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MR and Cerebrospinal Fluid Enzymes as Sensitive Indicators of Subclinical Cerebral Injury after Open-Heart Valve Replacement Surgery

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PURPOSE: To evaluate MR imaging and lumbar cerebrospinal fluid enzymes as potential sensitive indicators of cerebral injury after open-heart valve replacement surgery. **METHODS:** Thirty-four patients with cardiac valvular disease were prospectively entered into this study and then underwent valve replacement or repair under cardiopulmonary bypass using a membrane oxygenator. In 26 patients, MR head images were obtained 12 to 24 hours before surgery; repeat MR images were obtained between 1 and 2 weeks after surgery. In 18 patients, lumbar puncture cerebrospinal fluid was analyzed 24 to 48 hours after surgery; the analyses included measurement of lactic dehydrogenase, creatine phosphokinase, adenylate kinase, and neuron-specific enolase. **RESULTS:** After surgery, MR imaging showed new ischemic lesions in 15 (58%) of 26 patients: 7 with deep white matter hyperintense lesions; 5 with brain stem, caudate, cerebellar, or thalamic/basal ganglia infarcts; 1 with intraparenchymal hemorrhage; 1 with a subdural hematoma and cortical infarct; and 1 with a corpus callosum lesion consistent with calcium or air. These new ischemic lesions seen on MR images were associated with a focal neurologic deficit in only 4 (27%) of the 15 patients. Neuron-specific enolase and lactic dehydrogenase were abnormally elevated after surgery in 5 (28%) of 18 patients. Adenylate kinase and creatine phosphokinase (brain isozymes) were elevated in one (67%) of the patients. Two (40%) of the five patients with abnormally high neuron-specific enolase or lactic dehydrogenase after surgery also showed a new focal neurologic deficit. **CONCLUSIONS:** MR imaging is a sensitive measure of subclinical cerebral ischemia after cardiac valve replacement under cardiopulmonary bypass. Cerebrospinal fluid neuron-specific enolase and lactic dehydrogenase are less sensitive than MR imaging for detecting subclinical cerebral ischemia, but these values were elevated after surgery more frequently than was adenylate kinase in our patients.

Index terms: Brain, ischemia; Cerebrospinal fluid; Heart; Iatrogenic disease or disorder; Magnetic resonance, postoperative

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Cardiac surgery using cardiopulmonary bypass is among the most frequently performed operations in North America, with over 450 000 procedures done annually in the United States (1). Despite significant improvement in surgical, anesthetic, and medical management, patients undergoing open-heart surgery under cardiopulmonary bypass are at risk for developing cerebral complications and stroke. The percentage of such patients experiencing postoperative cerebral complications depends on the type of cardiac surgery and on the neurologic outcome measure that is evaluated. The neurologic complication rate has been estimated to be between 3% and 79%, using various methods of assessment including overt neurologic signs, psychometric testing, computed tomographic (CT) brain scanning, cerebrospinal fluid (CSF) enzyme analysis, electroencephalographic monitoring, or pathologic examination

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at autopsy (1–8). Magnetic resonance (MR) imaging has been shown to be a sensitive measure of cerebral ischemia (9), but it has not been used extensively to assess the patient's neurologic status before and after cardiac surgery. Some studies have shown elevations in CSF enzymes, including creatine phosphokinase (CPK), adenylate kinase (AK), and lactic dehydrogenase (LDH), after cardiopulmonary bypass. However, the sensitivity of these enzymes in detecting postoperative cerebral injury is controversial (3, 10). This prospective study examined the sensitivity of head MR imaging and several CSF enzymes as measures of cerebral injury after aortic and mitral valve surgery on cardiopulmonary bypass. Preliminary results have been reported elsewhere in abstract form (Steinberg GK, DeLaPaz R, Mitchell RS, Albers G, Choi D, Bell T, "Magnetic Resonance Imaging and CSF Enzymes as Sensitive Indicators of Subclinical Cerebral Injury following Open-Heart Valve Replacement Surgery," *Stroke* 1992;23:161, abstract).

