

# Blood Filtration During Cardiopulmonary Bypass

R. Thomas Solis, M.D.

Particulate microembolization during extracorporeal circulation is thought to contribute to cerebral, pulmonary and other post-operative complications following cardiac surgical procedures.<sup>1-10</sup> Factors which have been implicated in microembolic phenomena during cardiopulmonary bypass include: 1) transfusion of stored blood,<sup>1, 2, 8, 11, 13-22</sup> 2) formation of platelet aggregates in the patient or in the extracorporeal circuit,<sup>8, 11, 22, 24, 25</sup> 3) air embolization,<sup>4, 7</sup> 4) denaturation of plasma proteins,<sup>26</sup> 5) infusion of fat, fibrin and other foreign material through the coronary suction system.<sup>23, 27-29</sup> In order to quantitate the relative contribution of each of these sources of microemboli, we have utilized a particle size analyzer.<sup>18, 20, 21, 30, 31</sup> These studies have indicated that infusion of stored blood and the extravasated blood collected in the coronary suction system is the predominant source of microembolization in patients undergoing cardiac surgery. The present study reviews factors controlling the formation and removal of these two types of microemboli.

## FILTRATION OF STORED BLOOD

Since the beginning of blood banking, blood filters have been used to remove the microaggregates that develop in stored blood.<sup>32-34</sup> These particles were thought to consist of fibrin, red cells, platelets, and other amorphous material.<sup>32, 35</sup> By 1955, the currently used plastic disposable mesh filters with a pore size of 170  $\mu$  were in widespread clinical use.<sup>36, 37, 38</sup> These clot filters were preferred because of the rapid flow rates with which they allow stored blood to be transfused.<sup>39</sup> Although considerable material was known to pass through these filters, it was not thought to be harmful to the recipient.<sup>34, 40</sup>

In 1961, Swank introduced the screen-filtration pressure (SFP) technique to quantitate the microaggregates in stored blood.<sup>16</sup> The SFP is the pressure required to force blood at a constant rate through a 20  $\mu$  pore mesh filter with a fixed area. The SFP was noted to increase during the first ten days of storage of blood under standard blood-bank conditions and to remain high after passage through the standard clot filter, but to be reduced by wool filters consisting of glass, Nylon, or Dacron.<sup>16</sup> In later studies, the high SFP in stored blood used during heart-lung bypass was noted to fall to normal after passage of the blood through the patient.<sup>1</sup> In addition, the SFP of blood drawn from patients receiving transfusions was noted to fall progressively from central venous to arterial to peripheral venous samples.<sup>41</sup> These observations imply that the material infused is removed by the microcirculation of the recipient and are consistent with pathologic findings of multiple microemboli in patients who had recently received massive transfusions.<sup>2, 42</sup>

Although many contributing factors—such as shock, fat embolism, overhydration, and pulmonary trauma itself—have been implicated in the development of pulmonary insufficiency after trauma, the microaggregates infused with stored blood have also been thought to play a role.<sup>1, 2, 8, 11, 15, 41-43</sup> Clinical studies in combat casualties have shown a significant arterial hypoxemia in patients who

The Departments of Medicine, Baylor College of Medicine

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receive over eight units of blood.<sup>41-44</sup> However, because of the many complicating factors usually present during massive transfusion in man, most of the evidence that suggests that infusion of the microaggregates in stored blood may be harmful to recipients has been experimental. Transfusion of stored blood with a high SFP caused pulmonary hypertension<sup>8, 13, 45</sup> and transient increases in dead-space ventilation<sup>46</sup> in dogs and severe alterations in the electroencephalogram in cats.<sup>47</sup> Ultrastructural studies of the lungs of dogs after they received large quantities of stored blood filtered with the standard clot filter have shown lesions similar to those noted after hemorrhagic shock.<sup>11</sup> These pulmonary lesions, which consist of interstitial edema and degeneration of the capillary endothelial and type I alveolar cells,<sup>11</sup> and evidence of obstruction to pulmonary blood flow<sup>8</sup> were prevented by Dacron-wool filtration of the stored blood.

