METHODS

With IRB approval, blood samples from 17 CPB patients were collected at six time points during surgery. Test results were performed in duplicate on 8 different ACT devices (ACTalyke, Gem, HMS, Hemochron 801, Response, Jr. Signature, Rapidpoint, and Sonoclot) and compared to results of anti Xa activity (STA Rotochrom Heparin assay). The average of the duplicate samples was used for comparison to the anti Xa results.

RESULTS

Correlation of results to anti Xa activity (1.1–5.75 IU/ml) for each device produced a range of r = .071 to .502. Conclusion: No device correlated with the laboratory anti Xa data.

CONCLUSION

In summary, the ACT test is a whole blood coagulation test which is useful for monitoring anticoagulation during CPB. It is affected by anything that affects coagulation, especially heparin, but also non heparin variables such as hemodilution, hypothermia, aprotinin and others. There are many automated devices available to the clinician for ACT monitoring. Each machine responds to anticoagulant variables uniquely and therefore it should not be assumed that the results from different machines are interchangeable. Each institution should develop clinical parameters based on the device they are using and their clinical environment.

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From Trash To Leucocytes: What Are We Filtering and Why?

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INTRODUCTION

A filter processes non-homogeneous matter to allow the free passage of some elements, whilst preventing downstream passage of specific others. In the context of cardiac surgery, blood is the most commonly filtered "matter."

Filters can be classified as either "screen filters" or "depth filters" (1). Screen filters are typically comprised of material "woven" into a "screen" with a carefully calibrated pore size. Consistency of pore size is a characteristic of screen filters, and they are frequently named by this parameter, for example, a "40 micron filter." Clearly, they are designed to remove matter larger than the screen pores. Depth filters are typically comprised of material that is not precisely woven and through which the filtered matter must pass, typically over a longer distance and greater time when compared to screen filters. In these devices, the removal of matter occurs by several possible means that are discussed later.

Potential filtration sites in cardiopulmonary bypass (CPB) are itemized in Table 1 along with examples of the targets for removal. The majority of relevant research has been focused on filtration of arterial blood, and arterial line filtration will occupy most of this review.

Table 1. Filtration sites and targets in cardiopulmonary bypass

Site or Substance	Target
1. CPB circuit prime	Manufacture-related particulates, spallation material, bubbles
2. Arterial blood	Potentially everything, but mainly aggregates, bubbles, leucocytes, spallation material
3. Venous blood	Bubbles, leucocytes
4. Cardioplegia	Leucocytes
5. Pericardial suction blood	Aggregates, bubbles, bone, other tissue, surgical material, lipid, leucocytes
6. Allogenic blood	Leucocytes, aggregates
7. Autologous blood	Leucocytes, aggregates, bubbles
8. Sweep gas	Bacteria, particulates

ARTERIAL LINE FILTRATION

The use of arterial line filters gathered momentum in the 1960s, driven by concerns over the introduction of bubbles into arterial blood by bubble oxygenation. The earliest filters were Dacron wool depth types (2). A stainless steel screen filter developed around the same time was not used clinically because it caused haemolysis (3). Nevertheless, polyester mesh screen filters did achieve wide acceptance in the 1970s (4), and by the early 1980s 99% of arterial line filters used were of the screen type (5). Around the millenium, arterial line filters were used in more than 99% of cases in the USA (6), but interestingly, only 57% of cases in the UK (7).

The most recent comprehensive review of the use of arterial line filters in cardiac surgery was published by Whitaker et al. in 2001 (4). They defined 6 separate outcome goals that have driven the recent use of arterial filters as follows: reduction of microemboli; improvement of cerebral outcome; reduction of the inflammatory response to CPB; improvement of cardiac outcomes; improvement of pulmonary outcomes; and improvement in hospitalisation-related indices such as length of stay. These same outcome goals are adopted for this review.

