Cerebral Aneurysms

AB-14350-99

Objectives—The effect of intra-arterial papaverine (IAP) on the basilar artery (BA) and cerebral perfusion pressure (CPP) during the chronic period of the cerebral arterial vasospasm in rats was investigated.

Material and Methods—The study was carried out on male, Swiss-Albino rats, the weight of each varied between 200–340 g. A large volume (0.3 cc) of nonheparinized, autolog blood was used in order to cause a subarachnoid haemorrhage. For the measurement of the changes in BA diameter, the angiograms were made prior to the subarachnoid haemorrhage, 48 h after the subarachnoid haemorrhage, and in 1, 15, 30, and 60 min after papaverine infusion into the vertebral artery. The BA vascular index was found separately for each angiogram. At each stage of the procedure mean arterial blood pressure (MAP) and intracranial pressure (ICP) were monitored.

Results—BA diameter measurements were found to be 226±32 μm in pre-haemorrhage angiograms and 145±44 μm in angiograms 48 h after the subarachnoid haemorrhage. In the angiograms immediately after IAP, it was found that the BA diameter reached about 92% (206±41 μm) of control values. But, in the angiograms 15 min after IAP, it was observed that BA underwent a spasm again.

Conclusion—The dilatator effect of IAP on BA was temporary. Additionally, in the chronic vasospasm period when cerebral autoregulation mechanisms are impaired and CPP decreased significantly, IAP has adversely affected CPP decreasing MAP.

Clinical

AB-14351-99

Thrombosis may play an important role in the pathophysiology of certain complications of sickle cell disease (SCD), including stroke and avascular necrosis (AVN). Currently there is no laboratory or clinical parameter that can identify patients who are at highest risk of developing these thrombotic complications. We hypothesized that some patients with SCD have an inherited hypercoagulable state that results in an increased risk of developing stroke or AVN. We examined the role of two common inherited thrombophilic mutations that, in other populations, have been associated with arterial and venous thrombosis and are amenable to screening with DNA restriction enzyme analysis. The C677T mutation in the methylene tetrahydrofolate reductase (MTHFR) gene and the C1565T mutation in the platelet glycoprotein IIb (GPIIb) gene were evaluated. We analyzed genomic DNA from 86 children and adults with SCD, including 16 patients with a history of a clinical stroke and 14 patients with AVN, for the presence of these mutations. The C677T MTHFR mutation was found in 19% of patients with stroke, 14% of patients with AVN, and 14% of patients with neither complication (P=NS). The C1565T GPIIb mutation was found in 25% of patients with stroke, 14% of patients with AVN, and 18% of patients with neither complication (P=NS). Although each of these mutations is relatively common in patients with SCD, neither is independently associated with an increased risk of developing stroke or AVN.

AB-14352-99
Inherited DNA Mutations Contributing to Thrombotic Complications in Patients With Sickle Cell Disease—Zimmerman SA (Box 2916, Duke Univ Medical Center, Durham, NC 27710), Ware RE—Am J Hemanal. 1998;133:777–781. Copyright © by Mosby, Inc.


Objective: Resistance to activated protein C (APC) has been identified as a risk factor for thrombotic disease in adults. In over 90% of cases, the basis for the APC resistance is a mutation in the coagulation factor V gene (factor V Leiden) that renders the protein more resistant to inactivation by APC. We sought to determine the prevalence of the factor V Leiden (FVL) mutation in neonates and children who had experienced an arterial or venous thromboembolic event.

Study design: We retrospectively analyzed the clinical records of 33 neonates and 52 children with thromboembolic disease. Screening for the FVL mutation was performed by DNA analysis, allowing for identification of patients as normal, heterozygous, or homozygous.

Results: Of the 85 patients studied, 12 (14.1%) were heterozygous for FVL; none were homozygous. Of the 47 patients who had arterial central nervous system events, 8 (17%) were positive for the FVL mutation.
including 6 of 22 (27%) neonates. Of those patients who had a venous thrombosis, 4 of 32 (12.5%) were FVL positive. None of the 85 patients had protein C deficiency, 3.5% had protein S deficiency, 1.2% had antithrombin III deficiency, and 16.5% had anti-phospholipid antibodies.

