Efficacy of a New Oxygenator-Integrated Fat and Leukocyte Removal Device

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ABSTRACT

We evaluated the effectiveness of a new oxygenator-integrated device for removing lipid particles and leukocytes from shed mediastinal blood in 20 patients undergoing elective cardiac surgery under cardiopulmonary bypass. Another 20 patients undergoing cardiac surgery without the device served as controls. After filtration with the RemoveLL device, lipid particles, leukocytes, and fats were significantly reduced compared to preoperative levels. In the control group, blood fats and lipid particles at the end of cardiopulmonary bypass were significantly increased compared to preoperative levels. Leukocyte counts at the end of bypass were significantly lower in patients who had the filtration device compared to the control group. Platelets counts and hematocrit changes were not significantly different between the 2 groups.

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KEYWORDS: Cardiopulmonary Bypass, Embolism, Fat, Leukocyte Count, Platelet Count, Triglycerides

INTRODUCTION

Despite recent improvements in cardiopulmonary bypass (CPB) techniques, brain damage remains a significant cause of morbidity after cardiac surgery. The incidence of neurocognitive deficits ranges from 6% to 30% in patients undergoing CPB.[1,2] Microemboli have been demonstrated in brain tissue after CPB in animal and human cadavers.[3] Clinically, such embolization is considered responsible for neurocognitive dysfunction. Bronden and colleagues[4] reported the potential role of lipid particles in damaging other organs, particularly the kidneys and lungs. The shed mediastinal blood is the main suspect as the lipid emboli source and one of the factors responsible for activation of the fibrinolytic and inflammatory cascades.[3]

Biomedical industries have been trying to solve this problem by developing new devices capable of removing lipid particles and leukocytes from the pericardial suction blood. Various strategies are under investigation, including particle separation by ultrasound, sedimentation-based separation, and filter strategies.[5–7] The objective of this study was to evaluate the effectiveness of a new oxygenator-integrated device for removing lipid particles and leukocytes from shed mediastinal blood in a clinical setting. This device, integrated with the reservoir, combines 2 different strategies: filtration and physiologic fat separation from blood, with the creation of a supernatant.

PATIENTS AND METHODS

After approval by the local ethics committee and written consent, 40 patients undergoing elective cardiac surgery with cardiopulmonary bypass (CPB) were included in the study. Patients with preexisting renal insufficiency,

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Table 1. Preoperative data of 40 patients undergoing cardiac surgery

	Group 1		Group 2	
Variable	No. of patients	Range	No. of patients	Range
Male	13 (65%)		15 (75%)	
Mean age (years)	68.3 7.6	56–77	71.5 5.4	55–84
Hypertension	11 (55%)		10 (50%)	
Dyslipidemia	5 (25%)		8 (40%)	
Diabetes	4 (20%)		4 (20%)	
Smoking history	9 (45%)		6 (30%)	
EuroSCORE	5.4 3.2	2–11	6.3 3.6	2–15
Ejection fraction	54.6% 7.7%	33%–65%	52.8% 5.7%	30%–55%
COPD	3 (15%)		2 (10%)	
Vasculopathy	3 (15%)		3 (15%)	
Previous MI	8 (40%)		7 (35%)	

COPD ¼ chronic obstructive pulmonary disease, MI ¼ myocardial infarction.