REDUCTION IN MICROEMBOLI BY ARTERIAL LINE FILTRATION

Not surprisingly, there is irrefutable evidence that filters reduce microemboli both downstream in the CPB arterial line (8,9) and when measured at cerebral arterial sites in patients (10). In the study by Loop et al. (8) a dacron wool depth filter was most efficient (99% emboli removed) and a 40 micron screen filter the least efficient (72% emboli removed). Nevertheless, one of the depth filters became obstructed, and concerns about such events have seen screen filters with pore sizes around 40 micron become the most widely used. It is notable that the study by Mitchell et al. (9) was one of the few in which the emboli had been positively identified as bubbles, and it showed that a significant proportion of bubbles can be stopped by a 40 micron screen filter.

It is appropriate at this point to reflect on the potential value of reducing the number of emboli to which patients are exposed during CPB. The vast majority of studies investigating the potential for harm by arterial emboli in CPB have correlated peri-operative emboli exposure against post-operative neuropsychological (NP) outcomes, and there are now a number of studies that, independent of any manipulation of filtration, have demonstrated that NP outcomes are worse if emboli exposure is greater (11–17). This raises an obvious question: if emboli cause NP impairment, and arterial line filters reduce emboli, will arterial line filtration therefore reduce NP impairment?

IMPROVEMENT OF CEREBRAL OUTCOMES BY ARTERIAL LINE FILTRATION

Two early studies that used retrospective controls suggested improved NP outcomes in filtered patients, but are difficult to interpret because of their methodology (18,19). The study published by Pugsley et al. (20) is the most widely quoted and provides the most convincing evidence that filtration improves NP outcomes. The "filtered patients" (40 micron screen filters) were exposed to less emboli and exhibited less NP deficits than the non-filtered controls. In addition, there was a step-wise correlation between emboli exposure (measured by middle cerebral artery Doppler) and the incidence of NP deficits when patients were assessed 8 weeks after surgery. It must be emphasized that this study was performed using pH stat acid—base control and CPB circuits with bubble oxygenators. Most recently Whitaker et al. (21) demonstrated less emboli exposure and a strong trend toward less NP decrement in patients who had a leukocyte depleting arterial line filter compared to patients who had a standard 40 micron filter, but it is difficult to interpret the meaning of this finding given that emboli reduction and anti-inflammatory effects are both potential contributors.

It is notable that none of these studies have investigated an advantage for standard arterial line filtration vs. no filtration under the CPB conditions most prevalent in modern cardiac surgery theatres, viz: membrane oxygenation and alpha-stat acid-base management. Indeed, the only relevant study in this regard was that by Taggart et al. (22), which showed a smaller post-operative rise in serum s100β levels in patients whose arterial line included a 43 micron heparin coated filter. However, the s100β protein has become a controversial marker for brain injury in cardiac surgery, and the significance of this result is unclear. It is possible that this lack of data demonstrating a need for filters in modern CPB circuits may account for the lower uptake of filtration in the UK (4).

REDUCTION OF INFLAMMATION BY ARTERIAL LINE FILTRATION

There has been intense interest in the inflammatory response to CPB over the last decade. Cellular and biochemical mediators of inflammation are activated in CPB by a variety of means which are summarized by deVroege et al. (23). This occurs to some extent in all patients undergoing CPB, but with a combination of homeostatic correction and skilful clinical management, there may be no consequences of any significance in most patients. On the other hand, some patients may develop exaggerated manifestations of inflammation known as the "systemic inflammatory response syndrome" (SIRS). This is characterized by widespread microcirculatory failure with associated morbidity.

Strategies for preventing SIRS can be classified as either biomaterial dependent or independent (24). "Biomaterial dependence" refers to the manipulation of CPB circuit blood-contact surface modification to minimize activation of inflammatory cascades, and is beyond the scope of this review on filtration (though some filters may incorporate biocompatible surfaces). Filtration strategies fall into the category of "biomaterial independent" interventions, and almost without exception, the literature describing a reduction in the inflammatory response to CPB by filtration has focused on leukocyte filtration. It is therefore relevant to briefly discuss the role of leukocytes in CPB-related inflammation.

