Cerebral / Aneurysms

**AB-14066-98**


It has been recognised that the level of superoxide dismutase (SOD) significantly increases in CSF as the result of cerebral ischaemic damage. The aim of this study was to correlate the CSF levels of SOD enzymatic activity to the patterns of subarachnoid haemorrhage with regards to ischaemic complications due to vasospasm.

A series of 78 patients operated on for intracranial aneurysms was studied; all patients were monitored with serial TCD measurements every second day after SAH. CSF samples were obtained at surgery by cisternal puncture of the subarachnoid cistern nearest to the aneurysm. SOD activity was assayed spectrophotometrically. Mean cisternal CSF level of SOD in 12 control cases (12.99±2.33 U/ml) is significantly higher (p<0.01) than in 26 patients operated on between day 1 and 3 from last SAH episode (4.44±0.7 U/ml) and in 40 patients treated by delayed surgery (7.64±0.92 U/ml). In 13 patients presenting neurological deterioration related to arterial vasospasm mean cisternal SOD level was 12.23±1.86 U/ml; in 27 cases without vasospasm mean level was 5.43±0.7 U/ml (p<0.001).

The present results suggest that (a) cisternal CSF levels of SOD significantly decreases after SAH, probably in relation to an impaired synthesis in the brain compartment and that (b) a substantial elevation of SOD levels is present in patients treated by delayed surgery (7.64±0.92 U/ml) is significantly higher (p<0.001) than in 26 patients operated on between day 1 and 3 from last SAH episode (4.44±0.7 U/ml) and in 40 patients treated by delayed surgery (7.64±0.92 U/ml). In 13 patients presenting neurological deterioration related to arterial vasospasm mean cisternal SOD level was 12.23±1.86 U/ml; in 27 cases without vasospasm mean level was 5.43±0.7 U/ml (p<0.001).

**AB-14067-98**


**Background:** The Saguenay-Lac-Saint-Jean (SLSJ) region is a geographically isolated area (population 285,955) located in the northeastern part of the Province of Québec, Canada. Using a population-based register, the genealogical reconstruction of 502 individuals with ruptured intracranial aneurysm (RIA) showed a familial aggregation (the presence of aneurysm in two or more first- to third-degree relatives) for 144 (28.7%) of them; this proportion is much higher than reported elsewhere.

**Objective:** In order to assess the genetic predisposition to RIA in the SLSJ population, the objective of the present study is to compare familial and non-familial cases and to provide an estimate of the recurrence risk ratio for siblings.

**Results:** The age at the time of rupture, the number of intracranial aneurysms for each patient and the location of RIAs were not statistically different in the familial versus the non-familial group. Of the 3449 siblings, 20 (0.58%) had suffered a RIA. The recurrence risk ratio calculated for siblings (defined as the risk of disease among siblings divided by the estimated population prevalence) is 1.6 (CI 95% 1.0—2.4).

**Conclusions.** The overall mortality rate was 22.2% (46 of 207 patients). Subarachnoid hemorrhage and its neurological sequelae accounted for the principal mortality in this series. Medical (nonneurological and nontreatment-related) complications accounted for 37% of all deaths. Systemic inflammatory response syndrome with associated multiple organ dysfunction syndrome was the leading cause of death from medical complications. The authors conclude that respiratory failure is related to neurological outcome, although it is not commonly the primary cause of death from medical complications.

**AB-14069-98**

**Reversal and Prevention of Cerebral Vasospasm by Intracarotid Infusions of Nitric Oxide Donors in a Primate Model of Subarachnoid Hemorrhage**—Plutz RM, Oldfield EH (Surgical Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bldg 10, Rm 5D-37, 9000 Rockville Pike, Bethesda, MD 20892), Bosco RJ—*J Neurosurg.* 1997;87:746—751.

Decreased endothelium-derived relaxing factor, nitric oxide (NO), in the arterial wall has been hypothesized to be a potential cause of cerebral vasospasm following subarachnoid hemorrhage (SAH). The authors sought to determine whether intracarotid infusions of newly developed NO-donating compounds (NONOates) could reverse vasospasm or prevent the occurrence of cerebral vasospasm in a primate model of SAH. Twenty-one cynomolgus monkeys were studied in two experimental...
settings. In an acute infusion experiment, saline or NONOate was infused intracarotidly in four normal monkeys and in four monkeys after onset of SAH. During the infusions regional cerebral blood flow (rCBF) was measured in eight animals and CBF velocity in two. In a chronic infusion experiment, saline (four animals) or NONOate (diethylenetramine-NO [three animals] or proli-NO [six animals]) was infused intracarotidly in monkeys for 7 days after SAH. In acute infusion experiments, 3-minute intracarotid diethylenetramine-NO infusions reversed arteriographically confirmed vasospasm of the right middle cerebral artery (MCA) (as viewed on anteroposterior projection, the decrease in area was 8.4±4.3% in the treatment group compared with 5.5±12% in the control group; p<0.004), increased rCBF by 31±11% (p<0.002), and decreased the mean systolic CBF velocity in the right MCA. In a long-term infusion experiment, the area of the right MCA in control animals decreased by 63±5%. In animals undergoing a 7-day continuous glucantime-NO intracarotid infusion, the area of the right MCA decreased by 15±6%, and in animals undergoing a 7-day proli-NO infusion, the area of the right MCA decreased by 11±2% (p<0.05). The mean arterial blood pressure decreased in the glucantime-NO group from 75±12 mm Hg (during saline infusion) to 70±10 mm Hg (during glucantime-NO infusion; p<0.05), but it was unchanged in animals undergoing proli-NO infusion (76±12 mm Hg vs. 78±12 mm Hg). Results of these experiments show that cerebral vasospasm is both reversed and completely prevented by NO replacement. However, only the use of regional infusion of the NONOate with an extremely short half-life avoided a concomitant decrease in arterial blood pressure, which could produce cerebral ischemia in patients with impaired autoregulation of CBF after the rupture of an intracranial aneurysm.

