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Original Articles

Quantification of Fat Mobilization in Patients Undergoing Coronary Artery Revascularization Using Off-pump and On-pump Techniques

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Abstract: Fat mobilization during cardiopulmonary bypass (CPB) is a recognized risk of the procedure. Intravascular mobilization of fat emboli subsequent to CPB has been implicated in some of its recognized pathophysiologies, particularly with regard to cerebral embolic injury. The aim of this study was to investigate whether fat mobilization is still a real issue in modern perfusion practice and to determine whether off pump coronary artery bypass techniques minimize this risk. Thirty patients undergoing routine elective coronary artery bypass graft (CABG) surgery were divided into two groups. Group 1 patients underwent off pump coronary artery bypass (OPCAB) procedures, and group 2 underwent CABG supported with CPB. Blood samples were taken from the CPB patients at the beginning, middle, and end of the procedure, from the suction line, from the arterial line, and from the venous line for measurement of fat emboli present. Samples were taken at corresponding timepoints from the OPCAB patients for similar measurements. Fat emboli were counted manually using Oil red O staining and light microscopy. The fat emboli were sized using calibrated microspheres as a visual size contrast. No fat emboli were observed in any of the blood samples taken from the OPCAB patients. There were fat emboli present in all samples taken during CPB from all sources. The count was highest in the suction system and lowest in the venous blood and tended to increase during CPB. There was an absence of large fat emboli in the venous blood, which tends to indicate that the larger fat emboli lodge in the microvasculature. OPCAB surgery eliminates the risk of fat embolization in patients undergoing coronary revascularization. The suction system is the major source of fat emboli during CPB, and despite the multiple filtration components of the CPB system, fat emboli of various and significant sizes do reach the patient. Fat embolization remains a risk in routine elective CABG surgery. Cardiotomy suction should be eliminated where possible. **Keywords:** fat emboli, off pump, on pump. *JECT. 2006;38:116–121*

Despite innovative treatment regimens involving new classes and types of drugs and interventional cardiology techniques such as intra-coronary balloon dilatation, stenting, and laser angioplasty, routine treatment of ischemic heart disease is still carried out using surgical revascularization with or without cardiopulmonary bypass (CPB). In excess of one million coronary artery bypass graft (CABG) procedures are performed globally each year (1,2). Despite the increase in alternative, less invasive techniques, the number of CPB-supported open heart surgical procedures has remained relatively stable. However, there has been a shift in the average age of patients presented for conventional cardiac surgery. This older patient population often present with more concomitant disease and carry a significantly higher mortality and morbidity than those from younger patient groups. This older patient population carry a greater risk of neurological injury associated with CPB (1). Neurological dysfunction and injury associated with conventional CPB procedures is one of the most common complications, with a reported incidence of between 36% and 90% depending on the investigative technique used. Severe neurological dysfunction is relatively rare, affecting only around 1%–2% of patients, however less severe, but debilitating neurological sequelae are more common with up to 60% of patients in some studies reported with visual field defects, hyper-reflexias,

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or primitive reflexes (2,3). Although many of these manifestations are transient, there have been recent reports in the literature of long-term persistent neurological deficits in CPB patients (4). There is little doubt that the cause of neurological injury in CPB patients is multi-factorial; however emboli, from various extrinsic and intrinsic sources, play a major part in its etiology (5). Advances in the filtration technology used during CPB has led to a decrease in the incidence of micro- and macro-emboli from a number of sources, particularly air emboli, cellular aggregates, and manufacturer's debris (6,7). However, fat emboli are particularly difficult to remove using in-line filtration technology caused by their fluid and deformable nature and do persist as a challenge to patients undergoing conventional CPB procedures. The importance of mobilized fat emboli has been recognized, and techniques and technologies do exist for removing fat emboli as the use of cell savers and fat-adsorbing filters; however, these are expensive and may require that blood is removed from the main perfusion circuit for processing before reinfusion (8). With the advent of modern miniaturized perfusion technology with very low priming volumes, these techniques may not always be suitable.

The source of fat emboli has been the focus of considerable research effort over the years, and the sternotomy, commonly used during CPB procedures, reportedly results in more fat mobilization in the blood and tissues than does a thoracotomy (9). However, perhaps the most important source of fat emboli in the context of CPB is fat that is introduced into the circulation through the cardiotomy suction system (10). A strong association has been reported between the re-use of this scavenged blood and the negative outcome of CPB (11), including inflammatory and neurological outcomes (12), and superior results have been shown when the cardiotomy suction blood is discarded.

