Subclinical Cerebral Complications After Coronary Artery Bypass Grafting

Prospective Analysis With Magnetic Resonance Imaging, Quantitative Electroencephalography, and Neuropsychological Assessment

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**Objective:** To analyze the frequency and severity of subclinical cerebral complications associated with coronary artery bypass grafting (CABG).

**Design:** A prospective controlled study using preoperative and postoperative magnetic resonance imaging (MRI) of the brain, quantitative electroencephalography (QEEG), and detailed neuropsychological and neurologic examinations as potentially sensitive indicators of subclinical cerebral injury associated with CABG.

**Setting:** Multimodality evaluation in a tertiary care unit (Kuopio University Hospital, Kuopio, Finland).

**Patients:** Thirty-eight patients undergoing elective CABG and 20 control patients undergoing other major vascular surgery, mostly operations on the abdominal aorta.

**Main Outcome Measures:** Coronary artery bypass grafting–associated cerebral complications assessed preoperatively and postoperatively by brain MRI, QEEG, detailed neurologic examination, and a neuropsychological test battery that evaluates cognitive functions in major areas known to be vulnerable to organic impairment (learning and memory, attention, flexible mental processing, and psychomotor speed).

**Results:** There were no major neurologic complications. A mild hemisyndrome developed in 1 patient who underwent CABG and in 1 control patient. Overall, there was no decline in mean cognitive performance 3 months after surgery. Electroencephalographic slowing of 0.5 Hz or more in at least 2 channels occurred in 11 patients who underwent CABG and in 1 control patient ($P = .03$). The postoperative brain MRI scan revealed new small ischemic lesions in 8 patients (21%) in the CABG group but in none of the control group ($P = .03$). These new cerebral MRI lesions did not explain deterioration in neuropsychological test performance or the QEEG slowing.

**Conclusions:** Coronary artery bypass grafting causes more QEEG alterations and small ischemic cerebral lesions that are detectable by MRI than does other major vascular surgery. The effect is mainly subclinical, because no statistically significant deterioration in mean neuropsychological test performance was detected.

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**Original Contribution**

From the Departments of Clinical Radiology (Drs Vanninen, K. Partanen, and Manninen), Neurology (Ms Äikä and Drs Hartikainen and Enberg), Clinical Neurophysiology (Ms Kononen and Dr J. Partanen), and Surgery (Drs Tulla and Hippeläinen), Kuopio University Hospital, Kuopio, Finland.

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PATIENTS AND METHODS

STUDY DESIGN

A total of 38 patients undergoing elective CABG were included in this prospective study. They underwent neuropsychological examination, MRI of the brain, and QEEG approximately 2 weeks before surgery and detailed neurologic examination approximately 2 days before surgery. Patients older than 75 years were excluded, as were those who underwent associated valve replacement, those who had unstable angina, and those who underwent emergency surgery. Magnetic resonance imaging of the brain was repeated before the patient left the hospital, approximately 8 days after surgery. The postoperative QEEG and neuropsychological examination were performed 3 months after surgery. Selective carotid angiography was performed in association with the preoperative coronary arteriography.

The control group consisted of 20 patients undergoing other major vascular surgical procedures, mostly major aortoiliac or aortofemoral vascular reconstructions. The patients in the control group underwent detailed neuropsychologic and neuropsychological examinations, MRI of the brain, and QEEG before and after surgery within a time interval similar to that of the CABG group. In the control group, the degree of carotid artery stenosis was assessed noninvasively using magnetic resonance angiography, Doppler ultrasonography, or both.

All patients gave their informed consent before participating in the study. The study was approved by the ethics committee of the hospital.

PATIENTS

The basic characteristics of the patients who underwent CABG and the control subjects are listed in Table 1. In the CABG group, there were 2 occluded, 1 severely stenosed, and 16 moderately stenosed carotid bifurcations. Six patients had at least moderate stenoses bilaterally. According to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) measurement criteria, the mean degree of carotid stenosis degree was 14%/13% (right/left). In the control group, there were 2 occluded, 5 severely stenosed, and 4 moderately stenosed carotid bifurcations, and 4 patients had bilateral stenoses. One patient in the CABG group refused both the postoperative QEEG and the neuropsychological examination, and 3 patients in the CABG group refused the postoperative QEEG.

ANESTHESIA AND SURGERY

The patients who underwent CABG were operated on with standard anesthesia techniques and surgical procedures. The procedures were performed through a median sternotomy, and the left mammary artery and, if needed, 1 or 2 saphenous vein grafts were used. The mean number of peripheral anastomoses was 4.9 (range, 1-8). The mean ± SD operation time was 215 ± 46 minutes; the mean ± SD cardiopulmonary bypass time was 122 ± 27 minutes; and the mean ± SD aortic cross-clamp time was 110 ± 26 minutes. Lactated Ringer solution (2000 mL) was used as the priming solution for the heart-lung machine. Heparin sodium was administered before cannulation and added to the priming solution. A 20-µm filter was used in the heart-lung machine’s reservoir. Thiopental sodium was administered before cannulation of the ascending aorta, as well as at the start of rewarming. A single venous cannula and a cardioplegia-aortic root vent were used. Patients were cooled to a core temperature of 32°C. During perfusion, nonpulsatile flow was kept at the level of 2.5 L/min per square meter of body surface area at 37°C and 2.25 L/min per square meter at 32°C, respectively. The perfusion pressure was kept above 50 mm Hg. Membrane oxygenators (Compac filho 703, Dideco, Mirandola, Italy) were used. No patient received aprotinin. Careful de-airing was carried out before the aortic clamp was released. No patient required an intra-aortic balloon pump. During the operation, the patients received an average of 4.7 U of blood (range, 0-16 U). After surgery, the patients were observed in the intensive care unit and weaned from mechanical ventilation before the first postoperative morning. The control group received anesthesia and postoperative care similar to that of the patients in the CABG group, except for 1 patient undergoing axillofemoral bypass who had standard general anesthesia.

