Cerebral Emboli Detected by Transcranial Doppler During Cardiopulmonary Bypass Are Not Correlated With Postoperative Cognitive Deficits

Rosendo A. Rodriguez, MD, PhD; Fraser D. Rubens, MD, MSc; Denise Wozny, BA; Howard J. Nathan, MD

Background and Purpose—High-intensity transient signals (HITS) are the transcranial Doppler representation of both air and solid cerebral emboli. We studied the frequency of HITS associated with different surgical maneuvers during cardiopulmonary bypass for coronary artery bypass graft surgery and their association with postoperative cognitive dysfunction (POCD).

Methods—We combined 356 patients undergoing coronary artery bypass graft from 2 clinical trials who had both neuropsychological testing (before, 1 week and 3 months after surgery) and transcranial Doppler during cardiopulmonary bypass. HITS were grouped into periods that included: cannulation, cardiopulmonary bypass onset, aortic crossclamp-on, aortic crossclamp-off, side clamp-on, side clamp-off, and decannulation. POCD was defined by a decreased combined Z-score of at least 2.0 or reduction in Z-scores of at least 2.0 in 20% of the individual tests.

Results—Incidence of POCD was 47.3% and 6.3% at 1 week and 3 months after surgery. There was no association between cardiopulmonary bypass counts of HITS and POCD at 1 week ($P=0.617$) and 3 months ($P=0.110$). No differences in HITS counts were identified at any of the surgical periods between patients with and without POCD. Factors affecting HITS counts were surgical period ($P=0.0001$), blood flow velocity ($P=0.012$), cardiopulmonary bypass duration ($P=0.040$), and clinical study ($P=0.048$).

Conclusions—Although cerebral microemboli have been implicated in the pathogenesis of POCD, in this study that included low-risk patients undergoing coronary artery bypass surgery, there was no demonstrable correlation between the counts of HITS and POCD. (Stroke. 2010;41:2229-2235.)

Key Words: cardiac surgery ■ cardiopulmonary bypass ■ cognitive impairment ■ embolism ■ outcomes ■ TCD ■ transcranial Doppler ■ ultrasound

It is commonly believed that cerebral emboli during cardiopulmonary bypass (CPB) are associated with postoperative cognitive dysfunction (POCD).1,2 This hypothesis has been supported by findings of microscopic clots in the aortic cannula after decannulation in patients undergoing CPB3 and the presence of fat emboli, as evidenced by small arteriolar dilatations, in the brains of patients who died after CPB.4 Transcranial Doppler (TCD) has become 1 of the principal tools to document cerebral emboli during surgery in clinical studies assessing strategies to improve neurological outcome after CPB.5 This technology detects cerebral emboli by the ultrasonic characteristics of the embolus–blood interface in the form of high-intensity transient signals (HITS).5,6 Although a large number of HITS occur during CPB, there are no large studies confirming that these embolic signals are correlated with POCD.

During CPB, both air and solid emboli (ie, fat, clots, platelet aggregates, atherosclerotic plaque material) may be delivered to the brain.2–4 Solid emboli in particular are more likely associated with adverse neurological events such as stroke2 and perhaps cognitive deficits.2,4,6 Some studies2,3,5,6 have suggested that during CPB, solid emboli are more frequently released during certain surgical maneuvers. If solid emboli represented by HITS are in fact associated with POCD, then this association would be best detected during such maneuvers. To explore this association, we studied the time course and distribution of HITS occurring during different surgical maneuvers during CPB and their association with POCD. We had the opportunity to study a large number of patients by combining data from 2 recently completed randomized clinical trials. It was anticipated that with such a large prospective database of HITS, we would be able to confidently assess the correlation of HITS with POCD for the entire duration of CPB and also evaluate this correlation during periods of CPB when solid emboli are most likely.
single period of aortic crossclamping (single-clamp technique).

Constructing the distal anastomoses during a single period of aortic crossclamping and the proximal anastomoses through a single period of aortic crossclamping and the proximal anastomoses during a single period of aortic crossclamping and the proximal anastomoses during a single period of aortic crossclamping.