Although much information has been obtained with canine models, primate studies are of greater interest, because the microaggregates that develop in baboon blood during storage are similar to those in human blood, whereas those in dog blood are smaller.<sup>48</sup> Transfusion of stored autologous baboon blood into an isolated perfused lung has been found to increase the pulmonary vascular resistance and lung water and to decrease arteriovenous oxygen gradients.<sup>14</sup> However, massive exchange transfusion with stored type-specific blood in unanesthetized baboons after a 2-hour period of severe hypotension did not cause alterations in arterial blood oxygenation within 1 hour.<sup>48</sup> These studies have shown that transfusion of stored blood causes alterations in primate pulmonary function and that an unanesthetized baboon can compensate for these effects immediately after the transfusion. The more chronic effects of massive transfusion on the intact baboon and the effects of the newer blood filters on the development of the abnormalities in the isolated lung model are currently under investigation.

The studies mentioned above show that considerable material is infused with stored blood; however, quantitation of this material has been difficult. The SFP method is sensitive to the adhesiveness, as well as the aggregation, of blood cells and platelets<sup>49</sup> and does not indicate the size distribution of the material that obstructs the 20  $\mu$  pores of the filter. Another method of quantitation of the material in stored blood consists of weighing the amount of material retained by a filter.<sup>18, 40, 43</sup> Moseley and Doty<sup>43</sup> placed a filter with the same pore size (170  $\mu$ ) in line with the standard clot filter and found that as much as 0.86 g of material per unit of blood was retained by the second filter. However, this method does not reflect the smaller particles that pass through both filters and yet may be large enough to occlude the microcirculation of the recipient. Many turbidimetric,<sup>50</sup> filtration,<sup>51</sup> and other<sup>52</sup> techniques have been developed for the study of platelet aggregation, but these methods are restricted to the study of aggregates in plasma and do not give quantitative information on the size and number of aggregates in whole blood.

To quantitate the material in stored blood more precisely, a method has been developed to measure the size and number of microaggregates in blood with a Coulter Counter (Model T, Coulter Electronics, Hialeah, Fla.).<sup>18, 31</sup> This instrument simultaneously measures the number or volume of particles in 15 different sizes, each twice that of the previous, to cover a size range of about 1-16,000 by volume. The principle of the measurement is similar to that of the Model B Coulter Counter and plotter.<sup>53</sup> The size range of particles measured with a 200  $\mu$  aperture is 3-80  $\mu$  in equivalent spherical diameter (or 24-388,700  $\mu$  by volume), and with the 400  $\mu$  aperture, 8-161  $\mu$ . The operation of the instrument and analysis of the data are described in detail elsewhere.<sup>18, 31</sup> Figure 1 shows the size distribution of particles in fresh blood immediately after being drawn into acid-citrate-dextrose (ACD) and after 14 and 21 days of storage at 4° C. In this figure, the cumulative

number of particles of each size is plotted against the particle size in microns. There was a significant increase in the number of particles of each size by the fourteenth day of storage. During the third week of storage, the number of larger particles increased, and the number of smaller particles remained relatively constant.

The physical characteristics of the microaggregates in stored blood differ markedly from those of platelet aggregates induced in fresh blood. This can be seen in Figure 2, where the cumulative number of particles 32-80  $\mu$  in size in either stored blood or fresh blood containing platelet aggregates induced by adenosine diphosphate (ADP) is plotted. Each analysis was begun 30 seconds after dilution of the blood in saline that contained increasing concentrations of saponin. The concentrations of platelet aggregates in this size range in fresh blood and of the

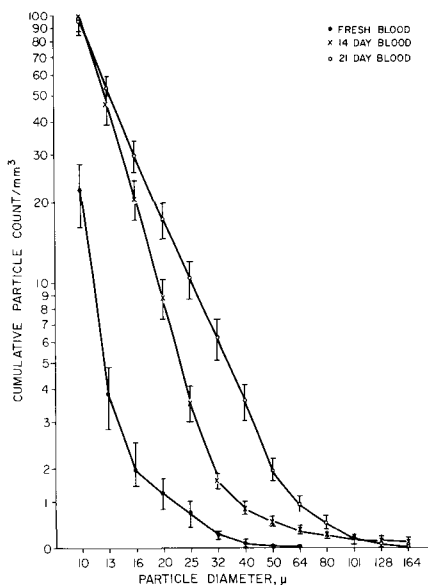


FIGURE 1.

Cumulative number of particles per cubic millimeter of blood plotted on log scale against particle size in microns in 8 units of human blood immediately after drawing into ACD plastic bags and after 14 and 21 days of storage at 4° C. Analysis was performed in 120 sec. after dilution in saline containing saponin (200 mg./100 ml).

microaggregates in stored blood with saponin (50 mg/100 ml) were not significantly different. However, as the saponin content increased, the concentration of platelet aggregates in the fresh blood progressively decreased. This is in contrast to the concentration of microaggregates in stored blood, which remained relatively constant. Similar studies have shown that, by 120 seconds after dilution, platelet aggregates completely deaggregate when the saponin content is 50 mg/100 ml, whereas the microaggregates in stored blood remain relatively stable.<sup>21</sup> These results indicate that the microaggregates in stored blood are more tightly bound than are the acutely induced platelet aggregates and would presumably be more damaging to the tissue to which they embolize.