The operation was uneventful in all the patients who underwent CABG. In the control group, some patients experienced hypotension during the operation (systemic pressure lower than 80 mm Hg), but none of those episodes lasted more than 5 minutes.

CLINICAL EVALUATION

A comprehensive clinical examination, including medical history, physical and detailed neurologic examinations, and assessment of mental state with the Mini-Mental State Examination (MMSE), was performed twice during the study by the same neuroligist approximately 2 days before and 3 months after surgery.

NEUROPSYCHOLOGICAL ASSESSMENT

The neuropsychological test battery assessed cognitive functions in major areas known to be vulnerable to organic impairment: learning and memory, attention, flexible mental processing, and psychomotor speed. The Vocabulary subscale of the Wechsler Adult Intelligence Scale was used as an estimate of verbal intellectual abilities and was performed only before surgery. In the tests of learning and memory, parallel sets of tests were used to minimize the retest effect. To control possible systematic errors caused by minor differences between the sets, the order of the 2 sets was alternated according to each patient’s number of inclusion into the study.

Learning and Memory

The Wechsler Memory Scale Logical Prose subtest, Story A, was used as a measure for logical verbal memory. A paragraph of 23 verbal ideas was read to the patient, and scores for immediate and delayed recall after a 1-hour delay were based on the story units recalled. The List Learning Test (modified from the Auditory-Verbal Learning Test) was used to test learning and memory. The test consisted of an oral presentation of 15 semantically unrelated words that the patient was requested to learn and recall in 4 consecutive trials. The score for learning and immediate recall was...
the sum of correctly recalled words. The score for the delayed recall was the number of words recalled after 1 hour, and the score for delayed recognition was the number of correctly recognized words (15 targets and 15 distractors). The Wechsler Memory Scale Visual Reproduction subtest was used as a test for immediate and delayed recall of nonverbal drawings. In this task, simple drawings were shown for 10 seconds, after which the subject was asked to draw the figure immediately as well as 1 hour later.

Attention, Flexible Mental Processing, and Psychomotor Speed

The Digit Symbol subtest of the Wechsler Adult Intelligence Scale is a task requiring sustained attention and visuomotor speed. The score was the number of correctly transcribed geometric symbols. In the Alternating S Task, the subject was asked to write the letter S and the reversed letter S alternately for 60 seconds. The score was the number of correct items. Reaction times (in milliseconds) and finger tapping were measured with the FePsy computerized neuropsychological test battery. Simple reaction time was measured on either auditory or visual stimuli that were presented at random intervals by the computer. In the Binary Choice Reaction Time Task, the subject had to react differentially to a red or a green square presented on either the left or the right side of the screen. Simple psychomotor speed was measured by the Finger Tapping Task in 3 consecutive trials for the index finger of the right and left hand separately.

The Stroop Test (was used to evaluate sustained attention and resistance to interference. In Form A, the subject was asked to read 50 color names (eg, red, green, and blue) printed in black; in Form B, to name the color of 50 colored dots; and in Form C, to name the color of 50 words printed in a color other than that spelled by the letters. The scores were the time to complete each task.

Mood

Mood and emotional status were measured by a Finnish modification of the Profile of Mood States, an adjectival checklist filled out by the patient.

MRI SCANS

Magnetic resonance imaging of the brain was performed using a standard 1.5-T whole-body imaging system (Magnetom, Siemens, Erlangen, Germany). Transaxial T2-weighted images (repetition time, 2200 milliseconds; echo time, 80-12 milliseconds; slice thickness, 5 mm; field of view, 230 mm; and matrix, 192 x 256) were obtained. The postoperative imaging was performed approximately 8 days after the operation. Both the T2-weighted and proton density images were recorded on film. The presence of previous cortical or lacunar infarcts was evaluated. Ventricular and sulcal enlargement, periventricular hyperintensities, and deep white matter hyperintensities were scored. The ventricular-to-intracranial width ratio was also measured. Also, the preoperative and postoperative films were independently analyzed by 2 neuroradiologists who looked for the presence of any new lesions in the postoperative study. This was done blind to both case and control status as well as to whether the scans were performed before or after surgery. A consensus reading was held between the 2 readers in cases of discrepancy.

QEEG PARAMETERS

A standard 21-channel EEG (Elema, Siemens, Solna, Sweden) was recorded as the subjects lay awake, first with their eyes closed and then with their eyes open. The EEG was recorded as the subjects lay awake, first with their eyes closed and then with their eyes open. The EEG was recorded for 10 minutes in each condition, with the subjects instructed to remain quiet and relaxed. The EEG was recorded for 10 minutes in each condition, with the subjects instructed to remain quiet and relaxed.

