Diffusion- and Perfusion-Weighted Magnetic Resonance Imaging of the Brain Before and After Coronary Artery Bypass Grafting Surgery

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Background and Purpose—Coronary artery bypass grafting (CABG) is a frequently performed surgical procedure that can be associated with neurological complications. Some studies have demonstrated that new focal brain lesions, detected by MRI, can develop after CABG. Furthermore, it has been suggested that the presence of such new lesions is associated with a decline in neurocognitive test scores. Advanced MRI techniques, including diffusion- (DWI) and perfusion-weighted imaging (PWI), offer important diagnostic advantages over conventional imaging in the assessment of patients undergoing CABG. We sought to determine whether focal PWI and DWI abnormalities could occur after CABG, particularly in patients without any measurable neurological deterioration.

Methods—Thirteen patients prospectively underwent MRI with DWI and PWI before and after CABG. A battery of neurocognitive tests was administered before and after surgery. Demographic, clinical, and radiographic characteristics of the patients were collected and compared.

Results—Four patients developed new DWI defects after CABG. The lesions were small, rounded, and multiple (3 of 4 patients). One of these patients was diagnosed with stroke on clinical grounds. The patients with new lesions had a larger neurocognitive decline than their counterparts with stable MRI. Other clinical characteristics of patients with new DWI lesions, including stroke risk factors, were similar to those of patients without MRI changes. No focal perfusion abnormalities were observed on preoperative or postoperative scans.

Conclusions—Postoperative DWI abnormalities can occur after CABG, even in patients without overt neurological defects. The PWI scans remained unchanged. Larger prospective studies are required to determine whether the new lesions are clearly associated with neurocognitive decline or with specific perioperative stroke risk factors. (Stroke. 2002;33:2909-2915.)

Key Words: bypass surgery • magnetic resonance imaging, diffusion-weighted • magnetic resonance imaging, perfusion-weighted

Coronary artery bypass grafting (CABG) is a frequently performed surgical procedure, with more than half a million operations performed every year in the United States. Although CABG provides definite clinical advantages in patients with coronary artery disease, the surgery may be associated with neurological complications. The incidence of such complications is 0.4% to 5.7% for stroke, 10% to 28% for delirium, and 33% to 83% for persistent cognitive dysfunction and behavioral change. The mortality rate of patients with such complications is considerably higher than for the remainder of patients. Furthermore, the length of stay in the intensive care unit and hospital ward is significantly greater for patients with neurological complications, resulting in a 2-fold increase in the total cost of care. Several risk factors for postoperative stroke have been postulated, including hypertension (HTN), diabetes mellitus (DM), carotid stenosis, previous stroke, and age ≥65 years. However, current predictive models of postoperative stroke may not necessarily identify all patients who eventually experience other neurological complications such as delirium.

The application of the MRI techniques of diffusion- (DWI) and perfusion-weighted imaging (PWI) to the study of the neurological complications of CABG is of particular interest because cerebral ischemia is thought to be a central pathophysiological factor underlying postoperative delirium and more persistent neurocognitive changes. Cerebral ischemia during CABG can be induced by hypoperfusion,
intraoperative aortocardiac embolization, coexistent cerebral vessel atherosclerosis, or a combination of such factors.

DWI is more sensitive than CT and conventional MRI sequences for the detection of early signs of ischemia, disclosing areas of brain infarction within a few hours after symptom onset in ≈95% of acute stroke patients.4–9 PWI, on the other hand, uses a bolus of gadolinium to generate changes in signal intensity throughout the brain in a time-dependent fashion, paralleling cerebral blood flow.6 PWI, however, does not provide an absolute estimate of cerebral blood flow but rather uncovers regions of relative focal cerebral hypoperfusion compared with equivalent contralateral areas.6 Nevertheless, the localization of perfusion defects thus detected correlates well with focal neurological dysfunction, which in some cases may be reversible.10,11 Some patients may exhibit a perfusion-diffusion “mismatch,” which suggests the presence of salvageable brain tissue.6 Therefore, the information provided by the combination of DWI and PWI has relevant therapeutic implications.12

