ABSTRACTS

15th International Joint Conference on Stroke and Cerebral Circulation

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Cosponsoring Organizations:

JOINT SECTION OF CEREBROVASCULAR SURGERY OF THE
AMERICAN ASSOCIATION OF NEUROLOGICAL SURGEONS
AND THE CONGRESS OF NEUROLOGICAL SURGEONS

CANADIAN STROKE SOCIETY
Canadian Heart Foundation

AMERICAN NEUROLOGICAL ASSOCIATION

THE SOCIETY FOR VASCULAR SURGERY
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<td>Vladimir C. Hachinski, London, Ontario, Canada</td>
<td>Has the concept “TIA” served its purpose?</td>
<td>Chairmen: Vachtang Pipia, Tbilisi, Georgia, USSR</td>
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<td>Symposium: Part I</td>
<td>James F. Toole, Winston-Salem, NC</td>
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<td>Brain temperature and cerebral ischemia</td>
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<td>Cellular mechanisms of hypothermia</td>
<td><strong>LACUNAR INFARCT OR SMALL STROKE?</strong></td>
<td>Among patients with first cerebral infarct in Rochester, MN in 1960-1984, the age- and sex-adjusted average annual incidence rate for lacunar infarct was 13.4 per 100,000 population, 13% (180/1382) of cerebral infarcts. The characteristics of patients with lacunar infarcts were similar to those for patients with nonlacunar infarcts, that is, the trends of incidence rates, the recurrent stroke rate, prevalence of diabetes, and causes of death, given 30-day survival. The frequency of a cardiac source for an embolus was 12% (9/78) versus 28% (144/516) in patients with lacunar and nonlacunar infarcts respectively (p=.002). The frequency of hypertension was 81% (63/78) in patients with lacunar and 70% (361/516) in those with nonlacunar infarcts (p=.05). Survival in patients with lacunar infarcts was equal to expected survival, determined in part by less disability in patients with lacunar infarcts. Small deep cerebral infarcts are caused by the same mechanisms that produce other infarcts.</td>
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LACUNARY INFARCTION: CLINICAL-CT CORRELATIONS IN THE STROKE DATA BANK

Lacunar syndrome (LAC) was diagnosed in 337 (27%) of 1273 infarct cases in the Stroke Data Bank. LAC had more hypertension (p<.001) and diabetes (p<.001) than did cardioembolism, and fewer prior strokes (p<.001) and TIA's (p<.001) than did atherosclerotic large artery strokes. No stroke risk factors separated the classical LAC syndromes.

CT within 30 days showed infarction in only 35%, 68% involving the internal capsule or corona radiata. For Pure Motor Stroke, mean infarct volume was 4.0 ml, for Sensorimotor, 4.3 ml. Size correlated directly with motor deficit in the 23 posterior capsular infarcts. Another 3 with small anterior choroidal territory lesions had severe weakness. The capsular infarct syndromes did not conform to the classical homuncular pattern. They ranged from plegia (5/23) to paretic combinations of face, arm and leg with variable proximal vs distal weakness (13), to isolated weakness of the arm & leg (3), arm (1), or face (1).

LACUNARY INFARCTION IN YOUNG ADULTS
Patrizia Nencini, M. Cristina Baruffi, Giovanni Pracucci, Domenico Inzitari, University of Florence, Florence, Italy.

We investigated lacunar infarction in a continuous series of 110 young adults (<45 yrs) with cerebral ischemia. All the patients underwent a standard clinical and laboratory assessment. Based on clinical and CT criteria, 7 (6.4%) cases of lacunar infarction were identified. They were men, with a mean age of 41.6 yrs (range 39-43).

Clinical and laboratory findings were evaluated in lacunar vs. non-lacunar patients. After controlling for age and sex, lacunar infarction was significantly associated with history (OR=6.4; 95% CI 1.3-31.2) and more than 1 year duration (OR=6.3; 95% CI 1.6-25.01) of hypertension, and with non-stenosing carotid ulcerated plaque (OR=11.3; 95% CI 2.0-65.4). Both hypertension and arterial embolism were considered as possible pathologic factors for lacunar infarction in this series of young adults.
Large cerebral arteries undergo hypertrophy with reduced distensibility during aging. To determine effects of aging on cerebral arterioles, we measured pressure (servo-null) and diameter in pial arterioles in adult (9 month old; n=10) and aged (24 month old; n=11) Fischer rats. Cross-sectional area of the vessel wall, measured histologically, was less in aged than adult rats (1239±91 vs 1832±180 μm² [mean±S.E.]; p<0.05). The slope of elastic modulus vs stress after EDTA in vivo was greater in aged than adult rats (6.8±0.6 vs 5.3±0.3; p<0.05), which indicates that distensibility of arterioles is reduced by aging. Using point counting stereology to quantitate smooth muscle (SM), elastin (E), collagen (C) and basement membrane (BM), we found that cross-sectional area of distensible components (SM+E) was less in aged than adult rats (841±115 vs 1309±170 μm² for SM; 63±12 vs 116±18 μm² for E; p<0.05), whereas cross-sectional area of nondistensible components (C+BM) was not different. Thus, during aging, 1) cerebral arterioles undergo atrophy, 2) the relative proportion of the more distensible elements, elastin and smooth muscle, is reduced, and 3) arteriolar distensibility is reduced. We speculate that changes in cerebral arterioles during aging may reduce both constrictor and maximal dilator responses, and thus impair responses in the cerebral circulation.

This study used an in vitro cannulation method to examine the response of rat intracerebral arterioles to ethanol (EtOH). Arterioles were cannulated and pressurized to 60 mm Hg (n=6). The vessels developed spontaneous tone and did not require pre-contraction (resting diameter = 40.8±12.6 μm). Viability was assessed by reactivity to pH changes. EtOH caused vasoconstriction in a dose dependent manner (expressed as % of resting diameter in the figure at left). Significant vasoconstriction occurred at concentrations between 10 and 30 mM EtOH, which corresponds to a low to moderate dosage of alcohol.

Vasomotion has been described mainly in peripheral arterioles. In this study, we examined mechanisms of vasomotion in a large cerebral artery in vivo. Spontaneous vasomotion (rhythmic contraction) of the basilar artery was observed in 33 of 41 anesthetized rats through a cranial window. Under control conditions, the frequency of vasomotion was 4.7±0.2 cycles/min (mean±SE) and the amplitude was 18±2% of mean diameter. Acute hypertension increased the frequency of vasomotion, and hypotension decreased the frequency. Nisoldipine and Ca²⁺-free cerebrospinal fluid (CSF) produced moderate dilatation and abolished vasomotion. Potassium-free CSF and ouabain produced moderate vasoconstriction and abolished vasomotion. Thus, 1) the basilar artery exhibits pronounced vasomotion in vivo, and 2) vasomotion is dependent on transmural pressure, extracellular Ca²⁺, K⁺, and on the activity of Na-K ATPase.

The sympathetic nerves of cerebral arteries are known to take up serotonin (5-HT) after subarachnoid hemorrhage (SAH). This study examined the effects of SAH on neuronal uptake and metabolism of 5-HT in the sympathetic nerve. Basilar arteries were incubated in 10⁻⁸M [3H]5-HT for 1 hr. Extracted [3H]amines were separated by column chromatography. Radioactivity of 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) were: 52.7±4.9 and 22.9±1.9 x 10⁻² dpm/mg tissue in the control group (n=8); 32.3% and 18.3% of control after denervation with 6-hydroxydopamine (n=6); 99.4% and 11.5% of control after treatment with monoamine oxidase (MAO) inhibitor (pargyline, n=7). After SAH (3 days, n=7), radioactivity of 5-HT and 5-HIAA decreased significantly to 65.1% and 75.9%. These results suggest that the majority of 5-HT is taken up by sympathetic nerves and that MAO is mainly responsible for degradation of 5-HT. Impairment of the inactivation mechanism of 5-HT after SAH is expected to play a role in developing vasospasm.

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ENDOTHELIN INDUCED VASOCONSTRICTION OF HUMAN CEREBRAL ARTERIES-IMPLICATIONS FOR CEREBRAL VASOSPASM

Stephen M. Papadopoulos, R. Clinton Webb
University of Michigan, Ann Arbor, MI

We have studied the vasoactive properties of endothelin in human cerebral artery strips. Endothelin typically produces intense sustained increase in tone over a physiologic dose range (ED₅₀= 10⁻⁶M). The response is resistant to selective antagonists of norepinephrine, serotonin, isoproterenol, histamine, acetylcholine and angiotensin II. Sodium nitroprusside verapamil and dithiothreitol inhibit the constrictor response. Endothelium dependent vasodilation produced by the calcium ionophore A23187 is diminished following pretreatment with endothelin. These physiologic properties are similar to those found in CSF from patients with cerebral vasospasm. Decreased endothelium-dependent vasodilation following experiment subarachnoid hemorrhage has been demonstrated by several investigators. The time course of the induction of endothelin production is consistent with the temporal sequence of vasospasm, further supporting the hypothesis that endothelin is involved in this pathologic process.

CORTICAL HYPEREMIA FOLLOWING SEVERE ISCHEMIA IS MARKEDLY DECREASED BY TRIGEMINAL(V) LESION

MA Moskowitz, DE Sakas, M Kano, EP Wei, HA Kontos. MGH, Boston 02114; Med Coll VA, Richmond 23298.

Hyperemia (HYP) can follow cardiac arrest, stroke, head injury, and classic migraine auras. The mechanism is poorly understood. 16 cats were subjected to chronic left V section or V sham, or left V rhizotomy. CBF (microspheres) was normal and symmetrical at rest in 10 regions. After 10/30 min of 4-vessel occlusion, marked HYP developed which was similar in the sham and rhizotomy group and on right side in chronic V section animals. Flx was attenuated by >60-80% in cortex grey matter on the left, corresponding to V innervation. These data suggest that cortical HYP is mediated via axon reflex-like mechanisms and relates V activation and headache to biochemical events that occur during ischemia.

IDENTIFICATION OF SATURATED FATTY ACIDS OF HUMAN CEREBRAL ARTERIES AS VASODILATORS

Gregory F. Ricca, Richard P. White and James T. Robertson. Univ. Tennessee, Memphis, TN 38163

Certain saturated fatty acids (SFA) are released with cerebral ischemia in large quantities, are present in high concentrations in some patients (e.g., diabetes, Reye's), are synthesized de novo by arteries, and increase CBF 100% in laboratory animals. The present experiments were performed on isolated rings of human basilar arteries and on canine basilar and femoral arteries. Sustained contractions were first produced by submaximal concentrations (EC₅₀) of PGF₂α. Then the relaxant effect of AX10⁻⁶M to 4X3 M of each SFA from C₄ (butyric) and upward in carbon length was quantified. The results show (N=5 to 11) that the cerebral arteries were more sensitive to all SFA than the femoral artery, that only C₈, C₁₀, and C₁₂ would relax 100% and that C₁₀ (capric) was the most potent (EC₅₀=4.9⁻⁶M). Thus medium chain SFA are effective dilators which could reduce cerebrovascular tone physiologically, in cerebral ischemia, and in other diseases that elevate lipid metabolism.

UNESTERIFIED CHOLINE DURING METABOLIC STRESS IN VITRO.

David Lust, Bogdan Djuricic¹, Steven Olson¹, Hussein Assaf, Tim Whittington, Lester Drewes¹.
Div. of Neurosurgery, Case Western Reserve Univ. Cleveland, OH and ¹Dept. of Biochemistry, Univ. of Minnesota, Duluth, MN.

Phosphatidylcholine (P) is a membrane phospholipid which is broken down to choline (C) during ischemia (I), apparently by the action of phospholipase D. To determine if other metabolic stresses would also elicit P degradation, C levels were determined in both hippocampal slices (n=4-6/group) and media at 30 min after incubation in anoxic, aglycemic and I medium and also in the presence of 60 mM potassium. Total C was significantly (p<0.05) increased by 2-fold in 60 mM K+, aglycemia and anoxia and by 7-fold in I over that of control (1.37 nmol/mg protein, n=8). The intracellular/extracellular distribution of the liberated C varied among the 4 experimental groups. C efflux increased 2-fold over that of control in aglycemia, 4-fold in elevated K+ and anoxia, and 11-fold in I. Physostigmine increased (p<0.05) the media C by 40% during I, suggesting that the source of C was not acetylcholine (Ach) and further that Ach may stimulate the increase of C. The results indicate that loss of membrane integrity through a greater P catabolism and efflux during I may account for the more extensive brain injury observed after this metabolic stress.
THE CEREBRAL ARTERIES OF PATIENTS WITH INTRACRANIAL ANEURYSMS

James C. Grotta, Carmela M. Picone, LiPing Yao, Univ Texas Med School, Houston, TX

We used an in vivo immunohistochemical assay of calcium-calmodulin (Ca-CaM) binding to indirectly determine the effect of GGS 19755, a competitive NMDA receptor antagonist 10 mg/kg IP begun immediately before or after global ischemia on the distribution and time course of Ca influx into neurons. Groups of 3-6 rats in control and 2 treatment groups were sacrificed immediately, 2 hours, and 24 hours after ischemia, and 40 μm sections incubated in a CaM-antibody recognizing only unbound CaM. Pre-treated animals had less Ca-CaM binding than controls (p<.01) at all 3 time intervals especially in CA1 and CA3 (p=.001) after 24 hours where histologic protection was also found. Post-treated animals had less Ca-CaM binding after 2 hours but this effect did not persist. We conclude that in regions such as CA1 and CA3 where prominent Ca entry occurs in ischemic controls, substantial and long lasting prevention of Ca influx through the NMDA ion channel by systemically administered GGS results in protection from ischemia.

