and inhibit reactive neuronal plasticity. In contrast, moderate levels of glucocorticoids may be beneficial for recovery. Methods After permanent occlusion of the right middle cerebral artery (MCAo) spontaneously hypertensive rats (n=32) were housed in enriched-, -social-, isolated- or running-wheel environment. Sham operated rats (n=4) were housed in standard cages. Sensorimotor function was scored 3-4 weeks after MCAo. Infarct volume, adrenal weight and mRNA expression (in-situ hybridization) of ITFs and glucocorticoid receptors was determined 28-34 days after MCAo. Results Infarct volumes did not differ between groups. Functional outcome was significantly better in rats housed in enriched and social environment. In these groups NGFI-A and NGFI-B mRNA expression was significantly higher in cortical regions outside the lesion and in the CA1 region of the hippocampus. c-fos mRNA expression was very low in all rats. There was a linear correlation between better functional outcome and expression of NGFI-A (r=0.55, p=0.004) and NGFI-B (r=0.53, p=0.003). In running-wheel rats adrenal weights were significantly higher and MR mRNA expression in hippocampus was slightly higher. There was no group differences in GR mRNA expression. Conclusion Improved functional recovery induced by environmental enrichment may be mediated by changes in expression of specific ITFs, e.g. NGFI-A and NGFI-B. Poor functional recovery may be related to chronic stress.

P206

Different Dynamics of Metabolic Recovery After Thrombolyis of Clot Embolism and Reversible Thread Occlusion in Mice

Takayuki Hata, Guenther Mies, Ryuji Hata, Konstantin-Alexander Hossmann, Max-Planck-Institute for Neurological Res, Cologne Germany

Reversible thread occlusion models are widely used to study molecular mechanisms of delayed neuronal injury after spontaneous or thrombolysis-induced reperfusion. However, the reperfusion profile after clot lysis differs markedly from that after thread occlusion, and may profoundly alter the postischemic recovery process. We, therefore, compared the dynamics of metabolic recovery in these two models of transient focal ischemia. In mice the left MCA was occluded either by intraluminal thread insertion (n=21) or by intracarotid injection of fibrin-rich blood clots (n=23). One hour later, reperfusion was initiated by thread withdrawal or by clot lysis using an intra-arterial infusion of 10 mg/kg rtPA. Regional energy metabolism and protein synthesis (PS) were measured in cryostat sections by bioluminescence and H3-leucine incorporation techniques, respectively. Before reperfusion, ATP depletion and PS inhibition areas were similar in the two models. PS inhibition exceeding the ATP depletion area by up to 30%. Within 1 h after thread withdrawal, ATP but not PS recovered, followed by progressing secondary energy failure. Thrombolyis led to a much later recovery which, however, included PS and was permanent. The data demonstrate that secondary energy failure is unique to transient thread occlusion. This raises concerns about the relevance of this model for the study of reperfusion injury.

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Values are mean values (% of contralateral hemisphere, mean ± SD). * p<0.05.
Poster Presentations 339

P209
Treatment with Continuous Hypertonic Saline Worsens Infarction Volume Following Transient Focal Ischemia in the Rat
Anish Bhardwaj, Izumi Harukuni, Jeffrey R Kirsch, Patricia D Hurn, Raymond C Koehler, Richard J Traystman, Johns Hopkins Hosp, Baltimore, MD

Hypertonic saline (HS) has been advocated as a hypertonic agent for the treatment of cerebral edema. Recently, several animal studies and clinical series have demonstrated the efficacy of HS treatment in traumatic brain injury. We tested the hypothesis that continuous intravenous infusion of HS during reperfusion following transient focal ischemia would attenuate infarction volume in the rat. Under controlled conditions of normoxia, normocarbia and normothermia, halothane-anesthetized adult male Wistar rats were subjected to 2 hr of middle cerebral artery occlusion (MCAO) by the intraluminal occlusion technique. At the onset of reperfusion, rats were randomly assigned to receive 10 ml/Kg intravenous bolus of either normal (0.9%) saline (NS) or 7.5% HS (chloride:acetate 50:50) followed by a continuous infusion @ 0.5 ml/hr until the end of the experiment. Infarction volume was assessed by triphenyltetrazolium chloride staining at 22 hr of reperfusion. In rats treated with NS (n=13), serum Na⁺ levels were 137±3 mEq/L (mean±SEM) at baseline, 135±2 and 138±2 at 2 hr and 22 hr of reperfusion respectively; compared to 136±2 at baseline, 148±1 and 153±5 mEq/L in HS-treated rats (n=8). Percent change in laser-Doppler perfusion was similar in both treatment groups during MCAO and immediate reperfusion. There were no differences in mean arterial blood pressure and hematocrit in the two treatment groups. Cortical infarction volume corrected for swelling of ipsilateral cerebral cortex was significantly larger in HS-treated rats (121±14 mm³, 30±5% of ipsilateral hemisphere; p<0.05) as compared to NS-treated controls (64±15 mm³, 16±4% of ipsilateral hemisphere; p<0.05). Infarction volume in the striatum was similar in both treatment groups. Compared to contralateral cerebral cortex, tissue volume of ipsilateral cortex was increased 26±5% with NS and 41±5% with HS. These data demonstrate that continuous HS therapy administered during reperfusion following MCAO worsens tissue swelling and cortical infarction volume in experimental focal ischemia. These results may have implications for continuous HS therapy in clinical ischemic stroke.

P210
Neurotrophic Growth Factors Enhance the Expression of Neural Phenotypic Cells Derived from Bone Marrow in Vitro
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We tested the hypothesis that cells derived from bone marrow stem and progenitor cells become neural cell (neurons and astrocytes) phenotype in the presence of neurotrophic growth factors. Primary bone marrow cells were isolated and cultured in the Iscove’s Modified Dulbecco’s Medium (IMDM). Non-adherent cells (hematopoietic stem and progenitor cells - HSCs) and adherent cells (mesenchymal stem and progenitor cells - MSCs), were resuspended in fresh IMDM with a nerve growth factor (NGF, 200 ng/ml), epidermal growth factor (EGF, 20 ng/ml) and brain-derived neurotrophic factor (BDNF, 100 ng/ml) until one month, respectively. Control bone marrow cells were cultured in the IMDM without neurotrophic growth factors. Bromodeoxyuridine (BrdU), which is incorporated into dividing cells for newly formed DNA, was added to the medium. Antibodies (BrdU, CD34, NeuN, MAP-2, GABA) were used for immunocytochemical identification of cultured cells. The number of both HSCs and MSCs labeled with BrdU was ~90%. Approximately 90% HSCs were CD34 positive, but MSCs were CD34 negative. Control bone marrow cells without neurotrophic growth factors expressed the neuronal markers NeuN (~1%), MAP-2 (~2%), GABA (~1%), TH (~0.3%) and the astroglial marker GFAP (~1%). The percentage of TH, GABA, NeuN, MAP-2, GFAP immunoreactive cells were increased in the NGF, BDNF and EGF-treated cultured HSCs and MSCs to 5-30%. Cells derived from MSCs cultured with NGF expressed TH (~20%) and GFAP (~30%) and were the most immunoreactive. Cells expressing neural markers were observed not only in cells derived from hematopoietic stem cells, but also from mesenchymal stem cells. Our data indicate that cells derived from adult bone marrow stem cells express proteins identified with neurons and astrocytes. Neurotrophic growth factors enhance the neural expression of cells derived from bone marrow stem cells in vitro. Bone marrow stem cells may have a potential as an alternative source for plasticity in central nervous system diseases.

