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Original Article

Embolic Activity During In Vivo Cardiopulmonary Bypass

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Abstract: Neurologic injury after cardiac surgery is principally associated with emboli. Although much work has focused on surgical sources of emboli, less attention has been focused on emboli associated with the heart–lung machine. We tested whether emboli are associated with discrete processes during cardiopulmonary bypass (CPB). One hundred patients undergoing cardiothoracic surgery were enrolled between April 2008 and May 2011 at a single medical center. During each surgical procedure, emboli were counted in three CPB locations: the venous side (Channel 1), before the arterial line filter (Channel 2), and after the arterial line filter (Channel 3). We used prespecified event markers to identify perfusionist interventions. Identical circuits were used on all patients. Of the 100 patients enrolled, 62 underwent isolated coronary artery bypass grafting (CABG), 17 underwent isolated valve operations, and 21 underwent CABG plus valve. Median counts across Channels 1, 2, and 3 were 69,853, 3,017, and 1,251, respectively. The greatest contributor to emboli in Channels 1, 2, and 3, respectively, were achieving the calculated CPB flow, opening of the electronic arterial line clamp, and introducing a hemofilter. The circuit technology was efficient in reducing total emboli counts from Channels 1–2 irrespective of the size of the emboli. Nearly 71% of all emboli 30–100 μm in size were removed from the circuit between Channels 2 and 3. No significant association was found between emboli counts and S100B release. Emboli occur frequently during CPB and are predominantly associated with the initiation of bypass, operation of the electronic arterial line clamp, and the initiation of a hemofilter. Continued work to reduce the occurrence of emboli is warranted.
Keywords: cardiopulmonary bypass, CPB, embolism, coronary artery bypass grafts, CABG. *JECT. 2014;46:150–156*

Neurologic injury is a leading cause of morbidity subsequent to cardiac surgery and is thought to be principally the result of embolization (1–4). Within the realm of embolization, most attention has focused on atheroembolic debris arising largely from manipulation of a diseased aorta (5). Nonetheless, other types of emboli (including gaseous microemboli emanating from the cardiopulmonary bypass [CPB] circuit) may contribute to neurologic injury (6).

A number of articles have focused on documenting the occurrence of emboli. Taylor and colleagues (6) identified emboli associated with perfusionists' techniques, including drug administration and blood sampling. Subsequent investigators have undertaken in vitro studies to quantify the air-handling characteristics of a variety of perfusion technologies (7–9). Groom and colleagues (10), although not able to discriminate between non- and gaseous microemboli, documented reduction of emboli subsequent to changes in CPB technique and devices. Recently Lynch (11) reported findings from a preliminary study of 30 patients who were monitored throughout their coronary artery bypass grafting (CABG) or valve operation and found emboli associated with initiation of CPB, manipulation of the heart, drug administration, and clamp insertion/removal.

We undertook a prospective observational cohort study of 100 patients undergoing elective or urgent CABG and/or valve surgery to test the hypothesis that emboli are a frequent occurrence during CPB and may be associated with discrete processes of perfusion care during CPB.

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METHODS

Data Sources

A total of 100 patients were enrolled in this prospective observational study. The patient cohort was restricted to those aged 30–89 years, irrespective of gender, receiving CABG and/or valve surgery on a nonemergency basis. An urgent patient was defined as one whose medical condition warrants being kept in-hospital until surgery can be scheduled, but does not necessitate an emergent procedure. All procedures were performed by the same team of four surgeons and three perfusionists at Dartmouth Hitchcock Medical Center, Lebanon, NH. All patients received identical CPB circuits: Sorin PrimO$_2$x® hollow-fiber oxygenator, Sorin VVR4000i hard-shell venous reservoir, Dideco D732 27-μm arterial line filter, and Sorin Revolution® centrifugal pump (Sorin Group, Arvada, CO). The normothermic CPB prime was circulated for a minimum of 1 hour at flows of at least 3 L per minute (LPM); neither prebypass filters nor afterload were used during recirculation. All circuits were flushed with carbon dioxide at 5 LPM for at least 2 minutes through the arterial line filter stopcock before priming. Patients for aortic valve replacement and/or CABG were cannulated using a three-stage cavoatrial cannula; those for mitral valve repair or replacement received bicaval cannulation.

