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Use of Leukocyte-Depleting Filters During Cardiac Surgery With Cardiopulmonary Bypass: A Review

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Abstract: Numerous researchers and clinicians have shown that cardiopulmonary bypass (CPB) plays a large role in the initiation of the systemic inflammatory response during cardiac surgery. The activation of leukocytes during this process has been implicated as one of the major contributors to multi-organ dysfunction experienced by some patients after cardiac surgery. Thus, in an attempt to attenuate the systemic inflammatory response and to reduce the amount of activated leukocytes from the systemic circulation during CPB, leukocyte-depleting filters were developed in the early 1990s. Since the clinical introduction of these filters into the CPB circuit, several articles have been published evaluating the effectiveness of leukocyte filtration; however, the results have been conflicting. This article will review some of the most recent literature, ~40 papers published within the past 10 years, regarding the use of leukocyte-depleting filters during CPB and its effectiveness in preserving organ function. In addition, the effect of different filtration strategies and the effectiveness of the filter to attenuate the systemic inflammatory response in combination with other mechanical and pharmaceutical strategies will be reviewed. **Keywords:** cardiopulmonary bypass, leukocytes, leukocyte filter, leukocyte filtration, leukocyte depletion, cardiac surgery, inflammation, inflammatory response. *JECT. 2008;40:27–42*

It has been well documented that the use of cardiopulmonary bypass (CPB) during cardiac surgery is associated with the activation of a multitude of cellular and humoral substances caused by various events such as contact of the patient's blood with the artificial surface of the CPB circuit, ischemia/reperfusion, endotoxemia, surgical stress, and other stimuli (1–3). Collectively, these activated substances produce a whole body systemic inflammatory response, which can result in a variety of effects from severe, moderate, or undetectable harm to the patient. Activation of the systemic inflammatory response during CPB has been a major problem for clinicians because of the potential deleterious effects on organs such as the heart, lungs, kidneys, and brain (2). Not only does this affect patient outcome, but also the costs associated with postoperative care and length of ICU and hospital stay. Although the pathologic mechanism of this response has been attributed to the activation of several biochemical pathways, at the cellular level, activated leukocytes have been implicated as a key factor in the progression of the inflammatory response and the subsequent postoperative morbidity (2–4). In an attempt to attenuate this potentially harmful reaction, many clinicians, researchers, and component manufacturing companies have introduced various pharmacologic and mechanical strategies to minimize the systemic inflammatory response and the related consequences during CPB. One of these novel strategies has been the use of leukocyte-depleting filters within the CPB circuit during cardiac surgery. Because these filters were clinically introduced into the CPB circuit in the 1990s, numerous papers have been published showing the effects of these filters with conflicting results (20–60; Table 1). Some authors reveal promising and clinically beneficial results, whereas others have shown no benefit or potentially harmful results (20–60). The purpose of this paper is to review the updated literature, ~40 published papers, regarding the use of leukocyte-depleting filters during cardiac surgery with CPB.

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SYSTEMIC INFLAMMATORY RESPONSE TO CPB

Although the systemic inflammatory response can be initiated by several processes during cardiac surgery such as operative trauma (i.e., surgical incision, manipulation of the aorta), ischemia-reperfusion, and endotoxins, blood contact with the foreign surface of the CPB circuit continues to play a major role in the initiation of the inflammatory response (1–3) (Figure 1). Initially, when the patient's blood comes into contact with the CPB circuit, several

Table 1. Clinical studies investigating the use of leukocyte-depleting filters during cardiac surgery in humans.

Study	Study Design	Sample Size	Study Groups	Conclusion
Myocardial function—leukocyte filtration in arterial line				
Matheis et al. (20)	Prospective, randomized, blinded; Pilot study	38	LG6 filter; standard filter (40 μm)	Strategic leukocyte depletion during reperfusion phase reduced myocardial damage
Di Salvo et al. (21)	Pilot Study	20	Pall leukocyte filter in arterial + transfusion lines; standard filter	Activated neutrophil depletion may be beneficial to patients with unstable angina with impaired left ventricular function
Whitaker et al. (22)	Prospective, randomized, controlled double blinded,	60	LG6 filter; standard filter (Avecor-38 μm)	Leukocyte filtration increased neutrophil elastase and did not decrease leukocyte count or show a cardioprotective effect
Leal-Noval et al. (23)	Prospective, randomized, controlled, blinded	159	LG6 filter; standard filter	No beneficial effects of leukocyte filtration on postoperative myocardial function. Non-significant decrease in rate of perioperative infections, hyperdynamic states, and postoperative fever in leukocyte filtered group
Sahlman et al. (24)	Prospective, randomized	60	LG6 filter; no filter	No effect of leukocyte filtration CK-MB values
Myocardial function—leukocyte filtration in cardioplegia line				
Heggie et al. (25)	Prospective, randomized	14	BC1 filter; no cardioplegia filter	The filter is safe and effective in removing leukocytes from blood cardioplegia
Roth et al. (26)	Prospective, randomized, double blinded	32	2 Pall BC1B filters; two dummy filters	Two BC1B serial filters are effective in decreasing myocardial cell injury in patients with severe left ventricular dysfunction
Suzuki et al. (27)	Prospective, randomized	40	BC1B filter; no filter	BC1B filter is safe and effective in decreasing reperfusion injury
Palatianos et al. (28)	Prospective, randomized	160	Purecell RC 400 filter; no filter	Neutrophil-filtered blood cardioplegia/controlled reperfusion is effective in reducing myocardial reperfusion injury
Murai et al. (29)	Prospective	22	BC1B filter; no filter	Leukocyte-depleted blood cardioplegia may attenuate reperfusion injury and may increase cytokine activity
Sawa et al. (30)	Prospective, randomized, blinded	30	Whole blood reperfusion (WB); terminal blood cardioplegia (TC); leukocyte-depleted terminal blood cardioplegia (LDTC) (Cellsorba-80P)	LDTC was the most effective in attenuating reperfusion injury and can be used as a potential adjunct to TC in patients undergoing cardiac surgery with severe left ventricular hypertrophy.
Hayashi et al. (31)	Prospective, randomized	54	Leukocyte-depleted terminal blood cardioplegia (LDTC) (Pall BC1)- short (S) and long (L) cross-clamp times; no terminal cardioplegia (CONT)-short (S) and -long (L)	LDTC is provided superior myocardial protective effects for patients with longer aortic cross-clamp times (>120 minutes)
Browning et al. (32)	Prospective, randomized	40	BC1B filter; no filter	Leukocyte-depleted cardioplegia does not significantly improve myocardial protection
Lung function— leukocyte filtration in arterial line				
Alexiou et al. (33)	Prospective, randomized	50	LG6 filter; conventional filter (Sorin Biomedica D754)	Leukocyte depletion seems to limit lung injury and improve lung function in low-risk patients
Chen et al. (34)	Prospective, randomized	32	LG6 filter; standard filter	Leukocyte-filtered group experienced better lung preservation
Alexiou et al. (35)	Prospective, randomized	110	LG6 filter; conventional filter (Sorin Biomedica D754)	Continuous arterial line leukodepletion is effective in significantly reducing the rate of alveolar production of exhaled NO

