Review

The effects of various leukocyte filtration strategies in cardiac surgery

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Summary

It is known that cardiopulmonary bypass causes an inflammatory reaction with an associated morbidity and mortality. Several anti-inflammatory strategies have been implemented to reduce this response, including leukocyte removal from the circulation using specialised filters. The aim of this study is to systematically review the available evidence on leukocyte filtration in cardiac surgery, focusing on its effect on systemic inflammation and whether this has influenced clinical outcomes. Five electronic databases were systematically searched for studies reporting the effect of leukocyte filtration at any point within the cardiopulmonary bypass circuit in humans. Reference lists of all identified studies were checked for any missing publications. Two authors independently extracted the data from the included studies. Whilst systemic leukodepleting filters do not appear to consistently lower leukocyte counts, they may preferentially remove activated leukocytes. Small improvements in early post-operative lung function in patients receiving systemic leukodepletion have been reported, but this does not lead to reduced hospital stay or decreased mortality. There is substantial evidence that cardioplegic leukocyte filtration attenuates the reperfusion injury at a cellular level, but this has not been translated into clinical improvements. Finally, whilst various strategies involving multiple leukocyte filters, or the incorporation of pharmacological agents into leukocyte-depleting protocols have been evaluated, the current available results are not conclusive. Our study suggests that there is not enough high quality or consistent evidence to draw guidelines regarding the use of leukocyte-depleting filters within routine cardiac surgical practice.

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Keywords: Leukocytes; Cardiopulmonary bypass (CPB); Inflammation; Cardiac

1. Introduction

Cardiopulmonary bypass (CPB) is an essential component of open-heart surgery and is used widely in surgical coronary revascularisation. However, CPB is associated with an inflammatory reaction that involves activation of plasma proteins and cells, and release of pro-inflammatory molecules, enzymes and cytotoxic substances\textsuperscript{[1–4]}. Activation of leukocytes, in particular neutrophils, is an important step in this inflammatory process, directly contributing to tissue and organ injury.

To reduce CPB-related morbidity, several anti-inflammatory strategies have been used with variable efficacy. These include the peri-operative administration of drugs (corticosteroids, aprotinin and anti-oxidants) and technical alterations (reduction of PaO\textsubscript{2} during reperfusion, ultrafiltration and heparin coating of the CPB circuit). More recently, leukocyte removal with specialised filters has been proposed as a means of reducing the unwanted effects of CPB.

Leukocyte-depleting filters for CPB were developed from the technology already used to filter allogeneic blood transfusions. Animal studies using blood transfusion filters showed that if leukocytes were removed from the circulating blood, pulmonary injury was attenuated\textsuperscript{[5,6]}, the myocardium was protected\textsuperscript{[7]} and organ transplant survival increased\textsuperscript{[8]}.

In the early 1990s, a leukocyte-depleting filter that is attached to the arterial line of the CPB circuit and filters all the arterial blood was introduced for clinical use (LeukoGuard 6 (LG-6), Portsmouth, UK)\textsuperscript{[9]}. More recently systemic leukodepletion has been trialled from the venous side of the circuit\textsuperscript{[10]}. Devices were also developed to filter the blood cardioprotective solution\textsuperscript{[11]} (Pall Medical LeukoGuard BC1), and the residual or salvaged blood after bypass (Pall Medical LeukoGuard RS Filter)\textsuperscript{[12]}.

Elsewhere, work has focused on leukocyte filtration using a separate veno-venous extracorporeal circuit, both
intra-operatively [13], and post-operatively [14], and on filtering the blood used for priming the circuit [15] or all the transfused blood received during a hospital admission [16]. In an attempt to improve the inconsistent results observed in these earlier studies, more intricate leukodepletion strategies have been developed. These include altering the timing of filtration [17,18], the temperature at which filtration occurs [19], and combining filtration techniques with each other [20] or with various pharmacological interventions [21].

The effect of all these leukocyte-depleting interventions was assessed in experimental and clinical studies. Initially work focused on molecular inflammatory mediators and a wide variety of markers of neutrophil activation [17,22,23]. However, later work measured biochemical markers of organ injury [24—26] and examined the impact of leukodepletion on post-operative clinical course and the hospital costs [11,27—30].

2. Aim and scope of review

Whilst there are previous review articles pertaining to the use of leukocyte filters [18,30—34] they are either not systematic, or focus on just one strategy or site for the filter. Furthermore, they are dated. Our aim was to systematically review the literature on the various types of leukocyte-depleting filtration strategies that are used intra-operatively during cardiac surgery, by classifying use of leukocyte depletion in the following categories: systemic, cardioplegic and strategic.

We attempted to answer the following questions: first, does systemic leukofiltration have an effect on leukocyte count and other biological markers of systemic inflammation or tissue injury? Further to this, does it improve peri-operative outcomes?

Secondly, does leukocyte filtration of the cardioplegia line reduce markers of cardiac reperfusion injury and subsequently improve peri-operative outcomes?

Thirdly, can certain strategies, where the timing or temperature at which filtration occurs is manipulated, affect the efficacy of leukofiltration? Can simultaneous pharmacological leukocyte suppression improve the impact of leukocyte filtration? Finally, does total leukocyte control, a technique where multiple filters are placed within the circuitry, improve efficacy?

