Relation Between Neurocognitive Impairment, Embolic Load, and Cerebrovascular Reactivity Following On- and Off-Pump Coronary Artery Bypass Grafting*

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Objectives: To evaluate the effect of on-pump and off-pump coronary artery bypass grafting (CABG) on postoperative cognitive impairment and cerebrovascular reactivity, with attention for the perioperative high-intensity transient signals (HITS).

Design: A prospective comparative study.

Setting: Urban university hospital.

Patients: Candidates for cardiac surgery.

Methods: Measurement of HITS as a reflection of embolic load was performed in 50 patients (on-pump CABG, n = 32; off-pump CABG, n = 18). To measure cognitively induced cerebrovascular reactivity, cerebral blood flow velocity (BFV) was measured preoperatively in 66 patients, early postoperatively (after 6 days) in 63 patients, and late postoperatively (after 6 months) in 44 patients during five cognitive tasks. In the same session, seven standardized neuropsychological tests were administered.

Results: A higher embolic load was found in the on-pump group (p < 0.01). In the on-pump group, aortic cannulation was the most important HITS-prone surgical maneuver. Repeated-measures multivariate analysis of variance (using surgical technique as between-subjects factor and significant differences between both groups as covariates) on the group data revealed no significant differences in neuropsychological performance and BFV immediately after surgery or at 6 months after surgery, compared with preoperative performance. No main effect of surgery was found for neuropsychological performance and BFV. No significant correlations were found between the number of HITS and the degree of postoperative neuropsychological impairment. Individual comparisons revealed that 60% (59.4% in the on-pump group; 61.1% in the off-pump group) of the patients undergoing CABG showed evidence of cognitive impairment soon after surgery. In 24.2%, the cognitive sequelae persisted at 6 months follow-up (31.8% in the on-pump group; 9.1% in the off-pump group). The cognitive impairment index (sum of impaired neuropsychological tests) showed a significant difference after 6 months between both surgery groups with fewer neurocognitive tests that remained impaired in the off-pump group.

Conclusions: In off-pump surgery, significantly fewer HITS were observed. On an individual level, more favorable results in neuropsychological test performance were demonstrated in the off-pump group after 6 months. The number of HITS showed no correlation with degrees of early and late postoperative neuropsychological impairment.

Key words: cerebrovascular reactivity; cognitive impairment; coronary artery bypass grafting; emboli; neuropsychology; off pump; on pump; ultrasonography

Abbreviations: BFV = blood flow velocity; CABG = coronary artery bypass grafting; CBF = cerebral blood flow; CII = cognitive impairment index; CPB = cardiopulmonary bypass; ECC = extracorporeal circulation; HITS = high-intensity transient signals; IQ = intelligence quotient; MANCOVA = multivariate analysis of covariance; MCA = middle cerebral artery; NLV = Nederlandse Leestest voor Volwassenen; TCD = transcranial Doppler ultrasonography

Neuropsychological impairment is a common complication of coronary artery bypass grafting (CABG). Although the cause of this cerebral injury is unclear, one of the frequently discussed pathophysiological features in relation to conventional CABG with extracorporeal circulation (ECC) is focal dysregulation caused by cerebral emboli. The advent of transcranial Doppler ultrasonography (TCD) provided a sensitive tool for the detection of emboli in the majority of patients during traditional CABG with ECC. Furthermore, several studies using TCD have reported a correlation between the count...
of high-intensity transient signals (HITS) and neuro-psychological outcome. This suggests that surgical techniques should be improved to reduce the number of emboli. CABG without ECC (off-pump surgery) on a beating heart is an increasingly common procedure and an interesting alternative to traditional revascularization, avoiding some of the morbidity of on-pump CABG surgery. Evidence for the reduction of cerebral HITS load in off-pump surgery has already been described. Nevertheless, inconsistent results were shown when the cerebroprotective effect of off-pump procedures was compared to conventional CABG. In the present study, we monitored the occurrence and frequency of HITS and compared the number of HITS resulting from CABG with ECC (on-pump CABG) or without ECC (off-pump CABG). We also wanted to determine whether a higher number of HITS is associated with an increased risk of short-term (6 days) and long-term (6 months) postoperative cognitive impairment.

TCD cannot only detect HITS; the device also permits the continuous and simultaneous assessment of blood flow velocity (BFV) in the middle cerebral arteries (MCAs) through a “temporal window” in the intact skull. BFV may serve as a surrogate measurement of cerebral blood flow (CBF) since changes in flow velocities correlate closely with alterations in CBF, even when cerebral autoregulation is disturbed. Bilateral BFV measurements can evaluate the cognitively induced cerebrovascular reactivity by using cognitive tasks to elicit cerebral activation. The changes in BFV that result from this activation are sensitive enough to demonstrate lateralized mental activity (for a review of cerebral activation studies with functional TCD, see Stroobant et al8). The second purpose of this study is to investigate the functional hemodynamic response by means of BFV measurements during rest conditions and during cognitive activation in patients before, early (6 days) and late (6 months) after the surgery. We assumed that reduced cognitively induced cerebrovascular reactivity could corroborate the observed neuro-psychological deficits on a more metabolic level.

**Materials and Methods**

**Patient Selection**

Patients ≤ 70 years old had to be free of known carotid artery stenosis as determined by duplex B-mode Doppler ultrasonography to prevent possible bias from carotid stenosis on BFV measurements in our patients. Exclusion criteria for all Dutch-speaking subjects were a history of head trauma, seizures, stroke, or other serious neurologic or psychiatric diseases. None of the subjects received psychoactive medication. Additionally, no patients requiring emergency treatment or valve repair were passed. Each patient who qualified for the study signed an informed consent document approved by our institutional ethical committee. Procedures were in accordance with the recommendations found in the Helsinki Declaration of 1975.

