Continuing Education: Filtration

Extracorporeal Filtration of Blood

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The filtration of blood is a highly complex and controversial subject to which much research and clinical evaluation has been devoted in recent years and months.1-2,3 The conclusion one arrives at regarding extracorporeal filtration of blood must be constantly re-evaluated in light of the ever increasing data.

Why Filter?

Since the inception of extracorporeal circulation, the medical community has puzzled at the high occurrence of post-operative complications involving alteration in the function of various vital organs.4-5,6 These disturbances include pulmonary, renal, and even reported pancreatic abnormalities,7 cardiac lesions, neurological alterations or deficits, and alterations in hepatic function.4-8 Some of these phenomena remain abstract and ill-defined.6

The explanation for these varied and widespread occurrences may well lie in the alteration of the blood components resulting from the extracorporeal circuit and/or the trauma of surgery, which in turn results in microvascular occlusion.2-9,10 Effects of these microembolic events are often subclinical in nature or transient disturbances due to the body’s ability to withstand great insult.6 Nevertheless, these events do occur and sometimes lead to detectable and permanent damage.7,11 Therefore, attention must be directed toward the prevention or removal of microemboli if extracorporeal circulation is to become a physiological and atraumatic procedure.

Debate still exists in attempting to statistically correlate the origin of these emboli and their effects upon organ function.2,9 Researchers have cited various embolic mechanisms, some of which are platelet-leukocyte aggregation,2,8 denaturation of plasma proteins,12 particulate microemboli,2,13 fat emboli,14-15 microbubbles,9 and fibrin.6,17 Of special interest is the formation of platelet-leukocyte aggregates. It is now believed that these aggregates are the major source of morbidity associated with total cardio-pulmonary bypass.6,16

Inherent in extracorporeal circulation are several causal factors of these aggregates:

1. Blood trauma during suction,2-18 oxygenation,5 and pumping.19
2. The use of bank blood, containing an average of 100 aggregates per cubic millimeter, ranging from 10-200 microns in diameter.3
3. The admixture of donor and patient blood which always results in some degree of blood reaction and clumping.20,21
4. Hypotension and trauma, which cause tissues to release substances, (i.e., serotonin), which contribute to aggregate formation.21-27
5. Contact of blood with foreign surfaces, which results in aggregation.19,28-29

Platelets and leukocytes begin to become adhesive immediately upon withdrawal of blood from the body.29 This process is accelerated upon contact with foreign surfaces.5,28 In addition, erythrocytes are hemolyzed by the extracorporeal circuit18,19 and even by contact with the pericardium.20 Hemolyzed erythrocytes release substances which also promote aggregation.4,12 Blood and surgical trauma lead to plasma protein denaturation12,31 and an increase in circulating lipids,14 further aggravating the microembolic process. Platelets become adhesive as tissue perfusion becomes inadequate due to the selective ischemia reaction.20-27,31

Extracorporeal blood filtration has recently gained import and popularity because of widespread efforts to minimize the number of emboli which are generated and introduced by cardiac surgery and concomitant extracorporeal circulation.32 Several types of disposable blood filters have been developed for such use. Effectiveness of these products against most fat emboli14,16,33 is dubious, and removal of air emboli and
denatured proteins is still in question. However, they may be of enormous value in eliminating platelet-leukocyte aggregates and fibrin material from the blood.\textsuperscript{3, 32, 34}

THE FILTERS AND HOW THEY WORK

There are three popular locations or uses for blood filters during cardiopulmonary bypass (Figure 1):

1. in-line between the cardiotomy reservoir and oxygenator,
2. in the arterial line between the arterial pump head and the patient,
3. in a transfusion set to filter stored blood or blood from the oxygenator being returned to the patient after bypass,
4. occasionally venous return line filtration is used.

Requirements for the cardiotomy line filter include:

1. ability to filter foreign material picked up by the cardiac suction,
2. ability to remove great amounts of aggregates resulting from the trauma of suctioning (95-99\% of all hemolysis resulting from cardiopulmonary bypass occurs in this subsystem),\textsuperscript{32}
3. reasonable ease in gravity drainage (low resistance), at relatively high flow rates (1-2 liters per minute).