Vacuum-assisted venous drainage (VAVD) was used in all procedures with a maximum vacuum level of 30 mmHg. VAVD was started after initiating CPB and was discontinued before weaning. When initiation of a hemofilter (Sorn, Arvada, CO) was deemed necessary, it was interposed into the membrane recirculation line with return to a filtered port on the cardiotomy reservoir. These hemofilters did not require prerinsing (per the manufacturer's instructions). Flow through the device was achieved solely by the transmembrane pressure, and vacuum was not applied to the hemofilter.

Emboli were monitored in three places on the CPB circuit (Channel 1, the venous line; Channel 2, before the arterial line filter; Channel 3, after the arterial line filter; Figure 1) using the EDAC Quantifier (Luna Innovations, Roanoke, VA) with factory preset parameters. The EDAC device uses the principle of ultrasound backscatter to count and characterize emboli passing through sterile cuvettes added to the CPB circuit. As a result of the backscatter methodology and the different physical and reflective properties of bubbles and solids, the preponderance of emboli detected are gaseous microemboli (12–15). The EDAC monitoring screen was blinded to clinical staff during procedures so that no modifications in practice would occur during or subsequent to emboli detection.

Simultaneous data recordings were made using the EDAC and the Sorin Data Management System (DMS; Sorin Group) on the heart–lung machine. Before the start of each procedure, the internal clocks of the EDAC and DMS devices were adjusted to a standardized network clock in the operating suite. At the conclusion of each procedure, data were exported from the EDAC device. The EDAC recorded counts and embolic load in 2-minute intervals, broken down into 10-μm size categories. The DMS generated a record for each case that included perfusion parameters and patient hemodynamic data, recorded every 20 seconds. These data files were later merged to create a single unique deidentified record for each procedure.

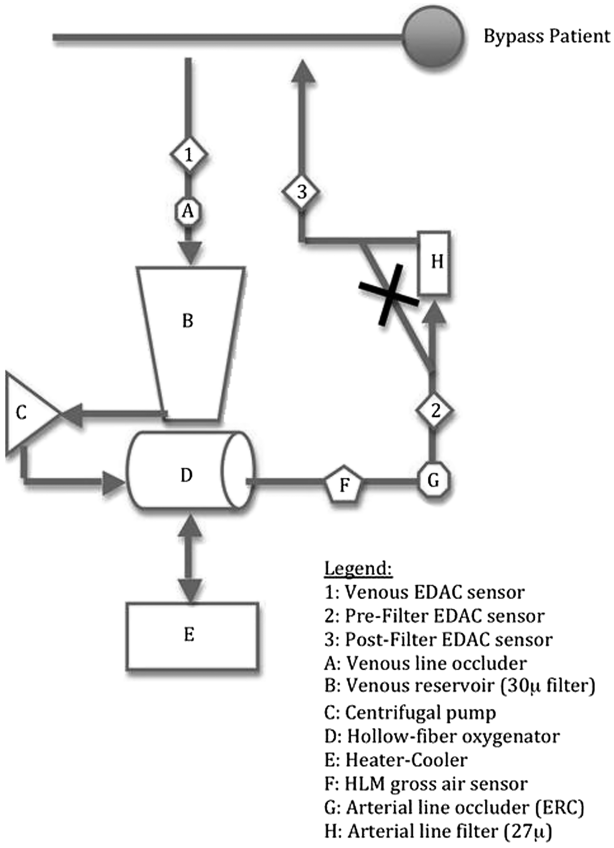


Figure 1. Cardiopulmonary bypass circuit diagram. Diagram of cardiopulmonary bypass circuit showing locations of major components and the sensors for the EDAC Quantifier.