3. Materials and methods

3.1. Literature search

A literature search was performed using Medline, Ovid, Embase, Google Scholar and Cochrane databases. All comparative studies published between 1990 and early 2006 on leukofiltration within the cardiopulmonary bypass circuit were included. The following mesh headings were used: 'leukodepletion', 'leukodepletion, cardiac surgery', 'cardiac', 'leukocyte', 'leukofiltration', 'leukofiltration, cardiac surgery', 'comparative study' and 'outcome'. The 'related articles' function was utilised to broaden the search, and all abstracts, studies, and citations scanned and reviewed. References of the articles acquired were also searched manually. No language restrictions were made. The latest date for this search was 1 April 2006.

3.2. Data extraction and validation of studies

Two reviewers (W.O. and M.R.), independently extracted the following data from each study: first author, year of publication, study population characteristics, study design, number of subjects operated on with each technique, equipment used and outcome measures.

3.3. Inclusion and exclusion criteria

In order to enter our review, studies had to be comparative, and report on the effect of leukocyte-depleting filtration within the cardiopulmonary bypass circuit, independent of where the filter was located. Studies assessing combined strategies were included as long as filtration occurred alongside other interventions. Non-comparative studies and animal studies were excluded.

4. Results

4.1. Eligible studies

Two hundred and ninety-nine publications were identified using the above search keywords, of which 91% were excluded following title and abstract review (76% animal studies, 2% non-filtering studies, 2% non-leukocyte-depleting filters, 4% non-cardiac studies, 1% transfusion-related studies, 1% non-comparative studies and 5% reviews). Nine percent of articles were thus investigated in detail. One further study was found to be non-comparative and thus excluded. Examination of the references of these studies provided a further 38 reports for evaluation. This left a total of 63 studies (54% systemic leukofiltration, 24% cardiopulmonary leukofiltration and 22% multi-strategy leukodepletion) for inclusion and data extraction, of which 86% were randomized studies and 14% were non-randomized/not clear (please see Fig. 1 for systematic search strategy and results).

4.2. Part A: systemic leukocyte-depleting filters

Our search strategy identified 34 clinical studies investigating the potential benefits of systemic leukocyte filtration using either the arterial or venous line. These papers are summarised in Table 1. Of these, 82% were randomised control trials, 18% non-randomized comparative studies (in one study it is not apparent as to the method of group allocation, so non-randomization was presumed [35]).

4.2.1. Does systemic leukofiltration reduce leukocyte counts?

Early in vitro work demonstrated the capability of leukodepleting filters to remove leukocytes from a stream of blood [36—38], and clinical studies supported this using electron microscopy of the filters post-operatively [10].
Palanzo et al. performed the first clinical trial to evaluate the impact of leukocyte-depleting filters on leukocyte counts (WCC), and found no significant reduction in treated patients [9]. Only eight studies within this section of the review did not record pre- and post-operative WCC. Of the 26 that did, 15 found no significant difference between filtered patients and controls at any point in the patients admission [9,22,23,27,39–50]. The remaining 11 papers found reduced WCCs in the filtered group mainly during CPB, although these differences tended to disappear after CPB [10,26,35,51–53]. Hachida et al. showed a significantly lower WCC in the filtered group only at 15 min post-bypass measurement [54]. Johnson et al. demonstrated lower WCCs at 1, 4 and 24 h post-operatively in the filtered cohort [55] and Efstathiou et al. found that both groups had significantly elevated WCCs post-operatively, but that these were significantly lower in the depleted group [56]. Karaiskos et al. reported a difference between the two groups on arrival in ITU but not thereafter [57], and although Patel et al. report lower WCCs ‘post-operatively’, they do not specify when the blood samples were taken [58].

4.2.2. Does systemic leukofiltration reduce markers of systemic inflammation, leukocyte activation, adherence and degranulation?

Two groups that used C-reactive protein as a marker to assess the overall systemic inflammatory response witnessed no difference between those filtered and controls [44,50].

Numerous studies also found no differences between the filtered and control groups in plasma levels of cytokines (e.g. IL-1, IL-6, IL-8 and TNF) during or after cardiac surgery [22,23,39,46,50,55]. The only study to show a significant effect utilized a venous line leukodepleting filter [10] and observed a significant decrease in IL-8 compared to controls.

Other workers, studying the expression of neutrophil adhesion molecules, reported mixed results. Hurst et al. found a decrease in CD18 expression on neutrophils in the filtered group, and suggested that the filter could selectively remove activated leukocytes [39]. In a study that included only three patients (one filtered and two controls), Thurlow et al. observed a gradient in the expression of CD11a and CD45RO across the filter not seen in the two control patients and also claimed that the filter selectively removed activated leukocytes [40]. The effect of filtration on CD-11b expression appears to be variable, with no difference [27,39], down-regulation [51] and up-regulation of CD-11b [48] all having been reported. In a clinical study on patients undergoing CABG surgery by Chen et al. [52], L-selectin, P-selectin, ICAM-1 and PECAM-1 were all significantly reduced by leukofiltration.

Finally, certain investigators have focused on markers of cell damage such as elastase, a lysosomal enzyme released by neutrophils, and malondialdehyde (MDA), a product of oxygen free-radical initiated lipid peroxidation, and thus a suitable method to screen for oxygen free-radical generation. Whereas some studies showed similar elastase levels in the filtered and control patients [9,10,46], others have unexpectedly showed higher elastase levels following leukocyte filtration [35,43,44] and suggested this reflects increased elastase release by neutrophils trapped within the filter, rather than a higher activation of neutrophils within the tissues. Chen et al. demonstrated a reduction in MDA [52] following leukocyte filtration, as did Allen et al. in cyanotic infants [59]. However, all others studies utilising MDA as an outcome variable for systemic leukofiltration have shown no significant effect.

