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Anticoagulation and Disorders of Hemostasis

Brian C. Bridges, MD, Marco Ranucci, MD, Laurance L. Lequier, MD

Introduction

One of the greatest challenges of providing ECLS is achieving and maintaining therapeutic anticoagulation. While the field of ECLS has advanced greatly, most of the complications involved with this support remain unchanged, and continue to involve clotting of the artificial circuit and patient bleeding. In this chapter we will discuss the types of anticoagulation used for ECLS, the monitoring of anticoagulation, blood product replacement, and the strategies for dealing with hemorrhagic and thrombotic complications.

Anticoagulation

Unfractionated Heparin

Historically, unfractionated heparin (UNFH) has been the anticoagulant of choice for the vast majority of ECLS. Heparin has been in clinical use since 1937 when it was first used to prevent pulmonary embolism in postsurgical and postpartum patients.[1] It remains widely used, relatively inexpensive, and easily available. UNFH is a mixture of mucopolysaccharide chains of various lengths that range from 5,000 to 30,000 daltons. UNFH undergoes hepatic metabolism, renal excretion, and has a plasma half-life of 30 to 60 minutes.[2,3] The anticoagulation effect of heparin is mediated via its interaction with antithrombin (AT) and tissue factor pathway inhibitor (TFPI).[4] Although AT inhibits all serine proteases except factor VIIa and protein C, most of its anticoagulant effect is through inhibition of thrombin and factor Xa. The inhibition of thrombin prevents the conversion of fibrinogen to fibrin, and ultimately, the formation of a cross-linked fibrin clot. The UNFH-AT complex increases the inhibition of coagulation proteins by 1000 fold compared to AT alone.[5] Patients with congenital or acquired AT deficiency often fail to achieve therapeutic anticoagulation with UNFH.[6] The administration of UNFH also results in a several-fold increase in the release of TFPI from the endothelium. TFPI is a major *in-vivo* inhibitor of coagulation that binds and inhibits both factor Xa and factor VIIa/tissue factor catalytic activity. Dilute prothrombin time assays reveal that TFPI contributes about one third of the anticoagulant effect of heparin, with the rest of the effect attributed to antithrombin.[7]

A bolus dose of UNFH ranging from 50 to 100 units/kg is given after the exposure of the vessels and before insertion of the cannulas for ECLS. Patients with transthoracic cannulation, severe coagulopathy, or active bleeding can receive an UNFH bolus at the lower end of this range. Subsequently, UNFH is administered as

or diagnosed HIT.[24-30] The maintenance dose is reported between 0.1-0.7 μg/kg/min with anticoagulation monitoring based on the aPTT (50-60 seconds) and ACT. Potential advantages of DTIs over UNFH are the prevention and treatment of HIT and the preservation of platelet and AT levels. The main disadvantages include the lack of antidotes and, for bivalirudin, the risk of local, intravascular clearance with thrombus formation in areas with blood stagnation.

When UNFH is replaced by a DTI, the initial dose should begin on the lower side of the reported range (0.05 mg/kg/hr for bivalirudin and 0.1 μg/kg/min for argatroban) progressively increasing the dose until the target aPTT is reached and maintained. DTIs represent a viable alternative to UNFH for ECLS anticoagulation that deserves additional study.

Anticoagulation Monitoring

Activated Clotting Time

The ACT has long been the standard measure of anticoagulation for both cardiopulmonary bypass and ECLS. It provides a measure of the clotting of whole blood. Advantages of ACT are that it can be done at the bedside, requires a drop of blood, and results are available within a few minutes. ACT continues to be the most commonly performed test of anticoagulation among ECLS centers. In an international survey study of ELSO centers, 97% reported using ACT for patients supported with ECLS.[31]

Despite its ease, ACT has limitations. ACT measures the time to clotting for a sample of whole blood. A prolonged ACT could be due to excessive anticoagulation, thrombocytopenia, coagulopathy, or any combination of these factors. In addition, variability in the ACT for a single sample of blood occurs, even when using the same measuring device.[32] Finally, considerable variability in results exists between different commercially available instruments that measure ACT.[33,34]

Traditionally, ACT has been used to initiate and titrate UNFH for ECLS. The UNFH infusion is typically started once ACT reaches 300 seconds or less. The initial standard Hemochron® ACT range is 180 to 220 seconds or 160 to 180 seconds with the ISTAT® analyzer with kaolin cartridge. This ACT range can then be adjusted based on factors including patient bleeding, circuit clotting, or the measured anti-factor Xa level.