Requirements for the arterial line filter include:

1. ability to function in a high flow (6 or more liters per minute) environment without undue hemolysis,\textsuperscript{35, 36}
2. ability to be primed and evacuated of air with ease,
3. provision for continuous monitoring of the pressure gradient across the filter to determine filter occlusion,
4. a bypass line in place to be employed in case of filter occlusion and failure.

Requirements for transfusion filter include:

1. low priming volume,
2. reasonably low resistance,
3. limited rate of loss of filtering surface area.\textsuperscript{37}

Figure 1. The popular locations for placement of extracorporeal blood filters in the cardiopulmonary bypass circuit.

Figure 2. A diagram of a typical screen filtration pressure measuring device. The pressure curves on the lower left indicate a typical pressure curve from stored citrated blood on the left and normal fresh drawn heparinized blood on the right.

Although variations and combinations exist, there are two basic types of filters: \textit{screen} and \textit{depth}. The actual filtering material of screen filters is a mesh material (nylon, dacron, etc.) and filtration depends upon the pore sizes of the mesh. A depth filter is composed of packed material such as polyurethane foam, nylon, glass wool, or dacron wool, and depends on adsorption for its filtration efficiency.\textsuperscript{23, 32}

METHODS FOR TESTING EFFICIENCY OF FILTRATION

The methods for determining the efficiency of filters are varied and complicated, but one should gain familiarity with them in order to evaluate the available clinical data. Probably the least complicated method of testing performance of a filter is by examining it after use. Gross examination gives very little if any, useful information, since the point of concern is the filter’s ability to remove \textit{microemboli}. Microscopic examination makes it possible to identify and perhaps estimate the size of the material removed by the filter.\textsuperscript{38} This is an appealing technique and a valuable one when used in conjunction with certain others.\textsuperscript{3, 39} Caution must be used, however, when drawing conclusions based on
filter examination only, because there is no data about the material not removed by the filter.

Calculation of the weight or volume removed by the filter has similar drawbacks. The only valid conclusion is that the filter does remove x weight or x volume of material from the blood. Examination of the filter can reveal the nature of the trapped matter, but filtration efficiency cannot be evaluated unless suitable data is ascertained about the blood before and/or after its passage through the filter.

One of the more popular methods for studying the effects of blood filtration during transfusion or extracorporeal circulation concerns pulmonary function. It has been documented in countless papers that many of the aggregates are filtered out of the circulation in the pulmonary ultrastructure. These substances, however, are harmful both to the interalveolar septum and the endothelium of the effected vessels. On biopsy and electronmicroscopic examination, extensive occlusion of capillary beds by aggregates of platelets and leukocytes in various stages of disintegration has been found. These damaged cells apparently release enzymes which, combined with local accumulation of acid metabolites, change the permeability of the basement membrane, and cause ultimate loss of membrane integrity. The small vessels in the lungs swell and may finally rupture, releasing blood elements and toxic substances into interalveolar and intraalveolar spaces. The lung tissues swell, further compromising pulmonary flow.

These events cause the decrease of gas exchange and, depending on the extent of their occurrence, often result in pulmonary insufficiency. One way of testing the efficacy of filters, therefore, is by studying pulmonary function and pulmonary ultrastructure in control and filter groups. Since this method involves one of the main clinically observable effects of aggregates, it is fairly valid. However, it is sometimes difficult to objectively grade and rate the severity of the morbidity.

The Screen Filtration Pressure (SFP) technique is one of the earlier devices for determining the efficiency of extracorporeal filters. It utilizes a screen with known surface area and pore size (usually 20 microns) and is based on the assumption that an increase in the pressure gradient across the screen is proportional to the increase in resistance caused by occlusion of the screen pores with aggregates (Figure 2). This method is valuable in tabulating the occlusive power of aggregates but not to indicate their individual sizes, their number, or their specific identity. Conversely, since the potential of microemboli to occlude microvasculature in the body is the motivation for their attempted elimination by blood filters, then the drop in SFP after passage of blood through a filter is a good index of the degree to which the filter reduced microembolic risk.

