
LECTURE

Ultrafiltration versus Cell Washing for Blood Concentration

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History of Autologous Blood Use

The concept of using the patient as his own blood donor is more than 100 years old. Autotransfusion was used sporadically in the past as an emergency measure when the patient's life was in danger due to sudden massive hemorrhage and lack of donor blood supply.

Autotransfusion is essentially credited to an English obstetrician/surgeon, Dr. James Blundell. In 1818, Dr. Blundell published research work done in his dog laboratory which suggested that autotransfusion might be a way of replenishing a patient's necessary blood volume (1). Interestingly, Dr. Blundell did not actually do any clinical autotransfusion cases. Instead, he is known for his work with homologous transfusion on his obstetrics patients. Most of his patients were wealthy and were brought to the hospital by a coachman. If bleeding became severe during labor and delivery and the patient became hypovolemic, Dr. Blundell would bring the coachman in and lacerate his brachial artery. He then collected the blood in a funnel, and syringed this blood back into the patient.

It was not until 1864 that Dr. John Duncan autotransfused about 50 ccs of blood from an amputated limb back into a patient. He based his clinical procedure on Dr. Blundell's work. The results of this procedure were published in a British medical journal two years later (2).

In the late 1800's, Dr. James Highmore, an English surgeon, advocated the use of intraoperative autotransfusion in cases of postpartum hemorrhage. He suggested that a patient's shed blood was an overlooked source that could be used to great advantage. This article appeared in the *Lancet* in 1874 (3). As a result of the large-scale use of banked donor blood, development of autotransfusion for use as a routine procedure has been neglected. A rapid rise in the use of donor transfusions came after Landsteiner's discovery of the ABO blood groups in 1900 and the development of adequate anticoagulant and preservative agents. The first blood bank was established in the United States by Lundy in 1935 at the Mayo Clinic (4).

Following World War II, problems with blood supplies such as availability and storage gave impetus to the development of many large civilian blood banks. This also brought about new techniques of storage and use of blood and its derivatives. These techniques became well established during the post war

years. During the ensuing 30 years, large amounts of data were accumulated regarding the use of banked blood and its complications. Many serious complications such as febrile or allergic reactions, circulatory overload, hemolytic reactions, and even cardiac arrest have been recorded. It is estimated that approximately one in 200 donors is a carrier of the hepatitis B virus. The incidence of hepatitis Non-A, Non-B can be as high as 1 in 10, according to some sources (5).

Only in the last two decades has interest in autotransfusion as a viable medical technique become intense. The Korean and Vietnam wars placed high demands on the blood donor pool. In addition, expanding surgical technologies such as open heart and orthopedic surgery further depleted the blood bank reserves. In the early 1980's when the AIDS virus was identified, public panic resulted in a decrease in blood donations, further adding to donor blood shortages.

The severe shortages during the Vietnam War stimulated military surgeons, such as Dr. Gerald Klebanoff, to develop autotransfusion equipment that would salvage blood for reinfusion (6). One of Klebanoff's machines was introduced commercially by Bentley Laboratories in the late 1960's. This first attempt to modernize autologous blood recovery in the late 1960's and early 1970's was effective but technically unsophisticated. These first units were plagued with problems of poor blood quality, damaged cells, risk of infection, coagulopathies, and air embolism. In addition, these first units required highly trained operators who had to devote their full attention to operating the equipment. Other significant problems associated with these early autotransfusion procedures such as the returned red blood cells not being as clean as they needed to be presented the danger of negative side effects. These problems prevented the growth of autotransfusion until appropriate washing techniques were developed in the mid 1970's.

History of Centrifugal Cell Washing

In 1975, Haemonetics Corporation introduced its first centrifugal cell washing system, the Cell Saver™ (7). The term Cell Saver™ is a registered trademark of Haemonetics Incorporated; however, the process of washing red cells has been referred to by many terms such as cell washing, cell processing, hemoconcentration, red cell washing, autotransfusion and IAT (Intraoperative AutoTransfusion). These terms may all be used interchangeably. Within the next several years, other companies introduced similar centrifuge-

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type, red cell washing systems. These first units still required close operator attention and in many cases, the blood salvage rate was not fast enough to keep up with reinfusion needs of the patient. In the late 1970's and early 1980's, the development and introduction of computerized autotransfusion models requiring less operator intervention, improved reliability, and a cleaner end product, brought a renewed interest in autotransfusion. The increasing problems of infection with hepatitis and AIDS, a decreasing blood supply, and increased cost of processing donor blood have also contributed to the increased interest in cell washing and autologous blood usage.