ELASTIN AND TYPE III COLLAGEN FIBERS IN THE CEREBRAL ARTERIES OF PATIENTS WITH INTRACRANIAL ANEURYSMS

Douglas Chyatte, Colleen Brophy, Jeffrey Reilly, M. David Yao, Univ Texas Med School, Houston, TX

Elastin and reticular fibers were identified using standard histologic stains and type III collagen fibers were identified immunohistochemically in middle cerebral arteries taken from patients who had died from subarachnoid hematomas (n=5) and control patients who did not have cerebral aneurysms (n=3). Examination of cerebral arteries from normal individuals revealed a dense network of fine reticular fibers in the arterial media that were uniformly distributed. Computerized morphometric analysis indicated that reticular fibers in the arterial media were significantly decreased in aneurysm patients (p<.01). In addition, these fibers were irregularly distributed and shortened when compared to those seen in control arteries. Changes observed in type III collagen fibers mirrored those seen in reticular fibers. In both aneurysm and control patients, elastin fibers were almost exclusively to the internal elastin lamina. No differences were observed in the appearance or content of elastin fibers in control and aneurysm patients. Although other explanations cannot be excluded, these observations are consistent with the hypothesis that "intrinsic" abnormalities in the walls of cerebral arteries lead to conditions which favor the formation and rupture of cerebral aneurysms.

PERIVASCULAR HEPARIN PREVENTS INTRATHecal PROLIFERATION IN RATS

Marc Mayberg, Don Bark, Tomohisa Okada. Department of Neurosurgery, University of Washington, Seattle, WA

Segmental endothelial desquamation of the common carotid artery was produced in 30 rats using a balloon catheter technique, and animals were treated with periadventitial application of heparin contained in a continuous release drug-delivery system using the polymer polyvinyl alcohol (PVA). At 5, 10 and 20 days after injury, there was a >50% reduction in intimal cross-sectional area and Thymidine Index (TI) in heparin/PVA-treated vessels compared to controls. Immunohistochemistry demonstrated the presence of immuno-reactive actin in the proliferating myointimal cells. Periodic vanous Proteinsin Time (PT) and Partial Thromboplastin Time (PTT) were unchanged in heparin/PVA treated animals compared to controls. Continuous-release polymer drug-delivery can be used to selectively apply heparin to the adventitial surface of vessels, and affect changes in the vessel wall over periods of up to three weeks. By this means, smooth muscle proliferation and subsequent vessel narrowing after endothelial injury were inhibited without systemic anticoagulation. This technique may be applicable to both clinical and research applications related to the pathophysiology of arterial injury.
Clinical and pathologic evaluation of focal brain ischemia after MCA occlusion in rats.

Mary K. Gumerlock and J. Charles Mace
University of Michigan, Ann Arbor, MI

Albinum extravasation in ischemic brain edema.

Stephen A. Menzies, Julian T. Hoff, A. Louis Beetz
University of Michigan, Ann Arbor, MI

Delayed opening of the blood-brain barrier (BBB) is a hallmark of ischemia. To evaluate BBB during post-ischemic reperfusion, 15 rats had bilateral carotid and pterygopalatine arteries ligated with the int. carotids occluded for 30 min followed by reperfusion for 15' and 9hrs. Evans blue (EB) 2% 2ml/kg IV and intracardiac saline perfusion, the brains were prepared for fluorescence study. Separate coronal slices had formamide EB extraction and quantitation by fluorescence spectrophotometer. Animals with 15' post-ischemic reperfusion showed bright red EB fluorescence perivascularly in and around ganglia neurons, but after 3.5 or 9hr reperfusion no fluorescence was observed. The EB content was significantly (p<0.02) higher in the 15' rats (1.4 ± 0.4 ug EB/gm brain) compared with those at 3-9hr (0.2 ± 0.8). These data demonstrate early BBB permeability to the EB-albumin complex during the first 15' of post-ischemic reperfusion and suggest a biphasic pattern of ischemic BBB opening with an intervening period of "intact BBB".

Albinum extravasation in ischemic brain edema.

Stephen A. Menzies, Julian T. Hoff, A. Louis Beetz
University of Michigan, Ann Arbor, MI

The time course (between 1 and 42 days) of changes in blood-brain barrier (BBB) permeability and albumin extravasation were examined in relation to the formation and resolution of ischemic brain edema in 97 rats with middle cerebral artery (MCA) occlusion. Measurements were made on a core of tissue centered on the MCA, and compared to similar samples from the non-ischemic hemisphere. BBB permeability (PS product) to H(1)-amino-3-3-hydroxybutyric acid (AIB) was significantly increased in the ischemic cortex compared to non-ischemic or sham cortices between 1 and 14 days. Peak permeability of 2.2 times the baseline was reached on the third day (p=0.05 paired t-test) which was maintained until day 14. No significant differences were found at or after 21 days.

On the same animals, the amount of albumin in brain tissue was quantitated by an enzyme-based immunologic technique. Brain albumin increased significantly from a baseline of 60-113 ug/g wet tissue to 1273 (1090-1449) ug/g during the first day, reached a peak on the 3rd day at 1974 (1316-2593) ug/g (p<0.001 paired t-test) then gradually declined until day 21. The baseline value was almost reached by the 28th day (18-129) ug/g. At its peak, brain albumin was about 25% of plasma albumin (10162 ug/ml).

Both PS product and albumin measurements were closely related to the severity of the stroke determined clinically and pathologically. Extravasation of plasma albumin plays a major role in the development and resolution of ischemic brain edema.

Memory loss following transient forebrain ischemia in the gerbil.

Dudley F. Fleeter and Robert B. Smith
University of Mississippi Medical Center
Jackson, MS

The gerbil model of transient forebrain ischemia has been extended to include behavioral sequelae. Gerbils underwent 5-7 min bilateral carotid (N=16) or sham (N=9) occlusion. Ischemia which produced severe bilateral loss of CA1 hippocampal cells led to significantly more re-entries in a radial arm maze (p=0.05). Total CAI loss disrupts memory processes required for short-term (within session) problem solving, but appears to have little effect upon previously acquired information which remains constant between test sessions. With more severe damage, both types of memory may be affected. Interventions which may provide even limited protection may be therapeutic if administered at the appropriate time and dose. This model currently is being used to explore these parameters.
MEDIAL GENICULATE DAMAGE in TRANSIENT FOREBRAIN ISCHEMIA

Histological damage in the cortex, striatum, hippocampus, lateral reticular nucleus of the thalamus and substantia nigra reticulata have been reported in animals after transient forebrain ischemia. Using silver degeneration staining, we found frequent fiber damage in the medial geniculate nucleus (MGN). Sixty-four rats underwent 10 minutes of bilateral carotid artery occlusion and hypotension. MGN damage was usually in fibers, but cell bodies were injured in 2 animals. As with hippocampal damage, MGN damage was delayed in onset with damage in 3 of 24 hemispheres (12.5%) at 24 hours after ischemia and 30 of 68 hemispheres (44%) at 7 days (P=.02; Fisher's exact test). These findings may reflect delayed axonal damage in fibers projecting to the MGN from other brain regions such as the inferior colliculus or auditory cortex. The different characteristics of selective neuronal damage in various brain regions suggest different underlying mechanisms.

EFFECTS OF EXCITATORY AMINO ACIDS ON BRAIN CALCIUM AND HISTOLOGY

The effect of N-methyl-D-aspartate (NMDA) and the NMDA receptor antagonist MK-801 on NMDA induced phenomena were investigated in 9 cats using fluorometric method for the measurement of [Ca$^{2+}$]. Superfusion of the exposed cortex with 50μM NMDA for 1 hour induced a significant elevation of the [Ca$^{2+}$] signal ratio (400/506nm) from 1.41±0.01 to 1.63±0.07 30 minutes after superfusion (P<0.01). The EEG amplitude was abruptly depressed to 24.3±4.0(%) 2 min after superfusion and gradually recovered to 63.5±8.4% by 30 minutes. Histopathological changes 3 hours later showed an intense inflammatory response in the subarachnoid space with infiltration of superficial neuropil. Neurons of layers 1-3 were chromatolytic or shrunken with pyknotic nuclei. When NMDA was superfused following treatment with MK-801 (2mg/kg i.v.), the [Ca$^{2+}$] change and the EEG alterations were almost completely blocked, the inflammatory response was blunted and neuronal injury was reduced. These data show that NMDA can cause neuronal damage, which may be due to increased [Ca$^{2+}$], and is blocked by an NMDA antagonist.
ALLOPURINOL AFFECTS LEUKOCYTE FILTERABILITY IN ACUTE CEREBRAL INFARCTION

M Mercori, G Cuffetti, G Alia, R Lombardini, D Recullini, U Semio, A Ventura. II Dept of Internal Medicine, University of Perugia, ITALY

The purpose of this study was to ascertain the nature of calcium and vascular permeability changes in cerebral ischemia and traumatic brain injury. Gerbils in groups of 10 were subjected to repeated carotid occlusions and to cryogenic injury of the cortex. Calcium was evaluated with autoradiography and by E.M. studies. The blood-brain barrier (BBB) was assessed by immunostaining for albumin. In repeated ischemia regional Ca accumulations were observed after several days. In cryogenic lesions foci of abnormal calcium uptake appeared in thalamos or bilaterally in hippocampi. Generally, Ca accumulation was associated with BBB dysfunction. EM observations revealed pattern of calcium uptake in dendritic structures, similar to that in convulsions associated with calcium accumulation. Our studies suggest possible involvement of transneuronal neuroexcitatory mechanisms in the final outcome of the post-ischemic and post-traumatic lesions.

SELECTIVE INCREASES IN HEAT SHOCK PROTEIN (HSP 70) GEN EXPRESSION DURING ISCHEMIA REPERFUSION

Koji Abe, Yoshihiko Uemura, Chaker Adra, Rudolph Tanzi, James Gusella, Michael Moskowitz. Massachusetts General Hospital, Boston, MA.

HSP 70 increases in ischemic brain and during other stressful conditions. Changes in mRNA were examined by Northern blots prepared from gerbil (n=70) hippocampus (CA1 and CA3) and parietal cortex following 10 minutes of ischemia and 1,4,8,24h,2,7 days reperfusion, using probes directed against HSP 70, tubulin (T) or amyloid precursor protein (APP). Our preliminary data indicate that T or APP expression do not change. However, HSP 70 expression increases in the 3 regions at 1 hr after reperfusion and sustains for as long as 2 days. These data suggest the importance of transcriptional mechanisms (selective mRNA synthesis) in the adaptive responses of brain cells to cerebral ischemia and indicate a potential role for this protein in stroke pathophysiology.

EFFECT OF FENTANYL ON RECOVERY FOLLOWING POST-ISCHEMIC CEREBRAL INJURY

Usha S. Vasthare, Sharon Rubin, Lynn A. Heinel, Robert H. Rosenwasser, Ronald F. Tuma Temple Univ. School of Medicine, Philadelphia, PA

The purpose of this investigation was to study the effect of fentanyl (δ opioid agonist) on recovery following cerebral ischemia in rats. A comparison was made of neurophysiological changes (SSEP) following transient, incomplete cerebral ischemia between a group of 6 rats anesthetized with a low dose of fentanyl (150ug/Kg) and 6 rats anesthetized with a high dose of fentanyl (100ug/Kg). Cerebral ischemia was produced by bilateral carotid occlusion and reduction of mean blood pressure to 50mm/Hg. There was no EEG/SSEP during ischemia in both groups. The SSEP was present in all of the animals anesthetized with lower dose of fentanyl 60 min. after reperfusion. However, in the rats anesthetized with higher dose of fentanyl, the cortical peak was absent at 60 min. and 120 min. after reperfusion. The results of this study indicate that the use of high doses of fentanyl exacerbates the damage caused during ischemia and reperfusion.
A CHLORIDE TRANSPORT INHIBITOR AMELIORATES FOCAL ISCHEMIA IN A RABBIT MODEL

James J. Kohut, Martin Bednar, Cordell Gross, Harold K. Kimelberg, Albany Medical College, Albany, NY

L644,711, a non-diuretic derivative of ethacrynic acid, has been shown to reduce astrocyte swelling in vitro and in a cat model of head trauma, putatively by blocking bicarbonate/chloride transport. Five rabbits were pretreated with 12mg/kg of L644,711 and 5 controls were given saline. Both groups were then embolized with a 5cm, aged autologous thrombus, followed by 45 min of hypotension. After 3 h the animals were sacrificed. In the treated group, infarct size was 16.0 ± 8.5% of the brain and intracranial pressure (ICP) at 3 h was 94.4 ± 52% of baseline. In the untreated group, infarct was 30.9 ± 11% and ICP was 235 ± 137%. The reductions in both ICP and infarct size were statistically significant (p<.05, students t-test). Thus L644,711, a drug known to reduce astrocyte swelling by blocking anion transport, appears to reduce infarct size and ICP in a rabbit model of focal ischemia.

RELATIONSHIP BETWEEN GLUCOSE, LACTATE AND pH IN CEREBRAL ISCHEMIA

David J. Combs, Robert J. Dempsey, Mary Maley, David Donaldson, Charles Smith. University of Kentucky Medical Center, Lexington, KY

The relationships between plasma glucose (GLU), brain lactate (LAC) and intracellular pH (pHi) before and during severe cerebral ischemia were studied in 86 anesthetized gerbils over a wide range of plasma glucose levels. Measurement of pHi was done using P-31 NMR spectroscopy. Ischemia increased final LAC linearly 4 μmol/g per 100 mg/dl increase in GLU up to 650 mg/dl (p<0.0001, R² = 0.9); beyond 650 mg/dl, saturation of the glucose transport/glycolysis system occurred. By simple linear regression, GLU (p=0.0002, R²=0.62) correlated better with ischemic pHi than LAC (p=0.002, R²=0.46). However, LAC vs. pHi during ischemia may be a threshold, rather than linear, relationship. Ischemic pHi decreased to 6.8-6.9 in gerbils with LAC<17 μmol/g. When LAC increased from 17 to 22 μmol/g, pHi decreased sharply to about 6.2. No further decrease in pHi was observed at LAC>22 μmol/g. The marked decrease in ischemic pHi when LAC>17 nmol/g suggests that this sudden drop in pHi may account for the "lactate threshold" for increased cerebral ischemic damage.