Perhaps the most valid method for evaluating the efficiency of filters involves counting the aggregates contained in blood before and after it passes through a filter. This is possible using a Coulter Counter or other similar device: equipment able to measure not only numbers but sizes of aggregates down to and including 10 microns. This technique is proving to be of great benefit in in vivo studies of filtration during clinical cardiopulmonary bypass.

There is some concern about the possible elimination or damage of desirable and functional blood elements by filters. An ideal filter should eliminate aggregates and damaged or nonfunctional cells from the blood but leave functional platelets, leukocytes, erythrocytes, and proteins intact. Cell counts in filtered blood immediately and hours or days after infusion of filtered blood are valuable tests of the effects of filters on these blood elements. One should not deduce from the cell counts, however, that the decrease in cell count is attributable solely to the use of the filter. For example, de Leval has shown that platelets migrate to the liver during perfusion and remain there until after termination of bypass. Function studies reveal more information than mere counts, for what is important is the overall performance of the remaining cells, not their concentration. Also beneficial are determinations of fibrin degradation products, plasma hemoglobin levels, coagulation studies, and certain other ancillary evaluations.

**THE FILTERS**

Whenever there is a demonstrated need for a new product, industry is usually quick to produce its own interpretation of the answer to suit that need. Although some of these products are clinically excellent, the users have an obligation to their patients to closely scrutinize the available objective data prior to choosing which product they will use.

The Ultipor Filter (formerly the Barrier Filter) is a disposable, screen-type filter which is available in two models: one for placement in either the arterial or

* Coulter Electronics, Hialeah, Florida.
** Pall Corporation, Glen Cove, New York.
cardiomyotomy return line of an extracorporeal bypass circuit (Figure 3), and a smaller transfusion filter. The larger filter consists of a cylindrical polypropylene case measuring 6 x 9 cm. containing an accordion-pleated mesh (the actual filtering material). There is a thick outer mesh and a thin inner mesh for graded filtration, both of a polyester material. The filtering surface area is 645 square cm.; pore size, 25-40 microns; and priming volume, 160-190 ml. The filter is available in a presterilized package, but can be autoclaved at 275° F (135° C). There are integral blood inlet and outlet connectors and a female luer vent into which a stopcock may be fitted for elimination of air. The interior design is such that all blood entering the filter must pass through the mesh before passing through the outlet (Figure 3). Theoretically, then, all particles larger than the pore size (25-40 microns) are caught by the mesh and removed from the blood.

The transfusion filter contains the same mesh, also fan-folded, encased in a 2 square inch polypropylene housing (Figure 4). The filtration surface is 25 square inches, priming volume is minimal, and the filter fits into a standard transfusion set.

Reul, et al., in a study of pulmonary function and fine structure after traumatic injury and massive transfusion, showed a reduced risk of pulmonary insufficiency when transfused blood was passed through Ultipor filters. Goldiner and co-workers also report prevention of pulmonary compromise by the use of Ultipor filters for blood transfusions, and demonstrated by electron microscopy that most of the particles trapped by the filters were 60 to 80 microns and consisted of damaged erythrocytes, fibrin strands, and platelet-leukocyte aggregates.

McNamara and associates, studying the weight of material removed by the Ultipor and Swank filters compared to the weight of all filterable debris in units of stored blood (QSFP). They found that the Ultipor filter removed all but about 0.6 mg/ml of filterable debris (45-78%). The quantity, however, was somewhat less than that removed by the Swank filter.

Solis, using a Coulter Counter to measure numbers and volumes of particles contained in unfiltered and filtered units of stored blood, found that the Ultipor filter virtually eliminated all particles larger than 32 microns, but left most in the 13-21 microns range. Swank, et al., varied this technique by combining tabulation of emboli using a Coulter Counter with SFP methods. They concluded that the Ultipor filter eliminated emboli larger than 100 microns from stored blood, but increased the number of emboli smaller than 50 microns.

