Retinal and Cerebral Microembolization During Coronary Artery Bypass Surgery
A Randomized, Controlled Trial

Raimondo Ascione, FRCS; Arup Ghosh, FRCS; Barnaby C. Reeves, DPhil; John Arnold, BA; Mike Potts, FRCS; Atul Shah, MBBch; Gianni D. Angelini, FRCS

Background—We sought to compare the effects on ophthalmic function of coronary artery bypass grafting (CABG) with cardiopulmonary bypass (CPB) and off-pump (OPCAB) grafting and to investigate whether retinal microvascular damage is associated with markers of cerebral injury.

Methods and Results—Retinal microvascular damage was assessed by fluorescein angiography and color fundus photography. Ophthalmic function was tested by the logarithm of the minimum angle of resolution visual acuity (VA), and cerebral injury, by transcranial Doppler ultrasound–detected emboli and S100 protein values. Twenty patients were randomized. Fluorescein angiography and postoperative VA could not be obtained for 1 CABG-CPB patient. Retinal microvascular damage was detected in 5 of 9 CABG-CPB but in none of 10 OPCAB patients (risk difference, 55%; 95% confidence interval [CI], 23% to 88%; \( P = 0.01 \)). Color fundus photography detected microvascular damage in 1 CABG-CPB patient but in no OPCAB patients; this lesion was associated with a field defect, which remained after 3 months of follow-up. There was no difference in postoperative VA. Doppler high-intensity transient signals (HITS) were 20.3 times more frequent in the CABG-CPB than in the OPCAB group (95% CI, 9.1 to 45; \( P < 0.0001 \)). Protein S100 levels were higher in the CABG-CPB than in the OPCAB group 1 hour after surgery (\( P < 0.001 \)). HITS were 14.7 times more frequent (95% CI, 3.5 to 62; \( P = 0.001 \)) and S100 level 2.1 times higher (95% CI, 1.3 to 3.5; \( P = 0.005 \)) when retinal microvascular damage was present.

Conclusions—The relative frequency of retinal microvascular damage between groups shows the extent to which the risk of cerebral injury is reduced with OPCAB. Imaging of part of the cerebral circulation provides evidence to validate markers of cerebral injury. (Circulation. 2005;112:3833-3838.)

Key Words: embolism ■ microcirculation ■ cerebrovascular disorders ■ extracorporeal circulation ■ surgery

Ophthalmic injury after coronary surgery has rarely been investigated. However, patients sometimes complain of postoperative transient loss of vision, poor reading, altered perception of colors, and reduced visual acuity (VA) for both near and distance.1 The eye provides a “window” on the cerebral circulation and the opportunity to observe effects on the cerebral microvasculature, because the retina develops as an outgrowth of the embryonic brain and the retinal artery is a branch of the cerebral artery. Abnormal fluorescein angiograms suggestive of retinal damage have been reported in patients having coronary artery bypass grafting (CABG) with cardiopulmonary bypass CABG-CPB,2,3 and “particles” in the blood (gas or microemboli) in the cerebral circulation detected with transcranial Doppler ultrasound have been observed more often during CABG-CPB than off-pump coronary artery bypass (OPCAB) surgery.4,5

Editorial p 3816

This randomized, controlled trial aimed to compare the effects of CABG-CPB and OPCAB surgery on ophthalmic function, retinal microvascular damage, and previously used markers of cerebral injury, ie, Doppler ultrasound findings and serum S-100 protein release. We have previously shown that levels of these markers are reduced during OPCAB compared with CABG-CPB.4–6 Here we were interested not only to replicate this finding but also to test the hypothesis that retinal microvascular damage is associated with markers of cerebral injury.

Methods

Patient Selection
Patients undergoing elective first-time CABG were eligible. Exclusion criteria included diabetes; previous history of cerebrovascular...
accident; significant carotid artery disease; previous history of ophthalmic, neurological, or peripheral vascular disease; recent myocardial infarction (<1 month); or poor ejection fraction (<30%). Random treatment allocations were generated in advance of starting the study and were concealed in sequentially numbered, sealed, opaque envelopes. The study was approved by the United Bristol Healthcare Trust Ethics Committee, and all patients gave informed consent (LREC reference number E5480).

