Cerebral Aneurysms

AB-14661-00

The effects of subarachnoid haemorrhage (SAH) on cerebral blood flow (CBF) autoregulation during induced hypertension were studied by positron emission tomography (PET) during chronic vasospasm in anesthetised Sprague-Dawley rats. SAH was induced by intracisternal injection of autologous blood. In the control animals saline was injected instead. This method produced angiographical vasospasm of major arteries 48 h after injection. During this period, CBF was measured at each side of the fronto-parametial and occipital sections using PET with or without induced hypertension. Mean arterial blood pressure (MAP) was increased from 94±2.4 to 140±3.3 mm Hg by the injection of phenylephrine. An autoregulatory index (AI) expressed as delta CBF (% per 10-mm Hg) increase in MAPB was employed to analyse CBF response. SAH significantly reduced (p<0.0001) basal CBF (ml/100 g/min) by 26.2% (control 60.0±1.9 n=24, SAH 44.3±4.5 n=20). A territorial CBF that decreased by 50% or more over the mean control value was used to define ischaemia and was identified in five out of 20 regions (25%) in the SAH group. AI (%10-mm Hg) was 13.5±2.4 in the control group (n=24). In the SAH group, AI decreased (p<0.05) to 4.5±2.5 in non-ischaemic areas (n=15), while in the ischaemic areas (n=5) AI increased (p<0.05) to 25±2.4. Since the spastic artery is intrinsically resistant to hypertension, the marked increase in CBF during hypertension can be attributable to ischaemia following SAH.

AB-14662-00

Objective. The reduction in the level of nitric oxide (NO) is a purported mechanism of delayed vasospasm after subarachnoid hemorrhage (SAH). Evidence in support of a causative role for NO includes the disappearance of nitric oxide synthase (NOS) from the adventitia of vessels in spasm, the destruction of NO by hemoglobin released from the clot into the subarachnoid space, and reversal of vasospasm by intracarotid NO. The authors sought to establish whether administration of L-arginine, the substrate of the NO-producing enzyme NOS, would reverse and/or prevent vasospasm in a primate model of SAH.

Methods. The study was composed of two sets of experiments: one in which L-arginine was infused over a brief period into the carotid artery of monkeys with vasospasm, and the other in which L-arginine was intravenously infused into monkeys over a longer period of time starting at onset of SAH. In the short-term infusion experiment, the effect of a 3-minute intracarotid infusion of L-arginine (intracarotid concentration 10–6 M) on the degree of vasospasm of the right middle cerebral artery (MCA) and on regional cerebral blood flow (rCBF) was examined in five cynomolgus monkeys. In the long-term infusion experiment, the effect of a 14-day intravenous infusion of saline (control group, five animals) or L-arginine (10–3 M; six animals) on the occurrence and degree of cerebral vasospasm was examined in monkeys. The degree of vasospasm in all experiments was assessed by cerebral arteriography, which was performed preoperatively and on postoperative Days 7 (short and long-term infusion experiments) and 14 (long-term infusion experiment). In the long-term infusion experiment, plasma levels of L-arginine were measured at these times in the monkeys to confirm L-arginine availability.

Vasospasm was not affected by the intracarotid infusion of L-arginine (shown by the reduction in the right MCA area on an anteroposterior arteriogram compared with preoperative values). However, intracarotid L-arginine infusion increased rCBF by 21% (p<0.015; PCO2 38–42 mm Hg) in all vasospastic monkeys compared with rCBF measured during the saline infusions. In the long-term infusion experiment, vasospasm of the right MCA occurred with similar intensity with or without continuous intravenous administration of L-arginine on Day 7 and had resolved by Day 14. The mean plasma L-arginine level increased during infusion from 12.7±4 μg/ml on Day 0 to 21.9±13.1 μg/ml on Day 7 and was 18.5±3.1 μg/ml on Day 14 (p<0.05).

Conclusions. Brief intracarotid and continuous intravenous infusion of L-arginine did not influence the incidence of degree of cerebral vasospasm. After SAH, intracarotid infusion of L-arginine markedly increased rCBF in a primate model of SAH. These findings discourage the use of L-arginine as a treatment for vasospasm after SAH.

AB-14663-00

OBJECTIVE: Accurate outcome prediction after high-grade subarachnoid hemorrhage remains imprecise. Several clinical grading scales are in common use, but the timing of grading and changes in grade after admission have not been carefully evaluated. We hypothesized that these latter factors could have a significant impact on outcome prediction.

METHODS: Fifty-six consecutive patients with altered mental status after subarachnoid hemorrhage, who were managed at a single institution, were studied retrospectively. On the basis of prospectively assessed elements of the clinical examination, each patient was graded at admission, at best before treatment, at worst before treatment, immediately before treatment, and at best within 24 hours after treatment of the aneurysm using the Glasgow Coma Scale (GCS), the World Federation of Neurological Surgeons (WFNS) scale, and the Hunt and Hess scale. Outcome at 6 months was determined using a modification of the Glasgow Outcome Scale validated against the Karnofsky scale. All grades and clinical and radiographic data collected were compared among good and poor outcome groups. Multivariate analyses were then performed to determine which grading scale, which time of grading, and which other factors were correlated with and contributed significantly to outcome prediction.