AB-14070-98

OBJECTIVE: Iron catalyzed generation of injurious free radicals has been implicated in the pathogenesis of cerebral vasospasm after subarachnoid hemorrhage (SAH). The present study assessed the effects of the iron chelator deferiprone on cerebral vasospasm in an in vivo rabbit model of SAH.

METHODS: Twenty-four rabbits were assigned to three groups as follows: SAH plus placebo (n=8), SAH plus deferiprone (n=8), or control plus placebo (n=8). Deferiprone was administered to an additional group of three rabbits that were not subjected to SAH. Drug administration was initiated 8 hours after SAH was induced and was repeated at 8-hour intervals. The animals were killed using perfusion fixation 48 hours after SAH. Cross-sectional areas of basilar artery histological sections were measured by an investigator blinded to the treatment groups.

RESULTS: In placebo-treated animals, the average luminal cross-sectional area of the basilar artery was reduced by 54% after SAH compared to controls (i.e., from 0.272 to 0.125 mm²). The vasospastic response after SAH was attenuated significantly in animals treated with deferiprone (0.208 mm², representing a 24% reduction).

CONCLUSION: Previous experimental studies suggested that iron chelation can be effective in attenuating cerebral vasospasm after SAH. Deferiprone is a recently developed iron chelator that has been extensively evaluated for the treatment of patients requiring chronic blood transfusions. The present study demonstrates that deferiprone is effective in attenuating experimental cerebral vasospasm. Because of its stability, lipophilicity, and ability to penetrate the blood-brain barrier, deferiprone represents an attractive candidate for the treatment of cerebral vasospasm.

Clinical

AB-14071-98

Objectives.—To describe the clinical features of cardioembolic infarcts. Material & methods.—Cardioembolic infarct was diagnosed in 231 (15.4%) of 1500 consecutive stroke patients included in a prospective stroke registry over an 8-year period. Results.—Cardiac sources of emboli included isolated atrial dysrythmia (57.1%), valvular heart disease (20.3%), and coronary artery disease (18.2%). Patients with cardioembolic stroke showed a significantly higher (P<0.00001) frequency of sudden onset of neurological deficit (79.7%) and altered consciousness (31.2%) than patients with lacunar infarct (38% and 1.9%) and atherothrombotic infarction (46% and 24%). Eleven patients had a spectacular shrinking deficit and 6 a presumed cardioembolic lacunar infarct. Early recurrent embolisms occurred in 6.5% of patients mostly (60%) within 7 days of initial embolism. In-hospital mortality was 27.3% (0.8% in lacunar infarcts, 21.7% in atherothrombotic infarction, P<0.000001). Conclusion.—Cardioembolic infarction is a severe subtype of stroke with a high risk of early death. Clinical features at stroke onset may help clinicians to differentiate cerebral infarction subtypes and to establish prognosis more accurately.

AB-14072-98

Background: Hyperhomocysteinemia has been shown to be a mild independent risk factor for premature atherosclerosis, and there is evidence of an increased rate of peripheral vascular occlusive disease, myocardial infarction, and stroke.

Objective: To evaluate clinical, biochemical, and neurophysiological findings in patients with ischemic stroke with and without hyperhomocysteinemia.

Subjects: One hundred twenty-five consecutive patients with a history of stroke and 60 healthy control subjects.

Methods: Patients were divided into those with and those without hyperhomocysteinemia, which was defined as blood levels beyond the mean total plasma homocysteine level plus 2 SDs of the healthy control group. History, symptoms, cause, patterns of infarction, biochemical data, continuous and transcranial Doppler sonography, and event-related potentials were recorded in all patients.

Results: Twenty-seven patients had hyperhomocysteinemia. Compared with the 98 patients without hyperhomocysteinemia, they had an increased rate of hypertension (odds ratio, 3.5; 95% confidence interval, 1.0–12.6), an increased level of uric acid (P<0.007), an increased hematocrit (P<0.02), a higher rate of microangiopathy (odds ratio, 2.8; 95% confidence interval, 1.1–7.2), and a trend to a higher rate of multiple infarctions. Furthermore, the P3 latency of the event-related potential was significantly increased in hyperhomocysteinemia (P<0.004).

Conclusions: Hyperhomocysteinemia is probably an independent risk factor for stroke, with a prevalence of about 20% in all patients with a history of stroke; however, additional factors (eg, hypertension, hyperuricemia) may have an enhancing effect. There are significant differences in stroke patterns between patients with and without hyperhomocysteinemia, with a higher rate of lesions typical of cerebral microangiopathy and a trend to multiple infarctions in the former. Impairment of cognitive processing as measured by visual event-related potential is more pronounced in hyperhomocysteinemia.

AB-14073-98
Assessment of Mental Ability in Elderly Anticoagulated Patients: Its Reduction Is Associated With a Less Satisfactory Quality of Treatment—Palareti G (Dept of Angiology and Blood Coagulation, University Hospital S. Orsola, Via Massarenti 9, 40138 Bologna, Italy), Poggi...
Hyperhomocyst(e)inemia Is a Risk Factor For Arterial Endothelial Dysfunction in Humans—Woo KS (Department of Medicine, Prince of Wales Hospital, Shatin, Hong Kong), Chook P, Lolin YI, Cheung ASP, Chan LT, Sun YY, Sanderson JE, Metreweli C, Celemajer DS—Circulation. 1997;96:2542–2544. © 1997 American Heart Association, Inc.

Background Hyperhomocyst(e)inemia is associated with premature peripheral vascular, cerebrovascular, and coronary artery disease. Because homocysteine has been found to be damaging to endothelial cells in animal and cell culture studies, we evaluated the association between hyperhomocysteinemia and arterial endothelial dysfunction (a marker of early atherosclerosis) in asymptomatic adult subjects.

