

Elimination of Fat Microemboli During Cardiopulmonary Bypass

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Background. Fat emboli have been implicated in cerebral dysfunction after cardiopulmonary bypass (CPB). We sought to identify the source of fat emboli during CPB and devise a technique for their elimination.

Methods. Patients undergoing CPB were prospectively randomized to either cardiotomy suction (n = 7) or cell-saving suction device (n = 6). Blood was collected at various intervals during CPB, and the fat emboli were identified using oil red O stain. These emboli were grouped based on their diameter into 10- to 50- μm and more than 50- μm particles. The number of fat emboli per slide examined was graded according to the following scale: 1 (1 to 10), 2 (11 to 20), 3 (21 to 30), and 4 (> 30 emboli). In the second phase of the experiment, a 21- μm filter was attached in series, distal to the cardiotomy reservoir (n = 6), and fat emboli were quantified.

Results. Blood from the pericardial well was saturated

with fat emboli of both sizes. Patients randomized to the cardiotomy suction had a significantly higher number of fat emboli at the end of CPB when compared with those randomized to the cell-saving suction device and dual-filter group. Processed blood from both the cardiotomy reservoir and cell-saving device was noted to have an abundance of fat emboli when compared with blood processed through the dual filters.

Conclusions. Processed blood from both the cardiotomy reservoir and cell-saving device appear to have an abundance of fat emboli that are completely eliminated by using a 21- μm arterial filter in series with the cardiotomy reservoir. This intervention could potentially reduce neurocognitive dysfunction associated with CPB.

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Cardiopulmonary bypass has emerged as the standard of care for the treatment of various congenital and acquired cardiopulmonary disorders. One of the known complications of cardiopulmonary bypass is the occurrence of neurocognitive deficits. The incidence of neurocognitive deficits ranges from 6% to 30% [1, 2] of patients who undergo this procedure. The neurocognitive deficits range from postoperative delirium to depression, to changes in memory, to stroke. Fat microemboli have been implicated in type II neurocognitive deficits such as deterioration of intellectual function and memory deficits [3]. Several aspects of cardiopulmonary bypass have been implicated as the culprit. Various materials such as protein debris after denaturation, fat particles, platelet aggregates, and atheromatous debris have been implicated as potential sources of emboli [4]. In our study we chose to study the nature of fat microemboli in cardiopulmonary bypass and to devise a technique for their elimination. One of the ways in which fat emboli can be introduced into the cardiopulmonary bypass circuit is the use of the cardiotomy suction device that drains fat-laden pericardial well blood directly into the bypass circuit. The clinical problem of fat embolism has

been well studied in the orthopedic literature; orthopedic surgeons have illustrated the detrimental effect of fat emboli on the pulmonary status of patients who have undergone extensive musculoskeletal trauma [5]. Several innovations in the past decade, like the reduction or elimination of antifoaming agents and conversion to membrane oxygenator, have addressed this problem [6]. New catheters have also been developed to capture atheromatous debris from the aorta after cross-clamping. In this study we aim to compare the number and size of fat microemboli that are present in the arterial blood after randomizing patients to either the cardiotomy suction or the cell-saving suction device. In addition, we also compared the incidence of fat microemboli after the addition of an intervening filter distal to the cardiotomy reservoir.

Material and Methods

Institutional review board approval at the University of Virginia was obtained for conduction of this study. Voluntary informed consent was obtained from the patients enrolled in the study. The initial phase of the experiment involved the randomization of patients to the exclusive use of either the cardiotomy suction device or the cell-saving suction device. During the second phase of the experiment we sought to compare the incidence of fat microemboli after the addition of a 21- μm filter (Sentry