Table 1. *Continued.*

Study	Study Design	Sample Size	Study Groups	Conclusion
Sheppard et al. (36)	Prospective, randomized	50	LG6 filter; conventional filter (Sorin Biomedica D754)	Leukocyte filtration is effective in significantly reducing exhaled NO production, thus protecting the lung
Karaiskos et al. (37)	Prospective, randomized	40	LG6 filter; standard filter (Jostra Safeline)	Leukocyte filtration during the early reperfusion phase was effective in preserving lung function in patients with chronic obstructive pulmonary disease
Sheppard et al. (38)	Prospective, randomized, blinded	32	LG6 filter; conventional filter (Sorin Biomedica D754)	Leukocyte-depleting arterial line filters are beneficial for patients with mild lung dysfunction
Sutton et al. (39)	Retrospective, cohort	700	Pall LGB filter + conventional filter (Pall) + leukocyte-depleted cardioplegia; conventional filter	Continuous leukocyte filtration improves lung function and offers clinical benefits to patients undergoing valvular surgery
Mihaljevic et al. (40)	Prospective, randomized	32	LG6 filter; standard filter	Leukocyte filtration failed to improve any postoperative lung function parameters
Fabbri et al. (41)	Prospective, randomized	40	LG6 filter + standard filter (Dideco Microtrap D730); standard filter	Although there was a significant reduction of circulating leukocytes in the leukocyte filtered group, there was no clinical benefit observed
Leal-Noval et al. (23)	Prospective, randomized, controlled, blinded	159	LG6 filter; standard filter	No beneficial effects of leukocyte filtration on postoperative pulmonary function. Non-significant decrease in rate of perioperative infections, hyperdynamic states, and postoperative fever in leukocyte-filtered group
Sahlman et al. (24)	Prospective, randomized	60	LG6 filter; no filter	No effect of leukocyte filtration in terms of pulmonary function
Renal function— leukocyte filtration in arterial line				
Tang et al. (42)	Prospective, randomized	40	LG6 filter; standard filter (40 μm)	Leukocyte filtration significantly reduced the extent of differential renal injury and showed renoprotective benefits
Cerebral function—leukocyte filtration in arterial line				
Whitaker et al. (43)	Prospective, randomized, blinded	198	LG6 filter; standard filter (Avecor Affinity/Pall Autovent-6)	Leukocyte filtration significantly reduced the number of cerebral microemboli and the results suggest some neuroprotection
Matheis et al. (20)	Prospective, randomized, blinded; Pilot study	38	LG6 filter; standard filter (40 μm)	Strategic leukocyte depletion during reperfusion phase showed no significant difference in S100B values between the groups, but neuron-specific enolase was lower in the leukocyte filtered group postoperatively.
Inflammatory mediators—leukocyte filtration in arterial line				
Chen et al. (34)	Prospective, randomized	32	LG6 filter; standard filter	Leukocyte filters are effective in decreasing endothelial activation and neutrophil transmigration.
Chen et al. (44)	Prospective, randomized	24	LG6 filter; standard filter	Leukocyte filtration is effective in reducing the expression of CD-11b and L-selectin
Sahlman et al. (24)	Prospective, randomized	60	LG6 filter; no filter	The value of C3 was significantly lower in the leukocyte filtered group 24 hours postoperatively
Stefanou et al. (45)	Prospective, randomized	20	LG6 filter; standard filter (Pall AV-6)	No significant difference between the two groups in terms of inflammatory parameters. Blood and crystalloid requirements were statistically higher in the control group (standard filter). Leukodepletion provides early clinical advantage

Table 1. *Continued.*

Study	Study Design	Sample Size	Study Groups	Conclusion
Mair et al. (46)	Prospective, randomized	40	LG6 filter; standard filter (Pall AV-6)	No significant difference in inflammatory parameters measured except for plasma elastase concentrations, which were significantly higher during and immediately after CPB in leukocyte filtered group compared with controls. Results do not support routine use of leukocyte-depleting filters
Ilmakunnas et al. (47)	Prospective, randomized	50	LG6 filter; no filter	Leukocyte filtration is not effective in reducing phagocyte activation and is associated with increased neutrophil and monocyte activation
Baksaas et al. (48)	Prospective, randomized, blinded	40	LG6 filter; standard filter (Pall AV-6)	Leukocyte filter significantly reduced leukocytes during reperfusion period, but there was no difference in inflammatory parameters between the groups. No clinical benefits were observed in leukocyte filter group
Total leukocyte depletion				
Salamonsen et al. (49)	Prospective, randomized, single blinded	300	Leukocyte filters in five locations of circuit: cardioplegia line, arterial line, residual oxygenator retrieval line, blood and platelet transfusion lines; standard filter	No clinical benefit of total leukocyte depletion
Samankatiwat et al. (50)	Prospective, randomized, controlled, blinded	40	Systemic leukocyte depletion (LG6 filter); cardioplegic leukocyte depletion (standard + BC1B filter); total leukocyte depletion (LG6 filter + BC1B filter); standard filter	Cardioplegic leukocyte depletion provides sufficient myocardial protection. There is no additional advantage of adding a systemic leukocyte filter
Leukocyte filtration in venous line				
Gu et al. (51)	Prospective, randomized	40	2 Pall Duplex filter sets (J1647G); control	Circulating leukocytes and IL-8 production were significantly reduced in the leukocyte filtered group. No significance between the groups in pulmonary parameters. It is possible to use a leukocyte filter on the venous side of the CPB circuit at the start of rewarming, before aortic cross-clamp release
de Vries et al. (52)	Prospective, randomized	40	Arterial line leukofiltration (LG6 filter-high flow and pressure); venous line leukofiltration (Pall RS1 filter-intermediate flow/high pressure); leukofiltration of residual blood post-CPB (Pall RS1 filter-low flow and pressure); no leukofiltration	No clinical difference between the three strategies. Findings suggest that leukofiltration with low flow and low pressure is associated with a reduction in leukocyte damage and elastase release
Pharmacologic + mechanical strategy				
Olivencia-Yurvati et al. (53)	Prospective, randomized, non-blinded	122	LGB filter (arterial line) + BC1B filter (cardioplegia line) + RS1 filter (cell saver) + RCQT filter (packed red cell) + aprotinin; no leukocyte filters + aprotinin	Combined pharmacological and mechanical (strategic leukofiltration) strategy significantly reduced postoperative atrial fibrillation, and decreased length of hospital stay, recovery time and costs.

