Abstracts of Literature

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Cerebral Aneurysms

AB-14217-98


Object. The radical scavenger (±)-N,N’-propylenedinitocinamide (AVS) was shown recently to ameliorate delayed neurological deficits resulting from ischemia in patients who have had an aneurysmal subarachnoid hemorrhage (SAH). The aim of this study was to evaluate the effect of AVS administration after experimental SAH on 1) behavioral deficits; 2) angiographically confirmed basilar artery (BA) spasm; and 3) blood-brain barrier (BBB) permeability changes.

Methods. These parameters were measured by 1) using a battery of well-characterized chronic assessment tasks over a 5-day observation period; 2) assessing in vivo the mean vessel diameter 2 days after SAH; and 3) evaluating the extravasation of protein-bound Evans Blue dye by using a spectrophotofluorimetric technique 2 days after SAH. Groups of eight to 10 rats received injections of 400 µl of autologous blood into the cisterna magna. Within 5 minutes after the surgical procedures were completed the rats were treated with an intravenously administered continuous infusion of saline (Group III) or AVS (1 mg/kg/minute, Group IV). Results were compared with those in sham-operated animals treated with intravenously administered saline (Group I) or AVS (Group II). The AVS-treated rats had significantly improved balance beam scores on Days 1 to 2 (p<0.05), shorter beam traverse times on Day 1 (p<0.05), and better beam walking performance on Days 1 to 4 (p<0.01), but no significant effect was seen in terms of SAH-related changes in body weight. Treatment with AVS also attenuated the SAH-induced BA spasm (p<0.05) and decreased BBB permeability changes in frontal, temporal, parietal, occipital, and cerebellar cortices, and in the subcortical and cerebellar gray matter and brainstem (p<0.01).

Conclusions. These results demonstrate useful antivasospastic and brain-protective actions of AVS after induction of experimental SAH and provide support for observations of beneficial effects of AVS made in the clinical setting.

AB-14218-98

Enhanced Endogenous Antioxidant Activity and Inhibition of Cerebral Vasospasm in Rabbits by Pretreatment With a Nontoxic Endotoxin Analog, Monophosphoryl Lipid A—Toyoda T, Kwan A-L, Bavbek M, Kassell NF, Wanebo JE, Lee KS (Dept of Neurological Surgery, Box 420, Health Sciences Center, Univ of Virginia, Charlottesville, VA 22908)—J Neurosurg. 1998;88:1082–1087.

Object. Monophosphoryl lipid A (MPL) and diphosphoryl lipid (DPL) are derivatives of the lipopolysaccharide (endotoxin) of Salmonella minnesota strain R595. Monophosphoryl lipid A is relatively nontoxic and can stimulate the natural defense or immune system. Diphosphoryl lipid is relatively toxic; however, at higher concentrations, it can also stimulate an immune response. The purpose of the present study was to determine the effects of these endotoxin analogs on cerebral vasospasm after the onset of subarachnoid hemorrhage (SAH) in rabbits.

Methods. Intrathecal administration of MPL or DPL (5 µg/kg) was performed immediately before and 24 hours after induction of SAH in New Zealand White rabbits. Forty-eight hours after induction of SAH, the animals were killed by perfusion fixation for morphometric analyses of vessels or perfused with saline and assayed for superoxide dismutase (SOD) activity. Additional rabbits were administered MPL or DPL and killed 24 hours later for assessment of SOD activity; no SAH was induced in these animals.

Experimental SAH elicited spasm of the basilar arteries in each group. Vasospasm was markedly attenuated in animals treated with MPL (p<0.01 compared with vehicle-treated animals), but not in animals treated with DPL. A substantial reduction in SOD activity in the basilar artery accompanied the vasospasm; this loss of activity was significantly blocked by treatment with MPL, but not DPL. In animals that were not subjected to experimental SAH, MPL elicited a significant increase in SOD activity over basal levels, whereas DPL was ineffective.

Conclusions. These data provide evidence of a marked protective effect of the endotoxin analog MPL against vasospasm. Although the mechanism(s) responsible for the protective effect of MPL remains to be verified, an enhancement of basal antioxidant activity and an inhibition of SAH-induced loss of this activity are attractive candidates. An MPL-based therapy could represent a useful addition to current therapies for SAH-induced cerebral injury.

AB-14219-98


OBJECTIVE: Oxygen-derived free radicals may contribute to vasospasm after the rupture of an intracranial aneurysm through direct vasoconstricting effects occurring within the arterial wall or, secondarily, by causing lipid peroxidation in the subarachnoid erythrocytes with secondary induction of vasoconstriction. U74389G is a potent inhibitor of lipid peroxidation and a scavenger of oxygen-derived free radicals. This study determined the relative contributions of oxygen-derived free radicals and lipid peroxidation to vasospasm in the double-hemorrhage dog model.

METHODS: Sixteen dogs underwent baseline (Day 0) cerebral angiography and induction of subarachnoid hemorrhage by two injections of blood into the cisterna magna 2 days apart. They were randomized to receive drug vehicle (n=8) or U74389G (n=8, 3 mg/kg of body weight/d) intravenously. Drug administration and end point analysis were blinded. The end points were angiographic vasospasm, as assessed by comparison of angiograms obtained before and 7 days after subarachnoid hemorrhage, and the levels of malondialdehyde and salicylate hydroxylation products (dihydroxybenzoic acids) in cerebrospinal fluid and of malondialdehyde in subarachnoid blood clots and basilar arteries 7 days after hemorrhage.

RESULTS: Comparisons within groups of Day 0 and Day 7 angiograms and between groups of angiograms obtained at Day 7, showed significant vasospasm in animals in the vehicle group (mean±standard error, 51±4) but not in the U74389G group (25±11, P<0.05, unpaired t test). High-pressure liquid chromatographic assays of malondialdehyde and dihydroxybenzoic acids in cerebrospinal fluid, subarachnoid blood clots, and basilar arteries showed no significant differences between groups.