Methods and Results Using high-resolution ultrasound, we measured endothelium-dependent flow-mediated dilation (EDD) and endothelium-independent nitrovasodilator-induced dilation (GTN) of the brachial artery in 14 prospectively defined hyperhomocysteinemic (mean plasma homocysteine, 34.8±8.5 μmol/L), nonsmoking, healthy subjects aged 53±9 years and 14 control subjects with low plasma homocysteine levels (9.9±3.2 μmol/L). The two groups were well matched for age, sex, body mass index, blood pressure, blood cholesterol, folate, and vitamin B12 levels; and vessel diameter. EDD was significantly lower in hyperhomocysteinemic subjects (6.5±1.7%) than in subjects with low homocysteine levels (10.8±2.1%) (P<0.001). GTN responses were similar in the two subject groups (P=0.90). Multivariate analysis confirmed homocysteine level as the strongest predictor for impaired EDD, independent of age, sex, body mass index, or blood pressure, folate, vitamin B12, and cholesterol levels.

Conclusions Hyperhomocysteinemia is an independent risk factor for arterial endothelial dysfunction in healthy middle-aged adults.


Previous research has indicated that intraplaque hemorrhage is a significant pathogenetic factor in carotid artery disease. The present study was undertaken to evaluate whether the clinical presentation of patients with carotid artery disease could be correlated to quantitative histologic analysis of surgically removed carotid specimens. Two-hundred-seventy patients undergoing carotid endarterectomy comprised the material. Symptomatology was assessed prospectively. After removal, the carotid plaques were analyzed histologically for relative volume content of hemorrhage, fatty tissue, fibrous tissue, and calcification. There was no difference between asymptomatic and symptomatic patients. However, when the time interval between onset of symptoms and surgery was considered, plaques from patients with recent symptoms contained more hemorrhage compared with plaques from asymptomatic patients (p=0.0045). The paper supports the theory of intraplaque hemorrhage being related to clinical events in carotid artery disease.


Objectives—to better define the neuropathology of vascular dementia.

Methods—The neuropathological findings in 18 elderly, undemented subjects free of cerebrovascular disease were compared with 19 elderly undemented subjects who had cerebrovascular disease (many of whom had had a “stroke”) and 24 elderly demented subjects who had cerebrovascular disease, but no other pathology to account for dementia. Cases in all groups were selected for absence or no more than very mild Alzheimer type pathology.

Results—Microvascular brain damage in the form of severe cribriform change and associated subcortical white matter damage and microinfarction were correlated with a history of dementia. Severe cribriform change was much more common and microinfarction somewhat more common in the demented group with vascular disease than the undemented group with vascular disease (P=0.0006 and P=0.031 respectively). Other findings of note were that congophilic angioathy had a greater prevalence in the vascular dementia group than the control group, single cerebral infaracts were more common in the group who were undemented with vascular disease than in the group with dementia and vascular disease (P=0.0028), and the last group lacked evidence of macroscopic infarction more often than the first (P=0.034). There was a nonsignificant trend for the ratio of infarcted/uninfarcted tissue in one cerebral hemisphere to be higher in the group with dementia and vascular disease than in the group with vascular disease but no dementia.

Conclusions—Microvascular disease, not macroscopic infarction, was the chief substrate of vascular dementia in this series of cases.


We performed a case-control study to investigate the role of recent infection as stroke risk factor and to identify pathogenetic pathways linking infection and stroke. We examined 166 consecutive patients with acute cerebrovascular ischemia and 166 patients hospitalized for nonvascular and noninflammatory neurologic diseases. Control subjects were individually matched to patients for sex, age, and season of admission. We assessed special biochemical parameters in subgroups of stroke patients with and without recent infection (n=21) who were similar with respect to demographic and clinical parameters. Infection within the preceding week was a risk factor for cerebrovascular ischemia in univariate (odds ratio [OR] 3.1; 95% confidence interval [CI], 1.57 to 6.1) and age-adjusted multiple logistic regression analysis (OR 2.9; 95% CI, 1.31 to 6.4). The OR of recent infection and age were inversely related. Both bacterial and viral infection contributed to increased risk. Infection elevated the risk for cardioembolism and tended to increase the risk for arterioarterial embolism. Stroke patients with and without preceding infection were not different with respect to factor VII and factor VIII activity, fibrin monomer, fibrin D-dimer, von Willebrand factor, C4b-binding protein, protein S, anticardiolipin antibodies, interleukin-1 receptor antagonist, soluble tumor necrosis factor-α receptor,
interleukin-6, interleukin-8, and neopterin. In conclusion, recent infection is an independent risk factor for acute cerebrovascular ischemia. Its role appears to be more important in younger age groups. The pathogenetic linkage between infection and stroke is still insufficiently understood.

Epidemiology

**AB-14078-98**


**Objective:** To determine the influence of oral contraceptives (particularly those containing modern progestins) on the risk for ischaemic stroke in women aged 16–44 years.

**Design:** Matched case-control study.

**Setting:** 16 centres in the United Kingdom, Germany, France, Switzerland, and Austria.

**Subjects:** Cases were 220 women aged 16–44 who had an incident ischaemic stroke. Controls were 775 women (at least one hospital and one community control per case) unaffected by stroke who were matched with the corresponding case for 5 year age band and for hospital or community setting. Information on exposure and confounding variables were collected in a face to face interview.

**Main outcome measures:** Odds ratios derived with stratified analyses and unconditional logistic regression to adjust for potential confounding.

**Results:** Adjusted odds ratios (95% confidence intervals) for ischaemic stroke (unmatched analysis) were 4.4 (2.0 to 9.9), 3.4 (2.1 to 5.5), and 3.9 (2.3 to 6.6) for current use of first, second, and third generation oral contraceptives, respectively. The risk ratio for third versus second generation was 1.1 (0.7 to 2.0) and was similar in the United Kingdom and other European countries. The risk estimates were lower if blood pressure was checked before prescription.

**Conclusion:** Although there is a small relative risk of occlusive stroke for women of reproductive age who currently use oral contraceptives, the attributable risk is very small because the incidence in this age range is very low. There is no difference between the risk of oral contraceptives of the third and second generation; only first generation oral contraceptives seem to be associated with a higher risk. This small increase in risk may be further reduced by efforts to control cardiovascular risk factors, particularly high blood pressure.

