Correction of Hyperviscosity by Apheresis

Mirjana Zarkovic, M.D., Ph.D.,1,2 and Hau C. Kwaan, M.D., Ph.D.2

ABSTRACT

Therapeutic apheresis is an extracorporeal blood purification technique designed for the removal of either plasma (plasmapheresis) or cellular blood components (cytapheresis). One of the main indications for the use of apheresis is in the treatment of the hyperviscosity syndromes that can result from either the presence of abnormal plasma components, such as antibodies, immune complexes, paraproteins, and cryoglobulins, or the excessive increase in blood cells as seen in polycythemia, leukemias, and myeloproliferative diseases. Apheresis involves withdrawal of anticoagulated blood via a vascular catheter, separation of different blood components by either centrifugation or membrane filtration, removal of the undesired component, and reinfusion of the remaining components with replacement fluid into the patient. The centrifugal method can be intermittent or continuous, the latter being faster and fully automated, and is principally used in North America. The membrane filtration technique, mainly used in Europe and Japan, involves the filtration of blood by filters of different pore sizes. These are used sequentially in a process called double or cascade filtration, enabling removal of specific plasma pathogens without need for replacement fluids. In paraproteinemias, hyperviscosity syndrome is most commonly seen with Waldenström's macroglobulinemia, followed by immunoglobulin (Ig) A and IgG, multiple myeloma. Single plasmapheresis with one plasma volume replacement (about 3 L) usually results in a dramatic improvement in patients with macroglobulinemia because of its predominant intravascular distribution, whereas repeated plasmapheresis is necessary with other types of paraproteins. Cryofiltration apheresis using a high-capacity cryofilter is specific for the removal of cryoglobulins. In leukemias with hyperleukocytosis, there are no evidence-based guidelines for use of leukapheresis, but it is commonly initiated when white blood cells (WBC) are > 100,000/μL or even with lower counts if leukostasis symptoms are present, especially in acute myeloid leukemia. Erythrocytapheresis and plateletpheresis are mostly used in the acute management of symptomatic patients with polycythemia vera (PV), essential thrombocytosis, and sickle cell disease.

KEYWORDS: Plasmapheresis, leukapheresis, plateletpheresis, erythrocytapheresis, hyperviscosity

Objectives: On completion of this article, the reader should (1) understand the principles of apheresis and the different techniques currently in use, and (2) know its application in the management of different hyperviscosity syndromes as seen in paraproteinemias, cryoglobulinemias, leukemias, and myeloproliferative diseases.

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The management of the various syndromes associated with hyperviscosity, discussed elsewhere in this issue, is aimed at the removal of the causative factor in each syndrome. The therapeutic approach is generally directed at treatment of the specific underlying pathologic lesion. Thus, for example, cyto reducitive therapy would be used to reduce the excessive circulating blood cells in PV and in leukemia, whereas chemotherapy directed at the plasma cells would control the hyperviscosity due to excessive paraproteins. However, this process requires days to accomplish its objective. In the meantime, the hyperviscosity may be either symptomatic or may be abnormally high to pose an immediate threat of thromboembolic complications. Under these circumstances, the offending component in the blood can be removed by therapeutic apheresis (derived from the Greek word "aφαίρεσις" aphairesis, meaning removal).

Therapeutic apheresis is an extracorporeal blood purification technique designed for the removal of certain pathogenic blood components, either cells (cytapheresis) or plasma (plasmapheresis) that are directly responsible for the disease process. Cytapheresis can be further categorized into leukapheresis, in which leukocytes are depleted; plateletpheresis; and erythrocytapheresis. A variety of plasma pathogens can be removed by plasmapheresis, including antibodies, immune complexes, paraproteins, cryoglobulins, toxins, lipoproteins, and so on.

**PRINCIPLES OF THERAPEUTIC APHERESIS**

Apheresis involves the withdrawal of anticoagulated venous blood from the body via a rigid tubing system under negative pressure. By a system of either centrifugation or membrane filtration, plasma is separated from the blood cells. Theundesired component present in plasma or the excessive or abnormal cellular fraction is then removed and the remaining portion is returned to the patient. If a significant volume is removed, as in the case of plasmapheresis and in some cases of cytapheresis, the blood volume will be depleted. Replacement with a fluid, either albumin or plasma, is necessary and is carried out in the same procedure. The volume removed depends on the indication.

