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Leukocyte Filter Enhances Neutrophil Activation during Combined Aortic Valve and Coronary Artery Bypass Surgery

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ABSTRACT

Objective. Cardiopulmonary bypass–induced systemic inflammatory reaction involving the expression of neutrophil surface adhesion molecules is the main mechanism leading to myocardial ischemia-reperfusion injury as well as multiorgan dysfunction. Patients undergoing prolonged cardiopulmonary bypass are especially at risk in this regard. The aim of this prospective, randomized study was to evaluate the impact of continuous leukocyte filtration on the perioperative expression of neutrophil adhesion molecules along with the markers of systemic inflammation during combined coronary artery revascularization and aortic valve surgery due to aortic stenosis.

Patient and Methods. Twenty patients scheduled for combined coronary artery revascularization and aortic valve surgery due to aortic stenosis were randomized to undergo cardiopulmonary bypass with or without a leukocyte filter (LeukoGuard LG6). The expression of neutrophil adhesion molecules and proinflammatory cytokine response were measured.

Results. The use of the leukocyte filter significantly increased neutrophil CD11b expression (P_g = .003) compared to the control group, which was followed by a faster rise in interleukin-6 levels 5 minutes (median, 125 versus 34 pg/mL) and 2 hours after cardiopulmonary bypass (median, 158 versus 92 pg/mL, $P_{t \times g}$ < .001), respectively. No marked differences in terms of levels of CD11a, CD62L, cardiac troponin-I, or oxyhemodynamics were observed.

Conclusions. The observed increased neutrophil activation and enhanced inflammatory response do not support the use of continuous leukofiltration in patients undergoing prolonged cardiopulmonary bypass.

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INTRODUCTION

The use of cardiopulmonary bypass (CPB) is associated with well-recognized inflammatory responses. This complex systemic inflammatory reaction involves complement activation, generation of proinflammatory cytokines, and neutrophil activation along with the expression of adhesion molecules. Ischemia and reperfusion–induced endothelial activation, followed by neutrophil adhesion and transmigration across the endothelium, have been shown to have a key role in multiorgan ischemia/reperfusion injury [Kirklin 1983; Gillinov 1994; Edmunds 1998]. Combined coronary artery bypass grafting and aortic valve surgery for aortic valve stenosis is known to be associated with adverse postoperative events [Edwards 2001]. Prolonged CPB is suggested to be the main determinant of such a severe systemic inflammatory reaction. Furthermore, the outflow obstruction–induced left ventricular hypertrophy often associated with aortic valve stenosis makes the myocardium particularly vulnerable to ischemia/reperfusion injury [Friehs 2003].

Many efforts have been made to find a method to attenuate this systemic inflammatory response and the related neutrophil-endothelium interaction. The leukocyte filter has been enthusiastically employed to modulate the ischemia/reperfusion injury by removing activated neutrophils during CPB with different filtration strategies [de Vries 2003] and settings [Karaiskos 2004]. Until now, a number of clinical studies failed to show any major clinical benefit with the use of leukocyte filtration [Mihaljevic 1995; Lust 1996; Baksaas 1999; Fabbri 2001; Sahlman 2001; Chen 2002; Ilmakunnas 2005; Leal-Noval 2005; Salamonsen 2005), and a few showed somewhat better immediate postoperative outcomes when a leukocyte filter was used [Gu 1996; Roth 2000; Efstathiou 2003; Olivencia-Yurvati 2003; Patel 2003; Karaiskos 2004; Sutton 2005). The main benefit of leukocyte filtration seems to be related to a better postoperative preservation of pulmonary function.

We have previously demonstrated the neuroprotective efficacy of leukocyte filtration in an experimental model of hypothermic circulatory arrest [Rimpiläinen 2000] and the value of this method to decrease myocardial enzyme release after elective coronary artery bypass grafting surgery, although the expression of adhesion molecules suggested increased neutrophil activation [Koskenkari 2005a].