One of the implied advantages of off-pump coronary revascularization procedures is that the CPB-related complications are eliminated (e.g., those associated with blood contact with the foreign surfaces of the CPB circuit and hemodynamic effects). However, these potential advantages are not always apparent in clinical studies, and the matter remains controversial (13–17). This picture may be very different when fat mobilization is considered. Off-pump procedures generally do not require that suction blood taken from the operative field is returned unprocessed to the general circulation. This very important difference in technique may lead to a reduction in free circulating fat emboli with a consequent reduction in the incidence of neurological dysfunction in the post-operative phase in the off-pump population. Such a moderation in neurological outcome associated with off-pump surgery has been reported in the medical literature, although the mechanism responsible remains unclear; however, a reduced lipid embolic load implied with off-pump procedures may be at least partly responsible (18,19). This study aims to quantify the fat embolic load associated with each of these approaches to revascularization. Specifically, it aims to establish the source and magnitude of the lipid embolic load in our routine CPB practice and determine whether there is a difference in the level of free circulating fat emboli between the two techniques of revascularization.

MATERIALS AND METHODS

Thirty patients were recruited to the study and allocated to one of two groups. Group 1 patients ($n = 15$) underwent conventional CPB supported coronary heart surgery (CHS), whereas group 2 patients ($n = 15$) underwent CHS without CPB (OPCAB). A single surgical team performed the procedures in each group, eliminating inconsistencies associated with surgical technique. Written informed consent was obtained from all patients in line with the requirements of the local ethics committee.

Operative Procedures

Anesthetic Protocol: The anesthesia protocol was common to both arms of the study. Patients were induced using a fentanyl-based anesthesia used in combination with benzodiazepine and pancuronium. Anesthesia was maintained intra-operatively with isoflurane and intravenous propofol infusion. Active warming techniques were used in the recovery period to achieve a nasopharyngeal temperature of at least 37°C before extubation. Dopamine was used as the first-line inotrope to support low cardiac output where necessary.

OPCAB Procedure: Access through a median sternotomy was initiated in all cases. Partial systemic heparinization with a target activated clotting time of 300–400 seconds was used before any cardiac manipulation. Alternating Trendelenburg posture was used on initiation of distal anastomosis in which a single suture technique was used.

A mechanical suction-based myocardial tissue stabilizer (Octopus 3; Medtronic, Watford, UK) was used to stabilize the operative field during the process of distal anastomosis. Core temperature was maintained at 35°C throughout the procedure by using an active warming technique. The proximal anastomosis was carried out with the assistance of a side-biting clamp and arterial pressure manipulation. Suction blood was not returned to the patients circulation in the OPCAB procedures, rather it was sucked to discard. This was possible because of the extremely low volumes of blood encountered during the revascularization period.

CPB Procedure: A standard CPB protocol was used for all patients undergoing cardiac surgery with CPB, which

was established using a single venous cannula in all cases. An arterial cannula (Medtronic DPL; Medtronic) placed in the ascending aorta. Non-pulsatile CPB was conducted under moderate hypothermia (34°C) in all cases. A hollow-fiber membrane oxygenator was used, and an arterial line filter (AV6; Pall Biomedical, Portsmouth, UK) was incorporated into the arterial line of the CPB circuit. A Biocor model 200 HIS high-performance oxygenator with integrated hard-shell venous reservoir (Minntech Corporation, Minneapolis, MN) was used, and the circuit was primed with 1 L of Hartman's solution, 500 mL of gelofusine, and 5000 IU of sodium heparin. Intermittent antegrade cold blood cardioplegia (4°C) was administered through a 12G aortic root cannula in all cases. Blood cardioplegia containing St. Thomas Hospital No.1 solution (Martindale Pharmaceuticals, Essex, UK) was delivered at a dose of 12 mL/kg to induce cardiac arrest during CPB, and a maintenance dose of 3 mL/kg was administered after the completion of each anastomosis. The CPB flow was maintained at 2.4 L/min/m^2 using an α-stat protocol. During the process phenylephrine and phentolamine were used to maintain a mean blood pressure between 50 and 80 mm Hg. Patients were rewarmed to a nasopharyngeal temperature of 37°C before cessation of CPB. Critically, in terms of this study, blood sucked from the operative site either by vent or pericardial suction was returned to the circuit through the cardiotomy aspect of the integrated reservoir.