**Technique**

The two methods used in apheresis are the centrifugal and the membrane filtration methods, both requiring vascular access as well as anticoagulation of the extracorporeal blood (Fig. 1). The centrifugal method is used primarily in North America, whereas membrane separation is mostly used in Europe and Japan.

In centrifugal separation, whole blood is separated into various components based on the sedimentation coefficients of the components. Two methods are intermittent separation (manual and automated) and continuous separation, which takes place in an automated manner.

With intermittent centrifugation, sequential volumes of whole blood are removed, processed, and returned to the patient. This cycle is repeated as often as necessary to remove the desired volume of plasma. Blood is pumped from the patient at a flow rate of up to 100 mL/min into the processing unit that consists of a bell-shaped bowl that rotates at high speed. The denser cellular blood components are centrifuged against the lateral walls of the bowl while the plasma escapes steadily through a central outlet on top of the bowl. Each cycle removes about 400 to 700 mL of plasma, and packed cells are emptied from the bowl and returned to the patient. Advantages include relative simplicity of operation, portability of machines, and adequacy of a single-needle peripheral venipuncture. Disadvantages include slowness (the procedure typically takes more than 4 hours) and the relatively large extracorporeal volume removed each time. This may not be well-tolerated by patients with cardiovascular instability. Also, in the severely anemic patient, the plasma volume is much higher, resulting in a correspondingly greater amount of blood transferred extracorporeally in each cycle, giving rise to symptoms of volume depletion. Continuous flow centrifugation systems, on the other hand, are fully automated, with blood fed continuously into a rapidly rotating bowl, where components are separated, the desired layer or layers removed, and the remainder returned to the patient with replacement fluid. This method is faster and is more suitable for hemodynamically unstable patients. However, it is more costly and requires two venipunctures or insertion of a dual lumen catheter. Because the driving force for the extracorporeal circulation uses a negative pressure, the tubing used for the transport of blood has to be fairly rigid so that it will not collapse.

In the membrane filtration technique, blood is pumped through membranes that usually have pores of 0.2 to 0.6 μm in diameter, sufficient to allow passage of plasma while retaining cells. Membrane filtration can be done using hemodialysis equipment, with a blood flow rate of 100 (± 20) mL/min and an optimal transmembrane pressure of less than 70 mmHg. In another procedure, the separated plasma can be processed by a second membrane, also called a plasma fractionator, to remove macromolecules or immune complexes, a procedure known as double filtration or cascade filtration. The pore diameter of this second membrane is as small as 0.03 μm, the plasma components that cannot pass through this filter are discarded, and the cleared plasma is recombined with cells and returned to the patient. This technique, however, is not widely used.

Alternatively, affinity columns can be used in which the separated plasma is processed using special adsorption columns such as protein A columns that remove IgG antibodies and immune complexes or chemical affinity columns such as dextran sulfate that have negative
charges and are used to remove antibodies or other positively charged plasma pathogens such as low-density lipoproteins (LDL) and very low-density lipoproteins (VLDL). This is a selective procedure used to remove specific plasma components and does not require replacement fluid.

Successful execution of the apheresis procedure requires reliable venous access, which may be either two large, durable peripheral veins or a central line using a catheter that has a dual lumen and is rigid enough to withstand significant flow and pressures. A number of such devices are available (Vas-Cath, C.R. Bard Co., Mississauga, Canada).

Both centrifugation and membrane apheresis require anticoagulation to prevent activation of the coagulation system within the extracorporeal circuit. The most frequently used anticoagulant for centrifugation procedures is the acid-citrate-dextrose (ACD) solution (1/9 volume of solute per volume of solution [v/v]), given as a continuous intravenous (IV) infusion with infusion rate adjusted according to the blood flow rate (target ratio ranges from 1:10 to 1:25). Standard unfractionated heparin is most frequently used for membrane apheresis with the required dose of heparin about twice that needed for hemodialysis because a significant amount of infused heparin is removed along with the plasma. An initial loading dose of heparin (40 U/kg) is usually administered intravenously, followed by a continuous infusion (20 U/kg per hour) adjusted to maintain adequate anticoagulation in the circuit.