Table 1. Clinical and Operative Data in the Study Groups*

Risk Factors	Control Group, %	Leukocyte Filter Group, %	*P*
Age	70.3 (66.4-74.8)	69.6 (65.6-77.4)	.97
Male patients (%)	10 (100)	7 (70)	.21
New York Heart Association functional class			.58
II (%)	3 (30)	1 (10)	
III (%)	7 (70)	8 (80)	
IV (%)	0	1 (10)	
History of myocardial infarction (%)	0	4 (40)	.09
Hypertension (%)	6 (60)	6 (60)	1.00
Lower limb ischemia (%)	1 (10)	1 (10)	1.00
Diabetes (%)	1 (10)	0	1.00
Chronic obstructive pulmonary disease (%)	0	1 (10)	1.00
Cerebrovascular disease (%)	0	1 (10)	1.00
Renal failure	0	0	—
Left ventricular ejection fraction			1.00
≥50% (%)	8 (80.0)	8 (80.0)	
30-50% (%)	2 (20.0)	2 (20.0)	
Smoking (%)	1 (10)	0 (0)	1.00
Additive EuroSCORE	5.0 (4.0-7.0)	4.5 (3.7-5.2)	.28
Aortic clamping time, min	134 (105-167)	150 (133-158)	.39
Cardiopulmonary bypass time, min	167 (140-220)	189 (164-200)	.44
Myocardial ischemia time, min	12.0 (10.2-25.0)	21.0 (5.0-27.2)	.97
Amount of cardioplegia infusion, mL	850 (587-1125)	975 (875-1025)	.35
Length of operation, min	315 (300-365)	335 (330-360)	.46

*Continuous data are reported as the median and interquartile range (twenty-fifth and seventy-fifth percentiles). EuroSCORE indicates European System for Cardiac Operative Risk Evaluation; Myocardial ischemic time, duration of cardioplegia discontinuation during perfusion.

To further address the value of leukocyte filtration during CPB, we have herein evaluated the perioperative expression of neutrophil adhesion molecules and proinflammatory cytokine release along with markers of myocardial injury in patients undergoing prolonged CPB with and without a leukocyte filter.

PATIENTS AND METHODS

This prospective, randomized open, clinical study was approved by the local Ethics Committee. Written informed consent was obtained from all patients. Twenty patients scheduled for combined aortic valve replacement for aortic valve stenosis and coronary artery revascularization were randomized to undergo CPB with a leukocyte-depleting filter (LeukoGuard LG6, Pall Biomedical, Portsmouth, England) incorporated in the extracorporeal circulation arterial line (leukocyte filter group, 10 patients) or without such a filter (control group, 10 patients). Patients with severe chronic diseases, altered organ or immune function, or evident infection were excluded. Other exclusion criteria were urgent or emergency operation and a serum creatinine level higher than 150 mg/L.

Premedication, anesthesia, and intensive care were standardized and performed according to our normal practice [Koskenkari 2005b]. All patients received 2 g of tranexamic acid (Caprilon, Leiras, Finland) after induction of anesthesia and another 2 g of tranexamic acid were administered during protaminization. Before aortic cannulation, heparin (3 mg/kg) was administered to maintain activated clotting time longer than 400 seconds during CPB. Additional heparin was administered as necessary. At the end of CPB, heparin was antagonized with protamine sulfate (3 mg/kg). CPB was carried out by using roller pumps with nonpulsatile flow and a membrane oxygenator, and under moderate systemic hypothermia (34°C). The CPB circuit was open and phosphorylcholine coated (Ph.i.s.i.o., Dideco, Mirandola, Italy) and it was primed with Ringer acetate (1500 mL), 15% mannitol (250 mL), and heparin 75 mg. Immediately after aortic cross clamping, with hypothermic blood cardioplegia at 15°C, Ringer acetate (1000 mL with KCl 80 mmol/L) mixed with oxygenated blood from the arterial line was administered in a retrograde fashion through the coronary sinus and electromechanical asystole was facilitated by injecting 10 to 20 mmol of KCl into the aortic root. Total ischemia time was recorded as cardioplegia was interrupted for better surgical field visualization. Pump flow was maintained at 2.4 L/min per m^2 and perfusion pressure was kept at 50 to 70 mmHg with the aid of norepinephrine. Hematocrit was maintained over 0.25 during and after CPB, and only leukocyte-depleted packed red blood cells were used. Cardiotomy suction was returned to the CPB reservoir in all cases. Cardioplegic temperature was raised to 36°C at least 5 minutes before the removal of the aortic cross clamp.

