Operative strategies to reduce cerebral embolic events during on- and off-pump coronary artery bypass surgery: A stratified, prospective randomized trial

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ABSTRACT

Objective: To determine the impact of different aortic clamping strategies on the incidence of cerebral embolic events during coronary artery bypass grafting (CABG).

Methods: Between 2012 and 2015, 142 patients with low-grade aortic disease (epiaortic ultrasound grade I/II) undergoing primary isolated CABG were studied. Those undergoing off-pump CABG were randomized to a partial clamp (n = 36) or clampless facilitating device (CFD; n = 36) strategy. Those undergoing on-pump CABG were randomized to a single-clamp (n = 34) or double-clamp (n = 36) strategy. Transcranial Doppler ultrasonography (TCD) was performed to identify high-intensity transient signals (HITS) in the middle cerebral arteries during periods of aortic manipulation. Neurocognitive testing was performed at baseline and 30-days postoperatively. The primary endpoint was total number of HITS detected by TCD. Groups were compared using the Mann–Whitney *U* test.

Results: In the off-pump group, the median number of total HITS were higher in the CFD subgroup (30.0; interquartile range [IQR], 22–43) compared with the partial clamp subgroup (7.0; IQR, 0–16; *P* < .0001). In the CFD subgroup, the median number of total HITS was significantly lower for patients with 1 CFD compared with patients with >1 CFD (12.5 [IQR, 4–19] vs 36.0 [IQR, 25–47]; *P* = .001). In the on-pump group, the median number of total HITS was 10.0 (IQR, 3–17) in the single-clamp group, compared with 16.0 (IQR, 4–49) in the double-clamp group (*P* = .10). There were no differences in neurocognitive outcomes across the groups.

Conclusions: For patients with low-grade aortic disease, the use of CFDs was associated with an increased rate of cerebral embolic events compared with partial clamping during off-pump CABG. A single-clamp strategy during on-pump CABG did not significantly reduce embolic events compared with a double-clamp strategy. (J Thorac Cardiovasc Surg 2017;154:1278–85)

Off-pump CABG. Median HITS with the CFD versus partial clamp.

Central Message

Patients with low-grade aortic disease undergoing off-pump CABG had more embolic events with CFDs than with partial clamping. On-pump patients had comparable results with single or double clamping.

Perspective

Aortic clamping during CABG surgery is associated with cerebral atheroembolism, which is likely responsible for increased risk of periprocedural stroke in patients undergoing CABG. The findings of this study support the use of traditional clamping methods during on- or off-pump CABG for patients with low-grade aortic disease.

See Editorial Commentary page 1286.

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Abbreviations and Acronyms

ANOVA	= analysis of variance
CABG	= coronary artery bypass grafting
CFD	= clampless facilitating device
CNSVS	= CNS Vital Signs
HITS	= high-intensity transient signals
IQR	= interquartile range
RBANS	= Repeatable Battery for Neuropsychological Status
TCD	= transcranial Doppler ultrasonography

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Despite advances in no-aortic-touch multiarterial revascularization, extracorporeal perfusion techniques, and off-pump approaches to minimizing adverse neurologic events, these events remain a leading cause of morbidity associated with coronary artery bypass grafting surgery (CABG). Adverse neurologic events are frequently attributed to atheroembolism resulting from aortic manipulation,¹ which can occur at any part of the procedure, including aortic clamping, cannulation insertion and removal, and initiation of bypass. Thus, it would seem intuitive that minimizing aortic manipulation would result in less cerebral embolism. Although this is one of the potential benefits of off-pump CABG, off-pump approaches frequently use some degree of aortic manipulation for the construction of proximal aortocoronary anastomoses.^{2,3}

Transcranial Doppler ultrasonography (TCD) has been used to detect high-intensity transient signals (HITS) in the middle cerebral arteries. This technique is highly sensitive for cerebral microembolization, but the association with clinical outcomes and neurocognitive dysfunction has not been demonstrated. Most of the studies published to date have been observational in nature and thus subject to bias and confounding, whereas others have not examined the spectrum of proximal aortic strategies with different revascularization options. Thus, the purpose of this randomized trial was to compare the impact of different aortic manipulation strategies on the number of cerebral embolic events occurring during CABG.