RESULTS

COMPARABILITY OF THE STUDY GROUPS

There were no significant differences between the CABG and control groups in their age or sex distribution, cerebrovascular history, or history of hypertension, diabetes, atrial fibrillation, cardiac insufficiency, or previous myocardial infarction, nor in their preoperative MMSE scores, Wechsler Adult Intelligence Scale Vocabulary subtest scores, or MRI scores for periventricular or deep white matter hyperintensities, lacunae, or previous cortical infarcts. However, there were more current smokers in the control group (P = .01), and more of the patients in the CABG group had hyperlipidemia (P = .01). The control
patients had higher scores for ventricular and sulcal enlargement, and the ventricular-to-intracranial width ratio was higher in the control group (36.5) than in the CABG group (25.8, \( P = .02 \)). The patients in the CABG group had more years of formal education than the control subjects (7.7 ± 2.4 years [mean ± SD] vs 6.3 ± 1.9 years, \( P < .05 \)). The groups did not differ in their scores on the Profile of Mood States rating scale or, after education was controlled for, in their preoperative cognitive performance.

**NEUROLOGIC EXAMINATION**

There were no major hemispheric strokes in the study population. The number of patients with mild neurologic symptoms or signs did not differ between the CABG and control groups. Disorientation and confusion during the postoperative period in the intensive care unit was registered in 4 patients (2 in the CABG group and 2 in the control group; \( P = .50 \)). Four days after surgery, a 57-year-old man also demonstrated mild signs of a hemisyndrome during his postoperative neurologic examination. In the CABG group, the mean MMSE score was 27.7 preoperatively and 28.1 postoperatively. In the control group, the mean MMSE scores were 27.6 and 28.0, respectively.

**NEUROPSYCHOLOGICAL TESTS**

Overall, there was no decline in the mean postoperative cognitive performance. The results of the preoperative neuropsychological assessments and the observed change in the scores between the preoperative and postoperative assessments are given in Table 2. In general, a tendency toward slight improvement in the mean postoperative test scores was noticed, consistent with a normal practice effect. In the CABG group, minor decline was found in the delayed Visual Reproduction Task and in the Alternating S Task of psychomotor speed. In the control group, the mean finger-tapping rate of the right hand decreased. After surgery, the patients in the CABG group had significantly lower scores for tension (\( P = .001 \)), depression (\( P = .004 \)), and anger (\( P = .02 \)), while the controls demonstrated no change in the mood ratings (Table 3). Analysis of individual neuropsychological per-

The eye movements and electrocardiographic findings were also recorded. Epoephs with artifacts due to restlessness were rejected and corresponding new epochs rerecorded.

The epochs were divided into 3 half-overlapping 4-second periods, which were transformed to frequency domain with Fast Fourier Transformation. The amplitude and frequency parameters were calculated from the mean of these 12 spectra. The following frequency bands were used in the analysis: \( \delta \) (1.46-3.91 Hz), \( \theta \) (4.15-7.32 Hz), \( \alpha \) (7.57-13.92 Hz), \( \beta \) (14.16-20.0 Hz), and total (1.46-20.02 Hz). Absolute amplitudes were calculated for all these bands, and relative amplitudes were calculated for the \( \delta \), \( \theta \), \( \alpha \), and \( \beta \) bands. The mean frequency was calculated from the frequency band 1.46 to 20.02 Hz. A printout of the original QEEG sample was always combined with the amplitude spectra to enable rejection of specimens with disturbing artifacts due to excessive electromyographic or eye movements. An experienced clinical neurophysiologist validated the QEEG recordings blindly. For the analysis of the QEEG results, the relative amplitudes and frequencies with EC were used as the parameters of the background QEEG. Amplitude ratios (EC/EO) were used as parameters of reactivity. To normalize the distribution of data, the relative amplitudes were transformed to natural logarithm values.

**STATISTICS**

All analyses were performed with a statistical software package (version 5.01, SPSS Inc, Chicago, Ill). Differences were considered to be statistically significant if the \( P \) value was less than .05.

All neuropsychological and computed QEEG parameters were tested for normal distribution with the Kolmogorov-Smirnov 1-sample test. On the basis of acceptable normality, the differences between the CABG and control group means were analyzed with the independent Student \( t \) test, and differences between the preoperative and postoperative QEEG parameters and mood variable scores were analyzed with the \( t \) test for paired observations. As each QEEG parameter was used twice for 2 separate paired comparisons, ie, preoperative vs postoperative and patients vs controls, the multiple comparisons were corrected with Bonferroni adjustment, and the significant \( P \) value in these analyses was .05/2.25 The \( \chi^2 \) test for dichotomized discrete variables and the Mann Whitney \( U \) test for continuous variables with asymmetrical distribution were used.

As the educational level in general correlates with cognitive performance, the preoperative neuropsychological scores were analyzed by covariance analyses, with years of formal education as the covariate. Change scores of the neuropsychological measures, with 95% confidence intervals, were calculated and compared between groups. A neuropsychological impairment in a particular patient was defined as a decrease of 1 SD or more from the preoperative to the postoperative assessment in at least 3 tests.15,26,27 The influence of different primary risk factors and perioperative and postoperative incidents on the observed new MRI lesions and neuropsychological deficits was analyzed. Potential predictors that showed statistically significant associations with 1 of these findings in univariate analyses were further included in stepwise multiple logistic regression analyses.