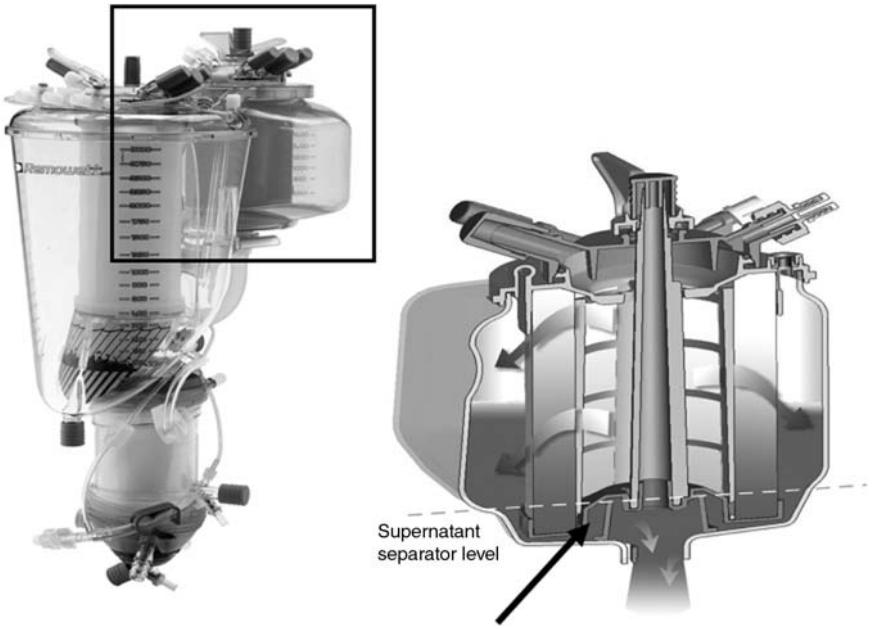

Figure 1. The RemoveLL system. Blood aspirated from the chest cavity is diverted into the RemoveLL reservoir. In the first phase, the blood is filtered through a 40-mm membrane. In the second phase, the blood passes into the sedimentation chamber where it is kept for at least 40 min to obtain a lipid supernatant. The blood may then be directed into the main reservoir or cell-saver device, or directly into the patient by a central venous line. The supernatant, rich in lipid particles, is blocked by the siphon at the base of the reservoir, and discarded.

severe lung disease, cerebrovascular disease, and those undergoing reoperation were excluded. Twenty patients were operated on with the new oxygenator-integrated device included in the CPB circuit (group 1). In the other 20 patients, we used a standard CPB circuit without a fat/leukocyte filter (group 2). Both groups were similar in terms of preoperative characteristics (Table 1). The clinical outcome of the patients was not investigated.

A narcotic-based anesthetic was used. CPB was conducted using a roller pump with a Stockert S3 heart-lung machine (Monaco, Germany). The RemoweLL oxygenator (Eurosets, Medolla, Italy) was used in group 1. A hollow-fiber oxygenator (Capiox, Terumo, Ann Arbor, MI, USA) was used in group 2. The mean circuit prime was 1,566 218 mL (range, 1,250–1,750 mL) of Ringer's lactate solution. Antegrade cold blood (20 C) cardioplegia was used in coronary bypass surgery, and a combination of antegrade and retrograde cold blood cardioplegia was used in valvular surgery. During perfusion, normothermia was maintained. Surgery was performed in the standard manner in both groups. The mechanism of the RemoveLL operation is detailed in Figure 1. Blood samples were taken before

Table 2. Operative and postoperative data of 40 patients undergoing cardiac surgery

	Group 1		Group 2	
Variable	No. of Patients	Range	No. of Patients	Range
Mean CPB time (min)	71.7 27.5	36–144	80.7 18.6	37–162
Crossclamp time (min)	55.4 22.1	27–109	57.5 20.1	27–132
CABG	6 (30%)	–	5 (25%)	–
AVR	9 (45%)	–	10 (50%)	–
MVR	3 (15%)	–	1 (5%)	–
AVR þ CABG	3 (15%)	–	4 (20%)	–
Priming volume (mL)	1,565.8 218	1,250–1,750	1,585 197	1,250–1,950
Cell-saver reinfusion (mL)	443 159	50–712	426 134	50–650
CPB diuresis (mL)	513 413	200–2,000	545 380	250–2,400
Transfusion during CPB	2 (10%)		2 (10%)	
Drainage (mL)*	318 169	50–700	430 210	50–1,200
Ventilation time (h)	5.4 2.4	2–12	5.6 2.2	2–14
Intensive care unit stay (h)	36.5 16.7	17–76	38.6 12.5	16–89

*In first 24 h postoperatively. AVR ¼ aortic valve replacement, CABG ¼ coronary artery bypass grafting, CPB ¼ cardiopulmonary bypass, MVR ¼ mitral valve replacement.