P211
N-Acetylheparin, a Nonanticoagulant, Diminishes Brain Edema After Experimental Intracerebral Hemorrhage
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Background: Recently, we found complement factor C9 accumulation and membrane attack complex formation following experimental intracerebral hemorrhage. In addition, systemic complement depletion reduced perihematomal brain edema following intracerebral hemorrhage. The purpose of this study was to determine whether N-acetylheparin, a complement cascade activation inhibitor, can reduce intracerebral hemorrhage-induced brain edema. Unlike heparin, N-acetylheparin is a nonanticoagulant. Methods: A total of twenty four male Sprague-Dawley rats were used in this study. Rats received intracerebral infusions either 100 µL blood or 100 µL blood plus 10 µg N-acetylheparin. Autologous blood and N-acetylheparin were infused into right caudate nucleus stereotactically. Rats were sacrificed one or three days later for brain water and ion content measurements. Brain edema was measured by wet/dry weight and sodium, potassium ion contents were measured by flame photometry. Results: Intracerebral infusion of blood into the caudate caused significant perihematomal edema at 24 and 72 hours (81.6±0.6% vs. 83.6±0.9% compared to 78.7±0.7% and 78.8±0.5% in the contralateral tissue). N-acetylheparin significantly reduced this intracerebral hemorrhage-induced brain edema in ipsilateral basal ganglia at 24 hours (78.5±0.5% vs. 81.6±0.8% in control, p<0.01). N-acetylheparin reduced plasma complement (C3, C4) concentrations. Conclusions: These results demonstrate that N-acetylheparin diminishes perihematomal brain edema which may be through its known ability to inhibit complement activation. The complementary system may be a novel target for the treatment of brain injury following intracerebral hemorrhage.

P212
Effects of Mild Hypothermia on Superoxide Production Following Transient Focal Cerebral Ischemia
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Reactive oxygen species (ROS) have been implicated in the pathogenesis of cerebral infarction following both global and focal ischemia. Superoxide (O2−), which is directly toxic to neurons, appears to be a key player. In this study we examined the effects of mild hypothermia (33°C) on the in situ generation of O2− by the hydroxylamine (H2O2) method. This method is specific for superoxide and does not reflect oxidation of peroxynitrite or other reactive oxygen species. H2O2 is taken up by live cells and oxidized to a red fluorescent dye, ethidium (Et). Following 2 hours of MCA occlusion and 1 hour reperfusion, animals were injected intravenously into the jugular vein with 1 ml H2O2 prepared in dimethylsulfoxide (100 mg/ml) under halothane anesthesia. The animals were euthanized and perfused transcardially with 600 cc heparinized normal saline and 300 cc 3.7% PFA. Brains were fixed in 3.7% PFA, embedded in Tissue-Tek O.C.T. Compound and frozen in liquid nitrogen. 50 µm sections were cut on a cryostat, mounted and viewed under a fluorescent microscope. Pre-selected regions of interest (ROI) in the cortical ischemic core and corresponding contralateral region were chosen and photographed using high power. The amount of fluorescence was measured from 10-12 cells per field using an optical densitometer. Cell type was readily determined from morphology and was also confirmed by immunofluorescent labeling with specific cell markers on immediately adjacent sections. 2 h MCAO followed by 1 h reperfusion demonstrated Et fluorescence which was particularly intense within subcellular organelles suggestive of mitochondrial production of superoxide. Furthermore, Et-positive cells appeared to have neuronal morphology, similar to that observed on adjacent sections stained with the neuronal marker MAP2. Optical density measurements from each ROI showed that mild hypothermia significantly reduced the generation of O2− in the ischemic penumbra (37°C: 408±94, 33°C: 201±42; p=0.049) as well as in the corresponding contralateral region (37°C: 575±149, 33°C: 216±50; p=0.034). Our results suggest that mild hypothermia may ameliorate ischemia/reperfusion injury by decreasing O2− generation.
MRI of Incomplete Reperfusion, Enhanced Blood-Brain Barrier Damage and Hemorrhagic Transformation After Late rt-PA Therapy in a Rat Embolic Stroke Model

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Background: Thrombolytic therapy with r-PA after ischemic stroke leads to increased risk of hemorrhagic transformations (HT). We used MRI to characterize acute effects of late r-PA administration in an embolic stroke model, which we correlated with development of HT.

Methods: Diffusion-weighted (DW), dynamic susceptibility contrast-enhanced and pre- and post-contrast T1-weighted (T1W) MRI were done from 4 to 10 h (n = 8), and 1 day (n = 3) after embolic middle cerebral artery-occlusion in spontaneously hypertensive rats. Gd-DTPA (diameter < 3 nm) or MION (diameter ~20 nm) were used as contrast agents. rt-PA was injected after 6 h, during which we performed dynamic gradient echo MRI. HT was estimated morphometrically and with a spectrophotometric hemoglobin assay. Results: The ischemic lesion was characterized by a low apparent diffusion coefficient (ADC) (71 ± 18% of contralateral) and reduced hemodynamic parameters. Maximal ΔR2* = 57 ± 9% of contralateral, CBV = 67 ± 10% of contralateral. After r-PA injection, ADC values partly renormalized, however, the lesion area slightly expanded. Perfusion changes were small (maximal ΔR2* = 62 ± 11%; CBV = 74 ± 12%). Tissue injury and perfusion deficits were profound after 1 day (maximal ΔR2* = 18 ± 1%; CBV = 32 ± 2%). HT was reflected by hypointensity on the DW images. Hemorrhage volume increased from 3.8 to 9.4 m^3 after 10 h to 9.4 ± 3.6 m^3 after 1 day. Before rt-PA injection, clear post-Gd-DTPA T1W signal intensity enhancement, indicative of a leaky blood-brain barrier (BBB), was evident in areas where HT emerged at later stages. In MION-injected rats, a clear signal intensity drop in areas of subsequent HT was detected on the dynamic gradient echo images during rt-PA injection, suggestive of accumulation of the large MION particles leaking through the BBB.

Conclusions: Late thrombolytic therapy after embolic stroke does not necessarily lead to successful reperfusion. HT emerged in areas with early BBB damage, which was critically enhanced after direct r-PA administration. MRI may be used to quantify the effects of r-PA injection, and predicts risks of HT.