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QEEG parameters were computed. Before the operation in neuropsychological test performance.

did not, however, significantly correlate with deterioration in neuropsychological test performance.

Ten of the 36 QEEG parameters showed significant change between the mean preoperative and postoperative values in the CABG group (Table 4). The electrical activity became slower, and there was less reactivity in the postoperative recordings. In the control group, none of the parameters showed significant change. Similarly, when the postoperative values for the CABG group were compared with those for the control group, it was evident that the patients in the CABG group had less activity and that the α reactivity was poorer (Table 5).

To identify the individual patients showing change in QEEG parameters, the mean frequency values of the amplitude spectrum (1.5-20.0 Hz) in 4 QEEG derivations (temporo-occipital and centroparietal) were used. A decrease of 0.5 Hz or more in at least 2 channels was interpreted as significant slowing of the QEEG parameters. Using this criterion, the QEEG slowed in 11 patients in the CABG group and in 1 patient in the control group (P = .03). In individual patients, this QEEG slowing did not significantly correlate with the occurrence of new cerebral lesions in the postoperative MRI scan or with deterioration in neuropsychological test performance.

**DETERMINANTS OF MILD CEREBRAL INJURY**

The following parameters were used as potentially sensitive indicators of mild cerebral injury: (1) new MRI lesions; (2) neuropsychological impairment, and (3) significant slowing of the QEEG (a decrease of 0.5 Hz or more in at least 2 channels). The influence of age, sex, several primary risk factors, perioperative parameters, and postoperative incidents was analyzed. The following unexpected incidents occurred in 7 patients (4 in the CABG group and 3 in the control group) in the early postoperative period: resternotomy because of bleeding (n = 2), atrial flutter or fibrillation after surgery (n = 2), low cardiac output (n = 2), and asystole and resuscitation (n = 1).

In univariate analyses, none of the parameters analyzed were statistically significant determinants of the QEEG alterations. In addition, the following parameters proved not to be statistically significant determinants of the new MRI lesions or of neuropsychological deterioration: sex, diabetes, hypertension, smoking history, history of transient ischemic attack or stroke, history of myocardial infarction, carotid bruit or degree of angiographic carotid stenosis, score of deep white matter or periventricular hyperintensities in the preoperative MRI scan, angina pectoris by New York Heart Association classification, decomposition of the heart, anticoagulant treatment, number of units of blood given, number of peripheral bypasses, duration of operation, bypass time, or aortic clamp time.

The following parameters did show statistically significant correlations in univariate analyses with the development of new MRI lesions: atrial fibrillation (P = .04), lacunar infarcts in the preoperative MRI scan (P = .02), hyperlipidemia (P = .04), stenosis of the main trunk (P = .02), and unexpected (nonneurologic) incidents after surgery (P = .001). Correspondingly, age (P = .04) and low scores for ventricular and sulcal enlargement in

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**Table 1. Patient Characteristics**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CABG</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>38 (100)</td>
<td>20 (100)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>32 (84)</td>
<td>18 (90)</td>
</tr>
<tr>
<td>Female</td>
<td>6 (16)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Mean age, y (range)</td>
<td>64 (55-73)</td>
<td>64 (55-75)</td>
</tr>
<tr>
<td>Cerebrovascular history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemisphere or retinal TIA</td>
<td>8 (21)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Nondisabling stroke</td>
<td>5 (13)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Carotid endarterectomy</td>
<td>2 (5)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Carotid artery bruit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>5 (13)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Left</td>
<td>8 (21)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Cardiac history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>38 (100)</td>
<td>9 (45)</td>
</tr>
<tr>
<td>NYHA 1-2</td>
<td>4 (11)</td>
<td>11 (55)</td>
</tr>
<tr>
<td>NYHA 3-4</td>
<td>3 (89)</td>
<td>9 (45)</td>
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<tr>
<td>Myocardial infarction</td>
<td>20 (53)</td>
<td>6 (30)</td>
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<tr>
<td>Cardiac insufficiency</td>
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<td>3 (15)</td>
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<tr>
<td>Atrial fibrillation</td>
<td>5 (13)</td>
<td>2 (10)</td>
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<tr>
<td>Previous CABG</td>
<td>0 (0)</td>
<td>4 (20)</td>
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<tr>
<td>Concomitant disease</td>
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<td></td>
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<tr>
<td>Hypertension</td>
<td>13 (34)</td>
<td>11 (55)</td>
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<tr>
<td>Diabetes</td>
<td>2 (5)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Claudication</td>
<td>5 (13)</td>
<td>15 (75)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>26 (68)</td>
<td>5 (25)</td>
</tr>
<tr>
<td>Smoking history</td>
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<tr>
<td>Current smokers</td>
<td>2 (5)</td>
<td>7 (35)</td>
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<tr>
<td>Exsmokers</td>
<td>22 (58)</td>
<td>7 (35)</td>
</tr>
<tr>
<td>Never smoked</td>
<td>14 (37)</td>
<td>6 (30)</td>
</tr>
</tbody>
</table>

* CAGB indicates coronary artery bypass graft; TIA, transient ischemic attack; and NYHA, angina pectoris by New York Heart Association classification. All data are presented as number (percentage) unless otherwise noted.