Diffusion abnormalities can be demonstrated in almost all patients with postoperative stroke and even in some patients with postoperative delirium.13 Using conventional MRI sequences, some investigators have observed new focal brain abnormalities developing after CABG in patients without apparent neurological impairment.14,15 However, the pathophysiological basis of such changes and their clinical significance remain speculative. It is unknown at present whether focal DWI or PWI abnormalities can also occur in patients without postoperative neurological symptoms or in those patients who develop postoperative neurocognitive decline. The purpose of this study was to determine whether brain diffusion and perfusion abnormalities can occur after CABG and, if so, their clinical relevance.

Materials and Methods

Patients

This study was reviewed and approved by the Institutional Review Board of the Johns Hopkins Hospital. Twenty-three patients undergoing elective CABG from January 2000 to March 2001 were prospectively asked to participate in our study. The study included any patient undergoing elective CABG with no contraindications for MRI (including allergy to gadolinium-DTPA, presence of pacemaker, aneurysm clips, and/or a history of shrapnel injury); no concomitant cardiovascular surgical procedures were contemplated, including carotid endarterectomy and valve replacement; and the patients had to be able to provide written consent. Informed consent was obtained from all subjects before the first MRI. Our protocol consisted of obtaining the brain MRIs within 8 days before and after the surgery.

Twenty patients underwent MRI before CABG; 13 completed both the preoperative and postoperative scans. Two patients could not complete the preoperative MRI because of scheduling problems, and 1 patient could not fit within the scanner. Seven patients did not complete the postoperative MRI: 1 patient did not have surgery, 4 patients refused the follow-up scan, and 2 patients were missed because of MRI scheduling problems.

Neurocognitive Testing

A battery of standardized neurocognitive tests was administered by 1 of 3 investigators (M.A.G., L.M.B., A.E.H.) within 1 week before and after CABG. The trail making test B was used to assess psychomotor speed. Language function was measured through the oral and written naming test and oral reading tests.16,17 Visual-spatial functions were evaluated with the line cancellation and Bells tests.16 All neuropsychological test scores were converted into z scores,18 as follows: z score equals individual test score minus mean baseline test score divided by the SD of the baseline test score (individual test score minus mean baseline test score divided by baseline test score).

The postoperative z scores were subtracted from the preoperative z scores to calculate the absolute change in the neurocognitive test scores. In addition to calculating z scores for each individual test, we also summed up and averaged all z scores of different tests in every particular patient to determine the overall cognitive performance of each patient (“composite” cognitive performance score). We defined short-term neurocognitive decline as a drop of >0.5 SD of the baseline mean z score of each individual test.

Neuroimaging Studies

All except 2 patients underwent preoperative carotid Duplex ultrasound examination of the extracranial carotid arteries. Brain MRI examination consisted of conventional T1 (time to repeat [TR], 800 ms; echo time [TE], minimum; field of view [FOV], 24 cm; number of excitations [NEX], 1; matrix, 256×192; slice thickness, 5 mm), axial fast-spin echo T2-weighted (TR, 4000 ms; effective TE, 85 ms; FOV, 24 cm; NEX, 2; matrix, 256×192; slice thickness, 5 mm), and axial fluid-attenuated inversion-recovery (TR, 8800 ms; TE, 133 ms; inversion time, 2200 ms; FOV, 24 cm; matrix, 256×192; slice thickness, 5 mm) sequences. Three-dimensional time of flight MR angiography of the circle of Willis was performed during the preoperative MRI scan with the following parameters: flip angle, 20°; TR, 43 ms; TE, 6 ms; slice thickness, 1 mm; FOV, 220 cm (3 of 4); matrix size, 512×192; 2 slabs of 54 slices each; scan time, 7.5 minutes.