METHODS**Trial Design and Oversight**

This trial was a randomized, single-center trial with 7 participating surgeons with expertise in both off-pump (each surgeon having performed at

least 100 off-pump cases) and on-pump CABG, as well as in the use of clampless facilitating devices (CFDs) for constructing proximal aortocoronary anastomoses. Data collection and management were handled by the Cardiothoracic Center for Clinical Research at Emory University. The Institutional Review Board of Emory University reviewed and approved the study. The trial was monitored by an independent Data and Safety Monitoring Board.

Study Population

Patients scheduled for elective or urgent, first-time multivessel sternotomy CABG were eligible for enrollment. All patients underwent a routine and standardized preoperative evaluation by the attending surgeon and a mid-level provider, including carotid artery ultrasound. Exclusion criteria included a history of preoperative stroke, preoperative or concomitant carotid endarterectomy, stenting, or known hemodynamically (>80%) significant stenosis; known left ventricular or left atrial thrombus; planned concomitant cardiac surgical procedure, salvage or emergency CABG, reoperative cardiac surgery, CABG with no planned aortocoronary proximal anastomoses, or the presence of a preoperative intra-aortic balloon pump; and unwillingness or inability to provide consent. All enrolled patients provided written informed consent.

Randomization and Treatment

The study was designed to study and compare the effects of different strategies of construction of proximal anastomoses; it was not designed to compare off- versus on-pump CABG. The decision to perform off- versus on-pump CABG was at the discretion of the operating surgeon. Randomization occurred intraoperatively after completion of sternotomy and epiaortic ultrasonography. Only patients with low-grade ascending aortic disease (grade I-II; Table 1) by epiaortic ultrasound were randomized, regardless of whether an off- versus on-pump approach was selected by the operating surgeon.⁴ Specifically, patients selected for off-pump CABG were randomized 1:1 to have proximal aorto-coronary anastomoses performed with a partial-occluding clamp or with a CFD (Heartstring Device; Maquet Cardiovascular, San Jose, Calif). Patients selected for on-pump CABG were randomized 1:1 to have proximal aorto-coronary anastomoses performed with a single clamp or a double clamp (cross-clamp for cardioplegic arrest and partial-clamp for proximal anastomoses). A randomized block design was used with blocks of 8; after epiaortic ultrasound confirmed grade I-II aortic disease, the randomization assignment was revealed via an opaque envelope by the research coordinator. Patients who were determined intraoperatively to have grade III-V ascending aortic disease by epiaortic ultrasound were excluded from randomization and the study. At an α level of 0.05, there would be 80% power to detect a treatment difference, if it exists, of 40 HITS with 31 patients per group using the Mann-Whitney *U* test. With an attrition rate of 10% due to dropouts and possible technical problems, the plan was to recruit 34 patients in each group.

Surgical Technique

All patients underwent sternotomy. Routine left internal mammary artery harvest was performed in all cases. Saphenous vein grafts were harvested using endoscopic techniques. Patients undergoing on-pump CABG underwent standard ascending aortic and right atrial cannulation for cardiopulmonary bypass. In patients randomized to a single-clamp strategy, proximal aortocoronary anastomoses were performed before release of the cross-clamp. In patients randomized to a double-clamp strategy, the cross-clamp was released after distal anastomoses, followed by application of a partial clamp for the construction of proximal anastomoses.

In patients undergoing off-pump CABG, distal anastomoses were performed using cardiac positioning and stabilizing devices. In patients randomized to the partial clamp subgroup, proximal aorto-coronary anastomoses were performed using a partial clamp on the ascending aorta.

TABLE 1. Epiaortic ultrasound grading system used at Emory University

Ultrasound grade of ascending aorta	Severity (atheroma thickness)	Description
1	Normal	Intimal thickness <2 mm
2	Mild	Mild (focal or diffuse) intimal thickening of 2-3 mm
3	Moderate	Atheroma <3-5 mm (no mobile/ulcerated components)
4	Severe	Atheroma >5 mm (no mobile/ulcerated components)
5	Complex	Grade 2, 3, or 4 atheroma plus mobile or ulcerated components

In patients randomized to the CFD subgroup, proximal anastomoses were performed using the Heartstring device.