CPB was accomplished either using the traditional technique of straight) or long-tip aortic cannula and a 2-stage right atrial cannula.

Our CPB equipment and management protocols have been described elsewhere.9,10 In the first study (Temp), patients were randomly assigned to maintain hypothermia (34°C) or normothermia (37°C) throughout blood, which had undergone centrifugal washing and lipid filtration.

The change scores for each test in the patient group were corrected for practice effect by subtracting the change scores determined in a 5-point scoring scale. Only patients with high-quality bilateral recordings (scores 4 and 5) were included in the final analysis.

The presence of POCD was determined using the method of the International Study of Postoperative Cognitive Dysfunction group.14 The change scores for each test in the patient group were corrected for practice effect by subtracting the change scores determined in a nonsurgical control group including patients with coronary artery disease.9 A combined Z-score was calculated by summing the Z-scores of each neuropsychological tests in the patient group and dividing by the SD of the sum of the Z-scores in the control group.14 Patients were considered to have had a cognitive deficit14 if (1) there was a decrease in the combined Z-score of at least 2.0; or (2) a reduction of ≥2.0 in the Z-scores of 20% of the individual neuropsychological tests. To provide an overall summary measure of cognitive performance, the individual psychometric test scores were reduced to 4 cognitive domains using factor analysis with orthogonal rotation as per Newman et al.15 The 4 domain scores were then summed to calculate a composite score.

**TCD Analysis**

An ultrasonographer (R.A.R.) who was unaware of the results of the cognitive assessment and patient treatment allocation reviewed the TCD recordings and classified ultrasonic signals into true or equivocal HITS, Doppler speckles, and artifacts according to pre-established criteria.13 Only true HITS were considered in the final counts of HITS. The quality of the TCD recording was assessed using a 5-point scoring scale. Only patients with high-quality bilateral recordings (scores 4 and 5) were included in the final analysis. To determine differences associated with the technique of aortic clamping, we compared the sum of HITS from the time of the application of the aortic crossclamp to the end of CPB between single and dual-clamp techniques. The effects of perfusionist’s interventions (ie, drug infusion, blood sampling)25 on the HITS counts during the period of Aortic X-clamp-on were documented by the sum of all counts of HITS that occurred within the next minute after any perfusionist’s intervention. Because perfusionist’s interventions represent sources of air for cerebral emboli,22 HITS associated with these interventions were excluded before determining the relationship between cerebral blood flow velocity and HITS counts.

**Definition of POCD**

Materials and Methods

Both clinical studies were approved by our Institutional Ethics Review Board. Patients undergoing elective coronary artery bypass graft (CABG) surgery who required CPB were asked for informed consent before their enrollment. The inclusion and exclusion criteria and their respective screening methods have been reported elsewhere.9,10 In the first study (Temp), patients were randomly assigned to maintain hypothermia (34°C) or normothermia (37°C) throughout CPB.9 In the second study (Cardio), patients were randomized to receive either unprocessed cardiotomy suction blood or cardiotomy blood, which had undergone centrifugal washing and lipid filtration.10 The primary outcome of both studies was the incidence of POCD.

Surgical Technique and CPB

Our CPB equipment and management protocols have been described elsewhere.9,10 In brief, CPB was achieved through a short (curved or straight) or long-tip aortic cannula and a 2-stage right atrial cannula. CABG was accomplished either using the traditional technique of constructing the distal anastomoses during a single period of aortic crossclamping and the proximal anastomoses through a single period of partial occlusion of the ascending aorta (dual-clamp technique); or both proximal and distal anastomoses were constructed using a single period of aortic crossclamping (single-clamp technique).

**Neuropsychological Testing**

Each patient underwent a standard battery of neurobehavioral tests, including those recommended by a consensus conference (Table 1).11 Patients were tested before surgery (baseline), before hospital discharge (1 week), and 3 months after the surgery.