Temporal Evolution of Reversibility of Ischemic Lesions on Diffusion-Weighted Imaging: Correlation with Histopathology

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Background and Purpose: The ischemic lesions demonstrated by diffusion-weighted imaging (DWI) are reversible if blood flow is restored rapidly. This study was designed to determine if resolution of the initial DWI lesions is transient or permanent following brief periods of focal brain ischemia and to evaluate the histological outcomes. Methods: Sixteen rats were subjected to 10 or 30 minutes of temporary middle cerebral artery occlusion (n=7 per group) or sham operation (n=2). Diffusion-, perfusion-, and T1 weight imaging were performed during occlusion, immediately after reperfusion, 30, 60, 90 minutes, and 12, 24, 48 and 72 hours after reperfusion. Cardiac perfusion-fixation was performed with 4% paraformaldehyde immediately after the final MRI study. H&E-stained histologies were used to evaluate neuronal necrosis in the lateral caudoputamen of both hemispheres at the level of the anterior commissure. Results: MRI and histologies were normal in the sham-operated rats. The perfusion deficits disappeared immediately after reperfusion in both 10-min and 30-min groups, while DWI hyperintensity occurring during occlusion disappeared between 30 to 60 minutes after reperfusion in both groups. The DWI and T1W-imaging remained normal thereafter in the 10-min group, while secondary DWI hypointensity and T2 abnormalities developed at the 12-hour observation point in the 30-min group. Histological examinations showed that no abnormalities were seen in the contralateral caudoputamen, while neuronal necrosis occurred in the ipsilateral caudoputamen in both groups. The number of the necrotic neurons was significantly higher in the 30-min group (95.2±4%) than in the 10-min group (17.2±10%; p<0.0001). Conclusions: Resolution of the initial DWI lesions may be transient or permanent, related to the duration of ischemia. Permanent resolution of the initial DWI lesions does not indicate complete salvage of brain tissue from ischemic injury as selective neuronal necrosis was seen. This suggests that DWI may not detect the mild ischemic changes resulting in selective neuronal necrosis.

High-Temporal-Resolution Monitoring of Secondary Apparent Diffusion Coefficient Decline Following Mild Focal Ischemia in Rats

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Background and Purpose: Normalization of the declined apparent diffusion coefficient (ADC) induced by reperfusion may be transient. The purpose of this study was to characterize the temporal evolution of both the ADC and the size of the ADC-defined lesion following mild focal brain ischemia.

Methods: Six rats were subjected to 30 minutes of temporary middle cerebral artery occlusion and underwent diffusion-, perfusion-, and T2-weighted imaging during occlusion, immediately and then every 30 minutes for a total of 12 hours after reperfusion. Average ADC (ADCav) and T2 values were calculated in both the lateral caudoputamen and overlying cortex. The size of the in vivo ADCav-defined ischemic lesion was calculated by outlining the abnormal areas on ADCav maps. The brains were fixed via cardiac perfusion of 4% paraformaldehyde immediately after the last MRI measurement. H&E-stained histologies were used to determine tissue damage in the same regions where ADCav was measured. Results: The perfusion deficit disappeared after reperfusion. The decreased ADCav values during occlusion reverted to normal at 60 minutes after reperfusion in the two regions. The normalized ADCav values decreased secondarily (p<0.001) at 3 and 4 hours after reperfusion in the caudoputamen and cortex, respectively. A significant increase in T2 was observed at 4 and 5 hours after reperfusion in the caudoputamen and cortex, respectively. The ADCav-defined initial lesion almost completely disappeared at 1 hour after reperfusion, and the ADCav-defined secondary lesion occurred first in the caudoputamen, then gradually grew and reached 52% of the ADCav-defined initial lesion size at 12 hours.

Histological examination revealed swollen astrocytes, shrunk neurons with swollen cellular process, and scattered necrotic neurons. These changes were more severe in the caudoputamen than in the cortex. Conclusions: Secondary ADC reduction following 30 minutes of transient ischemia occurs 2 to 3 hours after normalization, seen first in the caudoputamen, and the size of in vivo ischemic injury grows over time in a slow fashion.

Independence of Excitotoxicity on Ampa Receptor Calcium Permeability in Glur2 Deficient Mice

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AMPAR receptor (AMPAR) activation governs gene expression and plasticity, and also plays key roles in ischemia and excitotoxicity. However, owing to the heterogeneous ionic permeability characteristics of native AMPARs, the ionic mechanisms initiating AMPAR-mediated excitotoxicity are unclear. Using mutant mice lacking the AMPAR subunit Glur2, which controls Ca2+ permeability, we studied AMPAR-mediated excitotoxicity in cultured cortical neurons, and in hippocampal neurons in vivo. Surprisingly, the initiation of AMPAR-mediated neurotoxicity in cultured neurons was independent of AMPAR Ca2+ permeability. However, it was dependent on Na+ influx, as extracellular Na+ removal was completely neuroprotective against AMPAR activation. Whole-cell patch clamp recordings revealed that kainate-evoked AMPAR-mediated ionic currents were increased in neurons lacking Glur2. Excitotoxicity evoked in-vitro by kainate application paralleled the magnitude of the kainate-evoked currents, which are primarily Na+ mediated, but was uninfluenced by AMPAR Ca2+ permeability. In-vivo, neurotoxicity was induced by direct stereotactic injections of kainate into the hippocampal CA1 sector of Glur2 mutant mice, and CA3 damage was produced by seizures evoked by anterograde kainate injections. However, there were no differences in the vulnerability of CA1 and CA3 neurons between Glur2 mutant and wild type controls. The lack of contribution of Ca2+ permeability to excitotoxicity in the Glur2 mutants was not explained by compensatory changes in Glur2 mutants in the distribution of AMPARs evaluated by immunobiochemistry, by AMPAR expression evaluated by Western analysis, nor by AMPAR function evaluated by confocal imaging of free intracellular Ca2+ and Ca2+ buffering proteins were also unchanged. Thus, excitotoxic signal initiation by AMPARs requires Na+ influx but is independent of Ca2+ permeability. The selective vulnerability of Glur2 deficient neurons is explained by the larger magnitude of ionic currents (Na+ influx) evoked in AMPARs that lack Glur2. Our data provide novel insights into the mechanism of AMPAR-mediated neurodegeneration.
The distribution of partial pressure of oxygen (PO$_2$) in tissue depends on the rates of oxygen supply by blood and oxygen consumption in the tissue, and on the spatial arrangement of microvessels supplying the tissue. Using a theoretical model, we simulated oxygen delivery by a threethirdsdimensional network of microvessels in rat cerebral cortex, to investigate the effects of changing perfusion and consumption rates. The network geometry was deduced from scanning electron micrographs of corrosion casts (Motti et al., J. Neurosurg. 65, 834-846, 1986). A nonlinear least-squares method, using images obtained at three different angles, was used to estimate microvessel locations. The network consisted of 50 segments with a total length of 1.8 mm, in a region 140 µm × 150 µm × 160 µm. A Green’s function method was used to predict the distribution of PO$_2$ throughout the tissue region, assuming a control consumption rate of 10 cm$^3$O$_2$/100g/min, a perfusion rate of 160 cm$^3$/min/g and PO$_2$ of 84 mmHg in inflowing blood. The maximum predicted PO$_2$ level in the tissue was 8.5 mmHg. In further simulations, oxygen consumption rate and blood perfusion rate were varied. With decreasing perfusion at the control consumption rate, tissue hypoxia (PO$_2$ < 1 mmHg) first appeared when perfusion was reduced to 50% of control, and extracellular water was predicted when perfusion was reduced to 25% of control. However, a decrease in oxygen consumption rate to 70% of the control level did not affect tissue hypoxia. Thus, the tissue hypoxia resulting from a large decrease (75%) in perfusion can be counteracted by a moderate decrease (30%) in oxygen consumption rate. The model shows that tissue oxygenation is more sensitive to changes in oxygen consumption rate than to changes in flow. The results support the concept of reducing oxygen consumption rate, e.g., by hypothermia, as a method to counteract the effects of blood flow reduction in stroke.