RESULTS: A good outcome was achieved in 24 (43%) of 56 patients. Our study also had a 32% mortality rate. With the Hunt and Hess scale, only the worst pretreatment grade was significantly correlated with outcome. However, with the GCS and the WFNS scale, grading at all pretreatment times was significantly correlated with outcome, although outcome was best predicted before treatment, regardless of the scale used, if grading was performed at the patient’s clinical worst. Multivariate analysis revealed that the best predictor of outcome was WFNS grade at clinical worst before treatment. Used alone, a WFNS Grade 3 at worst pretreatment predicted a 75% favorable outcome, and a WFNS Grade 5 at worst pretreatment predicted an 87% poor outcome. No significant correlation was found between direction or magnitude of change in grade and outcome. Age was found to be significantly correlated with outcome, but it was only an

The abstracts in this section have been typeset for consistency with journal format but otherwise appear as in the original articles.
independent factor in outcome prediction when used in conjunction with the Hunt and Hess scale and not with the WFNS scale and the GCS.

CONCLUSION: Timing of grading is an important factor in outcome prediction that needs to be standardized. This study suggests that the patient’s worst clinical grade is most predictive of outcome, especially when the patient is assessed using the WFNS scale or the GCS.

AB-14664-00

OBJECTIVE: Intracranial aneurysm size is an important determinant of risk of rupture and outcome after rupture. Risk factors influencing aneurysm formation and growth are not well defined. In this study, we examined the association between known risk factors for cerebrovascular disease and size of intracranial aneurysms in patients with aneurysmal subarachnoid hemorrhage.

METHODS: We analyzed prospectively collected data from the placebo-treated group in a multicenter clinical trial conducted at 54 neurosurgical centers in North America. The presence, location, and size of intracranial aneurysms were determined by review of the admission angiograms. Pertinent information regarding the presence of various cerebrovascular risk factors was collected for each patient. Using logistic regression analysis, we identified independent determinants of aneurysm size from demographic, clinical, and angiographic characteristics of the participants. The impact of aneurysm size on 3-month mortality was analyzed after adjusting for potential confounding factors.

RESULTS: For 298 patients admitted with subarachnoid hemorrhage, the ruptured aneurysms were graded as small (<13 mm) in 235 patients (79%) and large (≥13 mm) in 63 patients (21%). In the logistic regression model, both smoking at any time (odds ratio, 2.2; 95% confidence interval, 1.4–4.5) and middle cerebral artery origin (odds ratio, 2.5; 95% confidence interval, 1.3–4.9) were independently associated with large aneurysms. Neither hypertension, diabetes mellitus, nor alcohol and illicit drug use were associated with large-sized aneurysms. After adjusting for initial Glasgow Coma Scale score and age in the logistic regression model, we identified independent determinants of aneurysm size from demographic, clinical, and angiographic characteristics of the participants. The impact of aneurysm size on 3-month mortality was analyzed after adjusting for potential confounding factors.

CONCLUSION: Cigarette smoking and middle cerebral artery origin seem to increase the risk for developing large aneurysms in patients predisposed to intracranial aneurysm formation. Further studies are required to investigate the mechanism underlying the association between cigarette smoking and intracranial aneurysm formation.

Clinical

AB-14665-00

Objectives—To compare the occurrence of lacunar infarcts in the very elderly (>85 years of age) and in patients below 85. Material and methods—Data of 374 consecutive patients with lacunar infarcts were analyzed after adjusting for potential confounding factors. Results—Lacunar infarcts were diagnosed in 39 (15%) of the 262 very elderly patients of our stroke registry. Lacunar infarcts in the very elderly accounted for 10.5% of all lacunes. There was no statistical difference in the occurrence of different lacunar syndromes between the very elderly patients and patients below 85. However, the very old group with lacunar infarct showed a significantly higher proportion of the female sex (56.4% vs 37.3%) and history of atrial fibrillation (28.2% vs 8.7%), chronic renal disease and pathologic condition and a significantly lower proportion of hypertension (61.5% vs 77.3%), diabetes (7.7% vs 28.4%), ischemic heart disease, hypercholesterolemia, and absence of neurologic deficit at discharge from the hospital than patients below 85. After multivariate analysis only atrial fibrillation (OR=3.77), female gender (OR=2.52), hypertension (OR=0.35), and diabetes (OR=0.16) were independent clinical factors for developing lacunar infarction in the very elderly.

Conclusion—In the very elderly the higher occurrence of atrial fibrillation, the lower prevalence of hypertension and diabetes, and the greater focal neurological impairment suggest that the cardioembolic pathogenic mechanisms may be more frequent than generally established for lacunar infarcts in stroke patients.

AB-14666-00

Objectives—The impact of stroke on the emotional outcome of patients is large. The aim was to describe the emotional outcomes among a cohort of patients which was of sufficient size to provide a precise estimate of their frequency and help identify those factors which are associated with poor outcomes after an acute stroke.

Methods—372 surviving patients, who had been referred to a hospital and entered into a randomised trial to evaluate a stroke family care worker, were asked to complete questionnaires at 6 month follow up. These included measures of emotional distress (general health questionnaire 30 item, hospital anxiety and depression scale) and physical functioning (modified Rankin, Barthel index). A regression analysis was used to identify factors which were independently associated with poor outcomes.