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For the analysis of the QEEG recordings, a total of 36 QEEG parameters were computed. Before the operation, none of the parameters differed significantly between the CABG and control groups.

Magnetic resonance imaging (MRI) of the brain revealed small new lesions in 8 (21%) of the patients in the CABG group, but no new lesions were found in the control group (P = .03). The new lesions had high-signal intensity in both the T1-weighted and proton density images, and the diameter of the lesions ranged from 5 to 11 mm. Two of the patients had multiple lesions, 1 of them bilaterally in the cerebral hemispheres. The new lesions were located in the cortical gray matter in 1 case, in the subcortical white matter in 3 cases, in the deep white matter in 2 cases, and in the basal ganglia in 2 cases. All the new lesions were interpreted as indicative of small perioperative infarctions. The appearance of new MRI lesions did not, however, significantly correlate with deterioration in neuropsychological test performance.

**QEEG FINDINGS**

For the analysis of the QEEG recordings, a total of 36 QEEG parameters were computed. Before the operation, none of the parameters differed significantly between the CABG and control groups.

Ten of the 36 QEEG parameters showed significant change between the mean preoperative and postoperative values in the CABG group (Table 4). The electrical activity became slower, and there was less reactivity in the postoperative recordings. In the control group, none of the parameters showed significant change. Similarly, when the postoperative values for the CABG group were compared with those for the control group, it was evident that the patients in the CABG group had less activity and that the α reactivity was poorer (Table 5).

To identify the individual patients showing change in QEEG parameters, the mean frequency values of the amplitude spectrum (1.5-20.0 Hz) in 4 QEEG derivations (temporo-occipital and centroparietal) were used. A decrease of 0.5 Hz or more in at least 2 channels was interpreted as significant slowing of the QEEG parameters. Using this criterion, the QEEG slowed in 11 patients in the CABG group and in 1 patient in the control group (P = .03). In individual patients, this QEEG slowing did not significantly correlate with the occurrence of new cerebral lesions in the postoperative MRI scan or with deterioration in neuropsychological test performance.

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The following parameters were used as potentially sensitive indicators of mild cerebral injury: (1) new MRI lesions; (2) neuropsychological impairment, and (3) significant slowing of the QEEG (a decrease of 0.5 Hz or more in at least 2 channels). The influence of age, sex, several primary risk factors, perioperative parameters, and postoperative incidents was analyzed. The following unexpected incidents occurred in 7 patients (4 in the CABG group and 3 in the control group) in the early postoperative period: resternotomy because of bleeding (n = 2), atrial flutter or fibrillation after surgery (n = 2), low cardiac output (n = 2), and asystole and resuscitation (n = 1).

In univariate analyses, none of the parameters analyzed were statistically significant determinants of the QEEG alterations. In addition, the following parameters proved not to be statistically significant determinants of the new MRI lesions or of neuropsychological deterioration: sex, diabetes, hypertension, smoking history, history of transient ischemic attack or stroke, history of myocardial infarction, carotid bruit or degree of angiographic carotid stenosis, score of deep white matter or periventricular hyperintensities in the preoperative MRI scan, angina pectoris by New York Heart Association classification, decompenation of the heart, anticoagulant treatment, number of units of blood given, number of peripheral bypasses, duration of operation, bypass time, or aortic clamp time.

The following parameters did show statistically significant correlations in univariate analyses with the development of new MRI lesions: atrial fibrillation (P = .04), lacunar infarcts in the preoperative MRI scan (P = .02), hyperlipidemia (P = .04), stenosis of the main trunk (P = .02), and unexpected (nonneurologic) incidents after surgery (P = .001). Correspondingly, age (P = .04) and low scores for ventricular and sulcal enlargement in
the preoperative MRI scans (P = .02) correlated significantly with neuropsychological deterioration in individual patients. These parameters were further included in the corresponding stepwise multiple logistic regression analysis as independent variables; however, a final model was not reached.

Table 2. Neuropsychological Test Scores Before Surgery and the Observed Change Between the Preoperative and Postoperative Scores in the CABG and Control Groups*