Blood samples were also taken from patients before incision and on the morning of postoperative day 1 (POD1) for biomarker analysis at a later date. We collected 75 matched pre- and postoperative samples among the 100 candidate patients. Serum S100B values were measured using two-site immunoassays (Sangtec® 100 IRMA, Liaison® Sangtec 100, Sangtec 100 ELISA) from DiaSorin AB (Bromma, Sweden).

Data files from the DMS and EDAC systems included keystroke event recording marks entered by a research assistant as well as events automatically recorded by the Sorin DMS or manually entered by the perfusionist.

In addition, the files could be annotated with remarks contained in a written paper record kept for each case. Given the 2-minute time window used by the EDAC device, it was assumed that embolic activity noted for the 2 minutes after an event was attributable to that event. When an event occurred between the 2-minute markers, data were proportionally taken from that time window and the ensuing window.

Statistical Analysis

All analyses were performed with Stata 12.0 (College Station, TX). We used χ^2 tests for categorical data and Kruskal-Wallis and *t* tests for continuous data. In secondary analyses, we stratified by type of procedure: CABG (n = 62) and valve with or without CABG (n = 38).

For the purpose of our analysis, we report median counts except when exploring the association between embolic counts and absolute changes in S100B (μg/L). For this latter analysis, we report the total embolic counts for the procedure rather than median counts.

Human Subjects

This study was approved by the Committee for the Protection of Human Subjects of Dartmouth College and the Dartmouth-Hitchcock Medical Center (CPHS #20307, "Redesigning Cardiac Surgery to Reduce Neurologic Injury"). A perfusionist, a cardiac physician's assistant, or a nurse research assistant obtained informed consent from each patient. Patients were issued a unique identifier; research data were not linked back to the patient's medical record.

RESULTS

Patient and disease characteristics for our patient population are detailed in Table 1.

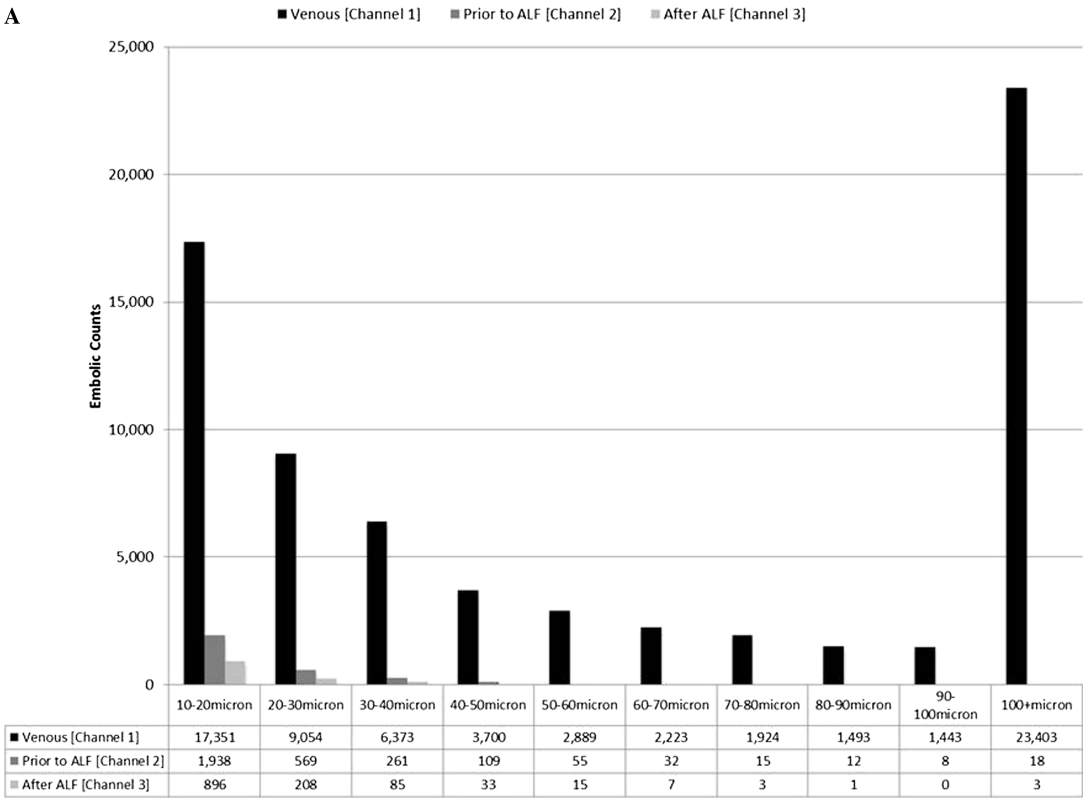
Table 1. Patient and disease characteristics.