4.2.3. Does systemic leukofiltration reduce biological markers of tissue injury?

4.2.3.1. Cardiac markers. The impact of systemic leukofiltration on peri-operative cardiac injury has been predominantly assessed by measuring plasma levels of creatine
<table>
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</table>

* E: elective; U: urgent


C: cardiac group; C1: control group one; C2: control group two; CPB: cardiopulmonary bypass; Cya.: cyanotic; Excl.: exclusion; F: filter; Incl.: inclusion; LDALF: leukocyte-depleting arterial line filter; LDVF: leukocyte-depleting venous line filter; LDF: leukocyte-depleting filter; n: number; Ref.: reference; yrs: years.

* a: Normal pulmonary function; b: age < 75 years; c: severe left main stem disease > 70%; d: poor LV function (EF < 40%); e: failed PTCA; f: unstable angina; g: LVEF > 40%; h: age < 70; i: age < 80 years; j: CABG > 60 min; k: normal renal function; l: serum creatinine < 135 umol/L; m: non-diabetics; n: stable angina; o: pre-operative cardiac function; p: low LVEF; q: pre-operative lab. variables; r: trisomy 21; s: aortic cross clamp time; t: CPB time; u: cardiac arrest time; v: rewarming time; w: pre-operative pulmonary hypertension; x: lowest temperature (rectal or nasal); y: previous MI/PTCA; z: drug dosage (steroids/nitrates); A: pre-operative lung function; B: pre-operative risk stratification.
kinase-MB (CK-MB) and Troponin T or I. Most studies reported a ‘trend’ towards a decrease in these markers for filtered patients without, however, recording statistically significant differences [44,48,54]. In a recent large ($n = 159$) randomized trial, there was no difference between the filtered and control groups, for either cardiac marker [49]. Some studies, nevertheless, identified a significant effect due to leukofiltration. Di Salvo et al. found significantly elevated levels of Troponin T on the third post-operative day in the control group [25], and Matheis et al. reported Troponin T to be significantly raised in controls immediately after aortic clamp removal and 24 h post-operatively [22]. Koskenkari et al. after initially finding no difference between groups for Troponin T levels performed a linear regression analysis to remove the effect of aortic cross clamp time, and then found significantly lower levels in the treated group on the first post-operative day [50].

4.2.4. Does systemic leukofiltration improve clinical peri-operative outcomes?

4.2.4.1. Cardiac function. Johnson et al. [55] documented a higher mean arterial blood pressure at 4 h post-operatively in the leukofiltration group compared to controls, but the groups were similar in all other parameters. The significance of this finding is probably limited, as no other study demonstrated different haemodynamic parameters in filtered patients compared to controls. Hachida et al. witnessed less catecholamine usage in the treated group within the first 24 h [54], a finding replicated by Efstathiou et al. [56]. Conversely, many other investigators found no impact on catecholamine or vasopressor use [27,43,49,53]. No study supported by Johnson et al., who measured PaO₂ and intra-pulmonary shunt (Qs/Qt) and found both to be worse in controls, although only in the first 4 h post CPB [55]. Subsequent studies report no impact on pulmonary function post-operatively, using a variety of indices [9,26,43,44,46]. More recent studies, however, describe beneficial effects of leukofiltration. Efstathiou et al. found the oxygenation index to be significantly improved in the leukodepleted group at 4, 6 and 10 h post-operatively ($p < 0.05$) and this was accompanied by a reduced intubation period ($p < 0.01$). Patel et al. also reported a significantly shorter time to extubation ($p = 0.009$) and improved respiratory quotient [43]. Chen et al. reported a significantly better oxygenation index at 10 h in filtered patients, but this was not mirrored in a shorter intubation period. Sheppard et al. [60] and Alexiou et al. [61] used exhaled nitric oxide (NO) as a marker of lung inflammation and demonstrated a statistically significant attenuation in the post CPB rise in exhaled NO (from the pre-operative baseline) in the LD group ($p = 0.002$ and $p = 0.02$, respectively). Although neither published clinical outcomes, in further studies Alexiou et al. did not identify any clinical advantage of LD despite demonstrating much better Alveolar arterial Oxygenation indices in the first 18 h post-operatively in the LD group [53].

Three studies have focused on certain sub-groups of patients. Englander et al. on an infant cohort found no difference between groups in the ventilation time or respiratory index [41]. In patients with chronic obstructive pulmonary disease, Karaïkos et al. reported significantly better respiratory indices for 12 h after cessation of CPB [57] coupled with significantly shorter intubation times for LD patients. Likewise, in patients with mild lung dysfunction (AaOi > 1.25) Sheppard et al. [62] found better AaOi ($p < 0.05$) up to 8 h post CPB and a significantly shorter ventilation time in favour of leukofiltration.

4.2.4.3. Renal function. Using urine output as a marker for renal function, most workers found no significant difference in the urine output over the first 24 h between the groups [9,45,56] whereas Smit et al. (1999) found a smaller difference between fluid input and output over the first 24 h in filtered patients, suggesting less extracellular fluid accumulation compared to controls. Tang et al. focused their study on renal function and found daily fluid balance, serum creatinine and blood urea to be comparable between groups. However, more sensitive indicators of renal injury (urinary microalbumin, urinary retinol binding protein) were significantly higher in those who were not leukocyte depleted ($p < 0.001$) [63] suggesting the control patient had suffered a greater degree of injury to renal tubules and glomeruli.