Ultrastructural examination of ACD-anticoagulated blood shows that, during the first few days of storage at 4° C, only platelet aggregates are present, but that, later in storage, granulocytes begin to stick to each other and to the platelets to form microaggregates consisting of platelets, granulocytes, and the nuclear material of decomposed granulocytes.<sup>54</sup> Fibrin, lymphocytes, and red cells do not contribute to the formation of these particles.<sup>54</sup> These findings agree with the results of quantitative studies of various components of blood—such as platelet-poor and platelet-rich plasma, the buffy coat, and saline-washed red cells—which show that both platelets and white cells must be present for microaggregates to form.<sup>55</sup> These studies confirm earlier work using microscopy and special staining techniques, which described the clumping of platelets and white cells during storage.<sup>16, 56</sup>

Many factors undoubtedly affect the extent of microaggregate formation.

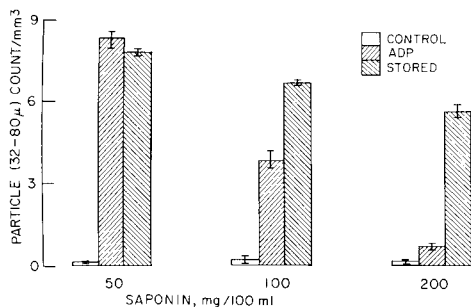


FIGURE 2.

Effect of increasing the saponin concentration in the saline diluent on the cumulative number of particles 32-80  $\mu$  in size per cubic millimeter of blood measured 30 sec. after dilution of (1) stored blood, (2) fresh sodium-citrated (0.32%) whole human blood 1 min. after adding ADP in saline ( $2 \times 10^{-6}$  M), and (3) fresh citrated blood (control) 1 min. after adding an equal volume of saline without ADP to blood (1:10).

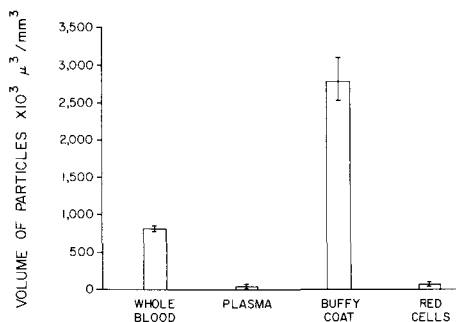


FIGURE 3.

FIGURE 3.

Volume of particles 13-80  $\mu$  in size per cubic millimeter in aliquots of ACD-stored human blood before and in plasma, buffy coat, and red-cell layers after centrifugation at 2,000 g for 5 min. (n = 5).

Among these are the technique with which the blood was drawn, the recent medical and drug history of the donor, and the conditions of storage. The extent of the formation of the microaggregates can be altered by the anticoagulant used or by pretreatment of the blood. For example, blood drawn into heparin or citrate-phosphate-dextrose develops more platelet aggregates than that in ACD,<sup>55, 57</sup> and treatment of blood with prostaglandin E<sub>1</sub> reduces the formation of aggregates and improves the recovery of platelets early in storage.<sup>58</sup>

Microaggregates can be removed from blood by means other than filtration. During storage, the microaggregates settle into both the red-cell and the buffy coat layers of the blood bag, with the buffy coat containing the larger microaggregates.<sup>55</sup> After centrifugation, the microaggregates settle exclusively into the buffy coat (Figure 3), indicating that these particles have a density similar to that of platelets and white cells. The buffy coat can then be removed to render the red cells and plasma relatively free of the microaggregates.<sup>16, 55</sup> Because of their markedly adhesive nature, resuspension of blood after centrifugation results in a change in the size distribution of the microaggregates, such that those smaller than 100  $\mu$ , which would ordinarily pass through the standard clot filter, aggregate to form larger particles that can then be effectively removed by the 170 pore mesh.<sup>18</sup> Another method of removing the particles is to wash the blood. Figure 4 shows that the volume of particles in stored blood can be markedly reduced by washing the red cells with saline. Similar results were obtained with fresh and 21-day-old ACD human blood after being frozen, thawed, and deglycerolized.<sup>59</sup>

