Cerebral Aneurysms

**AB-14531-99**


**Object:** To describe the clinical and angiographic results of endovascular occlusion of basilar bifurcation aneurysms with electrolytically detachable coils and to identify factors which should be considered in deciding upon surgical or endovascular treatment. **Methods:** We report our experience with 40 patients in whom occlusion of basilar bifurcation aneurysms with electrolytically detachable coils was attempted. All patients underwent superselective angiography and attempted embolization with Guglielmi detachable coils (GDCs). Angiographic and clinical results were prospectively recorded. Twenty-eight aneurysms presented with subarachnoid hemorrhage (SAH), 2 were symptomatic and 10 were incidental. **Results:** Coils were not placed in 10 patients (25%) because of unfavorable anatomy. Complete aneurysm occlusion was achieved at the time of the initial procedure in 13 (32.5%), small neck remnants were present in 13 (32.5%), and in 4 (10.0%) there was obvious residual contrast filling of the aneurysm body. Of 23 patients successfully coiled after SAH, 20 were Grade 1 to 3 and 3 were grade 4 or 5 at the time of treatment. Eighteen (78%) made a good recovery. Procedural mortality was 25% and permanent morbidity was 7.5%. There were no permanent complications in patients with unruptured aneurysms. Complete aneurysm occlusion was possible in 10 (56%) of 18 aneurysms with small necks and 3 (14%) of 22 with large necks. Follow-up angiography in 25 of 28 surviving patients (mean, 12 months) demonstrated stability of all completely occluded aneurysms. Incompletely coiled aneurysms had variable results on follow-up angiograms: 15.4% improved, 69.2% worsened, and 15.4% were stable. No aneurysm bled after treatment during clinical follow-up averaging 22 months. **Conclusions:** Endovascular treatment of basilar bifurcation aneurysms appears to prevent early aneurysm rebleeding with acceptable rates of morbidity and mortality, but long-term follow-up is required.

**AB-14532-99**


**Object.** The histopathological characteristics of aneurysms obtained at autopsy or surgery 3 days to 54 months after being treated with Guglielmi detachable coils (GDCs) were assessed. **Methods.** Seventeen aneurysms were obtained at autopsy and one was removed at surgery. Fourteen were examined histologically with the coils in situ. Naked coils embedded in an unorganized thrombus were found in those aneurysms that had been treated with coils within 1 week earlier. An incomplete replacement of the intraluminal blood clot by fibrous tissue and a partial membranous covering at the aneurysm orifice were observed in those aneurysms that had been treated with coils between 2 and 3 weeks prior to examination. One small aneurysm treated 6 weeks before harvesting showed formation of an endothelium-lined layer of connective tissue at the orifice. Collagen-rich vascularized tissue surrounding the coils was found in an aneurysm removed at surgery 54 months after coil implantation. Interestingly, six (50%) of 12 aneurysms (two small, three large, and one giant) that had been deemed 100% occluded on initial angiography showed tiny open spaces between the coils at the neck on gross examination. **Conclusions.** Endothelialization of the aneurysm orifice following placement of GDCs can occur; however, it appears to be the exception rather than the rule. In large aneurysms the process of intraneurysm clot organization seems to be delayed and incomplete; tiny open spaces between the coils and an incomplete membranous covering in the region of the neck are frequently encountered. Further longitudinal studies are required to establish the spectrum of healing profiles that may direct our efforts in modifying the GDC system to produce a more stable long-term result.

**AB-14533-99**


**Object.** To enhance visual confirmation of regional anatomy, endoscopy was introduced during microsurgery for cerebral aneurysms. The risks and benefits are analyzed in the present study. **Methods.** The endoscopic technique was used during microsurgery for 54 aneurysms in 48 patients. Forty-three aneurysms were located in the anterior circulation and 11 were in the posterior circulation. Thirty-eight aneurysms (70.4%) had not ruptured. All ruptured aneurysms in the present series produced Hunt and Hess Grade I or II subarachnoid hemorrhage. After initial exposure achieved with the aid of a microscope, the rigid endoscope was introduced to confirm the regional anatomy, including the aneurysm neck and adjacent structures. The necks of 43 aneurysms were clipped using microscopic control or simultaneous microscopic/endooscopic control. After clipping, the positions of the clip and nearby structures were inspected using the endoscope. Use of the neuroendoscope provided useful information that further clarified the regional anatomy in 44 cases (81.5%) either before or after neck clipping. In nine cases (16.7%), these details were available only with the use of the endoscope. In five cases (9.3%), the surgeons reapplied the clip on the basis of endoscopic information obtained after the initial clipping. There were two cases in which surgical complications were possibly related to the endoscopic procedures (one patient with asymptomatic cerebral contusion and another with transient oculomotor palsy). **Conclusions.** It is the authors’ impression that the use of the endoscope in the microsurgical management of cerebral aneurysms enhanced the safety and reliability of the surgery. However, there is a prerequisite for the surgeon to be familiar with this instrumentation and fully prepared for the risks and inconveniences of endoscopic procedures.

**AB-14534-99**


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This study is designed to determine whether patients with aneurysmal subarachnoid hemorrhage have mutations in the phospholipase C-δ 1 (PLC-δ 1) gene, which was identified as a gene responsible for hypertension in spontaneously hypertensive rats. Seventy-two cases (31 male and 41 female) with intracranial saccular aneurysms were analyzed. The mean age was 60.1±11.5 years (mean±SD) (range 24–85 years). There were 35 patients (48.6%) with hypertension, 5 (6.9%) with diabetes mellitus, 12 (16.7%) with hyperlipidemia, 8 (11.1%) with ischemic heart disease, and 25 (34.7%) who were active smokers. The location of aneurysm was distributed as follows: 33 (33%) were at anterior cerebral artery, 23 (23%) were at middle cerebral artery, 28 (28%) were at internal carotid artery, and 16 (16%) were at vertebro-basilar artery. Six patients (8.3%) had a family history of intracranial aneurysms. There were 20 patients (27.8%) with multiple aneurysms, and 8 patients (11.1%) with a large or giant aneurysm. The four regions of PLC-δ 1 gene previously implicated in hypertensive factor in rats may not be the case with human patients and therefore may be poorly related with aneurysmal subarachnoid hemorrhage.