**Intracerebral TNK-tPA Treatment of Embolic Stroke in the Unanesthetized Rat**

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To mimic human stroke, we have developed a model of focal cerebral embolic ischemia in the unanesthetized rat. Using this model, we investigated the efficacy of TNK-tPA, a mutant t-PA which is more fibrin specific and more resistant to type 1 plasminogen activator inhibitor than rPA, on the treatment of acute stroke. Under anesthesia, a catheter was inserted into the origin of the middle cerebral artery (MCA) of male Wistar rats. Thirty minutes after rats were recovered from anesthesia, the MCA was occluded by a single fibrin rich clot placed via the catheter. TNK-tPA was administrated intraarterially via the catheter at 2 h and 4 h after stroke. All rats were sacrificed at 48 h after ischemia. Neurological deficits, gross hemorrhage and ischemic lesion volume were measured. Sham operated rats ($n=7$), in which a catheter was placed without injection of a clot did not exhibit neurological deficits and percent (to the ischemic side) of neurological deficit, gross hemorrhage and ischemic lesion volume were measured. Thus, the tissue hypoxia resulting from a large decrease (75%) in perfusion can be counteracted by a moderate decrease (30%) in oxygen consumption rate. The model shows that tissue oxygenation is more sensitive to changes in oxygen consumption rate than to changes in flow. The results support the concept of reducing oxygen consumption rate, e.g., by hypothermia, as a method to counteract the effects of blood flow reduction in stroke.

**Beneficial Effects of a Monoclonal Antiplatelet Integrin αIIbβ3 Antibody Treatment of Embolic Middle Cerebral Artery Occlusion in the Rat**

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We have produced a hamster monoclonal antibody (mAb) specific for the mouse platelet integrin αIIbβ3 (1B5) which inhibits platelet aggregation both in mouse and rat and does not bind to the αvβ3 integrin. Using the Fab$_2$ fragment of mAb 1B5, we investigated the effect of this antibody on embolic focal cerebral ischemia. Rats were subjected to middle cerebral artery (MCA) occlusion by intracranial placement of a single fibrin rich clot. One hour before MCA occlusion, rats ($n=5$) were treated with 1B5 Fab$_2$ (1 mg/kg, i.p.). Platelet counts and platelet function assays in a rapid platelet function assay ($n=4$) were measured before, 1 h and 7 h after administration of 1B5 Fab$_2$. Occlusion of MCA, changes in CBF and ischemic lesion were measured by MR angiography, perfusion and diffusion weighted MRI, respectively. Ischemic counts ($n=10$) without any treatment were used as a control group. All rats were sacrificed at 24 h of stroke. Ischemic lesion volume, gross hemorrhage and fibrin deposition were measured. Platelet counts did not change after administration of 1B5 Fab$_2$, compared with pretreatment. However, platelet function was inhibited by 91% of pretreated levels at 1 h and 80% at 7 h after administration of 1B5 Fab$_2$. Pretreatment with 1B5 Fab$_2$ resulted in a significant (p < 0.05) reduction of ischemic lesion volume (18.4 ± 4.7% of the contralateral hemisphere) compared with the control group (33.2 ± 5.6%). None of pretreated rats and 20% of the control rats had gross hemorrhage. The number of vessels with fibrin deposition was significantly decreased in the pretreated rats compared to the control rats. Our data demonstrate that pretreatment of embolic stroke with 1B5 Fab$_2$ reduces ischemic lesion size without increasing hemorrhage. These data suggest that platelet aggregation contributes to the ischemic damage in the rat model. Further work is needed to confirm this result and to investigate the mechanisms by which 1B5 Fab$_2$ reduces ischemic lesion size without increasing hemorrhage.
The Relationships Between MRI-Measured Parameters and Brain Tissue Damage Are Not Simple in a Rat Model of Brief Focal Ischemia

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Background and Purpose: Various reports have suggested that a significant percentage of patients with transient ischemic attacks (TIAs) have brain lesions or neuroimaging abnormalities, but evidence of this is limited. The purpose of this study was to seek for more such evidence in a rat model of TIA by measuring several MRI parameters and tissue injury.

Methods: One middle cerebral artery was transiently occluded for 10 min in ten male Sprague-Dawley rats. Sham occlusions were performed in 2 rats. Diffusion (DWI), perfusion (PWI), and T2-weighted imaging were performed during the occlusion and repeatedly over 72 hr after reperfusion. Tissue sections were taken at 72 hr for TUNEL (DNA survival) and HE staining. Immunohistochemical (IHC) probes were GFAP (astrocytes), ED1 and GSA (microglia). Histochemical stains were Beilchowsky's (axons) and LFB (myelin). The MRI maps were co-registered with the histologies and IHCs, and quantitative comparisons were made. Results: The MRI maps, histologies, and IHCs were normal in the sham-operated rats. PWI deficits and DWI hyperintensities were found in the caudoputamen (Cpu) and parietal cortex (PCx) of the 10 "TIA" rats during occlusion but returned to normal at 30 to 60 min of reperfusion, and remained normal up to 72 hrs after reperfusion. In contrast, T2 was normal.

In the Cpu of all TIA-rats, disseminated selective neuronal necrosis (SNX); a few weakly dITIP-positive dead neurons (DN); and mild glial responses were observed. In the PCx of 3 TIA rats, focal, progressing SNX; nuclear pyknosis and cytoplasmic eosinophilia with strong TUNEL positivity, and activated, ED1+ microglia were seen. In the remaining 7 TIA rats, only a few DN were found in the PCx. Mild demyelination with astrogliosis was observed in subcortical white matter of all TIA rats. Conclusion: DWI detected brief, fully reversible “ischemic lesions” in all TIA rats; tissue damage that differed between the caudoputamen and cortex and varied for the PCx among rats was found at 72 hr. The relationship among MRI-measured parameters and tissue damage may, thus, be rather complex for TIA and worthy of further experimentation.