TCD

All patients underwent TCD evaluation to detect cerebral embolic signals during all periods of aortic manipulation using the Compumedics DWL system and QL software (Compumedics, Singen, Germany). In the on-pump group, TCD monitoring measurements were recorded at (1) cannulation; (2) initiation of cardiopulmonary bypass; (3) aortic cross-clamping; (4) removal of the aortic cross-clamp; (5) application of a partial clamp (double-clamp group); (6) removal of the partial clamp (double-clamp group); (7) removal of the aortic cannula. For the off-pump group, TCD monitoring measurements were recorded at placement and removal of each CFD, or placement and removal of the partial clamp. The DWL system is a fully digital system that uses an automated event detector to identify HITS and is powered by the Doppler M-mode. The Doppler M-mode simultaneously receives and analyzes Doppler signals from a predefined range of depths. This allows for verification of emboli detection when an embolus passes through various depths. Microemboli traveling along an insonated vessel will appear as HITS on the TCD spectrum. The system uses a 2.0-MHz probe with a power range of 20 to 100 mW. Initially, an adequate temporal window was confirmed by locating intracranial arterial signals. The right middle cerebral artery was insonated at a depth of 50 to 65 mm. The middle cerebral artery was verified through visualization of the depth and flow direction. The spectra from each period of insonation were saved to the hard drive of the computer. The number and timing of HITS were monitored and recorded by dedicated research coordinators who were trained and experienced in TCD (Video 1). Differentiation between solid and gaseous HITS was not done, because the overall clinical accuracy of dual frequency and frequency modulation analyses were insufficient to accurately separate gas from solid emboli.⁵⁻⁷

All TCD data were reviewed and adjudicated by a staff neurologist at Emory University with expertise in TCD ultrasonography who was blinded to the treatment group. False-positive recordings that were recorded as HITS by the software were identified by our neurologist and excluded from the analysis.

Neurocognitive Assessment

Neurocognitive function was measured preoperatively and at 30 days postoperatively. Selection of the test battery likely to be sensitive to cognitive deficits in a cardiac surgery population was guided by previous studies of neuropsychological outcomes following cardiac surgery,^{8,9} as well as by research in our own laboratory.¹⁰ For this assessment, CNS Vital Signs computerized neurocognitive testing (CNSVS; CNS Vital Signs, Morrisville, NC) was used for the majority of patients. The

VIDEO 1. Video of actual recording obtained with TCD measurement during clamp removal. The sounds interspersed during the pulse wave recordings are recorded as HITS by the computerized software program. Video available at: [http://www.jtcvsonline.org/article/S0022-5223\(17\)31226-6/addons](http://www.jtcvsonline.org/article/S0022-5223(17)31226-6/addons).

neuropsychological test was changed from the Repeatable Battery for Neuropsychological Status (RBANS) test to CNSVS after the first 25 randomized patients to improve standardization of testing through computerized administration. Eliminating the handwritten RBANS test reduced potential variations in test administration among nurse coordinators. Neuropsychological testing was administered by clinical coordinators and scored by either computer (CNSVS) or neuropsychological technicians (RBANS) under the supervision of an experienced neuropsychologist. The CNSVS scoring algorithm detects normatively rare scores, which could reflect actual poor cognitive performance but also could be due to poor effort, subject distractibility, or other factors that could potentially invalidate the scores. Because we could not distinguish among these causes of normatively out-of-range scores, we excluded all such potentially invalid scores from our analyses.

The change from RBANS to CNSVS required us to exclude the neuropsychological data on individual RBANS subtests from the initial 25 subjects, because those scores were not on a comparable scale as the CNSVS subtests. This reduced the sample size for which subtest neuropsychological data were available and reduced the statistical power. Nonetheless, the improved standardization of test administration likely increased the reliability of available data. The RBANS and CNSVS both include a total score reflecting overall neuropsychological performance that is scaled comparably across the 2 batteries. We were able to include either the RBANS or CNSVS total score in a single analysis of overall neuropsychological performance across groups.