Subjects and Methods

Of 39 consecutive patients scheduled to undergo left-sided cardiac valve replacement, 34 agreed to participate in this study, and informed consent was obtained. All patients consented to the MR imaging portion of the study; however, postoperative MR images could not be obtained in eight patients because of the placement of cardiac pacemakers or because of postoperative medical instability. Eighteen patients consented to postoperative lumbar puncture for CSF analysis. Thus, 16 patients underwent preoperative and postoperative MR imaging without lumbar puncture, 8 patients had lumbar puncture without MR studies, and 10 patients participated in both the MR imaging and lumbar puncture parts of the study. Our protocol was approved by the Stanford University Medical Center Institutional Review Board. The 23 men and 11 women ranged in age from 21 to 85 years old (mean, 63 years). One patient had a history of transient ischemic attack, and 2 had a history of stroke. All patients had valvular heart disease (5 patients with mitral stenosis, 13 with mitral regurgitation, 11 with aortic stenosis, and 12 with aortic regurgitation). Thirteen patients had a history of congestive heart failure, 9 had angina, 12 had hypertension, 3 had diabetes mellitus, 8 had atrial fibrillation, 3 had previous myocardial infarction, and 1 had subacute bacterial endocarditis. Because of our referral pattern as a specialized cardiovascular surgery center, many of the patients were considered to have complex, difficult cardiac valvular lesions or to be high-risk surgical candidates.

Twenty-six patients underwent unenhanced MR head imaging on a 1.5-T scanner 12 to 24 hours before surgery. Images included sagittal sections (600/20 [repetition time/echo time]) and axial sections (2000/30, 2000/80); the thickness of the nonoverlapping sections was 5 mm. Unenhanced MR head imaging was repeated between 1 and 2 weeks after surgery in 21 patients, at 3 and 6 weeks after surgery in 2 patients each, and at 40 weeks after surgery in 1 patient. The mean time of postoperative MR imaging was 22 days; the median time was 9 days. Postoperative MR images were read without knowledge of the preoperative MR findings and then were compared with preoperative MR images. Any new lesions were noted.

Patients underwent cardiac valve replacement or repair under cardiopulmonary bypass using a membrane oxygenator, arterial filter, systemic heparinization, and hypothermia to esophageal temperatures of 22.6°C to 30°C (mean, 27.5°C). Conditions of bypass were low flow, hypothermia, and continuous systemic blood flow at 50 to 70 mm Hg systolic pressure; conditions of pH management were "pH stat." Anesthesia was induced with fentanyl and maintained with additional fentanyl supplemented with halothane and thiopental as needed; pancuronium bromide was used for muscle relaxation. Bypass times varied between 70 and 257 minutes (mean, 131 minutes). Valves replaced or repaired included aortic, mitral, and tricuspid; in some patients, more than one valve was replaced or repaired (Table 1). In one patient, the left atrium was opened, the mitral valve was inspected, and saline was flushed into the left ventricle to check the extent of mitral valve regurgitation; this valve was not replaced or repaired. In eight patients the valves involved had been previously repaired or replaced (so this surgery was a repeat procedure). Four patients also had coronary artery bypass grafting at the same time as their valve replacement (Table 1). Twenty-seven patients underwent anticoagulation procedures (using warfarin) after their surgeries.

Postoperative lumbar puncture was performed in 18 patients. In 16 patients, lumbar puncture was performed between 24 and 52 hours after surgery; in 2 patients, lumbar punctures were performed 5 days after surgery. The mean time for performance of lumbar puncture was 44 hours after surgery, and the median time was 28 hours. CSF was analyzed for white blood cell count (WBC), red blood cell count (RBC), protein, LDH, CPK, AK, and neuron-specific enolase (NSE). Normal values for these parameters were determined by the reference laboratory as follows: WBC, 0–5; RBC, 0–5; protein, 15–45 mg/dL; LDH, <45 U/L; CPK (brain isozyme fraction), <5 U/L (University of Washington Laboratory); AK, <20 U/L (Uni-

TABLE 1: Surgical procedures performed

Valve Replacement or Repair	No. of Patients
AV only	19 (3 with CABG)
MV only	9 (1 with CABG)
AV + MV	5
AV, MV, TV	1
Total	**34 (8 repeat valve surgery)**

Note.—AV indicates aortic valve; TV, tricuspid valve; MV, mitral valve; and CABG, coronary artery bypass graft.

versity of Washington Laboratory); and NSE, <21 ng/mL (Specialty Laboratories). Neurologic examinations were performed before surgery and daily after surgery as long as the patients were hospitalized (typically for at least 7 to 10 days).