The Integrity of Blood Brain Barrier Does Affect the Accuracy of Brain Water Measurements Using MRI

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Recently, we have demonstrated that an absolute estimate of brain water content (W) can be obtained non-invasively with MRI. However, one of the major concerns is the interference of macromolecules which have been attributed to have a short T2*, resulting in an underestimation of the true W.

In this study, cerebral ischaemia was induced in rats (n=67). The rats were assigned into two groups: MR (n=16) and vascular injury index (VII) groups (n=51) in which the cerebrovascular permeability to macromolecules was assessed via the extent of extravasation of fluorescein isothiocyanate-conjugated dextran (FITC-D). In the MR group, the right MCA was permanent occluded and imaged 24 hrs post-ischemia. Immediately after MR imaging, wet/dry measurements were performed. In contrast, VII was assessed at different time points post-ischemia. For rats (n=13) underwent reperfusion (90 min ischemia), VII was measured at 2, 4, 6, 24 hrs while VII was measured at 2, 4, 6, 24, 48, 72 and 168 hrs post ischemia for rats (n=38) underwent permanent MCAO. A sharp increase in VII 4hr post-ischemia was followed by a gradual recovery toward but not to the baseline value 168 hrs post-ischemia for reperfused rats. In contrast, a minimal increase in VII was observed up to 24 hrs post-ischemia for the permanent MCAO group, suggesting that the extravasation of FITC-D was negligible. The correlation between MR estimated W and that obtained from wet/dry measurements is shown in Fig. 1. A linear relationship with a slope of 0.986 (r=0.71) was obtained, identical to our previously reported results when a 90 min ischemia was utilized. Our results suggest that the accuracy of brain W measurements with MRI will not be affected by the integrity of BBB.

Overexpression of the Inducible 70 Kd Heat Shock Protein (HSP70) Worsens Injury After Transient Focal Cerebral Ischemia in Transgenic Mice

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The inducible stress protein, heat shock protein 70 (HSP70) has been suggested to be a potential neuroprotective agent in the central nervous system insults. We recently showed that gene transfer mediated HSP70 overexpression is neuroprotective against ischemia and ischemia-like insults in cultured astrocytes and in vivo models of stroke and epilepsy. From a strain of transgenic mice which overexpress human inducible HSP70, we found that glial and neuronal cultures were protected against hydrogen peroxide and substrate deprivation, but were less resistant to oxygen/glucose deprivation and glutamate toxicity. At the in vivo level, these animals were not protected against permanent middle cerebral artery (MCA) occlusion possibly due to the severity of the ischemic insult. We now examine whether these transgenic mice may be are protected against transient focal cerebral ischemia. Transgenic mice on a FVB/N background expressed hsp70 under the control of a beta-actin promoter. Genotyping was performed by polymerase chain reaction from extracts of tail or liver DNA, and confirmed at the protein level by Western blotting using an antibody which recognizes human, but not mouse HSP70. Heterozygotic HSP70 transgenic mice were generated by crossing a positive male with a wild type female. Positive offspring were presumed to be heterozygotic. These animals were subjected to transient (2 h) middle cerebral artery (MCA) occlusion via intraluminal occluding suture by advancing a 5.0 nylon blue monofilament suture 8 mm from the carotid bifurcation. Identical procedures were performed on wild type littermates. Twenty four hours after MCA occlusion, brains infarcts were delineated with triphenyl tetrazolium chloride (TTC). Among transgenic mice, infarct size was 62.5 +/- 5.5% (n=10) of the ipsilateral hemisphere versus 41.4 +/- 4.5% (n=9) among wildtypes (mean +/- SEM, p=0.0009). We conclude that although HSP70 may be involved in a cascade of events leading to neuroprotection, in some instances HSP70 overexpression may be associated with worsening of ischemic injury. The mechanisms underlying this worsening should be further elucidated.

Broad-Spectrum Cation Channel Inhibition by LOE 908 MS Reduces Infarct Volume in Vivo and Postmortem in Focal Cerebral Ischemia in the Rat


Background and Purpose: Cation channels conduct calcium, sodium, and potassium, cations that are likely deleterious in the evolution of focal ischemic injury. Diffusion-weighted magnetic resonance imaging (DWI) is a powerful tool for evaluation of acute cerebral ischemia. We studied the effects of a novel, broad-spectrum inhibitor of several cation channels, LOE 908 MS, on acute ischemic lesion development with DWI in vivo and on infarct size using TTC staining postmortem. Methods: Eighteen male Sprague-Dawley rats underwent middle cerebral artery occlusion (MCAO) and were randomly and blindly assigned to either LOE 908 MS (1mg/kg bolus 30 min after inducing focal ischemia and continuous intravenous infusion of 10mg/kg for 4 hr) or vehicle. Whole-brain DWI was done before initiation of treatment and repeated frequently for the next 3.5 h. The animals were reperfused 90 min after MCAO. At 24 h the animals were killed, and the brains were cut into six 2-mm-thick slices and stained with 2% TTC. Percent hemispheric lesion volume (%HLV) was calculated for each animal. Results: Physiological parameters, body weight, and premature mortality (3 in the placebo group and 1 in the LOE 908 MS group) did not differ between the two groups. No hypotension, abnormal behavior, or other adverse effects were seen. Pretreatment, the DWI-derived %HLV did not significantly differ between the groups (19.5+6.2 for controls and 17.9+7.9 for the treated group), whereas at 4 hr after MCAO, it was significantly smaller in the treated rats (21.3+5.5% versus 34.0+4.5%, p=0.03). The postmortem %HLV by TTC staining was significantly attenuated in the treated group (21.3+5.5% versus 0.03). Neurological score at 24 h was significantly better in the treated group (2.1+1.5 versus 4.0+6.0, p=0.02). Conclusions: LOE 908 MS significantly improved neurological outcome and reduced infarct size without observable adverse effects in rats as demonstrated in vivo by DWI and confirmed postmortem by TTC staining. Blocking several cation channels with LOE 908 MS showed significant neuroprotection in this focal ischemia model.
Interleukin-6 Related Brain Damage in Ischemic Stroke Is Independent of Acute Infections
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Background and Purpose: Acute infections and the proinflammatory cytokines have been implicated in cerebral ischemia. Since the synthesis of inflammatory mediators may be the result of both, brain injury and infections, we analyzed the independent role of interleukin-6 (IL-6) and infectious fever on infarct volume and stroke outcome. Methods: Plasma and CSF IL-6 were determined in 231 and 83 patients respectively, within the first 24 hours of an acute cerebral infarct. Stroke severity on admission was evaluated by the Canadian Stroke Scale, infarct volume was measured on a cranial CT performed on days 4 to 7, and poor outcome was defined as death or Barthel Index <80 at 3 months. Infections were investigated in patients with body temperature higher than 37.5°C within the first week after stroke. Results: There was a significant correlation between the infarct volume and IL-6 concentrations in plasma (r = 0.54) and CSF (r = 0.03). Poor outcome was observed in 55% of patients at 3 months. Mean concentrations of IL-6 were significantly higher in patients with poor outcome in comparison with those with good outcome, both in plasma (23.4 ± 17.0 versus 13.5 ± 11.3 pg/mL, p=0.0001) and in CSF (23.5 ± 23.5 to 16.4 pg/mL, p=0.015). Infections were detected in 42 patients (15.5%), and were associated with higher levels of IL-6 in plasma (p=0.03), but not in CSF. IL-6 in plasma (by 10 pg/mL, OR=1.9; 95%CI:1.5 to 3.7) with the initial volume of acute infarct, stroke severity at admission, and final infarct volume. This effect is independent of the concurrent infections during the acute phase of ischemic stroke.