4.2.4.4. Haematological disturbance, bleeding and blood transfusion requirements. One of the concerns regarding systemic leukodepletion is that simultaneous removal of platelets might adversely influence post-operative haemostasis [12]. However, a multitude of studies have shown leukocyte filtration to have no significant adverse impact on the degree of post-operative blood loss or the requirements for blood transfusion [9,23,46,49,53,56]. Contrary to this large body of evidence, Sahlman et al. found chest drainage in the first 24 h to be significantly higher in the filtered group ($p < 0.05$) [45], however this was not accompanied by an increased need for blood transfusion. Conversely, Stefanou et al. (2001) are the only group to suggest a positive impact of leukofiltration on haemostasis, as they found the blood transfusion requirements to be significantly reduced in filtered patients ($p = 0.034$). The volume of crystalloid infused was also significantly higher in the control group. However, the threshold for blood transfusion was not well defined, being either a haemoglobin < 8 g/dl or ‘haemodynamic parameter disturbance’.

4.2.4.5. Neurological outcomes/stroke. It is well recognised that CPB is an important contributor to post-operative neurological injury and that use of a standard arterial line filter reduces the incidence of microemboli and improves neuropsychological outcomes [64]. Three of the studies identified in our search recorded data on neurological outcome. Two found no difference in the incidence of stroke when a leukocyte-depleting filter was used [50,53]. In the third study, involving 198 patients, Whitaker et al. used trans-cranial Doppler and a battery of nine neurocognitive tests to assess a possible difference between two types of standard arterial line filters and leukodepleting filters. Whereas there was no difference between the two control
Table 2
Synopsis of cardioplegic leukocyte filtration studies

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<td>(1) CAXC &lt; 120 min vs (2) LDTBC AXC &lt; 120 min (3) CAXC &gt; 120 min (4) LDTBC AXC &gt; 120 min</td>
<td>1 E</td>
<td>4</td>
<td>C, L</td>
<td>f</td>
<td>a, h, j, k, d, p, q, e</td>
<td></td>
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<td>13 13 14</td>
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<tr>
<td>[80]</td>
<td>(1) C vs (2) LDC vs LDCPR</td>
<td>1 E</td>
<td>2</td>
<td>C, D, M, N, O</td>
<td>f</td>
<td>a, h, k, d, p, q, v, m, f</td>
<td></td>
<td>160</td>
<td>80 80</td>
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</table>

AXC: aortic cross clamp; C: control group; C1: control group one; C2: control group two; CPB: cardiopulmonary bypass; Cy.: cyanotic; EF: ejection fraction; Excl.: exclusion; Incl.: inclusion; LDC: leukocyte depleted cardioplegia; LDCPR: leukocyte depletion, cardioplegic reperfusate; LDTBC: leukocyte depleted terminal blood cardioplegia; TBCS: terminal blood cardioplegic solution; WBC: whole blood cardioplegia; yrs: years.

a: E: elective; U: urgent

A: <18 years age; B: any left ventricular assist device; C: associated cardiac disease requiring con-comitant surgery; D: recent acute coronary syndrome; D: recent acute coronary syndrome; E: cardiogenic shock/poor cardiac performance; F: coronary artery disease; G: PET confirmed non-viable myocardium; H: anaemia; I: immunodeficiency; J: leukocytopenia; K: thrombocytopenia; L: severe LV hypertrophy (LVMi > 150 g/m2 via echocardiography); M: severe co-morbidity; N: operated without cardiopulmonary arrest; O: pre-operative inotropes/IABP; P: unable to consent.

a: age; b: haemoglobin/haematocrit; c: no. of grafts; d: pre-operative laboratory variables; e: trisomy 21; f: aortic cross clump time; g: CPB time; h: cardiac arrest time; i: re-warming time; j: pre-operative pulmonary hypertension; k: lowest temperature (rectal or nasal); l: previous MI/PTCA; m: drug dosage (steroids/nitrates); n: pre-operative lung function; o: pre-operative risk stratification; p: no. of cardioplegic infusions.
filters, significantly fewer microemboli were detected in patients randomised to LD filters ($p < 0.0001$) [47]. At 6 weeks post-surgery there was a trend towards greater improvement in the neuropsychological performance of the LD group compared to controls, on all but one of the nine psychometric tests ($p < 0.07$).

4.2.4.6. Infection. A small number of studies recorded data on fever and post-operative sepsis at varying sites. Englander et al. in their small ($n = 12$) infant cohort study found significantly less fever in the first 24 h post CPB in those who were leukodepleted [41]. However, leukofiltration does not appear to impact in any other way on wound infection [27,56] or post-operative sepsis [49,50].

4.2.5. Length of intensive care unit stay, hospital stay and survival

Of the studies reviewed in this section only two have shown an impact on the intensive care unit and/or hospital stay. Patel et al. showed a significantly shorter length of hospital stay in the leukodepleted group ($p = 0.04$) [58] whereas Karamis et al., whose study was on 20 chronic obstructive airways disease (COPD) sufferers, found that ITU and hospital stay were also significantly shorter in the LD group [57]. It should be stressed, though, that numerous other studies have shown no benefit in terms of duration of ITU or hospital stay [9,10,25—27,41,45,46,49,50,53,56]. Also, there is no study to demonstrate a survival advantage for patients receiving systemic leukodepletion.