Conclusion: These data suggest that the FVL mutation plays a role in the development of arterial and venous thrombotic events in neonates and children.

AB-14354-99
Progressive Motor Deficits in Lacunar Infarction—Nakamura K (Second Dept of Internal Medicine, Faculty of Medicine, Kyushu Univ, Maidsahi 3-1-1, Higashi-ku, Fukuoka 812-8582, Japan), Saku Y, Ibayashi S, Fujishima M—Neurology. 1999;52:29–33. Copyright © 1999 by the American Academy of Neurology.

Objective: To study the clinical characteristics of the progression of motor deficits in lacunar stroke patients. Background: Some patients with lacunar infarction have progression of their neurologic deficits, but it is not known which patients will progress or why they progress. Methods: The authors evaluated 92 consecutive patients (47 men, 45 women; age, 69.4±10.9 years [mean±SD]) with first-ever stroke due to supratentorial lacunes in the internal capsule or the corona radiata. By defining lacunar infarction in which motor deficits progressed between admission and the day after admission as progressive lacunar infarction, the authors compared progressive lacunar infarction with stable lacunar infarction. Results: Of 92 patients, 25 (27%) had progression of deficits. Diabetes mellitus (p=0.02) and severity of motor deficit on admission (p=0.006) were related independently to progression in a logistic multiple regression analysis. Size of the infarct was slightly larger (1.2±0.4 cm² vs 0.9±0.5 cm²; p=0.01) and functional status at discharge was worse (median Barthel index, 45 versus 100; p=0.001) in patients with progressive infarction than in those without progression. There were no significant differences between the two groups regarding the site of the infarct or blood pressure or hematocrit levels on or after admission. Conclusions: The progression of motor deficits is associated with a relatively poor functional outcome. Diabetes mellitus and the severity of motor deficit on admission may predict progression of motor deficits.

Epidemiology

AB-14355-99
Lifestyle and 15-Year Survival Free of Heart Attack, Stroke, and Diabetes in Middle-Aged British Men—Wannamethee SG (Dept of Primary Care and Population Sciences, Royal Free Hospital School of Medicine, Rowland Hill St, London NW32PF, England), Shaper AG, Walker M, Ebrahim S—Arch Intern Med. 1998;158:2433–2440.

Background: To examine the relationship between modifiable lifestyle factors (smoking, physical activity, alcohol intake, and body mass index [BMI]) and the likelihood of 15-year survival free of major cardiovascular end points and diabetes in middle-aged men.

Methods: A prospective study of 7142 men aged 40 to 59 years at screening with no history of coronary heart disease, diabetes, and stroke drawn from 1 general practice in each of 24 British towns and followed up for 15 years.

Main Outcome Measures: Death from any cause and a combined end point, including survival free of heart attacks or stroke or the development of diabetes over a follow-up of 15 years for each man.

Results: During the 15-year follow-up, there were 1064 deaths from all causes, 770 major heart attacks (fatal and nonfatal), 247 stroke events (fatal and nonfatal), and 252 cases of diabetes among the 7142 men. After adjustment for age and each of the other modifiable lifestyle factors, the risk of the combined end point (death or having a heart attack, stroke, or diabetes) went up significantly with increasing smoking levels and from adjustment for age and each of the other modifiable lifestyle factors, the all causes, 770 major heart attacks (fatal and nonfatal), 247 stroke events