**AB-14079-98**

**Epileptic Seizures After a First Stroke: The Oxfordshire Community Stroke Project**—Burn J (Rehabilitation Research Unit, Southampton General Hospital, Southampton, SO9 4XY), Dennis M, Bamford J, Sandercock P, Wade D, Warlow C—BMJ. 1997;315:1582–1587.

**Objective:** To describe the immediate and long term risk of epileptic seizures after a first ever stroke.

**Design:** Cohort study following up stroke survivors for 2 to 6.5 years; comparison with age specific incidence rates of epileptic seizures in the general population.

**Setting:** Community based stroke register.

**Subjects:** 675 patients with a first stroke, followed up for a minimum of 2 years.

**Main outcome measures:** Occurrence of single and recurrent seizures.

**Results:** 52 patients had one or more post stroke seizures; in 25 the seizures were recurrent. The 3 year actuarial risk of a post stroke seizure in survivors (excluding 19 patients with a history of epilepsy and 3 patients in whom the seizure occurred shortly before death from another cause) was 11.5% (95% confidence interval 4.8% to 18.2%). The relative risk of was estimated at 35.2 in the first year after stroke and 19.0 in year 2. The risk of seizures was increased in survivors of subarachnoid and intracerebral haemorrhage (hazard ratio for intracranial haemorrhage vs cerebral infarction 10.2 (3.7 to 27.9)). The risk of seizures after ischaemic stroke was substantial only in patients presenting with severe strokes due to total anterior circulation infarction. Only 9 of 295 patients (3%) independent one month after stroke suffered a seizure between 1 month and 5 years (actuarial risk 4.2% (0.1% to 8.3%)�.

**Conclusion:** Stroke patients have about an 11.5% risk of single or recurrent seizures in the first 5 years after a stroke. Patients with more severe strokes or haemorrhagic strokes are at higher risk.

**AB-14080-98**

**A Triennial Comparison of Intracerebral Hemorrhage Mortality in Texas**—Morgenstern LB (Dept of Neurology, University of Texas Medical School, 6431 Fannin, Rm 7.044, Houston, TX 77030), Spears, WD—Ann Neurol. 1997;42:919–923. © 1997 by the American Neurological Association.

Intracerebral hemorrhage (ICH) is a significant cause of stroke death. Little is known about the relative risk of Hispanic Americans (HAs), African Americans (AAs), and non-Hispanic whites (NHWs) for ICH mortality. Based on the high prevalence of hypertension in AAs and the low prevalence of hypertension in HAs, we expected AAs to have the highest ICH mortality rates and HAs the lowest. Racial/ethnic age-specific ICH mortality rates were calculated from Texas vital statistics for the years 1980 through 1995. Rate ratios (RRs) are reported with NHWs as the referent group. There were 15,042 deaths due to ICH in Texas during this time. In the 45- to 59-year age group, AAs had an RR of 4. The RR for HAs was 1.9. In the 60- to 74-year age range, AAs had an RR of 1.7 and HAs had an RR of 1.3. In the 75+ age group, the rates were similar among all three race/ethnic groups. We conclude that there is a significant interaction of age and race/ethnicity for ICH. At younger ages, AAs and HAs have the highest ICH mortality rates. Access to care and socioeconomic status may play a role in the unexpectedly high ICH mortality rates in HAs.

**AB-14081-98**


**Objectives:** To study the association of apoE genotypes with dementia and cerebrovascular disorders in a population based sample of 85 year old people.

**Methods:** A representative sample of 85 year old people (303 non-demented, 109 demented) were given a neuropsychiatric and a medical examination and head CT. The apoE isoforms were determined. Dementia was diagnosed according to DSM-III-R.

**Results:** At the age of 85, carriers of the apoE ε4 allele had an increased odds ratio (OR) for dementia (1.9; p<0.01) and its subtypes Alzheimer’s disease (1.9; p<0.05) and vascular dementia (2.0; p<0.05). Among those categorised as having vascular dementia, the apoE ε4 allele was associated with mixed Alzheimer’s disease-multi-infarct dementia (OR 6.5; p<0.05), but not with pure multi-infarct dementia (OR 1.5; NS). Only carriers of the apoE ε4 allele who also had ischaemic white matter lesions on CT of the head had an increased OR for dementia (OR 6.1; p=0.00003), and its main subtypes Alzheimer’s disease (OR 6.8; p=0.002) and vascular dementia (OR 5.6; p=0.0007), whereas carriers of the apoE ε4 allele without white matter lesions had an OR for dementia of 1.0 (OR for Alzheimer’s disease 1.8; NS and for vascular dementia 0.6; NS) and non-carriers of the apoE ε4 allele with white matter lesions had an OR for dementia of 2.2; NS (OR for Alzheimer’s disease 2.7; NS and for vascular dementia 1.6; NS). The apoE allele variants were not related to mortality or incidence of dementia between the ages of 85 and 88. The ε2 allele was related to a higher prevalence of stroke or transient ischaemic attack at the age of 85 (OR 2.1; p<0.05) and a higher incidence of multi-infarct dementia during the follow up (OR 2.9; p<0.05).
Conclusions—Neither the apoE e4 allele nor white matter lesions are sufficient risk factors by themselves for dementia at very old ages, whereas possession of both these entities increases the risk for Alzheimer’s disease and vascular dementia substantially.

AB-14082-98

We used the Kaplan-Meier product limit method to estimate rates and Cox proportional hazards regression analysis with bootstrap validation to model significant independent predictors of and temporal trends in survival and recurrent stroke among 1,111 residents of Rochester, MN, who had a first cerebral infarction from 1975 through 1989. The risk of death after first cerebral infarction was 7% ± 0.7% at 7 days, 14% ± 1.0% at 30 days, 27% ± 1.3% at 1 year, and 53% ± 1.5% at 5 years. Independent risk factors for death after first cerebral infarction were age (p < 0.0001), congestive heart failure (p < 0.0001), persistent atrial fibrillation (p < 0.0001), recurrent stroke (p < 0.0001), and ischemic heart disease (p < 0.0001 for age ≥ 70, p < 0.05 for age > 70). The risk of recurrent stroke after first cerebral infarction was 2% ± 0.4% at 7 days, 4% ± 0.6% at 30 days, 12% ± 1.1% at 1 year, and 29% ± 1.5% at 5 years. Age (p = 0.0002) and diabetes mellitus (p = 0.0004) were the only significant independent predictors of recurrent stroke. Neither the year nor the quinquennium of the first cerebral infarction was a significant determinant of survival or recurrence. The temporal trend toward improving survival after first cerebral infarction documented in Rochester, MN, in the decades before 1975 has ended.