Anesthetic and Surgical Management
Anesthetic and operative techniques have been previously described. In brief, in the CABG-CPB group, heparin was given at a dose of 300 IU/kg to achieve a target activated clotting time of ≥480 seconds before commencement of CPB. Nonpulsatile flow at a rate reported. HITS were identified by use of a computerized detection transient signals (HITS) in the middle cerebral artery as previously described.7 In brief, in the CABG-CPB group, heparin was given at a dose of 300 IU/kg to achieve a target activated clotting time of ≥480 seconds before commencement of CPB. Nonpulsatile flow at a rate of 2.4 to 2.6 L·min⁻¹ was used with an arterial-line, 40-µm filter. Systemic temperature varied between 32°C and 34°C. Myocardial protection was achieved with intermittent antegrade warm blood cardioplegia. In the OPCAB group, heparin was administered before the start of the first anastomosis to achieve an activated clotting time of 250 to 350 seconds. Exposure and stabilization of the beating heart were performed as previously reported. For both groups, proximal aortic anastomoses when required were completed with a single application of a side-bite clamp. At the end of surgery, patients were transferred to the intensive care unit and managed according to our unit protocols. 7,8

Outcome Measures
Fluorescein Angiography
Fluorescein angiography findings were the primary outcome. A Zeiss fundus camera was modified so that it could be used in vertical alignment, as described by Arnold et al. Retinal fluorescein angiograms of the right eye were obtained in the CABG-CPB group (1) after opening the chest and before giving heparin and (2) before weaning from CPB; in the OPCAB group, they were obtained (1) after opening the chest and before giving heparin and (2) after completion of grafting. At both times in each group, the following steps were performed: (1) An eyelid retractor was inserted, and the cornea was kept moist with a flush of saline every 10 seconds; (2) then 5 mL of 20% sodium fluorescein was injected into the central venous line; (3) images were obtained at ~1-second interval for a period of ~15 seconds and subsequently with increasing intervals for a period of 50 seconds. The angiograms taken before surgery were used as within-patient controls. Fluorescein angiography is an intuitive, clinical outcome but one that is difficult to quantify. Therefore, the angiograms were simply reported for each patient as normal (no microvascular damage detected at either time point) or abnormal (microvascular damage present in the second angiogram that was not present on the first) by an independent ophthalmologist who was masked to the operative technique used.

Color Fundus Photographs
Stereoscopic 30° color fundus photographs of the disc, macula, and retina temporal to but including the fovea were taken before surgery and on postoperative day 5. When retinal emboli or other lesions were seen outside these 3 fields, additional fundus photographs were taken.

LogMAR VA and Visual-Field Assessment
VA for the right eye of each patient was measured as the logarithm of the minimum angle of resolution (logMAR) before surgery and at postoperative day 5 with an ETDRS chart. Patients’ visual fields were also assessed by a Humphrey visual-field (30-2) analyzer before and on postoperative day 5 after surgery. All ophthalmologic assessments were masked to the surgical technique.

Markers of Cerebral Injury
Transcranial Doppler ultrasound was used to detect high-intensity transient signals (HITS) in the middle cerebral artery as previously reported. HITS were identified by use of a computerized detection program with a threshold of 9 dB. HITS were defined as transient (<300 ms), high-intensity, unidirectional signals within the Doppler velocity spectrum. Serum protein S100 was measured preoperatively and at 1, 4, and 12 hours after the operation with a monoclonal 2-site immunoradiometric assay. 6

Sample Size and Statistical Analysis
On the basis of pilot work, we expected abnormal retinal microvascular changes to be observed in ~50% of CABG-CPB patients but only very rarely, if at all, among OPCAB patients. The sample size of 10 patients per group meant that the study had ~80% power to detect an absolute difference of 50% in the frequency of abnormal angiograms, providing 1 or no OPCAB patients had abnormal findings. This sample size also meant that the study had 80% power to detect an increase or decrease of 1.25 SDs in continuous outcomes (or logarithmically transformed outcomes, if the distributions were positively skewed), i.e., logMAR VA, number of HITS, and serum protein S100 values. These are large differences between groups, but the magnitude of difference was judged to be plausible based on previous studies. 3,7 No difference in VA was expected because for this to happen, retinal damage would have had to occur selectively at the macula.

The preoperative characteristics of the patients and their postoperative clinical outcomes were summarized by descriptive statistics (means and SDs for continuous variables and percentages for binary characteristics). Doppler HITS and S100 data were transformed into natural logarithms to normalize distributions before analysis. Outcomes were compared across groups by Fisher’s exact tests (for differences in proportions), Mann-Whitney rank-sum tests (for ordinal or continuously scaled data when there were no baseline data), or regression modeling to take into account baseline outcomes where available (models included only the baseline outcome and treatment group as covariates). Longitudinal S100 data were analyzed with a mixed model, with only the preoperative S100 level treatment group and time (ie, repeated measure) included as covariates.