CHRONIC INTRACELLULAR pH AS A FUNCTION OF ISCHEMIC INSULT IN THE RAT

Michael Chopp, Ana Vande Linde, Hua Chen, K.M.A. Welch
Henry Ford Hospital, Detroit, MI

Brain intracellular pH (pHi) was measured using in vivo 31P NMR spectroscopy, in a forebrain model ischemia of 8 (n=9) and 12 (n=7) minute duration and in sham (n=10) operated rats. pHi was measured prior to ischemia, and at 24, 48, 72, 96 hrs and 1 week after ischemia. The 8 and 12 minute ischemia groups exhibited significant increases in pH (p<0.003) above baseline. Mean maximum pH was 7.34±0.06, 7.38±0.14, and 7.16±0.06 for the 8 and 12 min. and sham groups, respectively. Baseline pHi for all groups was 7.07±0.04. A significant difference in the time course of pHi between groups was detected (p<0.04) using repeated measures analyses of variance. pHi and specific gravity measurements were also performed on control (n=7) and post ischemic animals, 24 hrs (n=4), 72 hrs (n=4) and 1 week (n=3). Conclusions 1) significant pHi increase 1-3 days after ischemia 2) pH profile over time reflects the degree of ischemia 3) no correlation between edema and pHi.

70 KDa STRESS PROTEIN mRNA IS INDUCED IN HIPPOCAMPAL CA1 NEURONS AFTER ISCHEMIA -- IN SITU HYBRIDIZATION ANALYSIS

Thaddeus S. Nowak, Jr., Laboratory of Neuropathology and Neuroanatomical Sciences, NINDS, NIH, Bethesda, MD

The time course of induction and distribution of mRNA encoding the 70 KDa stress / heat shock protein, hsp70, was evaluated in postischemic gerbil brain by in situ hybridization. Animals (n=48) were subjected to 5 min ischemia and recirculation for 3 h to 7 d. Hsp70 sequences were evident in all major hippocampal neuron populations within 3 to 6 h. Expression was transient (12-24 h) in dentate granule cells and CA3 neurons known to accumulate immunoreactive hsp70 protein. In contrast strong hybridization persisted through at least 48 h in CA1 neurons which fail to express the protein. Pretreatment with MK-801 (10 mg/kg) attenuated the early induction of hsp70 mRNA, but failed to prevent either its later expression in CA1 or the loss of these neurons. These results strengthen the link between hsp70 mRNA induction and proposed excitotoxic mechanisms of postischemic cell death.
GABA HOMEOSTASIS DURING ANOXIA AND ISCHEMIA IN VITRO

David Lust, Boğdan Djuricic1, Husein Assaf, Lester Drewes1, Linda Sternau and Robert Ratcheson. Div. of Neurosurgery, Case Western Reserve Univ., Cleveland, OH and 1 Dept. of Biochemistry, Univ. of Minnesota, Duluth, MN.

Glutamate toxicity has been implicated in delayed neuronal death (DND) after ischemia (I). Recently, Sternau et al. (Stroke, 1989) proposed that excess glutamate release is due to a down-regulation of GABA receptors elicited by extracellular GABA (G) during I. Since anoxia (A) does not cause DND, we examined the G response to determine if it differed between the 2 metabolic stresses. Slices (n=6/group) were incubated for 30 min in A and I media, and tissue (7.44 mmol/mg pr) and medium (2.72 mmol/mg pr) G was determined by HPLC. There was a significant (p<0.05) 2-fold increase in total G in both groups. The compartmental fate of accumulated G, however, differed between the 2 groups. Tissue G increased 2-fold in A, whereas it was unchanged after I. In contrast, medium G increased 7-fold during I, but only by 50% during A. Blocking G uptake with Nipecotic acid only affected medium G during A. The results indicate that the production of G was similar in A and I, but that the uptake system was perturbed by I, consistent with the concept that extracellular G may be a trigger to DND observed after I, but not after A.

AGE RELATED DIFFERENCES OF CO2 BLOOD FLOW RESPONSE AFTER COMPLETE CEREBRAL ISCHEMIA

M. Helfaer, S. Haun, J. Kirsch, R.C. Koehler, R.J. Traystman. Johns Hopkins University of Medicine, Baltimore, MD.

We tested if 1-2 wk (YOUNG) and 6-10 mo old pigs (OLD) had different cerebral vascular reactivity following complete ischemia. Pigs (n=7 for each group) were exposed to a Pco2 of approximately 25, 40, and 60 mmHg in random order prior to ischemia or following 60 or 120 min of reperfusion. Cerebral blood flow (CBF) was measured with microspheres. Ischemia (10min) was produced by aortic cross clamp. Reactivity was defined as ΔCBF/ΔPaco2 from Paco2 of 40 to 25 mmHg (LO) or 40 to 60 mmHg (HI). Results for forebrain (ml/min/100g/umHgSEM) are for:

YOUNG(LO/Hi)  OLD(LO/Hi)
CONTROL  5.2±2.2  5.2±2.4
REPERFUSION  60 min  1.1±1.3  1.4±2.3  3.2±2
120 min  1.2±2.5  2.5±2  5.2±2.8  1.5±1.3  5.5

We conclude, that OLD have quicker return of CO2 responsivity after complete ischemia as compared to YOUNG.

BLOOD FLOW AND EXTRACELLULAR POTASSIUM CONCENTRATION IN FOCAL CEREBRAL ISCHEMIA

Gerald P. Schielke and A. Lorris Betz
University of Michigan, Ann Arbor, MI

The relationship between brain extracellular fluid potassium concentration ([k+]e) and CBF was determined in rats under Ketamine/Rompun anesthesia after middle cerebral artery occlusion (MCAO). CBF was measured using the H2 clearance and [k+]e with ion selective micro-electrodes in 6 defined regions 1.5-2.5 hr. after MCAO. After sacrifice, electrocorticography was examined and the brains stained with triphenyl-tetrachloride (TTC) to identify lesioned areas. In regions where CBF was severely reduced (<10ml/100g/min, n=12), [k+]e was increased to 25.0 ± 12.8 mM. In regions with CBF between 10-20 ml/100g/min, (n=8), [k+]e was 14.3 ± 3.5 mM. TTC staining was absent at sites where CBF was <20ml/100g/min. In 10 of 14 ipsilateral regions with CBF between 20 and 50ml/100g/min, [k+]e was 4 mM (mean 6.8 ± 4.8, n=14). This was significantly elevated (p<0.02) compared to the sham operated animals which had [k+]e values of 3.2 ± 0.4 and CBF of 36.9 ± 13.4. TTC staining was present in the majority of these sites. We conclude that in focal ischemia, ion homeostatic mechanisms may be altered in areas with mild reduction in CBF.
Hyperglycemia can enhance ischemic brain injury. We studied the effect of moderate hyperglycemia on ischemic brain production of adenosine, a putative endogenous neuroprotector. Adult Sprague-Dawley rats (n=24) were either treated with 17% D-glucose (3 gm/kg) or normal saline i.p., 10 min prior to the onset of ischemia. Global incomplete ischemia was induced by bilateral carotid occlusion along with systemic hypotension to 50 mmHg for 15 min. Brain tissue was then sampled by the freeze-blow technique. HPLC analysis of adenosine, inosine, and hypoxanthine revealed significant decreases in ischemic production of these purine metabolites in the hyperglycemic animals (p < 0.01). Ischemic brain adenosine concentration was 270±37 nmoles/gm in the control group compared to 101±17 nmoles/gm in the hyperglycemic group (p < 0.005). We propose that altered ischemic adenosine production due to hyperglycemia may effect the pathogenesis of hyperglycemic ischemic brain injury.

CHARACTERISTICS OF FLOW IN THE ANTERIOR PORTION OF THE CIRCLE OF WILLIS IN PATIENTS WITH ANTERIOR COMMUNICATING ARTERY ANEURYSMS (ACA). Sean S. Hsu, Joseph R. Meno, H.R.Winn University of Washington, Seattle, WA

In order to identify a relationship between certain angiographic patterns of flow, ACA, and their clinical features we compared the angiograms of 51 patients with ACA to 50 matched controls. Exclusive filling of the ACA from one Al occurred in 78% (40/51). A dominant Al (filling both A2's) was found in 37/51 (72%) of ACA patients versus 14% (7/50) of controls (p<.001). Unilateral hypoplasia of Al (6%) was present in 25% (9/37 patients with unruptured ACA, or SAH but no vasoospasm) vs 6% (3/50) of controls (p<.01). No statistically significant relationship was found between the flow patterns studied and age, sex, rupture, or grade at time of presentation.

A dominant AI flow and AI hypoplasia are two angiographic findings significantly related to the presence of ACA, probably as a result of enhanced hemodynamic stress caused by such flow patterns.

THE USE OF CONTINUOUS PASSIVE MOTION TO AFFECT LOWER LIMB FUNCTION FOLLOWING STROKE

Patrick D. Lyden, Herbert P. von Schroeder, Richard D. Coutts, Veterans Administration Hospital, San Diego, CA

In an effort to determine the ability of repetitive patterning to stimulate functional recovery following stroke, continuous passive motion (CPM) was applied to the paretic leg of stroke patients who were randomly assigned to study or control groups. Study patients received an average of 23 hours of CPM per day to both legs(n=4) or only their paretic leg (n=5). Control patients received either no CPM (n=8) or 15 minutes of CPM per day (n=3). Weekly assessment consisted of the patient's ability to actively reproduce the same motion as the CPM using an instrumented CPM device that measured range of motion, velocity, and acceleration. Isometric knee flexion and extension force was also measured.

Recovery of the affected limb occurred in all patient groups, but was significantly greater for most parameters in the CPM group compared to the no CPM group (ANOVA p<0.05). The CPM group also had a shorter hospitalization (t-test p<0.05) and a dose-response effect between the hours of CPM received and test performance was demonstrated. These results indicate a useful role for CPM in stroke rehabilitation and illustrate the practical application of a quantified analysis system for monitoring the effects of therapy on recovery following stroke.

NON-INVASIVE PREDICTION OF CEREBRAL VENOUS HEMOGLOBIN SATURATION

Daniel F. Hanley, Klaus Cross, Karl Norris, Marco Ferrari, David A. Wilson, and Richard J. Traystman, Balto., MD

Scanning near infrared spectroscopy (730-960 nm) was utilized to determine canine cerebral venous hemoglobin saturation (Hb %S) with an extracranial sensor. This method was compared to "in vitro" photometry of sagittal sinus (SS) blood using an IL Co-Oximeter. Spectra were obtained from 13 animals under conditions of hypoxic hypoxia (150-20 torr), hypercapnia (30-80 torr), and anemia (18-3 g/dl Hb). These stimuli produced changes of SS Hb %S from 10% to 85%. Derivative transformation of the spectra produced a calibration of SS Hb %S. For n=92 spectra a linear regression between non-invasive infrared data and CO-Oximeter was demonstrated (r=.93). This algorithm was used to predict Hb %S for an additional 98 samples of SS blood. A significant correlation (r=.92) with a bias of 2% and standard error of determination of 8.5% was obtained. These studies suggest that non-invasive determination of human cerebral hemoglobin saturation might be performed using derivative near infrared spectroscopy.
A reevaluation of TIA as a risk factor for early mortality.

George Howard, John R. Crouse, Julia L. Thomas, Greg W. Evans, Jacqueline E. Ryu, Loretta Sanders, Joni K. Brockschmidt, James F. Tooie. Bowman Gray School of Medicine, Winston Salem, NC.

Transient ischemic attack (TIA) is widely viewed as a risk factor for cerebrovascular morbidity and mortality, based on reports comparing survival of TIA patients to that of age-race-sex adjusted general populations. Because concomitant diseases (e.g., ischemic heart disease, hypertension, diabetes) occur with higher frequencies among TIA patients than in the general population, this might be an inappropriate comparison. Therefore, we compared the survival of 338 TIA patients to that of a control group with a very similar risk factor profile - 7,031 patients evaluated for cardiac catheterization. Unadjusted survival estimates did not differ between the two groups; however, after proportional hazards adjustment for age, race, sex, and concomitant diseases the survival for TIA patients was significantly better than controls (p=0.0125). Adjusted and unadjusted three-year survival estimates were:

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<tr>
<th></th>
<th>UNADJUSTED</th>
<th>ADJUSTED</th>
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<tbody>
<tr>
<td>TIA</td>
<td>88.4%</td>
<td>94.2%</td>
</tr>
<tr>
<td>CONTROLS</td>
<td>88.8%</td>
<td>90.1%</td>
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These results suggest that TIA per se is not a risk factor for mortality, although it may identify patients at increased risk from coexisting conditions.

A phenotype of the complement C3 (C3F) has been shown to be a risk factor for cardiac disease and hypertension. We performed a case-control study in order to test whether C3F is a risk factor for stroke. 97 patients recruited over a 12 month period were matched by age and sex to randomly selected community controls. The C3 phenotype (C3SS vs C3SF and C3FF) were assessed by electrophoresis. Statistical analysis with the McNemar’s test for matched samples showed that C3F is not a risk factor for stroke. The unadjusted relative odds for the presence of C3F among cases was 1.2 (95% confidence interval: 0.6, 2.1), while the relative odds adjusted for history of hypertension, coronary heart disease, diabetes and smoking was 1.3 (95% confidence interval: 0.6, 2.7). A subgroup analysis for men or women only or atherothrombotic strokes of all other types was also negative.