**TCD Measurements**

TCD recordings were obtained from before aortic cannulation to immediately after aortic decannulation. Our TCD equipment and reviewing procedures have been previously described.12,13 Only embolic signals identified in the middle cerebral arteries with relative intensities >8 dB (intensity threshold) were accepted. Bilateral middle cerebral artery counts of HITS were grouped into periods that included the following surgical maneuvers: cannulation; defined from the time of aortic cannulation to before CPB initiation, CPB onset; from CPB initiation to immediately before the application of the aortic crossclamp, aortic X-clamp-on; from aortic crossclamping to immediately before declamping, aortic X-clamp-off; from aortic declamping to before aortic side-clamping, side clamp-on; from the application of the aortic side clamp to immediately before its release, side clamp-off; from aortic side clamp release to the end of CPB, and decannulation; from the time of CPB termination to immediately after aortic decannulation. For the single aortic crossclamp technique, the interval between the release of the aortic crossclamp and the end of CPB was considered as the period of Aortic X-clamp-off.

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**Statistical Analysis**

Normally distributed variables are reported as means and their SDs. Because the counts of HITS were nonnormally distributed, they are reported using median values (25th and 75th percentiles). Continuous variables were compared by unpaired t tests if normally distributed or Mann-Whitney tests for nonnormally distributed variables. Proportions were compared by chi² or Fisher exact tests. Logistic regression analysis was used to measure the relationship between total CPB count of HITS and incidence of POCD. The model was adjusted for age, duration of CPB, and study and treatment group. The interaction terms of the counts of HITS by age and treatment group were also tested. An analysis of variance for repeated measures evaluated the effects of different CPB periods on the counts of HITS including the study and the aortic...
Table 3. Median Count of HITS (25th, 75th Percentiles) in Patients With and Without POCD*

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>No POCD</th>
<th>P</th>
<th>With POCD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total count</td>
<td>169 (94, 290)</td>
<td>0.691</td>
<td>159 (90, 280)</td>
<td>0.112</td>
</tr>
<tr>
<td>Total CPB</td>
<td>150 (84, 278)</td>
<td>0.076</td>
<td>81 (56, 201)</td>
<td>0.009</td>
</tr>
<tr>
<td>Decannulation</td>
<td>1 (0, 4)</td>
<td>0.256</td>
<td>2 (1, 7)</td>
<td>0.848</td>
</tr>
<tr>
<td>Side clamp-off</td>
<td>31 (12, 61)</td>
<td>0.716</td>
<td>26 (4, 57)</td>
<td>0.027</td>
</tr>
<tr>
<td>Aortic X-clamp-off</td>
<td>12 (2, 41)</td>
<td>0.260</td>
<td>5 (1, 14)</td>
<td>0.060</td>
</tr>
<tr>
<td>Side clamp-on</td>
<td>15 (5, 43)</td>
<td>0.746</td>
<td>10 (4, 55)</td>
<td>0.048</td>
</tr>
<tr>
<td>Aortic X-clamp-on</td>
<td>12 (2, 35)</td>
<td>0.260</td>
<td>5 (1, 14)</td>
<td>0.060</td>
</tr>
<tr>
<td>CPB onset</td>
<td>15 (5, 33)</td>
<td>0.728</td>
<td>12 (3, 22)</td>
<td>0.048</td>
</tr>
<tr>
<td>Cannulation</td>
<td>6 (2, 14)</td>
<td>0.336</td>
<td>11 (4, 17)</td>
<td>0.027</td>
</tr>
</tbody>
</table>

Table 2. Baseline and Intraoperative Characteristics for Patients From Both Study Trials

