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Do Surface-Modifying Additive Circuits Reduce the Rate of Cerebral Microemboli During Cardiopulmonary Bypass?

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Abstract: The objective of this study was to determine if surface-modifying additive (SMA) cardiopulmonary bypass (CPB) circuits are associated with a lower rate of cerebral microemboli during CPB compared with standard circuits. In a 2 × 2 factorial design, patients undergoing coronary artery bypass graft surgery were randomized to SMA or standard CPB circuits (with and without methyl-prednisolone). Transcranial Doppler was used to detect high-intensity transient signals (HITS) in both middle cerebral arteries. HITS were counted from onset to end of CPB. Intervals of interest were as follows: period 1, from CPB onset to aortic cross-clamping; period 2, from aortic cross-clamping to immediately before de-clamping; period 3, from aortic de-clamping to before aortic side-clamping; period 4, from the application of the aortic side clamp to immediately before the release of the side clamp; period 5, from aortic side clamp release to the end of CPB. There were 14 patients in each circuit group. No significant differences were found on the partial and total counts of HITS (medians [25th, 75th percentile]) between patients exposed to standard (total count: 228 HITS [174, 280]) and SMA circuits (total count: 156 HITS [104, 356]; $p = .427$). The median of the sum of HITS per patient associated with perfusionist interventions was not different between both circuit groups (standard: 17 HITS [7, 80]; SMA: 43 HITS [13, 168]; $p = .085$). This study, with a sample size of 28 patients, indicates that it is unlikely to find any difference in the count of HITS during CPB that is greater than 117 HITS between the two CPB circuits. Moreover, our findings emphasize the relevance of minimizing additional sources of cerebral microembolization during CPB that are not directly related to the biocompatible nature of the SMA CPB circuit. **Keywords:** cardiopulmonary bypass, copolymers, biocompatible circuits, transcranial Doppler. *JECT 2006: 38:216–219*

Standard cardiopulmonary bypass (CPB) circuits can damage blood components and activate biologic cascades (1). These effects are attenuated when surface-modifying additive (SMA) copolymers are added to the circuits (2). SMA circuits may offer advantages over heparin-coated circuits by minimizing coagulation dysfunction (3,4). The SMA-CPB circuit takes advantage of the localization of alternating hydrophobic (polysiloxane) and hydrophilic (polycarprolactone) "domains" on the blood-contacting surface of the circuit (4). This increases the thromboresistant properties of the circuit, which may reduce both the possibility of clot formation and the risk of cerebral embolization.

Transcranial Doppler (TCD) is a method used in the detection of cerebral emboli from different anatomic sources (5). During TCD monitoring, air and solid emboli are recognized as high-intensity transient signals (HITS). In this study, TCD was used in a group of patients undergoing coronary artery bypass graft (CABG) surgery who were randomized to SMA and standard CPB circuits. We tested the hypothesis that SMA-CPB circuits would be associated with a lower rate of cerebral microemboli during CPB compared with standard circuits.

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MATERIALS AND METHODS

After approval by the Human Research Ethics Board and after obtaining informed consent, patients participating in a randomized clinical trial designed to assess the inhibitory properties of SMA-CPB circuits (with and without methyl-prednisolone [MPSS], 1 g intravenous given before CPB) on the systemic inflammatory response were enrolled. In the original trial, independent and combined effects of MPSS and the SMA circuit on tissue plasminogen activator (tPA) and bradykinin were evaluated using a 2 × 2 factorial design (4). Patients were randomized to one of four groups: group 1, standard CPB circuit and placebo; group 2, standard circuit and MPSS; group 3,

SMA-CPB circuit and placebo; group 4, SMA circuit and MPSS.

The original trial was powered to detect a significant difference in tPA and bradykinin using a sample size of 17 patients per group. However, the TCD equipment was available for only 28 of the cases. Because there were no differences in anticoagulation among the groups in the initial study, the placebo and MPSS arms of the study were grouped by type of circuit, resulting in an equal number of patients ($n = 14$) for both standard and SMA circuits.