Results—184 (60%) surviving patients scored more than 4 on the GHQ-30, 55 (22%) more than 8 on the HAD anxiety subscale, and 49 (20%) more than 8 on the HAD depression subscale. Patients with severe strokes resulting in physical disability were more likely to be depressed whereas there was a less strong relation between disability and anxiety. Patients with posterior circulation strokes had consistently better emotional outcomes than those with anterior circulation strokes.

Conclusion—These data may help identify those patients at greatest risk of poor emotional outcomes and thus help in planning trials and delivering appropriate interventions.

AB-14667-00

Objective: To characterize the risk factors for stroke in children and their relationship to outcomes. Methods: We reviewed charts of children with ischemic and hemorrhagic stroke seen at Hôpital Sainte-Justine, Montréal between 1991 and 1997. Results: We found 51 ischemic strokes: 46 arterial and 5 sinovenous thromboses. Risk factors were variable and multiple in 12 (24%) of the 51 ischemic strokes. Ischemic stroke occurred in 3 (8%) patients with a single or no identified risk factor and in 5 (42%) of 12 patients with multiple risk factors (p=0.01). We also found 21 hemorrhagic strokes, 14 (67%) of which were caused by vascular abnormalities. No patient with hemorrhagic stroke had multiple risk factors. Hemorrhagic stroke occurred in two patients (10%). Outcome in all 72 stroke patients was as follows: asymptomatic, 36%; symptomatic epilepsy or persistent neurologic deficit, 45%; and death, 20%. Death occurred more frequently in patients with recurrent stroke.
(40%) than in those with nonrecurrent stroke (16%). Conclusions: Multiple risk factors are found in many ischemic strokes and may predict stroke recurrence. Recurrent stroke tends to increase rate of mortality. Because of the high prevalence and importance of multiple risk factors, a complete investigation, including hematologic and metabolic studies and angiography, should be considered in every child with ischemic stroke, even when a cause is known.

AB-14668-00

Objective: To investigate the incidence and prognostic significance of fever on presentation and during the subsequent 72 hours in patients with spontaneous supratentorial intracerebral hemorrhage (ICH). Methods: We analyzed 251 patients. On admission, body temperature, Glasgow Coma Scale (GCS) score, age, sex, blood pressure, blood glucose level, and presumed origin of hemorrhage were analyzed. From the initial CT scan, hematoma volume, location, and presence of intraventricular hemorrhage were determined. From the first 72 hours, hematoma enlargement, duration of increased temperatures, blood pressure, and blood glucose level were determined. Outcome was classified on discharge with the Glasgow Outcome Scale (GOS) score. Results: Outcomes included no symptoms in 23 (9%), moderate disability in 64 (26%), severe disability in 104 (41%), vegetative state in 5 (2%), and death in 55 (22%) patients. Prognostic factors retained from a logistic regression model with a dichotomized GOS scale (GOS score of 1 or 2 versus GOS score of 3 to 5) as response variables were GCS score of 7 or less, age older than 75 years, hematoma volume of more than 60 cm³, ventricular hemorrhage, and presence of a coagulation disorder (p<0.05). Fever was associated with intraventricular hemorrhage. From 196 patients, data from the first 72 hours were analyzed. A total of 18 patients (9%) had normal temperatures throughout the study. The duration of fever (≥37.5 °C) was less than 24 hours in 66 (34%), 24 to 48 hours in 70 (36%), and more than 48 hours in 42 patients (21%). Independent prognostic factors during the first 72 hours were duration of fever, secondary hemorrhage, GCS score of 7 or less, ventricular hemorrhage, hematoma volume of more than 60 cm³, duration of increased blood pressure of more than 48 hours, and duration of increased blood glucose of more than 48 hours. Conclusions: The incidence of fever after supratentorial ICH is high, especially in patients with ventricular hemorrhage. In patients surviving the first 72 hours after hospital admission, the duration of fever is associated with poor outcome and seems to be an independent prognostic factor in these patients.

Epidemiology

AB-14669-00

Purpose: In recent years, several studies have shown the presence of vascular, cardiac, and other organ pseudoexfoliative material in patients with ocular pseudoexfoliation. The purpose of this study was to determine whether an association exists between ocular pseudoexfoliation and cardiovascular, cerebrovascular, or all-cause mortality.

Methods: This retrospective study included 472 residents of Olmsted County, Minnesota, who were diagnosed with pseudoexfoliation syndrome or pseudoexfoliative glaucoma at Mayo Clinic from 1976 through 1997. Of these 472 cases, 151 subsequently died from 1976 through 1997. Cause of death for these patients, as determined by the National Center for Health Statistics was compared with the entire Rochester, Minnesota, population using Kaplan-Meier analysis.

Results: Of the 472 patients with ocular pseudoexfoliation, 358 (76%) were female and 114 (24%) were male. The mean age at diagnosis was 74 years, with a SD of 10 years and a range from 39 to 106 years. Cardiovascular disease resulted in 40 deaths, with a 15-year cumulative probability of cardiovascular mortality of 22%, compared with an expected 20% (no significant difference with P=.19). Cerebrovascular disease resulted in 26 deaths with a 15-year cumulative probability of cerebrovascular mortality of 12%, compared with an expected 10% (no significant difference with P=.38). Finally, the 15-year observed all-cause cumulative mortality was 53% versus an expected rate of 59% (significant difference with P=.0002).