Results

MR Findings

In 16 (62%) of the 26 patients undergoing preoperative MR examination, MR images showed abnormalities suggestive of chronic cerebral ischemia, including small periventricular lesions, deep white matter lesions, or small infarcts. In 15 (58%) of the 26 patients who had both preoperative and postoperative MR imaging, the MR images showed new lesions after the surgery that were compatible with brain ischemia (Table 2). These 15 patients included 7 with small (2–5 mm) periventricular or deep white matter hyperintense lesions; 4 with small (3–5 mm) brain stem, caudate, or cerebellar infarcts; 1 with a large infarct in the thalamus, basal ganglia, and internal capsule; 1 with an intraparenchymal hemorrhage from a ruptured mycotic aneurysm; 1 with a parietal subdural hematoma with an underlying large cortical infarct; and 1 with a small lesion in the corpus callosum consistent with either calcium or air (Figs 1–3). The 2 patients with the postoperative intracranial hemorrhages were anticoagulated after surgery.

TABLE 2: Classification of new postoperative MR ischemic lesions

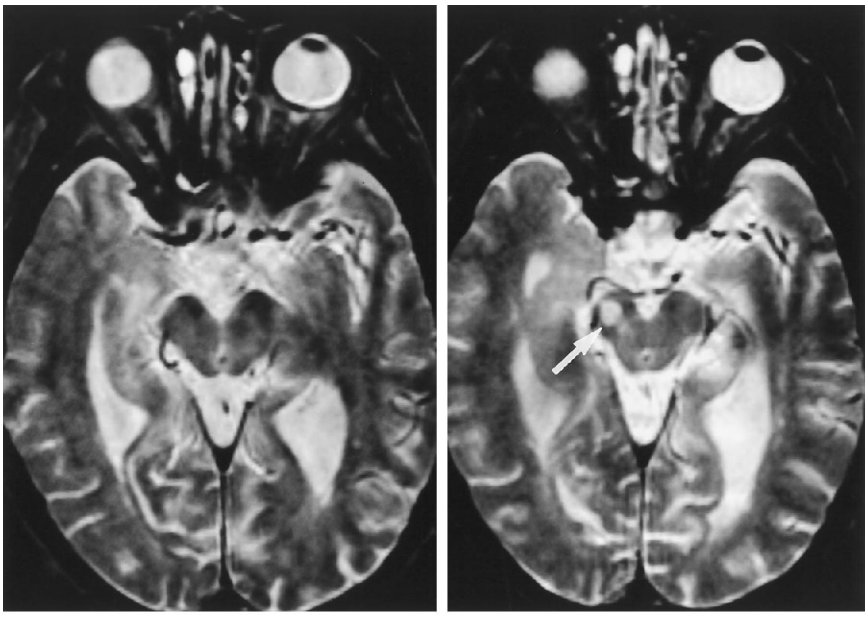
New MR Lesion	No. of Patients*
Small (2–5 mm) periventricular or deep white matter hyperintensity	7
Small (3–5 mm) brain stem, caudate, or cerebellar infarct	4
Large infarct (thalamus, basal ganglia, internal capsule)	1
Subdural hematoma with underlying cortical infarct	1
Intraparenchymal hemorrhage (mycotic aneurysm)	1
Corpus callosum lesion (calcium or air)	1
Total no. (%) of patients with new MR lesion	15 (58)
No. (%) of patients with no new MR lesion	11 (42)

Note.—"New MR lesion" indicates new lesion seen on postoperative MR images.

* Only one category of new MR lesion was observed in each patient.

Lumbar Puncture Findings

Of the 18 patients who had postoperative lumbar puncture, 5 (28%) had abnormal elevations in NSE (22–89 ng/mL), 1 (6%) had abnormal elevation in AK (21 U/L), 5 (28%) had abnormal elevations in LDH (49–79 U/mL), and 1 (6%) had a rise above normal values in CPK (brain isozyme, 5 U/L) (Table 3). The five patients with elevated NSE also had elevated LDH. The 1 patient with abnormally high AK and the 1 patient with elevated CPK (brain isozyme)



A B

Fig 1. The preoperative T2-weighted MR image (*A*) in this 85-year-old woman shows a normal midbrain and mild atrophic ventricular enlargement. The postoperative MR image (*B*), obtained 16 days after aortic valve replacement, shows a new right midbrain subacute infarct centered on the cerebral peduncle (*arrow*). After surgery, the patient had a new left hemiparesis.