Table 1. *Continued.*

Study	Study Design	Sample Size	Study Groups	Conclusion
Olivencia-Yurvati et al. (54)	Prospective, randomized, controlled, blinded	225	LGB (arterial line) + leukocyte filtered cardioplegia + leukoreduced autologous blood (RS1 filter) + leukoreduced allogenic blood + aprotinin; no leukocyte filters + aprotinin	Strategic leukocyte filtration with aprotinin administration significantly improved postoperative lung function
Olivencia-Yurvati et al. (55)	Part 1: prospective, randomized, controlled Part 2: retrospective, cohort	Part 1: 180 Part 2: 130	Part 1: LG6 filter (arterial line) + BC1 filter (cardioplegia line) + RS filter (cell saver) + RCQT filter (Allogenic blood) + aprotinin; no leukocyte filters + aprotinin	Part 1: strategic leukocyte filtration with aprotinin administration significantly reduced the incidence of atrial fibrillation and lessened postoperative impairment of pulmonary gas exchange. Part 2: a strong (non-significant) trend toward lower incidence of atrial fibrillation in on-pump dual treatment group compared to off-pump group. Combination of mechanical and pharmaceutical strategies could reduce incidence of arrhythmic and pulmonary complications post-CPB
Baksaas et al. (56)	Prospective, randomized	40	LG6 filter + heparin-coated circuit; standard filter (AV-6 filter) + heparin-coated circuit	Leukocyte filter did not reduce the level of WBCs and inflammatory markers.
Gott et al. (57)	Prospective, randomized, preoperatively risk stratified	400	Standard group: methylprednisolone pre-CPB; standard group + aprotinin; standard group + LeukoGuard arterial line filter + BC1B filter + RS1 filter + RC400 filter + PXLAR filter + LPS filter; methylprednisolone pre-CPB + heparin-bonded circuit + centrifugal pump	Heparin-bonded circuit group: significantly decreased complement activation; Leukocyte filtered group: significantly less postoperative leukocytosis and reduced length of hospital stay and mean charges in low risk patients; Aprotinin group: significantly less fibrinolysis and reduced length of hospital stay and mean charges in high risk patients. Pharmacologic and mechanical strategies reduced the inflammatory response to CPB and improved patient outcome
Hamada et al. (58)	Prospective, randomized	30	Conventional filter+ uncoated circuit (C); conventional filter + heparin coated circuit (H); LG6 filter + heparin-coated circuit (HF)	Combination of heparin-coated circuits with arterial line leukocyte filters significantly reduced the inflammatory response to CPB and improved pulmonary function
Gunaydin et al. (59)	Prospective, preoperatively risk stratified	225	Polymethoxyethylacrylate (PMEA)-coated circuit + LG6B filter (strategic) + BC2 filter (1); uncoated circuit + LG6B filter (strategic) + BC2 filter (2); uncoated circuit with no leukocyte filtration (3)	Low-risk patients: no significant differences between the groups. Medium-risk patients: groups 1 and 2 had significantly lower WBC counts; group 1 had significantly better platelet and fibrinogen levels preservation; groups 1 and 2 had significantly less IL-2 levels and C3a levels than group 3. High-risk group: groups 1 and 2 had significantly lower WBC counts, IL-2 and C3a levels than group 3; group 1 had significantly better platelet, fibrinogen, and albumin preservation
Timing of leukocyte filtration				
Scholz et al. (60)	Prospective, randomized	80	Standard filter; leukofiltration at onset of CPB; leukofiltration starting 5 minutes. before cross-clamp removal; leukofiltration starting with cross-clamp removal	Leukocyte filtration at any time point did not reduce neutrophil activity

LG6, LeukoGuard-6; BC1(B), blood cardioplegia.

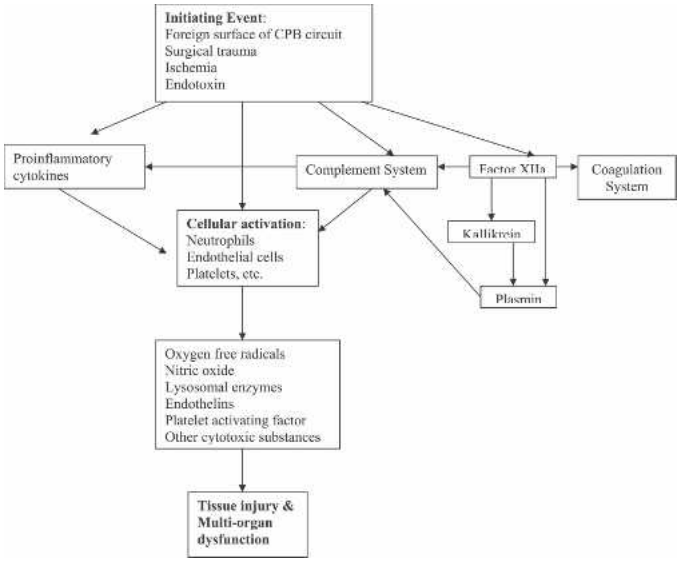

Figure 1. The systemic inflammatory response to CPB. [Adapted from: Wan S, LeClerc J, Vincent J. Inflammatory response to cardiopulmonary bypass: mechanisms involved and possible therapeutic strategies. Chest. 1997;112:676–92].

events occur such as the release of inflammatory mediators, the activation of neutrophils, and the initiation of the classic and alternative pathways of the complement system (2). Activation of the alternative pathway is of great significance because it results in the formation of the anaphylatoxins C3a and C5a (2). When these anaphylatoxins are released along with the other products of complement activation, an array of events can occur such as leukocyte activation, chemotaxis and adhesion, histamine release, increased respiratory burst in neutrophils, increased vascular permeability, and the intensification of other inflammatory and immune responses (2–6). In particular, C5a, along with adhesion molecules, and cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), are responsible for recruiting leukocytes to the site of injury or inflammation (3,5).

Stages of Endothelial Activation

Initially, inflammatory cytokines stimulate the synthesis of endothelial cell adhesion molecules (selectins) to which neutrophils transiently attach to (1,3,5,7). The neutrophils slowly roll across the vascular endothelium, which brings them into close contact with the endothelium (5,7). After this initial step, the neutrophils firmly attach to the endothelium through the interaction of the cell adhesion molecule CD11b/CD18 (β2-integrin receptor) with the intracellular adhesion molecule-1 (ICAM-1) expressed on the endothelium (1–3,7,8). Once they are attached, transmigration of the neutrophils occurs as a result of the production of chemoattractants and cytotoxins (3,7). Finally, when the neutrophils reach their target site (i.e., in the lungs, heart), they release cytotoxic substances and powerful enzymes such as lysosomal enzymes, myeloperoxidase, elastase, reactive oxygen species, lactoferrin, and a host of other endothelial-damaging substances to the newly reperfused tissue (1,3,4). It is this complex process that researchers and clinicians believe is responsible for much of the postoperative organ dysfunction associated with CPB.

It should also be noted that leukocytes are not only activated by the complement system and by direct contact with the CPB circuit but also by platelet-activating factor and leukotriene B4 (9). Furthermore, throughout CPB, other processes such as the fibrinolytic pathway and the coagulation cascade are activated. For example, when the contact system is activated, factor XIIa and kallikrein are formed, which in turn initiates the intrinsic coagulation pathway and activates neutrophils, the complement system, and the fibrinolytic system (2,9).

STRUCTURE AND MECHANISM OF LEUKOCYTE-DEPLETING FILTERS

The first leukocyte-depleting arterial line filter developed for use in the CPB circuit was created by Pall Biomedical Products Company (East Hills, NY) in 1991. Referred to as the Pall LeukoGuard-6 (LG6) Arterial Blood Filter, many researchers and clinicians have evaluated this filter's leukocyte-depleting capability during CPB and its effectiveness in reducing the postoperative morbidity associated with CPB. The Pall LeukoGuard-6 filter is made up of a 40-μm rated polyester screen with a clear, surface-modified polycarbonate housing and leukocyte-reducing polyester cartridge (10). This filter also has a three-stage system for gas separation with automatic venting, allowing flow rates of up to 6 L/min (10).

Additionally, Pall Biomedical Products Company developed the first leukocyte-reducing blood cardioplegia filter: the Pall LeukoGuard BC filter. Like the LeukoGuard-6™, this filter contains a 40-μm screen, which has the ability to capture gaseous and particulate microemboli and has a nonwoven polyester layer aimed at reducing circulating leukocytes (11,12). This filter is designed to tolerate flow rates of up to 500 mL/min, and the leukocyte-reducing capability is dependent on the volume of cardioplegia delivered to the patient and the conditions under which the cardioplegia is administered (11).

The main mechanism by which these filters remove circulating leukocytes from the blood is adhesion (13). Van der Waals forces and electrostatic forces on the material of the filter attract the negatively charged leukocytes, causing them to adhere to the filter (13). Factors that can affect the efficiency of adhesion include the filter material, surface charge, and hydrophilicity of the filter (13).

Although these filters have been shown to reduce the number of circulating leukocytes during CPB, they have been shown to become saturated during the course of CPB, rendering them ineffective in capturing circulating

leukocytes (14). They have also been shown to cause activation of the leukocytes, resulting in the release of toxic substances (14). Also, their efficacy in removing leukocytes depends on the contact time of the leukocytes with the filter. It has been noted that an increase in contact time with the filter improves leukocyte filtration (15). Thus, shorter contact time may impair the efficiency of the filter.