All patients were potential candidates for off-pump surgery except in case of unstable angina, severe left main stenosis (≥ 95%) and/or hemodynamic instability, or anatomic inaccessibility. In multiple-vessel disease, complete revascularization, especially in the region of the distal circumflex or right coronary artery, using the off-pump technique necessitates important prolonged tilting of the heart, sometimes leading to hazardous hemodynamic instability. As a consequence, more patients with multiple distal anastomoses in the region of the circumflex and right coronary arteries were selected to be included in the on-pump group. However, since the beginning of the study, the used types of stabilizers have improved considerably, thus broadening the indications for off-pump surgery.

One patient died before the early postoperative examination (due to a cerebrovascular accident) and was not included in the HITS study. One other patient died before the late postoperative examination (sudden death). Both patients had undergone on-pump surgery. For the other patients, we observed no in-hospital psychiatric complications, and none of the patients had postoperative neurologic complications such as transient ischemic attacks or strokes.

**Anesthesia and Surgical Management**

Anesthesia was induced and maintained with benzodiazepines, propofol, and opioids. For the conventional CABG, all patients underwent a midline sternotomy. Cardiopulmonary bypass (CPB) with moderate hypothermia was achieved by cannulation of the ascending aorta, and venous cannulation through the right atrium into the inferior vena cava. After cross-clamping of the ascending aorta, anterograde crystalloid cold cardioplegia was administered. Roller pumps and a membrane oxygenator were used for CPB. The proximal anastomoses of the veins or free arterial grafts were performed to the ascending aorta during reperfusion during one single aortic cross-clamp. An arterial filter was incorporated in the circuit.

For the off-pump CABG, midline sternotomy was undertaken in all patients. Under normothermia, venous or free arterial grafts were first of all secured (with partial cross-clamping) to the ascending aorta before tilting the heart, allowing immediate restoration of blood flow to the distal target coronary. Sutures were stabilized at the distal coronary anastomotic site in all patients (Octopus II; Medtronic; Minneapolis, MN).

**Intraoperative HITS Counting**

HITS detected by a 2-MHz, pulsed-wave TCD unit (Multidop X4; DWL Elektronische Systeme GmbH; Sipplingen, Germany)
were recorded in 50 CABG patients (46 men and 4 women; mean age ± SD, 59.9 ± 7.5 years). The sex ratio of this sample reflects the usual gender distribution in the population undergoing cardiac surgery. Patients were classified into two subgroups: all patients undergoing on-pump surgery \( (n = 32) \) were compared to patients undergoing off-pump CABG \( (n = 18) \) 6 days after surgery. A Dutch version of the National Adult Reading Test (Nederlandse Leestest voor Volwassenen [NLV]) was used to obtain an estimated the intelligence quotient (IQ). State anxiety was measured by the Dutch version of the Spielberger state anxiety questionnaire. For further details about this patient group, we refer to Table 1. Six months after surgery, the on-pump group consisted of 22 patients and the off-pump group consisted of 11 patients. Some of the reasons for not coming back were difficulties in transport to revisit the hospital, and lack of interest/motivation. Interestingly, a statistical analysis with belonging or not belonging to the dropout group as a between-subjects factor was performed. We found no statistical differences for demographic, intraoperative, or postoperative variables.

Patients underwent preoperative identification of both MCAs. Two 2-MHz transducers fitted on an elastic headband (DWL 40389; DWL Elektronische Systeme GmbH) were placed on each of the left and right temporal skull windows transmitted the ultrasonic signal and received the echoes. Details of the insonation technique and the correct insonation of the MCA have been described elsewhere. Starting from insonation depths of 50 mm and 55 mm, depth and angles of insonation were adjusted to obtain the highest signal intensity of the M1 segment of the MCA. HITS were continuously and bilaterally recorded by a sonographer from the moment of induction of heparin until 5 min after aortic decannulation (on-pump) or 5 min after the last distal anastomosis (off-pump). HITS were defined as having high amplitudes (greater than flow velocity), unidirectional, transient signals lasting \(< 0.1 \) s, greater than nine decibels, and associated with a characteristic chirping sound. The sonographer was informed of major procedural events, and HITS distribution was recorded accordingly. For on-pump CABG, eight categories of surgery manipulation were noted, and if a HITS signal was detected in the immediate 1-min period after one of these categories, it was considered to be associated with that event. The categories were aortic cannulation, aortic decannulation, cross-clamp on, cross-clamp off, ECC on, ECC off, partial clamp on, and partial clamp off.

### Neuropsychological Testing

One examiner (N.S.) administered a battery of seven standardized neuropsychological tests 1 day before, 6 days after, and 6 months after surgery. The tests included:

- **On-Pump Group (n = 32)**
  - Mean age, yr: 59.1 ± 7.7
  - Male gender: 90.6
  - IQ estimate (NLV): 94.9 ± 9.6
  - State: 42.3 ± 14.6

- **Off-Pump Group (n = 18)**
  - Mean age, yr: 61.3 ± 7.1
  - Male gender: 94.4
  - IQ estimate (NLV): 84.4 ± 10.2
  - State: 44.5 ± 16.7