**Clinical**

**AB-14535-99**

**Coagulation Activation in Patients WithBinswanger Disease**—Tomimoto H (Dept of Neurology, Faculty of Medicine, Kyoto Univ, Kyoto 606-8507, Japan), Akiguchi I, Wakita H, Osaki A, Hayashi M, Yamamoto Y—Arch Neurol. 1999:56:1104–1108.

**Background:** A hypercoagulable state is often associated with an acute stroke in cerebrovascular disease (CVD). However, inBinswanger disease (BD), no information is available on the coagulation-fibrinolysis pathway except for the presence of high plasma fibrinogen levels.

**Objective:** To determine the association of BD and coagulation-fibrinolysis pathway activation.

**Patients and Methods:** We examined the levels of fibrinogen, thrombin-antithrombin complex, prothrombin fragment 1, or cross-linked D-dimer in 17 patients with BD, 24 neurologically patients without CVD, and 26 patients with lacunar infarction in either the acute or chronic stage.

**Results:** As compared with the non-CVD and lacunar infarction groups, the patients with BD had significantly elevated levels of thrombin-antithrombin complex (P<0.01), prothrombin fragment 1, or cross-linked D-dimer (P<0.05). There was also a significant increase in fibrinogen levels compared with the non-CVD group (P<0.05). In the BD group, 8 patients in stable condition (ie, those without obvious neurologic deficits in the past 3 months) showed normal levels or a mild increase in their fibrinogen, thrombin-antithrombin complex, prothrombin fragment 1, or cross-linked D-dimer levels. In contrast, 9 patients with BD with a subacute aggravation of their focal or subcortical cerebral functions (deteriorating group) showed a significant increase in their thrombin-antithrombin complex levels compared with the stable patients (P<0.01). Similarly, the fibrinogen, prothrombin fragment 1, or cross-linked D-dimer levels were elevated in the deteriorating patients, but this trend did not reach statistical significance.

**Conclusions:** These results indicate that the coagulation-fibrinolysis pathway is activated in patients with BD with a subacute aggravation.

**AB-14536-99**


**Objective:** To describe the prevalence at baseline and the 5-year incidence of retinal emboli, associated risk factors, and the relationship of retinal emboli at baseline to stroke and ischemic heart disease mortality.

**Methods:** The Beaver Dam Eye Study is a large (N=4926) population-based study of persons aged 43 to 86 years at the baseline examination. Retinal emboli were detected at baseline (1988–1990) and at a 5-year follow-up (1993–1995) by grading of stereoscopic 30° color fundus photographs using standardized protocols. Cause-specific mortality was determined from death certificates.

**Results:** The prevalence of retinal arteriolar emboli was 1.3%, and the 5-year incidence was 0.9%. After adjustments were made for age and sex, the prevalence of retinal emboli was associated with higher pulse pressure, hypertension, diabetes mellitus, past and current smoking, cardiovascular disease, and the presence of retinopathy. After adjustments were made for age and sex, the incidence of retinal emboli was associated with past and current smoking and a history of coronary artery bypass surgery. After age, sex, and systemic factors were controlled for, people with retinal emboli had a significantly higher hazard of dying with a mention of stroke on the death certificate (hazard ratio=2.61, 95% confidence interval=1.12–6.08) than those without retinal emboli.

**Conclusions:** Persons with retinal emboli are at an increased risk of stroke-related death. Data also show an association of smoking, hypertension, and cardiovascular disease with the prevalence of retinal emboli.

**Clinical Relevance:** Data from this population-based study suggest that after detection of retinal emboli in the asymptomatic patient, referral for possible medical intervention to control hypertension, if present, may be beneficial.

**AB-14537-99**

**Risk Factors for Early or Delayed Stroke After Cardiac Surgery**—Hogue CW Jr (Dept of Anesthesiology, Washington Univ School of Medicine, 660 S Euclid Ave, Box 8054, St Louis, MO 63110), Murphy SF, Schechtman KB, Dávila-Román VG—Circulation. 1999;100:642–647. Copyright © 1999 American Heart Association, Inc.

**Background:** Stroke after cardiac surgery is a devastating complication that leads to excess mortality and health resource utilization. The purpose of this study was to identify risk factors for perioperative stroke, including strokes detected early after cardiac surgery or postoperatively.

**Methods and Results:** Data were obtained from 2972 patients undergoing coronary artery bypass graft and/or valve surgery. Patients ≥65 old and those with a history of symptomatic neurological disease underwent preoperative carotid artery ultrasound scanning. Intraoperative epiaortic ultrasound to assess for ascending aorta atherosclerosis was performed in all patients. New strokes were considered as a single end point and were categorized with respect to whether they were detected immediately after surgery (early stroke) or after an initial, uneventful neurological recovery from surgery (delayed stroke). Strokes occurred in 48 patients (1.6%); 31 (65%) were delayed strokes. By multivariate analysis, prior neurological event, aortic atherosclerosis, and duration of cardiopulmonary bypass were independently associated with early stroke, whereas predictors of delayed stroke were prior neurological event, diabetes, aortic atherosclerosis, and the combined end points of low cardiac output and atrial fibrillation. Female sex was associated with a 6.9-fold increased risk of early stroke and a 1.7-fold increased risk of delayed stroke. In-hospital mortality of patients with early (41%) and delayed (13%) strokes was higher than that of other patients (3%, P<0.0001).

**Conclusions:** Most strokes after cardiac surgery occurred after initial uneventful recovery from surgery. Women were at higher risk to suffer early and delayed perioperative strokes. Atrial fibrillation had no impact on postoperative stroke rate unless it was accompanied by low cardiac output syndrome.