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Temp (n=356)</th>
<th>P</th>
<th>Cardio (n=247)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>325 (91)</td>
<td>0.458</td>
<td>247 (93)</td>
<td>0.009</td>
</tr>
<tr>
<td>Age, years</td>
<td>63 ± 9</td>
<td>0.694</td>
<td>65 ± 7</td>
<td>0.009</td>
</tr>
<tr>
<td>Hematocrit before CPB</td>
<td>0.36 ± 0.04</td>
<td>0.701</td>
<td>0.36 ± 0.04</td>
<td>0.009</td>
</tr>
<tr>
<td>Hematocrit after CPB</td>
<td>0.26 ± 0.04</td>
<td>0.701</td>
<td>0.26 ± 0.04</td>
<td>0.009</td>
</tr>
<tr>
<td>Single cross clamp technique</td>
<td>103 (29)</td>
<td>0.701</td>
<td>101 (28)</td>
<td>0.009</td>
</tr>
<tr>
<td>Retrograde cardioplegia</td>
<td>22 (6)</td>
<td>0.701</td>
<td>22 (6)</td>
<td>0.009</td>
</tr>
<tr>
<td>Long tip aortic cannula</td>
<td>70 (20)</td>
<td>0.701</td>
<td>70 (20)</td>
<td>0.009</td>
</tr>
<tr>
<td>Sternal bone wax not used</td>
<td>137 (39)</td>
<td>0.701</td>
<td>137 (39)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Results

Table 2 summarizes demographics and intraoperative characteristics of the patients. Of the 514 patients who participated in the studies (Temp: 267; Cardio: 247), 356 patients (Temp: 188; Cardio: 168) showed good quality bilateral TCD recordings. Of these, 353 (99.1%) completed the 1-week and (Temp: 188; Cardio: 168) showed good quality bilateral TCD recordings. Of these, 353 (99.1%) completed the 1-week and 322 (94.1%) the 3-month postoperative cognitive testing. Of these, 353 (99.1%) completed the 1-week and 356 patients (Temp: 267; Cardio: 247), 356 patients participated in the studies (Temp: 267; Cardio: 247), 356 patients.

POCD, HITS Counts, and Surgery

Table 3 summarizes the counts of HITS by surgical period in patients with and without POCD and Table 4 illustrates the linear regression analysis between the change scores corrected for practice on each of the 15 neuropsychological tests and the CPB count of HITS adjusted by age and duration of CPB. There was no association between the CPB counts of HITS and the incidence of POCD (1 week: P=0.617; 3 months: P=0.110) or the composite cognitive score (1 week: P=0.458; 3 months: P=0.694). Additionally, there were no differences in the number of HITS between patients with and without POCD at 1 week and 3 months during any of the surgical periods or the entire CPB period. Moreover, no association was found between the corrected change scores from any neuropsychological test and the CPB counts of HITS at 1 week or 3 months. Also, no significant differences in the CPB counts of HITS (P=0.277) were observed in older patients (≥75 years) with and without POCD.

During the first week, 54.5% of patients who underwent surgery with the single-clamp technique were classified with POCD compared with 44.4% of patients with the dual clamp technique as between-subject factors. Associations between continuous variables were examined using correlation and linear regression analyses. Four patients whose CPB counts of HITS were greater than 3 SDs from the group mean were identified as outliers and their values removed before regression analysis. All tests used P<0.05 as the critical value of statistical significance. Analyses were performed using SPSS (Version 16.0).

POCD was identified in 47.3% of the patients before discharge, but this incidence decreased to 6.3% at 3 months after surgery. The incidence was similar in patients who were excluded from the analysis either due to poor-quality TCD recordings or absent TCD monitoring (1 week: 49.3%, P=0.701; 3 months: 5.8%, P=0.848). The rates of POCD were similar between the 2 study groups at 1 week (Cardio: 49.7%; Temp: 45.2%; P=0.400), but it was slightly higher in patients in the Cardio group at 3 months (Cardio: 9.9%; Temp: 2.9%; P=0.009). During the first postoperative week, POCD were more frequent in patients whose age at the time of surgery was ≥75 years (65.9%) compared with those younger (P=0.008).

