Background: Coronary artery bypass grafting (CABG) is associated with a risk for focal neurological deficits and neuropsychological impairment postoperatively.

Objectives: To examine the brain damage after CABG using diffusion-weighted magnetic resonance imaging and 1H-magnetic resonance spectroscopy (MRS) and to correlate the results with neurological and neuropsychological findings.

Patients and Methods: Thirty-five consecutive patients undergoing elective CABG were included. Patients underwent a neurological and neuropsychological examination before and after CABG. The magnetic resonance protocol was applied before and after (mean, 3 days) surgery and included a diffusion-weighted sequence and single-voxel MRS measurements in the frontal lobes.

Results: None of the patients revealed a new focal neurological deficit after surgery. Diffusion-weighted magnetic resonance imaging demonstrated new ischemic lesions in 9 (26%) of the patients. The presence of an ischemic lesion was not related to impaired postoperative test performance ($P > .50$). The apparent diffusion coefficient values in the cerebellum and the centrum semiovale exhibited an increase after surgery ($P < .01$), consistent with vasogenic edema. Following surgery, MRS revealed a significant decrease in the metabolite ratio of N-acetylaspartate–creatine (mean ± SD, 1.69 ± 0.20 vs 1.52 ± 0.19; $P < .001$). The extent of deterioration in neuropsychological test performance after surgery was closely related to the degree of the N-acetylaspartate–creatine ratio decrease ($P < .01$). A follow-up MRS scan revealed a normalization of the N-acetylaspartate–creatine ratio, which accompanied the recovery in psychological test performance.

Conclusions: Postoperative impairment in neuropsychological test performance is associated with a transient metabolic neuronal disturbance. Focal ischemic lesions after CABG are more frequent than the apparent neurological complication rate; however, they are not related to the diffuse postoperative encephalopathy.

Arch Neurol. 2002;59:1090-1095

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PATIENTS AND METHODS

PATIENTS

Thirty-five consecutive patients undergoing elective CABG with cardiopulmonary bypass without magnetic resonance contraindication or a major psychiatric or neurological disease were included in this prospective study. Only patients without an increased perioperative risk (as outlined by McKhann et al19) were selected to avoid dropouts during early postoperative testing. Thus, this was a positive patient selection without prior stroke, with normal carotid Doppler findings, without a severely depressed left ventricular function (ejection fraction, <35%), with medically controlled hypertension and diabetes mellitus, and younger than 70 years. Informal written consent was obtained from all participants. The study was approved by the local ethics committee. The characteristics of the patients are shown in the Table.

ANESTHESIA AND SURGERY

Cardiopulmonary bypass-assisted surgery was performed with standard anesthesia techniques and surgical procedures. For general anesthesia, a combination of midazolam hydrochloride, fentanyl citrate, and vecuronium bromide was used. After a median sternotomy, left mammary artery and/or saphenous grafts were used. The procedures were performed under moderate hypothermia (32°C), using a nonpulsatile pump flow of 2.4 L/m² per minute at maximal pump force, a membrane oxygenator, and 40-µm membrane filters. Anticoagulation was adjusted at an activated clotting time of longer than 400 seconds. Mean arterial pressure was maintained at 60 mm Hg or higher. Bypass graftings (range, 2-5; mean, 3.8) were performed within a bypass time of 68 to 222 minutes (mean±SD, 129±37 minutes) and an aortic cross-clamp time of 37 to 105 minutes (mean±SD, 78±21 minutes). The mean±SD overall operation time was 230±46 minutes. Following the day after surgery, the patients did not receive opioids or sedative medication.

CLINICAL EVALUATION

The clinical examination was performed 2 days before and on days 1, 3, and 9 after surgery. For all subjects, it was performed by the same neurologist (W.M.) and included the medical history, a physical examination, and a detailed neurological examination.

NEUROPSYCHOLOGICAL EVALUATION

The neuropsychological test battery included the following tests: d2-letter cancellation test (examining sustained concentration and attention)21; Benton19 visual retention test, instruction A (testing visual short-term memory and visuomotor abilities); Reitan trail-making test A (assessing attention, psychomotor tracking speed, and hand-eye coordination)21; and the block design test from the Wechsler Adult Intelligence Scale (testing clumsiness and visuospatial and constructive abilities)21. The tests were performed by the same neurologist (W.M.) and applied 2 days before surgery and on days 3, 6, and 9 after surgery.