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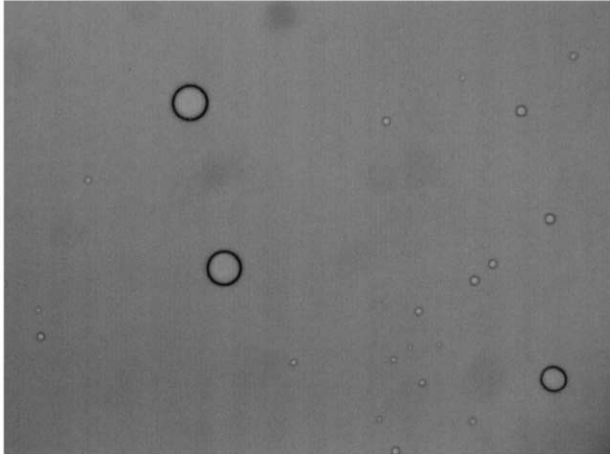


Fig 1. Appearance of fat microemboli after oil red O staining.

Arterial Filter, Cobe Cardiovascular, Arvada, CO) in series, distal to the cardiotomy reservoir (dual-filter group). This particular filter was chosen because it does not impede rapid transfusion of shed blood, and the flow rates through the dual-filter setup were comparable to the flow rates through the cardiotomy reservoir alone. The cardiopulmonary bypass circuit used during this experiment was a standard setup consisting of cardiotomy suction that drained into a reservoir equipped with a 30- μm filter (Cobe Cardiovascular). This reservoir is then connected to the venous reservoir, which drained into the oxygenator. The cell-saving suction device was connected to a continuous cell-saving device (Brat 2, Cobe Cardiovascular) that is used to spin the shed blood, and this blood is given back to the patient through the cardiotomy reservoir in the bypass circuit.

Detection of Fat Microemboli

Oil red O stain was prepared by mixing 100 mL of 100% methanol with 1 g of oil red O powder; 200 μL of 1% oil red O stain was then added to 2 mL of blood and mixed gently. The mixture was then allowed to mix gently for 15 minutes. The sample was centrifuged at 2,500 rpm for 20 minutes at room temperature. Thirty microliters of the supernatant was then added to a slide, and the slide was examined using a light microscope for detection of fat microemboli. The fat microemboli appear as orange-red-stained particles (Fig 1).

Blood was collected at various intervals during cardiopulmonary bypass; after being processed in the cardiotomy reservoir, cell-saving device, and distal to the dual-filter setup; and finally from the patient's arterial catheter at the end of cardiopulmonary bypass. The total number of fat microemboli on a slide were then quantitated by a blinded evaluator using a light microscope fitted with a size reticule. We chose to evaluate fat microemboli based on the size of the particles. Particles that were less than 10 μm in diameter were not counted because they could traverse the capillary space and thus do not pose a

clinically significant risk. We stratified the microemboli into small, those between 10 and 50 μm in diameter, and large, those greater than 50 μm in diameter, particles.

Cardiotomy Group

Patients randomized to this group were limited to the use of the cardiotomy suction device during cardiopulmonary bypass. The cardiotomy reservoir was equipped with a 30- μm arterial filter that drained directly into the venous reservoir. Blood was collected distal to this reservoir at various intervals during the procedure and just before completion of bypass. The arterial blood from the patient was also sampled after discontinuation of bypass.

Cell-Saving Device Group

Patients randomized to this group were limited to the use of the cell-saving suction device during cardiopulmonary bypass. All the shed blood was then processed in the cell-saving device using standard protocol, and the processed blood was sampled. The arterial blood from the patient was sampled after discontinuation of bypass and after the cell-saving device-processed blood had been infused into the patient by means of the cardiotomy reservoir or through a venous catheter.

Dual-Filter Group

Patients were sequentially assigned to this group after they were randomized into the two other groups. The intervention in this group consisted of a 21- μm filter that was added distal to the cardiotomy reservoir in series in the bypass circuit (Fig 2). Blood was sampled distal to this dual filter set-up and also from the patient's arterial catheter just after discontinuation of bypass.