**AB-14538-99**

**Relation Between Carotid Intima-Media Thickness, Platelet Surface Activation and Endothelial Cell Markers**—Ramsis N (75 Osman Eb
Background: The role of platelet activation and endothelial cell damage in the pathogenesis of atherosclerosis was investigated. Methods: Flow-cytometric detection of platelet activity was accomplished by measuring the surface expression of activated platelet glycoprotein IIb/IIIa (activated CD41) and the lysosomal integral membrane protein (CD63). Levels of thrombomodulin (TM) and von Willebrand factor (vWF) were estimated by the ELISA technique as markers of endothelial cell damage. These procedures were performed in healthy male subjects without obvious signs of atherosclerosis. Also, the intima-media thickness of the carotid artery was measured with high-resolution B-mode ultrasound to quantitate the presence and/or the extent of carotid atherosclerosis. Results: According to ultrasound findings patients were divided into those with apparent evidence of atherosclerosis (AS+) with intima-media thickness >1.1 mm (n=19) and those without such evidence (AS−) with intima-media thickness <1.1 mm (n=17). The percentages of activated CD41 and CD63 surface antigen expression were significantly increased in the AS+ compared to AS− subjects. TM levels were elevated in the former group compared to the latter, while vWF levels were not different in the two groups. Multivariate analysis indicated the independent association of carotid atherosclerosis with each of the expression of activated CD41, CD63 as well as TM levels after adjustment of other risk factors. Conclusion: This study demonstrates that platelets circulate in an enhanced activation state in asymptomatic atherosclerosis, which is closely related to the degree of endothelial cell damage as expressed by increased plasma levels of TM. The detection of platelet activation can be used as a potential marker for oncoming atherosclerosis.

Epidemiology


Objective: To determine the risk of cardiovascular events and death in patients receiving statin treatment for cholesterol regulation. Methods: Systematic review and meta-analysis of all randomized controlled trials that were published as of April 15, 1997. Primary or secondary prevention studies or regression trials were eligible. Main Outcome Measures: All-cause mortality, fatal myocardial infarction (MI) or stroke, nonfatal MI or stroke, angina, and withdrawal from the studies. Both random- and fixed-effects models were run for the outcomes of interests, and results are expressed as odds ratios (ORs). Sensitivity analyses tested the impact of the study type and duration, statin treatment type, and control arm event rates. Intent-to-treat denominators were used whenever they were available, and the number needed to treat was calculated when appropriate.

Results: Seventeen studies (21 303 patients) were included (2 secondary prevention studies, 5 mixed primary-secondary prevention population studies, and 10 regression trials). Treatment groups included lovastatin (t=5), pravastatin (t=10), and simvastatin (t=3). For all-cause mortality, the OR was 0.76 (95% confidence interval [CI], 0.67–0.86) in favor of receiving statin treatment; for fatal MI, the OR was 0.61 (95% CI, 0.48–0.78); for nonfatal MI or stroke, angina, and withdrawal from the studies. Both random- and fixed-effects models were run for the outcomes of interests, and results are expressed as odds ratios (ORs). Sensitivity analyses tested the impact of the study type and duration, statin treatment type, and control arm event rates. Intent-to-treat denominators were used whenever they were available, and the number needed to treat was calculated when appropriate.

Conclusions: Patients who received statin treatment demonstrated a 20% to 30% reduction in death and major cardiovascular events compared with patients who received placebo. This advantage was generally present across study types and statin treatment types and for patients with less severe dyslipidemias. The benefit in clinical outcomes was noticeable as early as 1 year.


An increased risk of intracerebral hemorrhage among heavy consumers of alcohol has been demonstrated in several epidemiologic studies. The effect of moderate or intermediate intakes is, however, unclear. Although several studies provide evidence for a protective effect, this conclusion may be spurious, resulting from the inclusion, within the zero intake (reference) group, of past drinkers who have recently abstained for health reasons. The present study describes the relation between alcohol consumption and intracerebral hemorrhage among 331 case-control pairs recruited in Melbourne, Australia. Heavy drinking was associated with an increased risk of intracerebral hemorrhage (odds ratio (OR) 3.4, 95% confidence interval (CI)=1.4–8.4). The odds ratio of intracerebral hemorrhage with moderate drinking, when compared with never drinkers, was 0.7 (95% CI=0.4–1.2) and was 0.6 (95% CI=0.4–1.0) when compared with nondrinkers (never drinkers plus past drinkers). Wine drinkers were apparently protected from intracerebral hemorrhage (OR 0.5, 95% CI=0.2–0.9). These results are consistent with the possibility that moderate drinking may confer protection from intracerebral hemorrhage, but this protection may be less than that previously reported.

AB-14541-99 Impact of Nativity and Race on “Stroke Belt” Mortality—Lackland DT (Dept of Biometry and Epidemiology, Medical Univ of South Carolina, Charleston, SC 29425), Egan BM, Jones PI—Hypertension. 1999;34:57–62. Copyright © 1999 American Heart Association, Inc.

The southeastern region of the United States has been recognized for 6 decades as an area of excess cerebrovascular mortality rates. While the reasons for the disease variation remain an enigma, South Carolina has consistently been the forerunner of the “Stroke Belt.” To determine the effects of nativity (birthplace) on stroke mortality rates in South Carolina, proportional mortality ratios (PMRs) were calculated for stroke deaths in South Carolina during 1980–1996 according to birthplace and stratified by gender, race, age, and educational status. The analyses revealed a graded risk of stroke by birthplace, with the highest PMRs (95% CI) among individuals born in South Carolina (104.8 [103.4 to 106.3]), intermediate PMRs in those born in the Southeast other than South Carolina (92.5 [90.2 to 94.9]), and lowest PMRs for those born outside the Southeast (77.4 [74.9 to 80.1]). The lower stroke PMRs for individuals born outside the Southeast were more striking in blacks (51.8 [45.2 to 59.3]) than in whites (84.9 [82.0 to 88.0]) and for men (73.3 [69.5 to 77.3]) than women (83.5 [79.9 to 87.3]). The findings, particularly in blacks, were not explainable by gender, differences in age, and/or markers of educational and socioeconomic status. These findings suggest that nativity is a significant risk marker for the geographic variation in stroke mortality. Moreover, the regional disparities for nativity and subsequent stroke mortality appear to be greater in blacks than in whites and for men than for women. An understanding of factors linking birthplace to risk for cerebrovascular mortality could facilitate efforts directed at stroke prevention.