Experimental Pathology

AB-14083-98
Effects of 17β-Estradiol on Glucose Transporter 1 Expression and Endothelial Cell Survival Following Focal Ischemia in the Rats—Shi J (PO Box 100487, JMHMC, College of Pharmacy, University of Florida, Gainesville, FL 32610), Zhang YQ, Simpkins JW—Exp Brain Res. © Springer-Verlag 1997.

Estrogen replacement therapy in postmenopausal women is associated with a decreased mortality and morbidity from stroke. The present study was undertaken to investigate the effects of estrogen on endothelial cell glucose transporter 1 (GLUT 1) and on the cell viability during focal ischemia in a rat model. Female rats were ovariec-tomized (OVX) and 2 weeks later 17β-estradiol (E2) was injected subcutaneously at a dose of 100 μg/kg 2 h before unilateral middle cerebral artery (MCA) occlusion. Ischemic lesion size was quantified using 2,3,5-triphenyl tetrazolium chloride (TTC) staining and GLUT 1 protein was analyzed by Western blotting. E2 treatment decreased ischemic lesion size in slices taken at 9 and 11 mm posterior from the bregma. Ischemic lesion size increased by 46.3% and 44.1%, respectively (P < 0.05). GLUT 1 protein decreased in both OVX and E2, and 11 mm posterior from the olfactory bulb by 46.3% and 44.1%, respectively. A semiquantitative analysis of GLUT 1 protein expression in the ipsilateral hemisphere. Delaying the onset of ischemia increased GLUT 1 transporters and protects BCEC loss which may in turn reduce focal ischemic brain damage.

AB-14084-98

In anesthetized piglets, endothelial and neuronal nitric oxide synthase (eNOS and nNOS, respectively) levels were investigated after global cerebral ischemia. Increased intracranial pressure was used to produce 5 or 10 minutes of global ischemia, which was verified visually by observing pial arteriolar blood flow and by a microsphere technique. At 4 to 6 hours of reperfusion, parietal cortex, hippocampus, and cerebellum were collected for immunohistochemical or immunoblot analysis. Immunohistochemical examination localized eNOS only to blood vessels and nNOS only to nonvascular cells, which were primarily neurons in all regions examined. Analysis of immunoblot data revealed significant increases in eNOS levels from 47 ± 22 pixels/μg protein for time controls to 77 ± 36 pixels/μg protein (75% increase) for ischemia in parietal cortex (n = 9 to 10) and 22 ± 10 for control to 40 ± 16 pixels/μg protein (40% increase) for ischemia in hippocampus (n = 7 to 8). Levels of eNOS in cerebellum also tended to be higher but were variable and not significant (n = 5 to 6). In contrast, changes in nNOS levels were not detected at 4 or 6 hours. The increase in eNOS levels detected on immunoblots also was apparent on tissue sections as an increase in intensity of staining. Cyclooxygenase-dependent mechanisms were investigated with respect to the ischemia-induced increase in eNOS levels. Pretreatment with the cyclooxygenase inhibitor indomethacin (5 mg/kg intravenously) abolished the ischemia-induced eNOS increase in parietal cortex and hippocampus (n = 7). Thus, we conclude that the eNOS response is rapid, specific to vessels, and involves an indomethacin-sensitive mechanism.

AB-14085-98

To investigate long-term adaptations after unilateral carotid artery ligation, the effect of forebrain ischemia on cerebral blood flow and ATP levels was determined at various times after ligation. Unilateral carotid artery ligation was performed in male Wistar rats 0, 3, or 7 days before forebrain ischemia. Laser-Doppler blood flow was monitored bilaterally over the parietal cortex and ATP was measured in the subjacent cortex of both hemispheres at the end of a 10-minute episode of ischemia. In the 0-day group, forebrain ischemia reduced cortical blood flow to 12 ± 8% (mean ± SD) of preischemic values and lowered cortical ATP to 26 ± 35% of control levels in the ipsilateral hemisphere. Delaying the onset of forebrain ischemia for 3 days after carotid artery ligation significantly improved cortical blood flow (29 ± 12%, P < 0.05) and ATP levels (92 ± 11%, P < 0.05) in the ipsilateral hemisphere. Delaying forebrain ischemia for 7 days also significantly improved ipsilateral blood flow (36 ± 1%, P < 0.05) and ATP levels (81 ± 29%, P < 0.05) compared with the 0-day group. In the contralateral hemisphere, the reduction in blood flow and ATP levels was not significantly altered by delaying the onset of forebrain ischemia for 3 or 7 days. These results show that unilateral carotid artery ligation induces long-term vascular adaptations that improve the collateral circulation and preserve ATP levels during a subsequent episode of ischemia.

AB-14086-98

The present study was undertaken to determine if estrogens protect female rats from the neurodegenerative effects of middle cerebral artery
(MCA) occlusion. The rats were ovariectomized and 7 or 8 days later various estrogen preparations were administered before or after MCA occlusion. Pretreatment with 17β-estradiol (17β-E2) or a brain-targeted 17β-E2 chemical delivery system (CDS) decreased mortality from 65% in ovariectomized rats to 22% in 17β-E2-treated and 16% in 17β-E2 CDS–treated rats. This marked reduction in mortality was accompanied by a reduction in the ischemic area of the brain from 25.6 ± 5.7% in the ovariectomized rats to 9.8 ± 4% and 9.1 ± 4.2% in the 17β-E2–implanted and the 17β-E2 CDS–treated rats, respectively. Similarly, pretreatment with the presumed inactive estrogen, 17α-estradiol, reduced mortality from 36 to 0% and reduced the ischemic area by 55 to 81%. When administered 40 or 90 minutes after MCA occlusion, 17β-E2 CDS reduced the area of ischemia by 45 to 90% or 31%, respectively. In summary, the present study provides the first evidence that estrogens exert neuroprotective effects in an animal model of ischemia and suggests that estrogens may be a useful therapy to protect neurons against the neurodegenerative effects of stroke.