For most conditions in which plasmapheresis is used, it is considered acceptable to perform a 1 to 1.5
times plasma volume exchange per procedure, which will lower plasma macromolecule levels by 60 to 75%, respectively. Higher exchange volumes will double or triple the time required to perform the procedure without significant clinical benefit. The formula that can be used to estimate plasma volume in an adult is as follows: 

\[ \text{Estimated plasma volume (in liters)} = 0.07 \times \text{weight (in kg)} \times (1 - \text{hematocrit (Hct)}) \]

The typical replacement fluid is 5% human albumin solution or an equal mixture of albumin and 0.9% saline, except in the case of hemolytic-uremic syndrome or thrombotic thrombocytopenic purpura, in which fresh frozen plasma is used because it can replenish a deficient putative plasma factor (recently believed to be the von Willebrand factor cleaving metalloproteinase or ADAMTS-13 protein). Fresh frozen plasma may also be preferable in patients at risk for bleeding or those requiring daily exchanges for several weeks because frequent replacements with albumin solution will eventually result in postpheresis coagulopathy and a net loss of immunoglobulins. Blood flow rates when using albumin replacement are generally around 80 mL/min but are generally lower when using fresh frozen plasma to prevent untoward reactions because of rapid infusion of citrate anticoagulant.

**PLASMAPHERESIS FOR HYPERVERSICOSITY SYNDROMES DUE TO ABNORMALITIES OF PLASMA COMPONENTS OF BLOOD**

These conditions include paraproteinemias, such as multiple myeloma, Waldenström's macroglobulinemia, and light-chain disease, as well as cryoglobulinemia.

**Paraproteinemias**

Hyperviscosity syndrome is seen in less than 5% of multiple myeloma patients and depends on both the quantity and the quality of paraprotein. It is most commonly seen with IgA paraprotein because of its frequent polymerization, followed by IgG, class M protein and kappa light chains, which both tend to form aggregates and complexes. In IgA myeloma, the syndrome is seen at 6 to 7 g/dL with the polymeric form of IgA, whereas with the monomeric form the level has to reach 10 to 11 g/dL for symptoms to occur. In IgG3 myeloma, the syndrome is seen at a plasma level of 4 to 5 g/dL of this paraprotein, but in other forms of IgG, hyperviscosity is encountered only at levels above 15 g/dL.

In Waldenström's macroglobulinemia, hyperviscosity syndrome has been reported in 10 to 40% of patients who usually have an IgM level above 5 g/dL. The degree of hyperviscosity is assessed by measurement of serum viscosity, with the results expressed as units of relative viscosity as compared with water that is assigned a viscosity of 1.0. The relative viscosity of normal serum is 1.4 to 1.8, whereas the viscosity of the symptomatic patient is generally greater than 5. Viscosity rises with increasing concentrations of paraprotein, but, at some critical point, small increases in the amount of M-protein can disproportionately raise the viscosity. Serum viscosity does not always correlate with symptoms and some patients...
can be asymptomatic even with high serum viscosity measurements. This is most likely related to the properties of the particular paraprotein and the protective effects of hypervolemia and anemia on the blood viscosity.12

Paraproteins in myeloma also increase red cell aggregation (seen as rouleaux formation in peripheral blood smears) and reduce red cell deformability, thus increasing whole-blood viscosity. Practically, it is important not to transfuse a symptomatic patient with a high burden of paraprotein until after institution of plasmapheresis because this might significantly increase the whole-blood viscosity with serious adverse consequences.

In addition, hemostatic function is impaired at high paraprotein levels because of inactivation of clotting factors and interference with platelet function, often resulting in prolonged prothrombin times, activated partial thromboplastin times, and abnormal platelet function assays.13

The clinical symptoms of hyperviscosity syndrome are due to vascular occlusions and impaired hemostasis with neurological and visual symptoms the most frequent. They manifest as headache, dizziness, tinnitus, decreased hearing, impaired mentation up to coma, seizures, peripheral neuropathy, and blurry vision or visual loss due to retinal vein thrombosis or retinal hemorrhage. Bleeding diathesis manifests as ecchymoses; epistaxis; oozing from mucosa, particularly gingiva; and gastrointestinal bleeding. Patients with hyperviscosity also have expanded plasma volume and may develop congestive heart failure.