Statistical Analysis

TCD outcomes. For power analysis, the expected number of HITS in each subgroup was estimated to be 50 for CFD, 90 for partial clamp, 100 for single clamp, and 160 for double clamp based on pilot data¹¹ for off-pump CABG as well as on previously published reports for on-pump CABG.¹² For the off-pump group, given a significance level of 0.05, we would have 80% power to detect a treatment difference of 40 HITS with 31 patients per subgroup using the Mann-Whitney U test. Assuming an attrition rate of 10% due to dropouts and technical problems, 34 patients were needed in both the CFD and partial-clamp subgroups. For the on-pump group, assuming a significance level of 0.05, we would have 80% power to detect a treatment difference of 50 HITS with 31 patients per subgroup. Assuming an attrition rate of 10% due to dropouts and technical problems, 34 patients would be needed in both the single-clamp and double-clamp subgroups.

The same data analyses were performed in the CFD and partial-clamp subgroups for off-pump CABG and for single-clamp and double-clamp

subgroups for on-pump CABG. Numeric variables were summarized using mean $\pm$ standard deviation or median and interquartile range (IQR), as appropriate. Categorical variables were summarized as count (percentage). Group averages were compared using the Student *t* test or Mann–Whitney *U* test, as appropriate. Group proportions were compared using the χ^2 test or Fisher's exact test, as appropriate. The Mann–Whitney *U* test was used to assess the difference in the average number of HITS between groups. To graphically compare HITS distributions, boxplots were drawn after log-transforming the number of HITS. Log transformation compresses the scale for high values and stretches the scale for low values and provides a better visual comparison between 2 right-skewed distributions. Comparative analyses of the total number of HITS between the CFD and partial-clamp subgroups and between the single-clamp and double-clamp subgroups were intention-to-treat. Secondary questions comparing, for example, 1 CFD and >1 CFD were as-treated. Tests of hypotheses were 2-sided, and a significance level of 0.05 was used throughout. All data analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

Neurocognitive testing. Invalid CNSVS scores on given variable were excluded from analysis. All planned comparisons were conducted on pretreatment and posttreatment raw and age-adjusted scaled scores, as well as on change scores (pretreatment score subtracted from posttreatment score).

RESULTS

Enrollment and Patient Characteristics

Between 2012 and 2015, 193 patients were enrolled and 142 patients underwent randomization. For the patients enrolled, the main reasons for exclusion were the inability to obtain a TCD signal over the middle cerebral artery and

a grade III–V aorta on epiaortic ultrasound (Figure 1). In the off-pump group, 72 patients were randomized to have proximal aortocoronary anastomoses performed using either a CFD or a partial clamp. In the on-pump group, 70 patients were randomized to either a single cross-clamp or a double-clamp strategy for construction of aortocoronary proximal anastomoses. Baseline characteristics were similar across the groups (Table 2). For randomized patients in the on-pump group, all patients received the treatment that they were assigned. For all patients in the single-clamp subgroup, no additional clamping was done after release of the cross-clamp. All patients in the double-clamp subgroup received only 1 application of the cross-clamp and only 1 application of the partial clamp. For the off-pump group, 2 patients who were randomized to the partial clamp subgroup received a CFD, and 2 patients who were randomized to the CFD subgroup received a partial clamp. The 30-day postoperative follow-up was completed in 129 patients (91%).

Clinical Outcomes

No 30-day mortality, postoperative myocardial infarction, or deep sternal infection occurred in any group. Superficial sternal infections occurred in 3 patients (8.3%) in the partial-clamp subgroup and in 2 patients (5.6%) in the

FIGURE 1. CONSORT diagram of trial enrollment, randomization, and treatment received. CABG, Coronary artery bypass grafting; TCD, transcranial Doppler ultrasonography.