Inflammatory Mechanisms in Acute Cerebral Hemorrhage Are Associated with Poor Outcome and High Volume of Residual Necrosis
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Background and Purpose: There is no evidence for an ischemic penumbra in the early acute phase after intracerebral hemorrhage (ICH), so other mechanisms for acute neuronal injury may be involved in the surrounding regions. This study was conducted to identify the role of the inflammatory mediators on the residual brain necrosis and poor outcome after ICH. Methods: We evaluated Canadian Stroke Scale (CSS) score, volume of hematoma with CT, plasma interleukin-6 (IL-6), tumor necrosis factor (TNF-α), and intercellular adhesion molecule-1 (ICAM-1) within the first 24h from the onset of symptoms in 124 patients who survived 3 months after an ICH. Results: The initial volume of the ICH was 66.1 ± 44.9 cc. An encircling edema on the second CT carried out on days 3 to 4 was observed in 84% of patients (mean volume: 22.1 ± 22.8 cc), and a focal area of tissue necrosis was seen at 3 months in 81% (mean volume: 24.9 ± 27.8 cc). Linear regression analyses showed a significant correlation of IL-6 and TNF-α concentrations with the volume of the surrounding hypodensity on days 3-4 (r=0.33, p=0.0002; and r=0.85, p<0.0001, respectively), the volume of the focal hypodensity at 3 months (r=0.65, p=0.0001; and 0.31, p=0.0001, respectively) and CSS score at 3 months (r=0.63, p=0.0001; and r=0.26, p=0.0004, respectively). IL-6 was the only factor related to the volume of tissue necrosis at 3 months in multiple linear regression analysis (p=0.0001) and was the most important predictor of poor outcome (CSS score <7) in a logistic model after controlling for age, CSS on admission and initial volume of ICH (by 10 pg/mL, OR:1.6; 95%CI:1.3 to 2.7). Conclusions: High IL-6 plasma concentrations within the first 24h of ICH are associated with increased residual necrosis and poor outcome. These findings support an early inflammatory response in ICH that may contribute to the surrounding neuronal injury.
A Quantitative Analysis of Injured, Necrotic and Apoptotic Cells in a New Model of Intracerebral Hemorrhage in Rats

Abstract

Introduction: Intracerebral hemorrhage (ICH) is a significant cause of morbidity and mortality. The pathophysiology of ICH is complex and involves hemorrhage, inflammation, and secondary tissue damage. However, the current therapeutic options are limited and are focused on acute hemorrhage control. This study aimed to develop a new model of ICH in rats and to evaluate the effects of recombinant tissue plasminogen activator (rt-PA) on hemorrhagic transformation (HT) and cellular damage.

Methods: The study was conducted in accordance with the Guide for the Care and Use of Laboratory Animals. Male Sprague-Dawley rats (n = 48) were used. The rats were divided into six groups: sham, ICH, ICH + rt-PA, ICH + TUNEL staining, ICH + histology, and ICH + immunohistochemistry. ICH was induced by injecting 1.5 ml of saline into the right hemisphere. The rats were sacrificed at 24 hours after ICH induction. The brains were removed and sectioned for histological and immunohistochemical analysis.

Results: In the sham group, no hemorrhage or cell damage was observed. In the ICH group, significant hemorrhage and cell damage were observed. In the ICH + rt-PA group, a significant reduction in hemorrhage and cell damage was observed. In the ICH + TUNEL staining group, a high burden of apoptotic cells was observed. In the ICH + histology and ICH + immunohistochemistry groups, a high proportion of swollen cells was observed.

Conclusions: This study demonstrates that rt-PA can reduce hemorrhagic transformation and cellular damage in a new model of ICH. These findings suggest the potential of rt-PA for the treatment of ICH.

Oxidative Injury After Transient Middle Cerebral Artery Occlusion in the Neonatal Rat

Background: Oxidative stress plays a crucial role in the pathogenesis of cerebral ischemia-reperfusion injury. However, the mechanisms underlying oxidative stress in neonatal rats are not well understood. The current study aimed to investigate the oxidative stress response in neonatal rats after transient middle cerebral artery occlusion (tMCAO).

Methods: Neonatal Sprague-Dawley rats (P7) were subjected to 3 hr MCAO followed by reperfusion. The brains were removed at 24 hours after reperfusion for histological and histochemical analysis.

Results: In the control group, no histological changes were observed. In the tMCAO group, significant histological changes, including neuronal loss, gliosis, and edema, were observed. In addition, increased levels of oxidative stress markers, such as 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA), were detected in the tMCAO group compared to the control group.

Conclusions: The current study demonstrates that transient middle cerebral artery occlusion induces oxidative stress in neonatal rats. These findings highlight the potential role of oxidative stress in the pathogenesis of cerebral ischemia-reperfusion injury in neonatal rats and suggest the importance of targeting oxidative stress as a therapeutic strategy.

The Transcription Factor E2F Represents a Novel Molecular Checkpoint in Post-Mitotic Cells

Introduction: The transcription factor E2F is known to regulate cell cycle progression. However, its role in post-mitotic neurons is less well understood. The current study aimed to investigate the role of E2F during nitric oxide (NO) induced programmed cell death (PCD) in post-mitotic neurons.

Methods: Primary hippocampal neurons were cultured and exposed to NO. The expression of E2F and its target genes was determined by qPCR and Western blot analysis.

Results: In primary hippocampal neurons, E2F expression was decreased in response to NO exposure. Downstream targets of E2F, such as p21 and p15, were upregulated following NO exposure.

Conclusions: The current study demonstrates that E2F plays a role in regulating the expression of genes involved in PCD in post-mitotic neurons. These findings suggest that E2F may represent a novel molecular checkpoint in PCD.

Bone Marrow Transplantation with BDNF Reduces Dysfunction Following MCAo in Rats

Introduction: Stroke is a major cause of disability and mortality. Bone marrow transplantation (BMT) has been shown to improve functional outcomes after stroke. However, the mechanisms underlying this effect are not well understood. The current study aimed to investigate the effects of BDNF on functional outcomes after BMT.

Methods: Male Sprague-Dawley rats were subjected to MCAo and received either intravenous injection of BDNF or saline. The rats were sacrificed at 24 hours after MCAo. The behavioral function was assessed using the Neurological Severity Score and the BBB Motor Score.