Imaging

**AB-14087-98**


**PURPOSE:** We sought to determine the prevalence of coexistent occult vascular malformations (OVMs) and developmental venous anomalies (DVAs) and to investigate the relationship between them.

**METHODS:** One hundred two patients with OVMs were examined with precontrast and postcontrast T1-weighted MR imaging and with noncontrast T2-weighted MR imaging. Seventy-two patients had surgery, with subsequent pathologic confirmation of the final diagnosis.

**RESULTS:** Coexistent DVAs and OVMs were present in 23 (23%) of 102 patients. Seventy-nine patients had OVMs without DVAs, and in this population, multiple OVMs (from two to 10 or more) were seen in 13 patients (16%). In contrast, multiple OVMs were seen in 10 (43%) of 23 patients with coexisting OVMs and DVAs. Twenty-five (83%) of 30 OVMs coexisting with DVAs were infratentorial. In 72 patients with surgically resected OVMs, 49 (68%) had pathologically confirmed cavernous malformations. Among the patients with coexistent DVAs, seven (46%) had cavernous malformations, four (27%) had arteriovenous malformations, and four (27%) had vascular malformations that were not classifiable.

**CONCLUSION:** Our study revealed a high prevalence of OVMs with coexistent DVAs, and a high percentage of these were in the posterior fossa. Contrast-enhanced MR imaging may increase the probability of finding these lesions, and therefore should be considered part of the preoperative evaluation, since the finding of unexpected coexistent lesions may affect surgical management.

**AB-14088-98**


**PURPOSE:** We examined age-related changes in baseline regional cerebral blood volume (rCBV) and response to acetazolamide stimulation by using dynamic contrast-enhanced MR imaging.

**METHODS:** Thirty healthy volunteers ranging widely in age (23 to 82 years) were examined before and after intravenous injection of acetazolamide with dynamic susceptibility contrast-enhanced MR imaging. rCBV values were normalized for intersubject and intrasubject comparison by estimating an arterial input function directly from the imaging data. Preacetazolamide baseline rCBV and the percentage volume change index (PVCV) of the postacetazolamide to preacetazolamide state were calculated and examined as a function of age.

**RESULTS:** Older adults (>50 years) had lower baseline rCBV per unit tissue than did younger adults (<50 years), but higher rCBV after acetazolamide stimulation. Baseline rCBV tended to decrease with age in the medial frontal and frontoparietal gray matter regions. Response to acetazolamide stimulation, measured by PVCV, showed a significant age-related increase in gray matter, approximately 0.5% per year.

**CONCLUSION:** rCBV can be significantly increased after acetazolamide stimulation in the healthy aged. These results support the notion that age-related decreases in rCBV measured at rest reflect reduced regional metabolic requirements rather than reduced capacity for regional substrate delivery. These data serve as a normative baseline for comparison studies of rCBV vascular reserve in aging persons with various cerebrovascular disorders.

**AB-14089-98**

Natural History of the Spontaneous Reperfusion of Human Cerebral Infarcts as Assessed by 99m Tc HMPAO SPECT—Bowler JV (Dept of Clinical Neuroscience, Charing Cross and Westminster Medical School, St Dunstan’s Road, London W6 8RP, UK), Wade JPH, Jones BE, Nijran KS, Steiner TJ—J Neurol Neurosurg Psychiatry. 1998;64:90–97.

**Objective**—Little is known about the effect of spontaneous reperfusion of human cerebral infarcts. Single photon emission computerised tomography (SPECT) data were analysed from a study using 99m Tc–labeled hexamethylpropyleneamine oxime in human cerebral infarction for the frequency of reperfusion and to see if it affected infarct size, oedema, haemorrhagic transformation, or functional outcome.

**Methods**—Fifty sequential cases of ischaemic stroke were studied with 124 99m Tc HMPAO SPECT at around one day, one week, and three months after stroke along with detailed clinical and functional assessments.

**Results**—Visually apparent reperfusion occurred in 14 of 50 patients (28%) with a mean delay of 5.8 days and reperfusion was seen in seven others in whom it was identified on the basis of changes in perfusion deficit volume. It occurred in 13 of 23 embolic events but only in three of 23 other events. In only two cases did spontaneous reperfusion occur early enough to preserve tissue or function. Reperfusion did not otherwise reduce infarct size, or improve clinical or functional outcome, and was not associated with oedema but an association with haemorrhagic transformation was suggested. Reperfusion significantly decreased the apparent perfusion deficit as measured by SPECT one week from the ictus, but was mostly non-nutritional and transient. The mean volume of tissue preserved by nutritional reperfusion was 10 cm3, but this was unequally distributed between cases. Late washout of 99m Tc HMPAO from areas of hyperaemic reperfusion may be a good prognostic marker but is a rare phenomenon and too insensitive to be of general applicability.

**Conclusions**—Spontaneous reperfusion after cerebral infarction occurs in 42% of cases within the first week but is associated with clinical improvement in only 2%. It has few adverse consequences although it may be associated with haemorrhagic transformation.

**Neurosonology**

**AB-14090-98**


The purpose of this study was to analyse the cerebral haemodynamic changes brought about by trial occlusion of the internal carotid artery (ICA). Sixteen patients with surgically inaccessible cerebral aneurysms, carotid cavernous fistulas or neck neoplasms were monitored with transcranial Doppler ultrasonography (TCD) during 90–120 s angi-
graphic ICA balloon occlusion or ICA closure with a Seldinger valve. The blood velocity (V) was registered continuously in both middle cerebral arteries (MCAs) while the pulsatility index (PI MCA) and haemodynamic tension (U hem MCA) were calculated.