Variables	No.	Percent
Number of procedures	100	100
Primary procedure		
CABG		62
Valve		21
CABG + valve		17
Age (years), % by group		
<60		22
60–69		39
70–79		28
≥80		11
Sex, % female		25
Body surface area (m^2), % by group		
<1.70		9
1.70–1.99		32
≥2.00		59
Body mass index (kg/m^2), %		
<31		69
31–36		20
≥37		11
Preoperative HCT, % by group		
<36		46
36–39		24
40–42		21
≥43		9
Preoperative WBC >12,000, % yes		6
Prior CABG surgery, % yes		4
Prior PCI, % yes		29
Comorbid disease, % yes		
Vascular disease		24
Diabetes		37
COPD		14
CHF		19
Dialysis or creatinine ≥2		7
NYHA Class 4		10
Ejection fraction, %		
<40		14
40–49		14
50–59		19
≥60		53
Coronary artery disease, % yes		
Left main stenosis ≥50%		27
Three-vessel disease		29
MI within 7 days		13
Priority at surgery, %		
Elective		38
Urgent		62

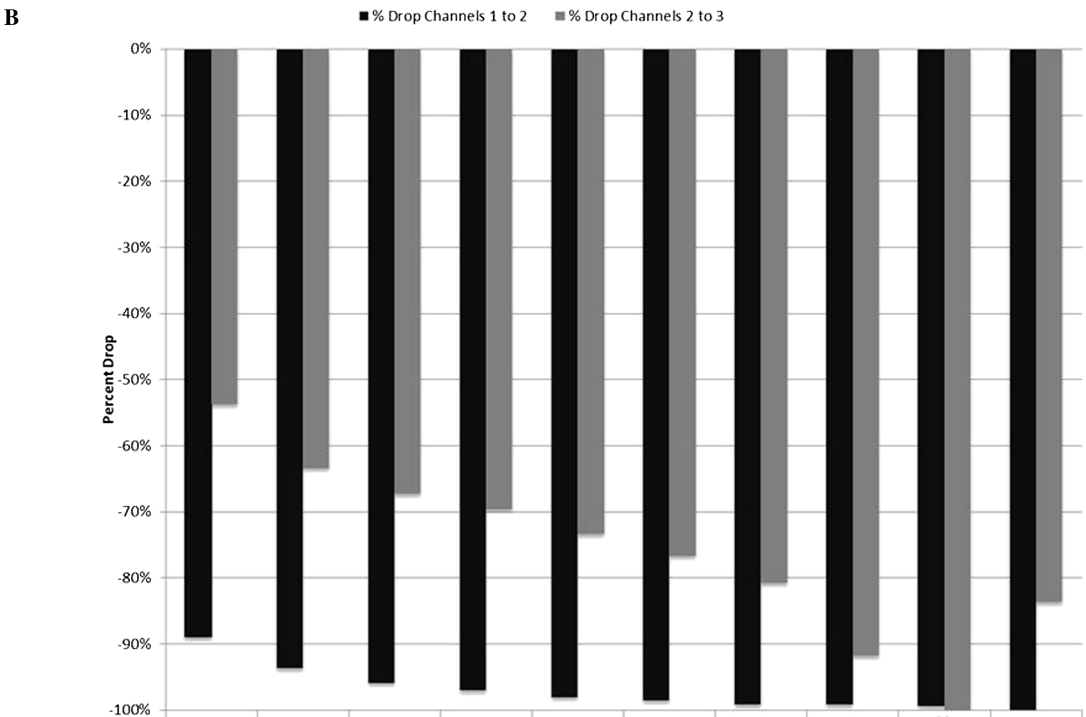
Data supplied by crosslink with the Northern New England Cardiovascular Disease Study Group's Cardiac Surgery Registry.
CABG, coronary artery bypass grafting; HCT, hematocrit; WBC, white blood cell count; PCI, percutaneous coronary intervention; COPD, chronic obstructive pulmonary disease (requiring medication); CHF, congestive heart failure; NYHA, New York Heart Association; MI, myocardial infarction.