DWI was performed by use of single-shot, multislice, spin-echo, diffusion-weighted echo planar imaging of the whole brain (TR, 10 000 ms; FOV, 24 cm; NEX, 1; matrix, 128×128; slice thickness, 5 mm). Apparent diffusion coefficient maps showing restricted diffusion were used to confirm that regions of DWI abnormality matched perfusion abnormalities.20–22 DWI abnormalities were used to calculate the volume of putative salvageable brain tissue.23

Five patients had postoperative MRA or digital subtraction angiography of the carotid arteries. The MRA was performed at 1.5 T using a 3-channel head coil. Three-dimensional time of flight MR angiography from the circle of Willis to the extracranial carotid arteries was performed using a 3D fast gradient echo sequence (TR, 43 ms; effective TE, 6 ms; flip angle, 90°; FOV, 24 cm; NEX, 1; matrix, 128×64; slice thickness, 5 mm; axial slices, 17). Injection of gadolinium was followed by 20 cm³ of normal saline at 5 cm³/s with an MRI-compatible power injector (Spectris, Medrad Inc).

All volumes were measured by a trained technician under the supervision of a neuroradiologist (N.J.B.). All volumes were measured by a trained technician under the supervision of a neuroradiologist (N.J.B.). Both were blinded to the outcome and the identity of all patients. Volumes of any DWI and PWI abnormalities were manually delineated by region of interest with the Scion Imaging program (Scion Corp, 1998). A perfusion abnormality was defined as a region with a time-to-peak (TTP) on the TTP map with a delay compared with the contralateral side on the time-to-peak (TTP) map. We chose this threshold on the basis of our previously published data showing that detailed language and neurocognitive test scores strongly correlate with the PWI volume of regions exhibiting a TTP delay of 2.5 seconds.11,19 Nevertheless, we also calculated regional cerebral blood volume (rCBV), regional cerebral blood flow (rCBF), and mean transit time (MTT) for all available PWI scans (11 patients) to compare them qualitatively with the TTP map. The PWI scans of the 2 remaining patients were not available to generate rCBV, rCBF, and MTT because of archival problems and therefore had only TTP sequences. MTT images were generated from the following equation20,21:

\[
\text{MTT} = \frac{\text{VOI} \times \text{TR}}{\text{Flux}}
\]

where VOI is the perfusion volume, TR is the time between two TRs, and Flux is the cerebral blood flow.20

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where $c(\tau)$ is the relative pixel contrast agent concentration estimated from $\Delta R_2^*$. The areas of abnormality (in cm$^2$) on each slice were summed, and the sum was multiplied by the interslice spacing to determine volume in cubic centimeters. Volumes of abnormal signal hyperintensity were calculated similarly on DWI images through manual tracing.

### Surgical Procedure

All patients had cardiopulmonary bypass support with heparin-coated arterial line filters and membrane oxygenators. Crystalloid cardioplegia was used in all patients, and anesthesia management usually consisted of a combination of benzodiazepines, inhalation agents, and intravenous opiates. Further details of the procedure have been published elsewhere.4

### Data Collection and Statistical Analysis

A standardized questionnaire, designed to identify risk factors for postoperative stroke, was administered by 2 investigators (M.A.G., L.M.B.) on each patient. We calculated the probability of postoperative stroke using an algorithm previously validated by McKhann et al.,3 which takes 5 items into account: history of previous stroke, chronic HTN, presence of a carotid bruit, DM, and age $\geq$65 years. With this predictive model, stroke risk is classified into low ($<2\%$), medium (2% to 5%), or high (>5%). The development of any possible postoperative neurological complication was monitored by a neurologist on a daily basis. The diagnosis of stroke was made by a neurologist from our institution through consultation. We used Fisher’s exact test and Pearson’s $\chi^2$ test to examine associations in 2 tables. Differences between z scores were determined from Student’s $t$ test and/or the $t$ test when appropriate.