Conclusions: No association was found between ocular pseudoexfoliation and cardiovascular or cerebrovascular mortality. All-cause mortality was significantly less in patients with ocular pseudoexfoliation.

AB-14670-00
J-Shaped Relation Between Blood Pressure and Stroke in Treated Hypertensives—Voké Z, Bots ML, Hofman A, Koudstaal PJ, Wittelman JCM, Breteler MMB (Erasmus Univ, School of Medicine, Dept of Epidemiology & Biostatistics, POB 1738, NL-3000 Dr, Rotterdam, Netherlands)—Hypertension. 1999;34:1181–1185.

The objective of this study was to investigate the relationship between hypertension and risk of stroke in the elderly. The study was performed within the framework of the Rotterdam Study, a prospective population-based cohort study. The risk of first-ever stroke was associated with hypertension (relative risk, 1.6; 95% CI, 1.2 to 2.0) and with isolated systolic hypertension (relative risk, 1.7; 95% CI, 1.1 to 2.6). We found a continuous increase in stroke incidence with increasing blood pressure in nontreated subjects. In treated subjects, we found a J-shaped relation between blood pressure and the risk of stroke. In the lowest category of diastolic blood pressure, the increase of stroke risk was statistically significant compared with the reference category. Hypertension and isolated systolic hypertension are strong risk factors for stroke in the elderly. The increased stroke risk in the lowest stratum of blood pressure in treated hypertensive patients may indicate that the therapeutic goal of “the lower the better” is not the optimal strategy in the elderly.

AB-14671-00

Background: Warfarin dramatically reduces the risk for ischemic stroke in nonvalvular atrial fibrillation, but its use among ambulatory patients with atrial fibrillation has not been widely studied. Objective: To assess the rates and predictors of warfarin use in ambulatory patients with nonvalvular atrial fibrillation. Design: Cross-sectional study. Setting: Large health maintenance organization. Patients: 13428 patients with a confirmed ambulatory diagnosis of nonvalvular atrial fibrillation and known warfarin status between 1 July 1996 and 31 December 1997. Measurements: Data from automated pharmacy, laboratory, and clinical-administrative databases were used to determine the prevalence and determinants of warfarin use in the 3 months before or after the identified diagnosis of atrial fibrillation. Results: Of 11082 patients with nonvalvular atrial fibrillation and no known contraindications, 55% received warfarin. Warfarin use was substantially lower in patients who were younger than 55 years of age (44.3%) and those who were 85 years of age or older (35.4%). Only 59.3% of patients with one or more risk factors for stroke and no contraindications were receiving warfarin. Among a subset of “ideal” candidates to receive warfarin (persons 65 to 74 years of age who had no contraindications and had previous stroke, hypertension, or both), 62.1% had evidence of warfarin use. Among our entire cohort, the strongest predictors of receiving warfarin were previous stroke (adjusted odds ratio, 2.55 [95% CI, 2.23 to 2.92]), heart failure (odds ratio, 1.63 [CI, 1.51 to 1.77]), previous intracranial hemorrhage.
AB-14672-00


Memantine, an uncompetitive NMDA open-channel blocker, has been shown to be effective in preventing neuronal damage after permanent focal cerebral ischemia. Reperfusion after a long period of ischemia may aggravate the progression of neuronal damage. Those drugs that show protective effects after permanent cerebral ischemia, therefore, might fail to do so against ischemia-reperfusion injury. In this study we evaluated the effects of memantine on brain edema formation and ischemic injury volume after transient cerebral ischemia. Male Spontaneously Hypertensive Rats (SHR) weighing 250–300 g were anesthetized with halothane and subjected to 1 hour of temporary middle cerebral artery occlusion by an intraluminal suture. 20 mg/kg of memantine or saline were injected intraperitoneally 5 min. after the induction of ischemia. Physiological parameters and regional cerebral blood flow were monitored during the surgical procedure. Brain water content and ischemic injury volume were measured with the wet dry method respectively, at 24 hours after occlusion. There were no statistically significant differences between the groups regarding physiological parameters during the procedure. Memantine treatment (n = 9) reduced the brain water content significantly in the cortex compared to saline treatment (n = 8; 83.1±0.7% vs. 84.5±1.5%, respectively, p<0.05). The total volume of ischemic brain injury was 300±49 mm³ in the animals treated with saline (n = 13). Treatment with 20 mg/kg memantine (n = 14) reduced the ischemic injury volume to 233±61 mm³ (P<0.01). These results demonstrate that the harmful effects of reperfusion after a period of ischemia can be attenuated by the treatment of memantine, perhaps by its action at the NMDA receptors.