<table>
<thead>
<tr>
<th>Test</th>
<th>CABG (n = 37)</th>
<th>Control (n = 20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate story recall</td>
<td>7.9 ± 3.5</td>
<td>6.9 ± 3.5</td>
<td>.78</td>
</tr>
<tr>
<td>Delayed story recall</td>
<td>6.3 ± 4.0</td>
<td>5.3 ± 3.9</td>
<td>.45</td>
</tr>
<tr>
<td>List learning</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate recall</td>
<td>24.7 ± 5.7</td>
<td>22.7 ± 5.6</td>
<td>.68</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>4.1 ± 2.7</td>
<td>3.1 ± 2.4</td>
<td>.75</td>
</tr>
<tr>
<td>Delayed recognition</td>
<td>10.4 ± 1.9</td>
<td>9.9 ± 2.6</td>
<td>.23</td>
</tr>
<tr>
<td>Visual reproduction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate recall</td>
<td>8.5 ± 2.0</td>
<td>6.9 ± 3.1</td>
<td>.29</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>6.8 ± 2.8</td>
<td>4.7 ± 3.9</td>
<td>.05</td>
</tr>
<tr>
<td>Digit symbol</td>
<td>30.4 ± 9.1</td>
<td>26.4 ± 7.6</td>
<td>.36</td>
</tr>
<tr>
<td>Alternating S Task</td>
<td>28.8 ± 11.7</td>
<td>22.5 ± 12.8</td>
<td>.04</td>
</tr>
<tr>
<td>Stroop A</td>
<td>31.6 ± 6.2</td>
<td>28.1 ± 3.9</td>
<td>.27</td>
</tr>
<tr>
<td>Stroop B</td>
<td>42.9 ± 13.4</td>
<td>45.2 ± 12.6</td>
<td>.24</td>
</tr>
<tr>
<td>Stroop C</td>
<td>81.2 ± 21.8</td>
<td>87.3 ± 37.1</td>
<td>.52</td>
</tr>
<tr>
<td>Reaction time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Auditory</td>
<td>304.5 ± 92.4</td>
<td>299.0 ± 83.8</td>
<td>.75</td>
</tr>
<tr>
<td>Visual</td>
<td>284.4 ± 46.5</td>
<td>274.5 ± 81.4</td>
<td>.28</td>
</tr>
<tr>
<td>Binary choice</td>
<td>518.1 ± 105.4</td>
<td>491.6 ± 76.9</td>
<td>.46</td>
</tr>
<tr>
<td>Tapping right hand</td>
<td>55.7 ± 7.6</td>
<td>55.7 ± 7.0</td>
<td>.04</td>
</tr>
<tr>
<td>Tapping left hand</td>
<td>49.1 ± 5.8</td>
<td>49.7 ± 6.1</td>
<td>.56</td>
</tr>
</tbody>
</table>

* For all tests, a positive change value denotes improvement. CABG indicates coronary artery bypass graft; CI, confidence interval. Baseline values are presented as mean (±SD).

Table 3. Mood Variables in CABG and Control Groups Before and After Surgery*

<table>
<thead>
<tr>
<th>Test</th>
<th>CABG (n = 37)</th>
<th>Control (n = 20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>POMS tension</td>
<td>4.5 ± 2.8</td>
<td>4.8 ± 3.0</td>
<td>.12</td>
</tr>
<tr>
<td>POMS depression</td>
<td>5.5 ± 4.7</td>
<td>4.7 ± 3.4</td>
<td>.39</td>
</tr>
<tr>
<td>POMS anger</td>
<td>5.9 ± 4.5</td>
<td>5.8 ± 4.6</td>
<td>.41</td>
</tr>
<tr>
<td>POMS vigor</td>
<td>11.1 ± 5.0</td>
<td>11.7 ± 5.0</td>
<td>.52</td>
</tr>
<tr>
<td>POMS fatigue</td>
<td>4.9 ± 2.9</td>
<td>3.9 ± 2.6</td>
<td>.80</td>
</tr>
<tr>
<td>POMS confusion</td>
<td>3.9 ± 2.4</td>
<td>4.5 ± 2.1</td>
<td>.08</td>
</tr>
</tbody>
</table>

* CABG indicates coronary artery bypass graft; POMS, Profile of Mood States. All data are presented as mean (±SD).

Several large studies have previously assessed the incidence of perioperative stroke and milder clinically evident adverse outcomes associated with CABG. To be able to increase cerebral safety in CABG operations, the goal should be to eliminate all perioperative and postoperative cerebral injury, including subtle changes in intellectual function. To understand the risk factors, all available clinical and investigative information is needed. The strength of the present study is the meticulous assessment of data prospectively collected by multiple modalities known to be sensitive to subclinical cerebral incidents. Our study design thus fulfilled the expectations proposed by Moody.28 However, we did not examine cerebrospinal fluid enzyme levels, because adding an invasive lumbar puncture to our protocol would have decreased the consent and participation rates. In routine clinical work, lack of technical experience in detailed neuropsychological assessment and the time required for such assessment as well as for QEEG and MRI hinder the larger-scale use of this kind of heavy study protocols.

We selected a 3-month interval between the operation and the postoperative assessment of cognitive performance and QEEGs. At an early stage after surgery, performance in the neuropsychological tests is influenced by postoperative factors such as tiredness, pain, analgesic effects, and pulmonary atelectasis. In addition, anesthesia and medication for pain, sleep, and sedation may have immediate QEEG effects. Even if the patients who underwent CABG obviously had less cardiac medication 3 months after surgery, there was no such difference in the postoperative medication, psychotropic or...
other, that might have an impact and would bias the QEEG and neuropsychological assessments. Magnetic resonance imaging was performed approximately 8 days after surgery to detect even small lesions early on, while their interpretation is most distinct. It has been shown that while the majority of strokes complicating cardiac surgery have occurred by postoperative day 2, as many as 39% may occur between postoperative days 3 and 9.20

The preoperative MRI was always performed after the diagnostic coronary and carotid angiography to avoid the possibility that a new lesion in the postoperative MRI scan would be directly attributable to the angiographic procedure rather than to CABG. It is theoretically possible that both the intraventricular and the unselective proximal aortic injections, as well as the selective common carotid injections, might be associated with subclinical lesions in the brain.28 Gerraty et al31 studied 24 patients during selective carotid angiography and confirmed the presence of numerous cerebral microemboli of air using transcranial Doppler examinations during injections. One of their patients had angiographic stroke, but in no other patient did the microemboli lead to new lesions on the MRI scans.