#### Table 1—Patient Characteristics*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>On-Pump Group (n = 32)</th>
<th>Off-Pump Group (n = 18)</th>
<th>F Test</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age, yr</td>
<td>59.1 ± 7.7</td>
<td>61.3 ± 7.1</td>
<td>0.98</td>
<td>0.327</td>
</tr>
<tr>
<td>Male gender</td>
<td>90.6</td>
<td>94.4</td>
<td>0.47</td>
<td>0.641</td>
</tr>
<tr>
<td>IQ estimate (NLV)</td>
<td>94.9 ± 9.6</td>
<td>84.4 ± 10.2</td>
<td>13.05</td>
<td>0.001†</td>
</tr>
<tr>
<td>State</td>
<td>42.3 ± 14.6</td>
<td>44.5 ± 16.7</td>
<td>0.20</td>
<td>0.656</td>
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<tr>
<td><strong>Preoperative risk factors</strong></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>43.8</td>
<td>61.1</td>
<td>1.17</td>
<td>0.247</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>56.3</td>
<td>50</td>
<td>0.42</td>
<td>0.678</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>12.5</td>
<td>16.7</td>
<td>0.4</td>
<td>0.691</td>
</tr>
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<td>Diabetes</td>
<td>31.3</td>
<td>33.3</td>
<td>0.15</td>
<td>0.583</td>
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<tr>
<td>Tobacco use</td>
<td>71.9</td>
<td>94.4</td>
<td>2.3</td>
<td>0.026†</td>
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<td>Recent myocardial infarction</td>
<td>21.9</td>
<td>33.3</td>
<td>0.88</td>
<td>0.386</td>
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<tr>
<td>Ejection fraction</td>
<td>67.3 ± 14.9</td>
<td>71.7 ± 12.5</td>
<td>1.08</td>
<td>0.304</td>
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<td>COPD</td>
<td>6.3</td>
<td>5.6</td>
<td>0.10</td>
<td>0.923</td>
</tr>
<tr>
<td>No. of diseased vessels</td>
<td></td>
<td></td>
<td>2.06</td>
<td>0.049†</td>
</tr>
<tr>
<td>1</td>
<td>3.1</td>
<td>16.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>18.8</td>
<td>33.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>78.1</td>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td>26.9 ± 4.8</td>
<td>28.3 ± 3.9</td>
<td>1.16</td>
<td>0.257</td>
</tr>
<tr>
<td><strong>Perioperative and postoperative factors</strong></td>
<td></td>
<td></td>
<td>3.85</td>
<td>0.001†</td>
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<tr>
<td>No. of grafts</td>
<td></td>
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<td></td>
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<tr>
<td>1</td>
<td>5.6</td>
<td></td>
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<tr>
<td>2</td>
<td>16.7</td>
<td></td>
<td></td>
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<tr>
<td>3</td>
<td>50.0</td>
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<tr>
<td>4</td>
<td>27.8</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>5</td>
<td>21.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>6.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Operation time, min</td>
<td>188.8 ± 42.5</td>
<td>160.6 ± 28.7</td>
<td>2.91</td>
<td>0.095</td>
</tr>
<tr>
<td>Anesthesia time, min</td>
<td>245.5 ± 46.9</td>
<td>230.0 ± 38.0</td>
<td>2.04</td>
<td>0.16</td>
</tr>
<tr>
<td>Ventilation time, h</td>
<td>113.5 ± 5.1</td>
<td>106.4 ± 4.4</td>
<td>0.29</td>
<td>0.596</td>
</tr>
<tr>
<td>Stay in ICU, h</td>
<td>44.1 ± 40.3</td>
<td>44.2 ± 32.0</td>
<td>0.00</td>
<td>0.989</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>18.8</td>
<td>16.7</td>
<td>−0.20</td>
<td>0.846</td>
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</table>

*Data are given as mean ± SD or % unless otherwise indicated.
†Significant at 0.01 level.
‡Significant at 0.05 level.
months after surgery in the 50 patients with emboli measurement. This group was part of the larger group of 66 patients. At the time of the first assessment, it was unknown whether an on-pump or off-pump strategy would be used. The tests were selected to sample a broad range of cognitive abilities and included measures of attention and concentration, verbal and nonverbal memory, language, visuospatial functions, executive functions, and motor and psychomotor speed. To reduce test-retest effects, we used alternate test versions when possible. The tests used in the study are listed in Appendix 1.

Definition of Cognitive Decline

Since direct comparisons of the group means of preoperative and postoperative neuropsychological measurements usually show improvement rather than cognitive decline, researchers have focused on preoperative and postoperative differences in cognitive performance on an individual level. This allows each patient to serve as his/her own control. If these differences exceed a certain threshold, a patient is considered to have a cognitive decline. Several thresholds have been proposed. We used the “20% definition” because it is believed to be the most sensitive method for identifying patients with signs of cognitive decline. The 20% definition implies that a decrease in test scores by at least 20% from the preoperative baseline is said to constitute significant decline. Studies have also varied in the number of tests that a patient’s score must have declined on, before a subject can said to be declined. For this study, we defined cognitive decline as having 20% on two or more tests.

To further refine our results, we described the severity of neuropsychological test decline by counting the number of impaired test performances for each individual (possible range, 0 to 7). This is called the cognitive impairment index (CII).

Measurement of BFV

Cerebral BFV changes in the MCAs were continuously and simultaneously recorded with the same TCD device as for emboli measurement. Following an initial rest phase, subjects were confronted with three verbal and two visual-spatial tasks, most of which were presented on a computer screen. Each activation and rest condition lasted 120 s and was delineated on the TCD record by a set of markers. The speed of the stimulus presentation was individualized to reduce frustration with stimulus pacing (either too slow or too fast) and to maximize the mental activity of the individual. As soon as the subject gave a response, the next item was shown. To obtain a stable measurement during activation, only the middle 60 s of each 120-s activation condition were used to determine the mean BFV for that task. During the rest periods, subjects were asked to look at an illuminated blank computer screen, to relax and breathe regularly without falling asleep, and to clear their thoughts. They were not allowed to move or speak, nor were they spoken to. The first 60 s of each rest period served as a recovery period in which posttask activation could subside. Only the last 60 s of the rest period served as the baseline measurement for the subsequent activation phase. We always used the immediately preceding rest period to determine the BFV change of the cognitive task under study. Because TCD cannot detect the differences between real asymmetries in BFV and differences caused by slightly different insonation angles, we calculated the relative increase from baseline to activation: \(\frac{BFV_{\text{baseline}} - BFV_{\text{activation}}}{BFV_{\text{baseline}}} \times 100\).