DW-MRI AND 1H-MRS

All measurements were performed on a 1.5-T device (Magnetom Vision; Siemens AG, Erlangen, Germany). The Continued on next page
protocol was applied 1 to 3 days before surgery (median, 2 days) and repeated on days 3 to 5 (median, day 3) after surgery. The MRI scan included an axial T2-weighted double-echo spin-echo sequence (repetition time, 2000 ms; echo time, 20/80 milliseconds; and slice thickness, 6 mm) and an axial DW sequence (using echoplanar imaging) (orthogonal axis DW images: b=0, 500, and 1000 s/mm²; repetition time, 3400 milliseconds; echo time, 103 milliseconds; and slice thickness, 6 mm). Apparent diffusion coefficient (ADC) maps were calculated for every slice, and mean ADC values were bilaterally determined in a round region of interest (4 mm in diameter) in the cerebellar hemispheres, thalamus, and supraventricular white matter of the hemispheres.

The MRS protocol consisted of a single-voxel point resolved spectroscopy sequence (repetition time, 1500 ms; echo time, 135 ms; 128 acquisitions; and voxel size, 40 × 30 × 20 mm³) bifrontally. To achieve a reproducible position, the voxel was placed on a midsagittal image with its inferior edge at the callosomarginal sulcus and on an axial image with its posterior edge at the central sulcus. The voxel position and representative spectra are shown in Figure 1.

DATA ANALYSIS

Analysis of MRI and MRS data was performed blinded to the clinical and neuropsychological data and to the time of the examination (presurgery or postsurgery). Two neuroradiologists (M.W.-M. and L.S.) independently evaluated the MRI scans for diffusion abnormalities on DW images and preexisting vascular abnormalities and brain atrophy on T2- and proton-density–weighted images.

Spectral postprocessing was performed on a workstation using software provided by the manufacturer (Luis; Siemens AG) and included 4k-space zero filling, gaussian apodization, Fourier transformation, water reference processing, and frequency shift, phase, and baseline corrections. Peak integral values were determined by a fit-curve algorithm at 3.0 ppm for creatine (Cr), 3.2 ppm for choline-containing compounds, 1.35 ppm for lactate, and 2.0 ppm for N-acetylaspartate (NAA). Peak integral values were normalized to the internal Cr peak.

All statistical analyses were performed with a statistical software package (Statistical Product and Service Solutions, version 9.0; SPSS Inc, Chicago, Ill). Differences were considered to be statistically significant at P<.05. Metabolite ratios were tested for normal distribution with the Kolmogorov-Smirnov test. Based on an acceptable normal distribution, differences between the preoperative and postoperative values were analyzed with the t test for paired observations. Correlation between metabolic and surgical data (operation, bypass, and aortic cross-clamp times) was assessed using the Pearson product moment coefficient. To assess the neuropsychological impairment after surgery, the differences between preoperative and postoperative values were calculated for each test, and a median split was performed to separate patients with a more severe or a less severe psychological deterioration after surgery. Both groups were tested for significant differences in metabolic data, lesions on DW images, and preexisting vascular damage on T2-weighted images using either a nonpaired t test or a Wilcoxon signed rank test. The group of patients with lesions on DW-MRI was compared with the group of patients without lesions concerning metabolic and surgical data and preexisting vascular damage using a nonpaired t test or a Wilcoxon signed rank test after fulfillment of appropriate prerequisites. Data are given as mean±SD unless otherwise indicated.

Figure 1. A, An axial T2-weighted localizer image demonstrating the position of the frontal voxel. Representative preoperative (B) and postoperative (C) spectra demonstrate a decline in the NAA/Cr ratio 3 days postoperatively (preoperatively: NAA/Cr ratio, 1.9; Cho/Cr ratio, 0.64; postoperatively: NAA/Cr ratio, 1.3; Cho/Cr ratio, 0.62). This patient revealed a marked decline on test performance for each test on the third postoperative day. NAA indicates N-acetylaspartate; Cr, creatine; and Cho, choline.