The top five perfusion processes contributing to median emboli counts at each location in the circuit were ascertained and are listed in descending order. In the venous line, these include achieving calculated CPB flow, adding albumin to the circuit, initiating VAVD, the onset of CPB, and deairing of the heart. Before the arterial line filter, the events include opening of the electronic arterial line clamp (ERC), onset of CPB, closing of the ERC, VAVD initiation, and starting a hemofilter. Distal to the arterial line filter, the events include initiation of a hemofilter, addition of albumin to the circuit, opening of the ERC, closing of the ERC, and onset of CPB. Blood gas sampling and drug injections by the perfusionist were not found to significantly contribute to embolic events. Venous air lock was noted in only one patient in our series.

Although larger (>100 μm) emboli were regularly seen in the venous line, they accounted for only 33.5% of total count (Figure 2A). Over one-third (37.8%) of the emboli registered in the venous line were in the 10- to 30-μm range. By the time the blood had transited the venous reservoir and membrane oxygenator, less than .6% of the emboli were characterized in the >100-μm range, and that proportion was only approximately .2% after the arterial line filter (ALF). Emboli counts were significantly reduced in all size categories as they progressed through the CPB circuit; the combination of the venous reservoir, centrifugal pump, and membrane compartment



	10-20micron	20-30micron	30-40micron	40-50micron	50-60micron	60-70micron	70-80micron	80-90micron	90-100micron	100+micron
Venous [Channel 1]	17,351	9,054	6,373	3,700	2,889	2,223	1,924	1,493	1,443	23,403
Prior to ALF [Channel 2]	1,938	569	261	109	55	32	15	12	8	18
After ALF [Channel 3]	896	208	85	33	15	7	3	1	0	3



	10-20micron	20-30micron	30-40micron	40-50micron	50-60micron	60-70micron	70-80micron	80-90micron	90-100micron	100+micron
% Drop Channels 1 to 2	-89%	-94%	-96%	-97%	-98%	-99%	-99%	-99%	-99%	-100%
% Drop Channels 2 to 3	-54%	-63%	-67%	-70%	-73%	-77%	-81%	-92%	-100%	-84%

Figure 2. (**A**) Distribution of emboli counts by size category. Median microemboli counts by location in the cardiopulmonary bypass circuit. Counts and size categories determined by the EDAC Quantifier. (**B**) Mitigation of emboli counts by size category. Percentage change in median microemboli counts as blood progresses through cardiopulmonary bypass circuit. Counts and size categories determined by the EDAC Quantifier.

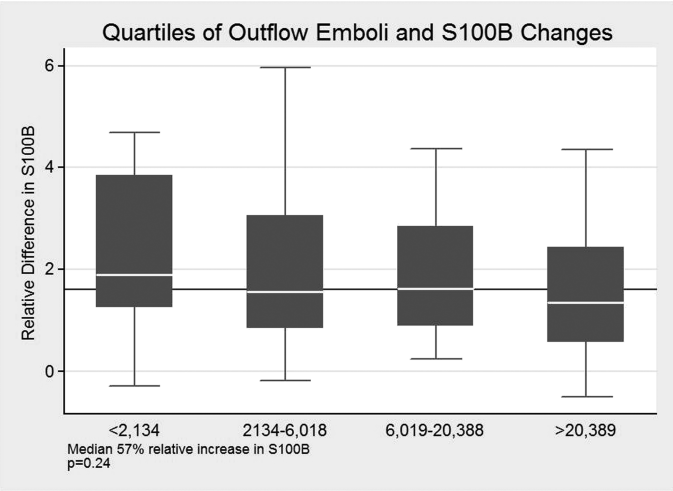


Figure 3. Absolute changes in S100B and postarterial embolic counts. Interquartile range of changes between preoperative and postoperative S100B values (μg/L) across quartiles of total postarterial line filter embolic counts.

accounted for >95% reduction. Figure 2B shows mitigation of embolic activity by size category during transit through the CPB circuit.