We selected cognitive tasks that had demonstrated potential for lateralized cognitive activity (and lateralized cerebral hemodynamics) in previous functional imaging or TCD research. The cognitively induced cerebrovascular reactivity tasks are listed in Appendix 2.

Preoperative BFV measurements were obtained for 66 patients, early postoperative BFV measurements for 63 patients (on-pump CABG, \(n = 41\); off-pump CABG, \(n = 22\)) and late postoperative measurements for 44 patients (on-pump CABG, \(n = 30\); off-pump CABG, \(n = 14\)). The total patient group was divided into the on-pump and the off-pump groups.

Statistical Analysis

All continuous variables are expressed as mean ± SD. Categorical variables are expressed as a percentage of those exhibiting the trait out of all patients for whom data were available. Statistical analysis (SPSS/PC+; SPSS Chicago, IL) was based on two independent groups of patients (on-pump vs off-pump groups). Baseline characteristics, outcome measures, and complications between the two groups were compared. Normally distributed data (ratio scale) were compared with independent \(t\) tests. If the data were not normally distributed, the nonparametric Mann-Whitney test was used. Nominal data were analyzed with \(x^2\) statistics if all expected cell frequencies were greater or equal to five. Otherwise, Fisher Exact Test was used.

Analyses of neuropsychological and BFV data between groups were analyzed with repeated-measures multivariate analysis of variance and corrected for between-groups differences with the proper covariates (multivariate analysis of covariance [MANCOVA]). Associations between the number of HITS and neuropsychological and BFV data were calculated by Spearman \(p\) and Pearson correlation coefficients. In the parametric tests, dependent variables were checked for normal distribution by Kolmogorov-Smirnov tests and transformed if necessary. Detailed information about each statistical procedure follows.

Results

HITS

In the on-pump group, the mean number of HITS was 335.1 ± 333.5 (range, 24 to 1,229), whereas in the off-pump group, the mean number of HITS was 144.7 ± 180.4 (range, 5 to 632). This difference was significant (Z = -2.698; \(p < 0.01\)).

Since all patients were monitored bilaterally, we could compare the HITS detection in the left and right MCAs. For the on-pump group, we counted 179 ± 227 HITS (53%) in the left MCA and 156 ± 151 HITS (47%) in the right MCA. This difference was not significant. In off-pump patients, HITS tended to be more numerous on the right MCA (106 ± 149; 73%) compared to the left MCA (39 ± 62; 27%), although this trend failed to reach significance (\(p = 0.057\)). After square-root transformation of the HITS count to obtain a normal distribution, a repeated-measures, multivariate analyses of variance with eight different surgical maneuvers of on-pump CABG as within-subjects factor was performed and revealed a main effect of surgical maneuver (\(F = 8.128, p < 0.01\)). When the different surgical maneuvers of on-pump CABG were assessed separately with paired \(t\) tests, significantly more HITS were detected immediately after aortic cannulation (Table 2). Significantly fewer HITS were
found after cross-clamping. When cumulating the percentage of HITS associated with the different stages of the operation, 13.9% of the total number of HITS was explained.

**Effect of Surgical Technique on Cognition**

The neuropsychological testing results for the preoperative, early, and late postoperative periods are presented in Table 3. Neuropsychological data were analyzed on a general level. Patients in the on-pump group showed a higher IQ ($p < 0.01$), less tobacco use ($p < 0.05$), a higher number of diseased vessels ($p < 0.05$), and a higher number of grafts ($p < 0.01$). For further analysis of cognitive measures in this group, these variables were included as covariates. MANCOVAs with time of neuropsychological assessment (preoperative vs early postoperative and preoperative vs late postoperative) as within-subjects factor, type of surgery as between-subjects factor, and differences between both groups as covariates revealed no main effect of time, no main effect of surgery, and no interaction effects.

According to the 20% definition, 60% from the total group had a cognitive decline 6 days after surgery, 59.4% in the on-pump group and 61.2% in the off-pump group. After 6 months, 24.2% still had a cognitive decline, 31.8% in the on-pump group and 9.1% in the off-pump group.

For the results according to the CII, we refer to Tables 4, 5. Early neurocognitive impairment was most frequently observed on the blocks tap test and the line bisection test. Six months after surgery, the CII was significantly different in the on-pump group vs the off-pump group ($Z = -2.24$, $p < 0.05$) with less neurocognitive tests that remained impaired in the off-pump group. Neurocognitive impairment was most frequently observed on the line bisection test (on-pump group), trail-making test, and blocks tap test (on-pump and off-pump groups) after 6 months.