The effectiveness of therapeutic apheresis of the paraproteins depends on the distribution of the proteins, whether they are intravascular or extravascular. In case of monoclonal IgM protein, 70 to 80% of which is contained within the intravascular space, a single plasmapheresis session can result in significant clinical improvement and serum viscosity reduction by 50% or more.11 In hyperviscosity syndrome caused by IgG or IgA M-proteins, additional procedures are necessary to reduce the total amount of M-protein because of the large extravascular volume of these immunoglobulins. A small study has shown the superiority of conventional plasma exchange as compared with cascade filtration in hyperviscosity syndrome due to Waldenström's macroglobulinemia.14 Daily or every other day single plasma volume exchanges are generally used initially until symptoms are relieved. Delivered alone or in combination with drug therapy, plasmapheresis may be repeated on a less frequent basis, such as once per week, as needed for control of symptoms.36 In addition, drug therapy should be withheld until after plasma exchange so that plasma protein-bound drugs are not removed from circulation by this treatment.

Cryoglobulinemias

Cryoglobulins are cold-precipitable proteins in serum that might cause occlusion of vessels in the cooler parts of the body, such as the skin in the extremities, the digit tips, the ears, and the tip of the nose.11 These obliterative lesions manifest as Raynaud's phenomenon, cutaneous ulcerations, purpura, livedo reticularis, myalgia, arthralgia, renal involvement, and peripheral neuropathy. The relationship between concentration and precipitation of cryoglobulins is direct and linear: the higher the protein concentration, the higher the temperature at which precipitation may occur. The incidence of cryoglobulinemia has changed dramatically in the last decade from being a complication of plasma cell dyscrasias and other lymphoproliferative diseases to one that is associated with hepatitis C.15 Cryoglobulins are classified according to their composition. Type I cryoglobulins are monoclonal immunoglobulins, with IgM being the most common followed by IgG and IgA. Type II cryoglobulins are composed of monoclonal IgM, which has rheumatoid factor activity and a polyclonal IgG. Type III cryoglobulins are known as mixed polyclonal cryoglobulins and are composed of polyclonal immunoglobulins often complexed with complement and viral and other antigens. They are seen in infections, the most prominent being hepatitis C and autoimmune diseases, similar to type II cryoglobulins, whereas type I cryoglobulins are seen in myeloma, chronic lymphocytic leukemia, lymphomas, and other lymphoproliferative diseases.

Treatment of cryoprotein-related disease includes therapy for the underlying disease causing the cryoprotein excess, such as ribavirin and interferon for hepatitis C or steroids plus alkylating agents in lymphoproliferative disorders, concomitantly with plasma exchange with 5% human albumin solution replacement.16 If a patient experiences symptoms with only a slight decrease in temperature, plasmapheresis may require the use of in-line blood warmers to avoid precipitation of the protein in the cell separator. Cryofiltration apheresis using the high-capacity cryofilter is the most selective procedure to remove cryoglobulins and is specific for the treatment of cryoglobulinemia. In this method, the plasma is cooled to 4°C and the precipitated cryoproteins are removed by the cryofilter. The cryoprotein-free plasma is subsequently rewarmed to body temperature, mixed with the cells and returned to the patient.17

**CYTOPHERESIS FOR HYPERVISCOSITY SYNDROMES**

These conditions include acute and chronic leukemias with extreme leukocytosis (WBC > 100,000/μL), polycythemia, sickle cell disease, and essential thrombocytois.