AB-14356-99

Hyperhomocysteinemia is an independent risk factor for atherosclerotic disease in the middle-aged. We investigated whether a high serum homocysteine level is a risk factor for vascular disease in 878 elderly men (mean age at baseline, 71.5 years; range, 64 to 84 years) in a population-based, representative cohort followed up for 10 years in Zutphen, the Netherlands. Thirty-one percent had nonfasting homocysteine levels ≥17 μmol/L. After adjustment for other major risk factors, high homocysteine levels at baseline (the third compared with the first tertile) were associated with an increased baseline prevalence of myocardial infarction (odds ratio [OR], 1.81; 95% confidence interval [CI], 1.07 to 3.08; P for trend, 0.03) and with a marginally significant increase in the risk of dying of coronary heart disease (relative risk [RR], 1.58; 95% CI, 0.93 to 2.69; P for trend, 0.09) but not with an increased risk of first-ever myocardial infarction. In addition, high homocysteine levels at baseline were associated with an increased baseline prevalence of stroke (OR, 4.61; 95% CI, 1.79 to 11.89; P for trend, 0.002) and with an increased risk of dying of cerebrovascular disease in subjects without hypertension (RR, 6.18; 95% CI, 2.28 to 16.76) but not in those with hypertension. High homocysteine levels were associated with an increased risk of first-ever stroke among normotensive subjects that was not statistically significant (RR, 1.77 [95% CI, 0.83 to 3.75; P for trend, 0.14]). In a general population of elderly men, a high homocysteine level is common and is strongly associated with the prevalence of coronary heart disease and cerebrovascular disease. It is a strong predictive factor for fatal cerebrovascular disease in men without hypertension but less so for coronary heart disease.

Experimental Pathology

AB-14357-99
Insular Cortex Lesions Alter Baroreceptor Sensitivity in the Urethane-Anesthetized Rat—Zhang ZH, Rashba S, Oppenheimer SM (Laboratory of Neurocardiology, Meyer 5-185, The Johns Hopkins Hospital, 600 N Wolfe St, Baltimore, MD 21287-7585)—Brain Res. 1998;813:73–81. Copyright © 1998 Published by Elsevier Science B.V.

Cardiovascular representation has been demonstrated within the insular cortex and lateralization has been previously inferred. In this study, baroreceptor gain was investigated in response to the systemic injection of the pressor agent phenylephrine (PE) and the depressor agent sodium nitroprusside (SNP) in 57 urethane-anesthetized, male Sprague-Dawley rats before and after single lesion placement. Lesions mainly confined to the anterior insula (left or right) or the adjacent cortex were without significant effect on baroreceptor gain. Left posterior insular lesions, however, significantly increased baroreceptor gain (p<0.0001) whereas right posterior insular lesions had no effect on baroreceptor gain although heart rate and blood pressure were both significantly increased after
lesion placement (p<0.05). These data suggest that: (1) the posterior insula (and not surrounding cortex or anterior insula) is primarily involved in cardiovascular control; (2) the left insular cortex may be chiefly concerned with parasympathetic cardiac regulation. Conversely, the right posterior insular cortex may regulate both cardiac and vasomotor sympathetic tone, as has been suggested in other species.

**AB-14358-99**

**Clopidogrel Inhibition of Stent, Graft, and Vascular Thrombogenesis With Antithrombotic Enhancement by Aspirin in Nonhuman Primates—Harker LA (Div of Hematology and Oncology, Emory Univ School of Medicine, 1639 Pierce Dr, WMB Room 1003, Atlanta, GA 30322), Marzec UM, Kelly AB, Chronos NRF, Sundell IB, Hanson SR, Herbert JM—Circulation. 1998;98:2461–2469. Copyright © 1998 American Heart Association, Inc.**

**Background—**A recent study showed that clopidogrel reduces thrombo-occlusive complications in patients with symptomatic atherosclerosis more effectively than aspirin.

**Methods and Results—**The effects of clopidogrel and aspirin have been compared, singly and in combination, for measurements of $^{111m}$In-labeled platelets and $^{125}$I-labeled fibrin deposition in baboon models of arterial thrombosis and related to platelet aggregation and expression of activation epitopes induced by ADP, collagen, and thrombin receptor agonist peptide (TRAP) and to template bleeding times (BTs). Low-dose oral clopidogrel (0.2 mg $\cdot$ kg$^{-1}$ $\cdot$ d$^{-1}$) produced cumulative (1) intermediate decreases in $^{111m}$In-platelet and $^{125}$I-fibrin deposition for segments of prosthetic vascular graft, deployed endovascular metallic stents, and endarterectomized aorta (P<0.009 in all cases); (2) elimination of ADP-induced platelet aggregation (P<0.001); (3) modest inhibition of collagen-induced platelet aggregation (P<0.01); (4) no reduction in TRAP-induced platelet aggregation; and (5) minimal prolongation of BTs (P=0.03). High-dose oral clopidogrel ($\geq$2 mg/kg) produced the same effects within 3 hours. The effects of clopidogrel dissipated over 5 to 6 days. Aspirin 10 mg $\cdot$ kg$^{-1}$ $\cdot$ d$^{-1}$ alone did not decrease $^{111m}$In-platelet and $^{125}$I-fibrin deposition on segments of vascular graft but detectably decreased $^{111m}$In-platelet and $^{125}$I-fibrin accumulation on stents (P<0.01), minimally inhibited ADP- and collagen-induced platelet aggregation (P<0.05 in both cases), and minimally prolonged BTs (P=0.004). Within 3 hours of aspirin administration, the antithrombotic effects of acute high-dose or chronic low-dose clopidogrel were substantially enhanced, and BTs were modestly prolonged without inhibiting platelet aggregation induced by TRAP (P<0.001 in all cases compared with clopidogrel alone).

