Prebypass filtration of cardiopulmonary bypass circuits: an outdated technique?

Frank Merkle, Wolfgang Böttcher and Roland Hetzer

Department of Cardiovascular Surgery and Academy for Perfusion, Deutsches Herzzentrum Berlin, Berlin, Germany

Filtration of cardiopulmonary bypass (CPB) priming fluid before connection of the circuit to the patient was first accomplished by arterial line filtration. When dedicated prebypass filters (PBFs) with smaller pore sizes became available, a large number of particles could be found on the filter surface. In recent years, modern manufacturing methods for CPB circuit components were believed to be associated with a reduced number of particles found in components of extracorporeal circuits, making separate filtration of CPB priming solution unnecessary.

Microemboli generated during the preparation and priming procedure of the CPB circuit may consist of either solid particles or gaseous emboli and may contribute to patient morbidity. Endotoxins found in infusion solutions and CPB priming solutions may trigger inflammatory responses when administered into the circulatory system.

Filtration of crystalloid CPB priming solutions with a PBF consisting of a filter membrane with a pore size of 0.2 μm was found to effectively reduce the number of microemboli. Infusion filters with a filter pore size of 0.2 μm were found to reduce the endotoxin contamination in infusion solutions. Prebypass filtration with filters containing pores of 0.2 μm should be a necessity for contemporary perfusion practice.


Introduction

Advances in the therapy of patients undergoing cardiac surgery with reduced mortality and morbidity related to surgical procedures have triggered further efforts to optimize patient treatment. Cardiopulmonary bypass (CPB), used for temporary circulatory and pulmonary support during cardiac surgery, has been associated with risks for patient morbidity.

Postoperative cognitive deficits in patients after coronary surgery with CPB have been explained with arterial emboli and hypoperfusion. Most of the emboli were detected by transcranial Doppler examination upon initiation of bypass, when the heart was defibrillated, when clamps were manipulated and when aortic cannulation was performed. The rate of total embolic events was found to be highest at initiation of CPB, while total embolic events were highest during aortic clamping. Early neuropsychological testing within 18 hours after cardiac surgery revealed that initial deficits occurred in 30% of fast track patients, with 10% of the patients still showing deficits 5 days after the procedure.

Cognitive decline may complicate early recovery after coronary artery bypass grafting (CABG). The effect of perioperative cognitive deterioration on longer-term cognitive function was determined in a recent study. Cardiac patients were followed up for five years after CABG. Cognitive decline was noted in up to 75% of patients at the time of discharge from the hospital, and still evident in a third of these patients after six months.

Emboli may be characterized by their sizes in diameter: emboli bigger than 200 μm may be defined as macroemboli and emboli smaller than 40 μm may be described as microemboli.

Arterial embolizations associated with CPB may be caused by either particulate or gaseous emboli. Particulate emboli consist of either inorganic material or biological aggregates. Blood vessels will be occluded when these emboli are transported into capillaries. Gaseous emboli resulting from the CPB circuit may consist of air, oxygen, carbon dioxide and anaesthetic gas. Both bubbles and particles in small capillaries have been shown to cause regional blood distribution problems.

With the start of CPB, rapid arterial infusion of a large volume of priming fluid occurs within a short time. In adult patients, 1600–2000 mL of CPB priming fluid are pumped into the arterial system, typically within less than one minute. A possible
Gaseous and particulate embolic load of the CPB circuit may lead to arterial microembolization at the start of the procedure.

A strategy to purify crystalloid CPB priming solutions consists of recirculating the solution through a dedicated prebypass filter (PBF). This text aims at reviewing the types of emboli found in CPB priming solutions and at giving recommendations for preventing such emboli entering the arterial circulation of the cardiac patient upon initiation of CPB.

**Microparticles**

Sources of particulate emboli originating from the CPB circuit upon initiation of the extracorporeal circulation may be residual debris from the fabrication and assembly of the disposable components of the CPB circuit, particles in infusion solutions used to prime and de-air the CPB circuit, as well as particles generated during the operation of the heart–lung machine, especially the arterial roller pump.

Particles smaller than 2 μm administered to the circulation via infusion solutions may form aggregates with thrombocytes and fibrin, causing formation of thrombi and thromboembolization of the microcirculation as well as destruction of endothelium and the formation of granulomas and foreign body giant cells. Particulate matter originating from CPB circuits may be a trigger for activation of mediator systems, causing dysfunction of organs involved, having a negative effect in the developing phase of multiorgan failure in severely ill patients.