AB-14673-00


The mechanisms underlying cerebral microvascular perfusion deficit resulting from occlusion of the middle cerebral artery (MCA) require elucidation. We, therefore, tested the hypothesis that intravascular fibrin deposition in situ directly obstructs cerebral microcirculation and that local changes in type 1 plasminogen activator inhibitor (PAI-1) gene expression contribute to intravascular fibrin deposition after embolic MCA occlusion. Using laser-scanning confocal microscopy (LSCM) in combination with immunofluorescent staining, we simultaneously measured in three dimensions the distribution of microvascular plasma perfusion deficit and fibrinogen immunoreactivity in a rat model of focal cerebral embolic ischemia (n = 12). In addition, using in situ hybridization and immunostaining, we analyzed expression of PAI-1 in ischemic brain (n = 13). A significant (p<0.05) reduction of cerebral microvascular plasma perfusion accompanied a significant (p<0.05) increase of intravascular and extravascular fibrin deposition in the ischemic lesion. Microvascular plasma perfusion deficit and fibrin deposition expanded concomitantly from the subcortex to the cortex during 1 and 4 hr of embolic MCA occlusion. Three-dimensional analysis revealed that intravascular fibrin deposition directly blocks microvascular plasma perfusion. Vascular plugs contained erythrocytes, polymorphonuclear leukocytes, and platelets enmeshed in fibrin. In situ hybridization demonstrated induction of PAI-1 mRNA in vascular endothelial cells in the ischemic region at 1 hr of ischemia. PAI-1 mRNA significantly increased at 4 hr of ischemia. Immunohistochemical staining showed the same pattern of increased PAI-1 antigen in the endothelial cells. These data demonstrate, for the first time, that progressive intravascular fibrin deposition directly blocks cerebral microvascular plasma perfusion in the ischemic region during acute focal cerebral embolic ischemia, and upregulation of the PAI-1 gene in the ischemic lesion may foster fibrin deposition through suppression of fibrinolysis.

AB-14674-00


We examined average apparent diffusion coefficient (ADCav) thresholds to define ischemic lesion size and characterized the temporal evolution of the ADCav thresholds. Thirteen Sprague-Dawley rats underwent permanent middle cerebral artery occlusion in the magnetic resonance imaging unit. Diffusion-weighted imaging was acquired before occlusion and 25, 60, 90, 150, 210, and 270 minutes after occlusion. Absolute ADCav values from 0.46 to 0.62×10⁻³ mm²/s and the percentage of the decline of ADCav values from −32% to −16% compared with the baseline values were used to define the percentage of hemispheric lesion volume (%HVL) at each time point. Twenty-four hours after occlusion, the rats were killed, and 2,3,5-triphenyl-tetrazolium chloride (TTC) staining was used to calculate the percentage of hemispheric infarction volume (%HIV), which was then used as the “gold standard” to determine ADCav thresholds. The ADCav-derived %HVL was identical to and best correlated with the TTC-derived %HIV when the absolute ADCav threshold was 0.62, 0.60, 0.54, 0.52, 0.50, and 0.50×10⁻³ mm²/s and the percentage of ADCav threshold was −16%, −18%, −24%, −28%, −30% and −30% at 25, 60, 90, 150, 210, and 270 minutes after occlusion, respectively. Our results suggest that both the absolute values and the percentage of ADCav thresholds can define the final lesion volume as early as 25 minutes and that these thresholds decrease over time and become constant 210 minutes after occlusion throughout the observation period.

AB-14675-00


Background: Human brains show widespread necrosis when death occurs after coma due to cardiac arrest, but not after hypoxic coma. It is unclear whether hypoxia alone can cause brain damage without ischemia. The relationship of blood oxygenation and vascular occlusion to brain necrosis is also incompletely defined. Methods: We used physiologically monitored Wistar rats to explore the relationship among arterial blood oxygen levels, ischemia, and brain necrosis. Hypoxia alone (PaO₂<25 mm Hg), even at a blood pressure (BP) of 30 mm Hg for 15 minutes, yielded no necrotic neurons. Ischemia alone (unilateral carotid ligation) caused necrosis in 4 of 12 rats, despite a PaO₂>100 mm Hg. To reveal interactive effects of hypoxia and ischemia, groups were studied with finely graded levels of hypoxia at a fixed BP, and with controlled variation in BP at fixed PaO₂. In separate series, focal ischemic stroke was mimicked with transient middle cerebral artery (MCA) occlusion,
and the effect of low, normal, and high PaO₂ was studied. Results: Quantitated neuropathology worsened with every 10 mm Hg decrement in BP, but the effect of altering PaO₂ by 10 mm Hg was not as great, nor as consistent. Autoradiographic study of cerebral blood flow with ¹⁴C-iodoantipyrine revealed no hypoxic vasodilatation during ischemia. In the MCA occlusion model, milder hypoxia than in the first series (PaO₂=46.5±1.4 mm Hg) exacerbated necrosis to 24.3±4.7% of the hemisphere from 16.6±7.0% with normoxia (PaO₂=120.5±4.1 mm Hg), whereas hyperoxia (PaO₂=213.9±5.8 mm Hg) mitigated hemorrhagic damage to 7.50±1.86%. Cortical damage was strikingly sensitive to arterial PaO₂, being 12.8±3.1% of the hemisphere with hypoxia, 7.97±4.63% with normoxia, and only 0.3±0.2% of the hemisphere with hyperoxia (p<0.001), and necrosis being eliminated completely in 8 of 10 animals. Conclusions: Hypoxia without ischemia does not cause brain necrosis but hypoxia exacerbates ischemic necrosis. Hyperoxia potently mitigates brain damage in this MCA occlusion model, especially in neocortex.