We conclude that C3F is not a risk factor for stroke.

Cerebral aneurysms are a rare occurrence in sickle cell anemia (SCA). We present 14 patients with SCA and subarachnoid hemorrhage from ruptured cerebral aneurysms. There was a high incidence of multiple aneurysms - 57.1% (8 of 14), and some of these were in unusual locations. Twelve patients underwent craniotomy. We propose that endothelial injury from the abnormal adherence of sickle erythrocytes is the initiating event in arterial injury. There is subsequent fragmentation of the internal elastic lamina and degeneration of the smooth muscle layer. Hemodynamic at these sites of arterial damage results in aneurysm formation and hemorrhage. We present our pathological material and data from the literature to support our hypothesis. These findings have provided a paradigm for acquired aneurysm formation that may be applicable to other intracranial aneurysms.
Vascular malformations of the brain stem are an historically heterogeneous collection of lesions which most often present with sudden and progressive neurologic deficit in young adults. The authors have treated eleven patients with brain stem malformations. Seven of the patients were treated with complete surgical extraposition of the malformation because of recurrent hemorrhage. Four additional patients made a full neurologic recovery and are being carefully observed for signs suggestive of the need for surgical treatment.

These malformations are accurately diagnosed by magnetic resonance imaging. They have a characteristic morphologic appearance which differentiates them from other diagnostic possibilities. All seven operated patients have returned to their previous occupations. For patients with progressive neurologic deficit secondary to recurrent hemorrhage complete surgical excision is mandatory.

Recent clinical studies emphasize very early treatment (<12 hrs) of patients (pts) with acute ischemic stroke (AIS). However, the rate of spontaneous improvement in such pts is unknown. We prospectively evaluated the course of 23 pts (15 M, 8 W) aged 33-82 who were seen within 12 hrs of AIS. Fourteen pts were first seen within 6 hrs and the remaining between 6-12 hrs. All pts were examined using a modified NIH Stroke Scale at baseline, 1 hr, 2 hrs, 3 hrs and 6 hrs. No specific treatment was given. Improvement (as defined by 2 or more points change from baseline score) was noted within 1 hr in 7 pts (30%). By 6 hrs, 13 pts (56%) had improved, 8 (35%) were unchanged and 2 (9%) were worse. These results prove that spontaneous, often dramatic improvement occurs with AIS, and should be taken into consideration in the design of any acute treatment trial.

This study consists of microscopic dissection via an eyebrow incision in cadavers to expose the anterior cerebral circulation. A lateral eyebrow incision provides adequate exposure to the MCA at its main branchings without brain retraction and allows preservation of the supraorbital branch of V and frontotemporal branches of VII. The craniotomy incorporates removal of the orbital rim and roof with portions of the temporal bone and sphenoid ridge. Widening the eyebrow incision medially allows exposure of anterior communicating aneurysms without resection of the gyrus rectus. This latter approach has been performed in 3 patients. This incision requires crossing one or both the aforementioned nerves. However in all operated patients there was eventual recovery and a satisfactory cosmetic results.

We conclude that an eyebrow incision provides adequate exposure for an orbito-cranial approach to some anterior circulation aneurysms.
PRE-SIGMOID, TENTORIUM-SPLITTING APPROACH GIVES GOOD EXPOSURE TO VERTEBRO-BASILAR ANEURYSMS WITHOUT SACRIFICE OF LATERAL SINUS OR HEARING

Robert M. Crowell, Arvind Kumar, Robert Gettleman, University of IL, Chicago, IL

To avoid lateral sinus division, Samii has recently described a pre-sigmoid tentorium-splitting approach for petro-clival tumors. We have successfully applied this approach for clipping of 3 vertebro-basilar aneurysms.

A postero-inferior temporal craniotomy and lateral suboccipital craniectomy are performed. Next the otoneurologist carries out radical mastoidectomy with sparing of the cochlea and semicircular canals. The dura is incised antero-lateral to the sigmoid sinus, across the coagulated superior petrosal sinus, and above the lateral sinus medially. The cerebellum and temporal lobe are retracted medially and the tentorium is divided. The vertebro-basilar aneurysm is dissected and obliterated. The dura is closed watertight with a pericranial graft.

In 3 cases we noted 1) superb exposure of the vertebo-basilar complex from PICA origin to SCA origin, 2) preservation of lateral sinus, 3) preservation of hearing, 4) absence of cerebro-spinal fluid leakage, and 5) satisfactory operative time.

SURGICAL EXPERIENCE WITH INTRACEREBRAL HEMORRHAGE SECONDARY TO CEREBRAL AMYLOID ANGIOPATHY

George M. Greene, John C. Godersky, Jose' Biller, Michael N. Hart, Harold P. Adams, Jr. University of Iowa, Iowa City, IA

Cerebral amyloid angiopathy (CAA) often presents as a lobar intracerebral hemorrhage (ICH) in elderly persons. We evaluated 11 patients (pts) since 1983 with CAA and ICH. Nine women and 2 men (mean age 73 years) experienced either a spontaneous ICH (3), or an ICH following a minor fall (5) or major trauma (1). Two were demented and 4 were receiving anti-thrombotic medications. The ICH was unilateral in 3 pts and multilobar in 8, involving the parietal (8), frontal (6), temporal (5), and occipital (3) lobes. Nine pts underwent ICH removal with no cases of abnormal bleeding or recurrent ICH. Six pts improved neurologically and 2 were unchanged after ICH evacuation; 1 pt had a fatal cardiopulmonary arrest post-operatively. The 2 pts treated non-operatively died prior to correction of underlying bleeding diatheses. During follow-up (mean 23 months, range 1 week to 74 months, n=7) no pt experienced a recurrent ICH and 4 continued to improve neurologically. This series suggests that pts with CAA may safely undergo ICH removal.

SURGICAL TREATMENT OF VERTEBRO-BASILAR INSUFFICIENCY DUE TO NON-SPECIFIC AORTO-ARTERITIS (TAKAYASU'S ARTERITIS)

Vachtang Pipia, Givi Tsitsuashvlli. Research Inst. of Surgery, Tbilisi, Georgia, U.S.S.R.

The most frequent type of nonspecific aorto-arteritis (NAA) involves the supra-aortic trunks, leading to reversed flow in the vertebral artery (subclavian steal syndrome - (SSS). Among 85 patients NAA was symptomatic in 17 (20%) cases. 13 females aged 21-39 years had occlusion (9 cases) or severe stenosis (4 cases) of the proximal subclavian artery; the vertebral arteries were intact. The duration of symptoms ranged from 4 to 7 years. All had an absent radial pulse, angiography typical of SSS, and 50% had vertebro-basilar TIAs. In 9 cases a carotid-subclavian bypass and in 4 cases a percutaneous transluminal angioplasty were performed. In all cases the radial pulse was restored, and the TIAs and brachial ischemia disappeared. Follow up ranged from 6 to 18 months. Surgery and balloon dilation are effective treatments of localized occlusion of the subclavian artery.

SESSION IV
Friday, February 16
6:45-7:45 AM

Breakfast Seminar:
New therapies in the treatment of cerebral vasospasm

Chairmen:
Robert R. Smith, Jackson, MS
Marc R. Mayberg, Seattle, WA

6:45 Thrombolytic therapy and clot removal
Max Findlay, Edmonton, Alberta, Canada

6:55 Calcium channel blockers
E. Clarke Haley Jr., Charlottesville, VA

7:05 Anti-inflammatory agents
Douglas Chyatte, New Haven, CT

7:15 Angioplasty
Joe Eskridge, Seattle, WA

7:30 Discussion

7:45 Recess
**Ativoventricular malformations and aneurysms**

Chairmen: 
Roberto Heros, Minneapolis, MN  
Gary G. Ferguson, London, Ontario, Canada

A REVIEW OF THE HELSINKI ARTERIOVENOUS MALFORMATION NATURAL HISTORY STUDY AND ITS IMPLICATIONS FOR SURGICAL THERAPY

Stephan L. Ondra, Eugene D. George, Henry Troupp, Neurosurgery Service, Walter Reed Army Medical Center, Washington, DC

This report updates a series of 166 prospectively followed symptomatic unoperated patients with cerebral arteriovenous malformations (AVM). Mean follow-up was 23.7 years. Data was obtained on 96% of the original population.

71% (119 of 168) presented with hemorrhage, 24% (41 of 168) with seizure, and 5% (8 of 168) with other symptoms.

The yearly bleed rate was 4%. The mortality rate was 1%. There was a combined severe morbidity and mortality rate of 2.7% per year. These values were the same in all presenting groups and remained constant over the entire length of study. By the end of the study 23% of the patients were dead of AVM hemorrhage.

Additional comments will be made regarding the timing of the first bleed and the severity of these.

**NATURAL HISTORY OF CAVERNOUS ANGIOMA**

John R. Robinson, John R. Little, Issam Awad. Cleveland Clinic, Cleveland, OH.

The objective was to determine the natural history of cavernous angiomas (CA) of the brain. Reports of magnetic resonance (MR) studies (13,000) performed over a 6 year period were reviewed for suspected CA. Seventy-one lesions with a typical MR appearance of a CA were identified in 62 patients (1 lesion incidence rate of 0.51%). Parenchymal hemorrhage associated with a CA was found in 5. Mean age was 34 years and male/female ratio was 34/28. The CA's were supratentorial in 82%. Eight CA's were in the brainstem. Clinical presentation included seizures in 55%, headaches in 29% and focal neurologic deficit in 18%. The CA was asymptomatic in 16%. Follow-up (cumulative survey of 110 lesion years) revealed continuing symptoms in 40%. Hemorrhage occurred in 8% (1e annualized bleed rate of 0.07% per year). All hemorrhages occurred in patients under 35 years. Hemorrhage in central regions or brainstem were associated with the most severe neurologic deficits. A therapeutic paradigm has been developed based on this data.

**SURGICAL MANAGEMENT OF CAVERNOUS MALFORMATIONS OF THE BRAIN STEM**

K. Stuart Lee, Robert F. Spetzler  
Barrow Neurological Institute  
Phoenix, AZ

A significant number of symptomatic cavernous malformations (CM) or angiomas occur in the brain stem; the management of these lesions is controversial. Nine patients (7 females, 2 males; mean age 32 years) had surgery for CMs of the brain stem at our institution from May, 1985-May, 1989. Indications for surgery were brain stem hemorrhage in 7 patients and progressive neurological dysfunction in 2 patients. Lesions were located in the medulla in 5 patients, the pons in 2 patients, and the midbrain in 2 patients. Gross total removal of the CM was accomplished in 8 cases, and approximately 90% resection was performed in 1 case. Three patients had transiently increased neurologic deficits postoperatively. Length of follow-up ranged from 3 to 46 months (median 7 months). All patients are ambulatory with relatively mild or no deficits. The results of this series indicate that many symptomatic CMs of the brain stem can be managed surgically.

ANGIOGRAPHIC PREDICTORS FOR HEMORRHAGE AND STEAL SYMPTOMS IN INTRACEREBRAL ARTERIOVENOUS MALFORMATIONS. Gary K. Steinberg, Michael P. Marks, Barton Lane, Paul Chang, Stanford University Medical Center, Stanford, CA

Sixty-five patients with high-flow intracerebral arteriovenous malformations (AVMs) seen at Stanford between 1984 and 1988 were retrospectively analyzed in an effort to delineate key features of the AVM architecture that correlate with a history of hemorrhage or symptoms of vascular steal. Biplane angiography was obtained on all patients and compared with MRI (46 cases) or CT (19 cases). Characteristics for analysis included: location, size, periventricular or intraventricular location, feeding vessel aneurysm, remote vascular territory aneurysm, intranidus aneurysm, arterial stenosis, A-V fistula, anomalous arterial supply via dilated collateral vessels (angiomatous change), venous drainage pattern, venous stenosis, venous variation, delayed venous drainage, and venous ectasia or aneurysm. Forty-five patients (69%) had a history of clinical hemorrhage (verified by CT, MRI or LP). Eight patients (12%) had symptoms of gradually progressive neurological deficit, characteristic of steal.

A history of hemorrhage was strongly correlated (Chi^2) with: central venous drainage (p=.0001), periventricular or intraventricular location (p=.0004) and intranidus aneurysm (p=.0310). Angiomatous change was negatively correlated with hemorrhage (p=.0001). Multivariate discriminant analysis showed three characteristics to be most predictive of hemorrhage: central venous drainage, angiomatous change (negatively predictive) and intranidus aneurysm. Using these variables hemorrhage was correctly predicted in 35 of 45 cases, with a false negative rate of 15% and a false positive rate of 0%. Symptoms of steal were highly correlated with angiomatous change (p=.001).

Certain features of AVM vascular architecture strongly correlate with clinical hemorrhage and steal symptoms. These characteristics may have important prognostic implications in predicting the natural history for some patients.

Angiographically occult vascular malformations (AOVMs) of the brain, including low-flow arteriovenous malformations and cavernous angiomas, can cause significant morbidity and mortality, particularly when located in a deep brain region such as the brainstem, thalamus, or basal ganglia. Since 1983 we have treated 35 patients with surgically inaccessible, symptomatic AOVMs using stereotactic heavy-charged-particle radiosurgery at the Lawrence-Berkeley Laboratory Synchro-cyclotron and Bevatron. AOVMs were located in the brainstem (19), thalamus or internal capsule (9), basal ganglia (3), deep cerebral hemisphere and motor area (3), or cerebellopontine angle (1). All patients presented with clinical and radiologic evidence of previous hemorrhage, usually with multiple episodes of hemorrhage. Treatment volumes ranged from 80 to 15,200 mm3 and treatment doses from 7.7 to 34.6 Gy.