Studies concerning the use of Ultipor filter in the cardiomyotomy return or arterial line during clinical cardiopulmonary bypass are limited. Solis and associates, using Coulter Counter techniques, studied the effects of placing various extracorporeal blood filters in the cardiomyotomy return line to filter suctioned blood. Results were reported in terms of per cent and amount of particulate volume removed by the filters. The study determined that the Ultipor filter removed 83% by volume of particles, 32-80 microns, but only 39% by volume of particles 13-25 microns.

Comparative qualitative and quantitative analysis of particle removal by Ultipor filters in the arterial line have escaped notice of these authors.
Gervin, et al., examined filtered stored blood for possible deleterious effects of filtration and found that a single pass of fresh or aged blood through an Ultipor filter did not significantly alter hematocrit, PTT, thrombin times, fibrinogen levels, Whole Blood Euglobulin Lysis Times (WBELT), fibrin split products, platelet counts, or platelet function. However, Reed et al., in a study utilizing filters in the cardiotomy return line during clinical perfusions noted a significant decrease of WBELT in a group of patients in which the Ultipor filter was used when compared to a group in which the Swank filter was employed. Although this decrease was transient and values returned to near normal levels shortly after bypass, it indicates that patients in the Ultipor filter group were exposed to more circulating biological debris during cardiopulmonary bypass.

For many years Swank and others have studied emboli and how they were effected by glass or Dacron wool. The Swank* filter, a product of this research, is a disposable, depth-type filter composed of Dacron wool packed in a clear plastic casing. There are three available models: one for each use previously described. Pore size is variable, but averages 80 to 100 microns. Pore size is not the important factor of this product's filtration characteristics, however, since removal of aggregates is primarily by adsorption to the wool fibers. Preliminary research by Ashmore and co-workers indicates that the degree to which the filtering material is packed may greatly influence its filtering efficiency, probably because channeling in loosely-packed wool interferes with its ability to perform its adsorptive function.

The filter designed for placement in the cardiotomy return line (Model CA-100) has a stated flow capacity of 5 liters per minute. The casing is cylindrical, 10 cm. in diameter by 2 cm. deep (Figure 5). There are integral 3/8" inlet-outlet connectors.

Figure 5. A diagram of the Swank perfusion filter showing (a) 3/8" inlet, (b) dacron-wool, (c) plastic grid, (d) 3/8" outlet connector.

Figure 6. A diagram of the Swank transfusion filter showing the gross clot filter and the two different densities of dacron-wool.

Stopcocks on both the inlet and outlet sides of the filter enable air to be eliminated from the filter. The Dacron wool is contained by a 100 micron nylon mesh held in place by plastic grids resting against the top and bottom of the cylinder. Early use of the cardiotomy line filter in the arterial line—a function for which it was not designed—produced problems involving extreme pressure build-up across the filter, especially at the beginning of bypass or after a hypotensive episode. This led to development of an arterial line filter (High Flow 6000). This filter is similar in design to the CA-100, except that its diameter is increased to 12 cm.: this means that the blood sees a face surface area 40% greater than that of the CA-100. Hill reports that pressure gradients across this arterial line filter have been within acceptable limits.

The transfusion filter, Model IL-200 (Figure 6), includes a gross clot filter (180 microns mesh) and Dacron wool packed at two different densities, the greater density being the last traversed by the blood before infusion. This gradation of filtering surfaces increases the filtering efficiency while minimizing loss of filtration area as stored blood passes over it. The filter fits into a standard transfusion set and has a stated flow capacity of 80-300 ml per minute. *Pioneer Filters, Beaverton, Oregon.
Connell et al.,8 employed electromicroscopic examination of pulmonary ultrastructure in post-operative cardiac patients. The patients were divided into four groups: (1) no filter, (2) Swank CA-100 in the cardiotomy drainage line, (3) all suction blood (as in group 2) and prime or added blood filtered, and (4) suction, prime, added, and arterial line blood filtered by Swank CA-100 filters. The study found that the more extensive the filtration, the fewer were the degenerative lesions detected in pulmonary ultrastructure, and that groups 3 and 4 differed only in that interstitial edema was seen significantly less often in Group 4.