In our secondary analysis, we found that embolic counts (of all sizes) on the venous side of the circuit were quantitatively higher for patients undergoing valve versus isolated CABG surgery (relative increase ranged from 83% to 193% higher across range of embolic sizes). However, differences between emboli counts by procedure in the pre- and post-ALF sides of the circuit varied in magnitude across embolic size categories (before ALF: minimum 5% decrease, maximum 90% increase; after ALF: minimum 13% decrease, 240% increase).

We found a nonsignificant (P trend = .24) inverse association between differences in S100B and the number of emboli detected post-ALF (Figure 3). The counts used for this analysis are total counts for the procedure, not median counts as used in Figure 2A–B. Findings were similar when restricting to emboli >20 μm in diameter.

DISCUSSION

In this prospective observational cohort study, we found large numbers of emboli associated with discrete processes of perfusionist care. Emboli were of variable size with most large emboli detected in the venous side removed from the circuit by the time the blood transited to the postarterial filter side of the circuit. We found no significant association between emboli returning to the patient and a biomarker of brain injury.

A number of authors have investigated the practice and technology of cardiovascular perfusion. One of the more widely reported studies, performed by Pugsley and colleagues (16), focused on technology assessment and emboli generation and documented the association between increasing number of emboli detected through transcranial Doppler and neurobehavioral injury. Albeit the authors used bubble oxygenators at the time of this study, they found reductions in the number of emboli associated with the use of a 40-μm arterial line filter. More recently, Taylor and colleagues (6) also used transcranial Doppler ultrasonography to document increases in Doppler activity when perfusionists drew blood samples and administered medications into the CPB circuit, a finding not replicated in our current study. Borger and colleagues (17) reported an increase in postoperative neurobehavioral impairment among patients undergoing elective CABG who also had procedures with a greater number of perfusion interventions (≥10 versus <10), even when controlled for prolonged CPB times. This finding was not replicated by Rodriguez and colleagues (18). Using the EDAC, Lynch (11) identified certain process associated with increases in embolic load during CPB, namely the initiation of CPB, manipulation of the heart, insertion and removal of aortic clamps, and the administration of drugs. Relative to the Borger study, Groom and colleagues (19) were able to demonstrate a relationship between increasing quartiles of arterial outflow emboli on bypass and a serum marker (S100B) for brain injury. Differences across studies may reflect differences in both the defined cohorts and methodological approach for detecting emboli.

In an effort to minimize the number of emboli generated by or introduced into the CPB circuit, investigators have undertaken a number of in vitro studies. Direct comparisons of emboli across studies should not be made given the use of different emboli detection devices and variable testing conditions. De Somer and colleagues (20), using a clear blood analog of glycerol and water under controlled laboratory conditions, demonstrated that the EDAC and the Gampt BC200 both under- and overestimated bubble sizes at different flow rates. In addition, both devices only partially counted the numbers of bubbles, especially as flow rates increased. In addition to showing differences between various commercial circuits, Dickinson (7) also demonstrated the increased sensitivity of the EDAC Quantifier as opposed to more traditional devices such as the Hatteland ultrasound. Riley (9) used the EDAC monitor to examine the performance of 10 different ALFs, generally concluding that smaller pore size improved gaseous microemboli separation efficiency. While examining the capabilities of different circuits, Liu (8) also demonstrated that embolic load increased at higher flows and temperatures in all circuits tested. Using such information, Groom and colleagues (10) changed their clinical practice by discontinuing the use of a dry venous line to initiate CPB, redesigned their circuit to incorporate lower

pore sizes of arterial and venous reservoir filters, and added a centrifugal arterial pump to achieve an 87.9% reduction in arterial outflow emboli. In an effort to minimize emboli at our own institution, we adopted the technology reported by Groom and colleagues and used this "optimized" circuit, as described in detail in our "Methods" section.