Mean follow-up was 34.6 months, with 31 patients followed for at least one year and 22 patients for at least two years. Clinical outcome at last follow-up was excellent 45%, good 32%, poor 16%, and dead 7%. Twenty-four patients in excellent or good condition prior to treatment remained stable or improved neurologically. Three patients initially in good condition worsened after treatment. Two patients initially in poor condition who had previously received conventional radiotherapy died 9 and 14 months after treatment. Six patients experienced recurrent hemorrhage 2-19 months following treatment. Four patients worsened from probable radiation-induced injury, 1-2 months after treatment; 2 of these patients made a complete recovery.

Although a larger number of treated patients must be followed over longer periods of time, stereotactic heavy particle radiotherapy may be a valuable treatment modality for surgically inaccessible intracranial AOVMs.

DOES VASOSPASM OCCUR IN SMALL PIAL ARTERIES?

Hiroshi Nihei, Neal F. Kassell, Douglas A. Dougherty, University of Virginia, Charlottesville, VA

Brainstem pial arteries from 15 perfusion-fixed rabbits (3 groups: control, experimental subarachnoid hemorrhage [SAH], or intracerebral injection of 10-5M/kg BaCl2) were analyzed morphologically. BaCl2 caused severe constriction of both basilar and small arteries, strongly suggesting that all arteries, regardless of size, have enough contractility for the corrugation of internal elastic lamina to be detected. After SAH all basilar arteries had highly corrugated internal elastic laminae and were constricted 34% of control (318±76 of 91±25 μm). However, small pial arteries did not show any vasoconstrictive configuration. Cerebral arteries of monkeys and rats after experimental SAH were reviewed, and only major conducting arteries were observed to be constricted. It is concluded that vasospasm after SAH tends to occur in large conducting arteries rather than small pial arteries. In other words, vasospasm might be size-dependent.

CEREBRAL BLOOD FLOW CHANGES AFTER SUBARACHNOID HEMORRHAGE IN THE RAT

Abraham Kader, William E. Krauss, Stephen T. Onesti, J. Paul Elliott, Robert A. Solomon, Columbia University, New York, NY

SAH was induced in adult male Wistar rats by transclival basilar artery puncture. Telencephalic blood flow (TBF) was measured in 24 rats, 23 sham operated rats and 10 controls using a 14C-butanol indicator fractionation technique. TBF was significantly reduced in SAH rats as compared to sham operated animals at 3 days (TBF of 78.7 ± 6.9 and 112.0 ± 8.5 ml/min - 100 gm respectively, P<0.01), 7 days (TBF of 74.9 ± 5.1 and 112.6 ± 4.6 ml/min - 100 gm, P<0.001) and 14 days (TBF of 81.9 ± 6.0 and 104.1 ± 5.4 ml/min -100 gm, P<0.01). Intracranial pressure was normal at 3 and 7 days after surgery. Histologically, there was evidence of cerebral vasculopathy or ischemia 7 and 14 days after SAH.

The basilar artery puncture method of SAH has advantages over other rat models: vessel wall injury, extensive blood clot formation in the basal cisterns and documented chronic changes in TBF.
Dilazep dihydrochloride (DD), a strong vasodilator which has a Ca^2+ blocking and an adenosine agonistic effect, was investigated for its effect on vasospasm. Eighteen New Zealand white rabbits (3-4 kg) were intracisternally injected with 5 ml of autologous non-heparinized blood, and sacrificed 2 days later. Half of the hemorrhaged rabbits were treated intravenously with 3 mg/kg of DD for 1 hr immediately before sacrifice. All rabbits, as well as 9 normal rabbits serving as a control group, were cardiac perfusion-fixed. The basilar arteries were embedded in Epon, stained with 0.5% toluidine blue, and morphometrically analyzed by an image analyzer. The mean diameter of the control group was 637±25 μm, while that of the non-treated hemorrhage group was 394±42 μm. The average diameter of the DD-treated hemorrhage group was 517±38 μm, which was significantly larger (p<0.05) than that of the non-treated group. Considering that these animals treated for only one hour showed a significant amelioration, continuous administration of DD could be an antivasospasm treatment.

EFFECTS OF MULTI-DOSE 21-AMINO-STEROID U74006F ADMINISTRATION ON CHRONIC CEREBRAL VASOSPASM IN PRIMATES

Kenji Kanamaru, Bryce K.A. Weir, Michael G. Grace. University of Alberta, Edmonton, Canada

The 21-aminosteroid U74006F is effective in preventing chronic cerebral vasospasm (VSP). We investigated the efficacy of U74006F using a dosage regimen design in a restricted, randomized, placebo-controlled trial. Forty monkeys were divided into 5 groups of 8: saline, vehicle, 0.3 mg/kg, 1.0 mg/kg and 3.0 mg/kg U74006F-treated groups. Each monkey underwent baseline cerebral angiography followed by right-sided craniotomy and subarachnoid clot placement around the middle cerebral artery. The drug was injected intravenously every 8 hours for 6 days. On day 7 angiography was repeated and animals were sacrificed. In the saline and vehicle groups significant VSP occurred in the middle cerebral arteries (P<0.01). VSP was significantly attenuated in the middle cerebral arteries of U74006F-treated groups (P<0.05).

HEART DISEASE AS A POTENTIAL CAUSE OF STROKE


Data concerning cardiac disease was abstracted from the medical records of all cases of first cerebral infarction in Rochester, MN, 1960-1984. Of 1382 cases, 318 (23%) had at least one major potential cardiac source of emboli (CSE). Lone atrial fibrillation/flutter was associated with 10% of cerebral infarcts. The average annual incidence rates of cerebral infarction with CSE did not change significantly from 1960-64 to 1980-84, despite a significant decline in incidence rates for other cerebral infarcts. The 30-day stroke recurrence rate was 1% for those with CSE, which was not significantly different from those without a source (2%). The risk of death in patients with CSE was 24 times the risk of recurrent stroke within 30 days. In a proportional hazards model, variables that were independently associated with recurrent stroke were sinus nodal dysfunction, age, systemic emboli, age-systemic emboli interaction, and myocardial infarction.
CAUSES OF STROKE IN PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION (NVAF)

J. Bogousslavsky, G. van Melle, F. Regli, L. Kappenberger, CHUV, Lausanne, Switzerland

Using systematic CT carotid (ICA) duplex scanning and echocardiography, we studied coexisting causes of stroke in 159 patients with NVAF and carotid infarct admitted to a population-based primary care center. In 107 (67%) patients, ICA disease ipsilateral to infarct was present, but it was severe (≥50% stenosis or occlusion) in only 18 (11%) patients. Another potential cardiac source of embolism, than NVAF was found in 22 (14%) patients. Small-artery disease was possible in 21 (13%) patients who had hypertension and a small deep infarct. Overall, though only 29 (18%) patients had NVAF as the only potential cause of stroke, NVAF-related cardio-embolism remained the most likely etiology of infarct in 101 (64%) patients. Brady-cardia, hypotension and syncope (22%) also emphasize hemodynamic failure.

EFFECT OF AGE ON CARDIAC AND AUTONOMIC RESPONSES IN THE RAT STROKE MODEL

David F. Cechetto, John X. Wilson, Karen E. Smith, Vladimir C. Hachinski. Robarts Research Institute, London, ONT, Canada

In humans the great majority of strokes occur in elderly individuals. We examined the cardiovascular responses in animals of different ages. Fifty-three urethane-anesthetized male rats were divided into 6 groups including middle cerebral artery occlusion (MCAO) and sham-operated for 3 ages (young, adult and aged). Heart rate, arterial blood pressure, renal nerve activity, EKG and plasma catecholamines were measured and analyzed using two-way ANOVA and t-tests (p<0.05). An acute increase in sympathetic nerve activity was found in the first hour following MCAO in the young and adult animals, but not in the aged group. In the aged group a prolongation of the QT interval at 4 hours after the MCAO was demonstrated, and a 61% (8 of 13) mortality rate at 6 hours. These results suggest that older animals may be at greater risk for cardiac electrophysiological abnormalities which could result in death, while ischemia itself induces only a transient increase in sympathetic function in younger rats.

ACUTE CEREBRAL INFARCTION IN NON-VALVULAR ATRIAL FIBRILLATION: EARLY RECURRENCE OF STROKE AND OTHER ISCHEMIC EVENTS.

Duncan M. McIlraith, Robert Côté, Christine Wolison. The Montreal General Hospital, Montreal, PQ, Canada.

We retrospectively determined the occurrence of cerebral and systemic ischemic events in the first 2 weeks following acute cerebral infarction in 134 patients, 67 with non-valvular atrial fibrillation (NVAF) and 67 comparable patients with normal sinus rhythm (NSR). Anticoagulated patients were excluded. The occurrence rate of all ischemic events in the NVAF group was 3.0% (2/67) and in the NSR group was 1.5% (1/67). The difference did not reach statistical significance (p>0.1).

This study does not show an effect of NVAF on the early recurrence of ischemic events following cerebral infarction.

THE INSULA AND CARDIAC ARRHYTHMIAS: IMPLICATIONS FOR STROKE.

Stephen M. Oppenheimer, Vladimir C. Hachinski, John X. Wilson, David F. Cechetto; Robarts Research Institute, London, Ontario, Canada.

Although cardiac arrhythmias account for significant mortality from stroke, the mechanism is unclear. Recently, we identified a site in the rat insula, where stimulation speeds or slows heart rate. Using a new method of ECG-linked, phasic microstimulation of this area in unventilated, urethane-anesthetised male Wistar rats, we consistently produced in sequence: Q wave broadening; R wave attenuation; Q wave loss; PR interval increase; complete heart block; bundle branch block; monomorphic ventricular tachycardia leading to a multimorphic format, and asystole (~200 stimulations per minute for a mean of 4 hours in 5 rats). None of the 6 control animals showed ECG changes. The mean ratio of the intraluminal to external left ventricular diameter was significantly greater in the stimulated animals (p=0.01). Plasma norepinephrine levels rose only in the stimulated group (p=0.02). These data suggest that the insula may be an important site for arrhythmogenesis in stroke, and that catecholaminergic mechanisms may be involved.
Hypertensive Intracerebral Hemorrhage
Does past hypertension or left ventricular hypertrophy predict size?
Conrado J. Estol, Louis R. Caplan, Philip Lee, William B. Young, Michael S. Pessin.
New England Medical Center, Boston, MA.
Caplan posited 2 mechanisms of hypertensive intracerebral hemorrhage (ICH): arteriolar damage from chronic high BP, and arteriole rupture caused by acute increased flow or pressure. We studied ICH size by computerized CT data in 34 patients to see if history of hypertension (HH) affected ICH volume or site. 20 patients had HH. Admission BP averaged 196/110. Average ICH volume 26.5cc. 14 had no HH. Admission BP averaged 186/107. Average ICH volume 42cc. 17 had no LVH by EKG or CXR. Average ICH volume 33.5cc. 17 had no LVH. Average ICH volume 36cc.
Data was analyzed relating HH and LVH. No HH, no LVH-33.6cc; HH-no LVH-38.4cc; HH and LVH-14.5cc; no HH, LVH-52.6cc. ICH site did not differ among groups. Patients with no HH and LVH had significantly (p < 0.01) larger ICH. The smallest ICHs were in patients with HH and LVH. Among 11 in this group, 7 were treated for high BP. The data suggests that size of ICH depends on HH, LVH and treatment of high BP.

THE BLACK-WHITE DIFFERENCE IN STROKE INCIDENCE IN THE NHANES-I EPIDEMIOLOGIC FOLLOW-UP STUDY
Steven J. Kittner, Lon R. White, Katalin G. Loaonczy, Philip A. Wolf.
University of Maryland, Baltimore, MD
In a 10-year follow-up study of a national sample, the risk of stroke among 1,298 blacks and 7,819 whites was compared. The results show: (1) That the black women in this cohort had a statistically significant increased age-adjusted risk of stroke compared to white women (RR = 1.8 with 95% CI 1.3-2.4). Black men also showed an excess risk of stroke compared to white men (RR = 1.3) but this was not statistically significant (95% CI 0.9-1.7). The small number of strokes among black men <n=43) limited the power of this study to detect a black-white difference among men. (2) The relative risks for stroke associated with hypertension and diabetes mellitus were unrelated to race or sex. (3) The excess stroke risk among black women remained significant even after adjusting for the effects of age, hypertension and diabetes mellitus.

Lunch
The annual business meeting of the Stroke Council will be conducted during lunch. Council Chairman Hermes A. Kontos will preside.

SESSION VII
Friday, February 16
1:30–3:30 PM
Cerebral ischemia
Chairmen:
Robert H. Ackerman, Boston, MA
Patricia A. Grady, Bethesda, MD
THE 'THERAPEUTIC WINDOW' IN A RAT MODEL OF REVERSIBLE FOCAL ISCHEMIA
Bruce A. Kaplan, Xing-Jie Wang, William A. Putznielli. Cornell Medical College, New York, NY
Treatment of focal ischemia requires knowledge of the time interval between stroke onset and development of infarction. We subjected spontaneously hypertensive rats to reversible tandem occlusion of middle cerebral and common carotid arteries (MCA-CCAO) for 1, 2, 3, 4 or 24 hours. Infarct volumes were measured at 24 hours. In separate rats, rCBF (laser-doppler) and DC potential were monitored; ATP and phosphocreatine (PCr) were measured fluorometrically at 15 min, 1 and 4 hr. Infarct volumes following ischemic periods of 1(n=5), 2(n=4), 3(n=6), 4(n=5) and 24(n=5) hours were 11±7, 99±9, 182±12, 178±37 and 187±21 respectively (mean ±SE in mm³). Measurement of DC potential at sites of metabolite sampling (n=10) showed persistent depolarization, and rCBF was reduced to 17.8±1.4% of the pre-occlusion baseline (n=13). At 15 min(n=8), 1(n=9) and 4(n=7) hours ATP was .15±.05, .20+.07 and .27±.05 (control=2.72±.09);PCr was .41±.06, .55±.11 and .81±.11(control=4.82±.19, mean±SE in µmol/g). In this model of focal stroke, rats can tolerate severe ischemia, with profound energy depletion and persistent anoxic depolarization, for up to 1 hour with minimal infarction. Therapy to reduce infarct volume in this model must be initiated no later than 1 to 2 hrs after the onset of ischemia.
VISUAL IDENTIFICATION OF THE ISCHEMIC PENUMBRAS

Adrian W. Gelb, Franco DeMonte, Sarah Henderson, Robarts Research Institute, London, Canada.