TABLE 2. Patient perioperative characteristics

Characteristic	Off-pump CABG			On-Pump CABG		
	CFD (n = 36)	Partial clamp (n = 36)	P value	Single clamp (n = 34)	Double clamp (n = 36)	P value
Age, y, mean $\pm$ SD	60.8 $\pm$ 10.3	60.6 $\pm$ 9.2	.93	62.3 $\pm$ 7.8	61.1 $\pm$ 8.6	.54
Female sex, n (%)	8 (22.2)	10 (27.8)	.59	6 (17.6)	5 (13.9)	.67
Caucasian, n (%)	28 (77.8)	21 (58.3)	.08	25 (73.5)	26 (72.2)	.90
Diabetes, n (%)	18 (50.0)	22 (61.1)	.34	13 (38.2)	14 (38.9)	.96
NSTEMI, n (%)	17 (47.2)	13 (36.1)	.34	7 (21.2)	10 (28.6)	.48
CCS angina 3/4, n (%)	19 (61.3)	20 (57.1)	.73	21 (70.0)	20 (62.5)	.53
NYHA class III/IV, n (%)	0	2 (5.9)	.22	2 (6.7)	4 (12.5)	.53
EF, mean $\pm$ SD	49.5 $\pm$ 15.1	51.3 $\pm$ 14.4	.61	52.6 $\pm$ 11.5	52.3 $\pm$ 12.1	.93
Renal insufficiency, n (%)	2 (5.6)	4 (11.1)	.53	4 (11.8)	5 (13.9)	.83
Dyslipidemia, n (%)	30 (83.3)	32 (88.9)	.50	32 (94.1)	29 (80.6)	.10
Hypertension, n (%)	31 (86.1)	34 (94.4)	.27	27 (79.4)	26 (72.2)	.48
Smoker, n (%)	21 (58.3)	15 (41.7)	.16	21 (61.8)	14 (38.9)	.06
Previous PCI, n (%)	11 (30.6)	11 (30.6)	1.00	13 (38.2)	5 (13.9)	.02
COPD, n (%)	3 (8.3)	2 (5.6)	.75	4 (11.8)	1 (2.8)	.17
PVD, n (%)	1 (2.8)	2 (5.6)	.68	1 (2.9)	2 (5.6)	.68
Diseased vessels, n, mean $\pm$ SD	3.1 $\pm$ 0.7	3.0 $\pm$ 0.7	.52	3.3 $\pm$ 0.8	3.5 $\pm$ 0.8	.27
Distal anastomoses, n, mean $\pm$ SD	3.2 $\pm$ 0.7	3.0 $\pm$ 0.8	.15	3.4 $\pm$ 0.7	3.5 $\pm$ 0.8	.42
Proximal anastomoses, n, mean $\pm$ SD	1.8 $\pm$ 0.6	1.6 $\pm$ 0.6	.11	2.1 $\pm$ 0.8	2.1 $\pm$ 0.8	.98

CABG, Coronary artery bypass grafting; CFD, clampless facilitating device; SD, standard deviation; NSTEMI, non-ST segment elevation myocardial infarction; CCS, Canadian Cardiovascular Society; NYHA, New York Heart Association; EF, ejection fraction; PCI, percutaneous coronary intervention; COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease.

double-clamp subgroup. Two postoperative strokes occurred in the single-clamp subgroup, compared with none in any of the other subgroups, for an overall stroke rate of 1.4%. Both of these strokes occurred in extubated, stable patients after an initial normal postoperative neurologic exam on postoperative day 1. The numbers of HITS in these 2 patients (10 and 43) were not outliers compared with the results for other patients. Postoperative atrial fibrillation occurred in 7 patients (19.4%) in the CFD subgroup, 10 (27.8%) in the partial-clamp subgroup, 6 (17.7%) in the single-clamp subgroup, and 8 (22.2%) in the double-clamp subgroup. The number of patients who received blood transfusions intraoperatively or postoperatively was 2 (5.6%) in the CFD subgroup, 4 (11.1%) in the partial-clamp subgroup, 5 (14.7%) in the single-clamp subgroup, and 6 (16.7%) in the double-clamp subgroup. The number of cases of postoperative renal failure was 0 in the CFD subgroup, 1 (2.8%) in the partial-clamp subgroup, 0 in the single-clamp subgroup, and 1 (2.8%) in the double-clamp subgroup. Thirty-day hospital readmission occurred in 3 patients (8.6%) in the CFD subgroup, 2 (5.7%) in the partial-clamp subgroup, 0 in the single-clamp subgroup, and 3 (8.3%) in the double-clamp subgroup.

TCD-Detected Cerebral Embolic Events

In the on-pump CABG group, TCD data were complete for 33 of 34 (97%) single-clamp patients and 35 of 36

(97%) double-clamp patients. In the intention-to-treat analysis, the median number of HITS detected during all periods of aortic manipulation was 10 (IQR, 3-17) for the single-clamp subgroup versus 16 (IQR, 4-49) for the double-clamp subgroup ($P = .10$) (Figure 2, A).