The European Pharmacopoeia, issued in the year 2000, defines the allowed particle content of parenteral preparations, i.e., infusions and injections. Resolution AP-CSP (00) 6 for parenteralia has been adopted by the EU member states and subsequently national regulations have been put into place. The allowed particle content for parenteralia with a volume of more than 100 mL has been set at 25 particles/mL of 10 μm and bigger, and three particles/mL of 25 μm or bigger. It is further stated that solutions for injection and infusion must be clear and practically free from particles.

**Roller pump**

Solid particles originating from the CPB circuit were found to be released from silicone rubber arterial pump boots during the course of extracorporeal circulation. The size of these silicone particles was described as a range from below 10 μm to above 50 μm. The presence of silicone particles in the liver, spleen and other organs in patients after chronic haemodialysis was traced back to haemodialysis roller pump heads with a silicone pump boot.

In a study comparing silicone tubing to polyvinylchloride (PVC) tubing in roller pump heads with varying flow rates and occlusion pressures, both materials were found to produce spallation and sequestration of particles in sizes up to 25 μm in diameter. In another report, the majority of particles resulting from PVC pump boots were found to be smaller than 5 μm. In addition to particles, plasticizers added to PVC may also be released from tubing inserted into roller pump heads. Pump boot tubing spallation seems to take place continuously in PVC tubing. The liberated particles have sizes from less than 2 μm up to 50 μm.

**Centrifugal pump**

While centrifugal pumps theoretically avoid the problem of spallation of tubing material, particles generated from a centrifugal pump head for an implantable ventricular assist device have also been found, although to a much lesser degree when compared to a standard roller pump. The mechanism for liberation of particles may create friction in impeller bearings, causing particles to be generated.

**Oxygenator**

Particles generated in vivo by oxygenators during CPB with heparinized blood have been described in a variety of studies. Particles in oxygenators found after the priming procedure with crystalloid priming fluid before connection of the circuit to the patient have also been documented. Linen fibres, originating from cloth used to wrap parts of the oxygenator before sterilization were found in primed and rinsed extracorporeal circuits. Particles visible in bubble oxygenators after the priming procedure led to an investigation of particulate matter in these devices. The majority of these particles were fibres. Further, an array of chemical elements, including silicon, aluminium and iron was analysed in circuits containing a bubble oxygenator.

In an analysis performed by Ueda et al. on modern membrane oxygenators, the number of particles was determined by a particle counter, operating with the light blocking method. Eight hundred and twenty-three particles per millilitre priming fluid of sizes between 2 and 50 μm were found to originate from the oxygenator, with the majority of particles being in the 2–5 μm range. Particles smaller than 2 μm were not analysed.
Venous and cardiotomy reservoir
A high number of particles were found to stem from the cardiotomy reservoir after recirculation with saline.\textsuperscript{25} Solid particles resulting from the manufacturing process could be isolated in cardiotomy reservoirs. The material included fibres, excess moulding material, plastic particles and antifoam sponge.\textsuperscript{26}

In the Ueda study, in which a cardiotomy reservoir was tested for particulate contamination, a total of 341.5 particles between 2 and 50 $\mu$m were present, with a majority of particles between 2 and 5 $\mu$m.\textsuperscript{24}

Tubing system
Particles ranging from 2 to over 50 $\mu$m were found in isolated CPB tubing without connected cardiotomy or venous reservoir or oxygenator.\textsuperscript{24} PVC tubing systems that had been filled with plasmalyte, which was recirculated through an arterial filter and a cardiotomy reservoir in a closed loop contained particles from 5 to 40 $\mu$m. A high number of particles smaller than 40 $\mu$m were found to pass through an arterial 40-$\mu$m filter.\textsuperscript{18} Assembly of the tubing system in the pump preparation room and cutting of the PVC tubing to insert components into the CPB system may be further mechanisms for introduction of solid particles.

Particles in priming solutions and additives
In a study on particulate contamination of intravenous infusion solution and other intravenous medication, intrinsic contamination from manufacture, packaging, transport and storage, and extrinsic particles introduced at the time of drug reconstitution and administration to the patient were named as mechanisms of contamination. Small volume parenterals in vials contained a very high number of particles as determined by light blocking method in comparison to large volume parenterals. However, only particles larger than 2 $\mu$m could be counted. A much higher particle content for particles smaller than 2 $\mu$m was hypothesized. As systemic effects of particles may be related to surface area rather than actual particle size, a large number of small particles administered into the circulatory system may potentially be most worrying. Final in-line filtration of intravenous drugs was, therefore, recommended. Interestingly, heparin was one of the drugs with the highest number of particles larger than 2 $\mu$m.\textsuperscript{27}

The addition of intravenous drugs to infusion solutions can lead to incompatibility reactions, caused by pH differences or alterations in buffer capacity. Drugs with added stabilizers that are injected into a solution may become unstable, because the stabilization agent is diluted as well and can, therefore, no longer perform its function. Also, drugs that require a specific pH for stabilization may become ineffective or may precipitate when brought into contact with a solution in a different pH range.