The ischemic penumbra is the region most likely to benefit from therapy but is difficult to measure. Our aim was to validate a simple technique to visually define the penumbral area. Nine cats had permanent MCA occlusion. Microspheres were used to measure rCBF. At sacrifice, carbon black (CB) was injected to show the area of non-perfusion. Sections of brain were incubated with triphenyl tetrazolium (TTC) which in the presence of viable dehydrogenases turns bright red. The areas of CB and TTC staining were calculated. The difference between the two represents areas with no perfusion but viable enzymes (i.e. penumbra). CBF in regions with both CB and TTC staining was 56.9±6.2; in areas with no CB or TTC (infarct) 2.8±0.85; in areas with CB but with TTC (penumbra) 21.6±6.6.

EXCESSIVE RELEASE OF GLUTAMATE IS NOT SUFFICIENT FOR THE DEVELOPMENT OF ISCHEMIC CELL DAMAGE IN VIVO

Mordecai Y.-T. Globus, Raul Busto, W. Dalton Dietrich, Elena Martinez, Isabel Valdes, and Myron D. Ginsberg. Cerebral Vascular Disease Research Center, University of Miami, FL.

Excessive release of glutamate is thought to play a major role in ischemic neuronal injury. Using a rat model of 10 min global ischemia induced by 2-vessel occlusion plus systemic hypotension (n=5), we compared ischemia-induced changes in glutamate release in a selectively vulnerable region (hippocampus) to changes occurring in an equally ischemic region (striatum) which is usually unaffected by a 10-min insult. Glutamate levels, measured by microdialysis, were significantly elevated during ischemia both in the hippocampus and the striatum. These levels continued to increase during the early recirculation period and gradually returned to baseline by 30 min of reperfusion. The total integrated amount of glutamate release over the time of ischemia and early recirculation was 5.9±1.2 pmoles in the hippocampus and 5.2±0.7 pmoles in the striatum (mean ± SE). These results demonstrate that elevated intra-ischemic glutamate levels of themselves are insufficient to engender ischemic damage, other injury mechanisms associated with glutamate may be operative.

PROTON MRE EVOLUTION OF DAMAGE AFTER FOCAL STROKE.

Warren Selman, Ralph Crumrine, Karen Seta, Don Kormor, Emanual Paleiaksky, Robert Rathbenson and David Lust; Div. of Neurosurgery, Case Western Reserve Univ, Cleveland, OH.

Experimental focal stroke investigation has been hindered by inter-animal variability in both the size and time course of ischemic damage. Recent evidence suggests that there is a more consistent pattern of injury in spontaneously hypertensive rats (SHR); however, this may be due to the absence of a penumbra, or area at risk. To evaluate the correlation between edema formation and evolution of focal ischemic damage in SHR's, the volume of edema was determined by proton MRI in 4 rats at 24 h after MCA occlusion and the volume of infarct was determined in H&E stained sections at 6 and 24 h after occlusion. The infarct volume at 6 and 24 h was, respectively, 143.6±31 and 207.2±29 mm³ (p<0.05), suggesting that a penumbral region does exist in SHR's with normal perfusion. The volume of edema at 24 h (265.0±22.8 mm³) was significantly greater than infarct volume (p<0.02), indicating that edema formation extended beyond the borders of the infarcted area. The differences in infarct volume with increasing time and persistence of an extended volume of edema suggest a window of opportunity for salvaging vulnerable tissue with therapeutic intervention in SHR stroke models.

TISSUE PO2 DETERMINES THE ISCHEMIC THRESHOLD FOLLOWING MCA OCCLUSION


These experiments examined the relationship between CBF, tissue PO2 and ischemic brain damage resulting from a 6 hour middle cerebral artery occlusion in cats. CBF and tissue PO2 were measured using paired platinum electrodes 1 mm apart placed in 3 preset locations in the ischemic cortex. Tissue PO2 was manipulated by infusing a 15 ml/kg bolus injection Fluosol-DA (20%) either prior to or at 5, 30 or 120 min postocclusion. Four control groups received an equal volume of Ringers solution. All animals were ventilated with 100% O2. After six hours, the brains were perfuse-fixed and examined histologically. Ischemic cell damage was found at 59% (71/120) of electrode sites in control animals and at 28% (32/116) in Fluosol treated cats. In control groups, ischemic damage occurred at flows below 18-20 ml/100g/min corresponding to a tissue PO2 of 7-8 mm Hg. The flow threshold was much lower in the Fluosol treated animals (14-15 ml/100g/min) but the PO2 threshold was identical. I conclude that it is hypoxia rather than oligemia which causes the tissue damage.

EXCESSIVE RELEASE OF GLUTAMATE IS NOT SUFFICIENT FOR THE DEVELOPMENT OF ISCHEMIC CELL DAMAGE IN VIVO

Mordecai Y.-T. Globus, Raul Busto, W. Dalton Dietrich, Elena Martinez, Isabel Valdes, and Myron D. Ginsberg. Cerebral Vascular Disease Research Center, University of Miami, FL.

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ADRENALECTOMY AFFECTS BRAIN TEMPERATURE AND FURTHER DELAYS HIPPOCAMPAL DAMAGE FOLLOWING TRANSIENT ISCHEMIA

Joanne K. Morse, James N. Davis, Duke University, Durham, NC

Adrenalectomy attenuates hippocampal CA1 pyramidal cell damage from a variety of insults including ischemia. However adrenalectomy disturbs body temperature regulation. Gerbils sham adrenalectomized 24 hours after 5 minutes of bilateral carotid occlusion followed by reperfusion and sacrificed on day 4 demonstrated moderate-severe hippocampal damage in 11 of 12 hemispheres (92%). By contrast, adrenalectomized gerbils demonstrated moderate damage in only 4 of 18 hemispheres (22%). Ischemic gerbils, adrenalectomized or sham adrenalectomized 24 hours after carotid occlusion and sacrificed on day 7 had damage in 10 of 10 (100%) and 5 of 6 hemispheres (83%) respectively. A decrease in brain and body temperature was observed in adrenalectomized gerbils. These results suggest that adrenalectomy does not permanently prevent cell death, rather adrenalectomy appears to delay ischemic neuronal cell death perhaps through its effect on temperature regulation.

SUPEROXIDE DISMUTASE REDUCES CAUDATE INFARCT VOLUME AFTER TRANSIENT FOCAL ISCHEMIA

N. Matsuniya, R.C. Kohler, J.R. Kirsch, R.J. Traystman. Johns Hopkins Medical Institutions, Baltimore, MD

We tested if polyethylene glycol-conjugated-superoxide dismutase (PEG-SOD) reduces infarct volume after transient focal ischemia in anesthetized cats. Left middle cerebral plus bilateral carotid arteries were occluded for 2 hr followed by 4 hr reperfusion. Caudate nucleus infarct volume (triphenyltetrazolium) was 568±35 (SEM) of ipsilateral caudate volume (249 mm³) in the placebo group (n=17). Pretreatment with PEG-SOD (10,000 U/kg, iv) 3 hr before ischemia (n=12), reduced infarct volume (283±5; P<.05). Caudate blood flow (microspheres) increased during occlusion with SOD (112±155 to 165±100 mg/100g at 60 vs 120 min ischemia; P<.01), but remained constant with placebo (82±100 mg/100g) throughout ischemia. Infarct volume in cortical grey was variable and not different (placebo-1391±404; SOD-930±281 mm³). Thus PEG-SOD can potentially ameliorate infarct volume in an end-artery region after transient focal ischemia and a vascular mechanism may be involved.

(H) GROWTH FACTOR PRETREATMENT AMELIORATES ISCHEMIC HIPPOCAMPAL NEURONAL INJURY

Alastair M. Bucher, Larry Williams and Barbara Burnetelden. Laboratory of Cerebral Ischemia, Toronto Research Institute, London, Ontario, Canada. *The Upjohn Co., Kalamazoo, MI.

Deafferentation studies show that while removing glutamate inputs did not protect the hippocampal CA1 cells from ischemic neuronal injury, sectioning the fimbria/forebrain (F/F) did. This effect is only seen 7-13 days following deafferentation, and the time course parallels the transient increase in hippocampal nerve growth factor (NGF) following F/F deafferentation. These experimental results performed in vitro suggest NGF can ameliorate ischemic CA1 neuronal injury without F/F deafferentation.

Male Wistar rats had a 14 day intra-ventriculur infusion of either NGF or vehicle through an implanted cannula connected to an Alzet pump. NGF was delivered at 1.2 mg/kg/day. After 10 days they were prepared for four vessel occlusion, and subsequently they were exposed to 15 minutes of transient forebrain ischemia and 72 hours of reperfusion. Infarct volume in the ischemic hemisphere was assessed by TTC staining. Ischemic injury was graded from 0 = normal, 1 = < 10%, 2 = 10-50%, 3 > 50% of CA1 neurons infarcted. A third group of contemporary sham operated controls were also exposed to 15 minutes of ischemia and 72 hours of reperfusion.

Mean Grade CA1 Damage ± SE

Control (n=6) 2.75 ± .1
Vehicle Infused (n=6) 2.35 ± .3
NGF Infused (n=6) 1.64 ± .3

The NGF infused animals appear to have less damage than those with vehicle infusion which in turn are less damaged than controls. It is possible that cortical irritation from prolonged vehicle infusion induced cyto-protection (perhaps through stimulation of glia) but the effect is enhanced by a decrease in hippocampal NGF levels, respectively.

The molecular explanation for the cyto-protective effect of prolonged infusions of nerve growth factor is unknown.

(S)-EMOPAMIL PROTECTS AGAINST GLOBAL ISCHEMIC INJURY IN RATS

Baowan Lin, W. Dalton Dietrich, Raul Bustos, and Myron D. Ginsberg. Cerebral Vascular Disease Research Center, University of Miami, FL, 33101

The calcium-antagonist and serotonin (S)-emopamil (E) markedly reduces infarct size in focal ischemia (Neurology 38:1667-73, 1988). To test its efficacy in preventing neuronal injury in global ischemia, we subjected rats to 10 min of bilateral carotid artery occlusion plus moderate hypotension (50 mmHg). Treated rats received E, 20 mg/kg i.p., 30 min before and 2 hr following ischemia. Quantitative cell counts following 3-day survival revealed a marked loss of pyramidal neurons in all subsectors of the hippocampal CA1 region of untreated rats (n=15). In contrast, in E-treated rats (n=15), numbers of normal neurons were increased by 2.4X, 1.8X, and 1.8X in the medial, mid-, and lateral subsectors of CA1 (P<0.02, P=0.02, and P<0.05, respectively; Mann-Whitney U test). For example, normal-neuron counts in medial CA1 were 34 ± 8 (SEM) in untreated ischemic vs. 82 ± 10 in E-treated ischemic rats. (Control non-ischemic value, 131 ± 6.) By semiquantitative grading, E also decreased ischemic changes in cerebral cortex (P<0.02). Thus, pretreatment with (S)-emopamil is beneficial in decreasing the severity of neuronal injury in global ischemia.

HBBVE GftOVTB FACTOR: PRBT&EATXEHT AMELIORATES IBCHEHIC HIPPOCAMPAL NEURONAL INJURY

Alastair H. Bucher, Larry Williams* and Barbara Burnetelden. Laboratory of Cerebral Ischemia, Toronto Research Institute, London, Ontario, Canada. *The Upjohn Co., Kalamazoo, MI.

Deafferentation studies show that while removing glutamate inputs did not protect the hippocampal CA1 cells from ischemic neuronal injury, sectioning the fimbria/forebrain (F/F) did. This effect is only seen 7-13 days following deafferentation, and the time course parallels the transient increase in hippocampal nerve growth factor (NGF) following F/F deafferentation. These experimental results performed in vitro suggest NGF can ameliorate ischemic CA1 neuronal injury without F/F deafferentation.

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The NGF infused animals appear to have less damage than those with vehicle infusion which in turn are less damaged than controls. It is possible that cortical irritation from prolonged vehicle infusion induced cyto-protection (perhaps through stimulation of glia) but the effect is enhanced by a decrease in hippocampal NGF levels, respectively.

The molecular explanation for the cyto-protective effect of prolonged infusions of nerve growth factor is unknown.
SESSION VIII
Friday, February 16
4:00-6:00 PM

Therapy

Chairmen:
Hermes A. Kontos, Richmond, VA
Richard J. Trastman, Baltimore, MD

RANDOMIZED DOUBLE-BLIND TRIAL OF NIMODIPINE IN OUT-OF-HOSPITAL RESUSCITATION.

Risto O. Rolke, Markku Kaste, Pertti Nikki, Ari Kiranen. Department of Neurology, Univ. of Helsinki, Finland.