Experimental Pathology

Background: Although the association between inflammation and atherosclerosis is well established, the biologic events that trigger the local inflammatory response within plaque are not fully understood. Cytotoxic free radicals and infectious agents, both of which are associated with an inflammatory response, have previously been implicated in the initiation and progression of atherosclerosis. In this study, we analyzed carotid plaque for evidence of oxidative vascular injury by determining the presence and distribution of inducible nitric oxide synthase (iNOS) expression and nitrotyrosine formation and for evidence of infection with cytomegalovirus.

Methods: Carotid plaque from 51 patients who underwent endarterectomy for either primary (n = 37) or recurrent (n = 14) stenosis were examined histologically (hematoxylin-eosin staining and Masson’s trichrome staining) and with immunohistochemistry with specific antibodies to α-smooth muscle actin, macrophages (CD68), T-lymphocytes (CD3), and T-cell activation (human leukocyte antigen–DR). Twenty-eight specimens from patients with primary (n = 15) and recurrent (n = 13) stenosis were examined for the presence of iNOS and nitrotyrosine with immunohistochemistry and in situ hybridization (iNOS). Twenty-three additional specimens (22 primary, and 1 recurrent) were analyzed with antibodies to p53, cytomegalovirus, and the polymerase chain reaction (cytomegalovirus, n = 8).

Results: Primary atherosclerotic lesions were either complex heterogenous cellular plaques (n = 29) or relatively acellular fibrous plaques (n = 8). Ten of 14 recurrent plaques were either complex or fibrous lesions, and the remaining four were typical of myoinstitial thickening. CD68-positive staining cells were detected in all specimens regardless of their structural morphology. CD3-positive cells were interspersed between macrophages in all heterogeneous cellular plaques and only infrequently noted in fibrous plaques. iNOS and nitrotyrosine immunoreactivity were detected in macrophages and smooth muscle cells in all complex and fibrous plaques and in two of four myoinstitial plaques. The presence of iNOS and nitrotyrosine in plaque correlated with the existence of symptoms in 80% of primary and 62% of recurrent lesions. Cytomegalovirus was detected in only two of 23 carotid specimens (9%).

Conclusion: The association between ischemic cerebrovascular symptoms and iNOS and nitrotyrosine immunoreactivity in complex primary and recurrent carotid plaque and the infrequent occurrence of cytomegalovirus in primary carotid lesions suggests that ongoing free radical oxidative damage rather than viral infection may contribute to plaque instability in patients with complex and fibrous carotid plaques.


The objective was to examine the effect of the nitric oxide synthase inhibitor, N–nitro-L-arginine methyl ester (L–NAME) on leukocyte adhesion in the cerebral microcirculation during reperfusion following partial forebrain ischemia in the rat. Intravital fluorescence video-microscopy through a closed cranial window was used to visualize leukocyte–endothelium interaction in small pial veins of 15–100 μm diameter. Forebrain ischemia was produced by the ligation of both carotid arteries plus elevation of the intracranial pressure to 20 mm Hg for 60 min. The number of leukocytes adhering to the endothelium for longer than 3 sec was determined during ischemia (5 min and 60 min) and during reperfusion (5 min and 60 min). Two experimental groups were treated with either L–NAME or its inactive enantiomer D–NAME (20 mg kg–1 i.v.) 30 min prior to reperfusion. In a third group, also treated with D–NAME, post-ischemic hyperemia was prevented by lowering the ICP without removing the occlusion of common carotid arteries (partial reperfusion). The velocity of flow adjacent to the endothelial surface of pial veins was measured by tracking the movement of fluorescently labeled red blood cells as flow markers before and after ischemia. During ischemia, the number of adhering leukocytes increased approximately two-fold at 5 min, and three-fold at 60 min. In the D–NAME-treated group with complete reperfusion, leukocyte adhesion returned to the baseline level by 60 min of reperfusion. However, in the L–NAME-treated group, leukocyte adhesion remained elevated at 60 min of reperfusion. Post-ischemic flow velocity was significantly decreased (−66%) from control after L–NAME treatment whereas it was increased (+53%) in the D–NAME-treated group. In the partial reperfusion group, leukocyte adhesion continued to increase after the first hour of ischemia and reached a level 2.7-fold over baseline at 60 min reperfusion. Flow velocity remained below control (−26%) at 60 min reperfusion. Leukocyte adhesion was absent in pial arteries and no plugging by leukocytes was observed in cortical capillaries. The results suggest that leukocyte adhesion in small pial veins increases during 1 h forebrain ischemia and continues to increase during reperfusion if the velocity of flow or shear rate is low. The increase in leukocyte adhesion is reversible if flow velocity is elevated during reperfusion. L–NAME prevents post-ischemic hyperemia and augments leukocyte adhesion principally via a decrease in velocity or shear rate.


OBJECTIVE: Murine models using intraluminal occluding suture to establish transient focal cerebral ischemia are becoming increasingly widespread, because of advances in transgenic technology and the advent of cerebroprotective strategies to ameliorate postischemic cerebrovascular no-reflow. We hypothesize that the degree of postischemic hyperperfusion is directly related to the severity of the initial ischemic insult.