Table 2. Postoperative Data*

Risk Factors	Leukocyte Filter Group (n = 10)	Control Group (n = 10)	*P*
Intensive care unit stay, d	1.0 (1.0-5.0)	2.5 (1.0-4.5)	.58
Surgical ward stay, d	5.5 (3.7-6.0)	6.5 (5.0-10.5)	.09
Intubation time, h	7.0 (4.0-14.2)	9.5 (6.9-14.2)	.39
Average Pa_{O_2}/Fi_{O_2}, kPa	42 (36-44)	41 (34-44)	.52
Weight gain on first postoperative day, kg (range)	4.8 (4.0-6.0)	4.5 (2.0-6.5)	>.9
Postoperative blood loss, mL	600 (257-712)	525 (287-825)	.74
Blood transfusion (%)	2 (20)	5 (50)	.35
Platelet transfusion (%)	1 (10)	1 (10)	>.9
Inotropic support (%)	3 (30)	8 (80)	.07
Vasopressor support (%)	4 (40)	7 (70)	.37
Myocardial infarction (%)	1 (10)	1 (10)	>.9

*Continuous data are reported as the median and interquartile range (twenty-fifth and seventy-fifth percentiles).

During the intensive care unit (ICU) stay, the goals of hemodynamic support were to maintain the cardiac index above 2.2 L/min per m^2, mixed venous oxygen saturation above 58%, and mean arterial pressure above 65 mmHg. These were achieved by dobutamin infusion as needed following an adequate preload (pulmonary capillary wedge pressure 10-14 mmHg), afterload, and heart rate optimization (>65 beats/min). Hypotension was managed by administration of noradrenaline. Cardiac rhythm and hemodynamic measurements were recorded before the induction of anesthesia, after perfusion, 0, 1, 2, 3, 4, 6, and 8 hours after admission to the ICU, and on the morning of the first postoperative day. Occurrence of atrial fibrillation and a need for inotropic or vasopressor medication were recorded as well. Other outcome endpoints were time to extubation, average oxygenation index (Pa_{O_2}/Fi_{O_2}), ICU and hospital stay, first postoperative day weight gain, perioperative blood loss, and postoperative morbidity (cardiac, pulmonary, infectious, renal, neurological). Myocardial infarction was defined as a new Q-wave or a depression of R-wave combined with a rise of serum cardiac troponin-I above 5.0 μg/L. Neurological complications were classified as focal neurological defects or depression of consciousness associated with signs of cerebral injury on computed tomography scan.

Blood samples were collected from the radial artery line for measurement of blood cell count, neutrophil adhesion molecules, and cytokine analysis before anesthesia induction, 45 minutes after start of perfusion, and 5 minutes, 2, 4, and 18 hours after the end of perfusion. Blood samples were collected into evacuated tubes containing acid-citrate-dextrose (Baxter Healthcare, Thetford, England) as an anticoagulant. Each tube was immediately cooled in an ice-cold water bath to prevent ex vivo leukocyte activation and subsequently kept at 0°C until staining of leukocytes for flow cytometry within 24 hours. Plasma was separated from each specimen within 4 hours of sampling and stored at –70°C for cytokine analysis. Interleukin (IL)-6 and IL-8 concentrations (pg/mL) were determined according to the manufacturer`s instructions by commercially available ELISA kits (DuoSet; R&D Systems, Minneapolis, MN, USA). Leukocyte surface antigens were stained by the whole-blood technique of the direct immunofluorescence method using a fluorescence flow cytometer analyzer (FACS). In brief, 50 μL of blood was mixed with 50 μL of phosphate-buffered saline (PBS) and double labeled by the addition of pretitered amounts of fluorescence dye–conjugated (fluorescein-isothiocyanate [FITC] or phycoerythrin [PE]) monoclonal antibodies. After 20 minutes incubation on ice in the dark, contaminating erythrocytes were lysed by adding 2 mL of ice-cold FACS lysing solution (BD Biosciences, San Jose, CA, USA). After 6 minutes of incubation on ice, leukocytes were collected by centrifugation, washed with ice-cold PBS buffer and suspended in PBS buffer containing 0.5% of formaldehyde. Monoclonal antibodies (BD Biosciences) were used as follows: anti-CD16b (neutrophils), anti-CD11a (integrin ($_L$ chain), anti-CD11b (integrin ($_M$ chain), anti-CD62L (L-selectin), and appropriate isotype control antibodies. Cells were measured on a dual-laser flow cytometer (FACSCalibur; BD Biosciences) and data were analyzed by the Cel-