**Leukapheresis**

Impaired microcirculation can result from either a high leukocyte count or abnormal leukocytes in acute leukemia. Sludging of leukocytes in the microcirculation, a phenomenon known as leukostasis, occurs when the whole-blood viscosity is increased from either a very high leuko-
cyte count, as in chronic leukemias, or a high myeloblast or lymphoblast count in acute leukemia and in high-grade non-Hodgkin’s lymphoma. Adhesive molecules are activated and participate in the leukocyte adhesion and extravasation. Whole-blood viscosity is increased when a leukocrit of 20 to 25% is reached.11 This corresponds to 4 to 6 x 10^5 myeloblasts/µL or 5 to 10 x 10^5 lymphoblasts or lymphocytes/µL. The occluded microcirculation can occur anywhere in the body but is most commonly seen in the brain and lungs with intracranial hemorrhages and respiratory failure, causing most early deaths.12 Clinical manifestations range from headache to coma and death, with signs of increased intracranial pressure, often accompanied by focal neurological deficits.18 Leukostasis in the pulmonary circulation presents with acute respiratory failure and bilateral pulmonary infiltrates prominent in the chest X-ray. If leukostasis is not recognized and treated promptly, the mortality rate can be as high as 40%.19

Hyperleukocytosis is seen most often with acute monocytic leukemia, followed by acute myelomonocytic leukemia and chronic myelogenous leukemia. It is also seen in the microgranular variant of acute promyelocytic leukemia (APL). The undesirable properties of blasts (large size, diminished deformability, and increased “stickiness”) are more often seen with myeloid than lymphoid blasts, which accounts for the lower incidence of leukostasis with acute lymphocytic leukemia (ALL) (2 to 6%).12 The severe anemia usually present in patients with acute leukemia counteracts the effect of hyperleukocytosis on whole-blood viscosity, and thus red cell transfusions should be generally avoided until the white cell count is reduced. Activation of cell adhesive molecules and interactions between leukemic blasts and endothelial cells are responsible for vascular disruption and hemorrhage. This process can be activated by inflammatory cytokines such as interleukin (IL)-1β and tumor necrosis factor (TNF)-α, which upregulate the expression of several adhesion molecules on endothelial cells, resulting in a progressive increase in the number of blasts attached to the endothelium.12,20 A local inflammatory process can often precipitate leukostasis, as seen for example in patients with pneumonia who might have only moderate leukocytosis.21,22 The adhesion molecules displayed by the leukemic blasts and their chemotactic response to the cytokines in the vascular microenvironment are probably more important in causing leukostasis than the cell number is.

Treatment of hyperleukocytosis by leukapheresis is commonly initiated in any acute myelogenous leukemia (AML) patient with blast counts greater than 100,000/µL, or even with lower counts if symptoms of leukostasis are evident, and is usually continued until counts have been reduced to less than 50,000/µL. Large numbers of leukocytes in the range of 10^11 to 10^12 cells can be removed in a single apheresis procedure.23,24 Because of the small volume of blood removed, the patient can tolerate leukapheresis quite well. However, there are no evidence-based guidelines as to when to start, how long to perform, and when to stop leukapheresis.19 It is rarely performed in ALL unless the patient is symptomatic or the blast count is greater than 300,000/µL. In addition, hydroxyurea at a dose of 50 to 100 mg/Kg per day in three to four divided doses, allopurinol, and IV fluids should be started concomitantly with leukapheresis, followed by more definitive chemotherapy. The disadvantages of leukapheresis include the necessity for placement of central venous catheter, further decrease in number of platelets that are removed in significant numbers together with the white cells, and the fact that blast counts often rebound quickly after leukapheresis unless additional cytoreductive medications are started. It is important to understand that early deaths and leukostasis may occur even after WBC counts have been significantly reduced and that this is due to the intrinsic nature of leukemic blasts and their vascular microenvironment.25 The prophylactic or therapeutic use of agents that target the leukocyte–endothelium interface is still under investigation. However, dexamethasone has proved to be effective in the management of the all-trans retinoic acid syndrome in APL, where its beneficial effect may result from modulation of adhesion molecules on APL blasts.26

Plateletpheresis

High platelet count, especially when greater than 1 x 10^6 cells/µL, is associated with a high risk for thrombosis or bleeding in patients who have underlying myeloproliferative diseases such as essential thrombocytosis, PV, and chronic myeloid leukemia. Risk is higher in patients older than 60 and in those with comorbid conditions such as hypertension, obesity, hyperlipidemia, diabetes, and with cigarette smoking.11 Patients with reactive thrombocytosis due to disseminated cancer, infection, or rebound from hemorrhage are at much lower risk for complications because they have essentially normal platelet function.