4.3. Part B: leukocyte filtration of the cardioplegia line

Blood cardioplegia is superior to crystalloid solutions with regard to oxygen supply and limiting myocardial oedema and warm blood cardioplegic solutions are used to limit the reperfusion injury following cardioplegic arrest [65,66]. However, blood cardioplegia contains leukocytes and platelets, which can worsen the myocardial reperfusion injury. This suggested a role for leukocyte filters in the cardioplegia line, an intervention that was first investigated with encouraging results in animal models [67—69].

Our search strategy identified 15 clinical studies investigating the potential benefits of leukocyte filtration of blood cardioplegia. These papers are summarised in Table 2. Fourteen were randomised control trials, and in one case the study design is not clear [70].

4.3.1. Does leukocyte filtration of blood cardioplegia reduce biological markers of reperfusion injury? Ichihara et al. [71] reported lower values of lipid peroxide, elastase, thromboxane B2 and 6-ketoPGF1α in the leukocyte filtration group compared to controls. Sawa et al. [11] found significantly lower malondialdehyde levels in the coronary sinus blood in leukocyte depleted patients and replicated this finding in their 1996 study, as did Hayashi et al. in later years [72,73]. Sawa et al. [74] and Peari et al. [75] used microscopy of ventricular muscle biopsies to grade ultra-structural damage after reperfusion, and found significantly better preserved myocardium in the treated groups. Browning et al. [76] used post-reperfusion oxidized glutathione ratios as a marker of myocardial injury in routine CABG patients and found no difference between the control and leukodepleted groups. Pala et al. [77] and De Vecchi et al. [78] used the same marker and again found no benefit for ‘routine’ patients but identified some benefit in emergency patients and those having pre-operative myocardial dysfunction. Hayashi et al. [73], using different markers showed less apparent myocardial damage in those leukocyte filtered compared to controls, when aortic cross-clamping was prolonged beyond 120 min. The evidence from the literature seems to suggest that there is a reduction in myocardial reperfusion injury at a cellular level in those receiving leukodepleted blood cardioplegia, and that this is more pronounced in patients having pre-operative left ventricular dysfunction and those subjected to prolonged myocardial ischaemia.

4.3.2. Does leukocyte filtration of blood cardioplegia improve clinical biological markers?

Twelve studies looked at the effect of a filter on leukocyte count in the reperfusate or aortic root at the time of cardioplegia, and found that it was significantly lower than in control groups. They also demonstrated that cardioplegic leukofiltration does not affect systemic circulating leukocyte counts post-operatively. Nearly all investigators measured CK-MB, and from 1998 simultaneously measured Troponin T as clinical markers of myocardial damage. Many studies demonstrated that release of CK-MB and Troponin is diminished in those patients in whom cardioplegia is leukodepleted, regardless of whether they are elective patients [71,79—81], transplant patients [82], emergency cases [11] or patients with pre-operative myocardial dysfunction [83]. Contrary to that, Pala et al. (1995) and Browning et al. (1999) found no significant difference in post-operative levels of CK-MB and Troponin T in their studies, and De Vecchi et al. (1997) and Hayashi et al. (2003) only witnessed significant difference in those patients with impaired cardiac function or prolonged ischaemic injury, not in their routine patients.

4.3.3. Does leukocyte filtration of blood cardioplegia improve peri-operative outcomes?

Nearly all trials recorded some clinical peri-operative outcomes and focused predominantly on the cardiac and pulmonary systems.