RISK FACTORS

Identification of the risk factors for adverse cerebral outcomes would be of great value to the cardiovascular surgeon, especially during the selection of patients with relatively marginal indications for CABG. The Multicenter Study of Perioperative Ischemia Research Group25 has recently reported the key preoperative predictors for major focal adverse neurologic events in a series of 2107 patients undergoing CABG. Age, history of previous neurologic disease, diabetes, history of vascular disease, previous coronary artery surgery, unstable angina, and history of pulmonary disease were found to be significant predictors.25 Lynn et al30 reported that a history of diabetes, the presence of mural thrombi, and aortic calcification carried a higher probability that the patient would have a permanent neurologic deficit after CABG. For subclinical neuropsychological impairment, perfusion time and unexpected intraoperative events were reported to be the most important factors in a series of 49 patients undergoing valvular replacement.14 In the present study, unexpected postoperative incidents, stenosis of the main trunk, atrial fibrillation, hyperlipidemia, and lacunar infarcts before surgery showed significant correlation with the development of new MRI lesions.

NEUROPSYCHOLOGICAL ASSESSMENT

Neuropsychological tests sensitive to subtle changes in intellectual function have detected impaired cerebral function in up to one third of patients after CABG. In the present study, analysis of group effects revealed no decline in mean cognitive performance. Cognitive performance slightly improved in general, as can be expected on the basis of normal practice effect. Only minor differences were found between groups, and their clinical relevance remains questionable.

Analyses of individual subject performance have been used in the field of cardiac surgery, but the definition of neuropsychological deficits has been somewhat arbitrary and the subject of much discussion. To identify the individual patients showing decline in a set of 17 neuropsychological tests, we selected a deterioration by 1 SD in at least 3 tests as our cutoff point. Even using this wide definition for neuropsychological impairment, no statistically significant difference was seen between the CABG and control groups. Correspondingly, Pugsley et al35 required a 1 SD decrease in performance on 2 or more tests in a set of 10 tests. A stricter criterion for statistically significant deterioration in neuropsychological performance could be defined using binomial distribution; at least 5 tests in a test battery of 17 tests should have a score
difference of 1 SD before the probability of chance is less than .08. Using this strict determination, 1 patient (3%) in the CABG group and no patients in the control group worsened, a result similar to that reported in a large multicenter study.1

Restricting analysis of neuropsychological performance to comparison of only group effects may blur virtual cognitive impairment in individual patients. In the literature, the amount of decline in a particular test score interpreted as deterioration varies, as does the number of tests in which the performance deteriorated, interpreted as indicative of a significant deficit.11,27,32 In addition, the neuropsychological test battery applied and the interval between the repetitive tests are variable, making direct comparisons difficult.7,10,33 Reaching a standardized neuropsychological evaluation would be desirable for comparing results between different patient populations.

We observed significantly lower postoperative scores for tension, depression, and anger in the patients who underwent CABG, while the mood ratings did not change in the controls. Increased anxiety scores in presurgical patients have been reported in several studies; also, many presurgical patients experience depressive symptoms that tend to increase after the operation.34 However, it has been shown that the significantly elevated emotional arousal in these patients has no relevant effect on their cognitive performance.34

MRI EVALUATION

Computed tomography has often been used to evaluate patients suspected of cerebral injury associated with open heart surgery. However, subtle ischemic lesions of the white or gray matter of the brain are not detectable on computed tomographic scans. Magnetic resonance imaging is by far the most sensitive imaging method for high-quality depiction of cerebral anatomy and abnormalities. Toner et al15 found new cerebral lesions in 5 of 12 patients, mainly deep white matter lesions. In a series of 29 patients who underwent CABG, postoperative MRI scans demonstrated a small infarction in 2 clinically asymptomatic patients.13 In another study of 31 patients who underwent CABG, however, no new cerebral lesions were detected on postoperative MRI scans, despite 1 patient with stroke and 8 patients with diffuse encephalopathic symptoms after surgery.35 In the largest series of Toner et al,36 6 (30%) of 20 patients had new ischemic lesions, while in another series of similar size, no patients did. The occurrence of new ischemic lesions in 21% (8/38) of our patients who underwent CABG was also far less frequent than the 58% (15/26) that was recently reported in patients who underwent complex valve replacement surgery.12 However, in another series, this procedure was associated with new MRI abnormalities in only 14.8% of patients.27,37 On the other hand, none of our control patients who were not subject to cardiopulmonary bypass or manipulation of the thoracic vascular system displayed any new lesions on their MRI scans. The majority of the new MRI lesions in our study were clinically silent, even when judged by detailed neurologic and neuropsychological workup. This was also the case in the valve replacement series of Moody et al38 but not in the patients who underwent CABG in the study of Toner et al36 in which all 4 patients with new MRI abnormalities had significant neuropsychological deficits. Some of the new ischemic lesions demonstrated on MRI scans may have resolved before the clinical follow-up studies 3 months after surgery. There is evidence that even the microscopic microvascular changes that are apparent after cardiopulmonary bypass may eventually resolve.30 However, we found it clinically more relevant to perform the clinical studies only after the patients had recovered from the immediate stress and fatigue associated with the surgical procedure. In earlier studies, it appeared that after valvular replacement surgery, the clinical neurologic outcome improved between postoperative days 10 and 60 and that it improved even more by the end of the first postoperative year.14

Moody et al39 suggested that microvascular alterations, such as small, empty capillary and arteriolar dilatations, in patients who had recently undergone cardiopulmonary bypass result from emboli that occur during the bypass. In their study, microvascular alterations occurred in such sufficient numbers and sizes that mental alterations might have been expected. In the study by Moody and colleagues, the prevalent microvascular changes were more often distributed throughout the cortical and deep nuclear gray matter than in the white matter; this was different from the present series, in which the new punctuate areas of hyperintensity were located mostly in the white matter.