Grading System

The particles were divided into two tiers based on the size of the fat microemboli. They were stratified into either small (10 to 50 μm in diameter) or large (>50 μm in diameter) size. The number of fat microemboli were graded according to the following scale:

- 1 to 10 microemboli/slide = 1;
- 11 to 20 microemboli/slide = 2;
- 21 to 30 microemboli/slide = 3;
- More than 30 microemboli/slide = 4.

Statistical Analysis

Data were analyzed using analysis of variance. Data are expressed as mean \pm standard error of the mean. Statistical significance was expressed as a *p* value.

Results

All patients randomized to this study underwent coronary artery bypass grafting using cardiopulmonary bypass. There were a total of 7 patients who were randomized to the cardiotomy group. Six patients each were randomized to the cell-saving device group and the dual-filter group. The duration of cardiopulmonary bypass was comparable among all three groups. We ana-

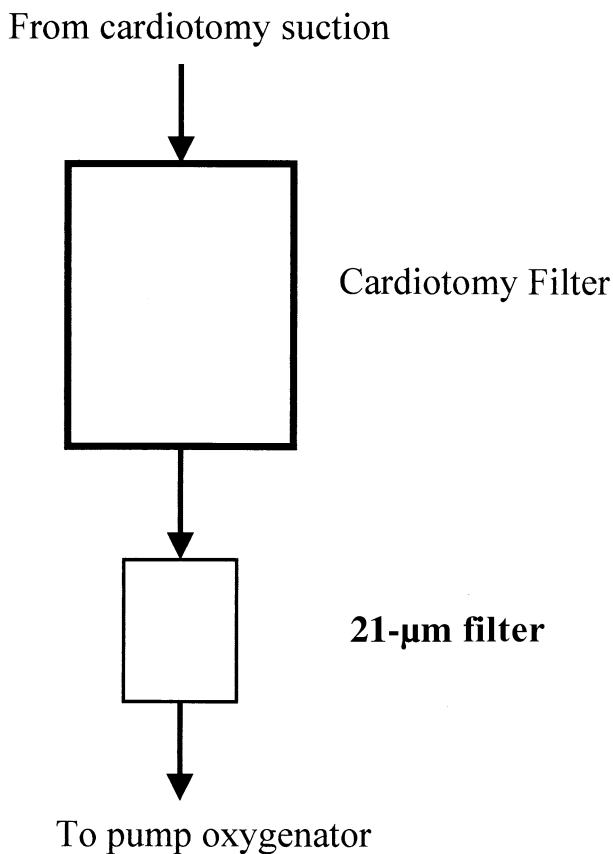


Fig 2. Schematic illustrating the dual-filter setup. The 21- μm filter is added in series, distal to the cardiotomy reservoir.

lyzed the data based on the size of the fat microemboli. The number of microemboli are stated according to the grading system described in the methods section.

Size 10 to 50 μm in Diameter

The pericardial blood was noted to be saturated with small fat microemboli (4.00). The number of fat microemboli in the processed blood from the cardiotomy group was 3.43 ± 0.20 . The number of fat microemboli in the cell-saving device-processed blood was 3.33 ± 0.33 . The number of fat microemboli in blood processed through the dual filters was 0.67 ± 0.21 . The dual-filter group was noted to have significantly fewer numbers of fat microemboli compared with both the cardiotomy and cell-saving device-processed blood ($p < 0.001$).

The arterial blood at discontinuation of cardiopulmonary bypass showed that the cardiotomy group contained 1.86 ± 0.14 particles. The cell-saving device group and the dual-filter group did not have any evidence of any fat microemboli. This was noted to be statistically significant ($p < 0.001$).