Table 3. Perioperative Changes in Leukocyte, Neutrophil, and Platelet Counts during the Study Intervals*

Group	Before Anesthesia Induction	Perfusion 45 Minutes	5 Minutes after Perfusion	2 Hours after Perfusion	4 Hours after Perfusion	18 Hours after Perfusion	P_g	$P_{t\times g}$
Leukocyte count, 1 × 10^9/L								
Leukocyte filter control	5.8 (4.2-7.3)	4.7 (3.0-8.1)	8.3 (7.2-10.1)	8.2 (6.8-8.9)	7.1 (5.9-8.3)	6.9 (5.5-9.7)	.40	.37
	5.3 (5.2-7.4)	6.0 (5.2-7.3)	9.6 (8.8-12.4)	6.7 (5.7-11.2)	6.7 (5.6-7.6)	7.9 (7.0-12.3)		
Neutrophil count, 1 × 10^9/L								
Leukocyte filter control	3.3 (2.0-4.5)	2.0 (1.3-4.3)	6.8 (5.2-7.7)	6.2 (5.2-7.6)	5.7 (4.7-7.0)	5.9 (4.2-7.0)	.45	.23
	2.9 (2.6-3.6)	3.1 (3.0-4.6)	6.9 (6.4-9.1)	4.8 (4.5-9.1)	5.3 (4.0-6.4)	6.4 (5.4-10.3)		
Platelet count, 1 × 10^9/L								
Leukocyte filter control	184 (178-240)	124 (115-170)	112 (85-140)	92 (71-141)	107 (90-137)	130 (100-151)	.67	.13
	183(151-213)	151 (114-170)	117 (86-137)	80 (70-105)	78 (65-118)	127 (82-139)		

*P_g indicates the level of difference between groups; $P_{t\times g}$, interaction between groups over time. Values are reported as median and twenty-fifth and seventy-fifth percentiles.

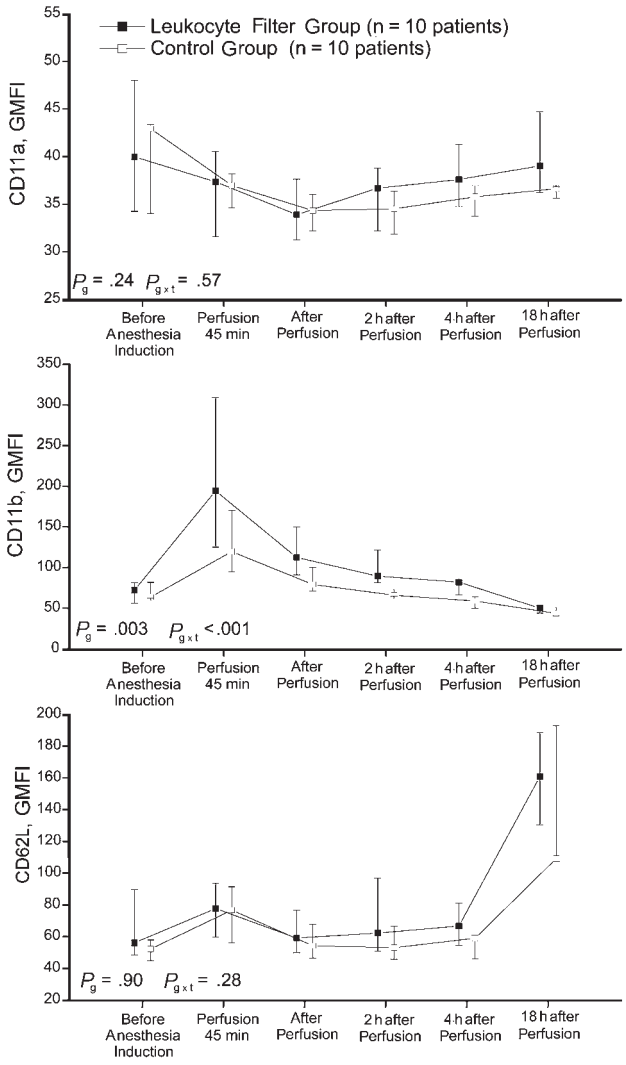

Figure 1. Perioperative neutrophil CD11a, CD11b, and CD62L expression in the study groups. Values are presented as the median and twenty-fifth to seventy-fifth percentiles.

lQuest software package (BD Biosciences). CD16b-positive neutrophils were gated and analyzed for the expression of CD11a, CD11b, and CD62L antigen. The results are expressed as geometric mean of the fluorescence intensity (channel number) of the FITC- or PE-positive histograms.