METHODS: Transient ischemia of 45-minute duration was produced using middle cerebral artery occlusion with 10-0 (n = 5), 9-0 (n = 5), 8-0 (n = 6), 7-0 (n = 8), 6-0 (n = 30), or 5-0 (n = 5) sutures. In separate experiments, transient vessel occlusion with 6-0 sutures was performed for 15 (n = 17), 30 (n = 16), or 45 (n = 30) minutes. Sequential laser Doppler measurements of relative cerebral blood flow were obtained, and stroke severity was assessed using neurological deficit scores and infarction volumes.

RESULTS: Although relative cerebral blood flow at the time of occlusion and 24 hours thereafter was diminished in parallel with increasing suture diameters, only the use of larger sutures resulted in postischemic no-reflow. As the suture diameter was increased, the resultant reflow was decreased and the stroke outcome worsened. A more than twofold increase in infarction volume (8.0 + 3 versus 19.7 + 3%, P < 0.05) resulted when ischemia duration was increased from 30 to 45 minutes.

CONCLUSION: Titration of the initial ischemic insult leads to corresponding variations in the magnitude of postischemic no-reflow and tissue damage. Therefore, critical control of the severity of the initial injury in studies using intraluminal suture occlusion is warranted.


BACKGROUND AND PURPOSE: Diffusion and perfusion MR imaging have been reported to be valuable in the diagnosis of acute ischemia. Our purpose was to ascertain the value of these techniques in the prediction of ischemic injury and estimation of infarction size, as determined on follow-up examinations.

METHODS: We studied 18 patients with acute ischemic stroke who underwent echo-planar perfusion and diffusion imaging within 72 hours
of symptom onset. Quantitative volume measurements of ischemic lesions were derived from relative mean transit time (rMTT) maps, relative cerebral blood volume (rCBV) maps, and/or apparent diffusion coefficient (ADC) maps. Follow-up examinations were performed to verify clinical suspicion of infarction and to calculate the true infarction size.

**RESULTS:** Twenty-five ischemic lesions were detected during the acute phase, and 14 of these were confirmed as infarcts on follow-up images. Both ADC and rMTT maps had a higher sensitivity (86%) than the rCBV map (79%), and the rCBV map had the highest specificity (91%) for detection of infarction as judged on follow-up images. The rMTT and ADC maps tended to overestimate infarction size (by 282% and 182%, respectively), whereas the rCBV map appeared to be more precise (117%). Significant differences were found between ADC and rMTT maps, and between rCBV and rMTT maps.

**CONCLUSION:** Our data indicate that all three techniques are sensitive in detecting early ischemic injury within 72 hours of symptom onset but tend to overestimate the true infarction size. The best methods for detecting ischemic injury and for estimating infarction size appear to be the ADC map and the rCBV map, respectively, and the diffusion abnormality may indicate early changes of both reversible and irreversible ischemia.

**AB-14546-99**  
Correlation of Neurologic Dysfunction With CT Findings in Early Acute Stroke—Scott JN, Buchan AM, Sevick RJ (Dept of Diagnostic Imaging, Foothills Hospital, 1331-29 St, NW Calgary, Alberta, Canada T2N 4N2)—Can J Neurol Sci. 1999;26:182–189.

**Objective:** To determine the frequency of early computed tomographic (CT) findings of ischemia and their relationship to symptom duration and neurologic dysfunction within 3 hours of ischemic stroke. **Methods:** The CT scans of 39 acute stroke patients were evaluated for signs of early ischemic change within 3 hours of symptom onset and without knowledge of the patient’s neurologic deficit or results of a 24 hour follow-up post-thrombolysis CT. Early CT signs of acute ischemic change or thromboembolism were hypodensity or hyperdensity middle cerebral artery sign. **Results:** Signs of acute ischemic change were seen on the baseline scan in 25/39 patients (64%). Hypodensity of the insular ribbon was seen in 11 patients, occurrence of the lentiform nucleus, cortical hypodensity/effacement, and hyperdense middle cerebral artery sign. **Conclusions:** Evidence of cerebral ischemia is frequently seen on CT within 3 hours of symptom onset. The degree of neurologic disability correlates with CT signs of ischemia.

AB-14547-99

Acute Cerebral Infarction: Quantification of Spin-Density and T2 Shine-Through Phenomena on Diffusion-Weighted MR Images—Burdette JH (Dept of Radiology, Wake Forest Univ School of Medicine, the Bowman Gray Campus, Medical Center Blvd, Winston-Salem, NC 27157), Elster AD, Ricci PE—Radiology. 1999;212:333–339.

**PURPOSE:** To quantify the relative contributions of spin density and T2 effects (“shine through”) on diffusion-weighted (DW) magnetic resonance (MR) images of acute and subacute cerebral infarction.

**MATERIALS AND METHODS:** In 30 patients, 1.5-T imaging was performed within the first 7 days after onset of cerebral infarction. Estimates of T2, spin density, and apparent diffusion coefficient (ADC) in the region of stroke and contralateral normal brain were computed by means of standard regression techniques after quadruple-echo conventional MR imaging and single-shot echo-planar DW imaging with a maximum b value of 1,000 sec/mm². Expected signal intensity (SI) enhancement ratios resulting from independent changes in T2, spin density, and ADC were then calculated for the DW sequence.

**RESULTS:** The overall SI of cerebral infarction on DW images was significantly higher than that of normal brain throughout the 1st week after stroke (mean relative SI enhancement ratio, 2.29; P < 0.001). During the first 2 days after stroke, decreased ADC within the stroke region made the dominant contribution to increased SI on DW images. By day 3, increased T2 values in the stroke region became equally important, and, from days 3–7, the contribution to SI from T2 effects became dominant. A slight increase of spin density in the stroke region made a relatively small and constant contribution to DW SI over the 1st week.

**CONCLUSION:** The increased SI of subacute cerebral infarction on DW images reflects not only a shortening of ADC but a prolongation of T2 and spin-density values.