Associations between outcome variables were also investigated by regression modeling because we wanted to test the hypothesis that retinal microvascular changes were associated with markers of cerebral injury. Therefore, in addition to the comparisons between randomly allocated groups, comparisons of geometric means for HITs and S100 were made between patients with and without abnormal fluorescein findings (after adjusting for the baseline level in the case of S100). All analyses were performed with STATA v8.2 or SAS v8.2 for the mixed-model analysis of S100.

Results
Twenty patients were randomized to CABG-CPB (n = 10) or OPCAB (n = 10). All patients received their allocated type of surgery, and no patient required conversion from OPCAB to CABG-CPB. The preoperative characteristics of patients in the 2 groups are summarized in the Table. The median number of grafts was 2 in both OPCAB and CABG-CPB groups (P = 0.86, Mann-Whitney rank-sum test). There were no in-hospital deaths or renal, gastrointestinal, hepatic, pancreatic, neurological, or pulmonary complications in either group. There were also no differences between groups in the clinical outcomes (eg, postoperative inotropes, use of blood products), although it should be noted that the study was not designed to detect such differences.

Fluorescein angiograms, color fundus photographs, and postoperative VA values could not be obtained for 1 CABG-CPB patient. All baseline fluorescein angiograms were normal in both groups. In postsurgery fluorescein angiograms, retinal microvascular damage was detected in 5 of the 9 CABG-CPB patients and in none of 10 OPCAB patients (risk difference, 55%; 95% confidence interval [CI], 23% to 88%; P = 0.01). Color fundus photographs taken on postoperative
day 5 were abnormal in 1 of 9 CABG-CPB patients but in none of 10 OPCAB patients. Figure 1 shows examples of retinal fluorescein angiograms in an OPCAB (normal) and a CABG-CPB (abnormal) patient. Figure 2 shows another abnormal fluorescein angiogram for the CABG-CPB patient who also had abnormal color fundus photographs at postoperative day 5. This patient had a persisting visual-field defect at 3 months after surgery.

There was no difference in postoperative VA, adjusted for baseline VA (mean OPCAB VA was 0.06 worse [equivalent to 3 letters]; 95% CI, −0.09 to 0.21; P=0.42). Mean VA was 0.01 in the OPCAB group and 0.04 in the CABG-CPB group (both approximately equivalent to 20/20 Snellen).

On average, Doppler ultrasound HITS were 20.3 times more frequent in the CABG-CPB than in the OPCAB group (95% CI, 9.1 to 45; P<0.0001). Geometric means of the number of HITS for the respective groups were 4 in the OPCAB group and 72 in the CABG-CPB group. The distributions of the numbers of HITS for the 2 groups did not overlap; the range of HITS detected was 0 to 8 in the OPCAB group and 15 to 237 in the CABG-CPB group.

Analyses of protein S100 levels included main effects of surgery type and time and the interaction of surgery type and time. The interaction was highly significant (P<0.0001) 1 hour after surgery, when S100 levels were 2.4 times higher in the CABG-CPB than in the OPCAB group (95% CI, 1.8 to 3.2 times; P<0.0001) but not thereafter (P>0.60).

Retinal microvascular damage was associated with transcranial Doppler HITS (HITS were 14.7 times more frequent when the fluorescein angiogram was abnormal; 95% CI, 3.5 to 62; P=0.001). Retinal microvascular damage was also associated with protein S100 levels 1 hour after the end of surgery (the level was 2.1 times higher when the fluorescein angiogram was abnormal; 95% CI, 1.3 to 3.5; P=0.005) but not 4 and 12 hours after the end of surgery.