Size More Than 50 μm in Diameter

The pericardial well was saturated with fat microemboli of this size (4.00). The cardiotomy processed blood had

2.57 ± 0.30 fat microemboli. The cell-saving device-processed blood was noted to have 1.50 ± 0.22 particles. Blood processed through the dual filters did not have any fat microemboli of this size. This was a statistically significant finding ($p < 0.001$). Analysis of the patients' arterial blood at the end of bypass revealed the cardiotomy group to have 1.00 ± 0.38 particles. Patients in the cell-saving device group and the dual-filter group did not have any fat microemboli of this size. Again, this was a statistically significant finding ($p < 0.001$).

Comment

Cardiopulmonary bypass has emerged as the standard of care for various congenital and acquired cardiopulmonary disorders. As the number of patients being treated using this modality increases, the related complications are also on the rise. Various culprits have been implicated in the pathogenesis of neurocognitive deficits after bypass. One of the explanations has been the inflammatory cascade that is initiated with the use of cardiopulmonary bypass. Various studies have also shown that particulate matter generated during various phases of bypass is a causative agent. There are several sources of particulate emboli during cardiopulmonary bypass. Atheromas and calcific deposits have been shown to dislodge during aortic cross-clamping and result in neurologic impairment. Several studies since the early days of cardiac surgery have implicated fat microemboli as a source of postoperative complications [7, 8]. Fat globules generated during dissection of subcutaneous tissue, sternal division, dissection of the pericardium, and dissection of the internal thoracic artery are all potential sources of emboli. The presence of such potential emboli is no more evident than when looking in the pericardial well during operation; enormous quantities of these particles are then transmitted directly into the bypass circuit using the cardiotomy suction device. In this study we chose to study the incidence of such fat microemboli and to develop a technique for the elimination of such microemboli during the use of the bypass circuit. To detect these fat microemboli we used the propensity of fat globules to take up oil red O stain.

In comparing the incidence of fat microemboli we divided them into small (10 to 50 μm in diameter) and large ($>50 \mu\text{m}$ in diameter) sizes. We noted that both the cardiotomy-processed blood and cell-saving device-processed blood had an abundance of small fat microemboli. The blood processed through the dual filters had significantly fewer numbers of microemboli. In addition, we noted that the arterial blood at the end of the operation consisted of fat microemboli in the cardiotomy group only. Similarly, we noted that both the cardiotomy-processed blood and cell-saving device-processed blood had an abundance of large microemboli. There was complete absence of large microemboli in the dual-filter group. Analysis of the arterial blood at the end of the case revealed that the cardiotomy group had a significant amount of large microemboli. The cell-saving device and

dual-filter groups had a near complete elimination of these large microemboli.

The complete absence of small and large microemboli in the arterial blood was noted in the cell-saving device group; this could be attributed to the fact that this blood is introduced into the bypass circuit through the cardiotomy reservoir, which is analogous to the dual-filter system. However, the exclusive use of the cell-saving device would deplete the shed blood of valuable clotting factors that are removed from the supernatant after the blood is processed in that device.

The basis for the addition of an arterial filter distal to the cardiotomy reservoir comes from several classic studies. Loop and colleagues [9] have demonstrated that the addition of an arterial line filter in the bypass circuit reduced the microembolic load. Egeblad and colleagues [10] had also demonstrated earlier that the addition of a Dacron wool filter in series in the arterial circuit diminished the presence of microemboli. Other studies have shown that the addition of a newer Dacron wool filter reduced postcardiotomy mortality from 19.8% to 6.5% [11].

Moody and colleagues [12] have shown the presence of small capillary and arterial dilatations in postmortem studies of the brains of patients who had undergone cardiopulmonary bypass. Furthermore, they found that these small capillary and arterial dilatations are indeed a result of fat microemboli using special staining techniques. They also noted that cardiopulmonary bypass of longer duration was associated with increased small capillary and arterial dilatations [13]. Their group had also shown that by using the cell-saving device as opposed to the cardiotomy suction, it is possible to reduce the number of small capillary and arterial dilatations [14]. However, in that study they point out the limitations of using the cell-saving device suction exclusively during cardiopulmonary bypass. They range from the inability to perform rapid transfusions to the inflammatory cascade that is activated by using the cell-saving device. In contrast to their study, we did not find the cell-saving device to be any more effective than the cardiotomy reservoir in the elimination of small and large fat microemboli. We did, however, find that the transfusion of the cell-saving device-processed blood through the cardiotomy filter does effectively remove the entire fat microembolic burden. But this is fraught with limitations that we mentioned above.