In the off-pump group, TCD data were complete for 35 of 36 (97%) partial-clamp patients and 33 of 36 (92%) CFD patients. The median number of HITS detected during all periods of aortic manipulation was 30 (IQR, 22-43) for the CFD subgroup versus 7 (IQR, 0-16) for the partial-clamp subgroup ($P < .001$) (Figure 2, B). For patients undergoing off-pump CABG with CFDs for construction of proximal anastomoses, the effect on HITS was positively related to the number of devices used (Figure 3, A-D).

Neurocognitive Function

Unfortunately, the exclusion of invalid CNSVS scores reduced the sample sizes available for some analyses. Loss of data due to invalid scores was comparable across the groups, so this factor did not introduce a systematic bias. Using the available valid data, we found no statistically significant between-group differences for any of the CNSVS domain scores preoperatively (Table E1). The groups did differ significantly in the preoperative CNSVS or RBANS Total Score, with the double-clamp subgroup showing higher scores than the other patient subgroups. Thus, the preoperative total score was used as a covariate

FIGURE 2. Intention-to-treat analysis of HITS data. A, On-pump CABG, single clamp versus double clamp. B, Off-pump CABG, CFD versus partial clamp. The number of HITS was log-transformed to compress the scale for high values and stretch the scale for low values, allowing for a better visual comparison between 2 right-skewed distributions. CABG, Coronary artery bypass grafting; HITS, high-intensity transient signals; IQR, interquartile range; CFD, clampless facilitating device.

in analyses of the corresponding postoperative scores in the on-pump group. In the analysis of both raw and age-adjusted (as well as covariate adjustment for the on-pump group) postoperative and change scores, no comparisons approached statistical significance.

DISCUSSION

Because of the large number of patients that would be required to demonstrate a difference in a postoperative stroke, a randomized trial with stroke as the primary outcome was impractical. In this study, the number of HITS detected during TCD ultrasonography was used as a surrogate for cerebral embolism and was the primary outcome.

Wolf and coworkers used TCD to detect cerebral microembolization in 42 patients undergoing off-pump CABG.¹³ They found no difference in total microemboli between the CFD group and the partial-clamp group, but there were significantly more solid microemboli in the partial-clamp group. Liu and associates also used TCD in a prospective observational study and found significantly higher numbers of microemboli in patients undergoing on-pump CABG compared with those undergoing off-pump CABG (median number of HITS, 430 vs 2; $P < .001$).¹² In a randomized study, Motalebzadeh and colleagues reported 1605 embolic signals in on-pump patients compared with 9 in off-pump patients with a partial clamp.¹⁴ Other studies have been relatively consistent with the foregoing reports.^{15,16}

The main findings of this study can be summarized as follows. For patients undergoing CABG with low-grade aortic disease determined by epiaortic ultrasonography, (1) there was no difference in cerebral embolic events between on-pump patients undergoing a single-clamp

technique and those undergoing a double-clamp technique; (2) in off-pump patients, more cerebral embolic events occurred when CFDs were used compared with the partial-clamp technique; and (3) the effect of using CFDs on cerebral embolic events was directly related to the number of devices used. Each insertion and removal of the device, much like with a partial clamp, is associated with some degree of cerebral microembolization. These results also suggest that the use of CFDs is another form of aortic manipulation and might not completely eliminate the risk of cerebral embolism. This study also contradicts previous studies that have reported a benefit from using CFDs in lieu of partial clamping in all off-pump patients.

Observational analyses,¹⁷ including one from our own institution,¹⁸ have shown a benefit from minimizing or avoiding aortic manipulation. Emmert and colleagues found a significant reduction in the incidence of stroke (0.7% vs 2.3%) with the use of the CFDs compared with a partial clamp in off-pump patients.¹⁹

The discrepancies noted between the aforementioned studies and our present study can be explained by several factors. First, the ubiquitous use of epiaortic ultrasound in this trial helped significantly reduce selection bias and confounding based on the burden of aortic disease. Therefore, patients who were selected for the on-pump or off-pump group at the discretion of the operating surgeon and then randomized to the aortic manipulation strategy were more likely to have a similar level of atheroembolic risk compared with patients in observational analyses that account for neither selection bias nor burden of aortic disease. The advantage of CFDs compared with partial clamping that has been observed in other studies may be partially related to their use in