Table 3. Median Count of HITS (25th, 75th Percentiles) in Patients With and Without POCD*

<table>
<thead>
<tr>
<th>HITS Counts 1-Week Testing</th>
<th>No POCD (n=186)</th>
<th>P</th>
<th>With POCD (n=167)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannulation</td>
<td>6 (2, 13)</td>
<td>0.779</td>
<td>6 (2, 15)</td>
<td>0.779</td>
</tr>
<tr>
<td>CPB onset</td>
<td>17 (5, 34)</td>
<td>0.994</td>
<td>15 (6, 33)</td>
<td>0.779</td>
</tr>
<tr>
<td>Aortic X-clamp-on</td>
<td>45 (20, 100)</td>
<td>0.544</td>
<td>42 (18, 92)</td>
<td>0.779</td>
</tr>
<tr>
<td>Aortic X-clamp-off</td>
<td>11 (2, 31)</td>
<td>0.352</td>
<td>11 (2, 41)</td>
<td>0.779</td>
</tr>
<tr>
<td>Side clamp-on</td>
<td>16 (6, 54)</td>
<td>0.258</td>
<td>13 (4, 36)</td>
<td>0.779</td>
</tr>
<tr>
<td>Side clamp-off</td>
<td>29 (13, 60)</td>
<td>0.531</td>
<td>39 (13, 61)</td>
<td>0.779</td>
</tr>
<tr>
<td>Decannulation</td>
<td>0 (0, 4)</td>
<td>0.256</td>
<td>2 (0, 5)</td>
<td>0.256</td>
</tr>
<tr>
<td>Total CPB</td>
<td>151 (89, 275)</td>
<td>0.583</td>
<td>144 (79, 266)</td>
<td>0.779</td>
</tr>
</tbody>
</table>

*Patients were considered to have had a cognitive deficit if they met at least 1 of these 2 criteria: (1) decrease in the combined Z-score of at least 2.0; or (2) reduction in the Z-scores of at least 2.0 in 20% of the individual neuropsychological tests.
Table 4. Linear Regression Analysis of the Corrected (for Practice Effect) Change Scores Against CPB Total Count of HITS With Age and CPB Duration as Covariates

<table>
<thead>
<tr>
<th></th>
<th>1 Week</th>
<th>3 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted $R^2$</td>
<td>$\beta$ Standardized</td>
</tr>
<tr>
<td>RAVTL total</td>
<td>−0.001</td>
<td>0.086</td>
</tr>
<tr>
<td>(T1-T5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAVTL Trial 6</td>
<td>0.0001</td>
<td>0.046</td>
</tr>
<tr>
<td>RAVTL Trial 7†</td>
<td>−0.004</td>
<td>0.055</td>
</tr>
<tr>
<td>Trails A</td>
<td>0.019</td>
<td>0.048</td>
</tr>
<tr>
<td>Trails B</td>
<td>0.006</td>
<td>0.082</td>
</tr>
<tr>
<td>Pegtime† d</td>
<td>0.037</td>
<td>0.031</td>
</tr>
<tr>
<td>Pegtime† nd</td>
<td>0.019</td>
<td>−0.021</td>
</tr>
<tr>
<td>SDMT§</td>
<td>0.001</td>
<td>−0.083</td>
</tr>
<tr>
<td>Digit span</td>
<td>−0.006</td>
<td>0.032</td>
</tr>
<tr>
<td>backward</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit span</td>
<td>0.005</td>
<td>−0.030</td>
</tr>
<tr>
<td>forward</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMS</td>
<td>Mental control*</td>
<td>−0.003</td>
</tr>
<tr>
<td>Letter Fluency</td>
<td>−0.003</td>
<td>0.001</td>
</tr>
<tr>
<td>(FAS) test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WORDTOT¶</td>
<td>−0.003</td>
<td>0.040</td>
</tr>
<tr>
<td>Finger Tapping, d*</td>
<td>0.018</td>
<td>−0.051</td>
</tr>
<tr>
<td>Finger Tapping nd*</td>
<td>0.027</td>
<td>−0.084</td>
</tr>
</tbody>
</table>

*Neuropsychological tests done only in the temp study (n=188); all other tests n=356.
†Combined patients from both Temp and Cardio studies.
‡Grooved pegboard.
§Symbol Digit Modalities Test.
¶Category fluency (animal).
RAVTL indicates Rey Auditory Verbal Learning Test; d, dominant hand; nd, nondominant hand.