History of Ultrafiltration

The first reported use of ultrafiltration was in 1929 when Brull connected an ultrafilter, made of filter paper and collodion, in-line in the internal carotid artery of a dog (8). In the 1970's ultrafiltration began to gain popularity for the removal of excess plasma water in conjunction with renal dialysis, or as an alternative to it. Romagnoli and associates reported on the first use of ultrafiltration to concentrate the blood remaining in the heart-lung machine in 1976 (9). The study reported that 700 cc's of blood with a mean hematocrit of 21% was ultrafiltered for 11 minutes, producing a final hematocrit of 31%. Over the past 14 years there have been many papers reporting the use of ultrafiltration in combination with cardiopulmonary bypass or with dialysis (10, 11, 12, 13, 14). Most studies report significant increases in hematocrit levels as well as a decrease in the positive fluid balance associated with CPB when compared to cases not utilizing ultrafiltration.

Basic Theory of Operation

The discussion of hemofiltration and/or centrifugal hemoconcentration in this paper is related mainly to their use during cardiac procedures involving cardiopulmonary bypass (CPB). Basically, we are considering the three phases of cardiac surgery: the pre-pump phase or that period prior to going on cardiopulmonary bypass, the actual bypass phase where the patient is on the heart lung machine, and the post-bypass phase, both in the operating room and the recovery room.

The relative function of these two types of blood concentration methods is discussed below.

Centrifugal Cell Washing

The collected blood is pumped from a collection reservoir into a spinning centrifuge bowl where the cellular components begin to separate into vertical layers which lie parallel to the axis of rotation in the centrifuge bowl. The outermost layer is composed of erythrocytes (red blood cells) and is separated from the lightest component (plasma) by the leukocyte/platelet layer (known as the "buffy coat"). As blood continues to enter the bowl, the amassing red cell pack begins to occupy more of the bowl volume. The excess plasma is pushed ahead of the advancing front of red blood cells and buffy coat layers, toward the center of the bowl. When the total volume of the bowl has been exceeded, the excess plasma is expressed from the bowl by continued cellular accumulation within the bowl. This "waste"

plasma is forced from the bowl through the exit port, on the upper central portion of the bowl, into the waste bag via connecting tubing. After the red cell pack has been isolated from the plasma and other cellular material, a saline solution is pumped into the red cell pack to free it from any traces of contaminating plasma and debris. After washing is complete, the resultant red cell pack is pumped into a holding bag for later transfusion to the patient. A schematic of the equipment and disposables utilized in a typical centrifugal cell washing system is shown in Figure 1. A summary of the advantages and disadvantages of centrifugal cell washing systems is shown in Table 1.

Ultrafiltration

The process of ultrafiltration utilizes a small, disposable ultrafilter which may be used during bypass and with some limitations, before or after bypass. Ultrafiltration has been referred to by many terms such as hemofiltration, hemo-ultrafiltration, diafiltration, or hemodiafiltration. All of these terms usually refer to the same thing, which is the concentration of blood utilizing an artificial kidney-type device. These terms may be used interchangeably.

One advantage of the ultrafiltration technique is that the operator has control over the rate and quantity of plasma water removed. A second advantage is that the ultrafilter can increase not only the concentration of red blood cells but that of other elements that are washed out in the centrifugation concentration process. One possible disadvantage of ultrafiltration is that usually a hemofilter needs to be operated by a perfusionist or someone experienced in extracorporeal circuits and familiar with hemofiltration techniques (15). Another disadvantage is that some ultrafiltration devices are packed in a glycerin compound to maintain fiber moisture during storage. This glycerin must be rinsed and discarded with at least 500 cc's of normal saline prior to use. Some perfusionists have reported that even a liter of saline rinse is not sufficient to prevent potential hemolysis and recommend using up to 2000 cc's of rinse solution (16). In any case, failure to rinse sufficiently may result in severe hemolysis with secondary acute renal failure.