**BFV Before and After Surgery**

Percentages change for the preoperative, early postoperative, and late postoperative period for the total group are presented in Table 6. MANCOVAs with time of BFV measurements (preoperative vs early postoperative and preoperative vs late postoperative on absolute rest values, absolute activation

<table>
<thead>
<tr>
<th>Variables</th>
<th>Average HITS Count (% of Total No. of HITS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic cannulation</td>
<td>9.24 (2.9)</td>
</tr>
<tr>
<td>ECC on</td>
<td>5.61 (1.8)</td>
</tr>
<tr>
<td>Cross-clamp on</td>
<td>0.67 (0.2)</td>
</tr>
<tr>
<td>Cross-clamp off</td>
<td>5.7 (1.8)</td>
</tr>
<tr>
<td>Partial clamp on</td>
<td>5.2 (1.6)</td>
</tr>
<tr>
<td>Partial clamp off</td>
<td>4.9 (1.6)</td>
</tr>
<tr>
<td>ECC off</td>
<td>6.6 (2.1)</td>
</tr>
<tr>
<td>Aortic decannulation</td>
<td>6.1 (1.9)</td>
</tr>
</tbody>
</table>

**Table 3—Neuropsychological Test Results in On-Pump Group Compared to Off-Pump Group After 6 Days and 6 Months**

<table>
<thead>
<tr>
<th>Tests/Groups</th>
<th>Preoperative</th>
<th>6 Days</th>
<th>6 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auditory verbal learning test</td>
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</tr>
<tr>
<td>On-pump</td>
<td>44.8 ± 8.5</td>
<td>42.6 ± 9.2</td>
<td>48.5 ± 9.5</td>
</tr>
<tr>
<td>Off-pump</td>
<td>41.72 ± 10.7</td>
<td>43.2 ± 7.9</td>
<td>49.6 ± 9.2</td>
</tr>
<tr>
<td>Block taps test</td>
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</tr>
<tr>
<td>On-pump</td>
<td>37.7 ± 19.9</td>
<td>43.9 ± 22.2</td>
<td>35.8 ± 22.5</td>
</tr>
<tr>
<td>Off-pump</td>
<td>41.8 ± 16.0</td>
<td>53.2 ± 18.9</td>
<td>34.5 ± 19.7</td>
</tr>
<tr>
<td>Trail-making test part B</td>
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<tr>
<td>On-pump</td>
<td>121.3 ± 67.1</td>
<td>134.4 ± 65.3</td>
<td>100.1 ± 38.7</td>
</tr>
<tr>
<td>Off-pump</td>
<td>154.8 ± 96.6</td>
<td>116.9 ± 30.1</td>
<td>123.2 ± 58.6</td>
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<td>Grooved pegboard test</td>
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<tr>
<td>On-pump</td>
<td>183.5 ± 50.2</td>
<td>209.9 ± 58.4</td>
<td>108.2 ± 53.7</td>
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<tr>
<td>Off-pump</td>
<td>197.3 ± 36.4</td>
<td>218.2 ± 52.4</td>
<td>123.2 ± 58.6</td>
</tr>
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<td>Judgment of line orientation</td>
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<tr>
<td>On-pump</td>
<td>23.7 ± 3.8</td>
<td>23.5 ± 4.5</td>
<td>24 ± 4.6</td>
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<tr>
<td>Off-pump</td>
<td>23.7 ± 4.2</td>
<td>23.1 ± 4.4</td>
<td>25.2 ± 3.9</td>
</tr>
<tr>
<td>Line bisection test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On-pump</td>
<td>68.2 ± 24.8</td>
<td>74.5 ± 28.5</td>
<td>65.9 ± 20.3</td>
</tr>
<tr>
<td>Off-pump</td>
<td>69.0 ± 27.7</td>
<td>71.9 ± 20.4</td>
<td>64 ± 34.4</td>
</tr>
<tr>
<td>Controlled oral word association test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On-pump</td>
<td>29.1 ± 8.5</td>
<td>25.6 ± 7.7</td>
<td>33.3 ± 8.9</td>
</tr>
<tr>
<td>Off-pump</td>
<td>22.4 ± 6.1</td>
<td>24.9 ± 8.7</td>
<td>25.9 ± 6.4</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD. For explanation of tests see Appendix 1.
values, and percentage change) as within-subjects factor, type of surgery as between-subjects factor and IQ, tobacco use, number of diseased vessels, and number of grafts as covariates revealed no main effect of time, no main effect of surgery, and no interaction effects.

Relation Between Number of HITS With Cognitive Performance and BFV

We tested whether patients showing significant cognitive decline (as defined by the 20% definition) received significant more HITS during operation than patients showing no significant decline. A t test with total number of HITS (log-transformed) as dependent variable and absence/presence of cognitive decline as independent variable showed no significant differences between both groups.

In addition, we tested if there was a significant association between HITS and CII. A Spearman ρ correlation was performed for total number of HITS and CII. No significant correlations were found.

With regard to the BFV variables, we investigated whether the number of HITS was related to changes in pre-cerebrovascular reactivity to post-cerebrovascular reactivity. We calculated Pearson correlations between the total number of HITS (log-transformed variable) and BFV values (preoperative BFV percentage change minus early postoperative BFV percentage change, and preoperative BFV percentage change minus late postoperative BFV percentage change). No significant correlations were found.

An explorative multivariate regression analysis with log-transformed number of HITS as the dependent variable and mean activation BFV value (sum of five BFV tasks left and right side divided by 10), left ventricle ejection fraction, age, hypertension, and number of diseased vessels as clinically relevant independent variables revealed that mean activation BFV value (β = −0.387, t = −3.037, p < 0.01), number of diseased vessels (β = 0.319, t = 2.469, p < 0.05), and left ventricle ejection fraction (β = −0.27, t = −2.125, p < 0.05) are significant predictors for number of HITS. The model explained 34.2% of the variance. We also found significant negative correlations between the number of HITS as well as between mean BFV activation value and left ventricle ejection fraction. This means that the lower the mean activation BFV value and left ventricle ejection fraction, the higher the embolic load.