Serum C-reactive protein levels (ADVIA 2400 Chemistry System; Bayer HealthCare, West Haven, CT, USA) were measured before the anesthesia induction, after the operation, and on the first postoperative morning. Serum levels of cardiac troponin-I (cTnI, Innotrac Aio!; Innotrac Diagnostics OY, Turku, Finland) were measured before surgery, upon arrival in the ICU and 8 hours later, and on the first postoperative morning.

Statistical analysis was performed using SPSS statistical software (SPSS 12.0.1; SPSS, Chicago, IL, USA) and SAS (version 9.1; SAS Institute, Cary, NC, USA). Summary statistics for continuous and ordinal variables were expressed as the median with twenty-fifth and seventy-fifth percentiles. The differences between the study groups were evaluated by the Fisher exact test and the Mann-Whitney *U* test. Linear mixed model was utilized for analyzing the repeated measures data. Complete independence was assumed across subjects. If measurements were done with uneven time intervals, the spatial covariance structure was defined for R matrix, with even time intervals first-order autoregressive covariance matrix as defined. Two-tailed *P* values are reported as follows: *P* and P_g indicate group (treatment) difference, and $P_{t\times g}$ indicates interaction between time and group.

RESULTS

Patient demographics and perioperative data are reported in Tables 1 and 2. The study groups were comparable with regard to the main pre- and intraoperative patient characteristics. None of the patients died postoperatively. Reoperation was required in 2 patients of the control group, one because of bleeding and another because of paravalvular regurgitation.

Leukocyte, neutrophil, and platelet counts are reported in Table 3. Figure 1 shows the expression of neutrophil adhesion molecules (CD11a, CD11b, and CD62L) along the study intervals. The baseline values were comparable between the study groups. The CD11b levels were elevated in both groups after 45 minutes of CPB, but the peak was far more prominent in the leukocyte filter group and lasted up to 2 hours after the end of CPB. Thereafter, the levels paralleled and returned to the baseline level in both groups (P_g = .003, $P_{t\times g}$ < .001). There were no remarkable changes in CD11a expression (P_g = .24, $P_{t\times g}$ = .57) and the expression of CD62L (L-selectin) did not differ between the groups either (P_g = .90, $P_{t\times g}$ = .28).

Figure 2 shows cytokine IL-6 and IL-8 levels along the study intervals. One patient in the control group had raised IL-6 and IL-8 levels at baseline, without any evident clinical or technical reason. Hence, differences in cytokine levels are presented both with and without this outlier. There was an enhanced increase of IL-6 with time in the leukocyte filter group 5 minutes (125 pg/mL, interquartile range [IQR] 59-163 versus 34 pg/mL, IQR 29-72) and 2 hours after the end of CPB (158 pg/mL, IQR 103-182 versus 92 pg/mL, IQR 63-107, P_g = .63, $P_{t\times g}$ <.001; outlier excluded, P_g = 0.09, $P_{t\times g}$ < .001). The increase in IL-8 levels was faster at these same intervals as well (67 pg/mL, IQR 32-83 versus 27 pg/mL, IQR 19-42 pg/mL; and 49 pg/mL, IQR 33-68 versus 38 pg/mL, IQR 23-51 pg/mL, P_g = .53, $P_{t\times g}$ = .19; outlier excluded, P_g = .16, $P_{t\times g}$ = .007). The median C-reactive protein values in the filter and the control groups were 78 mg/dL (IQR 53-99) versus 66 mg/dL (IQR 57-87) on the first postoperative day and 202 mg/dL (IQR 158-215) versus 182 mg/dL (IQR 180-245) on the third postoperative day (P_g =.12). Cardiac troponin-I levels were within normal limits in all patients before anesthesia induction. Median cardiac troponin-I values were 3.7 μg/L (IQR 3.1-5.8) versus 2.7 μg/L (IQR 1.9-4.4) at admission to the ICU, 3.4 μg/L (IQR 2.6-5.1) versus 3.6 μg/L (IQR 2.4-8.1) at 8 hours after arrival at the ICU, and 2.1 μg/L (IQR 1.1-2.6) versus 2.4 μg/L (IQR