FIGURE 3. As-treated analysis of HITS data in off-pump CABG. A, Number of CFDs used and HITS recorded. B, One CFD versus >1 CFDs. C, One CFD versus partial clamp. D, More than 1 CFD versus partial clamp. The number of HITS was log-transformed to compress the scale for high values and stretch the scale for low values, allowing for a better visual comparison between 2 right-skewed distributions. *HITS*, High-intensity transient signals; *CFD*, clampless facilitating device; *IQR*, interquartile range.

patients with varying levels of advanced aortic disease and surgeon selection. In our institution, patients who were identified with advanced aortic disease (epiaortic grade 3-5) were not eligible for randomization, because equipoise does not exist in our practice about how to manage these patients; we do not clamp the aorta and use either CFDs or in situ arterial grafts alone or as inflow for other conduits. Furthermore, there may have been more HITS in the CFD group compared with the partial-clamp group simply because there were more opportunities for measurement, given that 25 patients in the CFD group had multiple CFDs (4 measurement occasions vs 2 in the partial-clamp group).

In addition, because of the intricacies associated with TCD analysis, a dedicated neurologist with expertise in TCD (A.A.) reviewed and adjudicated our TCD findings. Similarly, based on his analysis and previous reports,^{5,6} we did not feel that we could accurately separate gaseous emboli from solid emboli in this study. Finally, the randomization of a large number of patients in this study minimized the confounding that may exist in observational retrospective and prospective cohort studies even with the use of advanced statistical analyses, such as propensity-score matching.

Similar to other studies,^{12,14,20} we failed to find a correlation between neurocognitive testing and cerebral microembolization. It is possible that cerebral microemboli that are detected by TCD do not result in persistent neurocognitive dysfunction, and that such properties as size and composition are more important than actual number.²¹

The main limitation of this study was the use of TCD as a surrogate for cerebral adverse events. TCD's limitations are well known and include no proven correlation with adverse neurologic clinical events, difficulty with data capture during surgery, difficulty differentiating artifacts from microembolic events, and difficulty distinguishing gaseous from solid microemboli. The use of diffusion-weighted magnetic resonance imaging would have strengthened this study, but was cost-prohibitive. The use of a dedicated neuropsychometrist to perform neurocognitive testing might have improved the ability to detect subtle differences in cognitive impairment among the groups.

The sample size calculations were derived from TCD data in previously published reports and preliminary data at our own institution (for off-pump CABG).^{11,12} Nonetheless, the number of HITS observed in this study was far lower than anticipated in all of the groups. This

raises the possibility of a type II error in the on-pump comparison, because the study was not powered to detect a smaller effect size. The likely main reason for the lower number of HITS in all groups was that our TCD recordings were reviewed and adjudicated by a neurologist with expertise in TCD. Many signals that were labeled as HITS by the computer software were in fact false-positive readings.

CONCLUSIONS

There was no significant difference with the use of 2 clamps compared with 1 clamp for patients undergoing on-pump CABG, and there was no advantage of using CFDs compared with a partial-clamp technique for patients undergoing off-pump CABG. Therefore, for off-pump patients with grade I-II aortic disease requiring aortocoronary proximal anastomoses, we recommend the use of partial clamping, especially when multiple proximal anastomoses are performed. For patients undergoing on-pump CABG, either a single-clamp or a double-clamp strategy can be used in patients with grade I-II aortic disease, depending on surgeon preference.

Conflict of Interest Statement

M.E.H. serves as a consultant for Maquet Cardiovascular. All other authors have nothing to disclose with regard to commercial support.