CONCLUSION: The significant prevention of vasospasm by U74389G without change in levels of indicators of free radical reactions suggests that the effect of the drug is related to other processes occurring in the arterial wall and that cerebrospinal fluid levels of oxygen radicals and lipid peroxides are not useful markers of vasospasm.
**AB-14220-98**

**Intra-Arterially Administered Papaverine For the Treatment of Symptomatic Cerebral Vasospasm—Polin RS, Hansen CA, German P, Chadduck JB, Kassell NF** (Dept of Neurosurgery, Univ of Virginia Health Sciences Center, Box 212, Charlottesville, VA 22908)—Neurosurgery. 1998;42:1256–1267.

**OBJECTIVE:** We examined the therapeutic benefits of intra-arterially administered papaverine for treatment of symptomatic cerebral vasospasm after subarachnoid hemorrhage (SAH). Recent advances in microcatheter technology have facilitated endovascular approaches to vessels experiencing vasospasm after SAH. However, despite numerous encouraging anecdotal reports, no rigorous examination of the efficacy of these procedures has been published. Intra-arterial infusion of papaverine has become part of the standard management of vasospasm at some centers.

**METHODS:** We examined a series of 31 patients undergoing papaverine infusion for the treatment of symptomatic vasospasm after SAH. The patients were a subgroup of the series enrolled in the North American Trial of Tirilizad for Aneurysmal Subarachnoid Hemorrhage. These individuals were matched with patients from the same trial who exhibited similar clinical characteristics (including the degree of vasospasm and the modified Glasgow Coma Scale scores measured at the time of admission and on the day of papaverine infusion) but received medical management alone for vasospasm.

**RESULTS:** Logistic regression analysis comparing these two groups showed no statistical difference in the 3-month Glasgow Outcome Scale scores between patients receiving papaverine and control subjects (58% favorable outcomes for control subjects versus 45% for patients receiving papaverine).

**CONCLUSION:** Although isolated series documenting clinical successes have prompted the increased use of papaverine as a treatment for vasospasm after SAH, the benefits of this treatment are not clearly established. We conclude that among the various types of mobile aortic lesions, the disrupted protruding plaques are a major risk factor for stroke and embolic events in the elderly.

**AB-14222-98**


**Background**—Right-to-left shunt through a patent foramen ovale is frequently diagnosed by contrast echocardiography and can be particularly prominent in the presence of elevated pressures in the right side of the heart. Its prognostic significance in patients with pulmonary thromboembolism, however, is unknown.

**Methods and Results**—The present prospective study included 139 consecutive patients with major pulmonary embolism diagnosed on the basis of clinical, echocardiographic, and cardiac catheterization criteria. All patients underwent contrast echocardiography at presentation. The end points of the study were overall mortality and complicated clinical course during the hospital stay defined as death, cerebral or peripheral arterial thromboembolism, major bleeding, or need for endotracheal intubation or cardiopulmonary resuscitation. Patent foramen ovale was diagnosed in 48 patients (35%). These patients had a death rate of 33% as opposed to 14% in patients with a negative echo-contrast examination ($P = .015$). Logistic regression analysis demonstrated that the only independent predictors of mortality in the study population were a patent foramen ovale (odds ratio [OR], 11.4; $P < .001$) and arterial hypotension at presentation (OR, 26.3; $P < .001$). Patients with a patent foramen ovale also had a significantly higher incidence of ischemic stroke (13% versus 2.2%; $P = .02$) and peripheral arterial embolism (15% versus 0%; $P < .001$). Overall, the risk of a complicated in-hospital course was 5.2 times higher in this patient group ($P < .001$).

**Conclusions**—In patients with major pulmonary embolism, echocardiographic detection of a patent foramen ovale signifies a particularly high risk of death and arterial thromboembolic complications.

**AB-14223-98**


We studied 25 patients with an acute thalamic stroke (infarct or hemorrhage) on CT or MRI scan and sensory dysfunction, among the 3,628 patients with first-time stroke included in the Lausanne Stroke Registry. Twelve patients had a right-sided infarct, 11 a left-sided infarct, and 2 a left-sided thalamic hemorrhage. Sensory symptoms or signs were the only clinical abnormality. The presumed causes of stroke were small artery disease in 21 patients including both cases of hemorrhage, embolicogenic heart disease in 2, while the etiology of ischemic stroke was undetermined in 2 patients. Nine patients had a loss of all modalities of sensation with fociobrachiooriculudrional, 5 patients suffered dissociated sensory loss with fociobrachiooriculudrional and 11 patients showed a dissociated involvement of sensation with a partial distribution pattern. The inferolateral region (thalomogeniculate arteries) was involved in all patients. Six patients complained of pain and/or dysesthesias during the stroke; 5 of them had involvement of the nucleus ventrocaudalis (in 3 with damage to the nucleus ventro-oralis intermedius, and in one to the pulvinar) and 1 patient had involvement of the nucleus ventro-oralis intermedius. Eighteen patients complained of paresthesias in the contralateral part of the body; 16 of them had involvement of the nucleus ventrocaudalis (in 4 with damage to the nucleus ventro-oralis...
intermedius, in 1 with damage to the nucleus ventro-oralis intermedius, and nucleus ventro-oralis externus, and in one with damage to the nucleus parvocellularis and pulvinar). Four patients developed delayed pain and/or dysesthesias; all of them had involvement of the nucleus ventrocaudalis (in 1 with damage to the nucleus parvocellularis and pulvinar). Time lag from stroke onset to developing pain ranged from 2 to 15 days (mean 10.5 days). One patient with dissociated involvement of sensation with a partial distribution pattern had paresthesias and disassociated hemisensory loss involving position sense without pain and temperature sensations. This patient had involvement of the posterolateral part of the nucleus ventrocaudalis. In conclusion, sensory dysfunction and delayed pain are more often found in thalamic lesions that involve the nucleus ventrocaudalis, and nucleus ventro-oralis intermedius. Restricted sensory abnormalities correlate with very small lesions located in critical areas within these nuclei.