Blood Sampling Protocol: Blood samples were taken from the suction, arterial, and venous lines where appropriate throughout the operative procedures. Blood samples from the OPCAB group were obtained from the venous and arterial sampling lines but not from the suction line, because this blood was discarded and cannot contribute to the overall fat mobilization profile at the following time-points in accordance with the approved protocol:

Time	Site of Sampling	Amount	CPB	OPCAB
Preopertive	Central venous line	10 mL	√	√
Mid-bypass	Suction line	10 mL	√	
(mid-procedure)	CPB venous line	10 mL	√	√
	CPB arterial output	10 mL	√	√
End-bypass	Suction line	10 mL	√	
(end-procedure)	CPB venous input	10 mL	√	√
	CPB arterial output	10 mL	√	√

The blood samples were stored on ice until they were processed in the laboratory.

Sample Preparation: Oil red O stain was used to stain the fat emboli present within the blood samples. This stain is a lysochrome (fat-soluble dye), predominantly used to show triglycerides and other forms of lipids in frozen sections, but also stain some protein-bound lipids in paraffin sections. Oil red O has been used in previous CPB studies (8); it stains with a deep red/orange color that is highly visible under optical microscopic conditions. The staining procedure is fairly simple: 2 mL of blood is placed into a test tube to each of the 2-mL samples, 0.2 mL of the Oil red O stain is added, and each sample is mixed thoroughly with a vortex mixer for at least 5 minutes. The samples are assembled on a test tube rack, and the batch of samples is placed on an orbital shaker for 15 minutes at 80 cycles/min. The samples are transferred to a refrigerated centrifuge and centrifuged at 4°C for ~15 minutes at 5000 cycles/min. To permit sizing of the fat droplets, 0.1 mL (300,000 microspheres) of violet 15-μm microspheres (Dye-track; Triton Technologies, Oxford, UK) were added to the sample supernatant. Using a pipette, samples of the supernatant were taken and introduced into improved Nehabauer Hemocytometer chambers. The samples were allowed to settle for 5 minutes and were examined with the aid of an optical microscope using low (×40) and high (×100) power to display the stained fat droplets. The fat droplets were graded into the following size bands, by visual contrast with the calibrated microspheres, by laboratory staff who were blinded to the source of the samples: (a) 0–10 μm; (b) 10–15 μm; (c) 15–20 μm; (d) >20 μm.

Statistical Analysis

Microsoft Excel spreadsheets were used for data management. Analysis was performed using an SPSS version 12.0 for Windows. Unpaired sample *t* test was used to compare the CPB with the OPCAB groups. A *p* value of 0.05 or less was considered to be statistically significant.

RESULTS

There were no differences between the groups in terms of the general demographic data, with the exception of patient age, which was lower in the OPCAB group (55.25 ± 5.94 years) than in the CPB group (65.88 ± 7.88 years; $p = .004$). The difference reflects the local tendency to recruit younger patients to OPCAB surgery. The patient demographic data are shown on Table 1.

Fat Emboli Analysis

There were no fat emboli detected in the off-pump group at any time-point. With the exception of the pre-

Table 1. Patient demographic data.

Mean	CPB Group	OPCAB Group	*p* Value
Age (years)	64.88 ± 7.88	55.25 ± 5.94	0.004
Height (cm)	168.88 ± 7.72	172.18 ± 5.98	0.465
Weight (kg)	81.34 ± 16.37	78.48 ± 6.07	0.470
Surface area (m^2)	2.05 ± 0.11	1.98 ± 0.08	0.154
Number of grafts	3.5 ± 0.27	3.0 ± 0.66	0.077
Bypass time (min)	64.5 ± 3.8	—	
Aortic cross-clamp time (min)	34.7 ± 2.83	—	

There were no significant differences between patients undergoing CPB and OPCAB, with the exception of age in which the OPCAB patients were generally and statistically significantly younger.

bypass samples in which no fat emboli were identified in any patient, fat emboli were detected in all remaining samples in the CPB group. A photograph of a typical example of a hemocytometer chamber showing fat emboli of various sizes in an arterial sample taken during CPB can be seen in Figure 1.

Analysis of the overall total counts for each time-point in the CPB group can be seen in Table 2 and is expressed graphically in Figure 2.