Results: In the saline group, no improvement in functional outcomes was observed. In the BDNF group, a significant improvement in behavioral function was observed. The improvement in functional outcomes was associated with increased expression of BDNF and its downstream targets in the brain.

Conclusions: The current study demonstrates that BDNF improves functional outcomes after stroke. These findings suggest that BDNF may serve as a therapeutic target for stroke.

Aspects of consciousness and behavioral recovery after ischemic stroke

Introduction: Ischemic stroke is a common cause of morbidity and mortality. The mechanisms underlying behavioral recovery after ischemic stroke are not well understood. The current study aimed to investigate the factors that influence behavioral recovery after ischemic stroke.

Methods: Male Sprague-Dawley rats were subjected to MCAo and sacrificed at 7 days after MCAo. The behavioral function was assessed using the Neurological Severity Score and the BBB Motor Score.

Results: In the control group, no improvement in functional outcomes was observed. In the ischemic group, a significant improvement in behavioral function was observed. The improvement in functional outcomes was associated with increased expression of neurotrophic factors in the brain.

Conclusions: The current study demonstrates that neurotrophic factors play a role in behavioral recovery after ischemic stroke. These findings suggest that targeting neurotrophic factors may improve functional outcomes after ischemic stroke.

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Conclusions: The current study demonstrates that BDNF improves functional outcomes after stroke. These findings suggest that BDNF may serve as a therapeutic target for stroke.
Effect of Hyperbaric Oxygenation on Spatial Learning and Memory After Focal Cerebral Ischemia in Rats

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Introduction: Treatment with hyperbaric oxygen (HBO) may be neuroprotective after focal cerebral ischemia. We determined whether HBO can improve cognitive deficits in spatial learning in a rat model of permanent middle cerebral artery occlusion (MCAO). Methods: SD rats (250-300g) underwent either sham surgery (negative controls) or MCAO by intraluminal filament. MCAO was confirmed by laser Doppler flowmetry. Anesthesia was maintained with isoflurane and HBO was randomized to treatment or positive control. HBO was initiated 60 min after occlusion (15 min descent to 3 ATA, 60 min at pressure, 30 min ascent). Testing of spatial memory by Y maze began 7 days after surgery (preliminary swim, 5 days of training with 3 swim/day, visible platform and probe trials on day 13). Latency to target, measured by computer, was the primary outcome. Results: Sham surgery animals had no evidence of cerebral ischemia. All animals with MCAO (HBO and control) showed similar initial motor deficits and decreases in cerebral blood flow. Initial motor deficits resolved by day 7. All 7 sham animals and 18 animals with MCAO (9 HBO, 9 control) were tested in the water maze. One animal in each MCAO group died during the testing period. As shown in the table, sham animals had shorter latencies than animals with MCAO. Animals treated with HBO had shorter mean latencies than positive controls every day. Many and on visible day MCAO was confirmed by angio graphy (p < 0.001). All groups had similar probe trial and swim speed data. Conclusions: In this model of focal cerebral ischemia, treatment with HBO, at 3 ATA delivered 1 hour after MCAO, reduced deficits in spatial learning and memory associated with stroke.

Poster Presentations 345

Maturation of Ischemic Neuronal Death Following Focal Cerebral Ischemia
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Introduction: Cerebral ischemia can result in selective neuronal death in both animal and human brains. In our previous ischemia study, we had shown that ischemic insults affects the maturation of neuronal injuries. In the present study, we examined the temporal evolution of cortical infarction following focal cerebral ischemia. Methods: Male spontaneously hypertensive rats were subjected to middle cerebral artery occlusion using aneurysm clips, followed by 1, 7, 14, or 21 days survival. The rat body temperature was kept at 37 ± 0.5°C during and following the ischemia. Regional cerebral blood flow was monitored and recorded. Volumes of cerebral infarction were examined using an image analyzing system. The percentage of infarct volume over normal hemisphere was calculated. Results: In the rat brains following 30 minutes of ischemia, scant selective cortical neuronal injuries were detected at 24 hours (n=5) and 7 days (n=5) post ischemically, and infarct lesions started to appear at the second and the third weeks, which was 1% (n=5) and 2% (n=5), respectively. The infarct volumes following 60, 90 and 120 minutes occlusion were 11 ± 4% (n=5), 17 ± 3% (n=6) and 20 ± 2% (n=5) at 24 hours, 16 ± 3% (n=5) (p < 0.001, 1d vs 7d), 21 ± 1% (n=9) (p < 0.001, 1d vs 7d) and 20 ± 1% (n=5) at 7 days, and 20 ± 2% (n=5), 20 ± 1% (n=5) and 21 ± 2% (n=5) at 14 days. Therefore, significant infarct volumes at 2 weeks survival in the animals following 90 and 120 minutes of ischemia. Conclusion: Duration of the ischemic insults determines the maturation rate of neocortical infarction. Brief duration of ischemia usually leads to selective neuronal death, while small infarcts gain in size after a latency of many days following the more prolonged ischemia.

Indefatigable Protection with Prolonged Mild Hypothermia Following Experimental Focal Cerebral Ischemia in Rats
Zongzheng Zhao, Alberta Stroke Program, Foothills Hosp, Calgary, AB Canada; Frederick Colbourne, Univ of Lethbridge, Lethbridge, AB Canada; Dale Corbett, Memorial Univ of Newfoundland, St. John’s, NF Canada; Hui Li, Ping Sun, Alberta Stroke Program, Foothills Hosp, Calgary, AB Canada; Alastair M Buchan, Alberta Stroke Program, Foothills Hosp, Calgary, AB Canada

Introduction: Many reports have shown that mild hypothermia is one of the most effective treatments for ischemic injury. Recently we studied the therapeutic value of prolonged mild hypothermia induced after transient middle cerebral artery (MCA) occlusion in spontaneously hypertensive rats to determine whether it could induce neuroprotection, and whether this was prolonged over time. Methods: Core temperature telemetry probes were implanted several days before induction of ischemia which was produced by 90 min clipping of the MCA and ligating the right common carotid artery. Normothermia was maintained during ischemia. After ischemic surgery, rats were either kept at normothermia (n=5) or subjected to 48 hours of mild hypothermia starting at reperfusion (n=6) or 1 hour later (n=6). Rats were sacrificed after a prolonged period of survival (3-4 weeks) and the volume of cortical infarction was determined using image analysis. Results: The normothermia group had 13.9% ± 0.6% of contralateral side cortical infarction. In the hypothermic groups, cortical infarction was significantly reduced to 4.9% ± 0.6% and 9.5% ± 2.1% of normal side infarction respectively (both P < 0.001). Conclusion: These preliminary data add to the growing evidence that postischemic prolonged mild hypothermia achieves indefatigable protection of cortex following experimental focal ischemic injury, even when hypothermia is induced 1 hour following reperfusion.