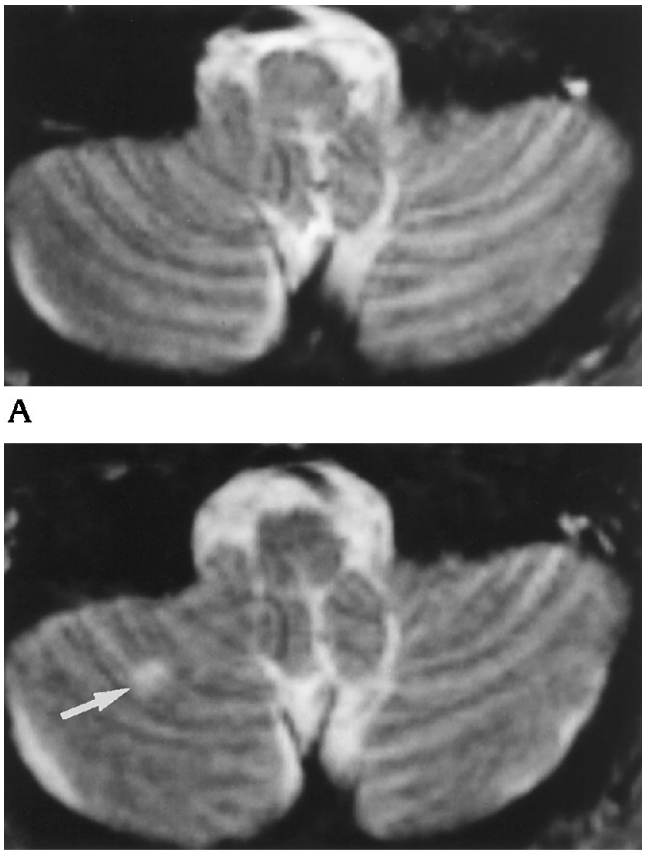


Fig 2. The preoperative T2-weighted MR image (*A*) in this 72-year-old man shows normal inferior cerebellar hemispheres. The postoperative MR image (*B*), obtained 9 days after aortic valve replacement, shows a new subacute infarct in the right cerebellar hemisphere (*arrow*). The patient experienced no new neurologic symptoms or signs after surgery.

also had abnormally high NSE and LDH. Postoperative CSF protein was elevated in 3 patients (72–139 mg/dL). Postoperative CSF WBC was normal (<5) in all patients, and CSF RBC was abnormally high (7–1210) in 7 patients.

Clinical Outcome

Six (18%) of the 34 patients had new focal neurologic deficits assessed by clinical examination 7 to 10 days after surgery. These included 4 patients with mild to severe hemiparesis, 1 with aphasia and hemiparesis, and 1 with a sixth cranial nerve paresis. One of these 6 patients made a complete recovery to her baseline neurologic status by the time she was discharged from the hospital, 1 patient recovered to her preoperative condition within 2 months, 1 patient recovered completely within 12 months, and 3 patients had recovered only partially at last follow-up (2–21 months after surgery).

TABLE 3: Postoperative lumbar puncture results (n = 18)

Cerebrospinal Fluid Enzyme, Cell Count, or Chemistry	No. (%) of Patients with Abnormal Elevation
Neuron-specific enolase	5 (28)
Lactic dehydrogenase	5 (28)
Adenylate kinase	1 (6)
Creatine phosphokinase (brain isozyme)	1 (6)
White blood cell count	0 (0)
Red blood cell count	7 (39)
Protein	3 (17)

Correlation of MR, NSE, LDH, and Neurologic Deficits

Table 4 shows the correlation of new neurologic deficits with the results of postoperative MR imaging and lumbar puncture. In the 15 patients with new postoperative MR ischemic lesions, 4 (27%) showed new focal neurologic deficits, but 11 (73%) had no new neurologic deficits. Among the 11 patients who had no new lesions on postoperative MR imaging, 1 (9%) had a new neurologic deficit, and 10 (91%) were neurologically unchanged. Abnormal NSE or LDH values were predictive of a new focal neurologic deficit in 2 (40%) of 5 patients but unassociated with a new deficit in 3 patients (60%). Among the 13 patients with a normal postoperative CSF NSE or LDH, 2 (15%) had new neurologic findings, and 11 (85%) were unchanged from their preoperative neurologic condition.