ICA closure led to an instantaneous drop in the ipsilateral VMCA, PI MCA and U hem MCA. The VMCA thereafter increased gradually until reaching a stable level. The subjects were grouped into those with initial drops in VMCA to ≥60% of pre-occlusion value (group 1) and those that fell to <60% (group 2), respectively. In group 1 autoregulatory mechanisms made the PI MCA decline further, while the U hem MCA remained unaltered during ICA closure. In group 2, however, the PI MCA did not change further, while the U hem MCA increased slightly. The cerebral haemodynamic features during ICA test occlusion were thus essentially different in the two groups. On re-opening the ICA, there was an overshoot in VMCA and U hem MCA. Contralaterally, the VMCA was increased during ICA occlusion.

Seven of the patients later had their ICA closed permanently. While none of five group 1 patients developed haemodynamic complications, two group 2 individuals experienced haemodynamic stroke. Assuming ICA sacrifice is feasible when test occlusion results in an ipsilateral initial reduction in VMCA to ≥60% of preocclusion value, the corresponding limit for the U hem MCA is ≥40%. In the pre-operative evaluation of the haemodynamic risk related to ICA loss, TCD emerges as a reliable method. It also seems to allow for the reduction of test occlusion time to 90–120 s.

AB-14091-98


To compare blood flow velocity changes within the middle cerebral artery (MCA) during hyperventilation, as measured with both by transcranial Doppler sonography and MR imaging, with the diameter of the MCA as measured with MR imaging alone. METHODS: The studies were performed in six healthy volunteers ranging in age from 22 to 31 years (mean, 27 years). Transcranial Doppler sonography was carried out with a range-gated 2-MHz transducer. MR examinations were done on a 1.5-T imaging unit. MR angiography was performed using the time-of-flight technique. MR flow measurements were carried out by using the phase-mapping technique with an ECG-triggered phase-contrast sequence. RESULTS: During hyperventilation, the mean blood flow velocity of the proximal MCA declined by 49.6% ± 5.7% (mean ± standard deviation) as measured with Doppler sonography, and by 47% ± 4.6% as measured with MR flow calculation. The diameter of the MCA (3.4 ± 0.3 mm) remained unchanged on MR imaging studies (3.3 ± 0.3 mm). CONCLUSION: We found a good correlation between relative flow velocity changes measured by transcranial Doppler sonography and MR techniques. MR imaging revealed no significant changes in the diameter of the proximal MCA during normal versus hyperventilation. Relative changes in flow velocity in the MCA would thereby reflect relative changes in cerebral blood flow, at least during hyperventilation.

AB-14092-98


Transcranial Doppler measurement (TCD) of cerebrovascular reserve (CVR) is usually performed by the CO2 test, the acetazolamide test, or the breath-holding test. Since these tests are time-consuming and labor-intensive, alternative methods such as the hand-gripping test are of interest. Twenty-one normal persons and 25 patients with unilateral carotid artery disease were studied. Flow velocity changes in both middle cerebral arteries (MCAs) during bilateral hand gripping were measured by TCD and compared with acetazolamide test results. The increase in MCA mean flow velocity (FVmean) during hand gripping was 18.0 ± 6.3% in normal persons; the increases in the poststenotic MCA were 15.8 ± 9.7% in all patients and 9.4 ± 5.4% in patients with impaired CVR as determined by the acetazolamide test. Only in the group with impaired acetazolamide reactivity was the increase in the poststenotic MCA significantly lower compared to that in controls (p < 0.01) and to the contralateral, nonstenotic side (p < 0.01). Nevertheless the FVmean increases in both tests showed a weak, but significant correlation (r = 0.59, p < 0.01). All FVmean increases during hand gripping were significantly (p < 0.01) lower than those during the acetazolamide test. The test appears as a weaker stimulus for MCA blood flow velocity increase than the acetazolamide test. Thus, only a substantial reduction of acetazolamide reactivity leads to a reduced MCA FVmean increase using hand gripping. Although it is highly specific but less sensitive, hand gripping does not appear to be suitable as a screening measure of CVR, but might be useful in addition to standard tests.

Pharmacology / Therapeutics

AB-14093-98


Aspirin is only modestly effective in the secondary prevention after cerebral ischemia. Studies in other vascular disorders suggest that anticoagulant drugs in patients with cerebral ischemia of presumed arterial (noncardiac) origin might be more effective. The aim of the Stroke Prevention in Reversible Ischemia Trial (SPIRIT) therefore was to compare the efficacy and safety of 30 mg aspirin daily and oral anticoagulation (international normalized ratio [INR] 3.0–4.5). Patients referred to a neurologist in one of 58 collaborating centers because of a transient ischemic attack or minor ischemic stroke (Rankin grade ≤ 3) were eligible. Randomization was concealed, treatment assignment was open, and assessment of outcome events was masked. The primary measure of outcome was the composite event “death from all vascular causes, nonfatal stroke, nonfatal myocardial infarction, or nonfatal major bleeding complication.” The trial was stopped at the first interim analysis. A total of 1,316 patients participated; their mean follow-up was 14 months. There was an excess of the primary outcome event in the anticoagulated group (81 of 651) versus 36 of 665 in the aspirin group (hazard ratio, 2.3; 95% confidence interval [CI], 1.6–3.5). This excess could be attributed to 53 major bleeding complications (27 intracranial; 17 fatal) during anticoagulant therapy versus 6 on aspirin (3 intracranial; 1 fatal). The bleeding incidence increased by a factor of 1.43 (95% CI, 0.96–2.13) for each 0.5 unit increase of the achieved INR. Anticoagulant therapy with an INR range of 3.0 to 4.5 in patients after cerebral ischemia of presumed arterial origin is not safe. The efficacy of a lower intensity anticoagulation regimen remains to be determined.

AB-14094-98

Objective: To assess optimal control of blood anticoagulation to maximize antithrombotic protection after mechanical cardiac valve replacement.

Design: A population-based study of 96 patients with a mean follow-up of 7.7 years (range, 1 month to 23 years) was performed in Olmsted County, Minnesota, and 10,301 prothrombin time (PT) ratios were determined after mechanical heart valve replacement.