Neurosonology

**AB-14548-99**  

Postprostaglandins are believed to play an important role in the regulation of resting cerebral blood flow and in the vasodilatory response to hypercapnia. Recently, we reported an increased CO2 reactivity (CR) in premenopausal women and, in the past, evidence has accumulated that estrogens might increase basal levels of prostaglandin secretion from endothelial cells. Therefore, one may speculate that gender differences in CR are possibly mediated by higher prostaglandin levels in women. Using transcranial Doppler sonography, we assessed CR before and 90 min after a single dose of 100 mg of indomethacin in 22 healthy volunteers (11 men, 11 women). Before intake of indomethacin, women had a significantly higher CR (4.53 ± 0.49 vs. 3.61 ± 0.74, P < 0.01). Ninety minutes after indomethacin administration, CR decreased to 1.53 ± 0.93 in women and 1.60 ± 0.92 in men, respectively. The change of CR was 3.00 ± 1.29 in women vs. 2.01 ± 1.06 in men (P = 0.07). For the entire study population, the decrease of CR was linearly correlated with the initial value of CR (r = 0.74, P < 0.001). This gender-related difference possibly relates to higher prostaglandin levels as mediators of an increased CR in premenopausal women, although the exact features remain to be clarified.

**AB-14549-99**  

Cerebrovascular hemodynamics during postural changes have been sparsely investigated despite the fact that abnormal responses may contribute to the risk of stroke. The aim of this study was to determine the effect of acute 80° head-down tilt (HDT) on cerebrovascular hemodynamics in humans using transcranial Doppler sonography (TCD). In 13 healthy volunteers (2 female, 11 male, age 19–37 years, mean age 26.8 years) left midcerebral artery blood flow velocities (CBFVs) were continuously monitored using TCD during 180 sec in horizontal position and during 60 sec of 80° HDT. Simultaneously systolic, diastolic, mean CBFVs, pulsatility index (PI), heart rate, beat-to-beat blood pressure (BP) and transcutaneous pCO2 were measured. In five volunteers, the procedure was repeated the next day to test the repeatability of the results. Mean BP increased slightly but not significantly during tilt (from 80.5 ± 7.7 mm Hg to 85.9 ± 14.1 mm Hg, p < 0.05). Heart rate decreased significantly during the first 20 sec of HDT (from 66.8 ± 9.9 min⁻¹ to 60 ± 11 min⁻¹; p < 0.05). Transcutaneous pCO2 was within physiological ranges during the whole procedure (mean pCO2 minimum 39.5 ± 2.9 mm Hg, mean pCO2 maximum 42.2 ± 3.3 mm Hg). Mean CBFV did not change significantly during tilt (from 70.1 ± 19.1 cm sec⁻¹ to 68.1 ± 19.1 cm sec⁻¹)

**PURPOSE:** To examine the variability of Doppler measurements along the extra-cranial courses of the nondiseased common carotid artery (CCA) and internal carotid artery (ICA) and determine the effect of this variability on assessment of carotid arterial stenosis.

**MATERIALS AND METHODS:** During the study period, 580 patients were referred for carotid arterial ultrasonography (US), including Doppler measurements of flow velocities in the proximal, middle, and distal portions of the CCA, in the bulb, and in the proximal and distal portions of the ICA. Eighty-five patients (average age, 59 years) with normal ICAs and CCA formed the cohort for this study.

**RESULTS:** The range of peak systolic velocity (PSV) measurements (maximum minus minimum) averaged 20 cm/sec (maximum minus minimum) averaged 20 cm/sec at the last 40 sec of tilt (Plsupine = 0.92±0.11; Plsitting = 0.15±0.18; Plsitting = 0.15±0.18; Plsupine = 66 sec) 1.03±0.16; p = 0.001; p = 0.017). The HDT results were found to be reproducible in the five volunteers. During 80°–HDT mean BP and pCO2 did not change significantly. This observation combined with the significant decrease in heart rate during the first 20 sec of HDT, suggests that there is no sympathetic activation. The significant PI increase during HDT indicates a vasocostruction of the cerebral resistance vessels. We assume that this vasoconstriction is due to the myogenic mechanism of cerebrovascular autoregulation triggered by a rapid, passive intracranial blood volume influx during HDT.

**CONCLUSION:** Variability of Doppler measurements in the CCA and ICA in patients without visible disease is substantial and could lead to inaccuracies in carotid arterial stenosis assessment.

Pharmacology / Therapeutics

**AB-14550-99**

Bleeding During Warfarin and Aspirin Therapy in Patients With Atrial Fibrillation: The AFASAK 2 Study—Gullow AL, Koefoed BG, Petersen P (reprints not available from the authors)—Arch Intern Med. 1999;159:1322–1328.

**Background:** Treatment with warfarin sodium is effective for stroke prevention in atrial fibrillation but many physicians hesitate to prescribe it to elderly patients presumably because of the associated risk for bleeding and the inconvenience of frequent blood tests for the patients.

**Methods:** In the Second Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation (AFASAK 2) Study, we studied the rate of bleeding events associated with the incidence of thromboembolic events in patients receiving warfarin sodium, 1.25 mg/d; warfarin sodium, 1.25 mg/d, plus aspirin, 300 mg/d; aspirin, 300 mg/d; or adjusted-dose warfarin therapy aiming at an international normalized ratio of the prothrombin time ratio (INR) of 2.0 to 3.0. The study was scheduled for 6 years from May 1, 1993, but owing to evidence of inefficiency of low-intensity therapy plus aspirin from another study it was prematurely terminated on October 2, 1996. Minor and major bleeding events were recorded prospectively. The rate of bleeding was calculated using the Kaplan-Meier method and risk factors were identified by the Cox proportional hazards model.