The blood for ultrafiltration can be removed from either the venous or arterial source on the bypass circuit. Usually a venous source is not recommended because air bubbles may be in the venous blood and may obstruct some of the fibers in hollow fiber type devices. Also, in some bypass situations, venous pressure may become too low, making blood withdrawal difficult or impossible. Arterial blood may be obtained from the coronary perfusion port of the oxygenator or from a connector placed in the arterial tubing between the oxygenator and the arterial pump head. The problem with this technique is that it requires an additional pump head to move the blood through the hemoconcentrator. Connecting the hemoconcentrator blood withdrawal line to the outlet port on the arterial filter works well and requires no additional pump head for the hemoconcentration procedure. The arterial pump head must be in operation, however, for blood to be supplied to the hemoconcentrator for processing. In addition, the operator

Figure 1

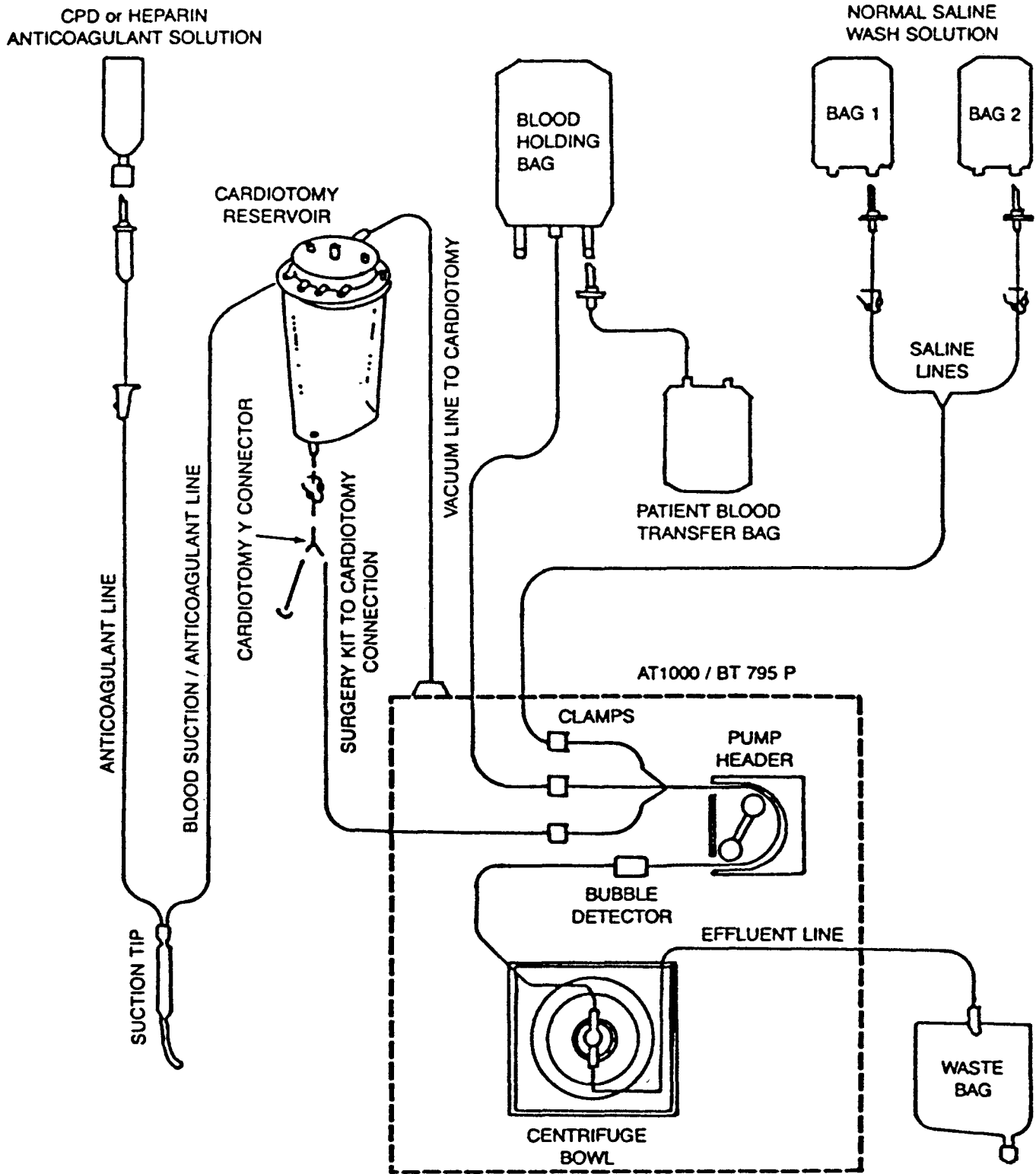


Figure 2

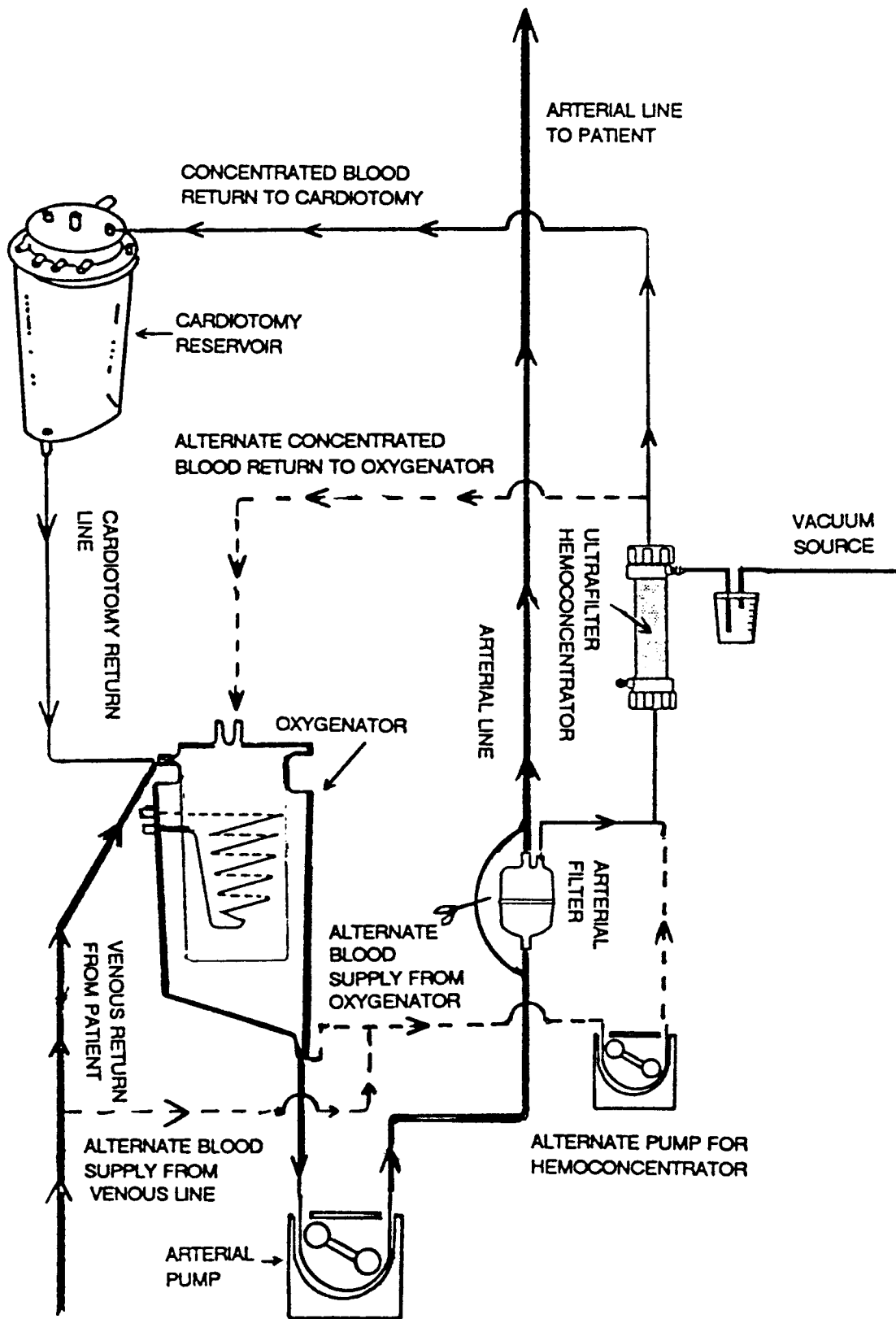


Table I

CENTRIFUGAL CELL WASHING

The **ADVANTAGES** of centrifugal washing are:

1. Thorough cleansing of debris from the red cells.
2. Removal of anticoagulants.
3. High concentration of red cells (hematocrits in the range of 60-80%).
4. Automated processing models require only minimum operator time and intervention and can be operated by non-perfusionist personnel.
5. Can be utilized on blood collected outside of the CPB system, i.e. blood suctioned from the wound or drainage device.

The **DISADVANTAGES** of centrifugal washing are:

1. Discards noncellular blood components such as proteins and coagulation factors.
 2. Removes platelets.
 3. Separate console with centrifuge equipment is required.
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Table II

ULTRAFILTRATION HEMOCONCENTRATION

The **ADVANTAGES** of Ultrafiltration are:

1. Removal of plasma water without removing plasma proteins, clotting factors, platelets, etc.
2. Small and compact. Can be added to the existing pump circuit with some additional tubing and connectors.

The **DISADVANTAGES** of Ultrafiltration are:

1. Must be utilized on uncontaminated blood from the CPB system or from blood obtained in a closed loop.
 2. More operator intense. Requires more background and knowledge to set up and operate. Usually a hemofilter would be operated by a perfusionist who should be familiar with the hemofilter techniques.
 3. Removal of plasma water only; no removal of any biochemical debris such as activated coagulation factors and activated complement proteins.
 4. Failure to remove any physical debris not previously filtered from the blood.
 5. Due to various connections required, there may be an increased risk of circuit contamination.
 6. Some hemofiltration devices are packed in glycerin compound to maintain fiber moisture during storage. These units must be rinsed with 500 cc's or more of saline which must be discarded prior to use. This further increases the possibility of contamination.
 7. Rebound hyperkalemia has been reported on cases where large amounts of blood were processed. Therefore, serial potassium levels should be closely monitored.
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Table III

REASONS FOR USE OF ULTRAFILTRATION

1. Controlling excess hemodilution from large volumes of cardioplegia or other crystalloid solutions which would result in massive quantities (<2000 cc's) of blood being processed from the oxygenator circuit, resulting in the loss of significant plasma volume if centrifugal cell washing is used.
 2. Pre- or peri-pump oliguria (the production of an abnormally small volume of urine) or anuria (failure of the kidneys to produce urine).
 3. Acute/Chronic renal failure.
 4. Known blood toxemia.
 5. Preoperative pulmonary edema.
 6. Clinical evidence of excess extravascular body or lung water either pre-bypass or during bypass.
 7. Prevention of excess fluid balance in patients who are on bypass longer than two hours.
 8. Controlling the concentration of serum potassium.
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should place a clamp between the filter and the hemoconcentrator to avoid backflow when the pump is turned off. Some users recommend when utilizing a hollow fiber ultrafilter, once the fibers have been exposed to blood flow, blood flow should be maintained through the ultrafilter fibers (17).

Processed blood may be returned from the hemoconcentrator to any of the many available connector sites on the cardiomy reservoir. Blood may be returned to the priming port on the oxygenator, but this may create bubbles, foam, poor mixing, and increased hemolysis. Blood should not be returned to the patient via an arterial source because of the risk of air emboli. Hemoconcentrated blood may be returned on the venous side of the circuit. The operator must keep in mind that when the blood reservoir is positioned higher than the ultrafiltration device, the outflow resistance from the hemoconcentrator may increase, causing an increase in the transmembrane pressure and reducing the ultrafiltration rate. Ultrafiltration depends on blood flow and transmembrane pressure, both of which can be precisely controlled. A diagram showing the circuit connections discussed above and their alternatives is shown in Figure 2 and a summary of advantages and disadvantages is outlined in Table 2.