Although occurring in only one patient in this cohort, venous air lock was associated with high embolic counts at all three locations in the CPB circuit. It was the largest source of emboli on the venous side and before the ALF and the second largest source after the ALF. Although such an event is rare, it does speak to the need for mitigating the entry of air into the venous side of the circuit. Similar to Lynch (11), we also identified that activities associated with the onset of CPB correlated with increased embolic activity. We note that operation of the electronic arterial clamp and the initiation of VAVD were also significant contributors of emboli. We postulate that operation of the ERC results in sudden changes in pressure within the membrane bundle itself, resulting in release of gaseous microemboli. When paired with level and bubble detection safety systems, an ERC represents an important safeguard against both gross gaseous embolism and retrograde arterial flow, yet caution may be warranted in their use for such activities as decreasing flow for clamp insertion and removal. Initiation of VAVD may pull gas in and around cannula pursestrings. VAVD has become common practice to decompress the heart but may need to be coupled with more attention to technique such as a double pursestring on the venous cannula or the use of umbilical tape.

Our findings suggest that emboli, generated while adding albumin to the venous reservoir, are particularly durable, because they appear distal to the ALF and then again in the venous line. We infer that these emboli are gaseous with their persistence perhaps resulting from the increase in surface tension for protein solutions and their subsequent resistance to fracturing (21). For those cases in which colloid administration might be anticipated, alternative practices may result in fewer emboli, including administration of albumin as a prime component with recirculation through a prebypass filter or administration through an intravenous line during the procedure. The return of volume from a hemofilter also enters through the venous reservoir, but those emboli do not appear to persist into the venous circulation. Hemofilters were not prerinsed before introduction into the circuit, but adoption of such a practice may be warranted. We did not find an association between increasing emboli and a marker of brain injury (S100B). This finding contradicts results from Groom and colleagues (19) (perhaps as a result of a difference in the method for detecting emboli), although it supports the findings from a number of other investigators (22,23). Although there are extracerebral sources of S100B as well as contamination from the surgical field, a number of investigators have found S100B associated with emboli during bypass (24) and especially during aortic management (25).

We acknowledge some limitations to our present study. First, although we used a readily available device to monitor emboli activity in the CPB circuit, we recognize that we are not able to definitively distinguish between gaseous and particulate emboli. Nonetheless, the probability for detection of gaseous emboli is much higher with the EDAC device than particulates given that air reflects ultrasound more strongly than particulates and particulates are more likely trapped at the bottom of a reservoir or within filter pores than gaseous emboli (12–15). Although not testable in our study, we anticipate that perfusionist interventions would most likely have an effect on gaseous emboli, exclusive of particulate debris in the aorta dislodged by arterial inflow. The EDAC software does not attempt to characterize the emboli as solid or gas. Second, we cannot rule out some degree of misattribution of emboli to discrete processes of care. Nonetheless, we have no reason to believe that such effect, if real, would be large or systematic.

In conclusion, we have demonstrated that even with the advances in circuit design, emboli may still be detected in large numbers on CPB and may be associated with discrete processes of the perfusionist's care. Changes in those processes should be undertaken in an effort to further reduce emboli. In addition, more sensitive markers may be helpful in assessing the overall impact of such interventions.

DISCLOSURES AND FREEDOM OF INVESTIGATION

Luna Innovations loaned the investigators the EDAC Quantifier and supplied all disposable cuvettes used for the study. The authors had full control of the study design, methods used, outcome parameters and results, analysis of data and production of the written report. Dr. Likosky was supported by a grant from the Agency for Healthcare Research and Quality (1K02HS015663-01A1). This work was partially funded by the Northern New England Cardiovascular Disease Study Group.

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