**Conclusions—**Clopidogrel produces irreversible, dose-dependent, intermediate reduction in thrombosis that is substantially enhanced by the addition of aspirin. The effects of combining aspirin and clopidogrel need to be evaluated in patients at risk of vascular thrombosis.

**Imaging**

**AB-14359-99**


**PURPOSE:** To determine the normal values and effects of age and sex on total cerebral blood flow (CBF) as measured with ungated two-dimensional phase-contrast magnetic resonance (MR) angiography.

**MATERIALS AND METHODS:** Volume flow rates in the basilar artery and both internal carotid arteries were measured on two-dimensional phase-contrast MR angiograms obtained in 250 subjects (age range, 19–88 years; mean age, 50 years) undergoing MR imaging because of indications other than cerebrovascular disease. Volume flow rates for the three arteries were summed to obtain the total CBF, and the values were analyzed in terms of age and sex.

**RESULTS:** Mean total CBF was 616 mL/min±143. There was a significant yearly decrease with age in total CBF of 4.8 mL/min (P<0.001). Mean total CBF ranged from 748 mL/min±121 to 474 mL/min±105 in subjects aged 19–29 and 80–89 years, respectively. No sex differences were found. Mean relative contributions of the right and left internal carotid arteries and the basilar artery to total CBF were 41%, 40%, and 19%, respectively, with no substantial change due to age.

**CONCLUSION:** Ungated two-dimensional phase-contrast MR angiography is a useful, noninvasive technique for assessing total CBF. By using this technique, a significant decrease in total CBF with age was demonstrated.

**AB-14360-99**

**Gray Matter and White Matter Perfusion Imaging in Patients With Severe Carotid Artery Lesions—Kluytmans M (Dept of Radiology, Image Sciences Institute, Univ Hospital Utrecht, Rm E01.334, Heidelberglaan 100, 3584 CX Utrecht, Netherlands), van der Grond J, Viergever MA—Radiology. 1998;209:675–682.**

**PURPOSE:** To determine, with dynamic susceptibility contrast-enhanced magnetic resonance (MR) imaging, changes in gray matter and white matter perfusion in patients with internal carotid artery (ICA) occlusions.

**MATERIALS AND METHODS:** Regional cerebral blood volume (CBV), mean transit time, arrival time (time for contrast material to arrive in the brain), and peak time (time to highest contrast material concentration in the brain) were determined in 44 patients and 33 control subjects. Patients were divided into three groups: patients with a unilateral ICA occlusion, patients with a unilateral ICA occlusion and a contralateral severe stenosis (>70%), and patients with bilateral ICA occlusions.

**RESULTS:** Compared with control subjects, patients with unilateral ICA occlusions had hemodynamic changes in the ipsilateral hemisphere: Mean transit time, arrival time, and peak time were increased in white and gray matter (P<0.001), and regional CBV was significantly increased in white matter only (P<0.01). Hemodynamic changes were more pronounced in patients with bilateral ICA occlusions: Compared with control subjects, mean transit time, arrival time, peak time, and regional CBV were increased in both white and gray matter in both hemispheres (P<0.001).

**CONCLUSION:** Dynamic susceptibility contrast-enhanced MR imaging can enable measurement of relative hemodynamic changes in patients with ICA occlusions, with the advantage that gray and white matter perfusion can be evaluated.