**Discussion**

Despite improvements in ECC apparatus and refinements in surgical techniques that have enormously reduced the mortality rate, subtle cognitive dysfunctions in CABG patients remain to be observed. This might be associated with the occurrence of cerebral microemboli generated during CPB. Several investigators have demonstrated that patients who receive less cerebral microemboli during CPB (on-pump surgery) have a lower incidence of postoperative neuropsychological impairment. It is assumed that CABG surgery without CPB will diminish the potential for emboli, particularly those associated with the disruption of atheromatous plaques due to cannulation, cross-clamping, and manipulation of the aorta. Moreover, the generation of gaseous microemboli from the CPB circuit and microparticulate emboli from the pump tubing would likewise be avoided. In essence, the avoidance of CPB during CABG surgery would be expected to reduce cerebral injury by reducing the cerebral embolic load, resulting in improved clinical outcomes.

HITS (as indicator of potential cerebral emboli) were observed in all patients, independently of type of surgery during CABG. This is in accordance with findings from the majority of previous TCD studies. The number of HITS was comparable to that of previous studies although methodologic differences have to be taken into account. For example, we defined HITS associated with a procedure if they occurred within 1 min of the latter, whereas other authors used a 4-min interval. Furthermore, in some studies, only the right MCA was intraoperatively monitored, whereas in our study a bilateral measurement in all patients was used. Nevertheless, together with Stump et al, we believe that the wide variety of HITS detection equipment used by differ-

### Table 4—Results According to CII After 6 Days*

<table>
<thead>
<tr>
<th>CII</th>
<th>Total Group</th>
<th>On-Pump Group</th>
<th>Off-Pump Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>18</td>
<td>15.6</td>
<td>22.2</td>
</tr>
<tr>
<td>1</td>
<td>22</td>
<td>25</td>
<td>16.7</td>
</tr>
<tr>
<td>2</td>
<td>34</td>
<td>37.5</td>
<td>27.8</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>12.5</td>
<td>27.8</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>6.3</td>
<td>5.6</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>3.1</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*Data are presented as %.

### Table 5—Results According to CII After 6 Months*

<table>
<thead>
<tr>
<th>CII</th>
<th>Total Group</th>
<th>On-Pump Group</th>
<th>Off-Pump Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>36.4</td>
<td>22.7</td>
<td>63.6</td>
</tr>
<tr>
<td>1</td>
<td>39.4</td>
<td>45.5</td>
<td>27.3</td>
</tr>
<tr>
<td>2</td>
<td>24.2</td>
<td>31.8</td>
<td>9.1</td>
</tr>
</tbody>
</table>

*Data are presented as %.
to our analyses of this (limited) group of patients, we
tween both surgery groups. Furthermore, according
ical performances on group level were found be-
Although more HITS were detected in the on-pump
of HITS could be related to declines in test scores.
before and after the surgery to determine if number
also performed a battery of neuropsychological tests
Watters et al17 described in a small study with
This supports the findings from previous TCD stud-
ECC is associated with significantly fewer HITS.
off-pump). Our results showed that CABG without
the type of surgery being performed (on-pump vs
5 to 1,229) both between patients and depending on
anastomoses, suggesting potential underlying con-
patients having less coronary artery disease likewise
contrasts to off-pump patients. It seems plausible that
patients having less coronary artery disease likewise
have less cerebrovascular disease and aortic ather-
sclerosis, logically suggesting that they are less pre-
disposed to subtle neurologic insult following CABG
surgery.4 In our patient group, there were indeed
differences between both groups according to a
higher number of diseased vessels and a higher
number of grafts for the on-pump group. Random-
ization of patients groups appears warranted in
further research.
In contrast to other authors1,14 who believe that
the number of ultrasonically detectable HITS deliv-
ered to the brain is the best predictor of neurobe-
havioral deficits, we suggest that the composition
and size of HITS might be more important for the
development of neurocognitive decline than is the
absolute number of HITS. An argument for this is
found in patients undergoing valve operations where,
despite the uniformly larger number of HITS, a

tent study groups makes comparison across studies on
the absolute number of HITS difficult because each
instrument produces quite different estimates of the
number of HITS depending on the physics of the
transducer, the arteries insonated, and the thresh-
olds imposed that define a HITS event.

More important than the absolute number of
HITS is the fact that their frequency differed (range,
5 to 1,229) both between patients and depending on
the type of surgery being performed (on-pump vs
off-pump). Our results showed that CABG without
ECC is associated with significantly fewer HITS. This
supports the findings from previous TCD studies.
Watters et al17 described in a small study with
unilateral measurements fewer emboli in the off-
pump group than in coronary surgery with CPB. This
was confirmed by Bowles et al3 with bilateral mea-
surements in a group of 40 patients (20 patients per
group). By eliminating the need for ECC, off-pump
surgery has theoretical advantages over conventional
on-pump procedures, partly due to the reduction of
the systemic inflammatory response elicited by ECC
during on-pump procedures.18–19 Adverse effects of
ECC can also occur in the CNS. The principal cause
of neuropsychological impairment is thought to be
diffuse microischemia secondary to cerebral micro-
emboli.20 As suggested in our previous study,21 we
also performed a battery of neuropsychological tests
before and after the surgery to determine if number
of HITS could be related to declines in test scores.
Although more HITS were detected in the on-pump
group, no significant differences on neuropsychologi-
cal performances on group level were found be-
tween both surgery groups. Furthermore, according
to our analyses of this (limited) group of patients, we
did not find a relation between degree of postoper-
ative neuropsychological impairment and number of
HITS. On an individual level, however, fewer neu-ocognitive tests remained impaired in the off-pump