During CPB leukocytes may be activated either primarily by contact with foreign surfaces or by trauma. They may also be activated secondarily by inflammatory proteins such as complement, or cytokines released by damaged tissue. Another important component of the CPB inflammatory response, and one of particular significance to leukocytes is the activation of

endothelium. This can occur in a variety of ways which include ischemia-reperfusion, and damage to endothelial surfaces by emboli. Anaerobic metabolism in the endothelial cell during ischemia results in production of hypoxanthine and the conversion of the enzyme xanthine dehydrogenase to xanthine oxidase. When oxygen supply is restored, xanthine oxidase converts hypoxanthine to xanthine, with superoxide and hydroxyl radicals produced as by-products. These highly reactive molecules may cause lipid peroxidation of the cell membrane, and cause expression of leukocyte binding molecules on the cell surface. Leukocytes that are pre-activated by other means as mentioned above marginate very readily on damaged endothelium, and are themselves capable of liberating large quantities of extracellular oxygen radicals which may further damage the endothelium. These processes are well summarized by Zamboni (25). This process of ischemia-reperfusion damage is particularly relevant to organs that undergo a period of relative ischemia during CPB, such as the heart and lungs.

Given the above, it is not surprising that removal of leukocytes from the CPB arterial blood has been proposed as a potential means of reducing inflammation, and protecting the heart and lungs during CPB. Leukocyte reduction (LR) filters for the arterial line were first developed by Pall in the late 1980s. The "archetypal" Pall LR filter is the "Leukoguard 6" (LG-6) device. This consists of a conventional 40 micron woven polyester screen, followed downstream by a non-woven polyester depth filter. Leukocytes are too small to be trapped by the screen filter, but may become trapped in the non-woven segment of the filter by processes such as *blocking* (where closely aligned fibers create a small "pore"), *bridging* (where two or more cells become obstructed together in a space that would normally allow passage of either alone), or by *adhesion* of activated cells to the fibers (1). The process of adhesion seems particularly important and it is not surprising that these devices appear selectively capable of removing pre-activated (and therefore readily adherent) leukocytes (26).

There are different strategies for employing LR filters during CPB (27). In respect of the arterial line, some use the filter throughout the period of CPB, while others bypass it until the period of organ reperfusion, which is usually defined as beginning at aortic declamping. Leukocyte reducingR filters have also been used in the venous line, cardioplegia line, and in filtration of residual CPB perfusate prior to return to the patient. These strategies will be mentioned briefly later.

In keeping with the sub-title of this section ("Inflammation") we next consider those controlled studies that have compared inflammatory indices in humans undergoing CPB with or without an arterial LR filter. These inflammatory indices take the form of either leukocyte counts or measurement of inflammatory markers or both, and the results can only be described as widely variable. Although tThis review has probably not cited all the relevant studies, there was no selection of those studies that are presented, and the outcome variability demonstrated here is almost certainly representative of the literature.

A number of studies have demonstrated that LR filters deployed in the arterial line throughout CPB do reduce leukocyte counts (28) and/or markers of inflammation post CPB (29–33). There is also one study that demonstrated mixed results when the period of filtration was limited to reperfusion (34) (positive for counts, but negative for markers). In contrast, there are as many studies that have failed to demonstrate any effect on inflammatory cell counts (21,35–39) or inflammatory markers (35–41) by arterial LR filtration throughout CPB.

There were no obvious reasons for this variation, though a more fastidious review of the relevant studies might uncover relevant issues, and is due. Variables that have been mentioned as potential confounders, and which would ideally be accounted for in such a review include: duration of use, pressure conditions, flow conditions, selection of markers, measurement of activated vs. non-activated leukocytes, and the use of other anti-inflammatory strategies such as aprotinin, steroids and biocompatible circuits in the respective studies.