There were significant differences in fat emboli load in blood samples taken from different sources and at different time-points during CPB. There were absolutely no fat emboli detected in the pre-bypass arterial and venous samples. During bypass, lower emboli numbers were detected in the arterial and venous samples than in the suction samples. Arterial emboli counts increased from 0 ± 0 in the pre-bypass samples to 411.1 ± 422.6 at the mid-bypass time-point and remained at 311.1 ± 750.7 at the end of bypass time-point. These arterial emissions were statistically significant higher than the pre-bypass level (p = .023 max), and there was no statistically significant difference between the mid and the end of bypass arterial emission rate ($p > .05$), suggesting that there is a fairly constant embolic emission rate to the patient during CPB. These results support the findings of other investigators (10,11) who suggested that there is a constant embolic load emitted during CPB, without identifying embolic species. The venous embolic counts suggests a slightly different picture. Once again, no emboli were detected in the pre-bypass samples (mean = 0 ± 0); this increased to 55.5 ± 133.3 at the mid-bypass time-point and further increased to 77.6 ± 230.3) at the end of bypass. These counts were not statistically significant to the baseline counts because of the large variations encountered in these samples (p = .34).

Figure 1. Image of a hemocytometer slide showing fat emboli present in an arterial blood sample taken at the mid-bypass time-point from a CPB patient. The arrows indicate large (>20 μm) emboli.

Table 2. Fat emboli size distribution in all samples at both time-points.

Sample	Site	0–10 μm	10–15 μm	15–20 μm	>20 μm
Mid-bypass	Suction	1610 ± 430	1314 ± 263	594 ± 180	85 ± 37
	Arterial	322 ± 107	61 ± 15	28 ± 7	0
	Venous	49 ± 14	6 ± 7	0	0
End-bypass	Suction	2650 ± 830	1830 ± 384	1003 ± 314	92 ± 43
	Arterial	289 ± 88	18 ± 11	4 ± 6	0
	Venous	66 ± 22	11 ± 7	0	0

Counts are shown as counts/dL, and are expressed as mean ± SD.

The suction samples, perhaps not surprisingly, showed the highest embolic load. Increasing from 3603 ± 3215.7 at mid-bypass to 5575.7 ± 4870.4 at the end of bypass time-point, the difference between these suction samples were not statistically significant (p = .4).

The embolic load in the arterial line of the circuit was significantly higher than that of the venous return line (411.13 ± 422.62 vs. 55.53 ± 133.31) at the mid-bypass time-point and (311.17 ± 750.74 vs. 77.6 ± 230.3) at the end of bypass time-point. The arterial-venous difference in count was statistically significant (p = .047) at the mid-bypass time-point but not at the end bypass time-point. These differences suggest that the emboli emitted by the circuit are retained by the tissues, resulting in a much lower embolic count in the venous return blood. The data tend to indicate that the suction system is the prime source of lipid emboli in the CPB system.

The spectrum of lipid emboli size was also studied in this work using calibrated microspheres to permit visual size contrast grading of fat emboli (Figure 3). The fat emboli were graded into four size categories, 0–10, 10–15, 15–20, and >20 μm (Figure 4; Table 2).

The majority of the emboli detected are of the 0–10 μm size range and found in all blood samples. Suction samples show by far the greatest quantity of emboli of all sizes; the highest number occurred at the end of bypass time-point

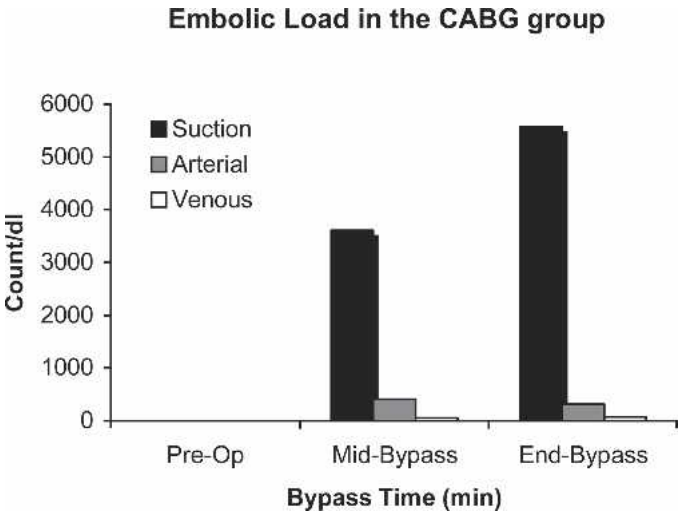

Figure 2. Emboli size distribution in all samples (CABG).