Thrombosis is more common in arteries than it is in veins, and the incidence is not directly correlated with the platelet count. Microcirculatory impairment may also give rise to the syndrome of erythromelalgia, which consists of erythematous, painful, and burning-skin manifestations in the extremities and acrocynosis. Extremely high platelet counts (> 1.5 x 10^6/µL) have been associated with increased risk of gastrointestinal bleeding, possibly as a result of acquired von Willebrand disease with loss of large–molecular–weight multimers.27

Treatment, in general, consists of antiplatelet agents such as aspirin or clopidogrel. Suppression of thrombocytosis with hydroxyurea or anagrelide should be initiated promptly because this usually takes days and some-
times weeks to accomplish. The role of plateletpheresis is to achieve rapid reduction in platelet counts in those patients with life-threatening organ dysfunction, particularly neurological and pulmonary, and in perioperative management. Plateletpheresis often results in dramatic clinical improvement.

Erythrocytapheresis

Whole-blood viscosity is commonly raised in clinical situations in which Hct is increased either because of shrunken plasma volume in dehydrated patients or because of erythrocytosis. The most common cause of erythrocytosis that gives serious concerns for thromboembolic complications is PV. At a moderately raised Hct level of 60%, the whole-blood viscosity is 2.5- to 3-fold that of blood with a Hct of 40%.\textsuperscript{11} Thrombosis is the most common cause of mortality in PV, accounting for 29% of the deaths. Cerebral vascular accidents were the most frequent (34%), followed by myocardial infarction (13%) and peripheral arterial occlusion (9%), whereas venous thrombosis accounted for 26% of these events.\textsuperscript{28} The management of PV principally involves frequent phlebotomies to bring the Hct to less than 45%. In PV patients with symptoms of hyperviscosity, hemorrhage, thrombosis, or congestive heart failure due to a Hct above 60%, or a combination of these, red cell removal should be carried out immediately, using erythrocytapheresis to bring the Hct below 60%. This will usually lead to rapid improvement.\textsuperscript{29} Pearson and Weterley-Mein\textsuperscript{30} demonstrated that, in patients with PV, a steep rise in thromboembolic complications occurs with Hct above 44%. Thus, this value should be the target of treatment. When the apheresis device is used for automated red cell removal, the procedure is similar to red cell exchange except that albumin (or saline) solution is infused in place of donor red cells. If the blood volume is based on 70 mL/kg, the following formula may be used to estimate the volume of red cells to be removed (VR):\textsuperscript{31} VR = actual Hct - desired Hct/79 \times 70 \text{ mL/kg} \times Wt (kg).

In patients with secondary erythrocytosis, corrective action may not be needed unless the Hct is above 60%, except when there are severe symptoms attributable to hyperviscosity. Normalization of Hct in these patients is not desirable because there is a need for extra oxygen-carrying capacity. In sickle cell disease, sickling of red cells increases the whole-blood viscosity and predisposes to episodes of tissue infarction caused by microvascular occlusions. Transfusion therapy, especially exchange transfusion, is usually recommended for the more severe forms of infarction crises, including stroke, acute chest syndrome, priapism, retinal infarction, and hepatomegaly. A rigorous goal would be to maintain Hb S at less than 30%. However, Hb S levels up to 50% have been shown to afford much protection against recurrent stroke while greatly reducing the requirement of transfusions and the risk of iron accumulation.\textsuperscript{32} Exchange of one red cell volume in a patient who has 100% Hb S should produce Hb A levels of about 65% and lower Hb S levels to 35%. The apheresis procedure in sickle cell patients is frequently complicated with transfusion reactions due to alloimmunization, and problems with vascular access because of frequent thrombosis of permanent catheters.

CONCLUSION

In recent years, therapeutic apheresis has been established as a sound therapeutic modality. Hyperviscosity syndrome is perhaps one of the most effective indications for this procedure. When hyperviscosity affects the microcirculation, the risks can be life threatening, either as a thromboembolic or a bleeding complication. When indicated, it is often carried out as an emergency procedure. However, apheresis is only one element of a comprehensive management plan. The underlying cause and any comorbid condition have to be treated at the same time.

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