METHODS

Articles were found by searching PubMed and electronic journals using the key words cardiopulmonary bypass (CPB), leukocytes, leukocyte filter, leukocyte filtration, leukocyte depletion, cardiac surgery, inflammation, and inflammatory response. The search was limited to human studies published within the past 10 years and selected based on the subtopics outlined for the review paper.

PRESERVATION OF MYOCARDIAL FUNCTION

Leukocyte Filtration in the Arterial Line

Numerous studies have shown that myocardial function can be impaired after cardiac surgery with CPB (16–19). The morbidity associated with this dysfunction has been shown to include left ventricular dysfunction, myocardial stunning, myocardial edema, atrial fibrillation, reduced cardiac output, cardiac failure, and much more (16–19). Several biochemical markers of myocardial damage such as cardiac troponin T (cTnT), cardiac troponin I (cTnI), and creatinine kinase-MB (CK-MB) have also been measured to assess the damage of the myocardium after CPB. In a pilot study using strategic leukocyte depletion to examine the potential beneficial effects on reperfusion injury, Matheis et al. (20) found that troponin T (TnT) plasma levels were significantly lower in the group with a leukocyte-depleting filter compared with controls (standard arterial filter) after 24 hours. However, they noted that there was no significant difference in creatinine kinase (CK) level, CK-MB level, or white cell counts between the two groups (20). It should be noted that heparin-coated oxygenators and tubing were used for both groups in this study (20). Moreover, a pilot study by Di Salvo et al. (21), using intermittent cross-clamping and fibrillation, showed that the measurements of TnT and CPK-MB were lower in the leukocyte-filtered group than in the control group (standard filter). They also noted an increase in glutathione level in the leukocyte-filtered group, which indicated a reduction in oxidative stress on the myocardium (21). Based on their evidence, these authors concluded that leukocyte filters offered some myocardial protection.

In contrast, in a prospective randomized study using cross-clamp fibrillation and continuous leukodepletion, Whitaker et al. (22) found that there was no difference in TnT concentration at any time point up to 72 hours postoperatively between the leukocyte-filtered group and control group (standard arterial line filter). However, they noted a significant increase in neutrophil elastase in the leukocyte-filtered group during CPB and 10 minutes after CPB (22). They also reported that the leukocyte filter did not decrease the neutrophil count compared with the control group (22). Moreover, in a controlled, randomized trial by Leal-Noval et al. (23) using continuous leukocyte filtration, there was no significant difference in CK-MB, TnT, or cardiac index between the leukocyte filter group and the control group (conventional filter). However, they found that there was a non-statistically significant trend in the decline of fever, infection, and hyperdynamic states throughout the surgery in the leukocyte-filtered group (23). There was also no decrease in leukocyte count during or after CPB in the leukocyte-filtered group compared with the control group (23). Similarly, Sahlman et al. (24) found no difference in CK-MB levels between their leukocyte filtered group (during and after CPB) and control group (no arterial line filter). It should be noted that the blood left in the CPB circuit was re-infused using the Pall LeukoGuard RS filters in the treatment group and standard filters were used in the control group. Thus, in contrast to the articles mentioned previously, these papers showed that there were no beneficial effects of leukocyte-depleting filters in the arterial line in terms of myocardial damage based on their measurements.

Leukocyte Filtration in the Cardioplegia Line

With the development of the Pall LeukoGuard Blood Cardioplegia (BC1) filter, some researchers opted to add the BC1 filter into the cardioplegia line only, whereas others used the BC1 filter in addition to other leukocyte filters in different lines of the CPB circuit. Heggie et al. (25) examined the safety and efficacy of the Pall BC1 filter in 14 patients undergoing cardiac surgery. Their results showed that the average removal of leukocytes was in excess of 70%, with little effect on the levels of platelets and red blood cells (25). Thus, they concluded that the filter was safe and effective in removing leukocytes from blood cardioplegia (25).

In a double-blind randomized study, Roth et al. (26) used two serial BC1B filters in their experimental group and two dummy filters in the blood cardioplegia line of their control group in patients with severe left ventricular dysfunction undergoing coronary artery bypass grafting (CABG) surgery. They compared cardiac specific enzymes during the first 72 hours after surgery and from the coronary sinus blood at 30 and 60 minutes after aortic unclamping (26). They found that there were no significant differences between the groups in terms of the systemic release of cTnT, cTnI, and CK-MB mass during the

first 72 hours (26). However, there was a significantly lower amount of cTnT released from the coronary sinus 30 minutes after the aortic cross-clamp was released in the BC1B group and a moderate decrease after 60 minutes (26). Additionally, they found that significantly less dopamine was needed for weaning from CPB in the BC1B group (26). Furthermore, although both groups experienced a moderate and significant increase in left ventricular ejection fraction at 30 and 60 minutes after CPB, the differences in the increase at the different time intervals were significantly higher in the BC1B group (26). Also, there were no significant differences between the groups in hemodynamic parameters (heart rate, mean arterial pressure, cardiac index, stroke index, and left ventricular stroke work index) at any time (26). They also noted that the leukocyte filtration rate was 96.0% during the first dose of cardioplegia and 96.3% during the terminal dose (26). The authors concluded that serial leukocyte blood cardioplegia filters decreased myocardial cell injury.

Similarly, Suzuki et al. (27) showed the myocardial protective effects of leukocyte-depleted cardioplegia. Their experimental group incorporated the Pall BC1B filter into their circuit, whereas the control group did not have a filter in the cardioplegia line (27). Their results showed that TnT and CPK-MB values were significantly lower in the BC1B filter group (27). The total leukocyte reduction rates by the BC1B filter were 99.5%, 98.1%, and 94.7% when 1000, 2000, and 3000 mL of blood passed through the filter, respectively (27). The white blood cell (WBC) count decreased significantly after passage through the filter (27). Furthermore, Palatianos et al. (28) showed that myocardial reperfusion injury could be reduced by filtering neutrophils from the cardioplegia and during the initial period of myocardial reperfusion using a leukocyte-depleting filter (Purecell RC400). It should be noted that the filter was placed in a line that drained blood from the recirculation line of the oxygenator and that all patients received controlled myocardial reperfusion in the treatment group (28). The researchers found that there was significantly less reperfusion ventricular fibrillation, less need for electrical defibrillations, and less need for inotropic support and antiarrhythmics intraoperatively in the treated group when compared to the control group (28). There were also significantly lower CK-MB bands and TnT1 levels in the treated group postoperatively (28). Similarly, Murai et al. (29) showed that leukocyte-depleted blood cardioplegia may be effective in attenuating reperfusion injury of the myocardium in patients undergoing CABG surgery. Their results showed that plasma CK-MB and troponin T concentrations were significantly decreased in the leukocyte-filtered group compared with the control group (non-filtered blood cardioplegia) but were similar on return to the intensive care unit (ICU) (29). There were no significant differences between the two groups in terms of IL-6 and IL-8 concentrations, dopamine or dobutamine doses, or hemodynamic parameters post-CPB (29). However, it was noted that the cytokine concentrations were higher in the leukocyte-depleted group, indicating that cytokine activity may be increased during leukocyte filtration (29). The leukocyte filtration rate was ~85.8% during administration of antegrade cardioplegia; however, this rate decreased to ~39.9% during administration of terminal warm cardioplegia (29).