Effects of nimodipine on the neurological outcome in out-of-hospital ventricular fibrillation (VF) were studied in a randomized, placebo-controlled double-blind trial of 195 patients. Nimodipine or placebo was started prehospitaly as an i.v. bolus dose of 10 μg/kg 23.6±±.4 min postarrest, followed by an infusion of 0.5 μg/kg/min for 24 hours. Of the 118 eligible patients, 22/5 (90%) had good outcome (Glasgow Outcome Score 4 or 5) at 12 months in the nimodipine group and 18/63 (28%) in the placebo group (P=0.13). Of the 50 eligible patients with advanced life support delays > 10 min, 7/21 (33%) nimodipine patients had good outcome at 12 months as compared to 2/29 (7%) placebo patients (P=0.02, Odds ratio 6.5). Thus, nimodipine improves the 12 month outcome of out-of-hospital VF in patients with delayed advanced life support. A European multicenter trial is in progress.

EXPERIMENTAL FOCAL STROKE: EFFECT OF ANTIHYPERTENSIVE THERAPY

Andrew P. Slivka, The Ohio State University, Columbus, OH

Hypertension is a potentially treatable risk factor for stroke. Few prospective studies, however, have documented the efficacy of antihypertensive therapy in patients with stroke. To learn more about the effects of antihypertensive therapy, 10 week-old spontaneously hypertensive rats (SHRs) were treated with oral hydralazine (n = 18). The control group consisted of untreated SHRs (n = 17). After 10 weeks, focal cerebral infarction was produced by tandem right common carotid and middle cerebral artery occlusion. The hydralazine-treated group showed an average drop in systolic blood pressure from 180 to 145 mmHg. Infarct volumes in this group were 189±14 mm³ (mean ± S.E.). This was significantly smaller than the infarct volume in controls, 230±9 mm³ (P = 0.02, t-test) who exhibited an average increase in systolic blood pressure from 178 to 197 mmHg. These results support the importance of antihypertensive therapy which not only diminishes the risk of stroke, but also appears to reduce the extent of infarction when cerebral ischemia occurs in the setting of hypertension.
EFFECTS OF EXPERIMENTAL AMINO-STEROID ON OUTCOME OF CEREBRO-VASCULAR OCCLUSION IN CATS

Ronald E. Myers, Marla Kleinholz, Kenneth R. Wagner, Lovely Steele, Gabrielle M. de Courten-Myers. VAMC, Cincinnati, OH

In a blinded drug (U74006F from Upjohn Company) versus vehicle study, ischemic blood flow, infarct size and death rate from ischemic territory edema was examined in 22 hyperglycemic (23 mM) cats with permanent MCA occlusion. Drug or vehicle was injected IV (2 mg/kg) at 0.5 and 3 and IP (4 mg/kg) at 12 and 24 hrs after occlusion.

<table>
<thead>
<tr>
<th>End-Point</th>
<th>Drug</th>
<th>Vehicle</th>
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<tbody>
<tr>
<td>Edema death rate</td>
<td>25% (3/12)</td>
<td>30% (3/10)</td>
</tr>
<tr>
<td>Infarct size (2 wks survival)</td>
<td>16 ± 5</td>
<td>19 ± 6</td>
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<tr>
<td>% MCA territory</td>
<td>60 ± 7</td>
<td>71 ± 6</td>
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<tr>
<td>CBV, % reduction at 0.5 hrs</td>
<td>54 ± 7</td>
<td>62 ± 8</td>
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<tr>
<td>CBV, % reduction at 3 hrs</td>
<td>51 ± 7</td>
<td>60 ± 9</td>
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<td>(Values = means ± SE)</td>
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No result differed significantly between the 2 groups. Thus, as administered, U74006F failed to significantly affect collateral blood flow or infarct development in this model.

THE EFFECT OF AMPHETAMINE ON FUNCTIONAL BRAIN ACTIVATION

W. Dalton Dietrich, Raul Bustos, Myron D. Ginsberg. Cerebral Vascular Disease Research Center, Dept. Neurology, Univ. Miami School Medicine, Miami, FL

Amphetamine (AMP) accelerates recovery of function following stroke. In normal rats, we determined the effects of AMP (4 mg/kg) on the metabolic responsiveness of the somatosensory cortex (SSC) to physiological activation. Control (n=8) and treated (n=4) rats underwent 45 min of unilateral vibrissae stimulation combined with 2-DG autoradiography. In control rats, metabolic activation of the contralateral SSC was restricted to the posterior barrel-field (BF) region. In 1 hr pre-treated rats, increased glucose utilization induced by stimulation was more widespread, including cortical areas outside the BF. For example, a 31% increase above control was seen in cortical areas representing the lower lip and forepaw (p < 0.01, 1-way ANOVA). Thus, AMP enlarged the receptive field size of the SSC to tactile stimulation, a pharmacological property which may be advantageous for post-injury recovery.

EVIDENCE OF PLATELET-ACTIVATING FACTOR (PAF) AS A MEDIATOR IN STROKE

Perttu J. Lindberg, Tian-Li Yue, Kai U. Frerichs, John M. Hallembeck, Gloria Pfeuerstein. USUHS, Bethesda, MD

PAF is a potent mediator of inflammation and tissue injury, and possesses untoward cerebrovascular effects. While PAF-antagonists have already been shown to reduce ischemic neuroinjury, no study to date has demonstrated PAF production in CNS ischemia. In rabbit spinal cord injured by 25 min (n=12) of ischemia followed by 2 h of reperfusion (laser-Doppler flowmetry), we observed PAF-levels 20-fold higher than controls (TLC-isolation, platelet 5HT-release, PLC-confirmation; p<.01). Elevated PAF-levels coincided with edema (p<.001) and hypoperfusion (-35±7%, p<.01). Both derangements were blocked by the PAF-antagonist BN 50739 (ip 10 mg/kg, n=7), given 15 min prior to reperfusion (25 min ischemia). BN 50739 also prevented the initial impairment of reperfusion, which was observed in the model. Our data suggests a role for PAF in mediation of microcirculatory failure in CNS ischemia and justifies further interest in PAF-antagonists in stroke.

DRUGS INFLUENCE THE RECOVERY OF FUNCTION AFTER STROKE

Larry B. Goldstein, David B. Matchar, Joel C. Morgenlander, James N. Davis. Duke University, Durham, NC

Certain drugs clearly impair recovery after brain injury in laboratory animals. We analyzed recoveries in a patient cohort with ischemic stroke to determine whether these same drugs have similar effects in man. Patients receiving phenytoin, benzodiazepines, dopamine receptor antagonists, clonidine, or prazosin ("detrimental" drugs, n=24) were compared with all other patients ("neutral" drugs, n=34). Sensorimotor function (Fugl-Meyer score) and activities of daily living (ADL's, Barthel Index) were measured. The two groups had similar initial functional deficits and clinical characteristics. Thirty days after the stroke, patients receiving "detrimental" drugs had poorer sensorimotor function (Mann-Whitney U, p=.04) and were less independent in ADL's (Mann-Whitney U, p=.02) compared to those receiving "neutral" drugs. These data are consistent with the detrimental effects of these drugs on recovery in laboratory animals and suggest that drugs can have profound effects on recovery of function after stroke in man.
PLATELET-ACTIVATING FACTOR ANTAGONIST PROTECTIVE IN FOCAL BRAIN INJURY

Kai O. Frerichs, Perttu J. Lindsberg, John W. Hallenbeck, Giora Z. Feuerstein, USUHS, Bethesda, MD

Enhanced phospholipid metabolism in the penumbral zone of ischemic stroke provides opportunity of platelet-activating factor (PAF) production. We report the effects of a PAF antagonist in a model of focal brain injury (Nd:YAG laser) in anesthetized rats, which features highly reproducible characteristics of an "ischemic penumbra". Pretreatment with the PAF antagonist BN 50739 ameliorated the severe post-injury hypoperfusion: CBF improved from 40.5±8.3% to 80.2±7.8% (n=12, p<0.01) while edema was reduced by 70% (n=10, p<0.05) at 2 h after injury. Progression of neuronal damage was substantially reduced in the penumbral area in the cortex from 88.0±3.9% to 49.8±4.2% and in the hippocampus (CA-1) from 40.2±5.0% to 13.2±2.1% at 24 h after injury (n=30, p<0.05). No significant neutrophil accumulation was observed in the pretreated group (n=30; p=0.35). Therefore, PAF antagonists may provide significant protection in ischemia related delayed neuronal death.

Presentation of the Robert G. Siekert Young Investigator Award in Stroke and Recognition of Honorable Mentions.

SESSION X
Saturday, February 17
8:00–10:00 AM

Thrombosis and thrombolysis
Chairmen:
Livia Candelise, Milan, Italy
Justin A. Zivin, San Diego, CA

THROMBUS LOCALIZATION WITH EMERGENCY CEREBRAL COMPUTED TOMOGRAPHY
Thomas Tomsick MD, Thomas Brott MD, William Brous MD, Joseph Broderick MD, Clarke Haley MD, David Levy MD, George Sheppard MD, University of Cincinnati, Cincinnati, OH

Hyperdensity of the middle cerebral artery on CT (Hyperdense Middle Cerebral Artery Sign, or HMCS), indicating intraluminal thrombus, was identified in 14 of 50 patients analyzed thus far from a treatment study of intravenous tissue plasminogen activator (tPA) for treatment of acute nonhemorrhagic stroke (n=74). The neuroradiologist was originally blinded to clinical data. By seven days, this HMCS group developed infarcts of larger volume (mean 135cm^3; range 6-285cm^3) than patients not exhibiting the sign (mean 39cm^3; range 0-301cm^3). Infarct volume further correlated with the extent of MCA hyperdensity. Patients with proximal or complete M1 hyperdensity (n=3, mean volume = 117cm^3) or isolated M2 branch involvement (n=4, mean vol. = 74cm^3). Arteriographic correlation in patients with HMCS (n=9) suggests an inverse correlation between volume of infarction and the collateral circulation into the occluded distribution.

We conclude that the detection of the HMCS on an emergency basis provides early clues regarding thrombus localization and eventual cerebral infarct volume.

SESSION IX
Saturday, February 17
6:45–7:45 AM

Breakfast Seminar: Medical and surgical management of acute intracerebral hemorrhage
Chairmen:
John R. Marler, Bethesda, MD
Harold P. Adams Jr., Iowa City, IA

6:45 Matthew E. Fink, New York, NY
7:05 Arthur L. Day, Gainesville, FL
7:25 Discussion
7:45 Recess

SELECTIVE UPTAKE OF HEPARIN BY SMOOTH MUSCLE CELL NUCLEI AFTER ENDOTHELIAL INJURY
Marc Mayberg, Don Bark, Tomochika Okada, Department of Neurosurgery, University of Washington, Seattle, Washington.

A model has been established in which perivascular heparin in the carotid-adventitia region produces localized inhibition of smooth muscle cell proliferation without systemic anticoagulation. The model involves the use of detached smooth muscle cells in vitro, and suggests that heparin acts at the smooth muscle cell nucleus to inhibit proliferation after endothelial injury.
ENDOGENOUS FIBRINOLYTIC ACTIVITY AFTER STROKE

William M. Feinberg, Monette Jeter, Denise C. Bruck, James J. Corrigan.
Arizona Health Sciences Ctr., Tucson, AZ

To characterize endogenous fibrinolytic response after stroke we assayed tissue plasminogen activator antigen (TPA-Ag), tissue plasminogen activator activity (TPA-Act), and plasminogen activator inhibitor activity (PAI-Act) in 13 patients within one week of acute stroke and in 10 normal controls. Mean ± S.E.M values were compared using Student's two-tailed t-test.

TPA-Ag (ng/ml) was greatly increased following stroke (19.3 ± 2.7 vs 4.2 ± 0.8, p < .001). TPA-Act (IU/ml) increased but to a lesser degree (0.17 ± 0.02 vs 0.10 ± 0.02, p = 0.02). This suggests a circulating inhibitor of TPA activity. This was demonstrated by an increase in PAI-Act (IU/ml) (5.2 ± 0.7 vs 1.7 ± 0.12, p < .001).

These data indicate that endogenous plasminogen activator is released following stroke, but its effect is limited by inhibitors.

HEMORRHAGIC INFARCT CONVERSION IN EXPERIMENTAL STROKE

Gabrielle M. de Courten-Myers, Marla Kleinholz, Patricia Holm, Ronald E. Myers. U.C. Col. of Med. Cincinnati, OH

The conversion of ischemic to hemorrhagic infarcts may cause clinical deterioration. We analyzed this phenomenon in 35 normo- (6 mM) and 35 hyperglycemic (20mM) cats with permanent or reversible MCA occlusion for 4 or 8 hrs. Among these 70 animals, 50 developed infarcts of which 19 contained multiple petechial hemorrhages and small hematomas. Hemorrhagic infarcts occurred 13 times more often in brains with total territory infarcts, edema and early death (15/16) than in animals that survived with oc without infarcts (4/54) (p<0.001); 8.5 times more often in hyper- (17/35) than normoglycemic cats (2/17) (p<0.001); and only 3 times more often in reperfused (16/45) than in permanently occluded cats (3/25) (p<0.001). Thus, hemorrhage into infarcts, like brain edema, seems to result from the vascular damage caused by marked tissue acidosis as occurs in hyperglycemic animals.

SAFETY AND POTENTIAL EFFICACY OF TISSUE PLASMINOGEN ACTIVATOR (tPA) FOR STROKE

Thomas Brott MD, Clarke Haley MD, David Levy MD, William Barsan MD, George Sheppard MD, Joseph Broderick MD, Robert Reed MD, John Marler MD, University of Cincinnati, Cincinnati, OH

In an open-label, dose-escalation study of tPA for ischemic stroke, 74 patients received I.V. tPA within 90 minutes of symptom-onset (dose range=10-87mg). CT scans were performed pre-tPA, at 24 hours, 7 days, and at 3 months. Intracerebral hematomas occurred within the presumed region of infarction in two patients (parietal lobe—clinically mild; thalamus—asymptomatic). Hematomas occurred outside the region of infarction in one patient (cerebellum—required surgery). Neurological improvement (IMP) within 6 hours of tPA occurred in 29 patients.