Table 3. Sample composition before and after use of RemoveLL device in 20 patients

	Before RemoveLL		After RemoveLL		
Variable	Median	25–75 Percentiles	Median	25–75 Percentiles	p Value
Leukocytes (10^3 mL ^{1})	5.6	3.3–6.6	2.6	3.2–6	0.001
Neutrophils (10^3 mL ^{1})	76.2	56–78	69.7	56–77	0.03
Platelets (10^3 mL ^{1})	127	88–184	99	68–144	0.05
Hematocrit	20.8%	15.4%–25.4%	24.6%	17.9%–36.3%	0.05
Cholesterol (mg dL ^{1})	163	138–204	89	74–121	0.0001
Triglycerides (mg dL ^{1})	136	119–189	104	99–140	0.004
Lipid particles per dL	2,850	1,200–6,400	950	400–2,800	0.001

and after use of the RemoveLL in group 1. In group 2, blood samples were collected directly from the cardiotomy reservoir when the activated clotting time was 400 sec just before starting extracorporeal circulation, and from the residual blood in the CPB circuit at the end of the operation.

We collected the following data: collected cardiotomy blood volume, mean sedimentation time, lipid particle concentration, cholesterol and triglyceride levels, leukocyte, neutrophil, and platelets counts, and hematocrit. The lipid particle counting was performed with a microscope using a Thoma-Zeiss counting chamber, after diluting 1:100 with physiologic saline to allow particle counting.

All data were collected prospectively. All continuous variables are presented as mean standard deviation and/or the median with the 25th to 75th percentile range. The hypothesis of Gaussian distribution was tested with the Shapiro-Wilk W test. As the data were not normally distributed, we switched to the nonparametric Wilcoxon signed-rank test for paired samples. Statistical significance was considered at $p < 0.05$. All analyses were performed using SPSS version 16.0 software (SPSS, Inc., Chicago, IL, USA).

RESULTS

Operative data did not differ between the 2 groups (Table 2). There was no significant difference in the amount of lipid particles in blood collected before filtration in patients undergoing valvular or coronary surgery. The mean lipid particle size was 15 4.8 mm in group 1, and 14 6.6 mm in group 2 (p 0.05). The mean sedimentation time into the cardiotomy was 74 21.6 min (range, 39–116 min; groups 1 and 2) and was related to the CPB time. Mean collected blood cardiotomy volume was 498 65.84 mL in group 1 and 422 55.76 mL in group 2 (p 0.05). There were no significant differences in blood sample composition between the 2 groups pre-CPB. After filtration with the RemoveLL device in group 1, lipid particles, leukocytes, and fats were significantly reduced (Table 3).

Table 4. Sample composition before and after cardiopulmonary bypass in 20 control patients

	Before Bypass		After Bypass		
Variable	Median	25–75 Percentiles	Median	25–75 Percentiles	p Value
Leukocytes (10^3 mL ^{1})	5.0	9.8–13.9	5.6	9.8–15.7	0.05
Neutrophils (10^{3} mL ^{1})	74.8	49–77	82.3	63–87	0.05
Platelets (10^3 mL ^{1})	132	96–212	135	94–198	0.05
Hematocrit	20.6%	13.2%–26.4%	25.3%	16.7%–33.9%	0.05
Cholesterol (mg dL ^{1})	211	143–251	329	88–398	0.003
Triglycerides (mg dL ^{1})	136	121–201	202	101–227	0.004
Lipid particles per dL	2,949	1,450–7,788	4,090	1,830–9,983	0.0001

Lipid particle concentration was reduced by 63% 8.4%, and leukocytes by 52% 9%. The efficacy of lipid separation was related to the sedimentation time ($p < 0.004$). In contrast to group 1, blood fats and lipid particles at the end of the CPB were significantly increased in group 2 (Table 4). The difference in leukocyte counts post-filtration in group 1 and at the end of CPB in group 2 was statistically significant ($p \frac{1}{4} 0.001$). Platelets counts and hematocrits were not significantly different between the 2 groups. One patient who underwent aortic valve surgery in group 1 had mild postoperative renal insufficiency, one patient in group 2 who underwent coronary surgery had a transient neurologic ischemic attack. Reoperation for bleeding was necessary in 3 patients (2 in group 2, 1 in group 1); in all cases, a source of surgical bleeding was found. One patient in group 2 died from acute pulmonary embolism on the 6th postoperative day. The 2 groups were similar with respect to CPB diuresis, blood loss, intensive care unit time, and lung function (Table 2).