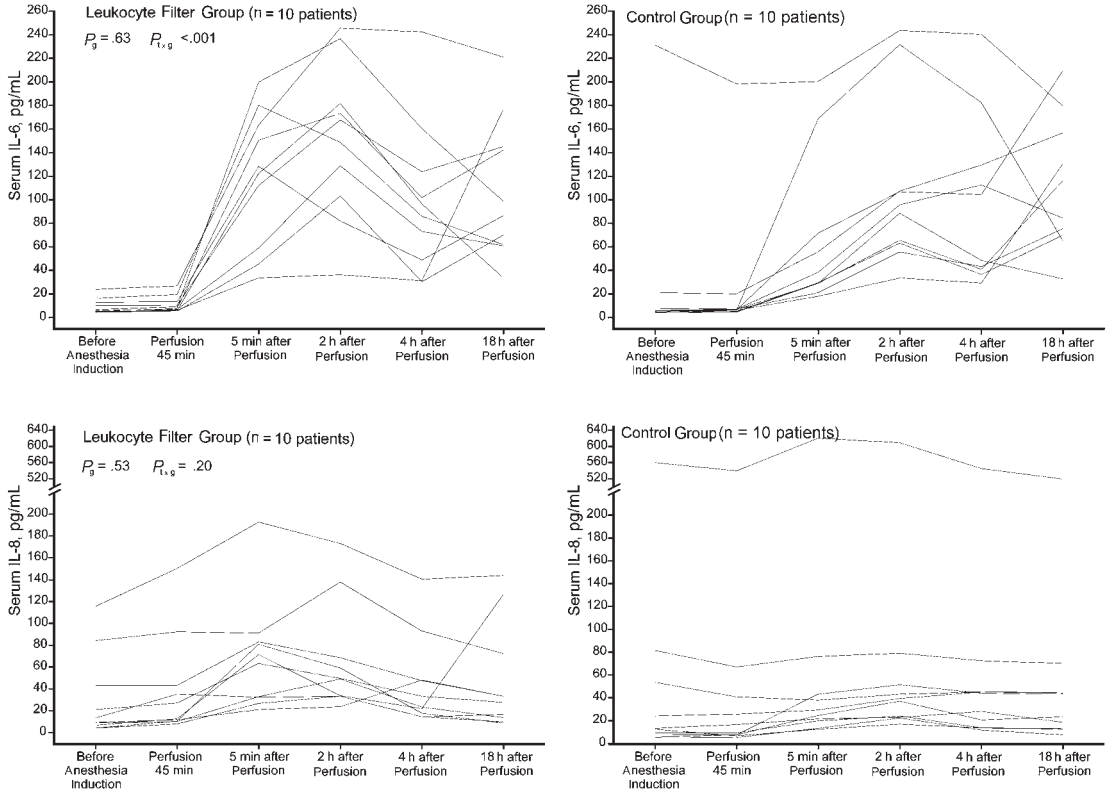

Figure 2. Perioperative serum cytokine level changes in each patient of the study groups. IL-6 indicates interleukin-6; IL-8, interleukin-8.

1.0-6.2) (P_g = .27) on the first postoperative day, respectively. There were no remarkable differences between the study groups in terms of cardiac indexes (P_g = .9), pulmonary capillary wedge pressures (P_g = .37), or systemic (P_g = .44) and pulmonary vascular resistance indexes (P_g = .66) during the study period (data not shown).