Although the above methods of removing microaggregates from stored blood are effective, the simplest means of removal is by filtration with one of the recently developed blood filters.<sup>18, 19, 66</sup> Previous studies<sup>18</sup> with the particle size analyzer have shown that the standard clot mesh filter with 170  $\mu$  pores cannot remove particles smaller than 80  $\mu$  from stored blood. Figure 5 shows particle measurements of eight units of stored blood before and after passage through the newer blood filters. The 40  $\mu$  pore filter, which contains a large surface of polyester mesh with 40  $\mu$  pores,<sup>60</sup> removed virtually all particles larger than 32  $\mu$  in size, but most of the smaller particles were not removed. The size distribution of the particles in blood after passage through the foam filter, which contains three layers of polyurethane foam with decreasing pore sizes (150, 75, and 30  $\mu$ ), was similar to that after passage

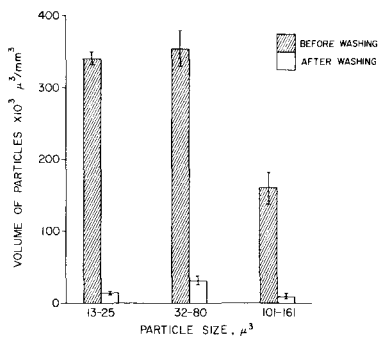


FIGURE 4.

Effect of washing aliquots from a unit of stored blood three times with equal volumes of saline after centrifugation for 5 min. at 650 g. Hematocrit: 41% before, 68% after washing (n = 8).

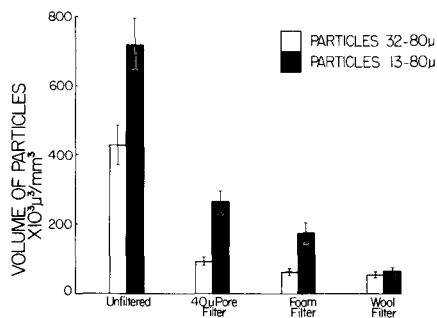


FIGURE 5.

FIGURE 5.

Volume of particles in 8 units of whole human blood stored 21-27 days in ACD before and in 100 ml aliquots after passage through (1) A 40 μ pore mesh filter (Ultipore, Pall Corporation, Glen Cove, N.Y.), (2) Polyurethane foam filter (PF 127, Bentley Laboratories, Santa Ana, Ca.) and (3) Dacron wool filter (Pioneer Filters, Hillsboro, Or.).

through the 40 μ pore filter. The Dacron wool filter, however, removed microaggregates of all sizes larger than 13 μ.

The mechanisms by which the new filters remove particles from blood differ. Dacron wool is a depth filter that functions by providing a large surface to which particles may stick, and its efficiency is determined by the adhesiveness of the particles being filtered. This is illustrated by the fact that the relatively nonadhesive platelets and white cells in fresh ACD blood are not removed, whereas, those present after 14 days of storage, which are more adhesive, are filtered by Dacron-wool.<sup>18</sup> However, the efficiency of the 40 μ pore mesh surface filter is determined by the relation between the size of the pores and the size of the particles being filtered. There is evidence that it may also be determined by the binding forces that hold the particles together. For example, the 40 μ pore filter completely removes pecan pollen (40 μ) and significantly lowers the concentration of 32 to 80 μ microaggregates in stored blood. However, platelet aggregates of this same size formed *in vivo* during hemostasis or after infusion of ADP are not removed by this filter.<sup>21</sup> This evidence indicates that platelet aggregates larger than 40 μ break up at the surface of the 40 μ pore mesh and reform after filtration. The foam filter removed particles larger than 32 μ but was less efficient in removal of particles that were smaller (Figure 5). This suggests that the foam removes particles as a result of the size of the smallest pore of the foam elements rather than by providing a large surface to which adhesive particles will stick.

Clinical experience with the use of the more effective blood transfusion filters has been limited. In a study of traumatized patients receiving more than 10 units of stored blood,<sup>15</sup> Ruel et al. noted a lower incidence of pulmonary insufficiency in a group of patients who received blood administered through the 40 μ pore mesh filter than in a group whose blood was administered through the standard mesh clot filter with 170 μ pores. In addition, lung biopsies obtained from the two groups of patients revealed ultrastructural lesions similar to those described by Connell and Swank in experimental animals,<sup>11</sup> which were not present in patients whose blood has been effectively filtered. Although these studies suggest that intravenous infusion of the microaggregates in stored blood may cause lung injury in man, the clinical situations which would require the use of the newer filters remain to be determined. This is because the lung has a great filtering capacity and many patients have received large quantities of blood without significant pulmonary complications. However, in situations such as cardiopulmonary bypass,

where all infused microemboli would enter the systemic circulation prior to filtration by the lungs, the most effective filter should probably be used.