**AB-14224-98**


**Background/Purpose:** The Baltimore—Washington Cooperative Young Stroke Study is the largest biracial urban-suburban population-based study to examine the etiology of strokes in children. **Methods:** We identified all children aged 1 to 14 years discharged from all 46 hospitals in central Maryland and Washington, DC with a diagnosis of ischemic stroke and intracerebral hemorrhage in the years 1988 and 1991. Each medical record was reviewed by two neurologists for appropriateness of the diagnosis of stroke and for information on the patient’s history, clinical presentation, pertinent investigations, hospital stay, and outcome at time of discharge. **Results:** Eighteen children with ischemic infarction and 17 with intracerebral hemorrhage were identified. The most common cause of ischemic stroke was sickle-cell disease (39%), followed by vasculopathy (33%) and indeterminate (28%) causes. Causes of intracerebral hemorrhages were arteriovenous malformation (29%), hematologic (23%), vasculopathy (18%), surgical complication (12%), coagulopathy (6%), and indeterminate (12%). The overall incidence for childhood stroke was 1.29 per 100,000 per year, with ischemic stroke occurring at a rate of 0.87 per 100,000 and intracerebral hemorrhage occurring at a rate of 0.71 per 100,000. The incidence of stroke among children with sickle-cell disease was estimated to be 0.28% or 285 per 100,000 per year. **Conclusion:** Sickle-cell disease plays a disproportionately high role in childhood stroke when a biracial population is surveyed.

**Epidemiology**

**AB-14225-98**

**Variation Between Studies in Reported Relative Risks Associated With Hypertension: Time Trends and Other Explanatory Variables**—Marang-van de Mheen PJ (Institute of Social Medicine, Academic Medical Center, Meibergdreef 15, 1105 AZ Amsterdam, Netherlands), Gunning-Schepers J—*Am J Public Health.* 1998;88:618–622.

Hypertension is an important risk factor for cardiovascular diseases, which are still the major killers in Western countries. Given the availability of effective blood pressure-lowering drugs, the rationale of (secondary) preventive programs can easily be understood. To estimate the potential health benefit of such programs in times of changing cardiovascular epidemiology, both with regard to risk factors and with regard to interventions, good estimates of the prevalence of hypertension and its associated relative risks are necessary. However, to obtain such estimates is difficult because of the large interstudy variation in both reported prevalences and reported relative risks. For studies in the Netherlands we recently showed that the variation in reported prevalences between studies was explained by differences in study populations and in study design, and by a period effect indicating a declining prevalence of hypertension over time, although we were not able to identify the underlying cause for this decline.

There are various sources for interstudy variation in relative risk estimates. One source is the definition of the exposure and outcome variables, e.g., the number of blood pressure measurements on which the definition of hypertension is based. A second source of variation is the difference in study design. Relative risks estimated in cohort studies may, for instance, differ from those estimated in case-control studies because of differential recall of exposure between case and control subjects. Furthermore, the average duration of follow-up may differ between studies, and the relative risks will be closer to 1 with longer duration of follow-up.

A third source of variation concerns true changes, for instance, changes with calendar time. In the case of increased accuracy of blood pressure measurements over time, the relative risk estimates would be expected to increase with calendar time. Alternatively, the relative risk estimates may decrease with calendar time owing to improved treatment over time. Previous studies have shown increasing proportions of the population treated for hypertension and increasing proportions in which hypertension is controlled over time. Finally, if the incidence of hypertension were to decrease over time, the relative risk estimates would be expected to remain the same with calendar time.

The purpose of this study was to examine the variation in reported relative risks of coronary heart disease (CHD) and stroke associated with hypertension, and to attribute the interstudy variation to differences in definitions and duration of follow-up and to time trends in diagnostic possibilities and treatment. The latter is not just an academic exercise, since decisions regarding future efforts to reduce hypertension are based on the part of the burden of disease attributable to hypertension, which is dependent upon the magnitude of the relative risk estimate.

**AB-14226-98**

**Depressive Symptoms and Increased Risk of Stroke Mortality Over a 29-Year Period**—Everson SA (Dept of Epidemiology, School of Public Health, Univ of Michigan, 109 S Observatory St, Ann Arbor, MI 48109-2029), Roberts RE, Goldberg DE, Kaplan GA—*Arch Intern Med.* 1998;158:1133–1138.

**Background:** Several lines of evidence indicate that depression is importantly associated with cardiovascular disease end points. However, little is known about the role of depression in stroke mortality. **Methods:** This study examined the association between depressive symptoms and stroke mortality in a prospective study of behavioral, social, and psychological factors related to health and mortality in a community sample of 6676 initially stroke-free adults (45.8% male; 79.1% white; mean age at baseline, 43.4 years) from Alameda County, California. Depressive symptoms were assessed by the 18-item Human Population Laboratory Depression Scale. Cox proportional hazards regression models were used to evaluate the impact of depressive symptoms after controlling for age, sex, race, and other confounders. **Results:** A total of 169 stroke deaths occurred during 29 years of follow-up. Reporting 5 or more depressive symptoms at baseline was associated with increased risk of stroke mortality, after adjusting for age, sex, and race (hazard ratio, 1.66; 95% confidence interval, 1.16–2.39; <0.006). This association remained significant after additional adjustments for education, alcohol consumption, smoking, body mass index, hypertension, and diabetes (hazard ratio, 1.54; 95% confidence interval, 1.06–2.22; <0.02). Time-dependent covariate models, which allowed changes in reported depressive symptoms and risk factor levels during follow-up, revealed the same pattern of associations.