Inclusion and Exclusion Criteria

We included patients scheduled for CABG surgery under CPB. Exclusion criteria consisted of those patients on steroids or Coumadin (warfarin sodium) and those undergoing emergency, reoperative surgery, or other cardiac procedures in addition to CABG. We excluded patients who had evidence of preoperative coagulopathy, bleeding diathesis, thrombocytopenia (<140,000 μL), severe chronic obstructive pulmonary disease ($FEV_1 < 1.5$ L), history of recent peptic ulcer disease (<6 months), chronic renal failure (creatinine > 120 μmol/L), or steroid dependency. Patients taking angiotensin II converting enzyme inhibitors (ACEIs) had these drugs discontinued 3 days before surgery and were switched to an angiotensin II receptor antagonist to limit the effect of ACEIs on measured plasma bradykinin levels.

CPB Protocol

Extracorporeal circulation was achieved with the use of a non-pulsatile roller pump (Cobe Cardiovascular, Arvada, CO). All the components of the two CPB circuits were identical except for the coating of the SMA copolymer. The CPB circuit consisted of a flat sheet polypropylene (1.3 m^2) membrane oxygenator (COBE DUO; Cobe Cardiovascular), a closed venous reservoir bag, and an arterial line filter (43 μm; Cobe Sentry with prime Guard). The circuit was primed with 1300 mL of Ringer Lactate (5000 IU of unfractionated Heparin) and continuously recirculated through the filter to remove any impurities before cannulation. Pump flow rates under CPB were maintained between 2.4 and 3.2 L/m^2/min, and cooling was achieved at target temperatures of 32°C (nasopharyngeal). Myocardial protection consisted of intermittent (20-minute intervals) antegrade cold crystalloid cardioplegia complemented by topical pericardial saline irrigation. Once on CPB, active venting was continuous, and the activated clotting time (ACT) was monitored using an ACT II machine (Medtronic, Minneapolis, MN). Blood aspirated from the surgical field was collected intraoperatively and up to 4 hours after surgery, and was subsequently processed by filtration (30-μm filter) and centrifugal washing (BRAT; Cobe Cardiovascular) before being returned to the patient.

In the SMA-CPB circuit, all blood-contacting surfaces were coated "tip-to-tip," including the cannulae with the SMA copolymer ($SMAR_xT$; Cobe Cardiovascular). MPSS and placebo were given at the time of insertion of the central line and before the incision. All members of the surgical and anesthetic teams were blinded to the use of MPSS and to the CPB circuit assignment. In addition, the number and type of perfusionist interventions (i.e., blood sampling, drug boluses, and volume infusions) during the period that the aorta remained clamped were documented (6).

Transcranial Doppler

A dual-gated pulse-wave TCD system (MDT2; DWL, Sipplingen, Germany) equipped with two 2-MHz probes was used for insonation of both middle cerebral arteries (MCAs). An adjustable headband (Marc 600; Spencer Technologies, Seattle, WA) secured the TCD probes on the temporal windows. TCD recordings were performed using the following parameters: 58% overlapping, Fast Fourier Transformation resolution of 128 Hz, dynamic range of 60 dB, inter-gate separation of 5 mm, sample volume of 10 mm, and high-pass filtering with a cut-off frequency of 100 Hz.

TCD Data Analysis

An experienced ultrasonographer (RAR) who was blinded to the circuit assignment reviewed the Doppler recordings several weeks after surgery. Doppler signals were classified as true HITS, equivocal HITS, artifacts, and Doppler speckles according to pre-established criteria (7,8). Our degree of inter-observer agreement for discriminating true HITS from other non-embolic signals during CPB has been excellent (6,8). Equivocal HITS, artifacts, and Doppler speckles were not included in the final analysis.