IMPROVEMENT OF CARDIAC OUTCOMES BY ARTERIAL LINE FILTRATION

The few studies that have considered cardiac outcomes in the context of arterial line filtration have investigated the effect of LR filters in comparison to simple screen filters. In fact, the cardioplegia circuit is a more common filtration target where the aim is improving cardiac outcomes by LR filtration, and this will be considered shortly.

The use of an arterial line LR filter throughout CPB vs. similar use of a standard 40 micron screen filter was associated with a reduction in enzyme markers of myocardial injury in two studies (42,43). The study by Hachida et al. (43) also demonstrated a reduced requirement for post-operative inotropic support in the LR filter group. The same findings were reported by Matheis et al. (33) in a study where both groups underwent CPB with a standard 40 micron arterial line filter except for a period of 15 minutes after aortic declamping when one group had LR filtration while the controls continued with 40 micron filtration, but via a new filter. It should be noted that these were all small studies (less than 40 patients) and the reduced requirements for inotropic support were small differences in the proportions of patients requiring or not requiring support.

IMPROVEMENT OF PULMONARY OUTCOMES BY ARTERIAL LINE FILTRATION

As with the investigation of cardiac outcomes, virtually all studies that have investigated improvement in pulmonary outcomes by filtration have compared LR filters to simple screen filters. Once again, there is a dichotomy of opinion on the optimal period over which to remove leukocytes; some studies applied LR filtration throughout CPB whilst others restricted it to the period of reperfusion. Pulmonary function indices shown to be improved by LR filtration of the arterial line either throughout CPB or during reperfusion are: indices of oxygenation (such as PaO2, A-a gradient, PaO2/FiO2 ratio) (throughout 28, 43–45; reperfusion only 46); reduced duration of post-operative ventilation (throughout 28,44, reperfusion only 46,47); improved pulmonary microvascular pressures (reperfusion only 47); and reduced extravascular lung water (throughout 44).

Some studies have reported no pulmonary benefit from LR filtration of the arterial line (35,39,41), but these were all small studies, and hopelessly underpowered to show anything other than large differences between the groups.

IMPROVEMENT IN HOSPITALIZATION INDICES BY ARTERIAL LINE FILTRATION.

Once again, those sStudies that have recorded hospitalization indices in controlled trials have investigated the impact of LR in comparison to "standard" arterial line filtration. It has been shown that the use of a LR filter in the arterial line is associated

with reduced hospital stay in the order of 1–2 days (28,46–48). Not surprisingly this is associated with reduced per patient cost (reduction of $2000–$9000 per patient) (47,48). A reduced requirement for transfusion and fluid administration has also been noted (33,36).

NON ARTERIAL FILTRATION STRATEGIES

Filtration in the Cardioplegia Circuit

It is not surprising, given the earlier discussion of ischemia-reperfusion injuries, that there may be potential for enhancing the myocardial protection afforded by blood cardioplegia if leukocytes are removed from the perfusate. Moreover, given the comparatively low volumes and flows involved (in comparison to arterial line parameters), leukocytes may be removed more efficiently. Indeed, using the Pall BC1B cardioplegia LR filter, Heggie et al. (49) demonstrated that more than 90% of leukocytes were removed. However, others have shown that these filters may begin to fail after a threshold filtered volume in the vicinity of 1000–1300 ml (50).

The overwhelming majority of human studies that have addressed this issue suggest that plasma markers of myocardial injury are reduced post-operatively when a LR cardioplegia filter is used (50–56). Indeed, only one study was found in which no such reduction was demonstrated (57). It is notable that the study by Sawa et al. (53) included the collection of left ventricular biopsies which demonstrated reduced leukocyte adherence in capillaries in LR cardioplegia patients.

Perhaps not surprisingly, this apparent benefit has been reflected in improved post-operative myocardial performance indicators such as cardiac index, ejection fraction, and inotrope requirements (50,51,53,55,56). A more detailed review of this issue (58) suggests that the greatest benefits for LR filtration of cardioplegia are to be gained in the sickest hearts or most complicated surgical procedures where, for example, the cross clamp times are prolonged. Another recent review also suggested that there may be merit in withholding filtration until administration of the terminal dose of cardioplegia (the "hotshot") (59).