Material and Methods: PT ratios were analyzed in a new time-dependent Cox proportional-hazards model by defining an algorithm for comparing variability in PT ratios at each month of follow-up and relating these to thromboembolic events. The new method was compared with several conventional time-independent definitions.

Results: During 740 person-years of follow-up, 19 of 96 patients (20%) had 27 thromboembolic events. Of these 19 patients, 8 (42%) had events within 3 months after valve replacement. Freedom from any thromboembolic event was 72% at 15 years. The event rate was high (7.5% per year) during high variability and low (0.9% per year) during low variability in the PT ratio. This relationship was lost when time dependence was removed. More PT ratios were less than 1.5 during high (27%) than during low (19%) variability. Several conventional definitions of adequacy of anticoagulation that averaged PT ratios before a thromboembolic event or throughout follow-up or that compared the proportion of PT ratios above or below a fixed ratio did not define or only partially defined different thromboembolic risks.

Conclusion: Periods of high and low variability of PT ratios define high and low risk of thromboembolism, respectively.

Surgery

AB-14095-98

Objective: To evaluate whether the patterns of inpatient care and patient characteristics have changed for patients undergoing a carotid endarterectomy across a group of academic medical centers from 1990 through 1995. If changes occurred, we investigated whether they had an impact on patient outcomes.

Design: Retrospective evaluation of patients undergoing a carotid endarterectomy using a hospital discharge data set compiled by the Academic Medical Center Consortium.

Setting: Ten academic medical centers.

Patients: A total of 7019 hospital admissions for patients who had 1 carotid endarterectomy performed as a principal procedure from January 1990 to December 1995.

Main Outcome Measures: Trends in patient demographics, comorbidities, length of stay, days in the intensive care unit, and inpatient cerebral arteriogram use were determined. Patient outcomes included inpatient mortality, discharge to an institution, 30-day readmission rate, and selected diagnoses (postoperative hemorrhage, infection, or seizure; acute myocardial infarction; or cranial nerve palsy) and postprocedure diagnostic tests (computed tomography and magnetic resonance imaging of the head and electroencephalogram) indicative of complications.

Results: Over the 6-year study period, the number of carotid endarterectomies performed more than doubled and the percentage of hospital admissions for patients 65 years or older increased from 65% to 75%. The mean and median length of stay halved and the percentage of admissions with transfers to the intensive care unit decreased from 56% to 26% of cases. In addition, the percentage of cases with a cerebral arteriogram during the same admission but prior to the day of the carotid endarterectomy decreased from 52% to 27%. There were no trends in inpatient mortality, discharge to an institution, or 30-day readmission rate. There were no significant trends indicative of poorer quality of care as measured by the frequency of secondary diagnoses or postprocedure diagnostic test use.

Conclusions: Despite dramatic changes that have occurred in patient characteristics and in hospital management practices for patients undergoing a carotid endarterectomy from 1990 to 1995, we were unable to detect any measurable impact on patient outcomes. These data have implications for monitoring and evaluating the impact of systemwide change on the overall quality of care for patients undergoing a carotid endarterectomy.

AB-14096-98

Background: The number of carotid endarterectomies (CEAs) performed in the UK, and thus the need to train surgeons in this operation, has increased markedly in recent years and may continue to do so. The aim of the present study was to assess the quality, clinical outcome and case-mix of supervised training in CEA in this unit.

Methods: The study was an analysis of a prospectively gathered database of all CEAs performed in this unit since 1975.

Results: Between 1 January 1975 and 31 December 1991, 247 CEAs were performed of which only 12 were done by supervised trainees. By contrast, between 1 January 1992 and 1 July 1996, 219 CEAs were performed, 92 (42 per cent) by supervised trainees (P<0.0001). In cases performed since 1 January 1992, there was no significant difference between trainee and consultant operations with regard to age and sex of patient, smoking history, ischaemic heart disease, hypertension, diabetes, presence of preoperative infarction on computed tomography, indications for operation, degree of ipsilateral carotid stenosis, status of the contralateral carotid artery, use of a shunt or patch angioplasty. Since 1 January 1992, the total perioperative neurological event rate for supervised trainees was seven of 92 (76 per cent) of which one was fatal (cerebral infarction). The total neurological event rate for operations done by a consultant was nine of 127 (71 per cent), of which one was permanent and disabling and two were fatal (one cerebral infarction and one haemorrhage).

Conclusion: Since 1991 there has been a tenfold increase in the proportion of CEAs being performed by supervised trainees. This has been accomplished without deterioration in clinical outcome. With adequate supervision, training in CEA can be safe, even when trainees are exposed to a true cross-section of low-, medium- and high-risk cases.

AB-14097-98

Background: Some patients may be more predisposed to develop an ulceration of atherosclerotic plaque in the carotid artery, and emboli. These patients should be more at risk for a late stroke even after carotid endarterectomy than patients who are not.

Materials and methods. Six-hundred thirty-eight patients had 750 carotid endarterectomies. Excised plaque specimens were examined for gross ulceration. The degree of stenosis was determined by duplex scan and/or angiography, and at operation. The median follow-up time was 3.6 years. The risk of a stroke occurring >30 days after carotid endarterectomy was calculated. Within 1 year, an endarterectomy of the contralateral artery was done in 77 patients (Subgroup) at a median time of 60 days.

Results. Late stroke occurred in 48 patients. Patients who had had ulcerated plaque had a stroke at a median time of 2.0 years, and patients who had had no ulcers had a stroke at a median time of 5.2 years (P<0.025). The 14-year stroke-free curve was lower (P<0.05) if there was plaque ulceration. In the Subgroup, plaque ulcers were found in 55 patients (71%) at the first endarterectomy and later in 46 of the 55
patients (84%) in the contralateral artery. No ulcers were found in 22 patients (29%) initially, but later 50% had ulcers in the contralateral artery. The risk of an ulcer in the contralateral artery was increased (P<0.005) in those patients who had ipsilateral carotid ulcers.

Conclusions. Some patients appear to be predisposed for plaque ulceration and late stroke.

Items of Interest


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Abstracts of Literature
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