### Results

Thirteen patients completed the preoperative and postoperative MRI examinations. There were 3 women and 10 men, ranging from 51 to 81 years of age (mean, 65±9 years). The initial MRI was performed an average of 1.8±2 days before CABG (range, 0 to 8 days), and the follow-up scan was done on average 4±1.6 days after CABG (range, 3 to 8 days). At least 1 risk factor for postoperative stroke was present in 11 of 13 patients: 4 had 2 risk factors, and 7 had $\geq$3 risk factors. Eight patients were considered preoperatively as having a high risk for postoperative stroke (Table 1). Among such risk factors, the most common was HTN (10 of 13), followed by extracranial carotid stenosis (4 bilateral, mostly low-grade; 3 were unilateral; only 1 had a high-grade stenosis) and DM (5 of 13). The most relevant clinical and radiological characteristics are summarized in Table 2.

Four of the patients (31%) had new diffusion abnormalities on the postoperative MRI. These lesions were small (0.6±0.2 cm$^3$; range, 0.2 to 0.8 cm$^3$) and rounded. They were multiple in 3 patients and solitary in 1 patient. The number of lesions ranged from 1 to 4 (the Figure). Two patients had lesions dispersed within the same cerebral artery territory, whereas 1 patient had involvement of multiple territories. One patient (patient 2, Table 1) had a small area of diffusion restriction on the preoperative scan, which persisted on the postoperative MRI sequences (the Figure). The patient had a cardiac catheterization 2 days before the preoperative MRI scan but did not have a clinical stroke as consequence of the procedure. This patient, however, developed new DWI lesions on the postoperative scan that were dispersed into different brain territories. No areas of abnormal perfusion on TTP maps were detected either in isolation or accompanying the diffusion defects, even in those patients with evidence of carotid stenosis. Side-by-side qualitative comparison of TTP scans with rCBV, rCBF, and MTT maps failed to reveal any areas of perfusion asymmetry.

One of the patients had a clinically evident postoperative stroke, whereas the other 12 patients had no apparent neurological abnormalities, including delirium. This patient with postoperative stroke had multiple stroke risk factors and had subclinical (old) infarcts on the preoperative MRI. All patients with postoperative DWI abnormalities had a history of HTN and postoperative atrial fibrillation. However, this was not statistically different from the rest of the patients (Table 2). Other variables, including age, risk factors for preoperative stroke, and preoperative risk classification, did not differ between the patients with new DWI lesions and those without changes (Table 2).

Most patients (10 of 13) experienced a decline in the score of at least 1 neurocognitive test. Usually only 1 test caused a drop in the postoperative scores (7 of 13 patients had postoperative decline in 1 test, 2 patients had a decline of $>1$ test, and 1 patient had a decline in 5 different tests). When the z scores of each individual patient were averaged across tests, it was noted that 3 of 13 patients had a decline in their composite z score calculation. Two of these patients had new DWI lesions. Patients with new focal diffusion lesions had a larger postoperative z score change than their counterparts without new DWI abnormalities (mean difference, 0.31 versus $-0.44$; $P=0.04$; 95% confidence interval, 0.017 to 0.6). The number of multiple new DWI lesions was associated with a larger decline in composite z score (Pearson’s $\chi^2$, 7.993; $P=0.046$). Furthermore, the number of new postoperative DWI lesions was significantly associated with a decline in $>1$ neurocognitive test (Pearson’s $\chi^2$, 26.894; $P=0.008$; Pearson’s r, 0.467; $P=0.107$). The most affected tests were the oral naming (Pearson’s $\chi^2$, 7.993; $P=0.005$), written naming (Pearson’s $\chi^2$, 3.704; $P=0.054$), and line cancellation (Pearson’s $\chi^2$, 5.318; $P=0.021$; Pearson’s $r$, 0.64; $P=0.019$). Nevertheless, 1 patient with new focal postoperative DWI changes (patient 9) had no discernible decline in any of the neurocognitive tests.

### Discussion

This study demonstrates that focal brain diffusion abnormalities can occur after CABG, even in patients without clinically identified stroke or delirium. Nevertheless, the development of focal postoperative DWI abnormalities was often associated with objective evidence of neurocognitive decline and/or a definite stroke syndrome in our cohort.