These incompatibility reactions may range from alterations in pharmacokinetics and pharmacodynamics, toxic effects of metabolites and irritation of tissue to embolization of aggregates.\textsuperscript{28}

The wide range of priming solutions employed makes testing of drug incompatibilities with additives to CPB priming problematic. In a recent survey on paediatric perfusion practice, the components of priming solutions were listed. The additives used vary, but it seems evident that more than just one additive is used apart from the crystalloid priming solution and heparin.\textsuperscript{29} Drug incompatibilities may only be reliably determined when additives in a defined quantity are mixed with a defined basic solution. Any alteration of concentration of the drug or the pH of the solution and addition of other drugs may lead to incompatibility reactions. The effects of the various materials found in CPB circuits, together with the very large surface area of components such as cardiotomy reservoirs and membrane oxygenators, have yet to be determined. Coating of CPB tubing with heparin or other means of surface modification may also contribute to pharmaceutical incompatibilities.

The amount of particles in infusion solutions may be largely underestimated, as particle counters for studies on these solutions with a measuring capacity for particles smaller than 2 $\mu$m were not available until recently. As particles smaller than 20 $\mu$m are invisible to the naked eye, particles in infusion solutions may not be apparent. In patients on intensive therapy units, the daily volume of 3 L of infusion solution was found to contain more than 400 000 particles smaller than 20 $\mu$m and the addition of small volume parenteral drugs injected intravenously added another 1 500 000 particles, of which 1 000 000 were found to be in the range 5–20 $\mu$m. The particles smaller than 2 $\mu$m are not included in these numbers.\textsuperscript{30}

Evidence of particulate contamination of priming fluids for CPB circuits was found by two other studies.\textsuperscript{31,32} Gaillard \textit{et al.} determined the degree of particulate contamination in priming solutions, parenteral drugs added to the priming solution and the effect of manipulation on these solutions. It could be demonstrated that, in addition to the particles originating from the solutions themselves, a high percentage of particles stem from manipula-
tion of infusion solutions used for priming the heart–lung machine (i.e., addition of drugs such as heparin). The authors conclude that usual perfusion solutions are not adapted for arterial perfusion.\textsuperscript{31}

Machin was able to show that the priming solution in two of six tested CPB circuits would no longer have passed the United States Pharmacopeia XXII standard after the priming procedure, although the infusion solutions complied with the standard before administration to the CPB circuit.\textsuperscript{32}

In the study already cited, Ueda\textit{ et al.} also found that infusion solutions for priming of CPB circuits contained a high number of particles ranging from 2 to over 50 \textmu m, with a total of 317.5 particles/mL average.\textsuperscript{24}

**Particles in cardioplegia solutions**
The effect of solid microparticles has been well studied in conjunction with administration of cardioplegia. It may be postulated that similar microvascular effects take place in other end organ capillary beds.

Particles in cardioplegia solutions may induce transient coronary vasoconstriction. Unfiltered St. Thomas’ Hospital cardioplegic solution caused considerable reduction in coronary flow, which could be limited by the incorporation of a 0.8-\textmu m cardioplegia filter. In hearts perfused with particle-containing solution followed by filtered solutions, the impairment of coronary flow was reversed.\textsuperscript{33}

It could be shown that filtration of cardioplegic solutions during repeated administration of crystallloid cardioplegia by a 0.8-\textmu m filter before they enter the coronary circulation resulted in a 90% recovery of their preischaemic functional capacity, whereas the unfiltered administration of cardioplegia resulted in a 30% recovery of preischaemic coronary blood flow. This effect was attributed to the presence of particles in the crystallloid cardioplegia solutions, although the particle content of the solutions complied with the United States Pharmacopeia and the British Pharmacopoeia.\textsuperscript{34}

Microparticles in myocardial capillaries after administration of unfiltered crystallloid cardioplegia were associated with adverse effects on restoration of cardiac function during reperfusion. Particles were found to be plugging coronary capillaries, to be adherent to the endothelial layer, or to be engulfed by apparently activated polymorphonuclear granulocytes. The number of particles in Bretschneider cardioplegic solution was assessed and particles of diameters between 0.2 and 20 \textmu m were found. An increase in the particle count was observed when the fluid was administered for clinical use, which resulted in the additional release of particles from the infusion kit. Filtration of the solution by a terminal in-line filter with a pore size of 0.2 \textmu m significantly reduced the number of particles.\textsuperscript{35}