**Conclusions:** This population-based study provides the strongest epidemiological evidence to date for a significant relationship between depressive symptoms and stroke mortality. These results contribute to the growing literature on the adverse health effects of depression.

Hypertension as a risk factor for intracerebral hemorrhage (ICH) is poorly quantified, particularly in the setting of the use of modern antihypertensive agents. To investigate this, we studied 331 consecutive hospital cases of primary ICH verified by computed tomography or autopsy, occurring during the period 1990 through 1992, and 331 age- and sex-matched community-based control subjects in a city-wide study involving 13 hospitals. Hypertension approximately doubled the risk of ICH (adjusted odds ratio [OR], 2.45; 95% confidence interval [CI], 1.61 to 3.73). The OR associated with hypertension was significantly greater among those who had ceased taking medications, supervised and supervised (OR, 4.98; 95% CI, 2.25 to 11.02), compared with those who had not (OR, 1.95; 95% CI, 1.20 to 3.16), were under the age of 55 years (OR, 7.68; 95% CI, 2.65 to 22.5), or were current smokers (OR, 6.12; 95% CI, 2.29 to 16.35). The presence of hypertension did not influence size or location of the hemorrhage. However, those dying from ICH displayed a greater risk of ICH due to hypertension than survivors, with the ratio of the two ORs being 5.47 (95% CI, 1.23 to 24.44). These findings provide evidence for a greater increase in risk of ICH due to hypertension among younger persons, current smokers, and those discontinuing antihypertensive therapy. This is the first direct evidence for a link between stopping antihypertensive medication use and stroke risk; targeting these individuals for more intensive monitoring and education on the importance of risk factor modification may help to reduce the impact of this form of stroke.


Coagulation factor V Leiden is a risk marker for venous thrombosis. For arterial thrombosis no large study to date has included population-based elderly patients. The Cardiovascular Health Study is a longitudinal study of 5,021 men and women over age 65. With 3, 4-year follow-up, we studied 373 incident cases of myocardial infarction (MI), justina, stroke, or transient ischemic attack (TIA), and 482 controls. The odds ratios for each event with heterozygous factor V Leiden were: MI, 0.46 (95% CI 0.17 to 1.25); justina, 1.0 (95% CI 0.45 to 2.23); stroke, 0.77 (95% CI 0.35 to 1.70); TIA, 1.33 (95% CI 0.5 to 3.55; any outcome, 0.83 (95% CI 0.48 to 1.44). Adjustment for cardiovascular risk factors did not change relationships. In older adults factor V Leiden is not a risk factor for future arterial thrombosis.

**Experimental Pathology**

Mild Hypothermia Disturbs Regional Cerebrovascular Autoregulation in Awake Rats—Niwai K, Takizawa S, Takagi S, Shinohara Y (Dept of Neurology, Tokai Univ School of Medicine, Bohsai, Isharara, Kanagawa 259-11, Japan)—Brain Res. 1998;789:68–73. © 1998 Elsevier Science B.V.

The effects of mild hypothermia on regional CBF (rCBF) and autoregulation were investigated in 60 awake and spontaneously breathing Wistar rats. They were divided into normothermic (rectal and brain temperatures: 37.0±0.5°C) and mildly hypothermic (33.0±0.5°C) groups. The temperature of the latter group was controlled by cooling a lead cast around each rat with ice-cold water. rCBF was measured by means of an autoradiographic technique with 14C-iodoantipyrine. In normothermia, rCBF in most of the supratentorial cortical regions was maintained down to a mean arterial blood pressure (MABP) of 50 mmHg, produced by exsanguination, while rCBF in most of the brain stem regions showed a tendency to increase despite this reduction of MABP (predysautoregulatory overshoot of CBF). In the mildly hypothermic group, pre-exsanguination rCBF values were lower than those in normothermia, and rCBF in all brain regions declined significantly in proportion to decreasing MABP, produced by exsanguination. It is, therefore, concluded that mild hyperthermia disturbs cerebrovascular autoregulation in awake rats.


**Object.** The authors previously demonstrated, in a large-animal intracerebral hemorrhage (ICH) model, that markedly edematous (“translucent”) white matter regions (>10% increase in water contents) containing high levels of clot-derived plasma proteins rapidly develop adjacent to hematomas. The goal of the present study was to determine the concentrations of high-energy phosphate, carbohydrate substrate, and lactate in these and other perihematomal white and gray matter regions during the early hours following experimental ICH.

**Methods.** The authors infused autologous blood (1.7 ml) into frontal lobe white matter in a physiologically controlled model in pigs (weiging approximately 7 kg each) and froze their brains in situ at 1, 3, 5, or 8 hours postinfusion. Adenosine triphosphate (ATP), phosphocreatine (PCr), glycerol, glucose, lactate, and water contents were then measured in white and gray matter located ipsi- and contralateral to the hematomas, and metabolite concentrations in edematous brain regions were corrected for dilution.

In markedly edematous white matter, glycerol and glucose concentrations increased two- to fivefold compared with control during 8 hours postinfusion. Similarly, PCr levels increased several-fold by 5 hours, whereas, except for a moderate decrease at 1 hour, ATP remained unchanged. Lactate was markedly increased (approximately 20 μmol/g) at all times. In gray matter overlying the hematoma, water contents and glycerol levels were significantly increased at 5 and 8 hours, whereas lactate levels were increased two- to fourfold at all times.