Moreover, Sawa et al. (30) examined whether leukocyte-depleted reperfusion as an adjunct to terminal cardioplegia can attenuate reperfusion injury in patients with severe left ventricular hypertrophy. One group received whole blood reperfusion (WB), another group received terminal blood cardioplegia (TC), and the last group received leukocyte depleted terminal blood cardioplegia (LDTC) (Cellsorba-80-P filter; Asahi Medical Co.) (30). The LDTC group showed better preserved myocardium, better recovery scores for myocyte damage and endothelial cell damage at reperfusion, significantly less number of leukocytes, and decreased neutrophil counts compared with the other groups (30). Also, lower CK-MB levels, lower pulmonary capillary wedge pressure, lower requirement for dopamine, and increased incidence of spontaneous defibrillation was observed in the LDTC group compared with the WB group (30). The authors concluded that LDTC is effective in reducing reperfusion injury and can potentially be used as an adjunct to TC in patients undergoing cardiac surgery with left ventricular hypertrophy (30).

Interestingly, Hayashi et al. (31) compared the myocardial protective effects of leukocyte-depleted terminal cardioplegia (LDTC) with prolonged (>120 minutes) and shortened (<120 minutes) aortic cross-clamp times in patients undergoing aortic valve replacement surgery. Patients in the LDTC group received 10 minutes of leukocyte-depleted terminal blood cardioplegia, whereas the control group did not receive any (31). The results showed that the LDTC group with the prolonged cross-clamp time had a significantly increased frequency of spontaneous defibrillation, increased plasma nitrate + nitrite in the effluent of the coronary sinus, decreased differences between the coronary sinus effluent and arterial blood in the percentage ratio of nitrotyrosine to tyrosine ($ONOO^-$ production), and decreased plasma polymorphonuclear-elastase and malondialdehyde(a marker of oxidative stress) compared with the control group after aortic declamping (31). Postoperatively, this group also showed decreased levels of the human-heart fatty acid-binding protein and CK-MB, and less need for catecholamines when compared to the controls (31). There were no significant differences in these measurements in the LDTC group with the shorter cross-clamp time; thus, the authors con-

cluded that LDTC is effective in preserving myocardial function in patients who undergo aortic cross-clamping for >120 minutes (31).

Additionally, Bowning et al. (32) compared the potential myocardial protective effects of leukocyte-filtered cardioplegia (Pall BC1B filter) with a non–leukocyte-filtered group in patients undergoing coronary artery bypass surgery. They found that there were no significant differences between the groups in terms of postreperfusion oxidized glutathione gradients, postoperative levels of CK-MB or troponin-T, or in the frequency of perioperative and postoperative complications (arrhythmia, myocardial infarction, and chest, wound, neurologic and gastrointestinal infections) (32). However, they noted at 1 and 5 minutes after the cross-clamp was released, there was a significant increase in transcardiac oxidized glutathione gradients in both groups (32). Although the filters had a mean cardioplegic leukocyte reduction of 90.7%, the authors concluded that they did not provide any significant myocardial protective effects (32).

PRESERVATION OF LUNG FUNCTION

Leukocyte Filtration in the Arterial Line

In a prospective randomized study by Alexiou et al. (33), pulmonary function was assessed in patients undergoing CABG surgery. They found that there was a significant difference in the total white cell count between the leukocyte-filtered group and the control group, and the activated white cell count was significantly lower across all sampled points in the leukocyte-filtered group (33). Also, the rate of alveolar exhaled NO production (a marker of lung inflammation) increased only slightly (nonsignificant) in the leukocyte-filtered group, whereas NO increased significantly in the control group after CPB (33). These differences were statistically significant between the two groups (33). In addition, whereas the alveolar-arterial oxygenation index (AaOI) increased in both groups, this value was significantly lower in the leukodepleted group (33). There were no differences in duration of mechanical ventilation, ICU and hospital stay, or frequency of heart and lung complications between the two groups (33). A study by Chen et al. (34) reported a significantly higher oxygen index 10 hours after CPB in the leukocyte-depleted group compared with the control group (standard arterial filter).

Both Alexiou et al. (35) and Sheppard et al. (36) studied the effects of leukodepletion on the rate of alveolar exhaled NO production in patients undergoing CABG surgery with normal preoperative lung function. These studies found that the rate of exhaled NO production increased in both the leukocyte-filtered groups and control groups (standard arterial line filters) after CPB; however, the increase in NO production was significantly less in the leukocyte-filtered groups (35,36). Both studies concluded that leukodepletion was effective in reducing the rate of alveolar exhaled NO production after CPB (35,36).

Additionally, Karaiskos et al. (37) showed that strategic leukocyte filtration is effective in preserving pulmonary function and improving oxygenation in patients with chronic obstructive pulmonary disease (COPD). The term strategic leukocyte filtration can imply that a filter is used at a certain time point throughout the surgery or that filters are placed at specific areas of the CPB circuit. In this study, the leukocyte filters were used 10 minutes before the aortic declamping and during the early reperfusion phase for up to 30 minutes in the treatment group (37). The authors noted a statistically significant increase in the respiratory index in the leukocyte-depleted group immediately after CPB compared with the control group, which remained significant when the baseline values were controlled for (37). Also, intubation and length of ICU and hospital stay were significantly lower in the leukocyte-filtered group than in the control group (37). The authors concluded that leukocyte filtration during the early reperfusion phase was successful in preserving lung function in patients with COPD (37). Similarly, Sheppard et al. (38) examined the effectiveness of leukocyte filtration in patients with mild lung dysfunction undergoing CABG surgery. They found that the alveolar-arterial oxygen index (AaOI) was significantly improved in the leukocyte-filtered group compared with the control group (standard arterial line filter) postoperatively (38). Also, the postoperative ventilation time and the amount of extravascular lung water were significantly less in the leukocyte filtered group than in the controls, indicating that leukocyte-depleting filters improved lung function (38).

Furthermore, in terms of patients undergoing valvular repair or replacement, Sutton et al. (39) performed a retrospective analysis on patients who underwent valvular surgery with an arterial line filter plus a leukocyte arterial filter and a leukocyte-depleted cardioplegia (study group) and those with a standard arterial filter only (control group). Their results showed that there was a significant improvement in PaO_2 in the immediate postoperative period in the study group compared with the control group (39). Also, the time to extubation, length of hospital stay, white blood cell count, and number of patients with prolonged intubation were significantly lower in the study group compared with the controls, indicating that leukocyte filters are clinically beneficial (39).

However, not all studies have been able to show that leukocyte filters are effective in preserving lung function. Mihaljevic et al. (40) evaluated postoperative pulmonary function in patients undergoing CABG surgery with normal preoperative lung function. Their results showed that there were no significant differences in postoperative lung function between the leukocyte-filtered group and the

control group in terms of oxygenation index, pulmonary vascular resistance, and intubation time (40). There was also no significant decrease in leukocyte counts between the groups (40). Fabbri et al. (41) also found no significant difference in postoperative lung function between their leukocyte-filtered and control groups as assessed by pulmonary respiratory index and intubation time. However, they noted a significant decrease in the number of circulating leukocytes during CPB and a smaller increase in leukocytes post-CPB in the leukocyte-filtered group, but there were no clinical benefits noted for the patients (41).Similarly, Leal-Noval et al. (23) found no significant difference in lung compliance, oxygenation index, and mechanical ventilation time between their leukocyte-depleted and control groups, rendering no measurable effects of leukocyte filters. There was also no difference in oxygen index before extubation and 45 minutes thereafter between the leukocyte-filtered group and control group in a study by Sahlman et al. (24).