Imaging

AB-14676-00

In major cerebral arterial occlusive diseases, patients with increased oxygen extraction fraction (OEF), which is measured with PET, may be at increased risk for cerebral ischemia. However, the clinical significance of increased OEF remains unclear. This study investigated whether increased OEF is an independent predictor of 5-y risk of subsequent stroke. Methods: We prospectively evaluated the relationship between the regional hemodynamic status of cerebral circulation and the subsequent risk of stroke in 40 patients with symptomatic internal carotid or middle cerebral arterial occlusive diseases who underwent PET. Patients were divided into two hemodynamic categories according to the mean hemispheric value of OEF in the hemisphere supplied by the artery with symptomatic disease: one group with increased OEF and one with normal OEF. All patients were followed for 5 y with medical treatment until the recurrence of stroke or death. Results: During 5 y, 11 total and 9 ipsilateral ischemic strokes occurred. The incidences of all ischemic strokes in patients with increased OEF and in those with normal OEF were 5 of 7 and 6 of 33 patients, respectively. There were 4 ipsilateral ischemic strokes in patients with increased OEF and 5 in those with normal OEF. Kaplan-Meier analysis revealed that the risks of all stroke and ipsilateral ischemic stroke in patients with increased OEF were significantly higher than in those with normal OEF (log-rank test; P<0.0002 and P=0.0018, respectively). Multivariate analysis with the Cox proportional hazards model showed that increased OEF significantly increased stroke recurrence: the relative risk was 7.2 (95% confidence interval [CI], 2.0–25.5; P=0.005) for all stroke and 6.4 (95% CI, 1.6–26.1; P=0.01) for ipsilateral stroke. An increase in the absolute OEF value was a better predictor of recurrent ischemic stroke than was OEF asymmetry. Conclusion: These findings suggest that an increased OEF is an independent predictor of 5-y risk of subsequent stroke. Identification of patients with increased OEF may have clinical significance in preventing recurrent stroke.

AB-14677-00

Purpose: To analyze the magnetic resonance (MR) imaging features of familial cerebral cavernous angioma in non-Hispanic families. Materials and methods: Between November 1996 and June 1997, 51 non-Hispanic families with familial cavernous angioma were identified. Cerebral MR images in 83 symptomatic subjects and 73 asymptomatic subjects were reviewed. Spin-echo (SE) and gradient-echo (GRE) MR imaging features of cavernous angioma were recorded and, in 91 subjects with both SE and GRE images, lesions were graded as type 1, 2, 3, or 4, according to a published classification scheme. MR imaging features were compared between symptomatic and asymptomatic subjects, and sensitivities of SE and GRE images were determined. Results: Multiple lesions were more common than single lesions in both symptomatic and asymptomatic subjects, with no difference in mean number of lesions between groups. More lesions were detected on GRE images than on SE images. Type 1 and type 2 lesions were more numerous in symptomatic than in asymptomatic subjects. The numbers of types 2, 3, and 4 lesions increased with age in both groups. Conclusion: The familial form of cavernous angioma is characterized by multiple lesions and by a correlation between lesion number and subject age. The clinical manifestation may be more closely related to the type of lesion than to the number of lesions. GRE MR images are more sensitive than SE images for demonstration of cavernous angioma.

Neurosonology

AB-14678-00

Background: Studies of aortic arch plaques with transesophageal echocardiography have demonstrated that complex aortic arch plaques (CAPs) greater than or equal to 4 mm in thickness are associated with ischemic stroke. Recent studies have demonstrated that the morphological features of plaques may aid in the identification of aortic plaques that are more likely to be associated with embolic stroke. Objective: To identify aortic plaques that are more likely to be associated with embolic stroke by means of their morphological features. Methods: Transcutaneous B-mode ultrasonography was used to image aortic arch plaques in 500 consecutive patients. The criteria used to identify the morphological features of carotid artery plaques that are more likely to be associated with ischemic stroke (heterogeneous rather than homogeneous) were applied to aortic arch plaques. Statistical comparisons were made using the Fisher exact test. Results: Ischemic symptoms (eg, stroke, transient ischemic attack, and amaurosis fugax) were present in 38% of 104 patients with CAP and in 34% of 391 patients without CAP. Nineteen (51%) of 37 patients with heterogeneous CAP were symptomatic. Twenty-one (31%) of 67 patients with homogeneous CAP were symptomatic (P=0.4). Conclusion: Transcutaneous B-mode ultrasonography of the aortic arch can help to identify heterogeneous plaques that are more likely to be associated with ischemic stroke using morphological criteria derived from studies of carotid artery plaque.