Discussion

Previous studies suggest that open-heart surgery under cardiopulmonary bypass carries a high risk of cerebral ischemic complications. The occurrence rate of overt stroke varies from 0.9% to 5.9%, whereas intellectual dysfunction or more subtle neurologic findings have been reported in 24% to 33% of patients (1–6, 11). If a detailed neuropsychological evaluation is used, up to 79% of cardiac surgery patients manifest new postoperative deficits (6, 7). However, many of these neurologic and neuropsychiatric problems resolve within 6 months after surgery (3, 6, 11).

Other measures of cerebral ischemia have been applied before and after cardiopulmonary

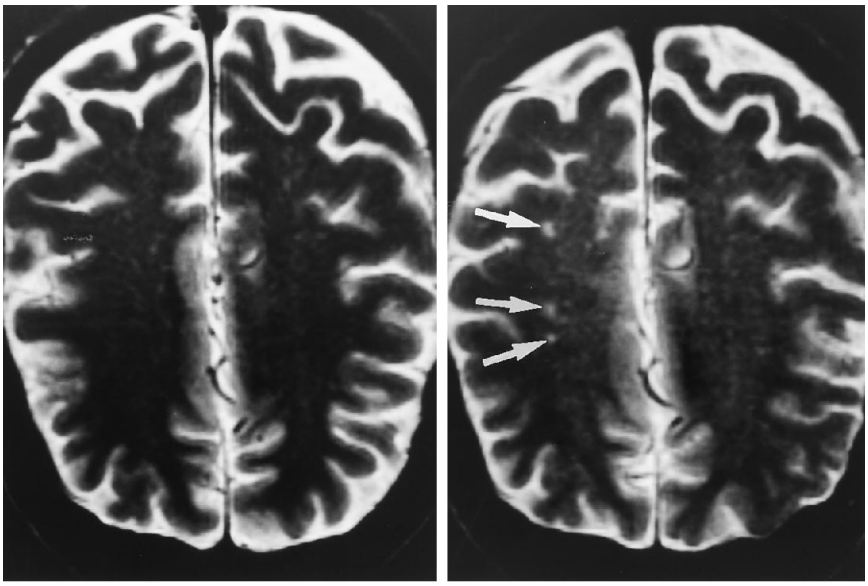


Fig 3. The preoperative T2-weighted MR image (*A*) in this 55-year-old man shows normal white matter in the centrum semiovale. The postoperative MR image (*B*), obtained 5 days after aortic valve replacement, shows three new lesions in the left centrum semiovale white matter (*arrows*). The patient experienced no new neurologic symptoms or signs after surgery.

bypass. Abnormal results on electroencephalogram readings occur in a large percentage of patients (12). Various CSF neuronally derived enzymes may become elevated by 24 hours after bypass, with AK perhaps being the most sensitive of those previously examined (up to 55% abnormal postoperative values) (3, 4). One report examining the CT head scans of patients before and after bypass suggests a 4% occurrence rate of new ischemic lesions (3). One study (13) evaluated CT head scans in 22 patients with new focal neurologic deficits or coma after cardiac surgery with cardiopulmonary bypass. Sixteen of these patients had CT-documented cerebral infarcts, and one had a subdural fluid collection, but preoperative CT scans had not been obtained for these patients. In a 1990 study (14), the use of a membrane oxygenator instead of a bubble oxygenator reduced the occurrence rate of retinal perfusion defects from 100% to 44%.

TABLE 4: Correlation of new ischemic lesion on MR images or abnormal NSE or LDH cerebrospinal fluid elevation with new postoperative focal neurologic deficit

Finding	Total No. of Patients	No. (%) of Patients with New Focal Neurologic Deficit	No. (%) of Patients with No New Focal Neurologic Deficit
New ischemic lesion on MR images	15	4 (27)	11 (73)
No new ischemic lesion on MR images	11	1 (9)	10 (91)
Abnormally elevated NSE or LDH	5	2 (40)	3 (60)
Normal NSE or LDH	13	2 (15)	11 (85)

Note.—MR indicates magnetic resonance; NSE, neuron-specific enolase; and LDH, lactic dehydrogenase.