Measurement of HITS

HITS were counted from onset to end of CPB. Also, we measured HITS at specific intervals during CPB. Intervals of interest were as follows: period 1, from CPB onset to aortic cross-clamping; period 2, from aortic cross-clamping to immediately before de-clamping; period 3, from aortic de-clamping to before aortic side-clamping; period 4, from the application of the aortic side clamp to immediately before the release of the side clamp; period 5, from aortic side clamp release to the end of CPB. The counts of HITS were generated by adding the counts for the right and left MCAs.

Statistical Analysis

Because HITS counts were not normally distributed, their values were presented as medians (25th, 75th percentiles). A Mann-Whitney test for two groups on continuous measures or the χ^2 for proportions assessed differences between the two CPB circuits regarding count of

HITS and several physiologic or demographic variables. All tests used $p < .05$ for the critical value of statistical significance. The median count of HITS associated with perfusionist interventions were compared with the Kruskal-Wallis test. This was followed by pair-wise comparisons with the Mann-Whitney test, adjusting for multiple comparisons (Bonferroni correction). The probability of incorrectly rejecting the null hypothesis was calculated by statistical power analysis. Analyses were performed using SPSS (SPSS Inc., Chicago, IL) version 13.0.

RESULTS

Table 1 summarizes patient distribution, demographics, and CPB parameters, and Table 2 shows the total and partial counts of HITS for each CPB circuit. No differences were found between the two circuit groups regarding the proportion of patients exposed to placebo or MPSS, age, use of the single cross-clamp technique, or number and type of perfusionist interventions per patient. The highest count of HITS during CPB was found during the time that the aorta remained clamped (Table 2, period 2). Blood sampling was associated with a higher median count of HITS per sample across patients compared with drug boluses (unadjusted: $p = .016$; Bonferroni adjustment: $p = .048$) or volume infusion (unadjusted: $p = .056$; Bonferroni adjustment: $p = .168$), but there was no difference between drug boluses and volume infusion ($p = .91$). No significant differences were found on the partial and total counts of HITS between patients exposed to standard and SMA circuits (Table 2). In addition, the median of the sum of HITS per patient associated with perfusionist interventions was not different between both circuit groups (standard: 17 HITS [7, 80]; SMA: 43 HITS [13, 168]; $p = .085$).

Because perfusionist interventions are not related to the effect of circuit choice, we subtracted HITS associated with perfusionist interventions on each patient from the number of HITS identified during the time that the aorta remained clamped (period 2). The mean count of HITS (±SD) in the absence of any intervention was 138 ± 157 HITS for the standard circuit and 83 ± 62 HITS for the SMA circuit ($p = .427$). With the current sample size, our study had an 80% power to detect a difference of 117 HITS or greater between the two CPB circuits, but only a 31% power for a difference of 55 HITS. Based on these findings, we estimated that at least 65 patients per circuit would be necessary to detect a difference of 55 HITS with 80% power and a significance level of .05 (two-sided).

Table 1. Demographics and CPB parameters according to the type of CPB circuit.

Variable	Standard CPB Circuit	SMA CPB Circuit	*p* Value
Patients	14	14	
Men	12 (86)	12 (86)	.990
Single aortic cross-clamp technique	6 (43)	6 (43)	.990
Placebo	6 (43)	8 (57)	.449
MPSS	8 (57)	6 (43)	.449
CABG with two or three proximal grafts	8 (57)	8 (57)	.647
Age (years)	56 ± 7	56 ± 8	.943
CPB time (min)	85 ± 33	85 ± 21	.645
Aortic cross-clamp duration (min)	59 ± 26	60 ± 19	.748
CBFV on CPB (cm/s)	43 ± 14	38 ± 12	.242

Values are means ± SD or number of patients (% total).
CABG, coronary artery bypass grafting; CBFV, cerebral blood flow velocity; CPB, cardiopulmonary bypass; SMA, surface modifying additive; MPSS, methyl-prednisolone.