Blood Components and Acute White Matter Edema Development Following Intracerebral Hemorrhage: Are Hemolysates Edemogenic?
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Introduction: White matter damage is an important cause of long-term morbidity following intracerebral hemorrhage (ICH). To develop effective treatments, better understanding of early pathophysiology is needed. Previously, we demonstrated that whole blood and plasma but not intact red cell infusions (N 10 kg; N 5) postischemically, and infarct lesions started to appear at the second and the third weeks, which was 1% (n=5) and 2% (n=5), respectively. The infarct volumes following 60, 90 and 120 minutes occlusion were 11 ± 4% (n=5), 17 ± 3% (n=6) and 20 ± 2% (n=5) at 24 hours, 16 ± 3% (n=5) (p < 0.001, 1d vs 7d), 21 ± 1% (n=9) (p < 0.001, 1d vs 7d) and 20 ± 1% (n=5) at 7 days, and 20 ± 2% (n=5), 20 ± 1% (n=5) and 21 ± 2% (n=5) at 14 days. Therefore, significant infarct volumes at 2 weeks survival in the animals following 90 and 120 minutes of ischemia. Conclusion: Duration of the ischemic insults determines the maturation rate of neocortical infarction. Brief duration of ischemia usually leads to selective neuronal death, while small infarcts gain in size after a latency of many days following the more prolonged ischemia.

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Transient Focal Ischemia (MCAo) Induces De Novo Neurogenesis in the Adult Rat Brain
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Introduction: Previous studies have demonstrated that in the adult brain, neural stem/multipotent progenitor cells are present within paramedian generative zones throughout the neuroaxis. In addition, we have recently shown that the postnatal cerebral cortex independent of the subventricular zone contains similar pools of multipotent progenitor species. Further investigations performed in the gerbil boxes found that transient global ischemia results in increased neurogenesis in the dentate gyrus of the hippocampus. The purpose of this study was to determine if transient focal ischemia also results in increased neurogenesis in the rat. Methods:Transient focal ischemia was induced in the adult rat using the intraluminal suture method (MCAo). Bromodeoxyuridine (BrdU) was injected intraperitoneally a day prior to sacrifice to identify neural progenitor cells that have newly entered the S-phase of the cell cycle. Histological and immunocytochemical analysis were performed at different time points following ischemia. Results: 7-12 days following 60 minutes of MCAo, histological analysis demonstrated ischemic infarction of the cerebral cortex and the subcortical white matter. Immunocytochemical analysis demonstrated a significant number of BrdU immunoreactive cells in the region of the infarction, particularly within the borderzone regions in the experimental animals as compared to the control animals. There was an increased BrdU staining in the adjacent non-infarcted parenchyma. Dual labeling revealed that a population of BrdU positive cells coexpressed the neuropherrophil marker nestin and the neuronal specific antigen NeuN. Conclusion: These data support the hypothesis that increased neurogenesis occurs in response to focal ischemia in the adult rat brain and that the new neurons are generated from the neural progenitor cells located outside of traditional paraventricular generative zones.

Multiparameter MRI Tissue Staging in Experimental Cerebral Ischemia Rat
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Background: After stroke, the brain tissue undergoes time-dependent histopathological change. These tissue alterations have resonance imaging (MRI) characteristics, which allow segmentation ischemic from nonischemic tissue. Moreover, MRI segmentation generates zones within the lesion that may reflect heterogeneity of tissue. Unsupervised segmentation methodologies may aid in the and staging of ischemic damage. Methods: MRI data sets of T2, T1 diffusion weighted (DWI), and cerebral blood flow (CBF) measurements using arterial spin tagging were obtained at 7T in a model of permanent middle cerebral artery occlusion (MCAo) on rats. Multiparameter (T2, DWI, T1) MRI are integrated and clusters MRI indices are segmented using an objective (unsupervised) computer algorithm implementing a modified version of the Iterative Organizing Data Analysis Technique (ISODATA) to define the ischemic zone. We test the utility of this model to characterize ischemic tissue stroke. Multiparameter ISODATA measurements of the ischemic tissue were compared to quantitative histological characterization of the tissue 4 hour to 1 week after stroke. Results: We demonstrate that the ISODATA segmentation of tissue identifies gradation of cerebral tissue damage independently of time. The scoring of ischemic tissue from 4 hour to 1 week post stroke all the animals were significantly correlated (r = 0.78, p = 0.01, n = 20) using a multiparameter (T2, DWI) ISODATA parameter, less (r = 0.73, p = 0.05, n = 20) when using T2 and T1 data set, and no (r = 0.01, p > 0.05, n = 20) when using only a DWI data set. The use of the multiparameter ISODATA was superior to that obtained T2, diffusion, and CBF measurements. Conclusion: Our data indicate that the ISODATA approach using an set of MRI parameters will distinguish and stage ischemic tissue an objective manner.

The Neurosteroid Dehydroepiandrosterone Sulfate Is Neuroprotective in a Rabbit Reversible Spinal Cord Ischemia Model
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Neurosteroids are a family of C19 steroids synthesized de novo by the CNS and PNS. One family member, DHEAS (5-androsten-3b-ol-17-one sulfate) is an allosteric modulator of a variety of CNS neurotransmitter receptors including GABA-A, NMDA and sigma receptors. In the CNS, DHEAS may also function as “neurotrophic” factor to protect neurons against a variety of insults. Thus, this study examined the effect of DHEAS in a model of spinal cord ischemia. DHEAS was administered (50 mg/kg) intravenously 5 minutes following the start of occlusion to groups of rabbits exposed to reversible spinal cord ischemia induced by temporary occlusion of the infrarenal aorta. The duration of occlusion for individual animals was varied from 15 minutes up to 60 minutes, providing a wide range of ischemia for each experimental group. The group P50 represents the duration (in minutes [min]) associated with 50% probability of resultant permanent paraplegia. Neuroneuroprotection was demonstrated if a drug prolonged the P50 compared to the control group. The P50 of the control group, when behavioral analysis was assessed 18 hours following aortal occlusion was 25.1 +/- 4.5 min. Treatment with intravenous DHEAS at 50 mg/kg significantly prolonged the P50 of the group to 43.3 +/- 4.9 min. In addition, the DHEAS effect appeared durable since there was a significant difference between the control and DHEAS-treated groups at the 4 day time point. The P50 of the control group was 39.9 +/- 3.1 min whereas the P50 for the DHEAS-treated group was 47.2 +/- 2.4 min. The physiological and apparent behavioral effects of DHEAS at the chosen dose was quite substantial and visible as DHEAS-treated rabbits had increased mobility, tactile sensation and use of their hind limbs. Thus, DHEAS exerts a prominent neuroprotective effect in the spinal cord ischemia model. Since steroids have been shown to be safe and effective for the treatment of spinal cord injury, our results suggest that neurosteroids like DHEAS may have substantial therapeutic benefit for the treatment of ischemic stroke. (Supported by NIH and the Veterans Administration)
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