PRESERVATION OF RENAL FUNCTION

Leukocyte Filtration in the Arterial Line

To date, there have not been many studies that have focused solely on the effect of leukocyte filtration in the arterial line in preserving renal function. In 2002, Tang et al. (42) conducted a prospective randomized study focusing on this aspect in a clinical setting. Their study included 40 patients randomized into two groups: a leukocyte filtered group and a control group (standard arterial line filter) (42). The patients were undergoing CABG surgery with normal preoperative renal function (42). Urinary excretion of microalbumin (MA) and retinol binding protein (RPB) indexed to creatinine (Cr; RBP:Cr) were used to evaluate renal glomerular and tubular injury (42). Although the results showed a dramatic and significant increase in the value of urinary RBP:Cr and urinary microalbumin in both groups, the increase was significantly higher in the control group (42). These values peaked on postoperative day 1 and returned to near baseline values at the end of the study (42). This temporal trend was also noted in the values of MA:Cr in both groups, again with a significantly marked increase in the control group compared with the leukodepleted group (42).There were no differences in daily fluid balance, serum creatinine, and blood urea between the groups (42). Based on these results, the authors concluded that leukodepletion is beneficial in providing renal protection during CPB (42).

PRESERVATION OF CEREBRAL FUNCTION

Leukocyte Filtration in the Arterial Line

As with renal function, there have not been many published studies that have examined the protective effects of leukocyte filters on cerebral function. In a randomized controlled clinical trial by Whitaker et al. (43), cerebral function was assessed by intraoperative microembolic load to the brain along with a battery of neuropsychologic (NP) tests in patients undergoing CABG surgery with cross-clamp fibrillation. They found that there were significantly less microemboli in the leukocyte-filtered group compared with the control groups (Avecor Affinity and Pall Autovent-6 filters) (43). There was also a non-statistical trend towards better NP scores in the battery of tests performed in the leukocyte-filtered group compared with the control group (43). Thus, the authors concluded that leukocyte filters were effective in decreasing the amount of microembolic events and the results also strongly suggested some neuroprotection (43).

In contrast, Matheis et al. (20) showed there was no significant effect of leukocyte filtration in preventing cerebral injury in patients undergoing CABG surgery. Their results showed there was no significant difference in the serum marker S100 (an inflammatory marker indicating cerebral injury) between the leukocyte-filtered group and control group (standard arterial line filter). However, they noted that a marker for neuronal damage, neuron-specific enolase, was lower in the leukocyte-filtered group 24 hours postoperatively (20). Heparin-coated circuitry and strategic leukodepletion were also used in this study (20).

ATTENUATION OF INFLAMMATORY MEDIATORS

Leukocyte Filtration in the Arterial Line

In 2004, Chen et al. (34) conducted a study that examined the effect of leukocyte filtration on endothelial activation and transendothelial neutrophil migration in patients undergoing CABG or heart valve operations. Their results showed that, although there was a significant increase in P-Selectin, ICAM-1, IL-8, and malondialdehyde (MDA) in both the leukocyte-filtered and control groups at various time points, the leukocyte filtered group displayed significantly less values than the control group (34). They also reported that the plasma platelet-endothelial cell adhesion molecule-1 (PECAM-1) rose significantly in the control group, but not in the leukocyte-filtered group, and the circulating plasma level of PECAM-1 was observed to be significantly lower in the leukocyte depletion group (34). The total WBC count was shown to be significantly reduced in the leukocyte filtered group and significant leukocytosis was observed in the control group after the reperfusion stage (34). They concluded that leukocyte filters were effective in decreasing endothelial activation and neutrophil transmigration (34). Similarly, in a previous study, Chen et al. (44) again showed the positive effects of leukocyte filtration during CPB. They examined the attenuation of neutrophil adhesion molecules by leu-

kocyte filters in patients undergoing various elective heart operations (44). The authors reported that CD11b expression on the neutrophils in the control group was significantly higher than the leukocyte-filtered group (44). The expression of L-selectin was observed to be down-regulated during and after CPB in the leukocyte filtered group, whereas the expression was significantly increased in the control group (44). The expression of CD11c was observed to be significantly lower during and after CPB in the leukocyte-filtered group; however, this decrease was not significantly different between the groups (44). Last, the authors found no significant difference in neutrophil cell surface CD11a expression between the leukocyte-depleted and control groups (44). Although there were no significant changes in total WBC and neutrophil counts during CPB in the control group, these values decreased markedly in the leukocyte-filtered group during CPB (44). The authors concluded that leukocyte filtration is effective in reducing the expression of CD11-b and L-selectin (44). Moreover, Sahlman et al. (24) evaluated complement activity pre- and post-CPB. They reported that C3 was significantly lower in the leukocyte-filtered group 24 hours postoperatively compared with the controls (24). No other parameters that they measured were significantly different between the groups (24).

In contrast, Stefanou et al. (45) studied the expression of CD11b on neutrophils and the production of myeloperoxidase and lactoferrin in patients undergoing CABG operations. In both the leukocyte-filtered group and the control group (standard filter), CD11b expression and myeloperoxidase and lactoferrin values increased but declined to preoperative levels by the third postoperative hour (45). There were no significant differences between the two groups in terms of these parameters (45). The WBC and neutrophil counts were reduced in the filtered group 3 hours postoperatively; however, the results were not statistically significant (45). The investigators reported that the leukocyte-filtered group required significantly less blood transfusions and less crystalloid fluid during the first 24 hours postoperatively compared with the control group (45). Furthermore, Mair et al. (46) examined the effect of leukocyte depletion on neutrophil activation and oxygen free radical generation in patients undergoing elective aortocoronary bypass surgery. They found no significant differences in terms of WBC count, plasma elastase, malondialdehyde, and C-reactive protein concentrations between the leukocyte-filtered and control groups (46). It was noted that plasma elastase concentrations were significantly higher during and immediately after CPB in the leukocyte-filtered group (46). This value was also significantly higher after CPB in both groups compared with the preoperative baseline value (46). Plasma concentrations of malondialdehyde were significantly lower during and after CPB in both groups (46). Moreover, Ilmakunnas et al. (47) studied the effects of leukocyte-depleting filters on phagocyte activation during CPB in patients undergoing CABG surgery. Their results showed that compared with the preoperative value, neutrophil and monocyte counts were lower in both groups, but more so in the leukocyte-filtered group than the control group (no arterial filter) at 5 minutes of CPB (47). Neutrophil count increased toward the end of CPB in both groups, but this value stayed significantly lower in the filtered group, whereas monocyte counts remained lower in the filtered group throughout this time (47). There was a small significant decrease in neutrophil count across the leukocyte filter at 30 minutes of CPB, whereas there was no difference in monocyte count across the filter at the same time (47). At 5 minutes of CPB, neutrophil and monocyte CD11b expressions were significantly higher in the leukocyte-filtered group compared with controls, and this value remained higher in the filtered group during CPB (47). Neutrophil hydrogen peroxide production and lactoferrin plasma levels were also significantly higher in the leukocyte-filtered group; however, neutrophil expression of L-selectin was lower in the filtered group (47). The authors concluded that the leukocyte filter played a role in increasing neutrophil and monocyte activation and was ineffective in reducing phagocyte activation (47).

All of the studies mentioned above used continuous arterial line leukocyte depletion. Baksaas et al. (48) conducted a study that measured complement and leukocyte activation in patients undergoing CABG surgery using strategic leukocyte filtration. Both groups used an identical circuit until aortic cross-clamp release, and the regular filter was occluded, and a leukocyte filter was incorporated into the treatment group's circuit and a standard arterial line filter was incorporated into the control group's circuit (48). Although the concentrations of myeloperoxidase, C3bc, terminal complement complex (TCC), IL-6, and IL-8 increased significantly in both groups at various time points, there were no significant differences between the two groups in terms of these parameters (48). However, the circulating WBC count during the reperfusion period and the total WBC count postoperatively were significantly lower in the leukocyte-filtered group compared with the control group (48).