(P=0.089). At 3 months, the prevalence of POCD was 7.2% and 6.0%, respectively (P=0.668). Furthermore, the use of a long-tip aortic cannula did not decrease the proportion of patients with POCD compared with those with the short-tip aortic cannula at 1 week (48.9% versus 40.6%; $P=0.212$) or 3 months (6.5% versus 6.2%; $P=0.95$) after surgery.

Factors Affecting HITS Counts
Table 5 summarizes the counts of HITS stratified by surgical period. The median count of HITS during CPB for all patients was 147 (81, 265) This represented 90.3% (±11%) of the total counts of HITS (160 HITS [91, 277]). Factors contributing to differences in the counts of HITS during CPB as identified by the analysis of variance included the surgical period ($P<0.0001$), CPB duration ($P=0.040$), and study group ($P=0.048$). The time from aortic crossclamping to immediately before declamping (Aortic X-clamp-on) and the period between the release of the aortic side clamp and the end of CPB (side clamp-off) were the 2 periods associated with the highest counts of HITS per period. Taking into account the duration of each surgical period, the median count of embolic signals was 4 HITS per minute (2, 9) during CPB onset, 1 HITS per minute (0, 2) when the Aortic X-clamp was on, 3 HITS per minute (1, 8) during Aortic X-clamp-off, 1 HITS per minute (0, 3) at the time of side clamp-on, and 4 HITS per minute (1, 9) for the period between the release of the side clamp and the end of CPB (side clamp-off; $P<0.001$). Patients who participated in the Cardio trial tended to have lower HITS counts from onset to

Table 5. Prevalence and Distribution of HITS Counts According to Surgical Periods and Their Durations*

<table>
<thead>
<tr>
<th>Surgical Period</th>
<th>Duration, Minutes</th>
<th>HITS Counts Combined Patients† (n=356)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannulation</td>
<td>9±5</td>
<td>6 (2, 14)</td>
</tr>
<tr>
<td>Cardiopulmonary bypass onset</td>
<td>5±4</td>
<td>16 (5, 33)</td>
</tr>
<tr>
<td>Aortic cross clamp on</td>
<td>52±19</td>
<td>42 (20, 57)</td>
</tr>
<tr>
<td>Aortic cross clamp off</td>
<td>6±7</td>
<td>11 (2, 35)</td>
</tr>
<tr>
<td>Side clamp on</td>
<td>17±7</td>
<td>14 (5, 42)</td>
</tr>
<tr>
<td>Side clamp off</td>
<td>10±7</td>
<td>31 (12, 60)</td>
</tr>
<tr>
<td>Decannulation</td>
<td>16±7</td>
<td>1 (0, 4)</td>
</tr>
<tr>
<td>CPB count</td>
<td>82±23</td>
<td>147 (81, 265)</td>
</tr>
<tr>
<td>Total count</td>
<td>106±27</td>
<td>160 (91, 277)</td>
</tr>
</tbody>
</table>

*HITS counts are expressed as median values (25th, 75th percentiles) and the durations of each surgical period as means±SD.
†Combined patients from both Temp and Cardio studies.
end of CPB and this difference was particularly noticeable at initiation of CPB \( (P<0.001) \). In the univariate analysis, longer durations of CPB were associated with higher CPB counts of HITS \( (R^2=0.02; P=0.009) \).