Table 2. HITS counts and number of perfusionist interventions according to type of CPB circuit.

Variable	Standard CPB Circuit	SMA CPB Circuit	*p* Value
Blood samples per patient	4 (2,6)	5 (4.7)	.126
Drug boluses per patient	4 (2,5)	4 (3,4)	.762
Volume infusions per patient	0 (0,2)	0 (0,3)	.176
HITS count, period 1	13 (5,24)	18 (8,27)	.84
HITS count, period 2	64 (31,115)	74 (34,196)	.91
HITS count, period 3	6 (1,31)	1 (0,4)	.180
HITS count, period 4	33 (13,37)	12 (3,25)	.094
HITS count, period 5	52 (39,56)	17 (8,55)	.336
Total HITS count on CPB	228 (174,280)	156 (104,356)	.427
HITS count, blood sampling*	3 (0,9)	3 (1,26)	.769
HITS count, drug injection*	2 (0,3)	1 (0,3)	.939
HITS count, infusions*	2 (0,3)	1 (1,3)	.818

Values are median (25th, 75th percentiles) number of patients (% total).
CPB, cardiopulmonary bypass; HITS, high-intensity transient signals; MPSS, methylprednisolone.
*Median counts of HITS per sample across patients: period 1, from CPB onset to aortic cross-clamping; period 2, from aortic cross-clamping to immediately before de-clamping; period 3, from aortic de-clamping to before aortic side-clamping; period 4, from aortic side-clamping to immediately before the release of the side clamp; period 5, from aortic side clamp release to the end of CPB.

DISCUSSION

Exposure of the patient's blood to standard CPB circuits has been suggested to be responsible for substantial morbidity after cardiac surgery, including postoperative bleeding and inflammation (1). SMA circuits improve biocompatibility with reduced thrombin generation and tissue plasminogen activation (2,4). It is believed that these beneficial effects may result in reduced clot formation and embolus generation during CPB (4). In this study, we did not find any differences between SMA and standard CPB circuits in the total or partial count of HITS measured in the MCAs at different time-points during CPB. Previous studies have found no differences in the rate of retinal emboli detected by fluorescein angiography (9) or in the counts of emboli trapped in brain and lungs (10,11) between heparin-coated and standard CPB circuits during

CPB. Our findings suggest that improving the biocompatibility of CPB circuits may not necessarily decrease cerebral microemboli during CPB. Several factors may explain this lack of association. First, air and lipid particulates account for the largest proportion of systemic emboli during CPB, whereas clots or platelet aggregates are only responsible for a smaller fraction (6,12). Second, large amounts of air bubbles derived from the surgical field or extracorporeal circuit may obscure any decline on the solid fraction of emboli (8). Third, the fact that TCD does not differentiate embolus composition may limit the assessment of any intervention directed to decrease the number of solid emboli (5,8). Finally, cardiotomy suction, which is active during cardiac surgery frequently accounts for an unknown amount of lipid microemboli during CPB (12).

Because cerebral embolization during CPB is a multifactorial phenomenon, clinical studies investigating single strategies aimed to decrease cerebral emboli may require large sample sizes. To have the statistical power necessary to show a significant difference of 55 HITS or greater associated with the type of circuit, our results suggest that a prospective randomized study should aim to a minimum of 65 patients per group.

In summary, this study, with a sample size of 28 patients, indicates that it is unlikely to find any difference in the count of HITS during CPB that is greater than 117 HITS between the two CPB circuits. Moreover, our study emphasizes the relevance of minimizing additional sources of cerebral microembolization during CPB that are not directly related to the biocompatible nature of the SMA-CPB circuit. Because our findings showed that most HITS during CPB occurred during the time that the aorta was cross-clamped and between the release of the aortic side clamp and the end of CPB, these two periods may represent the major opportunity to reduce the number of HITS during CABG surgery under CPB.

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