Total Leukocyte Depletion

A study by Salamonsen et al. (49) examined the effect of total leukocyte control in 300 patients undergoing elective CABG surgery. Total leukocyte filtration was achieved by including leukocyte filters in five different locations in the bypass circuit (cardioplegia line (BC1B filter), arterial return line (LG6 filter), residual oxygenator retrieval line (RS1 filter), and in the blood (RC400 filter) and platelet transfusion (LRP6 filter) lines (49). A standard 40-μm filter was used in the control group (49). The authors reported that postoperatively, leukocyte

counts increased in both groups (34% in leukofiltered group, 54% in control group) compared with preoperative values, but there was no significant intergroup difference (49). Neutrophil counts were less in the leukofiltered group immediately after surgery, but they were similar to the control group by the second postoperative day (49). Platelet level was significantly lower in the leukofiltered group in the immediate postoperative period and remained significantly lower on the second postoperative day compared with the controls (49). There were no significant differences between the groups in terms of length of ICU stay, hospital mortality, postoperative organ dysfunction, postoperative blood loss, use of blood or blood products, or any other outcome variables measured (49). The authors mentioned that the arterial line leukocyte filter blocked on two occasions in the leukofiltered group, resulting in one patient being weaned slightly early from bypass, whereas the other required replacement during bypass (49). The filter in the cardioplegia line also blocked on one occasion, which required replacement during CPB (49). The authors reported that these incidences did not affect the recovery of these patients (49). They concluded that, although total leukocyte filtration is safe, this strategy failed to improve clinical short-term outcome (49).

Furthermore, in a pilot study, Samankatiwat et al. (50) studied the effect of total leukocyte depletion (TLD) and compared this method to three other filtration strategies: systemic leukocyte depletion (SLD), cardioplegic leukocyte depletion (CLD), and a control group (standard filter) (50). The results showed that, although the plasma lactoferrin levels increased quickly in all groups at the beginning of CPB, this level was lowest in the TLD and CLD groups (50). Both groups had significantly lower lactoferrin concentrations than the SLD group at different time points (50). There were no significant differences between the groups in terms of troponin-I concentrations, blood loss, non-red blood cell volume replacement, and inotropic drug replacement, although the lowest level for each parameter was observed in the CLD group (50). Although there were no clear statistical differences between the groups, the results suggested that CLD may be the best strategy in attenuating neutrophil activation and myocardial ischemia reperfusion injury (50).

Leukocyte Filtration Through the Venous Line

Gu et al. (51) examined the effect of leukofiltration using two Pall Duplex filter sets located between the venous reservoir and the venous drainage line from the patient. Leukocyte filtration was used using a spare roller pump at the beginning of rewarming, but before the aortic cross-clamp was released and was completed within 10 minutes (51). The leukocyte filtered group and the control group consisted of 20 patients each (51). The authors reported that the mean leukocyte removal rate was 69%, and the circulating leukocyte count was significantly lower in the leukocyte-filtered group than in the control group when the cross-clamp was removed, resulting in a 38% decrease in circulating leukocytes (51). They also found that the leukocyte removal rate was positively correlated with the nasopharyngeal temperature and was negatively correlated with the cross-clamp time (51). Also, the leukocyte count increased quickly in the leukocyte-filtered group during the reperfusion phase, which was similar to the value in the control group (51). Although the value of IL-8 was very low in the two groups before CPB, this value increased in both groups during CPB and into the postoperative period (51). However, the value of IL-8 was significantly decreased in the leukocyte-filtered group (51). There were no significant differences between the groups in terms of the levels of leukocyte elastase, the soluble form of L-selectin, PaO_2 at any time point, intubation time, blood loss, or number of ICU and hospital days (51). The authors concluded that removing circulating leukocytes through the venous side of the CPB circuit with a low blood flow rate is possible (51).

Leukofiltration of the venous return blood was also shown in a study by de Vries et al. (52), in which three different leukofiltration strategies at different flows and pressures were compared in 40 patients undergoing CABG and valve surgeries. The groups were divided as follows: arterial blood leukocyte filtration during CPB with high flow and pressure gradients, leukocyte filtration of venous return blood during the rewarming phase of CPB with intermediate flow and high pressure, leukocyte filtration of residual heart-lung machine blood with low flow and pressure during transfusion at the end of CPB, and a control group without leukocyte filtration (52). The results showed that the circulating leukocyte and granulocyte counts significantly increased in all groups at the end of CPB to the first postoperative day, but there was no significant difference between the groups (52). The PaO_2 decreased in all groups with a significant time effect, while the A-a gradients increased with a significant time effect postoperatively (52). There were no significant effects between the groups. Also, the plasma elastase values were increased in the venous blood leukofiltered group and in the control group while these values decreased in the arterial and residual blood leukofiltered groups postoperatively (52). Scanning electron microscopy of the filters from each group revealed that the arterial filter group, with high flow and pressure gradients, had extensive platelet and protein deposits (52). Many of the leukocytes and red blood cells were damaged in the deeper layers of the filter and the platelets showed activation (52). The filters used under high pressure in the venous and residual blood groups showed extended protein deposits, damaged leukocytes in the middle and lower layers, and activated platelets (52). However, the filters used under low pressure in these two groups revealed leukocytes and platelets

mainly in the superficial layer of the filter, which declined in number as they examined the middle and lower layers (52). There were also very little protein deposits and more leukocytes trapped in the filter than platelets (52). They were unable to show that there was a clinical significance between the different filtration strategies; however, the results suggested that low flow and pressure may result in a smaller amount of leukocyte damage and less elastase release (52).

Leukocyte Filtration + Pharmacologic and/or Mechanical Strategies

There have been many studies in the literature that have combined the use of leukocyte-depleting filters with aprotinin, methylprednisolone, heparin-bonded circuits, and/or different types of pumps in an effort to reduce postoperative organ dysfunction. Olivencia-Yurvati et al. (53) recently published three papers that have specifically examined the use of leukocyte filtration in conjunction with aprotinin. In 2002, they tested whether combining these two strategies could decrease the post-CPB inflammatory response and the incidence of post-CPB atrial fibrillation (53). The treatment group was administered a full Hammersmith dose (Regimen A) of aprotinin and had leukocyte filters added to the arterial and cardioplegia lines (53). Residual pump volume and allogenic blood used during the surgery were also leukofiltered (53). The arterial line leukocyte filter was used strategically, ~30 minutes before the cross-clamp was released (53). The incidence of post-CPB atrial fibrillation in the treatment group was 7.6% compared with 27% in the control group (53). Thus, the combination of leukocyte filtration and aprotinin significantly decreased atrial fibrillation by 72% (53). Other outcomes such as length of hospital stay, recovery time, and cost were also reduced in the treatment group (53). In their following paper, published in 2003, they examined the effect of leukocyte filtration with aprotinin on postoperative pulmonary function (54). The same technique and CPB circuit design was used as described in their previous study (54). Their results showed that pulmonary microvascular pressures and pulmonary artery pressures were significantly reduced in the study group (leukocyte filtration + aprotinin) compared with the control group (aprotinin only) at 24 hours after CPB (54). Although the pulmonary shunt fraction increased in both groups after CPB, this rise was significantly less in the study group (54). Also, the average ventilator time was reduced by 47% in the study group (54). There was no significant difference between the groups in terms of pulmonary capillary wedge pressure (54). Furthermore, in their most recently published paper regarding leukocyte filtration and aprotinin, they divided the study into two parts (55). The first phase studied whether the dual treatment with leukocyte filtration and aprotinin could decrease post-CPB atrial fibrillation and pulmonary dysfunction using the design similar to their two previous studies (55). As with their previous study, their results showed that the study group (leukofiltration + aprotinin) significantly decreased the incidence of post-CPB atrial fibrillation (by 67%) compared with the control group (aprotinin only) (55). Pulmonary shunt fraction also increased in both groups; however, the increase was markedly reduced in the study group by 40% (55). In the second phase of the study, the study group was retrospectively compared with a cohort of patients undergoing off-pump surgery (55). The authors reported a strong trend (no significant difference) toward a decreased incidence of post-CPB atrial fibrillation in the on-pump study group vs. the off-pump group (55). In all three papers, the authors concluded that the combination of strategic leukocyte filtration with aprotinin is effective in reducing the post-CPB reperfusion inflammatory response and the arrhythmic and pulmonary complications associated with this complex reaction (53–55).