4.3.3.1. Cardiac function. Palatianos et al. in a large ($n = 160$) prospective randomized control trial of CABG patients demonstrated improvements in cardiac index, spontaneous defibrillation rates, and inotropic and antiarrhythmic support levels after CPB in the filtered group [80]. Roth et al. in a double blind randomized control trial, involving elective and emergency patients, also demonstrated a statistically significant difference between the groups in their need for inotropes and rates of spontaneous defibrillation [83]. This supported the findings of Sawa et al. [74], who had previously showed significantly lower doses of dopamine at weaning of CPB in the leukocyte-depleted group compared to controls but only in emergency cases [11]. Pala et al. showed a significant difference in post-operative cardiac index in favour of leukodepletion but only in a subgroup with a pre-operative EF < 35% [77]. Hayashi et al.
<table>
<thead>
<tr>
<th>Ref.</th>
<th>Study synopsis</th>
<th>Study design</th>
<th>Admission type</th>
<th>Surgical procedure</th>
<th>Excl. criteria</th>
<th>Incl. criteria</th>
<th>Matching criteria</th>
<th>n</th>
<th>Mean age (yrs) and gender</th>
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<td>[28]</td>
<td>(1) MP vs (2) MP + Aprot. vs (3) MP + TLC vs (4) MP + HCC</td>
<td>1 E</td>
<td>1, 2, 1 + 2, 15</td>
<td>E, H, T, Z, C*</td>
<td>p</td>
<td>a, h, b, k, n, e, p, q, y</td>
<td>400</td>
<td>112 109 112 67</td>
<td>n/a n/a n/a n/a n/a</td>
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<td>[84]</td>
<td>(1) C vs (2) LDALF filtration after AXC release</td>
<td>1 E</td>
<td>1</td>
<td>F, H, K, L, N, O, P, W</td>
<td>h</td>
<td>a, b, c, d, p, q, h, j</td>
<td>40</td>
<td>20 20 20 20</td>
<td>61 63 63 63 90</td>
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<td>[86]</td>
<td>(1) C vs (2) HCC + LDALF</td>
<td>2</td>
<td>n/a</td>
<td>1</td>
<td>F, H, K, L, P, Q, R, S, T, U, V, W</td>
<td>i</td>
<td>a, p, q, h, w</td>
<td>52</td>
<td>34 18 18 18 64.1 64.9 64.9 64.9 78.8</td>
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<tr>
<td>[85]</td>
<td>(1) C vs (2) HCC + (3) HCC + LDALF</td>
<td>1</td>
<td>E</td>
<td>1</td>
<td>H</td>
<td>n/a</td>
<td>a, c, h, k, p, q</td>
<td>30</td>
<td>10 10 10 10</td>
</tr>
<tr>
<td>[17]</td>
<td>(1) C vs (2) LDALF (onset of CPB) vs (3) LDALF (5 min before aortic declamping vs (4) aortic declamping)</td>
<td>1</td>
<td>E</td>
<td>1</td>
<td>H, L, P, W</td>
<td>r, s, t</td>
<td>n/a</td>
<td>80</td>
<td>20 20 20 20</td>
</tr>
<tr>
<td>[87]</td>
<td>(1) C vs (2) TLC + Aprot.</td>
<td>1</td>
<td>n/a</td>
<td>1</td>
<td>F</td>
<td>n/a</td>
<td>n/a</td>
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<td>55 65 65 65</td>
</tr>
<tr>
<td>[29]</td>
<td>(1) Aprot. vs (2) TLC + Aprot.</td>
<td>1</td>
<td>n/a</td>
<td>1</td>
<td>H</td>
<td>p</td>
<td>a, h, p, q, m</td>
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<td>[90]</td>
<td>(1) C vs (2) LDLF vs (3) cardiopulmonary LDF vs (4) TLC</td>
<td>1</td>
<td>E</td>
<td>1</td>
<td>A, E, H, P, Q, T,</td>
<td>b</td>
<td>a, h, j, k, g, m, c, w, p, q, f</td>
<td>40</td>
<td>10 10 10 10 10 66.7 61.8 61.8 61.8 82.5</td>
</tr>
<tr>
<td>[91]</td>
<td>(1) C vs (2) LDALF vs (3) LDLVF at rewarming vs (4) filtration of residual CPB machine blood</td>
<td>1</td>
<td>E</td>
<td>1</td>
<td>C, F, H</td>
<td>n/a</td>
<td>a, h, j, c, e, q</td>
<td>40</td>
<td>10 10 10 10</td>
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<tr>
<td>[88]</td>
<td>Part 1; (1) Aprot. vs (2) TLC vs (3) cardiopulmonary LDF vs (4) CABG cohort</td>
<td>1</td>
<td>E</td>
<td>1</td>
<td>F, H</td>
<td>n/a</td>
<td>a, h, m, p, q</td>
<td>180</td>
<td>90 90 90 90</td>
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<tr>
<td>[20]</td>
<td>(1) 28°C C vs (2) 28°C C</td>
<td>1</td>
<td>E</td>
<td>1</td>
<td>H</td>
<td>n/a</td>
<td>a, h, j, k, e, m, c, w, n, p, q</td>
<td>300</td>
<td>150 150 150 150</td>
</tr>
<tr>
<td>[89]</td>
<td>(1) C vs (2) LDLF</td>
<td>3</td>
<td>E</td>
<td>4, 5, 7, 12, 13</td>
<td>n/a</td>
<td>a, h, e, q</td>
<td>700</td>
<td>350 350 350 350</td>
<td>62.4 64.2 64.2 64.2 65.1</td>
</tr>
<tr>
<td>[19]</td>
<td>(1) 28°C C vs (2) 28°C C LDALF vs (3) 35°C C LDLVF</td>
<td>1</td>
<td>E</td>
<td>1</td>
<td>C, F, H, P, W, X</td>
<td>a, h</td>
<td>a, h, j, m, v, n, p, q, c, f</td>
<td>80</td>
<td>20 20 20 20</td>
</tr>
</tbody>
</table>

Aprot.: aprotinin; AXC: aortic cross clamp; C: control group; C1: control group one; C2: control group two; CPB: cardiopulmonary bypass; Cya.: cyanotic; EF: ejection fraction; Excl.: exclusion; HCC: heparin coated circuit; Incl.: inclusion; LDALF: leukocyte-depleting arterial line filter; LDVF: leukocyte-depleting venous line filter; LDF: leukocyte-depleting filter; MP: methylprednisolone; n: number; Ref.: reference; TLC: total leukocyte control; yrs: years.

a: E: elective; U: urgent


b: a: Normal pulmonary function; b: age < 75 years; c: severe left main stem disease > 70%; d: poor LV function (EF < 40%); e: failed PTCA; f: unstable angina, g: LVEF > 40%; h: age > 70; i: age > 60 years; j: CPB > 60 min; k: normal renal function; l: serum creatinine < 135 umol/L; m: non-diabetics; n: stable angina; o: non-smoker; p: > 18 years old; q: COPD; r: < 50 years; s: EF > 55%; t: Parsonnet score > 10; U: pregnant; D: MI in last month.