The risk of retinal microvascular damage in OPCAB patients was of interest, given the imprecision of the estimated proportion (ie, 0%; 95% CI, 0% to 31%). Therefore, we also estimated this risk from the association between retinal microvascular damage and HITS in the whole study population. The odds of retinal microvascular damage increased ≈30-fold for a 10-fold increase in HITS. Estimated

Preoperative and Bypass Graft Characteristics

<table>
<thead>
<tr>
<th></th>
<th>OPCAB (n=10)</th>
<th>CABG-CPB (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preoperative characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at surgery, y*</td>
<td>63.4±16.4</td>
<td>61.2±9.8</td>
</tr>
<tr>
<td>Body mass index, kg/m²*</td>
<td>28.4±3.9</td>
<td>28.8±5.3</td>
</tr>
<tr>
<td>Female</td>
<td>3/30</td>
<td>0/0</td>
</tr>
<tr>
<td>Canadian Cardiovascular Society class &gt;2</td>
<td>5/50</td>
<td>2/20</td>
</tr>
<tr>
<td>New York Heart Association class &gt;2</td>
<td>3/30</td>
<td>1/10</td>
</tr>
<tr>
<td>Triple-vessel disease</td>
<td>10/100</td>
<td>10/100</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>2/20</td>
<td>4/40</td>
</tr>
<tr>
<td>Past smoker</td>
<td>7/70</td>
<td>6/60</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1/10</td>
<td>0/0</td>
</tr>
<tr>
<td>Parsonnet score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–10</td>
<td>6/60</td>
<td>9/90</td>
</tr>
<tr>
<td>11–15</td>
<td>4/40</td>
<td>1/10</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7/70</td>
<td>8/80</td>
</tr>
<tr>
<td>Hypercholesteremia</td>
<td>9/90</td>
<td>7/70</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>2/20</td>
<td>4/40</td>
</tr>
<tr>
<td><strong>Bypass graft characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of grafts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>6/60</td>
<td>6/60</td>
</tr>
<tr>
<td>3</td>
<td>4/40</td>
<td>3/30</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>1/10</td>
</tr>
<tr>
<td>No. of proximal aortic anastomoses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1/10</td>
<td>0/0</td>
</tr>
<tr>
<td>1</td>
<td>5/50</td>
<td>4/40</td>
</tr>
<tr>
<td>2</td>
<td>4/40</td>
<td>6/60</td>
</tr>
<tr>
<td>&gt;1 Arterial conduit</td>
<td>1/10</td>
<td>2/20</td>
</tr>
<tr>
<td><em>Y</em> graft</td>
<td>1/10</td>
<td>1/10</td>
</tr>
</tbody>
</table>

*Mean and SD are shown for continuously distributed variables.
Discussion
There are 3 main findings of this study: (1) CABG-CPB causes retinal microvascular damage, which was not observed with OPCAB. One patient with an abnormal fluorescein angiogram also had evidence of retinal microvascular damage from color fundus photographs and had a corresponding visual defect that remained 3 months after surgery. (2) Compared with OPCAB, CABG-CPB also causes more transcranial Doppler HITS and elevated serum protein S100 levels 1 hour after surgery. (3) Retinal microvascular damage was strongly associated with transcranial Doppler HITS and,

Figure 1. Example of fluorescein angiography during OPCAB (upper) and CABG-CPB (lower) surgery: A, before surgery; B, after surgery, early phase; and C, after surgery, late phase. The arrow in each of the lower photographs indicates the site of a postoperative abnormality, ie, a branch of the retinal circulation with a vessel-wall injury leading to extravasation of fluorescein (B and C), which was not present before surgery (A).

Figure 2. A and B, Example of abnormal fluorescein angiogram during CABG-CPB surgery: A, before surgery; B, after surgery. The arrows indicate multiple sites of postoperative abnormalities (B), which were not present before surgery (A). C, Color fundus photograph in the same patient at postoperative day 5, showing a branch of the retinal artery with multiple, shiny emboli (arrowheads).
to a lesser extent, with serum protein S100 levels 1 hour after surgery.

Allocation to surgical technique was randomized, preventing selection bias. Results of fluorescein angiography and other assessments were interpreted by research staff who were masked to the surgical technique, thus preventing performance and detection bias. Despite the small sample size, the effects and associations reported are unlikely to have arisen by chance and are consistent with previous studies.2–5

We cannot rule out the possibility of retinal microvascular damage after OPCAB because of the small sample size. However, on the basis of the association between fluorescein abnormalities and transcranial Doppler HITS, we estimate the average risk of retinal microvascular damage in OPCAB patients to be ≈2%.