The cause of brain ischemia associated with open-heart surgery under cardiopulmonary bypass is not completely understood. However, there is substantial evidence that these complications relate to microemboli or macroemboli (platelet aggregates, leukocytes, thrombus, atherosclerotic plaque, antifoam particles, protein particles, particulate debris, calcium, air, or fat) from diseased vessels, valves, heart, or the oxygenator (1–5, 8, 15, 16). Intraoperative funduscopic florescein angiography during cardiopulmonary bypass reveals a high occurrence rate of retinal vessel occlusion, presumably from emboli (14). Transcranial Doppler imaging, a new technique for noninvasive monitoring of large-vessel blood flow at the base of the brain, may be exquisitely sensitive for detecting emboli during cardiac surgery (17). Hemodynamic insufficiency during the low-flow cardiopulmonary bypass state may also contribute to cerebral ischemic complications (1–5, 8). Because of the potential increased risk of embolizing particulate material into the aortic arch, valve replacement surgery carries a risk of cerebral ischemic complications that is higher than that of coronary artery bypass grafting alone (3, 4, 8, 11, 18). Advances in surgical and

anesthetic techniques, including the use of membrane oxygenators (rather than the bubble oxygenators) for the cardiopulmonary bypass machine (14), hypothermia (3, 4, 8), or barbiturate protection (8, 19) may reduce the risk of complications from brain ischemia.

MR imaging has been shown to be a sensitive indicator of cerebral ischemia both in experimental animal models and clinically (9). One report of 19 patients undergoing coronary artery bypass grafting found no difference between the patients' preoperative and postoperative cerebral MR images (20). Boyajian et al (16) obtained CT scans or MR images for 30 patients who had clinical neurologic impairment in the early postoperative period after cardiopulmonary bypass for a coronary artery bypass graft, valve replacement, or aortic arch repair. Eighteen (60%) of these symptomatic patients showed MR (11 patients) or CT (7 patients) evidence of acute ischemic injury (preoperative cerebral imaging studies had not been obtained). Another prospective study examined preoperative and postoperative brain MR images in 15 infants and children undergoing open-heart surgery under cardiopulmonary bypass for congenital heart disease (21). In this study, 4 (27%) of the patients showed a postoperative increase in the ventricular volume and subarachnoid space, 5 (33%) had new subclinical subdural hemorrhages, and 1 (7%) had a new postoperative infarct.

In a recent study, Simonson et al (22) used preoperative and postoperative MR images in a prospective study of 19 patients undergoing cardiopulmonary bypass. They found no new lesions on the postoperative MR studies. Muraoka et al (23) obtained preoperative and postoperative CT brain scans in 45 children with congenital heart disease who underwent open-heart surgeries under cardiopulmonary bypass. Four (15%) of 27 patients who had bubble oxygenators used for their procedures had new subclinical CT findings of ventricular dilatation or enlargement of the subarachnoid space. None of the 18 patients who had membrane oxygenators showed new postoperative findings on CT scans. A preliminary report assessing brain MR images 8 days before and 6 weeks after cardiopulmonary bypass in 10 patients older than 60 years of age found only one new lesion on the MR images: a clinically silent white matter hyperintensity (24).

Our study showed a 58% occurrence rate of new ischemic lesions seen on MR images after cardiopulmonary bypass and valve replacement surgery. However, only 27% of patients with new MR findings showed new focal neurologic deficits. Thus, MR imaging appears to be a sensitive indicator of subclinical ischemia. Clinical expression probably depends on whether the lesion is located in a critical or silent neurologic region. It is not known whether these new abnormalities seen on MR images would have correlated with new neuropsychiatric dysfunction. Eight of the 15 new lesions shown by MR imaging were unequivocal infarcts or hemorrhages, but 7 of the new lesions were small punctate white matter hyperintensities characteristic of ischemia. On the basis of previous MR-pathologic correlation studies (25–31), these white matter hyperintensities represent infarcts or areas of ischemic demyelination; however, they may represent small regions of ischemic edema that could resolve. We did not perform delayed, repeat MR imaging on these patients to determine whether these new lesions persisted.