**Conclusions.** These results, which demonstrate normal to increased high-energy phosphate and carbohydrate substrate concentrations in edematous perihematomal regions during the early hours following ICH, are qualitatively similar to findings in other brain injury models in which concentration in metabolic rate develops. Because an energy deficit is not present, lactate accumulation in edematous white matter is not caused by stimulated anaerobic glycolysis. Instead, glutamate concentrations in the blood entering the brain’s extracellular space during ICH are several-fold higher than normal levels, the authors speculate, on the basis of work reported by Pellerin and Magistretti, that glutamate uptake by astrocytes leads to enhanced aerobic glycolysis and lactate is generated at a rate that exceeds utilization.


The effect of the 5-HT1D receptor agonist sumatriptan on the volume of ischemic injury was studied in rats subjected to permanent middle cerebral artery (MCA) occlusion. Sumatriptan (2 mg/kg) was administered intravenously 5 minutes after MCA occlusion and the ischemic injury volume was determined 3 hours after MCA occlusion using regional adenosine-5′-triphosphate imaging. In addition, electroencepha-

AB-14230-98


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**Conclusions.** These results, which demonstrate normal to increased high-energy phosphate and carbohydrate substrate concentrations in edematous perihematomal regions during the early hours following ICH, are qualitatively similar to findings in other brain injury models in which a reduction in metabolic rate develops. Because an energy deficit is not present, lactate accumulation in edematous white matter is not caused by stimulated anaerobic glycolysis. Instead, glutamate concentrations in the blood entering the brain’s extracellular space during ICH are several-fold higher than normal levels, the authors speculate, on the basis of work reported by Pellerin and Magistretti, that glutamate uptake by astrocytes leads to enhanced aerobic glycolysis and lactate is generated at a rate that exceeds utilization.
lographic activity, direct current (DC) potential and cortical blood flow (CBF) was monitored throughout the experiment. In untreated animals, MCA occlusion resulted in a decline in penumbra CBF to 43.3% ± 7.6% of control, 21 spreading depression (SD)-like DC shifts with an average integrated depolarization negativity of 330.2 ± 297.4 (mV·min) and an ATP depletion volume of 61.8 ± 22.9 mm³ (mean ± SD). Three hours after MCA occlusion in sumatriptan-treated animals, penumbra CBF recovered to 63.5% ± 12.6% of control (P < 0.05), only 13 SD-like shifts were detected (P < 0.05) with a significantly reduced integrated depolarization negativity of 104.7 ± 98.4 (mV·min) (P < 0.05), and the volume of ATP depletion decreased to 16.6 ± 12.3 mm³ (P < 0.01). However, no significant neuroprotective effect was observed for the cavae nucleus (untreated, 19.7 ± 16.5 mm³; treated, 7.9 ± 8.5 mm³). The reduction in the volume of ischemic injury in sumatriptan-treated animals is explained by both the improvement of blood flow and the inhibition of SD-like shifts leading to an amelioration of the misrelationship between the depolarization-related energy demand and flow-dependent substrate delivery.

AB-14232-98

High Frequency of Apolipoprotein E e2 Allele is Specific for Patients With Cerebral Amyloid Angiopathy-Related Haemorrhage

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The apolipoprotein E (APOE) e2 allele is a putative risk factor for cerebral amyloid angiopathy-related haemorrhage. We explored the frequency of the APOE e2 allele in intracranial haemorrhage due to three different pathophysiological mechanisms to determine the specificity of the association. APOE genotypes in 207 autopsies with intracranial haemorrhage (96 subarachnoid haemorrhage, 71 deep intracerebral haemorrhage, 40 cerebral amyloid angiopathy (CAA)-related haemorrhage patients) were compared with 41 autopsy controls without neuro-pathological abnormalities and 406 living patients admitted to hospital following head injury. As identified previously the e2 allele frequency was significantly over-represented in CAA-related haemorrhage (frequency 0.24, P < 0.01): this association was stronger among patients with multiple CAA-related haematomas (0.31). The e2 frequencies of the deep haemorrhage (0.13) and subarachnoid haemorrhage (0.09) groups were not significantly different from the control autopsies (0.07) or live patients (0.08). The findings indicate that the e2 allele is associated with haemorrhage only in the context of cerebral blood vessels laden with amyloid.

Imaging

AB-14233-98


OBJECTIVE. Our objective was to evaluate a new scanning method, MR line scan diffusion imaging, and assess the apparent diffusion coefficient in the brains of healthy subjects and stroke patients.

SUBJECTS AND METHODS. Line scan diffusion imaging without cardiac gating or head restraints was implemented on low- (0.5 T) and medium- (1.5 T) field-strength scanners with conventional hardware. Diffusion-weighted images were obtained in six healthy subjects and eight stroke patients. Unidirectional diffusion encoding was used for fast localization of stroke lesions. For further characterization, orthogonal diffusion encoding was applied, and the trace of the apparent diffusion coefficient was calculated. Single-shot diffusion-weighted echoplanar imaging served as the reference standard. For healthy subjects, imaging was repeated four times on each scanner. Mean and relative precision of the apparent diffusion coefficient trace values were calculated for each pixel. In stroke lesions and adjacent normal tissue, apparent diffusion coefficient trace values were determined.

RESULTS. In the 108 scans obtained, line scan diffusion imaging proved to be robust, virtually free of artifact (independent of slice location and orientation), reproducible, and rapid for localization of a stroke. Scan time for 14 slices at 7-mm thickness was 8 min at 0.5 T and 7 min at 1.5 T. Image qualities with line scan diffusion imaging and single-shot diffusion-weighted echoplanar imaging were comparable. At 1.5 T, precision was essentially the same for line scan diffusion imaging (4.3%) and echoplanar imaging (4.7%). With line scan diffusion imaging at 0.5 T and 1.5 T, normal paraventricular apparent diffusion coefficient trace values averaged 0.71 µm²/msec, and with echoplanar imaging these values averaged 0.69 µm²/msec. In acute lesions apparent diffusion coefficient trace values were low, and in chronic lesions these values were high.