Vanninen et al40 previously detected new cerebral lesions in the postoperative brain MRI scans of 3 (16%) of 19 patients undergoing carotid endarterectomy. The degree of carotid stenosis in the present series did not show any significant correlation to the new cerebral lesions, nor to the neuropsychological deficits. Emboli from atheromatous plaques in the aorta remain a hazard in coronary surgery and may in part explain the lack of correlation to carotid disease.2

Theoretically, there are several potential mechanisms that may explain new cerebral lesions in the MRI scans after open heart surgery: (1) macroembolization of air, fragments of atherosclerotic plaque from the ascending aorta, or release of left ventricular thrombus; (2) microembolism of gas, fat, aggregates of blood cells, platelets, fibrin, or silicone; and (3) inadequate perioperative cerebral perfusion.5,40,41 Valvular surgery is believed to be more dangerous than CABG.42 In addition to the cerebral complications, clinical neurologic manifestations can result from brachial plexus or other peripheral nerve injuries associated with direct trauma during surgery. In the present series, microembolization was considered to be the most probable explanation for the new MRI lesions. An alternative mechanism in some cases may have been hypoperfusion associated with border zone edema and infarcts. The paradox is that in the low-flow situation, the brain’s embolic burden is likely to be much less than in higher-flow situations.28

QEEG ANALYSIS

Quantitative EEG analysis 3 months after the operation revealed significant postoperative increase in slow activ-
ity (θ and δ), a decrease of fast activity (α), and a decrease in EEG frequency in several channels, indicating general slowing of the EEG. In addition, the ratio parameters indicating EEG reactivity were also decreased postoperatively. This kind of deterioration was not observed in the postoperative EEGs of the controls. The most distinct postoperative QEEG differences between patients and controls were an attenuation of the α amplitude and a decrease of EEG reactivity. These observations reflect a general mild electrophysiological dysfunction in the CABG group after surgery. Eleven patients showed distinct decreases in the mean QEEG frequency, and this finding agrees with those of earlier studies in patients with open heart valvular replacement.

Although the criteria for postoperative electrophysiological deterioration in patients who have undergone CABG can be established, the effect is mainly subclinical because there are no significant correlations between QEEG deterioration and neuropsychological impairment or objective brain lesions revealed on MRI scans. However, we advocate the careful follow-up of patients who have undergone CABG to observe even subclinical subtle signs of brain function after surgery. Coronary artery bypass grafting causes distinctly more EEG alterations than does carotid endarterectomy, studied with the same QEEG technique. There are also other objective electrophysiological methods, eg, event-related potentials, that may be applied to the postoperative follow-up of patients who have undergone CABG.

Spurious significant findings may occur in multiple comparisons. In the analysis of QEEG data, we used Bonferroni adjustment to correct for multiplicity of comparisons. Recognizing that the probability of making an error in a statistical comparison is <.05 owing to chance alone, we can estimate that approximately 2 comparisons produce spurious significant differences in the 36 comparisons of QEEG data. However, in both Tables 4 and 5, the number of parameters with significant differences is clearly more than 2. Also, all the parameters with significant differences are seen only in the CABG group (Table 4) or only in the postoperative parameters (Table 5) and are linked together logically. Thus, our result indicating general slowing of the EEG in the CABG group after surgery is not a result of statistical distortion. On the other hand, only 3 neuropsychological parameters showed a significant difference in group comparison. As 1 of the 17 tests may show significant difference due to chance alone and the observed differences were not logically linked together (the performances on 2 tests in the CABG group and 1 in the control group deteriorated), no obvious decline in mean cognitive performance was found in the patients who underwent CABG.

CONCLUSIONS

As a tribute to the advances in cardiac surgery, major neurologic complications have become rare. To improve quality, even subtle but detectable changes in cognitive function that could be prevented should be assessed. We combined neuropsychological assessment with QEEG and MRI as objective measures of subclinical complications in a group of patients who underwent CABG and a group of controls and found that CABG was significantly more frequently associated with QEEG slowing and small ischemic cerebral lesions. However, these observations were not associated with clinical complications or statistically significant deterioration in neuropsychological test performance. The distress scale significantly improved after CABG, corresponding to the general recovery process.

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REFERENCES


**Correction**

In the article entitled “Sex Differences in Brain Aging: A Quantitative Magnetic Resonance Imaging Study,” published in the February issue of the *ARCHIVES* (1998;55:169-179), the coefficient for increased age associated with increased volumes of the lateral ventricles was incorrectly stated on page 172 in the paragraph subtitled “Age Main Effects,” last sentence. The sentence should have read as follows: “Increased age was also associated with increased volumes of the lateral ventricles (coefficient=0.88, *P*<.001) and the third ventricle (coefficient=0.05, *P*<.001).”