clamping time (P>.10). Moreover, there was no significant association between the presence of a new lesion and impairment in any neuropsychological test performance 3 days after surgery (median split, P>.50). However, patients with lesions on DW-MRI revealed more extensive preexisting diffuse white matter and periventricular hyperintensities on T2-weighted images (P=.02). In 6 patients with a new lesion on DW-MRI, a third MRI scan was performed 10 to 14 days following surgery. In these patients, the lesions seen on the first postoperative DW-MRI scan also became visible on T2- and proton-density–weighted images.
The ADC values in the cerebellum showed a significant increase 3 days after surgery, indicative of vasogenic edema (left side: 0.67±0.04×10⁻³ vs 0.69±0.04×10⁻³ mm²/s [P<.01]; and right side: 0.68±0.04×10⁻³ vs 0.70±0.04×10⁻³ mm²/s [P<.005]) (Figure 4); values were also increased in the paraventricular-supraventricular white matter (left side: 0.73±0.05×10⁻³ vs 0.76±0.05×10⁻³ mm²/s [P<.005]; and right side: 0.74±0.04×10⁻³ vs 0.76±0.05×10⁻³ mm²/s [P<.01]) (Figure 4). In the thalamus, there was no significant change of ADC values (left side: 0.82±0.05×10⁻³ vs 0.82±0.04×10⁻³ mm²/s [P>.50]; and right side: 0.81±0.04×10⁻³ vs 0.82±0.04×10⁻³ mm²/s [P>.50]) (Figure 4).

MRS RESULTS

Following surgery, the NAA/Cr ratio was significantly decreased compared with the preoperative values (1.52±0.19 vs 1.69±0.20; P<.001) (Figure 5), whereas the choline/Cr ratio remained unchanged (0.82±0.10 vs 0.81±0.10; P>.50) (Figure 5). Lactate or lipid signals were not detected in any patient. In 12 patients, a follow-up MRS scan was performed 10 to 14 days after surgery. At this time, there was a significant increase of the NAA/Cr ratio compared with the second examination (1.65±0.10, P=.01) (Figure 5) so that no significant differences to the preoperative values were found any longer (P>.10). The extent...
of the postoperative NAA/Cr ratio decrease was significantly correlated with the patient’s age ($r_p=-0.39$, $P=0.04$), the overall time of surgery ($r_p=-0.38$, $P=0.03$), the extracorporeal circulation time ($r_p=-0.43$, $P<0.01$), and the aortic cross-clamp time ($r_p=-0.36$, $P=0.03$). The NAA/Cr ratio decrease was significantly more pronounced in the half of patients with a more severe deterioration in the d2-letter cancellation test ($P=0.005$), the Benton visual retention test ($P<0.01$), and the Reitan trail-making test A ($P<0.01$) 3 days after surgery than in patients with a less severe impairment. In the block design test from the Wechsler Adult Intelligence Scale, no significant NAA/Cr ratio difference was found between both groups ($P=0.07$).

**COMMENT**

Coronary artery bypass grafting is one of the most common surgical procedures, performed on more than 800,000 persons per year worldwide. Even though mortality is relatively low, a considerable morbidity rate is found after CABG, especially affecting the central nervous system. Technical progress has reduced the incidence of severe perioperative stroke; nevertheless, postoperative impairment in neuropsychological performance is frequently found, which may persist for up to 6 months. Microemboli, hypoperfusion, and hypothermia have been suggested as causative factors, but the precise mechanism remains unclear. Recent studies have used MRI to examine the incidence of new lesions on T2-weighted images in relation to neuropsychological and clinical findings. These studies have shown highly variable results, ranging from no new lesions to an incidence of 42%. The reason for this discrepancy is the insensitivity of T2-weighted images for detecting new lesions, especially in patients with preexisting vascular lesions. The potential of DW-MRI in detecting clinically silent lesions after neuroangiography has been demonstrated because of its higher sensitivity and specificity for new ischemic lesions. A retrospective study of those with neurological symptoms following CABG has demonstrated ischemic DW-MRI findings in 10 of 14 patients. In the present study, we found new ischemic lesions in 9 (26%) of 35 patients following CABG with cardiopulmonary bypass, with an embolic lesion pattern in the absence of neurological symptoms. It remains unclear if the lesions were caused by air embolism or by thromboembolism. Transcranial Doppler ultrasonography has demonstrated many microembolic signals during cardiopulmonary bypass-assisted cardiac surgery. Historically, focal capillary dilations of 10 to 40 µm were found after cardiopulmonary bypass-assisted surgery, which possibly are caused by lipid microemboli. The sensitivity of DW-MRI is limited by the spatial resolution. Abnormalities smaller than the pixel size (2.0 × 1.8 mm) can hardly be detected reliably. Therefore, the lesions on DW-MRI are probably caused by thromboemboli or a macroscopic air embolism rather than by a microscopic air embolism generated by cavitation forces by the heart-lung machine or by temperature differences. As in previous studies, ischemic lesions were not associated with focal deficits or the prevalence of psychological impairment, and all lesions were found in noneloquent brain regions. Nevertheless, they represent structural ischemic brain damage because they became visible on T2-weighted images 10 to 14 days following surgery. As expected, patients with preexisting vasculopathy on MRI or older patients are particularly prone to new ischemic lesions following surgery.