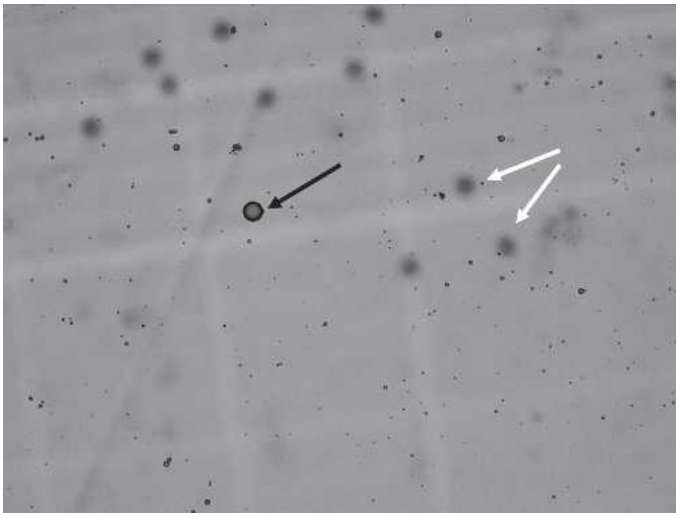

Figure 3. A larger fat globule (>20 μm) seen in comparison with multiple microspheres and many smaller fat emboli seen in a suction sample from the end of bypass. White arrows indicate microspheres, and black arrows indicate large fat emboli. The microspheres appear out of focus because of the fact that they tend to migrate to the upper layer of the slide. Correct grading is achieved by focusing on the microspheres and the fat emboli alternately.

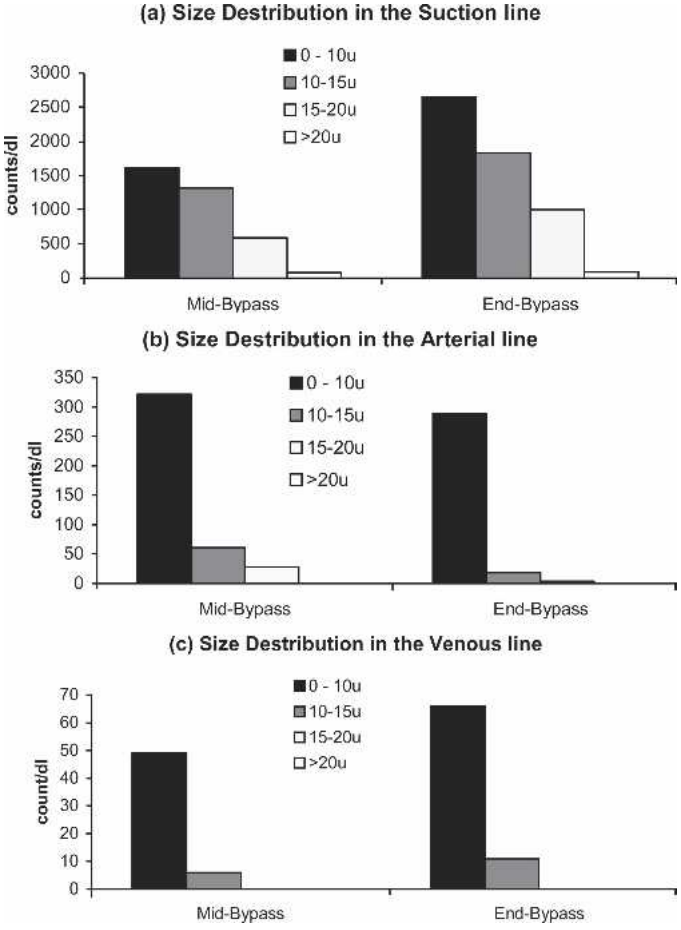

Figure 4. Fat emboli size distribution in (A) the suction line, (B) the arterial line, and (C) the venous line in CPB patients.

(2850 ± 830). The various filters of the perfusion apparatus reduce the lipid embolic load considerably as the blood passes through the system from the suction input to the arterial output. For example, the 0–10 μm embolic load fell from 2650 ± 830 in the suction input to 289 ± 88 ($p < .0001$) in the arterial output, representing a clearance ratio of ~86%. However, there was always a residual arterial embolic count.