The study of Solis et al.,2 determined that the CA-100 placed in the cardiotomy return line position removed 86% by volume of particles larger than 32 microns and 90% of the particles 13 to 25 microns. Reed et al.,1 found that the euglobulin lysis times were significantly higher (normal) during perfusions in which the CA-100 was used in the cardiotomy drainage line than when the Ultipor or no filter was used, indicating that patients in the Swank filter group were exposed to considerably less circulating biological debris.

McNamara et al.,43 in their determinations of percent by weight of filterable debris removed by filters from stored blood found that the Swank CA-100 removed 96% to 100% in comparison to the 45% to 78% removed by the Ultipor. One must wonder, however, if fluid absorption by the wool fibers could have accounted for some of the weight reported as particulate weight. Swank et al.,3 used Coulter and SFP techniques to determine the efficiency of the Swank transfusion filter in removing debris from stored blood. He found that the Swank filter removed all large aggregates and approximately 90% of all other aggregates including those 10 microns in diameter. There are no clinical studies available which quantitatively analyze the efficiency of the Swank High Flow 6000.

In regard to removal or damage of intact blood constituents by Swank filters, there remains much speculation and debate. Reed et al.,1 found that platelet counts were reduced significantly more during perfusion in the group of patients utilizing the Swank CA-100 in the cardiotomy line than in the Ultipor and no filter groups, but that there was no significant difference in the post-perfusion counts. Gervin et al.,42 found that a single passage of fresh stored blood through Swank filters reduced platelet counts an average of 36.8% compared to a 9% reduction by Ultipor filters. Despite this, platelet function remained normal. Removal of platelets from aged blood is of little interest hematologically since platelet function in this blood is abnormal.42 It may well be, however, that these nonfunctional platelets are the foci of microaggregates and in that case their removal would prove greatly beneficial.

Osborn et al.,4 reports a reduction of platelets by the extracorporeal circuit whether or not a Swank filter was used in the cardiotomy return line and states that the post-operative blood loss of the filtered group of patients compared favorably with that of the no filter group. Egeblad et al.,55 also reports a reduction in platelet counts with use of the Swank CA-100 in the arterial line, but found that the counts returned to about half the preperfusion level within 4 to 6 hours. Reed et al.,1 found no significant difference in hemolysis rates of perfusions with Swank filters, Ultipor filters, and no filter in the cardiotomy return lines.

The Polyfilter PF-427* (Figure 7) utilizes polyurethane foam in three progressively smaller pore sizes as the filtering material. The layers are stacked pancake fashion within a clear polycarbonate case. The topmost layer has a pore size of 150 microns; the middle layer 75 microns; and the bottom layer, 30 microns. The manufacturer states that the filter provides a total filtering surface area of 480,000 square centimeters.

The Polyfilter may be used in either the cardiotomy return or arterial line of the extracorporeal circuit. It has integral ¾” connectors and a female luer lock on both inlet and outlet sides for insertion of stopcocks to enable the removal of air.

The Polyfilter transfusion filter, the PF-127, contains the same three layered foam filter media, but precedes them with a standard 180 micron gross clot nylon mesh (Figure 8). Stated total surface area is 25,000 square cm. The Polyfilter 227 partial bypass filter (Figure 8) was designed primarily for use in a dialysis circuit. It is identical to the PF-127 with the exception that the gross clot nylon mesh is absent, the integral connectors are ¼” O.D., and there is a female luer port on the inlet side to facilitate removal of air.

Clinical data concerning the Polyfilter (PF-427) is limited. Solis et al.,2 included evaluation of the Polyfilter in his study analyzing filters in the cardiotomy return line

*Bentley Laboratories, Santa Ana, California.
with Coulter techniques. The study found that the Polyfilter removed 64% by volume of the microemboli present in suction blood compared to 58% removed by the Ultipor and 89% removed by the Swank. Solis concluded that since results of Polyfilter and Ultipor filtration were quite similar, the Polyfilter probably functions as a surface and not a depth type filter.

Figure 7. A diagram of the Polyfilter showing (a) \( \frac{3}{8} \)" inlet, (b, c, d) the layers of polyurethane foam, and (3) \( \frac{3}{8} \)" outlet.