Magnetic resonance spectroscopy revealed a decreased NAA/Cr ratio following surgery, which was significantly associated with a more severe impairment in postoperative neuropsychological test performance. The choline/Cr ratio remained stable, indicating a depletion of NAA as the cause for the NAA/Cr ratio decrease. The NAA/Cr ratio recovered until 10 to 14 days after surgery, which was accompanied by an improvement in psychological performance measures. N-acetylaspartate is exclusively found in neuronal tissue and is diminished in patients with conditions associated with loss of neurons, such as cerebral infarction. NAA is also reduced in potentially intact neurons with an impaired function, like in patients with an acute multiple sclerosis plaque. In this case, a decrease of the NAA/Cr ratio may be reversible. A similar decline and recovery of NAA has recently been demonstrated in patients following head trauma and after abstinence from long-term alcohol abuse. The reversible NAA decrease indicates a
transient disturbance in the metabolism of neurons, which was correlated with the extent of temporary neuropsychological deterioration. The amount of the NAA/Cr ratio decrease was related to various variables expressing the duration of surgery (extracorporeal circulation, bypass, and operation times). Moreover, the NAA/Cr ratio depletion showed a correlation with the preexisting vascular damage, which suggests an increased susceptibility for metabolic impairment of the preinjured brain. Prolonged anesthesia may be one reason for the metabolic disturbance, even though no significant metabolic changes occur during barbiturate anesthesia in healthy volunteers.34

Extracorporeal circulation causing a microscopic air embolism and cerebral and systemic inflammatory activation35–36 may also be responsible for the temporary metabolic disorder. A microscopic air embolism would result in diffuse cerebral hypoxemia with a consecutive reduction of attenuated diffusion coefficient values due to cytotoxic edema. By contrast, we found elevated ADC values in the cerebral white matter, consistent with vasogenic edema. This finding supports an activation of inflammatory processes in the brain that may be responsible for a transient disturbance of the neuronal metabolism. The NAA/Cr ratios recovered until 10 to 14 days after surgery and were accompanied by a normalization of neuropsychometric variables, again indicating a relationship between metabolic and functional variables. In future studies, MRS may allow for a more objective and quantitative evaluation of cognitive impairment following CABG than neuropsychological performance measures.

Accepted for publication January 9, 2002.

Author contributions: Study concept and design (Drs Bendszus, Koltzenburg, and Solymosi); acquisition of data (Drs Bendszus, Reents, Franke, Mullges, Babin-Ebell, Warmuth-Metz, and Solymosi); analysis and interpretation of data (Drs Bendszus, Mullges, and Koltzenburg); drafting of the manuscript (Drs Bendszus, Mullges, and Koltzenburg); critical revision of the manuscript for important intellectual content (Drs Reents, Franke, Babin-Ebell, and Warmuth-Metz); statistical expertise (Drs Bendszus and Koltzenburg); administrative, technical, and material support (Drs Reents, Franke, Mullges, Babin-Ebell, and Warmuth-Metz); and study supervision (Drs Bendszus, Koltzenburg, and Solymosi).

We thank Martin Klein and Tanja Horn for helping with the data analysis; and Kartheinz Reiners, MD, for critically reading the manuscript.

Corresponding author and reprints: Martin Bendszus, MD, Department of Neuroradiology, University of Würzburg, Josef-Schneider-Straße 11, D-97080 Würzburg, Germany (e-mail: bendszus@neuroradiologie.uni-wuerzburg.de).

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