c: a: A: valvular disease; B: congenital heart disease; C: acute or chronic pulmonary dysfunction; D: pulmonary hypertension; E: history of allergy; F: re-operation; G: recurrent pulmonary infection; H: unable to consent; I: intubated patients; J: pre-operative inotropes/IABP; K: recent or current infection; L: co-morbidity/malignancy; M: steroid/NSAID users; N: EF < 50%; O: LMS stenosis; P: renal disease; Q: EF < 30%; R: left ventricular aneurysm; S: atrial fibrillation; T: coagulopathy; U: > 6 u blood intraoperatively; V: use of tranexamic acid/aprotinin; W: cerebral insufficiency/stroke; X: haematological disease/abnormalities; Y: post-operative low cardiac output; Z: recent cardiac arrest; A: carotid bruit; B: Parsonnet score > 10; C: pregnant; D: MI in last month.

d: a: Normal pulmonary function; b: age < 75 years; c: severe left main stem disease > 70%; d: poor LV function (EF < 40%); e: failed PTCA; f: unstable angina, g: LVEF > 40%; h: age > 70; i: age > 60 years; j: CPB > 60 min; k: normal renal function; l: serum creatinine < 135 umol/L; m: non-diabetics; n: stable angina; o: non-smoker; p: > 18 years old; q: COPD; r: < 50 years; s: EF > 55%; t: Parsonnet score > 20; u: age > 70 years; v: stable coronary artery disease; w: estimated CPB time > 60 min.
have demonstrated a significantly lower maximum dose of inotrope at weaning of CPB in the leukodepleted group, but in their later study could only replicate this in patients who had extended aortic cross clamp time [73]. Other investigators, who predominantly studied uncomplicated elective cases, found no significant difference in any post-operative haemodynamic parameter [70,71,76,78,81].

4.3.3.2. Pulmonary function, length of intensive care unit stay, hospital stay and survival. A limited number of studies investigating the post-operative effect of cardioplegic leukodepletion on pulmonary function but could not demonstrate any impact on ventilatory support time [77,82], post-operative pulmonary capillary wedge pressure [83] or pulmonary infections [80]. No study found significant difference between the study groups in the length of intensive care unit stay, hospital stay or survival.

4.4. Part C: strategic leukocyte filtration

To maximise the impact of leukofiltration some groups have created novel strategies including altering the time course of filtration, adding in a pharmacological agent or altering the temperature at which filtration occurs. Others have performed various combinations of these. These papers are summarised in Table 3.

4.4.1. Isolated strategies

4.4.1.1. Timing. Schoitz et al. randomised 80 patients to four groups, one without filtration and three with different timing strategies, at onset of CPB, 5 min before aortic cross clamp release and at aortic declamping. None of the strategies reduced the number of activated neutrophils, or the levels of activity per cell [17]. Baksaas et al. incorporated a systemic leukocyte depletion filter only at the start of the reperfusion period, demonstrating a significant reduction in circulating leukocytes at 2 h post-operatively but no clinical difference between the groups [84].

4.4.1.2. Does temperature affect the efficacy of systemic leukofiltration?. Alexiou et al. studied the effect of temperature on leukofiltration on 80 patients undergoing elective CABG. Blood temperature was kept at 35 °C in one group and 28 °C in the other. Each group was then sub-divided, one half to a leukodepleting filter, the other half to a standard one. Patients undergoing leukodepletion had significantly lower total and activated leukocyte counts than controls, regardless of temperature. Whilst the filter removed more leukocytes at the warmer temperature than at 28 °C, the number of activated leukocytes removed was similar, irrespective of the temperature. No impact on peri-operative clinical outcomes, such as inotropic support, length of hospital stay or transfusion requirements was seen [19].

4.4.1.3. Does simultaneous pharmacological manipulation improve the impact of leukocyte filtration?. Three studies looked at heparin-coated circuits in combination with leukofiltration. Hamada et al. performed a three-limbed prospective randomized control trial on 30 patients, and measured cytokines and respiratory function peri-operatively. They found that compared to controls, patients with combined intervention had significantly better respiratory indices at weaning of cardiopulmonary bypass, an effect which disappeared by the end of the operation [85]. Similar trends were seen with interleukin levels. Martens et al. in a similar study found significantly less blood loss and thrombin formation in the first 24 h compared to controls (p < 0.05) but found no difference in transfusion requirements [86]. Gott et al. studied four different anti-inflammatory strategies in a prospective, randomised, pre-operatively risk stratified 400 patient study. One arm of this trial studied heparin-coated circuitry, and a second arm studied the impact of aprotonin and reported reduced mean length of stay (p = 0.02) and hospital charges (p = 0.0007) but only in high-risk patients [28].

4.4.1.4. Does total leukocyte control improve outcome?. In the final treatment arm of Gott et al.'s study the concept of 'total leukocyte control' (TLC) was introduced. This involved a three-tiered leukofiltration strategy with filters in the arterial line, cardioplegia line and for all blood products, both homologous and autologous. Complex multiple linear regression statistics were employed and this technique appeared to be effective in low-risk patients, reducing their hospital stay by 1 day and hospital charges by $2000–6000 [28]. However, Salamonsen et al. also compared a control group to a TLC group and found no significant difference in post-operative hospital stay, which was the primary outcome variable, nor in ICU stay, mortality, cardiac, pulmonary, haematological or renal function [20].