**Micro air**
The effect of micro air emboli on small capillary blood vessels consists of a reduction in perfusion pressure distal to the obstruction and an inflammatory response to the bubble, with triggering of a foreign body response through cellular and humoral immune mechanisms.\textsuperscript{36}

Gaseous emboli may dissolve, dependent on their size, temperature, type of gas and partial gas pressures. Small gas bubbles in blood with a diameter of less than 10 \textmu m are relatively unstable and may collapse.\textsuperscript{6} The gas composition is important when considering the effects of microbubbles, with CO\textsubscript{2} and O\textsubscript{2} bubbles considered less harmful than air with its high partial pressure of nitrogen.\textsuperscript{37} Practically all air introduced into the arterial circulation reaches tissue before it can be absorbed.\textsuperscript{38}

When reaching the capillaries of the brain, gaseous microembolization caused by the CPB circuit may contribute to postoperative cognitive impairment.\textsuperscript{39}

Microemboli generated during the priming procedure are most likely composed of air, if the CPB circuit has not previously been flushed with CO\textsubscript{2}. These microbubbles will be introduced into the arterial system of the patient if not otherwise eliminated. Micro air emboli resulting from the CPB circuit may be pumped into the cardiac patient at the start of CPB.\textsuperscript{2,40} Arterial line filters have proved to be inefficient in eliminating gaseous microemboli.\textsuperscript{31,42}

Vortex pumps used for routine cardiac surgery show decreased microbubble transmission compared to roller pumps.\textsuperscript{43} However, although centrifugal pumps will deprime and trap large volumes of air, microbubble transmission is still possible.\textsuperscript{37}

Other causes for gaseous microembolization during the operation of the heart–lung machine are entrained air in the venous line, or perfusionist interventions such as drug injection and blood sampling,\textsuperscript{40,41} use of vacuum-assisted drainage\textsuperscript{44} or inadequate CPB circuit design.\textsuperscript{45} Some variation in the handling of gaseous emboli exists with different types of membrane oxygenators.\textsuperscript{46} Spontaneous gas bubbling may occur in membrane oxygenators with microporous membrane, and when the priming procedure of the device is carried out in an inappropriate manner.\textsuperscript{47}
Contamination

Small doses of endotoxins of 2 ng/kg body weight administered intravenously are able to produce granulocytosis and fever.48 Endotoxin is a potent trigger of inflammatory and immunological reactions with activation of humoral and cellular mediators49 and has been shown to produce endothelial damage. Endotoxin may play an important role in the development of multiorgan failure.12

Postoperative respiratory distress syndrome has been associated with a sequence of multiple insults, such as systemic inflammatory response following CPB and subsequent exposure to endotoxin.50 In a study on priming fluid for CPB, endotoxins were also found. The total amount of endotoxins administered by 3000 mL of priming fluid ranged from 48 to 1500 ng. It was concluded that endotoxinemia found in cardiac patients was mainly associated with CPB and the intraoperatively administered fluids.48

The mechanism for endotoxin release during CPB was described as liberation of endotoxin from the intestines because of impaired microcirculation. The peak concentration may be influenced by CPB flow mode and medical pretreatment. Plasma concentration of endotoxin rises with the start of CPB, with an increase towards the end of the procedure.49 Any additional endotoxin load from the primed CPB circuit may potentially aggravate the negative effects of endotoxin.

Intravenous fluids administered during intensive care therapy are increasingly filtered by 0.2-vm infusion filters.51 Clinically, these infusion filters, made of a posidyne membrane, are successfully used to eliminate endotoxin contamination of infusion solutions.52 This filter membrane material is similar to the membrane employed in some PBFs for CPB.

A report on bacterial contamination of hospital-manufactured cardioplegic solution, with fatal outcome in five of eleven patients, further underlines the necessity for awareness of bacterial contamination in infusion solutions prepared at the hospital and administered during CPB.53 Mixing of infusion solutions for priming the heart–lung machine and addition of intravenous drugs to the circuit may hold risks for bacterial contamination or contamination with endotoxins.