While off-pump surgery continues to be explored
as an alternative to conventional CABG surgery in
many cardiac units worldwide, this revascularization
strategy continues to generate controversy. Several
studies17,22–23 identify no clear superiority of either
the on-pump or off-pump procedures. Instead, they
clearly suggest that patients undergoing these two
techniques are not clinically similar.24 CPB patients
tend to have higher mean numbers of coronary
anastomoses, suggesting potential underlying con-
trasts to off-pump patients. It seems plausible that
patients having less coronary artery disease likewise
have less cerebrovascular disease and aortic athero-
sclerosis, logically suggesting that they are less pre-
disposed to subtle neurologic insult following CABG
surgery.4 In our patient group, there were indeed
differences between both groups according to a
higher number of diseased vessels and a higher
number of grafts for the on-pump group. Random-
ization of patients groups appears warranted in
further research.

<table>
<thead>
<tr>
<th>Test/Side</th>
<th>Preoperative (n = 66)</th>
<th>Early Postoperative (n = 63)</th>
<th>Late Postoperative (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NLV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>6.15 ± 9.41</td>
<td>6.41 ± 6.75</td>
<td>6.36 ± 9.45</td>
</tr>
<tr>
<td>Right</td>
<td>4.21 ± 8.47</td>
<td>4.73 ± 7.07</td>
<td>5.47 ± 7.25</td>
</tr>
<tr>
<td>Visual searching</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>10.38 ± 7.81</td>
<td>8.56 ± 4.45</td>
<td>8.93 ± 7.15</td>
</tr>
<tr>
<td>Right</td>
<td>11.42 ± 8.46</td>
<td>8.93 ± 5.29</td>
<td>10.78 ± 8.15</td>
</tr>
<tr>
<td>Syntactic sentence construction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>9.62 ± 8.21</td>
<td>8.55 ± 4.49</td>
<td>8.17 ± 8.5</td>
</tr>
<tr>
<td>Right</td>
<td>7.17 ± 7.89</td>
<td>6.52 ± 5.69</td>
<td>6.89 ± 7.35</td>
</tr>
<tr>
<td>Three-dimensional puzzle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>14.22 ± 8.70</td>
<td>11.81 ± 6.11</td>
<td>15.00 ± 7.43</td>
</tr>
<tr>
<td>Right</td>
<td>17.07 ± 8.43</td>
<td>13.70 ± 7.08</td>
<td>16.85 ± 7.90</td>
</tr>
<tr>
<td>Controlled oral word association test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>7.36 ± 10.08</td>
<td>4.79 ± 6.36</td>
<td>7.91 ± 10.75</td>
</tr>
<tr>
<td>Right</td>
<td>3.45 ± 9.16</td>
<td>4.15 ± 11.87</td>
<td>5.10 ± 7.22</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD. For explanation of tests see Appendix 2.
higher incidence of cognitive decline is absent.\textsuperscript{12} Emboli can be particulate, air, or gaseous in nature. Obviously, large particulate emboli and massive air embolism will cause more injury than minor embolic events. Particulate emboli can cause stationary obstruction of cerebral vessels, whereas gas emboli have been reported to pass arterioles and capillaries and may pose less risk to the patient than solid atheroemboli dislodged during aortic manipulation. Furthermore, smaller particulate emboli, still large enough to occlude arterioles and capillaries, may not be detected and the total number of emboli would certainly be many times greater than our count. Until lately, it was impossible for TCD to determine the nature of the HITS recorded. A study\textsuperscript{24} was published that shows that it is now possible to differentiate between solid and gaseous cerebral HITS with multifrequency TCD. Although specific CPB components may be associated with increased risk of brain injury, it must be noted that non-CPB patients are not immune to neuropsychological deficits. It might be that other factors independent of CPB impart a greater independent risk than CPB alone such as hospitalization, sleep deprivation, and potential adverse effects of anesthesia.\textsuperscript{23}

We were also interested when and where cerebral HITS occurred. Previous research has demonstrated the occurrence of cerebral HITS in association with specific “surgical” events, \textit{i.e.}, aortic cannulation and decannulation, ECC start and end, cross-clamp application and removal, partial-occlusion clamp release, start of cardiac ejection after cross-clamp removal, and perfusionist interventions.\textsuperscript{2,14–16,20,25,26} In our study, the aortic cannulation was the most important HITS-prone surgical maneuver. Although manipulation does account for some of the emboli during on-pump surgery and especially during aortic manipulation, the vast majority (86.1\%) occurred when no specific surgical manipulation was identified. This percentage is comparable to that of the study of Bowles et al.\textsuperscript{3} In the study of Stump et al.,\textsuperscript{27} more than one third of HITS were not associated with any specific period or surgical manipulation, and occurred when the observer could not associate any act of the surgeon, perfusionist, or anesthesiologist as having a temporal relationship with the embolic signal. These data suggest that there are two separate major sources of emboli: (1) those secondary to surgical and manual manipulation of the heart and arteries and, (2) emboli from a nonobvious source.

The question remains where HITS occur in the brain? In our study, we found a tendency in the occurrence of HITS in the right MCA but only in off-pump surgery. This is in contrast with what would be anatomically expected. It is the left hemisphere that should have an increased susceptibility for receiving cardiogenic emboli caused by the asymmetrical anatomy in the branching patterns of the extracranial arteries on the aortic arch. Emboli coming from the heart have to pass through the brachiocephalic trunk that only exists on the right side. This divides the chance of embolization between the right subclavian artery and the right common artery, whereas the left common carotid artery of most individuals immediately originates from the aortic arch. Furthermore, the left internal carotid artery almost vertically originates from the arch and is therefore situated in the direct flow direction caused by every systolic contraction. Other authors\textsuperscript{28–30} reported an asymmetric distribution side difference for emboli, with a higher incidence of HITS in the left MCA.