After excluding HITS from perfusionist interventions in patients from the Temp study, higher counts of HITS during the period of Aortic X-clamp-on were significantly correlated with higher mean cerebral blood flow velocity \( (37°C: 46\pm12\text{ cm/s versus } 34°C: 36\pm8\text{ cm/s}; P<0.001) \). Patients with a 3°C reduction \( (37°C\) to \( 34°C\) \) in the nasopharyngeal temperature during CPB had an average 28% \( (\pm5\%\) decline in the mean cerebral blood flow velocity \( (37°C: 46\pm12\text{ cm/s versus } 34°C: 36\pm8\text{ cm/s}; P<0.001) \). The use of either clamping technique did not significantly affect the CPB counts of HITS \( (P=0.308) \), the total counts \( (P=0.415) \), or the number of HITS detected between the application of the aortic crossclamp and end of CPB \( (P=0.685) \). Additionally, no differences were found in the HITS counts due to the use of a short- or long-tip aortic cannula at any of the surgical periods \( (P=0.516) \) or the entire CPB \( (P=0.289) \).

**Discussion**

During CPB, solid and air emboli are released into the arterial circulation, but solid emboli are expected to be more likely to cause adverse postoperative neurological events, including POCD.\(^1,2\) Previous observations indicate that solid emboli are more likely released at certain surgical maneuvers during CPB.\(^2,3,5\) We sought to study the time course and distribution of HITS occurring at different surgical periods during CPB for CABG surgery and their association with POCD. Our findings in a large number of patients indicate that there is no correlation between the counts of HITS during either the entire CPB or at any of the surgical periods during CPB and the incidence of POCD after CABG surgery.

The association between HITS counts and POCD has been controversial.\(^5,8,9,13\) Some studies have found that patients undergoing CABG with higher HITS counts were more likely to experience cognitive deficits\(^1,2,5,6\) or higher rates of frontal lobe dysfunction,\(^16\) but others have found that there is no correlation between HITS counts and neurological symptoms or cognitive deficits.\(^6,8,17\) Several methodological issues may account for the variability among these studies, including small sample sizes,\(^1,6\) differences in intensity thresholds used to detect HITS,\(^13\) artery location (carotid versus middle cerebral artery),\(^1,8,12\) unilateral or bilateral recordings,\(^2,8,12\) type of ultrasound device,\(^15,18\) quality of TCD recordings,\(^18\) inconsistency of signal reviewing techniques (automatic versus manual),\(^13,18\) and the effects of several confounding variables such as the duration of CPB and core body temperature.\(^2\) We sought to overcome these limitations by studying a large number of low-risk patients undergoing

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**Table 6. Clinical Studies Reporting CPB Counts of HITS During CABG Surgery and Their Relationship With POCD**

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Median (Range)/Mean±SD HITS Counts*</th>
<th>Period of Highest Occurrence of HITS During CPB</th>
<th>Definition of POCD</th>
<th>HITS Counts and POCD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu et al(^20)</td>
<td>208</td>
<td>430 (155–2088)</td>
<td>Side clamp-off</td>
<td>Decreased combined Z-scores &gt;2.0 or Z-scores &gt;2.0 in ≥2 individual tests</td>
<td>No correlation. Study of on- and off-pump CABG</td>
</tr>
<tr>
<td>Motallebzadeh et al(^24)</td>
<td>104</td>
<td>1695 (750–2475)</td>
<td>Side clamp-off</td>
<td>Composite score differences at 6 weeks and 6 months compared with preoperative baseline</td>
<td>No correlation. Study of on- and off-pump CABG</td>
</tr>
<tr>
<td>Stroobant et al(^25)</td>
<td>50</td>
<td>335±333 (24–1229)</td>
<td>Aortic cannulation</td>
<td>Cognitive impairment index. 20% decline in ≥2 tests at 1 week and 6 months compared with preoperative baseline</td>
<td>No correlation. Study of on- and off-pump CABG</td>
</tr>
<tr>
<td>Fearn et al(^26)</td>
<td>70</td>
<td>75% of patients had HITS counts &gt;200</td>
<td>Start of CPB and defibrillation</td>
<td>Change of cognitive function over time at 1, 8, and 24 weeks compared with preoperative baseline</td>
<td>HITS associated with deficits in few memory tests</td>
</tr>
<tr>
<td>Stump et al(^†)</td>
<td>167</td>
<td>154±233</td>
<td>Manipulation of heart and aorta or no associated with any maneuver</td>
<td>A 20% decline in ≥2 tests at 1 week compared with preoperative baseline</td>
<td>Patients with POCD had more than twice HITS compared with those without POCD</td>
</tr>
<tr>
<td>Pugsley et al(^‡)</td>
<td>105</td>
<td>NR</td>
<td>NR</td>
<td>≥1 SD decline at 1 and 8 weeks compared with the preoperative baseline</td>
<td>Patients with &lt;200 HITS had 8.6% POCD; patients with &gt;1000 HITS had 43% POCD</td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass graft surgery; CPB, cardiopulmonary bypass.