DISCUSSION

Lipid microemboli have been implicated in type II neurocognitive disorders after CPB.[8] Moody and col- leagues[9] demonstrated small capillary and arterial dila- tation and obstruction due to fat microemboli in postmortem brains. The shed mediastinal blood has been shown to be a major source of lipid particles.[3,6]

In addition to fat particles and inflammatory mediators, shed mediastinal blood contains activated leukocytes.[10] All these factors are responsible for ''post-pump syndrome'' that affects not only the brain but also lung, kidney, heart, and the immunologic system.[11] Recently, various strategies to mitigate the deleterious effect of CPB have been investigated. Mini-extracorporeal circulation circuits, closed systems, and cell-saving devices have been introduced into clinical practice with promising results.[12,13] Other strategies to reduce lipid microembolization are still under investigation. Jonsson and colleagues[5] reported 81% removal of lipid particles using an ultrasonic device; a very satisfactory result compared to the approximately 50% capability of cell-saving technology and 30% to 40% filter-removal capacity.[12,13] Indeed the major limitation of the ''filter-only'' strategy is that the actual filter size of 40 mm fails to remove the majority of the lipid particles. In our study, we found that the mean lipid particle diameter was approximately 15 mm, well below the 40 mm filtration threshold.

Sedimentation-based separation is another promising technique.[6,14] Certainly, each strategy has advantages and disadvantages. For example, the use of filters with a very small pore diameter can decrease the charge on leukocytes, but at the same time it may create other problems such as high resistance in the circuit and loss of important blood components including platelets and red blood cells. Moreover, the ideal filter needs a short passage time and good biocompatibility.[15] Ultrasonic and sedimentation methods also have several drawbacks limiting their clinical application.[5,6,14,15] The RemoveLL technology combines 2 different strategies: filtration, which removes leukocytes and larger lipid particles (40 mm), and sedimentation which is responsible for smaller lipid particle (10–40 mm) removal. The combination of these 2 strategies is designed to achieve a synergistic effect, reducing the disadvantages of the individual methods.

In the evaluation of this new oxygenator-integrated device, our endpoints were the lipid particle and leukocyte-depleting capabilities. Our data show a considerable reduction of lipid particles (by 63% 8.4%) and leukocytes (by 52% 9.5%) after the filtration process, demonstrating the effectiveness of this new device. In the control group, we found an nonsignificant increase of lipid particles, cholesterol, and triglycerides in blood samples from the cardiotomy at the end of CPB, which confirm the efficacy of the new device. No differences were found in the control group in terms of leukocyte and neutrophil concentrations before and after CPB. In terms of platelet and red blood cell

reduction, our data show no significant difference before and after filtration. We found that the greatest drawback of this system was the time taken for the lipid-removal process of sedimentation. In the case of major bleeding or the necessity for high blood volume during CPB, the blood stored in the RemoveLL needs to be re-infused before obtaining effective lipid removal. Indeed, we noted that the lipid-removal ability depends on sedimentation time. Hence surgeons should be careful to avoid excessive sources of bleeding in the surgical field.

We found this new device to be effective in terms of lipid and leukocyte removal, but because of the small cohort and the design of the study, the clinical significance of lipid and leukocyte reduction was not determined. A superficial clinical evaluation did not find any difference in terms of morbidity and mortality between the 2 groups; however, further studies are necessary to assess the clinical impact of this device. After this preliminary evaluation, we are now performing a randomized study focused on clinical outcome, to determine the influence of lipid and leukocyte removal on organ function, and particularly on neurocognitive dysfunction after cardiac surgery.

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