**Neurosonology**

**AB-14361-99**


**OBJECTIVE:** Lumbar epidural anesthesia is associated with a transient elevation in intracranial pressure in both animals and humans and decreased cerebral blood flow in animals. We sought to determine the effect of medium-onset and slow-onset local anesthetic lumbar epidural anesthesia on maternal cerebral blood flow in normal human pregnancy.

**STUDY DESIGN:** In an Institutional Review Board–approved, double-blind study, 24 healthy, normotensive, nonlaboring, term gravidas undergoing elective cesarean section were prospectively placed into random groups to receive either 2% lidocaine with 8.4% sodium bicarbonate (1:10) or 0.5% bupivacaine lumbar epidural anesthesia. After prehydration with 20 mL/kg crystalloid and 15-degree left-wedge supine positioning with 15-degree head tilt, transcranial Doppler ultra-
Sound (Nicolet Pioneer EME) and simultaneous electrocardiogram, automatic blood pressure (Dinamap), and end-tidal CO₂ (SAR-Trans) monitoring were performed. Pulse, blood pressure, respiratory rate, end-tidal CO₂, middle cerebral artery blood flow velocity, and pulsatility index were measured at (1) baseline (once supine positioning was assumed); (2) immediately after administration of 20 mL local anesthetic; and (3) every 5 minutes for 25 minutes. Timing of the attainment of a T4 dermatome anesthetic level was noted. Comparisons were made by t test, rank sum tests, χ², and repeated measures analysis of variance. *P* < .05 was considered significant.

**RESULTS:** Maternal heart rate, blood pressure, respiratory rate, and end-tidal CO₂ were not significantly different within or between groups. No significant difference was found in baseline middle cerebral artery blood flow velocity or pulsatility index values between groups. Neither middle cerebral artery blood flow velocity nor pulsatility index changed significantly within or between groups up to 25 minutes after institution of epidural anesthesia.

**CONCLUSIONS:** Maternal middle cerebral artery blood flow velocity, as measured by transcranial Doppler ultrasonography, is maintained in normotensive, nonlaboring term gravid women receiving either lidocaine or bupivacaine lumbar epidural anesthesia, which supports intact cerebrovascular autoregulation in normal pregnancy.

**AB-14362-99**

**OBJECTIVE.** The purpose of this study was to assess the value of the ratio between the internal carotid systolic velocity (ICSV) at the carotid bulb and the distal internal carotid systolic velocity (DICSV) for the detection of carotid artery stenosis.

**SUBJECTS AND METHODS.** Two hundred eleven patients were enrolled in a prospective study comparing several Doppler measurements with carotid angiography. The following spectral measurements were obtained with Doppler sonography: ICSV/DICSV ratio, ICSV, ICSV/ common carotid systolic velocity (CCSV) ratio, and internal carotid (end) diastolic velocity (ICDV). Receiver operating characteristic curves were generated for two groups: the first group being 365 carotid arteries for which all Doppler measurements were successfully obtained and the second being a subgroup of 258 carotid arteries for which an ICSV of 100 cm/sec or greater was present.

**RESULTS.** In the group of 365 carotid arteries, the ICSV/DICSV ratio improved the detection of stenosis of 60% or greater as compared with the ICDV (*p* = .03). In 258 carotid arteries with an ICSV of 100 cm/sec or greater, the ICSV/DICSV ratio allowed for a better angiographic correlation for identifying stenoses of 60% or greater and 70% or greater as compared with ICSV (*p* = .006 and .023, respectively), ICSV/DICSV ratio (*p* = .0013 and .003, respectively), and ICDV (*p* = .0015 and .020, respectively).

**CONCLUSION.** Using the ICSV/DICSV ratio for the Doppler detection of carotid artery stenosis is advantageous when the ICSV is 100 cm/sec or greater.

**AB-14363-99**

**Background and objective:** Transcranial color-coded sonography (TS) allows a noninvasive, accurate evaluation of lateral displacement of the third ventricle. The authors studied the prognostic value of TS monitoring of the midline shift (MLS) in acute hemispheric stroke. **Method:**

Sixteen patients with acute middle cerebral artery (MCA) occlusion were investigated. On admission, the median modified Scandinavian Stroke Scale (mSSS) score was 6.0 (range, 5 to 8). Five patients died from cerebral herniation (group 1), 10 survived (group 2), and 1 patient (Patient 16) survived after decompressive surgery. TS was performed on days 1 to 4 (10±3, 32±4, 57±5, and 82±5 hours after onset of symptoms). Distance from the TS probe to the center of the third ventricle was measured both from the symptomatic (A) and asymptomatic (B) sides. MLS was calculated using the formula MLS = (A−B)/2.