Filtration of Pericardial Suction (PCS) Blood

Blood suctioned from the surgical field has "traditionally" been returned to the CPB circuit via a "cardiotomy reservoir." It is well recognized that pericardial suction **(**PCS) blood is "dirty", with potential contaminants including fat, bone, other tissue fragments, surgical debris such as bone wax, activated leukocytes and platelets, and others. A groundswell of concern has built in the literature over the potential for cerebral injury arising from the reinfusion of this blood. This reached a crescendo with the identification of so-called "small capillary and arteriolar dilatations" (SCADS) in the brain after CPB, and the further characterization of these as lipid from the pericardial suction (60,61). Lipid contamination was also identified as the cause for disadvantageous changes in the rheology of the PCS blood plasma fraction (62). As compelling as these findings seem, there is a paucity of data definitively linking them to functional brain injury. The only study which randomized patients to receive non-processed or processed PCS blood (from which most contaminants are removed) showed no difference in post-operative memory (63). Nevertheless, the appropriate handling of PCS blood remains an issue of high interest to those in the field.

It is well established that neither integral integrated cardiotomy reservoir filters nor arterial line filters are efficient in the removal of lipid emboli from PCS blood. One approach to avoiding any adverse effects of infusing these emboli is to avoid the reinfusion of PCS blood altogether. Another is to process scavenged blood through a cell saver. This has been shown to reduce the amount of lipid returned to the patient in human CPB (64) and to reduce the density of cerebral SCADs by more than 50% in vivo (65), but any neuroprotective benefit remains to be demonstrated (see above). There has also been advocacy for the use of accessory PCS blood filters, and one study suggested that these were more efficient at removing lipid than cell saver processing (66). Others, however, suggest that the efficiency of these filters is temperature dependent and that they might be prone to obstruction, somewhat paradoxically, when operated at the temperatures at which they are most efficient (67).

ISSUES THAT ARISE AND RESEARCH DIRECTIONS

1. It is almost 5 years since the literature on filtration in CPB was formally reviewed by Whitaker et al. (4) and they restricted their review to arterial line filtration. Similarly it is 4 years since the review of leukofiltration in cardiac surgery by Ortolano et al. (59). A large number of relevant papers have subsequently been published, especially in relation to clinical application of LR filtration. This is an area that is ready for review again. A fastidious systematic review might be rewarded by some interesting correlations. It is possible that there are now sufficient studies in the area of cardiac or pulmonary outcomes to justify a Cochrane type meta-analysis.
2. It is remarkable that there is still no study that addresses functional neurological outcomes in filtered vs. non-filtered CPB where a membrane oxygenator and alpha-stat acid base management are used. This is especially so given the regional disparity in uptake (implying differing opinions on the necessity for such filtration). The latter point would justify a randomized trial from an ethics standpoint.
3. The study by Whitaker et al. (21) raises the question as to whether or not LR filters are better filters of all material, as opposed to just leukocytes, than conventional arterial line filters. This reviewer has found no relevant formal evaluation (other than the Whitaker paper itself), and such an evaluation would be a very simple and cheap experiment to perform in vitro.
4. Given the magnitude of interest and concern surrounding the reinfusion of PCS blood, it is surprising that there is no comprehensive study of functional outcomes in processed vs vs. unprocessed perfusate. Such a trial may be justifiable given the recent negative (but small) study by Svenmarker et al. (63).
5. As a closing observation, the recent uptake of closed extracorporeal circuits (or "mini-CPB") must be acknowledged as an emerging trend (68). If this trend gains traction, it will generate a variety of questions with some relevance to the issue of filtration. Examples will include the appropriate way of dealing with PCS blood, the venous air handling capabilities of the circuit, and the implications of operating the circuit without an accessory arterial line filter.

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