## BLOOD FILTRATION DURING CARDIOPULMONARY BYPASS

The major source of microembolization during cardiopulmonary bypass is thought to result from infusion of particulate material in coronary suction blood and from induction of air bubbles and/or platelet aggregates in blood by bubble oxygenation.<sup>1, 2, 4, 7, 8, 23, 27-29</sup> *In vitro* studies have demonstrated that maintenance of a blood-gas interface causes platelet aggregation and a reduction in platelet counts.<sup>3, 8, 10, 24, 61</sup> However, the relevance of these studies to microembolic phenomena in man is not clear. In order to quantitate the extent of particulate microembolization, the volume of particles 13 to 80  $\mu$  in size was measured in the blood of patients undergoing cardiopulmonary bypass.<sup>31</sup> The gradient of particles in blood on passage through the bubble oxygenator was small and could be detected only during the first 10 minutes on bypass. In contrast, the volume of particles in coronary suction blood was several times greater and persisted throughout the procedure. The physical characteristics of the microemboli in coronary suction blood differed from those of platelet aggregates which could be induced *in vitro* in the arterial blood of the patients by ADP in that they were more resistant to deaggregation *in vitro* and a greater percentage floated into the plasma after centrifugation. This indicated that the microemboli were more firmly held together and consisted, in part, of lipid material.

Since the coronary suction blood contained the greatest concentration of microemboli, the ability of three commercially available in-line blood filters to remove these particles was determined.<sup>31</sup> The Dacron wool filter (CA 100, Pioneer Filters) was most effective, removing 89% of the microemboli, while a polyurethane foam (Polyfilter, Bentley Laboratories) and a 40  $\mu$  pore mesh (Barrier, Johnson & Johnson) removed 64 and 58% respectively.<sup>31</sup> The size distribution measurements indicated that the Dacron wool filter removed all particles larger than 13  $\mu$ , while the other two filters were most effective in removing particles larger than 32  $\mu$ .

Although an extensive literature exists documenting the adverse effects of particulate microembolization in experimental animals, few clinical studies have been performed. Dacron wool filtration of coronary suction<sup>5</sup> and arterial line blood<sup>6</sup> has been shown to reduce the incidence of cerebral non-fat microemboli and to reduce mortality. The 40  $\mu$  pore filter has been shown to improve the psychological performance of post-operative cardiac surgical patients;<sup>62</sup> however, objective improvement in neurological findings has not been noted.<sup>63</sup> Dacron wool filtration of the stored blood and the cardiotomy return blood infused into patients prevents the pulmonary ultrastructural changes which occur during cardiopulmonary bypass,<sup>22</sup> while arterial filtration does not significantly improve the results.

The considerations reviewed above indicate that effective filtration of autologous and homologous blood infused into patients undergoing cardiopulmonary bypass would reduce most of the microembolization. The major complication resulting from *in vivo* Dacron wool filtration is thrombocytopenia.<sup>5</sup> In considering filtration of stored blood, however, loss of platelets or white cells is of less concern because of their poor viability, even after a short period of storage.<sup>56, 64</sup> Clinical studies have shown that no significant changes in platelet counts were noted post-operatively after filtration of coronary suction blood with either the 40  $\mu$  pore mesh or the Dacron wool in-line filters when compared to a group of patients whose blood was not filtered.<sup>65</sup>

Although effective filtration of coronary suction blood seems indicated no controlled clinical studies have been reported to determine which system of blood filtration is most effective. Since the harmful effects of cerebral air embolization

may be prevented by arterial filtration,<sup>4</sup> an arterial filter may be needed. In addition to the site of filtration, the type of filter required also needs to be evaluated. The Dacron wool filter is most effective in removing the microemboli smaller than 32  $\mu$  and presumably would be most effective clinically. However, this is based upon the assumption that the smaller particles are damaging to tissue. Stored canine blood contains few microemboli larger than 32  $\mu$ ,<sup>48</sup> yet most of the experimental evidence demonstrating the adverse effects of microembolization have been performed using dogs.<sup>4, 8, 11, 12, 13, 25, 45, 46</sup> This suggests that the smaller particles may be harmful, but clinical comparisons of the various filters are needed to determine their efficacy in man.

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