*Total CPB counts.

†HITS were recorded unilaterally in the left common carotid artery.

‡HITS were unilaterally recorded in the middle cerebral artery.
CABG surgery through the use of uniform TCD parameters, good-quality bilateral TCD recordings, and consistent manual offline procedures for reviewing embolic signals.

The fact that we did not find any correlation between the counts of HITS and POCD may be related to several factors. First, previous reports have suggested that air microemboli are less damaging to the brain than solid emboli, but current TCD technology does not differentiate embolus size and composition (air versus solid). If the majority of cerebral microemboli during CPB are air microbubbles, then, the full effects represented by the total HITS counts on the patient’s neurological outcome would be minimal. Second, cerebral embolization during CPB may not be as important to neurological outcome as other mechanisms of brain injury such as inflammation, cerebral edema, response to the surgical insult, and ischemia. Third, comorbidities such as chronic hypertension, diabetes, or senile atherosclerotic disease may expose cardiac patients to regional cerebral hypoperfusion during surgery. Fourth, older patients may have higher rates of unrecognized cerebral vascular disease and this could contribute to the rapid deterioration of cognitive function after surgery. Fifth, the decreased amount of cerebral emboli achieved with off-pump CABG surgery has not resulted in a reduced incidence of POCD compared with on-pump procedures. Sixth, a follow-up study found similar rates of POCD between patients undergoing CABG and nonsurgical controls that perioperative factors may not be the cause of many POCD.

In our study, there were no differences in either the HITS counts or frequency of POCD associated with the aortic clamp technique or the type of aortic cannula. Our results obtained in low-risk CABG are different from Hammon et al who in higher-risk cases observed reduced rates of POCD with the modified single-clamp technique but no reduction in the HITS counts. Our findings are similar to those by Mullges et al who did not find any effect on the rates of POCD due to the length of the tip of the aortic cannula.

The use of different POCD definitions and techniques for counting HITS makes difficult to compare results among studies. We believe that our study achieved appropriate sensitivity by using scores corrected for practice effect and well-established criteria for POCD. In fact, our incidence of POCD at 1 week and 3 months is similar to that reported by others. Some studies (Table 6) with similar and different POCD definitions to our current study have found no association between HITS counts and POCD, but in others, which have reported a significant relationship, several issues regarding unilateral recording of HITS, sample size, or the comparison of POCD between groups with arbitrary classifications of HITS counts make this comparison more difficult. A limitation of our current study is related to differences in demographics and intraoperative characteristics between the 2 study groups. Although these factors may account for some variability in the number of HITS, we do not expect that it would change the relationship between HITS counts and POCD.

In summary, using data from 356 patients, we found that the number of HITS during the entire CPB period as well as during periods when solid emboli would be expected is not correlated with the incidence of POCD. Our findings indicate that the counts of HITS are associated with the type of surgical maneuver, cerebral blood flow velocity, duration of CPB, and type of clinical study but not related to the aortic clamp technique or length of the tip of the aortic cannula. The most likely explanation for our findings is that HITS identified during CPB mostly reflect air microemboli that have little effect on cerebral function as measured by cognitive testing. Although cerebral microemboli have been implicated in the pathogenesis of POCD, in this study that included low-risk patients undergoing CABG surgery, there was no demonstrable correlation between the counts of HITS and POCD. We believe that our findings underline the importance of developing and validating TCD devices that can distinguish solid from gaseous emboli.

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Disclosures
None.

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