The results of our study differ substantially from those of Simonson et al (22), who failed to show any new ischemic lesions on MR images after cardiopulmonary bypass. There are several possible explanations for this. Seventeen of their 19 patients underwent elective coronary artery bypass graft only (1 patient had mitral valve replacement, and 1 had aortic valve replacement plus coronary artery bypass graft), whereas all our patients underwent left-sided valve replacement (aortic valve replacement or mitral valve replacement), which carries a risk of cerebral ischemic complications that is higher than that for coronary artery bypass graft alone (3, 4, 8, 11, 18). Because of our referral base for complex cardiac valvular lesions, our patients may have posed greater surgical risks: many of the surgeries were nonelective, and 8 of the 34 patients in our study were undergoing repeat valve replacement procedures. The timing of postoperative MR images may also have contributed to the difference between our results and those of Simonson et al (22). They performed follow-up MR studies 3 to 7 days after surgery, and we performed those studies at least 1 to 2 weeks after surgery. Finally, some of their MR images were obtained on a 0.5-T scanner, which may be less sensitive than the 1.5-T machine used in this study.

CSF enzymes (including AK, LDH, and CPK brain isozymes) have been previously measured after open-heart surgery, with a variable occurrence rate of abnormal elevations (up to

55% for AK) (3, 4, 10). Experimental and preliminary clinical studies suggest that elevations in NSE or LDH may be highly correlated with neuronal damage caused by a variety of injuries, including cerebral infarction or transient ischemic attack (10, 32–36). The rate of elevated CSF NSE in clinical studies of ischemia varies from 18% to 89% (32, 34, 35). CSF NSE has not previously been recorded after cardiac surgery. Our study found 5 (28%) of 18 patients with abnormally elevated NSE and LDH. These two enzymes appeared to be more sensitive assays than the other enzymes measured (AK, 5%; CPK brain isozyme, 5%). Of patients with abnormally elevated NSE or LDH, 40% showed new focal neurologic deficits within the first 10 days. This suggests that increases in CSF NSE or LDH may indicate sufficient neuronal injury to produce a clearly observable focal neurologic deficit. However, the possible limitations of CSF NSE and LDH measurements include variability in the time course of their postoperative elevations; lack of sensitivity to deep, small cerebral infarcts nonadjacent to a ventricular or ependymal surface; and nonspecificity for ischemic lesions as opposed to traumatic, inflammatory, or neoplastic processes (32, 34–36).

There are other limitations of our study. No preoperative lumbar punctures were performed to provide values for comparison with the postoperative CSF values. We believed that preoperative lumbar punctures would be too much of a physical and psychological ordeal before cardiac surgery. However, data from Aberg et al (3, 4), who used lumbar punctures before and after cardiac surgery, suggest preoperative CSF-AK enzyme levels were consistently low in all patients. Also, we did not obtain long-term follow-up MR images in our patients, and it is possible that the new ischemic lesions shown on MR images in the first few weeks after surgery resolve over time. Finally, 16 of the 34 patients in our study did not consent to a postoperative lumbar puncture, and 8 patients who underwent lumbar punctures could not undergo a postoperative MR image because of the placement of a cardiac pacemaker or because of medical instability. MR and CSF enzyme data on all 34 patients might have allowed us to determine a correlation between these two measures of cerebral ischemia, but because only 10 patients underwent both procedures this type of analysis was precluded.

The new lesions seen on MR images and the CSF enzyme elevations after open-heart surgery in our study occurred in patients undergoing left-sided valve replacement under cardiopulmonary bypass. It is not known whether a similar rate of abnormalities would be found in patients with less complex cardiac valvular lesions, patients considered to be at lower surgical risk than those referred to Stanford, or patients undergoing coronary artery bypass grafting alone. The recent report by Simonson et al (22) suggests that there may be a lower rate of new ischemic lesions seen on MR images of patients who undergo coronary bypass grafting only.

Our prospective study suggests MR imaging is an easily performed, objective, and sensitive measure of subclinical cerebral ischemia; it can be applied to patients before and after cardiac surgery during cardiopulmonary bypass. Because these patients represent a population at significant risk for cerebral ischemia that can be shown on MR images, it may be possible to use MR imaging to test the efficacy of putative neuroprotective agents (given prophylactically) that have shown some promise in animal models of cerebral ischemia (37, 38). We hope the development of sensitive measures for detecting cerebral injury will help decrease the occurrence rates of both clinical and subclinical cerebral complications associated with cardiovascular surgery, cerebrovascular surgery, and cerebrovascular disease.

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