Dutton et al.,\textsuperscript{15} utilized a Coulter Counter to determine removal of emboli by a Polyfilter 427 placed in the arterial line. He found that the Polyfilter removed 60% of the emboli, 50 to 150 microns and 90% of the emboli larger than 150 microns but increased the number of emboli below 50 microns. This seems to concur with Solis\textsuperscript{2} in characterizing the Polyfilter a screen filter, and with Swank\textsuperscript{3} in finding that screen filters possess "punch-out" property and actually increase the number of microemboli smaller than 50 microns.

The most recently developed blood filter is the Intersept*. There are three available models, one for each use previously described.

The Intersept cardiotomy blood filter (Model 1331) (Figure 9) consists of a tapered clear plastic case in which Dacron felt is fan-folded around the central cavity. Pore size of the felt media is stated to be 10 to 40 microns, and surface area, 16,000 square centimeters with a frontal surface area of 430 square cm. The Dacron felt is held in place by large-pore, rigid nylon mesh on either side. Surrounding the hollow core and inside the Dacron wool is a woven nylon screen with 20 micron pores. There are integral \( \frac{3}{8} \)" connectors and a female luer-lock port for insertion of a stopcock on the top (tapered or inlet) side. The blood path through the filter is very similar to that of the Ultipor filter.

*Johnson & Johnson, New Brunswick, New Jersey.
The case of the Intersept arterial line filter (Model 1332) is similar to that of the cardiotomy line filter except that it contains an internal bypass valve to eliminate the need for an external bypass line. One can only speculate at the flow turbulence characteristics of this device. Filtration is accomplished by a woven nylon mesh with 20 micron pores (screen filtration). Frontal surface area is 600 sq. cm. and filtration surface area is 2,000 sq. cm.

Figure 10. A diagram of the Intersept transfusion filter showing (a) the inlet, (b) vent valve, (c) dacron felt and nylon mesh.

The Intersept transfusion filter also resembles the cardiotomy filter, except that it is smaller and possesses a vent valve near the inlet. The filtration materials, like the cardiotomy filters, are Dacron felt and nylon mesh. However, the outermost layer of the transfusion filter fan fold is a woven nylon screen, pore size 170 microns. The filter fits a standard transfusion set or can be obtained with attached administration set (Figure 10).

Clinical data about all three Intersept filters is not yet available.

The Fenwal* transfusion filter (Fig. 11) utilizes polyurethane foam and packed Dacron wool as its filtering material. Reed et al., studied this transfusion filter placed in the cardiotomy return line during pediatric perfusion. Free plasma hemoglobin levels were comparable to those in which the Swank transfusion was utilized in the cardiotomy line, and lower than in perfusions without filters. Platelet counts were similarly and transiently decreased in both filter groups as compared to the no filter group. No other clinical data about the Fenwal transfusion filter is available.

Figure 11. A diagram of the Fenwal transfusion filter showing the gross clot filter and the polyurethane foam and dacron-wool filtration media.

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SUMMARY

A review of various popular methods of evaluation, the literature, and the available extracorporeal filters has been presented. An attempt has been made to point out the questionable validity of certain conclusions drawn from specific testing of extracorporeal filters. An explanation of the filtration characteristics of these extracorporeal devices does not answer such basic questions as:

1. What is the optimal size of microemboli which should be removed by these filters?
2. Do microaggregates trapped by these filters de-aggregate, pass through the filter, and re-aggregate downstream?
3. Do these devices trap gaseous microemboli? And how effectively?
4. How effective are these devices in removal of fat emboli?
5. Do the merits of arterial line filtration outweigh the hazards?

*Fenwal Laboratories, Morton Grove, Illinois.
Even though sub-lethal red cell damage has not been documented, the available evidence indicates that these filters are not injurious to the blood components, and in fact remove damaged and/or non-functional cells. Overwhelming evidence is available supporting microfiltration of every unit of stored blood administered directly to the patient or used in the pump oxygenator. Continued clinical evaluation of extracorporeal filtration is certainly indicated. As specific requirements are delineated, one can only hope that design improvements will keep pace.

REFERENCES