<table>
<thead>
<tr>
<th>pre-tPA</th>
<th>7-day Infarction</th>
<th># exam score* exam score volume**</th>
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<tbody>
<tr>
<td>Early IMP</td>
<td>29</td>
<td>12±6(4a) 5±2 11±14cm²</td>
</tr>
<tr>
<td>No early IMP</td>
<td>45</td>
<td>14±6 10±7 6±7cm²</td>
</tr>
</tbody>
</table>

* NIH stroke scale, range 3-28 pre-tPA (0=no deficit) ** By CT at 7 days in the 43 scans analyzed to date

We conclude that IV tPA administration to ischemic stroke patients on an emergency basis is not without risk, but the potential for benefit justifies a randomized controlled clinical trial.

AN OPEN MULTICENTER STUDY OF THE SAFETY AND EFFICACY OF VARIOUS DOSES OF tPA IN PATIENTS WITH ACUTE STROKE: A PROGRESS REPORT

The tPA Acute Stroke Study Group

We report an ongoing dose-range finding safety and efficacy study of Burroughs Wellcome tPA (Prolysis®) in acute stroke. Patients received a 60 min. IV infusion of a preassigned dose of tPA within 8 hours of acute thrombotic or embolic stroke after a negative CT for blood, and angiographic documentation of an appropriate occlusion. Following tPA, repeat angiography, and serial CTs were performed. The primary positive efficacy response was angiographically documented reperfusion of the previous occlusion. The primary negative safety response was parenchymatous hemorrhage (PH). Results in 57 patients for 6 dose groups showed arterial recanalization in 22 (18 partial, 4 complete) at 60 mins. Hemorrhagic infarcts occurred in 23 but were not associated with clinical deterioration or recanalization. PH occurred in 4, with death in 3. These preliminary results are encouraging but consistent recanalization, and avoidance of PH remain major goals for continued study.

HEMORRHAGIC INFARCT CONVERSION IN EXPERIMENTAL STROKE

Gabrielle M. de Courten-Myers, Marla Kleinholz, Patricia Holm, Ronald E. Myers. U.C. Col. of Med. Cincinnati, OH

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INTRACEREBRAL HEMORRHAGE AFTER RT-PA AND HEPARIN FOR ACUTE MYOCARDIAL INFARCTION: THE TIMI II PILOT AND RANDOMIZED TRIAL COMBINED EXPERIENCE

Michael A. Sloan, Thomas R. Price, Anna M. Randall, Rachel E. Solomon, Michael L. Terrin and the TIMI Investigators, Maryland Medical Research Institute, Baltimore, MD

Of 908 pts treated with 150 mg rt-PA and heparin, 12 (1.3%) developed intracerebral hemorrhages (IH) compared to 11 (0.4%) of 3,016 treated with 100 mg rt-PA and heparin (p<0.01). IH size (range 1 to 166 cc), timing and site were similar for the two regimens. Of the 23 IH, 9 (39%) occurred during study drug infusion (<6 hours), 6 (26%) >6 but <12 hours after the start of infusion, 4 (17%) >12 but <24 hours, and 4 (17%) >24 hours. Sites of IH included the lobes (16), thalamus (4), brain stem and cerebellum (3); but not the putamen. Two pts (9%) made full recoveries; 5 (22%) partial recoveries with minor residual deficits; 4 (17%) partial recoveries with major residual deficits; 12 (52%) made no recovery and died within 1 week.

ANTIPHOSPHOLIPID ANTIBODIES AND CEREBRAL ISCHEMIA (CI) IN YOUNG PEOPLE

Robin L. Brey, Robert G. Hart, David G. Sherman, Charles H. Tegeler, UTHSC, San Antonio, TX

We examined 46 unselected CI patients < 50 years of age over 3 years for antiphospholipin antibodies (aCL) and lupus anticoagulants (LA). Age/sex matched patients with other neurologic disease served as non-CI controls to test whether (1) CI in young people is associated with aCL and/or LA and (2) their presence is specific to CI. In the CI group: 21 had aCL/LA and 25 had neither. In the control group: 2 had aCL and 24 had neither (p<.001,df=1). Nine patients with and 9 without aCL/LA and CI had other risks for CI. In conclusion, aCL/LA is significantly associated with CI in young adults, in many cases independent of other stroke risk factors, and is not due to non-specific brain disease.

SESSION XI
Saturday, February 17
10:30 AM-12:30 PM

COOPERATIVE STUDY OF ANTIPHOSPHOLIPID-IDS/LUPUS ANTICOAGULANTS IN STROKE

The Antiphospholipid Antibodies in Stroke Study Group (APASS)

APASS is a cooperative study group seeking to study the role(s) of antiphospholipid antibodies (aCL), and lupus anticoagulants (LA) in patients with cerebral ischemia (CI). Initially, a retrospective review from 12 centers has collected data on 128 aCL/LA-positive CI patients, the largest group to date. Entry criteria varied by center but clinical data was abstracted uniformly. There are 63 men and 65 women; 78 aged less than 50 y (61%). The index CI event was: stroke in 97, ocular ischemia in 5, transient CI in 26. Multiple CI at index was found in 37 (30%). Stroke risk factors (i.e. hypertension, diabetes, lupus) were noted in only one-third. These data show that CI alone may signal the initial presentation of aCL/LA-positive patients; further, multiple CI may be common. Subsequently, APASS intends to establish the epidemiology of aCL/LA in CI, and to assess possible therapies.

EFFECTS OF TREATMENT OF HYPERTENSION ON CEREBRAL ARTERIOLES

Gary L. Baumbach, Michael A. Hajdu, and Donald D. Heistad, Univ. of Iowa and VAMC, Iowa City, IA

Cerebral arterioles undergo hypertrophy and paradoxically become more distensible during chronic hypertension. To determine whether treatment of hypertension attenuates changes in arteriolar mechanics, we studied pial arterioles in 6 month old normotensive Wistar Kyoto rats (WKY; n=8) and stroke-prone spontaneously hypertensive rats (SHRSP) that were treated for 3 months with cilazapril (C; 10 mg/kg/day; n=10) a converting enzyme (ACE) inhibitor, hydralazine (H; 100 mg/kg/day; n=9), or untreated (U; n=12). Results (mean±SE; *p<0.05 vs WKY; »p<0.05 vs U-Shrsp):

<table>
<thead>
<tr>
<th></th>
<th>WKY</th>
<th>U-Shrsp</th>
<th>C-Shrsp</th>
<th>H-Shrsp</th>
</tr>
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<tbody>
<tr>
<td>AP (mmHg)</td>
<td>106±4</td>
<td>175±4</td>
<td>115±2*</td>
<td>162±6*</td>
</tr>
<tr>
<td>1.4±0.1</td>
<td>1.8±0.2*</td>
<td>1.2±0.1*</td>
<td>1.4±0.2*</td>
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<tr>
<td>CSA (μm²)</td>
<td>6.1±3</td>
<td>5.6±3.7*</td>
<td>4.8±0.2</td>
<td></td>
</tr>
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Values for cross-sectional area of the vessel wall (CSA) indicate that cilazapril and hydralazine prevented hypertrophy of pial arterioles in SHRSP, even though arterial pressure (AP) was reduced more effectively by cilazapril. Values for elastic modulus (EM) indicate that cilazapril, but not hydralazine, attenuated increases in arteriolar distensibility. Thus, both an ACE inhibitor and hydralazine achieved the goal of preventing vascular hypertrophy. In addition, the ACE inhibitor also attenuated alterations in vascular mechanics.
OUTCOME OF ASYMPTOMATIC CAROTID STENOSIS
Chang Z. Zhu, John W. Norris, University of Toronto, Toronto, Canada.

We previously reported outcome in patients with asymptomatic carotid bruits, but medical and surgical interventions involve patients with carotid stenosis, not bruits. We evaluated clinical outcome in 693 patients with asymptomatic carotid stenosis divided into mild (<50%), moderate (50%-70%), and severe (>75%). Mean follow-up 3.5 years.

Annual rate of all ischemic cerebral events (TIs and stroke) were 1.5% for the <50% group, 5% for 50%-70%, and 15% in the >75% group. Annual stroke rate was 1.3%. Annual ischemic cardiac events were 3%, 6%, 8% and annual vascular death rates were 2%, 3% and 6% respectively.

These data indicate that the major factor determining outcome is severity of carotid stenosis but only >75%

SERUM LIPIDS AND OTHER RISK FACTORS FOR ATHEROSCLEROSIS IN EXTRACRANIAL VESSELS OF PATIENTS WITH TIA AND MINOR STROKE
Heikki Palomaki, Markku Kaste, Rall Raininko, Olli Selonen, Antti Muuronen, Seppo Juvela, Department of Neurology, University of Helsinki, Finland

The association of atherosclerosis (AS) with serum lipids and other risk factors was studied in 271 patients with threatened stroke. The sum of the maximal thickness of all plaques in the anteroposterior views of extracranial arteries in aortic arch angiograms was used as an indicator of the severity of AS. Age, arterial hypertension, serum triglycerides, cholesterol, LDL-cholesterol, low HDL-cholesterol, smoking, male sex and diabetes were univariate risk factors for radiological AS. Age, smoking, arterial hypertension and serum triglycerides were independent risk factors in the multiple stepwise logistic regression analysis and explained the occurrence of AS in angiograms. Serum cholesterol was the only independent risk factor in the multiple linear regression analysis which explained the severity of AS in those 150 patients who had AS in angiography.

TRANSIENT MONOCULAR VISUAL DISTURBANCES AND INITIALLY OPEN CAROTIDS: 10 YEAR STROKE RISK
Robert H. Ackerman, Richard V. Brenner, Paul M. Katz, Massachusetts General Hospital, Boston, MA

This is a report of a 10-year follow-up on 139 of 195 patients (71%) who presented with transient monocular visual disturbances (TMD) in 1978/79. After 2.5 years' follow-up we suggested (1982) that patients with TMD and normal fundi are not at high risk for cerebral or ocular stroke from the carotids if non-invasive tests (direct/indirect) are normal. At 10 years, 8 cerebral (5.8%) and 3 ocular (2.2%) ischemic strokes ipsilateral to the carotid were identified. Of the 8 cerebral strokes, 5 occurred after onset of tight carotid disease. Only 1 cerebral and 1 ocular stroke patient had no known carotid stenosis and no identifiable cardiac embolic source. The data support our initial impressions, but suggest the need for ongoing non-invasive surveillance.

IMMUNOHISTOCHEMICAL DIFFERENCES BETWEEN CAROTID PLAQUE NEOVASCULARIZATION & VASA VASORUM
Camilo R. Gomez, Richard T. Kubiuk, Jerome B. Wade, Carlos Bedrossian, St. Louis University, St. Louis, MO

In an attempt to identify morphologic differences between carotid artery plaque (CAP) neovascularization (NV) and normal vasa vasorum (VV), 15 consecutive CAP surgical specimens were stained using factor VIII-related antigen technique. There were 12 men and 3 women, ages ranging 55-81 years (mean=67), and CAP-related symptoms in 9/15. Grading of NV was based in its appearance and location.

Mild NV (grade I) was found in 3/15 while moderate and severe (grades II & III) were each found in 6/15 cases. NV-III appeared more tortuous, showed thicker walls and was closer to the lumen than VV. Its severity didn’t correlate to plaque thickness (p>0.2) or to symptoms (p=0.4).

NV of CAP seems independent of the degree of atheroma and morphologically different than VV. Its origin, true incidence and role in the production of internal CAP hemorrhage, and increased stroke risk, are still uncertain. This is the first immunohistochemical study of CAP NV.
We microscopically investigated 134 plaques in 125 consecutive patients, and found 21 (15.7%) simple fibrous plaques versus 113 (84.3%) complicated plaques. The following plaque characteristics were present: intraplaque hemorrhage (73 plaques), ulceration (83 plaques), fresh thrombus (93 plaques), and recanalized thrombus (22 plaques). An average of 2.4 characteristics was observed in each complicated plaque. The only significant clinicopathologic correlation was the presence of fresh thrombi, found in 80% of the plaque of patients with previous transient ischemic attack, in 93% of those with amaurosis fugax. Analysing the localization of the fresh thrombus (mural or intraluminal), we found that fresh thrombus in symptomatic plaques was most frequently (71 to 77%) intraluminally exposed. Exulceration without fresh thrombus, plaque hemorrhage and recanalized thrombus were also found in a considerable number of asymptomatic patients, out of whom 85% (35/41) presented a form of complicated plaque.

PRELIMINARY FINDINGS ON ASPIRIN AND MIGRAINE IN THE PHYSICIANS' HEALTH STUDY

Julie E. Buring, Richard Peto, Charles H. Hennekens. Brigham and Women's Hospital and Channing Laboratory, Boston, MA

The Physicians' Health Study is a randomized, double-blind, placebo controlled trial testing low dose aspirin (325 mg every other day) in the primary prevention of cardiovascular disease and beta-carotene in decreasing cancer risks among 22,071 US male physicians aged 40 to 84. Annual follow-up questionnaires requested information on occurrence of numerous medical conditions including migraine. After an average of 60.2 months of follow-up, compliance with study medication was 83.0%, and morbidity follow-up was 99.7% complete. There were 689 self-reports of migraine in the aspirin group and 869 in the placebo group, representing a statistically significant 21% reduction in risk (relative risk = 0.79, 95% confidence interval, 0.72 to 0.88, p < 0.00001). These data support the hypothesis that regular low-dose aspirin reduces the occurrence of migraine.
It is the mission of the American Heart Association to reduce disability and death from cardiovascular diseases and stroke.