Ophthalmic injury after coronary surgery has rarely been investigated. Some patients complain of postoperative visual symptoms consistent with retinal vascular occlusions, which may persist.1 Although both embolism and hemodynamic compromise can lead to perioperative eye ischemia, we speculate that embolism may be considered the more likely mechanism because of the large amount of aortic manipulation needed during CABG-CPB surgery. Doppler HITS, which we have shown to be strongly associated with retinal microvascular damage, have been widely accepted as reflecting emboli, not the least because they peak at times when emboli are expected.11 OPCAB surgery has the advantage of limiting aortic manipulation to a single application of an aortic partial-occlusion clamp to perform the proximal anastomoses when necessary. In fact, aortic manipulation can be completely avoided during OPCAB surgery when using composite arterial revascularization.

Systemic embolization and circulatory disturbances are also a recognized hazard of CPB.12,13 Emboli-related infarcts, macro- and micro-hemorrhages, subarachnoid hemorrhages, or hypoxic/oxic damage have been observed in the brains of 49% of patients who died in hospital after cardiac surgery.14

Embolization of the retinal circulation was first demonstrated in the early 1970s by Williams,15 with optic fundoscopic studies in patients and in dogs during CPB. However, retinal vessels of <30-μm caliber are not discernible with optic fundoscopy,16 and detecting the effects of microemboli on this part of the retinal microcirculation requires a specialized imaging technique like fluorescein angiography. Blauth et al17 performed intraoperative fluorescein angiography in 10 patients undergoing CAGB-CPB, with the duration of extracorporeal circulation ranging between 40 and 160 minutes; retinal microvascular damage was observed in all of them. In a further study, those investigators demonstrated that flat-sheet-membrane oxygenation provided better protection against retinal microvascular damage than bubble oxygenation, although retinal microvascular damage was not eliminated.5

Retinal microvascular damage was frequent (>50%) in CAGB-CPB patients. Given that the retinal circulation is part of the cerebral circulation, we infer that similar damage would have been seen in the cerebral microcirculation had an appropriate imaging technique been available to visualize it. Previously, critics have questioned whether transcranial Doppler HITS should be interpreted as a marker of cerebral injury despite evidence that HITS are associated with neurocognitive outcomes.11 The strong association observed in this study between fluorescein angiogram microvascular changes and HITS provides evidence to support this interpretation. There has been similar skepticism about protein S100 levels, although again, this marker has been shown to be associated with neurocognitive outcomes.16,17 The association that we observed between fluorescein angiogram changes and protein S100 early release, though weaker, supports the interpretation of protein S100 levels as a marker of cerebral injury.

It is also important to reconcile our findings with other evidence from randomized, controlled trials of on- versus off-pump CAGB that have studied clinical outcomes. A recent meta-analysis showed a nonsignificant reduction in the odds of stroke (within 30 days) with OPCAB (n = 2859; odds ratio, 0.68; 95% CI, 0.33 to 1.40) and a statistically significant reduction in a dichotomous measure of neurocognitive dysfunction at 2 to 6 months after surgery (n = 393; odds ratio, 0.56; 95% CI, 0.35 to 0.89) but no evidence of dysfunction at 1 to 2 years (n = 334; odds ratio, 0.91; 95% CI, 0.57 to 1.46).18 To put this evidence in context, a trial would require 5000 to 10 000 participants to detect a halving of risk with prevailing stroke rates of 1% to 2%. Neurocognitive outcomes are not often measured and are not always reported in a standardized way, hence, the small sample size in the meta-analysis. It also becomes increasingly difficult to demonstrate continuing dysfunction with longer duration of follow-up because of statistical noise; other events that affect cognitive decline increase the variation in outcome between individuals, potentially obscuring differences between randomized groups. Even if dysfunction persists only to 1 year, this is still very important to those who are affected.

In conclusion, OPCAB surgery reduces the risk of retinal microvascular damage, as evidenced by the absence of abnormalities on intraoperative fluorescein angiograms. Such damage occurs frequently in CAGB-CPB patients. The associations between retinal microvascular damage, HITS, and S100 protein release support the interpretation that CAGB-CPB also causes cerebral microvascular damage.

Acknowledgment
Raimondo Ascione was supported by a 5-year Consultant Senior Lecturer Fellowship grant by the Garfield Weston Trust.

Disclosure
None.

References


Retinal and Cerebral Microembolization During Coronary Artery Bypass Surgery: A Randomized, Controlled Trial
Raimondo Ascione, Arup Ghosh, Barnaby C. Reeves, John Arnold, Mike Potts, Atul Shah and Gianni D. Angelini

Circulation. 2005;112:3833-3838
doi: 10.1161/CIRCULATIONAHA.105.557462

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/112/25/3833

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/