4.4.2. Combined strategies

Olivencia-Yurvati et al. have published three studies (2002, 2003, 2004) employing combined strategies. In 2002, the treatment group received full-dose aprotonin and 'total leukocyte control' (TLC) commencing 30 min prior to cross clamp release. They did show a considerable reduction in post-bypass atrial fibrillation from 27% in the control group to 7.6% in the treated group (p = 0.025). They suggested a decrease in hospital stay, and cost, but extrapolated this from the fact that, in general, patients with atrial fibrillation stay in hospital longer and cost $9000 more, not from data from their study groups [87]. In 2003 the same group studied the impact of this combined approach on post-bypass pulmonary function and found a statistically significant benefit in pulmonary artery pressure and pulmonary microvascular pressure at 24 h, and in shunt fraction at 6 h post-operatively. They have also reported reductions in ventilation time, hospital stay and cost, but no statistical significance was assigned to this [29]. The 2004 study by the same group assessed the combined outcomes of the first two studies, namely atrial fibrillation and pulmonary dysfunction. It appears that the patient groups were also the same, but in the second part of the report a retrospective comparison of the leukodepleted study group to 45 off-pump bypass cases was made, with no statistically significant differences found [88].

In a large (n = 700) retrospective matched cohort study, Sutton et al. (2005) employed simultaneous systemic and blood cardioplegia leukofiltration. Unlike previous studies, they did not simply replace the control filter with a LD filter, but kept the control filter as well. They recorded improved...
post-operative oxygenation \( (p < 0.04) \), and reduced time to extubation \( (p = 0.03) \) and length of hospital stay \( (p = 0.03) \) in the study group compared to controls \[89\].

Samankatiwat et al. conducted a small, randomized, control trial of 40 patients comparing systemic depletion, cardioplegic depletion and a combination of the two. There were no statistically significant findings, although the cardioplegic depletion group had the lowest Troponin I levels \[90\]. de Vries et al. contrasted arterial line systemic depletion, with venous line systemic depletion during the re-warming phase of CPB and finally leukofiltration of the residual heart—l lung machine blood during autologous transfusion. They demonstrated no clinical difference between groups \[91\].

5. Discussion

5.1. Systemic depletion

Although it is indisputable that leukocyte-depleting filters do remove leukocytes from a stream of blood, they do not appear to consistently lower leukocyte concentrations within the circulation, or do they only transiently \[55,57,90\]. Recognizing this, it has been claimed that any possible clinical effect of leukocyte-depleting filters may arise from their alleged propensity to preferentially remove activated leukocytes from the circulation. Given the presence of a large body of evidence in favour \[51,52,59,90\] and against such claims \[9,10,27,46\], the issue of preferential removal of activated forms of leukocytes by these filters remains controversial.

There exists no consensus on whether systemic leukocyte depletion reduces cardiac and pulmonary injury during and after cardiopulmonary bypass. It would appear that if there is a beneficial effect on cardiac function it occurs during the time of weaning from CPB and is transitory. It is probable that there is some benefit in early post-operative lung function in patients receiving systemic leukodepletion during CPB. However, it does not seem to be sustained beyond the first 24 h and it may well be that the effect is most pronounced in those with underlying pre-operative lung dysfunction \[57,62\]. Systemic leukodepletion may offer some renal protection \[63\] and more research involving patients with pre-existing renal disease is warranted. The bulk of the evidence suggests that systemic leukofiltration has no significant influence on blood loss, transfusion requirements, wound infection \[27,56\], post-operative sepsis \[49,50\] and neurological outcome. An overwhelming majority of studies have shown no benefit in the duration of ITU or hospital stay \[9,10,25—27,41,45,46,49,50,53,56\], and no study has recorded a survival advantage for patients receiving systemic leukodepletion.

5.2. Cardioplegic leukofiltration

Whilst controlled delivery of blood cardioplegia during aortic cross clamping provides an excellent opportunity for the application of leukocyte filters, the evidence that they affect clinical outcome seems to be weak. Although there is substantial evidence that they attenuate the reperfusion injury at a cellular level, and may improve cardiac recovery in the immediate peri-operative period (reduction in the requirement for electrical defibrillation or use of inotropes), this appears to be mainly in ischaemically compromised hearts or hearts with impaired left ventricular function, not in routine patients. There is also no evidence from randomized control trials that they reduce ventilation time, post-operative ITU and hospital stay, or improve survival. Consequently, their cost-effectiveness needs to be proven.

5.3. Strategic leukofiltration

In recent years various types of strategic leukodepletion have been used with encouraging results. It would appear that aprotinin and leukofiltration may have a synergistic effect, particularly in high risk patients \[28\]. Also, combining numerous filtration strategies seems to be safe \[20\] and effective at reducing post-operative atrial fibrillation \[87\] and there may be cost benefits \[28\].

6. Conclusions

Whilst there exists a large number of randomised controlled trials investigating the clinical use of this technology, most are small and have limitations in their methodology. Although some trials report positive findings in terms of reduction in various markers of organ injury, the great majority fail to report a statistically significant improvement in hard clinical endpoints such as time on ventilator, time in ICU, time in hospital and mortality. We feel that currently there is not enough high quality or consistent evidence to advocate the use of any leukodepletion filters within routine cardiac surgical practice. Nevertheless, there is evidence that some patients with certain co-morbidities, such as renal dysfunction, may benefit from leukocyte depletion, and if future research is to be performed it should be targeted at these sub-groups.

References


[43] livestream.