On an individual test level, 60\% of the patients showed cognitive decline 6 days after surgery. Six months after surgery, most patients returned to baseline level. We found that cognitive decline remained in 24.2\% of the patients. In particular, domains of nonverbal immediate memory and attention, visual attention, visual search, and mental flexibility were impaired. This is in accordance with other studies. In the study of Borger et al.,\textsuperscript{31} worse performance on tests of learning and memory and attention and concentration were seen. We agree with McLean et al.\textsuperscript{32} and Shaw et al.\textsuperscript{33} that the cognitive domains of learning, memory, and concentration are sensitive to the deleterious effects of CPB, but based on this study we add that the effect was also seen in patients without CPB.

Studies have been performed to evaluate the effect on CBF before and after the surgery. Abildstrom et al.\textsuperscript{34} found a significant, uniformly distributed decrease in CBF after coronary surgery that was not correlated to postoperative cognitive dysfunction. Smith and associates\textsuperscript{35} found a decrease in CBF in some patients 8 days after surgery. We studied the BFV, which is related to the CBF. We found no BFV differences between the on-pump and off-pump groups and no differences over the different time intervals. Interestingly, preoperative BFV during activation appeared to be a predictor, together with number of diseased vessels and left ventricle ejection fraction for the number of HITS. Since our patient group remains rather small, the relation between BFV and HITS load justifies further investigation before preoperative BFV may be employed as a predictor for HITS load during the operation. As far as we know, this is the first study that examines the association between the number of HITS and the BFV.

Our conclusions may be limited by several factors. First, we believe that the clinical relevance of cog-
Cognitive dysfunction is still uncertain. The real clinical impact of cognitive dysfunction, especially regarding quality of life and rehabilitation, needs to be confirmed by further investigations. Second, the study was limited by the fact that we investigated nonrandomized patient groups, because the decision regarding the surgical strategy (on-pump or off-pump) was left to the individual surgeon. However, including the patient for the neuropsychological test battery and BFV tasks was done without knowing which technique was going to be used. Third, we have to bear in mind that our patient group was limited to 50 patients. Research that includes more patients would undoubtedly give more representative conclusions.

To conclude, cerebral dysfunction after CABG operations remains an important possible complication of cardiac surgery. We used TCD to detect and quantify the number of microemboli in patients undergoing CABG. The technique may also alert the surgical team when HITs enter the cerebral circulation during surgery, thus allowing preventive measures to be taken. No relation was found between number of HITs and degree of postoperative neuropsychological impairment. We should bear in mind that the occurrence of neurologic complications after cardiac surgery cannot be attributed to a single causative element in most cases. As with most disease processes, the cause is multifactorial.

In the present study, no clear advantage in terms of neuropsychological test performance was demonstrated by the on-pump group when compared to the off-pump group, although less neurocognitive tests remained impaired in the off-pump group after 6 months when assessing the individual level. This supports the assertion that postsurgical neuropsychological deficits may not be so intimately related to the CPB circuit as suspected. Preoperative BFV, which can also be measured with TCD, should be further explored as one of the possible predictors for HITs load. Future research should focus on the relative importance of particulate matter and gaseous material.

**APPENDIX 1: NEUROPSYCHOLOGICAL TESTS**

1. The Rey auditory verbal learning test assesses verbal memory. The measure retained is the total number of words immediately recalled over the first five trials.
2. The trail-making test (part B) assesses speed for visual search, attention, and mental flexibility. The time to completion is the measure obtained.
3. The grooved pegboard test measures finger and hand dexterity. The sum of the times to completion of the left and right placement of all pegs is the measure taken.
4. The block taps test assesses nonverbal immediate memory and attention. The number of errors is the measure obtained.
5. The line bisection test assesses unilateral visual inattention. Total deviation from the true center is the measure obtained.
6. The controlled oral word association test (orthographic categories) assesses word fluency. The total number of words (with four given letters) is the measure obtained.
7. Judgment of line orientation examines the ability to estimate angular relationships between line segments. The measure obtained is the correct number of answers.

**APPENDIX 2: COGNITIVELY INDUCED CEREBROVASCULAR REACTIVITY TASKS**

1. Reading. Subjects were instructed to read a list of 50 words aloud. The list was a Dutch version of the National Adult Reading Test (NLV). The end score gives an estimation of the premorbid verbal IQ.
2. Visual searching. This task, which is part of the FEPSY computer program for neurocognitive assessment, consisted of finding a grid pattern (out of 24 similar designs) that matches the one in the center of the screen. Subjects had to point the identical grid with both index fingers simultaneously to avoid unilateral activation of the motor cortex. The quality of performance was expressed as the percentage of the correct answers.
3. Syntactic sentence construction. The words of a sentence were shown in a mixed-up order. Subjects were asked to whisper a grammatically correct sentence using as many words as possible. Whispering minimizes the acoustic interference on the TCD signal by preventing voice artifacts caused by the conduction of the normal voice spectrum via the cranial bones to the temporally placed probes. For the quality of the task performance, the absolute number of words was taken into account.
4. Three-dimensional puzzle. A commercially available three-dimensional puzzle was used (Eureka bvba; Mechelen, Belgium). Subjects were allowed 2 min to try to free the ring from the rope.
5. Word fluency (controlled oral word association test). The subjects were required to whisper as many words as possible (excluding proper names) beginning with a designated letter. For the quality of the task performance, the absolute number of words was taken into account.

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