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Key Words: CABG, stroke, neurocognitive outcomes

TABLE E1. Preoperative and postoperative neurocognitive results

Cognitive domain	Off-pump CABG			On-pump CABG		
	CFD	Partial clamp	P value	Single Clamp	Double clamp	P value
Psychomotor Speed Scale Score						
Preoperative	86.8 ± 19.2 (n = 15)	86.3 ± 12.8 (n = 15)	.94	92.1 ± 17.9 (n = 19)	89.1 ± 20.6 (n = 23)	.58
Postoperative	94.67 ± 20.2 (n = 12)	98.75 ± 10 (n = 16)	.52	93.29 ± 19 (n = 21)	91.92 ± 16.3 (n = 26)	.78
Change	9.9 ± 15.8 (n = 12)	11.5 ± 11.5 (n = 15)	.77	3.6 ± 12.6 (n = 18)	3.5 ± 15.8 (n = 22)	.98
Processing Speed Scale Score						
Preoperative	90.4 ± 16 (n = 15)	89.1 ± 14 (n = 20)	.80	99.3 ± 14.1 (n = 22)	92 ± 18 (n = 27)	.11
Postoperative	94.13 ± 17.2 (n = 16)	96.67 ± 13.4 (n = 21)	.61	103 ± 16.5 (n = 24)	98.25 ± 13.4 (n = 28)	.26
Change	5.5 ± 15.4 (n = 15)	9 ± 11.1 (n = 20)	.49	5.8 ± 13.6 (n = 22)	5.6 ± 16.9 (n = 25)	.98
Complex Attention Scale Score						
Preoperative	89 ± 22.6 (n = 12)	79.1 ± 26.6 (n = 11)	.36	83 ± 33.9 (n = 16)	95.9 ± 14.3 (n = 14)	.18
Postoperative	89.6 ± 21.4 (n = 9)	97.6 ± 16 (n = 13)	.47	96.3 ± 24.7 (n = 18)	89.2 ± 32.5 (n = 20)	.40
Change	1 ± 12.7 (n = 6)	15.9 ± 29.7 (n = 9)	.23	16.6 ± 29.1 (n = 13)	3.1 ± 10.6 (n = 12)	.15
Visual Memory Scale Score						
Preoperative	96.7 ± 14.3 (n = 17)	93.2 ± 13.6 (n = 21)	.53	91.9 ± 16.4 (n = 22)	94.4 ± 20.9 (n = 25)	.60
Postoperative	95.9 ± 14.6 (n = 15)	95.4 ± 14.5 (n = 19)	.94	91.79 ± 15.2 (n = 24)	93.9 ± 19.9 (n = 29)	.65
Change	-2.1 ± 23 (n = 15)	1.1 ± 18.3 (n = 19)	.62	0.59 ± 16.2 (n = 22)	0.13 ± 17.4 (n = 24)	.93
Verbal Memory Scale Score						
Preoperative	89.4 ± 21.5 (n = 17)	80.7 ± 20 (n = 20)	.21	93.1 ± 20.7 (n = 22)	87.8 ± 20.8 (n = 25)	.39
Postoperative	84.2 ± 24.4 (n = 17)	85.6 ± 21.5 (n = 20)	.81	94 ± 19.1 (n = 24)	92 ± 21.2 (n = 30)	.96
Change	-5.1 ± 24.5 (n = 17)	3.3 ± 14 (n = 19)	.20	2 ± 13.8 (n = 22)	3.7 ± 23.1 (n = 25)	.77
Cognitive Flexibility Scale Score						
Preoperative	89.4 ± 14.2 (n = 12)	82.8 ± 26.8 (n = 12)	.41	89.6 ± 18.4 (n = 16)	90.9 ± 17.5 (n = 18)	.84
Postoperative	91.2 ± 15.2 (n = 11)	98 ± 17.1 (n = 14)	.38	96.7 ± 21.3 (n = 20)	95.7 ± 19.9 (n = 20)	.87
Change	1.9 ± 9.4 (n = 8)	14.1 ± 25 (n = 9)	.08	11.1 ± 7.6 (n = 14)	9.4 ± 11.3 (n = 15)	.75
Executive Function Scale Score						
Preoperative	89.2 ± 13.1 (n = 13)	83.7 ± 26 (n = 14)	.47	94.8 ± 19.1 (n = 19)	89.2 ± 18.3 (n = 23)	.36
Postoperative	84.3 ± 16.7 (n = 13)	83.6 ± 25.1 (n = 15)	.93	88.6 ± 24.3 (n = 20)	86.2 ± 21.9 (n = 22)	.74
Change	5.7 ± 10.6 (n = 11)	10.5 ± 20.5 (n = 11)	.40	8.6 ± 7.8 (n = 17)	7.8 ± 12.5 (n = 20)	.85

CABG, Coronary artery bypass grafting; CFD, clampless facilitating device.