CONCLUSION. Line scan diffusion imaging on low- and medium-field-strength MR scanners equipped with conventional hardware was reliable and practical for measuring brain apparent diffusion values, which can be applied to the early diagnosis, and hence timely management, of stroke.

AB-14234-98


Objective: To analyze the frequency and severity of subclinical cerebral complications associated with coronary artery bypass grafting (CABG).

Design: A prospective controlled study using preoperative and postoperative magnetic resonance imaging (MRI) of the brain, quantitative electroencephalography (QEEG), and detailed neuropsychological and neurologic examinations as potentially sensitive indicators of subclinical cerebral injury associated with CABG.

Setting: Multimodality evaluation in a tertiary care unit (Kuopio University Hospital, Kuopio, Finland).

Patients: Thirty-eight patients undergoing elective CABG and 20 control patients undergoing other major vascular surgery, mostly operations on the abdominal aorta.

Main Outcome Measures: Coronary artery bypass grafting—associated cerebral complications assessed preoperatively and postoperatively by brain MRI, QEEG, detailed neurologic examination, and a neuropsychological test battery that evaluates cognitive functions in major areas known to be vulnerable to organic impairment (learning and memory, attention, flexible mental processing, and psychomotor speed).

Results: There were no major neurologic complications. A mild hemisindrome developed in 1 patient who underwent CABG and in 1 control patient. Overall, there was no decline in mean cognitive performance 3 months after surgery. Electroencephalographic slowing of 0.5 Hz or more in at least 2 channels occurred in 11 patients who underwent CABG and in 1 control patient (P = .03). The postoperative brain MRI scan revealed new small ischemic lesions in 8 patients (21%) in the CABG group but in none of the control group (P = .03). These new cerebral MRI lesions did not explain deterioration in neuropsychological test performance or the QEEG slowing.

Conclusions: Coronary artery bypass grafting causes more QEEG alterations and small ischemic cerebral lesions that are detectable by MRI than does other major vascular surgery. The effect is mainly subclinical, because no statistically significant deterioration in mean neuropsychological test performance was detected.

AB-14235-98

Relation Between Cerebral Blood Flow and Neurologic Deficit Resolution in Acute Ischemic Stroke—Firlik AD (Dept of Neurological

Background and objective: Early intervention remains the key to acute ischemic stroke therapy. Many patients whose deficits would later resolve without intervention are exposed to the risks of stroke treatment without benefit. The purpose of this study was to determine whether patients with transient deficits could be distinguished from patients with evolving strokes on the basis of acute cerebral blood flow (CBF) measurements before any clinical distinction could be made. Methods: Fifty-three patients who presented with acute hemispheric stroke symptoms and who underwent xenon-enhanced CT (XeCT) CBF studies within 8 hours of onset of symptoms (and before any clinical improvement) were studied. Results: Eight patients (15%) had a complete resolution of their symptoms within 24 hours (not related to treatment). All eight patients with deficits that resolved had normal CBF in the symptomatic vascular territories (mean time to XeCT = 3 hours, 51 min). Mean CBF in the regions of interest of the symptomatic vascular territories of patients who had deficits that resolved was 35.4 ± 8.1 mL · 100 g⁻¹ · min⁻¹ compared with 17.3 ± 9.3 mL · 100 g⁻¹ · min⁻¹ of patients with evolving strokes (p = 0.00058). Conclusions: Patients with ischemic neurologic deficits that will later resolve can be acutely distinguished from patients with evolving cortical infarctions using XeCT CBF measurements. CBF measurements may assist in the triage of patients for acute ischemic stroke therapy. Many patients whose deficits would later resolve without intervention are exposed to the risks of stroke treatment without benefit. To investigate whether the thickness of the layers of the carotid artery (externa, media, and intima) are affected by menopause and its treatment with hormone replacement therapy (HRT).

Methods: One hundred twenty-nine postmenopausal women were recruited sequentially and classified into three groups. Forty-six were taking oral HRT, 32 had estradiol implants, and 51 had never taken HRT. The three layers of the externa wall of the carotid artery were identified and measured by high-resolution ultrasound.

Results: Women with implants had thicker carotid artery wall measurements (0.84 ± 0.26 mm) than the other groups. The media (0.32 ± 0.11 mm) was significantly thicker in the implant group. This layer has a high connective tissue component, including collagen type I, collagen type III, and elastin fibers. The intima layer was thinner (0.25 ± 0.09 mm) in the oral HRT group compared with controls (0.29 ± 0.1 mm). A statistically significant higher intima-media ratio (1.17 ± 0.05) was calculated for the control group, compared with both the oral HRT (0.92 ± 0.04) and implant groups (0.94 ± 0.03).

Conclusion: Our findings suggest that HRT given to postmenopausal women influences differentially the layers of the carotid artery. Hormones seem to encourage thickening of the layers with the highest connective tissue component (externa and media) and to delay thickening of the atheromatous intima layer. These effects on the vascular system may be partly responsible for the cardioprotection attributed to HRT.

Pharmacology / Therapeutics

AB-14238-98
Different Effects of Heparin in Males and Females—Campbell NRC (Faculty of Medicine, Univ of Calgary, 3330 Hospital Dr NW, Calgary AB T2N 4N1), Hull RD, Brant R, Hogan DB, Pinoe GF, Raskob GE—Clin Invest Med. 1998;21:71–78.

Objective: To determine whether women have a pharmacological predisposition to bleeding and a worse outcome than men during heparin therapy, in light of recent studies showing that women have a higher risk of bleeding complications following antiocoagulant therapy for thrombotic disorders than men.

Design: Prospectively planned subgroup analysis of a double-blind randomized study.

Setting: Academic tertiary care hospitals in Hamilton, Ont.