Prebypass filtration

Dedicated filters with filter pores small enough to eliminate particles and gaseous emboli immediately prior to connection of the CPB circuit were developed in the 1970s. Filters with pore sizes of 3–8 vm were initially produced, later to be replaced by filters with submicronic pore sizes of 0.45–0.2 vm. The latter filter was designed to also trap bacteria.54 Before the advent of PBFs, arterial line filters were used to purify the priming solution of particles. However, the relatively large pores of arterial line filters are not able to capture the particles observed in the priming solution.18

Filtration of CPB priming fluid and removal of large quantities of foreign particles led to an improved postoperative neurological course, with a reduction of incidence of neurological deficits after open-heart procedures.22

In several other studies, the effective removal of microparticles from primed CPB circuits could be demonstrated.23,55,56 A PBF with a pore size of 0.2 vm was found to be effective in reducing the number of particles larger than 1 vm contained in the priming solution of clinically used CPB circuits.24 The use of PBFs was strongly advocated.26,32,57

In a survey carried out in 1997, the use of PBFs in German perfusion departments was investigated. Seventy-four percent of the perfusion departments in 53 hospitals routinely employed prebypass filtration, while arterial line filtration was employed in 94%.58 Similar numbers are reported from perfusion departments in the USA, where 83% of 524 centres were using PBFs in the adult, and 59% were using these devices in the paediatric age group. Arterial line filters in the adult population were used in 99% of all cases, with 88% for the paediatric patients.59 For the paediatric centres in the USA, another report found that the use of PBFs was 68.1% in 72 active paediatric centres, while arterial line filters were in use in 95.8% of paediatric centres.29

Until recently, particle counters capable of determining the number of microparticles in the 0.1–5 vm range were not available. In our own study, we were able to show that microemboli could be effectively eliminated by recirculating CPB priming fluid for two min with a flow rate of 5 L/min through a 0.2-vm PBF (Pall R3802 prebypass filter, Pall Biomedizin, Dreieich, Germany).

An in vitro study was performed in order to determine the quantity and sizes of possible microemboli in the crystalloid priming fluid of our routine adult CPB circuits. Three groups of test circuits were set up: in group A, priming fluid was analysed only; group B consisted of CPB circuits with membrane oxygenators; and group C circuits had no oxygenators, to determine the filtering effect of modern membrane oxygenators. While the prim-
ing solution contained a very large number of small particles in the range of 0.1 μm, some microemboli were added by the circuits themselves. Differences in the measured microembolic content between group A and groups B and C in the categories 0.2 μm, 0.5 μm and 0.8 μm may be explained by generation of microemboli from the CPB circuit components during recirculation. A comparison between groups B and C revealed some differences in the microembolic activity in the 1.5 μm and 3 μm category, with a discretely lower activity in some of the group B circuits. Inclusion of a 0.2 μm PBF led to a dramatic drop in microembolic counts in all test circuits, with virtually no more microemboli detected after 2 min of recirculation (Figure 1). With the particle measurement device employed (HIAC Royco 8000A particle counter, Silver Spring, MD, USA), we were able to demonstrate that the PBF effectively eliminated all microemboli above a size of 0.2 μm. Interestingly, the number of microemboli smaller than 0.1 μm was also reduced. \(^{60}\)

**Conclusion**

Although modern manufacturing methods for CPB circuits may have reduced the contamination of these circuits with macroemboli, absence of microemboli can not be assumed. In order to comply with regulations concerning particle content of infusion solutions, additional measures have to be taken to ensure the lowest possible level of contamination. Potentially harmful microemboli generated by the CPB circuit may contribute to neurological impairment and to triggering of inflammatory responses to CPB. Particulate and gaseous microemboli inherent in infusion solutions for CPB priming, endotoxins from infusion solutions used for the priming procedure as well as particles and gaseous microemboli generated during the priming procedure make prebypass filtration of the CPB circuit a necessity. Particles, gaseous microemboli and endotoxins introduced into the coronary system by administration of cardioplegia solution should also be eliminated with appropriate filtering devices.

Further, we suggest that manipulation of the CPB circuit prior to connection to the patient should be limited. For preoperative preparation, cutting and manual assembly of PVC and silicone tubing with the release of micro- and macroparticles should be avoided, as tubing connectors may cause abrasion of plastic material. Manipulation of CPB components and connection sites with powdered sterile gloves may also be of concern, as well as contamination of the inside of the CPB circuit by dust or contaminated air in the pump preparation room or the
operating theatre. After prebypass filtration of the CPB circuit with a 0.2-vm filter, drug injections and addition of fluids to the system should be accomplished via a 0.2-vm infusion filter to prevent contamination and addition of microparticles. Filtration of CPB priming solution with a PBF is not outdated; on the contrary, it is a necessary technique in the contemporary management of perfusion.

References

25 Liu JF, Su ZK, Ding WX. Quantitation of particulate microemboli during cardiopulmonary bypass: experi-


Copyright of Perfusion is the property of Arnold Publishers and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.