AB-14679-00

Reperfusion of intracranial arteries can be detected by transcranial Doppler (TCD). The authors report microembolic signals (MES) on TCD as a sign of clot dissolution and recanalization. Microembolic signals were detected during routine diagnostic TCD examination performed in the emergency room in patients eligible for thrombolytic therapy. Microembolic signals were found at the site of M1 middle cerebral artery (MCA) high-grade stenosis or near-occlusion. Transcranial Doppler was performed before, during, and after thrombolytic therapy. Of 16 consecutive patients, 3 (19%) had MES on TCD: All three patients had a severe MCA syndrome at 2 hours after stroke onset scored using the National
Institutes of Health Stroke Scale (NIHSS). In patient #1 (NIHSS 12), clusters of MES were detected distal to a high-grade M1 MCA stenosis preceding spontaneous clinical recovery by 2 minutes. Because of subsequent fluctuating clinical deficit, intraarterial thrombolyis was given with complete recovery. In patient #2 (NIHSS 20), TCD detected an M1 MCA near-occlusion. At 1.5 hours after intravenous tissue plasminogen activator, TCD showed minimal MCA flow signals followed by MES, increased velocities, and normal flow signals in just 2 minutes. She gradually recovered up to NIHSS 8 in 5 days. In patient #3 with NIHSS 22 and an M1 MCA near-occlusion, TCD detected MES 15 minutes after TPA bolus followed by MCA flow velocity improvement from 15 cm/sec to 30 cm/sec. The patient recovered completely by the end of tissue plasminogen activator infusion. The authors conclude that embolic signals detected by TCD at the site of arterial obstruction can indicate clot dissolution. Intracranial recanalization on TCD can be associated with MES and changes in flow waveform, pulsatility, and velocity if insomation is performed at the site of arterial obstruction.

AB-14680-00

The authors determined transcranial Doppler (TCD) accuracy for the proximal internal carotid artery (ICA), distal ICA, proximal middle cerebral artery (MCA), distal MCA, anterior cerebral artery (ACA), posterior cerebral artery (PCA), terminal vertebral artery (tVA), and basilar artery (BA) occlusion in cerebral ischemia patients. Detailed diagnostic criteria were prospectively applied for TCD interpretation independent of angiographic findings. Of 320 consecutive patients referred to the neurosonology service with symptoms of cerebral ischemia, 190 (59%) patients also underwent angiography (MRA or DSA). 48 of those 190 patients had angiographic occlusion and 12 of those 48 patients had involvement of multiple vessels. Median time from TCD until angiography was performed was 1 hour (41 patients had angiography before TCD). TCD showed 40 true positive, 8 false negative, 8 false positive, and 134 true negative studies with sensitivity 83.0%, specificity 94.4%, positive predictive value 83.0%, negative predictive value 94.4%, and accuracy 91.6% to determine all sites of occlusion. Sensitivity for each individual occlusion site was: proximal ICA 94%, distal ICA 81%, MCA 93%, tVA 56%, BA 60%. Specificity ranged from 96% to 98%. TCD is sensitive and specific in determining the site of the arterial occlusion using detailed diagnostic criteria, including proximal ICA and distal MCA lesions. TCD has the highest accuracy for ICA and MCA occlusions. If the results of TCD are normal, there is at least a 94% chance that angiographic studies will be negative.

Pharmacology / Therapeutics

AB-14681-00

Objective: To determine if 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are effective in preventing fatal and nonfatal strokes in patients at increased risk of coronary artery disease. Design: Meta-analysis of randomized controlled trials. Clinical trials were identified by a computerized search of MEDLINE (1983 to June 1996), by an assessment of the bibliographies of published studies, meta-analyses and reviews, and by contacting pharmaceutical companies that manufacture statins. Trials were included in the analysis if their patients were randomly allocated to a statin or placebo group, and reported data on stroke events. Thirteen of 28 clinical trials were selected for review. Data were extracted for details of study design, patient characteristics, interventions, duration of therapy, cholesterol measurements, and the number of fatal and nonfatal stroke events in each arm of therapy. Missing data on stroke events were obtained by contacting the investigators of the clinical trials. Main results: Among 19,921 randomized patients, the rate of total stroke in the placebo group was 2.38% (90% nonfatal and 10% fatal). In contrast, patients who received statins had a 1.67% stroke rate. Using an exact stratified analysis, the pooled odds ratio (OR) for total stroke was 0.70 (95% confidence interval [CI] 0.57, 0.86; p = .0005). The pooled OR for nonfatal stroke was 0.64 (95% CI 0.51, 0.79; p = .00001), and the pooled OR for fatal stroke was 1.25 (95% CI 0.71, 2.24; p = .4973). In separate analyses, reductions in total and nonfatal stroke risk were found to be significant only for trials of secondary coronary disease prevention. Regression analysis showed no statistical association between the magnitude of cholesterol reduction and the relative risk for any stroke outcome. Conclusions: The available evidence clearly shows that HMG-CoA reductase inhibitors reduce the morbidity associated with strokes in patients at increased risk of cardiac events. Data from 13 placebo-controlled trials suggest that on average one stroke is prevented for every 143 patients treated with statins over a 4-year period.

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Objectives. There is uncertainty amongst clinicians about the definitions of cobalamin and folate deficiency and therefore about the indications for treatment. In this report we present the results of systematic cobalamin and folate acid treatment based upon serum cobalamin, total homocysteine (tHcy) and methylmalonic acid (MMA) analyses in a population-based sample.

Subjects. A 20% random sample of persons 70 years or older in a defined geographical area were invited to a survey (n = 266). Sixty-nine persons who had serum cobalamin <300 pmol L−1 and serum MMA ≥0.37 μmol L−1 or serum tHcy ≥15 μmol L−1 and who had no cobalamin or folate acid substitution were selected for treatment.

Interventions. Initially all 69 patients were given cobalamin orally or intramuscularly. Those who remained high in tHcy were in addition given folate acid treatment.

Main outcome measures. Serum cobalamin, serum MMA and serum tHcy.