Patients: A total of 199 consecutive patients (105 women, 93 men) presenting with proximal deep vein thrombosis. (One patient was not included due to incomplete data.)

Outcome measures: Activated partial thromboplastin time (APTT) values and heparin levels were assessed every 4 to 6 hours after a standard heparin bolus and infusion. The effect of sex on heparin doses and levels was also assessed after stable therapeutic heparin infusions were achieved.

Results: The women had higher heparin levels than the men (0.560 [standard error of the mean, SEM 0.056] units/mL v. 0.347 [SEM 0.062] units/mL, p < 0.0001) and higher APTT values (94.9 [SEM 0.50] seconds v. 81.2 [SEM 0.53] seconds, p = 0.0002) 4 to 6 hours after being given the same heparin bolus and infusion doses. After achieving therapeutic APTT values, the women received lower heparin doses than the men (27.9 [SEM 0.24] 1000 units/24 hours v. 34.5 [SEM 0.24] 1000 units/24 hours, p < 0.0001) but had higher heparin levels (0.349 [SEM 0.035] units/mL v. 0.292 [SEM 0.036] units/mL, p = 0.034). The effect of sex was also determined after correcting for the known effects of weight and age on heparin therapy. After adjusting for patient weight, among the women, older women had higher heparin levels but, among the men, there was little effect of age. There were no sex differences with respect to bleeding complications or recurrent thromboembolic disease.

Conclusion: Women showed alterations in the pharmacokinetics of heparin, which could explain a predisposition to bleeding compli-
Surgery

**AB-14239-98**


Saphenous vein patch closure of carotid endarterectomies may decrease the risk of acute postoperative occlusion and recurrent stenosis. However, the disadvantages of a vein patch include postoperative rupture and pseudoaneurysm formation.

Object. The authors sought to assess the effectiveness of collagen-impregnated fabric grafts as substitutes for saphenous vein grafts.

Methods. In this report the authors prospectively analyzed 290 consecutive carotid endarterectomies in which a secondary closure was accomplished using a knitted double-velour graft. The 30-day major neurological morbidity and mortality rate was 1.7%. There were no postoperative occlusions or wound hematomas. The rate of recurrent carotid artery stenosis was less than 1%, and the graft site in one patient became infected.

Conclusions. For surgeons who prefer a secondary closure of carotid endarterectomies, the synthetic graft may prove to be a viable alternative to a saphenous vein.

**AB-14240-98**


The North American Symptomatic Carotid Endarterectomy Trial (NASCET) advocated the use of carotid endarterectomy (CEA) for transient ischemic attacks (TIAs), nondisabling strokes, and ipsilateral high-grade stenosis in highly selected patients. Whether similar results are achieved when CEA is applied to an entire geographically defined population is unknown but important if the NASCET recommendations are to be applied broadly to all community patients.

Methods: To determine the survival rate to ipsilateral stroke after CEA for all symptomatic patients in a defined population, we reviewed the medical records of all patients residing in Olmsted County, Minn. (approximately 100,000), who underwent a CEA for TIA or nondisabling stroke between 1970 and 1995. Their outcomes were compared with the NASCET results.

Results: In the community of Olmsted County, 297 patients (108 women and 189 men) underwent 322 CEAs during the study period. TIAs or nondisabling stroke was the indication in 254 patients (86%), whereas the remaining 14% had asymptomatic stenosis. After CEA for symptomatic lesions, survival rate free of ipsilateral stroke was 97% at 2 years, 93% at 5 years, and 92% at 10 years. These results are similar to the NASCET survival rates free of ipsilateral stroke at 2 years (91%). However, the 30-day postoperative stroke rate for patients older than 80 years was significantly higher than that for patients younger than 80 years.

Conclusions: When the NASCET results are compared with a population-based experience in which all symptomatic patients undergoing CEA were analyzed, the early outcomes were similar. Our population-based data also document the remarkably durable long-term results of CEA in preventing stroke and present another benchmark for carotid stent angioplasty.

**AB-14241-98**


This study was undertaken to determine the safety and efficacy of carotid endarterectomy (CEA) in the octogenarian population at the Cleveland Clinic.

Methods: From 1989 to 1995, 182 CEAs were performed among 167 octogenarians (98 men, 69 women) with a mean age of 83 years (median, 83 years; range, 80 to 93 years). One hundred procedures (55%) were performed for severe asymptomatic stenosis, whereas 48 (26%) were performed for hemispheric transient ischemic attacks (TIAs) or amaurosis fugax, 24 (13%) for prior stroke, and 10 (5%) for vertebrobasilar symptoms. Thirteen CEAs (7%) were combined with myocardial revascularization, and another five (3%) represented carotid reoperations. Nine arteriotomies (5%) were closed primarily, whereas the remaining 173 (95%) were repaired using either vein patch angioplasty (141, 77%) or synthetic patches (32, 18%). Two patients were lost to follow-up, but late information was available for 165 patients (180 operations) at a mean interval of 2.7 years (median, 2.4 years; maximum, 7.4 years).

Results: Considering all 182 procedures, there were five early (<30 days) postoperative neurologic events (2.7%), including three strokes (1.6%) and two TIAs (1.1%). An additional 15 neurologic events occurred during the late follow-up period, consisting of 11 strokes (6.1%) and four TIAs (2.2%). The Kaplan-Meier estimated 5-year rate of freedom from stroke was 85% (95% confidence interval [CI], 77% to 93%). There was one early postoperative death (0.6%) of cardiac complications 9 days after CEA. The estimated 5-year survival rate was 45% (95% CI, 33% to 57%), and the 5-year stroke-free survival rate was 42% (95% CI, 30% to 53%). Multivariable analysis yielded age at operation (p = 0.001), abnormal creatinine level (p = 0.025), and chronic obstructive pulmonary disease (p = 0.019) as variables that significantly influenced the survival rate. The presence of chronic obstructive pulmonary disease (p = 0.009) and, surprisingly, a lesser degree of contralateral internal carotid stenosis (p = 0.003) were found to be significantly associated with stroke after CEA. Causes of late death were cardiovascular in 16 patients (30%), unknown in 13 (24%), carcinoma in six (11%), stroke in six (11%), and miscellaneous in 13 (24%).

