

Anticoagulation for Therapeutic Apheresis

Apheresis procedures require anticoagulation to prevent clotting of blood in the extracorporeal circuit. The foreign surface of the tubing potently activates platelets and leads to contact-mediated activation of the hemostatic system.¹⁷ Citrate has become the anticoagulant of choice for centrifuge-based systems, whereas many membrane-based systems call for heparin.

Citrate-Based Anticoagulation and Calcium Regulation

Citric acid has been used as an anticoagulant since 1914. Citrate is the conjugate base of citric acid and is an intermediate conjugate in the citric acid cycle.¹⁸ The most commonly used citrate preparation in therapeutic apheresis is ACD formula A (ACD-A) (2.2 g/dL sodium citrate and 0.73 g/dL citric acid), although other preparations exist such as ACD-B (1.32 g/dL sodium citrate and 0.44 g/dL citric acid) and anticoagulant sodium citrate solution (4 g/dL sodium citrate), the latter of which is a common anticoagulant used for continuous renal replacement therapy.

Citrate reversibly chelates divalent cations, including calcium and magnesium. Ionized calcium is the physically active form of calcium and is a necessary cofactor for many cellular processes, including hemostasis, regulation of muscle contraction, and stabilization of cellular membranes.¹⁷ Of the total body calcium, 99% is found in bone; a small portion of this calcium can be rapidly mobilized to correct a circulating deficiency. Virtually all of the nonosseous calcium is extracellular, with the normal plasma concentration being about 10 mg/dL. Roughly 40% of plasma calcium is bound to plasma proteins, primarily albumin, and 13% is complexed to small anions such as lactate, phosphate, and endogenous citrate. The remaining half (47%) of plasma calcium is free, and it is this free (ionized) calcium fraction that participates in coagulation reactions and can be chelated by exogenous citrate.¹⁷ Normal ionized calcium levels range from 1.1 to 1.4 mmol/L (4.5-5.6 mg/dL) and do not vary with albumin levels. In the extracorporeal circuit, citrate con-

centrations of 15-24 mmol/L reduce ionized calcium levels sufficiently (to 0.2-0.3 mmol/L) to impair hemostasis and produce an anticoagulant effect. Additionally, using donor blood components as a replacement fluid involves even higher rates of citrate infusion; for instance, transfused plasma and Red Blood Cells each contain ~2 to 3 mmol citrate/unit.¹⁹

Although heparin can be used for centrifuge-based apheresis procedures, citrate is the preferred anticoagulant in low-flow circuits where delivery to the system is offset by clearance. The half-life of citrate is typically shorter than heparin (30 to 60 minutes vs 23 minutes to ~3 hours); the major site of metabolism is the liver and, to a lesser extent, the kidneys and skeletal muscle.^{20,21} Even though much of the citrate infused during TPE is discarded with the separated plasma, an exchange still produces a net loss of calcium. The net effect of citrate and parathyroid hormone levels on plasma calcium is that total calcium decreases most rapidly in the first 15 minutes of a procedure, reaching a 25% decrement by 90 minutes. Intact parathyroid hormone rises quickly, then levels off or decreases slightly during the remainder of the procedure.²² This pattern suggests that, in addition to body weight, TBV, and hematocrit, the rate and duration of citrate infusion may affect the severity of citrate-induced hypocalcemia (“citrate toxicity”) in the patient.

Modern apheresis instruments limit both citrate dose and flow rate on the basis of patient blood volume calculations. Newer machine models produce peak citrate and trough ionized calcium levels that are less extreme and that have a correspondingly lower incidence of citrate toxicity than reported with older technology. Many therapeutic apheresis centers routinely use prophylactic calcium replacement to prevent citrate-induced hypocalcemia. Calcium is typically run as a separate infusion with the return line, or calcium gluconate can be directly added to the albumin replacement fluid. The mild decreases in serum calcium that may be observed during the treatment do not result in a therapeutic anticoagulation of the

patient or significantly increase the risk of bleeding, in contrast to heparin anticoagulation.

Heparin Anticoagulation

Heparin anticoagulation is typically the anticoagulant of choice for membrane-separation techniques, such as membrane-based plasma exchange systems and dextran-sulfate-column-based lipoprotein apheresis systems, but it is also currently the standard protocol for the centrifuge-based ECP system. It is recommended that the dose be based on manufacturer guidelines for each system. Heparin exerts its primary anticoagulant effect by binding antithrombin and altering its conformation, thereby rapidly inactivating the clotting factors thrombin (Factor II), Factor IX, and Factor X.

Heparin sensitivity and half-life vary greatly in patients, and individual adjustment of dose is necessary. Heparin doses may need to be increased in patients with low hematocrit (increased volume of distribution) and when the plasma filtration rate is high (a high plasma filtration rate results in increased net removal of heparin, which has a sieving coefficient of 1.0). In membrane-based TPE, adequate anticoagulation is typically achieved with a plasma-heparin concentration of 0.5 to 2.0 IU/mL. In ECP, standard heparin for an adult patient is prescribed as 10,000 units of heparin in 500 mL of normal saline, given at a ratio of 10:1 (10 parts whole blood to 1 part heparin solution). The ratio of heparin delivered or the concentration of heparin solution can be adjusted according to the clinical situation (eg, reduced in the setting of concurrent systemic anticoagulation). Heparin administration via the currently available lipoprotein apheresis system in the United States is more similar to heparin administration in intermittent hemodialysis, where a heparin pump is programmed to deliver an initial bolus followed by an hourly infusion rate of heparin (eg, at 25 units/kg). With heparin anticoagulation, the patient is exposed to systemic anticoagulation following apheresis, the implications of which are discussed in greater detail in the section on adverse events.

Occasionally, a combination of heparin and citrate are used for certain procedures, particularly when there is evidence of insufficient anticoagulation in the circuit (“clumping”) and the patient cannot tolerate an increase in citrate delivered because of symptoms of hypocalcemia, or the machine will not allow the desired citrate flow rate (eg, pediatric apheresis or large-volume leukocytapheresis in adult patients).

Vascular Access for Therapeutic Apheresis

Adequate blood flow to and from the machine must be established to perform any type of apheresis procedure. The requisite vascular access may be obtained through peripheral veins, central veins, or a combination of the two. The blood flow rate for a procedure for an adult is usually between 30 and 120 mL/minute, depending on the procedure being performed and the type of replacement fluid; for small children and certain unstable patients, the flow rate will need to be lower. There are multiple options for vascular access in patients undergoing therapeutic apheresis, including peripheral venous catheters (PVCs), central venous catheters (CVCs), certain subcutaneous ports, and arteriovenous fistulas (AVFs) and grafts (AVGs).

PVCs are the preferred access point for apheresis, whenever possible. The advantages of PVCs include the following: 1) they may be placed with ease and rapidity, 2) they are less invasive and avoid the associated complications of central access, and 3) there is lesser possibility for recirculation. Potential disadvantages of PVC access include the following: 1) the blood flow rate in general is limited to a maximum of 80 mL/minute, so it may not be an option in membrane-based plasma exchange systems; 2) access may require multiple sticks to obtain, and pain, bruising, and vasovagal reactions can occur; and 3) the anticipated blood flow may be limited, lengthening treatment time and leading to more frequent alerts from the machine. The technique of ultrasound-guided PVC placement has been shown to significantly reduce the need for CVC in apheresis patients.²³