Discussion

Both centrifugation and ultrafiltration achieve hemoconcentration. The difference is that the centrifugal method removes the plasma and all its contents such as proteins, clotting factors, platelets, etc. The ultrafiltration hemoconcentration method with an artificial kidney retains this plasma fraction along with the red cells.

Normally, diuresis will offset the fluid administration and will control the concentration of blood components during cardiopulmonary bypass. When natural diuresis is inadequate, it can be supplemented by diuretic drugs. Many times the clinician may find that drug-induced diuresis is still not adequate, especially in view of the large additions of crystalloid cardioplegia used in some cardiac cases or in patients with renal insufficiency (18). During diuresis, plasma water is extracted by the patient's kidneys; however, the rate of removal is not easily controlled, and potassium loss may intensify or aggravate any cardiac rhythm disturbances. By using ultrafiltration, the operator can control the rate and quantity of plasma water removed while conserving plasma proteins (19).

The most frequently reported application for ultrafiltration hemoconcentration is in cardiac surgery. Following cardiopulmonary bypass, some patients develop normovolemic anemia. A patient with normovolemic anemia cannot withstand large quantities of fluid additions. Therefore, it is necessary to process (hemoconcentrate) the residual pump blood. This blood usually has a low hematocrit and must be hemoconcentrated to remove the excess water and condense the red cells. Red cells may then be returned to the patient without creating a circulatory overload condition (20).

During cardiopulmonary bypass, incorporating normal amounts of hemodilution blood components are diluted between

35 and 45%. The plasma proteins serve several physiological purposes. Some plasma proteins serve as clotting factors. Other plasma proteins are involved in maintaining the colloid osmotic pressure (COP) which helps to control fluid distribution in the body. A decrease in these plasma proteins may lead to third spacing.

When first looking at these two methods of hemoconcentration, it appears that ultrafiltration produces a larger volume of processed blood. This is, however, only an illusion since the ultrafiltration process produces a whole blood product with a hematocrit of approximately 35-40%. The centrifugal hemoconcentration process, on the other hand, produces packed red blood cells suspended in saline with a hematocrit in the 60 to 80% range. Some perfusionists find that it is easier to recover the residual volumes from the oxygenator circuit utilizing a centrifugal type of device rather than an ultrafiltration artificial kidney device (21).

One of the main concerns with centrifugal hemoconcentration deals with the loss of the plasma segment of the blood. Regardless of this theoretical concern, studies have shown that despite the loss of significant amounts of protein in the centrifugal cell washing process, (32.96 ± 2.95 grams), there was no significant difference between patients treated with the centrifugal cell washing process and those treated with ultrafiltration (22). In the two groups presented in this study (centrifugal hemoconcentration versus ultrafiltration), there was no significant difference in either the plasma protein concentration or the colloid osmotic pressure following transfusion of the processed blood. There was also no significant difference between groups in coagulation test data.

Three other valid items of concern were brought out in this study. The first was that the extra tubing, connectors, adapters, and blood bags required in the assembly of the ultrafilter circuit could increase the possibility of contamination. The second item mentioned was that since heparin does not cross the ultrafilter membrane, there is a potential for concentration of heparin via the ultrafiltration system. Therefore, in patients who are anticoagulated with heparin, the coagulation system should be closely monitored and protamine administered as required (23). The last point mentioned was the possible concentration of free hemoglobin via ultrafiltration. The author stated, "If a patient had an abnormally high plasma free hemoglobin following CPB, the potential for renal damage does exist if concentrated hemoglobin is transfused." This possibility of renal sequela following the infusion of concentrated plasma hemoglobin has been documented in a recent article which reported two patients who suffered renal dysfunction following infusion of blood that had a high hemolysis level (24).

Which is the Best Method?

The primary advantage of ultrafiltration is the preservation of the plasma proteins with the red blood cells during concentration. This helps maintain the colloid osmotic pressure and should help reduce third spacing. The primary disadvantage to ultrafiltration is that the contaminants (activated platelets, activated coagulation factors, free plasma hemoglobin, activated

complement, toxins, etc.) contained in blood salvaged from the surgical site are not removed, but returned to the patient (possibly concentrated) in the processed blood plasma (25). This precludes the use of ultrafiltration, except in a closed loop situation, such as cardiac surgery with the bypass pump.