Another finding of particular relevance was the absence of perfusion defects in our patients. A caveat is that PWI estimates relative brain perfusion compared with homolo-
gous regions of the contralateral hemisphere rather than providing a direct measurement of cerebral blood flow. Homogeneous bilateral perfusion changes are conceivable after CABG; for instance, a global augmentation of (ie, resulting from anemia) or reduction in (ie, secondary to heart failure) cerebral perfusion could occur after heart surgery. Therefore, relative perfusion maps using rCBV, rCBF, MTT, and TTP will not reveal abnormalities in the absence of perfusion asymmetry, spuriously resulting in a normal scan. Quantitative measures of cerebral blood perfusion with techniques such as PET or dynamic arterial spin-labeling MRI would be of interest but were not performed in the present cohort. Nevertheless, we have previously described regional hypoperfusion on TTP in other patients with clinical stroke after CABG.

In addition, hypoperfused brain regions may resolve over time as sufficient blood flow is reestablished. Because we obtained our follow-up scans an average of 4.1 days after CABG, it is conceivable that some of the observed DWI abnormalities were associated at some point with rCBF changes, which resolved by the time of the follow-up scan. On the other hand, the intrinsic technical constraints of PWI mapping may not permit the appropriate spatial resolution of hypoperfused brain regions caused by diminutive embolic debris, although color contrast manipulation can be used to improve the conspicuity of small perfusion defects. Another issue is the diagnostic accuracy of the PWI techniques used in the present study. Nevertheless, a recent study suggests that a combination of PWI parameters such as relative contrast bolus peak height and TTP are excellent...
predictors of infarct growth in acute stroke cases diffusion-perfusion mismatch. TTP has been shown to highly correlate with MTT, whereas rCBV and rCBF are needed to generate the MTT maps.

We hypothesize that the observed DWI abnormalities correspond to small areas of brain ischemia caused by emboli arising from the heart or aorta during surgical intervention. We base this opinion on the radiographic appearance of the lesions, particularly because of their multiplicity (3 of 4 patients had multiple areas of restricted diffusion). In addition, most patients did not have significant intracranial or extracranial arterial stenosis ipsilaterally that could serve as additional embolic source.

The possible embolic nature of the observed MRI lesions is suggested by prior pathological and neuroimaging studies. Pathological brain examination of patients who died after cardiac surgery has revealed the presence of embolic material diffusely lodged in the cerebral microcirculation. However, such material appears to be made up mainly of microscopic lipid fragments. Therefore, the terms "microemboli" and "macroemboli" have been proposed to differentiate the smaller embolic debris from larger particles, which have the potential to produce focal neurological and/or radiological abnormalities. In addition, studies using intraoperative transcerebral Doppler monitoring have demonstrated frequent microembolic signals detected at different stages during cardiac surgery. Although high counts of microembolic signals by transcerebral Doppler correlate with postoperative neurological complications (including stroke), most patients with microembolic signals do not develop neurological deficits after surgery.

Several studies have employed perioperative brain MRI to evaluate the neurological complications of CABG, some of which report asymptomatic focal brain lesions developing after surgery. The acuity and radiographic appearance of the new lesions suggest that such abnormalities constituted small infarcts, although the finding of discrete areas of increased signal on T2-weighted images is nonspecific. Some investigations report that the new postoperative MRI lesions were associated with a neurocognitive decline, although this claim was not confirmed by a subsequent study. Nevertheless, other investigations, including one using DWI, did not find focal brain postoperative changes.

Most investigations using MRI, including our own, have intrinsic methodological limitations, particularly small sample size (the largest study includes 38 patients). Only 2 previous studies have examined control subjects who did not undergo CABG. Other limitations of previous reports include the use of low-field-strength scanners (0.15-
the technical expertise of Charles Simpson, who performed the volumetric analysis of all MRI lesions. We are equally grateful to Jennifer Heidler, who participated in the neurocognitive testing of our patients.

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