Results. After 6 months of cobalamin treatment, serum MMA became normal in 13 out of 15 persons. Mean serum tHcy decreased but was still normalized in only 15 out of 56 persons. After 3 months of folate acid treatment added to those who still had an abnormal serum tHcy, serum tHcy had normalized in all but one person.

Conclusions. Cobalamin treatment normalizes increased MMA values and combined cobalamin and folate acid treatment normalizes tHcy, suggesting a pretreatment deficiency of tissue cobalamin and folate in spite of normal serum cobalamin and folate values in the majority of cases.

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Background. We have reported previously that, compared with use of second-generation oral contraceptives, the use of third-generation oral contraceptives is associated with increased resistance to the anticoagulant action of activated protein C (APC). Owing to the cross-sectional design of that study, these observations may have been subject to unknown bias or uncontrolled effects of the menstrual cycle. We aimed to overcome these sources of bias by doing a cycle-controlled randomised cross-over trial.
Methods The response to APC in plasma was assessed in 33 women who received two consecutive cycles of a second-generation oral contraceptive (150 μg levonorgestrel and 30 μg ethinylloestradiol) or a third-generation oral contraceptive (150 μg desogestrel and 30 μg ethinylloestradiol), and who switched preparations after two pill-free cycles. Normalised APC sensitivity ratios were calculated by measurement of the effect of APC on thrombin generation in the plasma of these women and in pooled plasma from 90 controls.

Findings Of the 33 women, five were excluded because not all required plasma samples were available. In the remaining 28 women, the normalised APC sensitivity ratio increased during treatment with both preparations. Compared with levonorgestrel, desogestrel-containing oral-contraceptive treatment caused a highly significant (p<0.0001) additional increase in normalised APC sensitivity ratio (0.51 [95% CI 0.37–0.66]). Normalised APC sensitivity ratios during oral-contraceptive treatment correlated with the values before oral-contraceptive use.

Interpretation Oral-contraceptive treatment diminishes the efficacy with which APC down-regulates in-vitro thrombin formation. This phenomenon, designated as acquired APC resistance, is more pronounced in women using desogestrel-containing oral contraceptives than in women using levonorgestrel-containing preparations. Whether acquired APC resistance induced by oral contraceptives explains the increased risk of venous thromboembolism in oral-contraceptive users remains to be established.

Surgery


Background: This study was undertaken to evaluate the role of eversion endarterectomy in the management of extracranial carotid occlusive disease.

Methods: A retrospective review was performed of all patients undergoing carotid endarterectomy between July 1994 and July 1998. After reviewing the records, patients were assigned to one of three groups: eversion (ECEA); open with primary closure (CEA°); or open with patch closure (CEAP). Statistical comparisons were made.

Results: The 190 index cases comprised 33 ECEA (17%), 15 CEA° (8%), and 142 CEAP (75%). Both ECEA and CEA° were more likely to be done on males versus females compared with CEAP (P = 0.01). For the entire 190 cases, stroke occurred in 1 patient (0.5%); and myocardial infarction in 2 patients (1%), resulting in death in both. Two patients (1.4%) in the CEAP group have undergone redo surgery at 8 and 24 months.

Conclusions: This study demonstrates that eversion endarterectomy achieves early results similar to open endarterectomy with and without patch closure.


Objective: To examine the relationship between carotid artery stenosis, other risk factors, and lacunar stroke. Background: Carotid artery stenosis in patients presenting with lacunar stroke may be coincidental or causal. The distinction by risk factor profile is uncertain. The risk and cause of subsequent stroke, and benefit of carotid endarterectomy (CE) is unknown. Methods: Stroke in patients entering the North American Symptomatic Carotid Endarterectomy Trial were classified as nonlacunar, possible lacune (symptoms without CT lacunae), or probable lacunae (symptoms with CT lacunae). Results: Of 1,158 patients with hemispheric stroke, 493 had features of lacunar stroke (283 possible and 210 probable). Lacunar stroke presented more commonly in patients with milder (<50%) degrees of internal carotid artery (ICA) stenosis (p = 0.003). History of diabetes and hyperlipidemia, not hypertension, were associated independently even after accounting for the degree of stenosis. Medically treated patients presenting with nonlacunar stroke had a low risk of subsequent lacunar events of 2.9% at 3 years in comparison with 9.2% for probable lacunar presentation (p = 0.03). For patients with 50 to 99% ICA stenosis, the relative risk reductions (RRRs) in stroke from CE were 35% when the presenting stroke was probable lacunar versus 61% when the stroke was nonlacunar. Patients presenting with a possible lacunar stroke had a 53% RRR. Conclusions: History of diabetes and hyperlipidemia were more important than arterial hypertension as risk factors for patients with lacunar stroke. Patients presenting with lacunar stroke more often had milder ICA stenosis. Although CE reduced the risk of stroke in all patients with 50 to 99% ICA stenosis, lesser benefits were observed in patients presenting with lacunar stroke.

Items of Interest


The Mississippi Stroke Education Consortium: A State-Based Template to Promote Stroke Awareness, Prevention and Emergency Treatment—Gordon DL (Center for Research in Medical Education, Univ of Miami School of Medicine, P.O. Box 016960 D-41, Miami, FL 33101)—Neuroepidemiology. 2000;19:1–12. Copyright © 2000 S. Karger AG, Basel.


Abstracts of Literature
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