In our study we note that the addition of the 21- μ m filter in series distal to the cardiotomy reservoir results in the nearly complete elimination of small and large fat microemboli. We believe that this is a result of the additional barrier function that this filter serves. Empiric examination of the filter from the cardiotomy reservoir indicated that there is membrane fatigue associated with the large fat globule load that this membrane is subjected to. The addition of the 21- μ m filter serves to alleviate this problem by subjecting the shed blood to a second barrier. The mechanism by which these fat microemboli are generated has been hypothesized by Lee and associates

[15] to be secondary to the denaturation of proteins and the subsequent release of free lipids. The presence of fat microemboli larger than the pore size is probably a result of coalescence of smaller fat globules in the postfilter stream; this phenomenon has been demonstrated in earlier studies [16]. In this study we have shown in a small cohort of patients that the addition of the second filter results in the complete elimination of small and large fat microemboli from the arterial blood of the patient. However, additional studies need to be performed to look at the impact of this intervention on the postoperative neurocognitive function. Finally, we believe that this simple intervention adds very little cost and resources to the cardiopulmonary bypass circuit and results in the elimination of fat microemboli that have long been implicated in postoperative cognitive deficits.

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DISCUSSION

DR JOHN J. HAMMON (Winston-Salem, NC): I want to congratulate Dr Kaza and his colleagues for a very innovative study, and I want to thank you very much for letting me see a copy of the manuscript in advance.

We are quite pleased that you have chosen to intervene on a phenomenon that we believe is a very important determinant of postoperative neurocognitive dysfunction as evidenced by magnetic resonance imaging studies of brain swelling in patients by Ken Taylor from the Hammersmith. We differ slightly in using a continuous cell-saving device, different from the cell-saving devices that you used, which allows one to reinfuse continuously during the operative period, and it also is very good at removing fat, even more so than the cell-saving devices that you use, as well as activated leukocytes and high levels of inflammatory cytokines, which are important determinants of the postoperative inflammatory reaction. I have three questions for you.

Number one, did this very small pore size filter offer obstruction to flow of blood from the cardiotomy reservoir into the oxygenator?

Number two, did you measure the amount of shed blood in your patients and compare the different groups, as this often is an important determinant in the amount of fat delivered to the patients?

And, number three, did you do any outcome studies on your patients to determine whether the patients having filtered blood had a better outcome postoperatively?

Thank you very much for letting me discuss this paper.

DR KAZA: Thank you for those comments, Dr Hammon. Answering your questions starting with the first question, we chose this particular filter just because it did not hinder our flow during cardiopulmonary bypass. Adding the second filter in series distal to the cardiotomy reservoir still maintained flow at approximately 6 L/min.

And the second question about measuring the amount of shed blood, we did not do that; however, the cardiopulmonary bypass and the pump run in all the patients was comparable.

And as far as the third question, we have not looked at postoperative neurocognitive outcomes. I think that is a study for the future.

DR WILLIAM A. BAUMGARTNER (Baltimore, MD): Congratulations on a great presentation and I think one of the first clinical demonstrations of what Dr Hammon and his group at Wake Forest have talked about for so many years. I have one question for you. From this observation, have you changed your practice? Do you now use this filter in all of your patients, and what is the cost?

DR KAZA: As far as using it in practice, I think the PI for this study is Dr Tribble. I think he uses it in his practice. I do not know about the other members of the department. I am not sure about the cost, Dr Baumgartner, it is a simple arterial filter; it is a Sentry filter manufactured by Cobe Cardiovascular.