The primary advantage of centrifugal cell washing is the complete cleansing of red cells from any contaminants such as activated platelets, activated coagulation factors, free plasma hemoglobin, activated complement, toxins, topical hemostatic agents, bone chips, metal fragments, antibiotic solutions, fibrin strands, red cell stroma (ghost) and enzymes (26). The primary disadvantage to centrifugal cell washing is the removal of the plasma proteins, platelets, and coagulation factors.

In low or moderate volume processing situations (500-1000 cc's) the loss of plasma proteins has not proven to be of significant consequence. It is acknowledged that in cases of large blood loss (35-40 % of the patient's blood volume) during trauma or intraoperative salvage in a difficult case, that homologous platelets and plasma containing coagulation factors and other proteins must be given to compensate for the loss of these components during centrifugal hemoconcentration (27). On the other hand, in high volume blood loss cases, the processing speed of the centrifugal system becomes a distinct advantage. An ultrafiltration system takes approximately 30 to 35 minutes to process 1800 cc's of blood with an initial hematocrit of 22-25% to a concentrated hematocrit of 40-45% (28). Another study utilizing an Amicon™ hollow fiber Diafilter™ reported the average ultrafiltration rate to be in the range of 31 ± 11.5 ml/min (range 5-85 ml/min) (29). At this rate it could take as long as 58 minutes to process the 1800 cc's of blood. A high speed centrifugal concentration system can process the same blood to a hematocrit of 60% in less than four minutes. In a high volume bleeding situation (200 cc's per minute or more), the ultrafiltration system would be of questionable value. In addition, if the blood loss is from a surgical wound, the ultrafiltration process should not be used in view of the contamination factors in the plasma mentioned above. This would logically limit the use of ultrafiltration to cardiac surgery cases or cases where blood could be obtained via an arteriovenous closed loop source.

The above facts suggest that the ideal situation for the use of ultrafiltration would be in the cardiac surgery patient as evidenced by the volume of literature available. The most effective situation for the patient would be to utilize BOTH methods of hemoconcentration. The centrifugal cell washing system could be set up and used during the pre-bypass period for collection of blood from the wound. During cardiopulmonary bypass the ultrafiltration method could be utilized in the bypass loop for the removal of excess water while maintaining the plasma proteins in the system. Following cardiopulmonary bypass, the excess pump volumes could be processed with either system basing the decision on the volumes involved, the need for returning the plasma proteins, and the time available for convenient processing in the operating room. Blood lost from the operative field should be collected and processed with the cell washing system. In the recovery room,

the blood collected in the chest drainage system should be processed with the cell washing unit as it is collected.

Unfortunately, in the cost-conscious atmosphere of today's medical systems, the expense of setting up both units simultaneously for an average case is usually prohibitive. Since the cell washing system can be utilized for operative wound blood salvaging, processing of excess pump volumes, and post-operative wound drainage cleansing, it would seem that this would be the most economical system to use for the average patient.

There are certain conditions under which the clinician should set up and utilize the ultrafilter during cardiopulmonary bypass even if the cell washer is used pre-and post-operatively. These conditions are outlined in Table 3.

Conclusion

Both hemoconcentration methods have been reported to be effective. The centrifugation technique offers flexibility for washing blood in all phases of blood collection, surgical wounds, excess pump volumes and postoperative drainage. This factor and the adaptability of centrifugal cell washing to all types of surgical procedures, make it the logical first choice hemoconcentration technique.

The ultrafiltration concentration method seems best suited to use in cardiac surgery cases (or in other cases where a closed blood loop system can be set up) and where there is an experienced perfusionist/operator trained in the use of ultrafiltration hemoconcentration. The ultrafiltration hemoconcentration technique should be utilized in patients who exhibit problems with excess hemodilution from large volumes of cardioplegia or other crystalloid solutions, pre- or peri-pump oliguria or anuria, acute or chronic renal failure, blood toxemias, etc. In these types of cases, the need for ultrafiltration is clearly documented (30, 31, 32, 33).

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