**Results:** Of 677 included patients, 130 (median age, 77 years; range, 67–89 years) experienced bleeding. One woman and 12 men experienced major bleeding. Four had intracranial bleeding: 2 cases were fatal and 2 were nonfatal. During treatment with mini-dose warfarin, warfarin plus aspirin, aspirin, and adjusted-dose warfarin, the annual rate of major bleeding was 0.8%, 0.3%, 1.4%, and 1.1%, respectively (P = 0.20). After 3 years of treatment the cumulative rate of any bleeding was 24.7%, 24.4%, 30.0%, and 41.1% (P = 0.003), respectively. Increasing INR value (P = 0.001) and prior myocardial infarction (P = 0.001) were independent risk factors for bleeding, whereas increasing age was not.

**Conclusions:** Fixed mini-dose warfarin and aspirin alone or in combination were associated with both minor and major bleeding. The small number of major bleeding events in patients receiving adjusted-dose warfarin therapy as compared with those receiving less intensive antithrombotic treatments and the finding of no significant influence of age on the risk for bleeding indicate that even elderly patients with atrial fibrillation tolerate adjusted-dose warfarin therapy (INR, 2.0–3.0).

**AB-14552-99**


Cervene (nalmefene), an opioid antagonist with relative kappa receptor selectivity, has shown neuroprotective effects in multiple experimental central nervous system injury and ischemic models. The agent already has a well-established safety profile in various clinical indications. Results from an earlier pilot study in 44 acute stroke patients suggest that Cervene administered by 24-hour maintenance infusion was safe and tolerable. The primary and secondary objectives of the current study were to assess the dose-related safety and preliminary efficacy of Cervene in patients with acute ischemic stroke. **Methods:** The present investigation was a Phase II, placebo-controlled, double-blind, randomized, dose-comparison, parallel-group study of a 24-hour administration of Cervene injection. Patients with acute ischemic stroke, onset of symptoms within 6 hours, and baseline score ≥ 4 on the National Institute of Health Stroke Scale (NIHSS) were randomized to 1 of 4 treatment groups: Cervene 6 mg, 20 mg, 60 mg or placebo. The primary efficacy outcome was the proportion of patients achieving a score of ≥ 60 on the Barthel Index and a rating of “moderate disability” or better on the Glasgow Outcome Scale at 12 weeks. Results: A total of 312 patients were randomized at 28 centers. All doses of Cervene were well tolerated. Overall, there was no significant difference in 3-month functional outcome for any dose of Cervene treatment compared with placebo. However, a prospective secondary analysis showed that both male and female patients less than age 70 years may have had an improved 3-month outcome. **Conclusions:** The results of this study indicate that the competitive kappa receptor opiate antagonist Cervene can be given safely to acute stroke patients at doses up to 60 mg/24 hr. Although overall there was no significant difference in the 3-month outcome, Cervene treatment may be associated with improved outcomes for patients younger than age 70.

**AB-14553-99**

Occupational Therapy for Stroke Patients Not Admitted to Hospital: A Randomised Controlled Trial—Walker MF (Div of Stroke Medicine, City Hospital NHS Trust, Nottingham NG5 1PB, UK), Gladman JRF, Lincoln NB, Siemonsma P, Whiteley T—Lancet. 1999;354:278–280.

**Background** Patients who have a stroke are not always admitted to hospital, and 22–60% remain in the community, frequently without coordinated rehabilitation. We aimed to assess the efficacy of an occupational therapy intervention for patients with stroke who were not admitted to hospital.

**Methods** In this single-blind randomised controlled trial, consecutive stroke patients on a UK community register in Nottingham and...
Derbyshire were allocated randomly to up to 5 months of occupational therapy at home or to no intervention (control group) 1 month after their stroke. The aim of the occupational therapy was to encourage independence in personal and instrumental activities of daily living. Patients were assessed on outcome measures at baseline (before randomisation) and at 6 months. The primary outcome measure was the score on the extended activities of daily living (EADL) scale at 6 months. Other outcome measures included the Barthel index, the general health questionnaire 28, the carer strain index, and the London handicap scale. All assessments were done by an independent assessor who was unaware of treatment allocation. The analysis included only data from completed questionnaires.

**Findings**
185 patients were included: 94 in the occupational therapy group and 91 in the control group. 22 patients were not assessed at 6 months. At follow-up, patients who had occupational therapy had significantly higher median scores than the controls on: the EADL scale (16 vs 12, P < 0.01; estimated difference 3 [95% CI 1 to 4]); the Barthel index (20 vs 18, P = 0.01; difference 1, [0–1]); the carer strain index (1 vs 3, P < 0.05, difference 2 [0 to 2]); and the London handicap scale (76 vs 65, P < 0.05, difference 7, [0.3 to 13.5]). There were no significant differences on the general health questionnaire between the patient or carer.

**Interpretation**
Occupational therapy significantly reduced disability and handicap in patients with stroke who were not admitted to hospital.

**Surgery**

AB-14554-99


**Purpose:** Macrophage accumulation is associated with aortic and coronary plaque instability. The macrophage content of carotid plaques removed at carotid endarterectomy (CE) was assessed, and the relevance to the onset of ipsilateral cerebral ischemic events (CIE) was examined.

**Methods:** Carotid plaques from patients undergoing CE were examined (group I, symptomatic stenoses, n = 28; group II, high-grade asymptomatic stenosis, n = 7). The plaques were stained with monoclonal antimacrophage antibody (HAM56), and the interval since the last CIE was recorded. The percentage area of the cap, shoulder, and entire sclerotic region was quantified by computerized planimetry.

**Results:** The macrophage content of the cap, shoulder, and sclerotic region in all 35 plaques was 1.14% (interquartile range, 0.56 to 3.86), 1.03% (0.51 to 2.15), and 0.49% (0.27 to 0.63), respectively (cap vs sclerotic, P < 0.01; shoulder vs sclerotic, P < 0.01; cap vs shoulder, P = 0.23). In 18 plaques that were removed less than 180 days after the last CIE, the macrophage content of the cap, shoulder, and entire sclerotic region was 2.41% (0.95 to 4.81), 0.83% (0.40 to 2.52), and 0.53% (0.38 to 0.71), respectively (cap vs sclerotic, P = 0.01; cap vs shoulder, P = 0.01). The content in the cap of these plaques was greater than in plaques removed more than 180 days after symptoms, or asymptomatic plaques (n = 17; 0.62% [0.44 to 1.25], P = 0.01). The cap macrophage content was inversely related to the time since the last CIE (r = –0.414, P = 0.029).