**Results:** Ten hours after stroke onset, MLS and mSSS scores were not significantly different between the two groups. At 32, 57, and 82 hours, MLS was higher in group 1 (32 hours, *p* = .0001; 57 hours, *p* = .0033; 82 hours, *p* = .023) whereas there was no difference in mSSS score after 32 hours. All patients with an MLS <4 mm at 32 hours survived, whereas patients with an MLS >4 mm died as a result of cerebral herniation, with the exception of the one patient who underwent decompressive hemicraniectomy.

**Conclusions:** The study of MLS at 32 hours after stroke onset in patients with severe MCA infarctions may identify patients who are unlikely to survive. The value of MLS in determining the indication of decompressive hemicraniectomy merits further study.

**Pharmacology / Therapeutics**

**AB-14364-99**

We performed a subgroup analysis of the first European Stroke Prevention Study including 1,306 patients recruited in a single center, Kuopio, Finland, to investigate whether or not antiplatelet therapy is effective in the secondary prevention of stroke in hypertensive patients with transient ischemic attack (TIA) or stroke. The patients were treated with aspirin, 990 mg/day, plus dipyridamole, 225 mg/day, or placebo for 2 years. The patients with high systolic blood pressure (≥140 mm Hg; *n* = 1,105) or high diastolic blood pressure (≥85 mm Hg; *n* = 1,120) at entry, were classified into subgroups by blood pressure level. The effect of treatment was statistically significant in all subgroups with high systolic (end-point reduction, 55.2–68.2%) and diastolic blood pressure (end-point reduction, 47.3–82.1%). Risk reduction was, however, greatest in patients with the highest diastolic blood pressure. One possible explanation is that platelets are more activated in these patients, and this can be effectively prevented by antiplatelet therapy. Further studies are needed to confirm this hypothesis.

**Surgery**

**AB-14365-99**
Carotid Endarterectomy for Asymptomatic Carotid Stenosis: A Meta-Analysis—Benavente O (Dept of Medicine, Div of Neurology, Univ of Texas Health Science Center, San Antonio, TX 78284-7883), Moher D, Pham B—*BMJ.* 1998;317:1477–1480.

**Objective** To assess the value of carotid endarterectomy for prevention of stroke in patients with asymptomatic carotid stenosis.

**Design** Systematic review and meta-analysis of randomised controlled trials in patients with asymptomatic carotid stenosis in which subjects were allocated to carotid endarterectomy or to medical treatment alone.

**Subjects** Five trials enrolled 2440 patients with stenosis ≥50%.

**Main outcome measures** Stroke ipsilateral to the stenosis, all strokes, and perioperative complications (stroke or death).

**Results** In patients who underwent carotid endarterectomy (*n* = 1215), there was a significant reduction in the odds of ipsilateral stroke plus perioperative stroke or death (odds ratio 0.62; 95% confidence interval 0.44 to 0.86), corresponding to a 2% absolute risk reduction over about 3.1 years. The prevalence of stroke in any location was also reduced (0.68; 0.51 to 0.9) in patients undergoing carotid endarterectomy. During
the immediate postoperative period there was an increased prevalence of stroke or death among such patients (4.51; 2.36 to 8.64).

**Conclusion** Carotid endarterectomy in patients with asymptomatic carotid stenosis unequivocally reduces the incidence of ipsilateral stroke, though the absolute benefit is relatively small. Given the modest benefit of surgery for unselected patients with asymptomatic carotid artery stenosis carotid endarterectomy cannot be routinely recommended for these patients pending reliable identification of high risk subgroups, and medical management is a sensible alternative for most patients.

**Items of Interest**


**Fifth ACCP Consensus Conference on Antithrombotic Therapy**—*Chest.* 1998;114(November, suppl):439S–769S.