Conclusions: We conclude that CEA may be safely performed in selected octogenarians with carotid stenosis, and that the majority of these patients live the rest of their lives free from stroke. Therefore, age alone should not exclude otherwise-qualified candidates from consideration for CEA.

**AB-14242-98**


Purpose: In carotid artery disease, correlation of carotid plaque morphology with the patient’s presenting symptoms has drawn conflicting conclusions. The purpose of this series was to correlate
carotid plaque characteristics with the presenting symptoms from a large cohort of patients who underwent operation for carotid artery disease.

Methods: From a series of 1252 consecutive patients who underwent carotid endarterectomy, presenting symptoms were divided into three groups: transiently symptomatic (transient ischemic attack [TIA] or amaurosis fugax), prior stroke, and asymptomatic. Plaque characteristics, including ulceration, intraplaque hemorrhage, and degree of stenosis, were recorded prospectively for 1008 procedures. All endarterectomy specimens were inspected during the procedure, and plaque characteristics were recorded immediately after operation.

Results: There was a higher incidence of plaque ulceration in the transiently symptomatic and prior stroke groups (391 of 508 [77%] and 91 of 115 [79%]) than in the asymptomatic cohort (231 of 385 [60%]; p < 0.0001, χ² test). There was no significant difference in the incidence of plaque hemorrhage between the transiently symptomatic and prior stroke groups compared with the asymptomatic patients. There was no statistical difference for ulcerated plaque or plaque hemorrhage between the transiently symptomatic and prior stroke groups. Intraplaque hemorrhage occurred more frequently in patients with high-grade stenosis (90% to 99%) than in those with less than 90% stenosis (202 of 299 [68%] versus 97 of 299 [32%]; p = 0.01, χ² test).

Conclusions: On gross examination of the carotid specimen in the operating room, plaque ulceration correlates with an initial presentation of amaurosis fugax, TIA, or prior stroke compared with patients operated on for asymptomatic disease. The presence of intraplaque hemorrhage is associated with more advanced stenosis of the internal carotid artery. These findings suggest that plaque morphology does play an important role in the presentation of carotid artery disease.

AB-14243-98

The risk of stroke and the risk of recurrent strokes in patients with patent foramen ovale (PFO) need a prevention that still remains a therapeutic problem. There are 4 preventive treatments: antiagregants, anti-coagulants, transcathereter closure, and surgical closure of PFO. The aim of this study was to demonstrate that surgical closure of PFO is safe and useful for prevention of strokes. Eight patients with stroke and PFO diagnosed by transesophageal echography (TEE) were prospectively selected for surgical closure. It was necessary to be younger than 70 years, not to have another cause of stroke, and to have either recurrent strokes or several ischemic lesions on MRI, isolated for PFO associated with an atrial septal aneurysm, and to have a Valsalva maneuver or cough inducing the stroke. For these reasons, these patients were considered to be an homogenous group with a strong relationship between the PFO and the stroke, and with a high risk of recurrence of stroke. The 8 patients had a direct suture of the PFO with a cardiopulmonary bypass. All patients were followed-up with clinical, MRI and TEE examinations during 12 months after surgery. No surgical complications were observed. After one year, without any anticoagulant treatment, no recurrent stroke or transient ischemic attack, no new ischemic lesions on MRI, nor neuropsycological disturbance were noted. No post-surgical inter-atrial right-to-left shunting was observed. In the absence of controlled studies to guide therapeutic options, our data suggest that surgical closure of PFO in patients with stroke, is safe and efficacious to prevent recurrent stroke without any anticoagulants in the first year of follow-up. Further studies are needed to evaluate the long-term role of surgical closure of PFO as an alternative to prolonged anti-thrombotic treatment.

AB-14244-98

Background: The natural history of cerebral venous malformations has not been well documented, and the clinical significance of these common lesions remains controversial. Objective: The objective of this study was to follow longitudinally the clinical course of patients with cerebral venous malformations to document the natural history of the lesion. Methods: Ninety-two patients with radiographically confirmed venous malformations were entered into the study between 1987 and 1996. Annual follow-up was maintained by clinic visits and/or phone interviews. Sixty-three patients (25 men and 38 women) with more than 1 year of follow-up were analyzed. McNemar’s test and logistic regression analysis was applied to prevalence of presenting symptoms over time. An average per patient follow-up of 4.2 years yielded 2,721 retrospective and 301 prospective lesion-years for analysis. Results: Average age at diagnosis was 39.1 years (SD, 18.7 years; range, 2 to 73 years). The most frequent lesion locations included the frontal lobe (55.6%, n = 35) and the cerebellum (27%, n = 17). The most frequent presentations included headache (50.8%, n = 32), focal neurologic deficits (39.7%, n = 25), and seizure (30.2%, n = 19). Prevalence of headache (p = 0.048) and seizure (p = 0.016) decreased over time without treatment of the lesion. A second cerebrovascular lesion was identified in 12 patients (19%). Two patients had a symptomatic intracerebral hemorrhage attributable to their venous malformation. Risk of hemorrhage was 0.15% per lesion-year (95% CI, 0.06 to 0.38%). Conclusions: This study establishes that the natural history of venous malformations is benign, that the risk of hemorrhage from these lesions is negligible, and that conservative therapy is warranted.

Items of Interest


Abstracts of Literature
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