Baksaas et al. (56) examined the effect of continuous leukocyte depletion on several biochemical and clinical parameters using heparin-coated circuits. The study group had a leukocyte-depleting arterial line filter, whereas the control group had a standard arterial line filter (56). Although the levels of myeloperoxidase, IL-6, C3 activation products, and the mean TCC significantly increased in both groups, there was no significant intergroup difference (56). There were also no significant differences in TNF-$\propto$ concentrations or mean platelet counts nor were there any shown differences in clinical outcome between the groups (56). Thus, the leukocyte filter with heparin-bonded circuits was not effective in reducing WBCs or inflammatory mediators (56).

Moreover, Gott et al. (57) conducted a study in which four anti-inflammatory strategies were used during CPB. All of 400 patients were divided into a standard group (methylprednisolone pre-CPB + roller pump), an aprotinin group (standard protocol + half-Hammersmith aprotinin dose), a leukocyte-filtered group (standard protocol + continuous leukofiltration in arterial and cardioplegia lines with all intra- and post-operative blood, platelets, and fresh frozen plasma filtered), and a heparin-bonded circuitry group (methylprednisolone + centrifugal pump) (57). The patients were also preoperatively risk stratified (57). There was no significant difference in renal dysfunction or pulmonary morbidity between the groups; however, lung function was significantly impaired in all of the groups after CPB (57). Chest tube drainage was significantly decreased in the aprotinin group, with high-risk patients having significantly lower hospital costs and length of stay (57). The hemoglobin level was significantly higher on the first postoperative day in the aprotinin group compared with the leukocyte-filtered group (57). The leukocyte filtered group had significantly lower leukocyte values immediately post-CPB compared with the other

groups (57). Lengths of hospital stay and hospital charges were also significantly reduced in this group in the low-risk strata with no significant difference in the medium-risk strata (57). In the heparin-bonded circuitry group, complement activation was highly significantly decreased, but there was no observed clinical benefit (57). The authors concluded that combining pharmacologic and mechanical strategies significantly reduced the inflammatory response to CPB and resulted in improved patient outcomes (57).

Additionally, Hamada et al. (58) combined various mechanical and pharmacologic strategies to determine whether the systemic inflammatory response could be reduced. Their study consisted of 30 patients divided into three groups: C group (conventional circuit + arterial line filter), H group (heparin-coated circuit + conventional filter), and HF group (heparin-coated circuit + leukocyte filter in arterial line) (58). Although the leukocyte count was lower in the HF group immediately and 4 hours after CPB, there was no significant decrease compared with the other groups (58). Also, in the HF group, plasma IL-6, plasma IL-8, and respiratory index were significantly lower than group C at various time points after CPB (58). The authors concluded that heparin-coated circuits with leukocyte-depleting arterial line filters are effective in attenuating the systemic inflammatory response and improving pulmonary function (58).

Furthermore, Gunaydin et al. (59) studied the effect of strategic leukofiltration in low-risk, medium-risk, and high-risk patients and divided the study groups as follows: leukofiltration + polymethoxyethylacrylate (PMEA)-coated circuits (group 1), leukofiltration + uncoated circuits (group 2), and no leukofiltration with uncoated circuits (group 3) (59). In the leukofiltered groups, the arterial line filter was replaced with a leukocyte filter, and another leukocyte filter was placed in the cardioplegia line (59). The arterial line leukocyte filter was used ~30 minutes before the aortic cross-clamp was removed (59). In the low-risk cohort, there were no significant differences between the study groups in terms of blood sampling and assays, hemodynamic evaluation, and perioperative follow-up (59). In the medium-risk cohort, the WBC counts were significantly lower in groups 1 and 2 compared with the controls, and platelet counts were significantly better preserved in group 1 compared with the other groups at various time points (59). Group 1 also showed significantly better preservation of fibrinogen levels and had significantly decreased serum IL-2 levels (as with group 2). There were also significant differences in C3a levels in groups 1 and 2 at certain time points (59). The incidence of atrial fibrillation was significantly decreased in groups 1 and 2 compared with group 3. Moreover, in the high-risk cohort, there were significant differences in WBC counts in groups 1and 2 and in platelet counts in group 1 at various time points (59). Group 1 also showed significantly better preservation of fibrinogen and albumin levels (59). Groups 1 and 2 showed significantly reduced serum IL-2 levels, and there were significant differences in both groups with regard to C3a levels (59). Although no difference was found in the low-risk cohort, the initial biochemical and hematologic parameters differentiated as the risk became higher, and the results showed that clinical outcome was much better in the filtered groups (59).

Timing of Leukocyte Filtration

The most beneficial and efficacious time to use leukocyte-depleting filters during CPB has been a major conflict among researchers and clinicians throughout the years. Inconsistencies can be seen in the existing literature concerning this issue, and there have been very few studies that have focused solely on this topic. Scholz et al. (60) studied three different filtration timing strategies in 80 cardiac surgery patients and measured functional neutrophil activity (60). The patients were allocated into the following groups: group 1, no leukocyte filtration (standard arterial line filter); group 2, leukocyte filtration starting at the onset of CPB; group 3, leukocyte filtration starting 5 minutes before aortic cross-clamp removal; group 4, leukocyte filtration starting with aortic cross-clamp removal (60). There were no significant differences between the groups in terms of leukocyte count, malondialdehyde level, percent of cells showing phagocytic activity, or oxidative burst assay (60). In fact, polymorphonuclear elastase and myeloperoxidase levels were significantly increased in groups 2–4 (60). The authors concluded that there were no clinical benefits of leukocyte filtration, and none of the filtration strategies were able to reduce neutrophil activity (60).

COMMENT

The implementation of leukocyte-depleting filters in CPB circuits has sparked much debate throughout the years as to whether they are truly effective in attenuating the systemic inflammatory response and improving clinical outcomes. A large body of evidence exists showing that leukocyte-depleting filters are capable of reducing organ dysfunction and markers of inflammation; however, there are also many other published studies that could not show any clinical benefit of using these filters (20–60). Until today, this debate remains unresolved because of the large variations in sample size, types of surgery, length of CPB time, age and other factors, making comparisons difficult between studies. There are still many unanswered questions and variables that need further exploration such as the timing of leukofiltration, the use centrifugal vs. roller pumps, and the effects of temperature, flow, and pressure through the filter, the location of the filter in the circuit, the number of filters to use, and the effects on low-high

risk patients. New strategies such as the use of leukocyte filtration in conjunction with pharmacologic and other mechanical strategies have shown much promise but still needs to be examined further to find the best strategy that will be the most beneficial to the patient. Until more clinically relevant studies are published, the decision to use leukocyte-depleting filters during CPB will remain controversial.

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