DISCUSSION

The main finding of the present study is that the continuous use of the leukocyte filter was associated with increased neutrophil CD11b expression during and after CPB, which was accompanied by enhanced proinflammatory cytokine IL-6 and IL-8 release during the first hours after CPB. The effects of activated neutrophils are largely mediated by the expression of neutrophil surface adhesion molecules, and increased expression of CD11b induced by CPB has been shown in several studies [Gillinov 1993; el Habbal 1997]. The up-regulation in CD11b is an important step in the formation of firm adhesion between activated neutrophil and endothelial cells and for the subsequent transendothelial migration and induction of tissue injury. Enhanced expression of CD11b is suggested to reflect increased neutrophil activity and some studies have demonstrated that it is associated with clinical adverse consequences [Rinder 2003]. Recent studies with the leukocyte filter have shown conflicting results with regard to the expression of neutrophil and endothelial cell adhesion molecules, particularly CD11b. Chen et al [2002] demonstrated decreased expression of CD11b by using a leukocyte filter during CPB and they suggested that this could be related to the removal of activated leukocytes by the filter. Opposite findings were reported by Ilmakunnas et al [2005] and recently by our group [Koskenkari 2005a]. Ilmakunnas et al [2005] showed that the leukocyte filter indeed increased CD 11b expression on neutrophils across the filter line, also resulting in elevated plasma lactoferrin levels as a marker of increased intravascular neutrophil activation. There is no evident reason to explain these conflicting results between the studies. However, one marked difference in the study protocol of Chen et al [2002] was the use of a normal arterial line filter in the control group, whereas no such filter was used either by us or Ilmakunnas and collaborators [2005]. The effect of a normal arterial line filter on neutrophil activation is unclear, but it might have some impact on the differing results.

Current opinions regarding different leukocyte filtration methods and the timing for filtration are contradictory [Scholz 2002; Patel 2003]. In this study, continuous filtration strategy was used as we aimed to achieve maximal removal of activated neutrophils. However, there is evidence that the activated neutrophils entrapped by the filter may still release deleterious substances such as inflammatory cytokines and proteases into systemic circulation [Scholz 2002]. Neutrophils may also become activated by the filter material itself. This was demonstrated by Ilmakunnas et al [2005] who

showed increased neutrophil and monocyte CD11b expression as early as 5 minutes after the initiation of CPB. These results are also supported by the current study, and the elevated proinflammatory cytokine levels after termination of CPB are indicative of an increased inflammatory response and strongly suggest enhancement of neutrophil activity by the leukocyte filter.

Neutrophil adherence to myocardial cells and release of oxygen-derived free radicals have been shown to induce myocardial cell injury and reduce the contractile response of cardiomyocytes. In this study, the use of a leukocyte filter failed to show any beneficial effect on myocardial reperfusion injury, as measured by troponin-I release and recovery of myocardial contractile function. Interestingly, our previous study on elective, isolated coronary artery bypass surgery with limited CPB duration demonstrated a significant reduction in peak cardiac troponin-I levels and also of C-reactive protein levels on the first postoperative day [Koskenkari 2005a]. This occurred without any attenuation of inflammatory response as measured by neutrophil surface antigens and cytokines. However, similarly to the present one, our previous study demonstrated enhanced CD11b and proinflammatory cytokine release in the leukocyte filter group. Perfusion duration was somewhat, but not significantly, longer in the current study than in our previous study, and the deleterious effects of enhanced inflammatory response due to this may have overshadowed the cardioprotective effects of leukofiltration during myocardial reperfusion.

There are potential limitations related to this study. Anesthesiologists and nurses involved in the intraoperative care were not blinded to patient allocation, but intensive care was provided in line with our normal standards by ICU nurses not involved in the study. Furthermore, this study was not powered to show any outcome benefit in the leukocyte filter group. Indeed, inclusion of only 10 patients per group is not likely to provide relevant data about any significant impact of this strategy on the immediate postoperative outcome, even in patients at high risk for adverse events. The main aim of this study, in fact, was to evaluate the impact of leukocyte filtration on inflammatory response. Furthermore, the interpretation of the present data can be biased by somewhat, but far from being statistically significant, longer perfusion duration and length of myocardial ischemia among patients of the leukocyte filter group. Indeed, the latter had shorter postoperative intubation duration and length of stay in the ICU along with a decreased need of inotropes, which could speak in favor of the use of leukocyte filtration. The length of stay in the ICU unit is, anyway, influenced by other factors such as the need of beds in the ICU or the lack of beds outside it for patient transferral. Thus, according to the present results, any benefit of leukocyte filtration in terms of immediate postoperative outcome can not be considered more than marginal.

In conclusion, the current study does not support the use of leukocyte filtration with continuous filtration strategy in cardiac surgery requiring prolonged CPB as it is associated with increased neutrophil CD11b expression during and after CPB, which is accompanied by enhanced proinflammatory cytokine IL-6 and IL-8 release.

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