**Conclusion:** In patients requiring CE, macrophage accumulation was maximal within the cap of carotid plaques and greatest in plaques removed less than 180 days after the last CIE. These findings and the inverse relationship between macrophage content and the interval since symptoms support the hypothesis that macrophage accumulation is associated with plaque instability.

AB-14555-99


**Purpose:** Symptomatic carotid disease resulting from generation of thromboemboli has been associated with plaque instability and intraplaque hemorrhage. These features of the lesion could be influenced by the fragility and position of neovessels within the plaque. The purpose of this study was to determine whether any association exists between neovessel density, position, morphology, and thromboembolic sequelae.

**Methods:** Carotid endarterectomy samples were collected from 15 asymptomatic patients with greater than 80% stenoses and from 13 highly symptomatic patients who had suffered ipsilateral carotid stenotic events within 1 month of surgery. Both groups were matched for gender, age, risk factors, degree of carotid artery stenosis, and plaque size. Samples were stained with hematoxylin/eosin and van Geison. Immunohistochemistry was performed by using an endothelial specific antibody to CD31. Plaques were assessed for histologic characteristics, and neovessels were counted and characterized by size, site, and shape.

**Results:** There were significantly more neovessels in plaques (P < 0.0001) and fibrous caps (P < 0.001) in symptomatic compared with asymptomatic plaques. Neovessels in symptomatic plaques were larger (P < 0.04) and more irregular. There was a significant increase in plaque necrosis and rupture in symptomatic plaques. Plaque hemorrhage and rupture were associated with more neovessels within the plaque (P < 0.017, P < 0.001) and within the fibrous cap (P < 0.046, P < 0.004). Patients with preoperative and intraoperative embolization had significantly more plaque and fibrous cap neovessels (P < 0.025, P < 0.001).

**Conclusion:** Symptomatic carotid disease is associated with increased neovascularization within the atherosclerotic plaque and fibrous cap. These vessels are larger and more irregular and may contribute to plaque instability and the onset of thromboembolic sequelae.

AB-14556-99


**BACKGROUND:** Endarterectomy benefits certain patients with carotid stenosis, but benefits are lessened by perioperative surgical risk. Acetylsalicylic acid lowers the risk of stroke in patients who have experienced transient ischaemic attack and stroke. We investigated appropriate doses and the role of acetylsalicylic acid in patients undergoing carotid endarterectomy. METHODS: In a randomised, double-blind, controlled trial, 2849 patients scheduled for endarterectomy were randomly assigned 81 mg (n = 709), 325 mg (n = 708), 650 mg (n = 715), or 1300 mg (n = 717) acetylsalicylic acid daily, started before surgery and continued for 3 months. We recorded occurrences of stroke, myocardial infarction, and death. We compared patients on the two higher doses of acetylsalicylic acid with patients on the two lower doses. FINDINGS: Surgery was cancelled in 45 patients, none were lost to follow-up by 30 days, and two were lost by 3 months. The combined rate of stroke, myocardial infarction, and death was lower in the low-dose groups than in the high-dose groups at 30 days (5.4 vs 7.0%, p = 0.07) and at 3 months (6.2 vs 8.4%, p = 0.03). In an efficacy analysis, which excluded patients taking 650 mg or more acetylsalicylic acid before randomisation, and patients randomised within 1 day of surgery, combined rates were 3.7% and 8.2%, respectively, at 30 days (p = 0.002) and 4.2% and 10.0% at 3 months (p = 0.0002). INTERPRETATION: The risk of stroke, myocardial infarction, and death within 30 days and 3 months of endarterectomy is lower for patients taking 81 mg or 325 mg acetylsalicylic acid daily than for those taking 650 mg or 1300 mg.

Purpose: After carotid endarterectomy, intraoperative findings and outcome of immediate reoperation of patients who had an intraoperative stroke were compared with those of patients who had an early postoperative stroke.

Methods: We retrospectively analyzed 2250 carotid endarterectomies performed between 1980 and 1997. Intraoperative stroke (group A) was detected after 41 of the 2250 operations (1.8%), whereas early postoperative stroke (group B) developed after 18 of the 2250 operations (0.8%). Patients from both groups were reoperated on within 1 hour after neurological examination.

Results: Positive intraoperative findings that could be corrected during immediate reoperation were: (1) thrombotic occlusion of the carotid artery that was operated on caused by technical error, which was found in nine of 41 patients (22%) in group A and in 11 of 18 patients (61%) in group B ($P<0.009$); (2) mural thrombus caused by technical error without occlusion, which was detected in seven of 41 patients (17%) in group A and in two of 18 patients (11%) in group B ($P>0.05$); and (3) technical error without a thrombus, which was found in eight of 41 patients (20%) in group A and in three of 18 patients (17%) in group B ($P>0.05$). A patent carotid artery was found in 17 of 41 patients (42%) in group A and in two of 18 patients (11%) in group B ($P=0.046$). Twenty of the 41 patients (49%) in group A died, and four of 18 patients (22%) in group B died ($P>0.05$). Major neurological deficit remained in nine of 41 patients (22%) in group A and four of 18 patients (22%) in group B ($P>0.05$). Total recovery occurred in seven of 41 patients (17%) in group A and in eight of 18 patients (45%) in group B ($P=0.058$).

Conclusion: Carotid artery thrombosis during immediate reoperation was more frequent in patients who had an early postoperative stroke than in patients who had an intraoperative stroke. It appears that patients who had an intraoperative stroke have a higher incidence of uncorrectable lesions.
Abstracts of Literature
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