Possibly of more importance is the reduction in the larger, potentially more harmful emboli. In the largest category (>20 μm), the reduction induced on the suction system compared with the arterial outlet was 92 ± 43 vs. 0 ± 0 ($p < .0001$). This represents a clearance ratio of more than 99.6%. Clearly the efficiency of the CPB apparatus in dealing with the larger emboli is considerably better that that of the smaller emboli. However, the embolic load is not eliminated, and significant numbers of fat emboli are passing through to the patient through the arterial line in most categories. This embolic load is a challenge to the CPB filtration system, and it is clear from this data that body tissues filter the emboli. The emboli present in the venous line, after blood has passed through the body vasculature, are significantly lower in numbers than those detected in the arterial line and in all size categories (66 ± 22 max [0–10 μm] vs. 289 ± 88 max [0–10 μm]; $p < .01$).

DISCUSSION

This study clearly shows that, despite modern techniques and technologies, fat emboli, generated most probably from the surgical site, remain a problematic issue in perfusion practice. Furthermore, these emboli are not present in off-pump coronary revascularization procedures. There were no apparent gross signs of embolic or neurological injury in either study group; however, specific study of this matter is beyond the scope of this pilot study. Further studies involving greater patient numbers, and neuro-psychological evaluations are planned in the future to determine the influence of fat embolic load on brain injury.

Comparative studies of off-pump and on-pump cardiac surgery for the correction of cardiac lesions continues to be at the forefront of cardiac research, and despite the increasing number of clinical studies focusing on this issue, the matter remains controversial. In particular, the degree to which the avoidance of the pathophysiology associated with conventional CPB improves the outcome in cardiac patients and whether these finite benefits are of real value when the added technical complexity of off-pump surgery are vectored into the decision-making process continue to raise questions in clinical practice. This study tends to support the application of OPCAB as a technique that will reduce the embolic load in cardiac patients. A number

of studies have highlighted a neuro-protective effect of OPCAB without determining the exact mechanism involved. This study suggests that protection from fat emboli may be one of these mechanisms.

In the CPB group, it was clear that the major source of fat emboli was cardiotomy suction. It was also clear that the filtration that takes place within the perfusion apparatus is capable of reducing this embolic load considerably, by up to 89% when comparing the suction load to the arterial load. However, although this is a significant reduction in fat emboli, the circuitry as used in this study does not totally eliminate the fat embolic load, and a significant amount of fat emboli, particularly of the smaller size band, does pass through to the patient, where almost all fat emboli are eliminated by the microvasculature, resulting in almost no embolic load in the venous circulation, a finding that is consistent with previous studies (14,15).

Previous studies have shown that fat liberated during the sternotomy procedure is a significant contributor to fat emboli during CPB (7,8); however, it is important to bear in mind that blood removed as a result of the sternotomy was eliminated in this study, and all blood evacuated from the chest cavity before CPB was sucked to discard. The fat emboli described in this study therefore represent either a residual fat content in the pericardium, the continued "ooze" of fat from the sternum during CPB, or another source of fat emboli as yet undetermined.

What is clear from this study is that fat emboli continue to be a challenge in clinical practice where revascularization is supported by CPB, and that fat emboli, particularly in the smaller size categories, continue to be emitted from the perfusion apparatus. Interestingly, these emboli seem to be almost entirely filtered by the tissues, resulting in virtually no fat emboli present in the venous system. This would suggest that they are being lodged in the tissues where they may be responsible for a degree of embolic damage.

In contrast to the CPB group, no fat emboli were discovered in the any of the blood samples taken from the OPCAB group, suggesting that this may be a surgical alternative in patients in who are susceptible to embolic injury (e.g., the elderly or those presenting with pre-existing cerebral complications). This is an issue that we will study more extensively in future investigations.

This pilot study was limited to patients undergoing CABG procedures so that direct comparisons could be made between the CPB and OPCAB groups; however, we recognize that the fat embolic load may be even more significant in patients undergoing combined or valve procedures supported by CPB, where more intensive use of cardiotomy suction is involved. The simple conclusion from this study is that, in terms of fat emboli, OPCAB is a better strategy than CPB with cardiotomy suction. Cardiotomy suction should be eliminated where possible to diminish the fat embolic load.

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