Activated Partial Thromboplastin Time

The aPTT assesses the intrinsic and final common pathway of coagulation and so is influenced by coagulation factors, heparin, and AT levels, and the presence of a lupus inhibitor. It has been the traditional means of measuring and titrating anticoagulation with UNFH. In a retrospective study of pediatric ECLS patients, titration of UNFH using aPTT versus ACT led to decreased hemorrhagic complications but increased circuit clotting complications.[35] As described previously, aPTT is the accepted means for titrating therapy with intravenous DTIs.

Of note, children have developmental differences in coagulation, and aPTT does not perform as reliably in neonatal and pediatrics patients compared to adults.[36,37] For neonatal and pediatric ECLS patients, aPTT values correlate poorly to anti-factor Xa levels and UNFH levels.[38-40] In a prospective observational cohort of pediatric ECLS patients, anti-factor Xa levels had a stronger correlation to UNFH dose than the ACT or aPTT.[39] Another prospective pediatric ECLS study found a positive correlation between anti-factor Xa levels and heparin dose but a poor correlation of anti-factor Xa levels to aPTT or ACT.[39] Additionally, the aPTT often becomes unreliable in critical illness, being affected by acute phase reactants such as C-reactive protein (CRP) and factor VIII. The aPTT is falsely prolonged in patients with el-

perform thromboelastography both with and without heparinase to determine the effect of UNFH.[45] Table 7-2 provides recommendations on approaches to abnormalities observed with thromboelastography and thromboelastometry, performed with heparinase for those patients anticoagulated with UNFH.

Antithrombin Level

AT is the most important inhibitor of coagulation *in vivo*. For ECLS patients, a primary deficiency of AT may exist or can may occur secondary to excessive peritoneal drain or chest tube losses. AT can be replaced in two ways: giving fresh frozen plasma (FFP) or commercially available AT concentrate. AT concentrate is available as a product pooled from human plasma or as a recombinant AT formulation. Healthy infants do not achieve normal adult levels of AT until approximately six months of life. Term neonates have an AT level of approximately 60% of adult values.[46] The "off label" use of AT concentrate for ECLS has increased greatly over the past decade,[47] but the evidence for this use is mixed. A retrospective study of neonatal and pediatric ECLS patients revealed increased in AT levels with AT concentrate administration, but no other clinically significant changes, including UNFH infusion rate, ACTs, chest tube output, or packed red blood cell (PRBC) transfusion volume.[48] In another single center pediatric ECLS study, supplementation with AT concentrate for activity levels of <70% resulted in higher anti-factor Xa levels without differences in UNFH infusion rates, but greater circuit failures.[49] Ryerson et al. conducted a retrospective study of pediatric ECLS patients that demonstrated supplementation with AT concentrate was associated with an increase in anti-factor Xa levels, decreased UNFH dose requirements, and no acute adverse events.[50]

FFP contains a relatively small amount of AT, approximately 1 unit of AT per ml.[51] Thus, a large volume of FFP is needed to change AT levels, increasing blood product exposure and fluid overload. For patients with a low AT level for age, heparin resistance, and sub-therapeutic anti-factor Xa level, supplementation with AT may help. For patients with coagulopathy or

Table 7-2. Thromboelastography/thromboelastometry with Heparinase Guidelines.

Abnormality	Approach
R >10 min (low clotting factors) or CT (extem) >100 sec	Administer FFP or prothrombin complex concentrate
MA <54 mm or MCF<45 mm and normal fibrinogen levels (decreased platelet function/count)	Administer platelet concentrate
Low fibrinogen at Functional Fibrinogen (<150 mg/dL) test or FIBTEM (<6 mm) test	Administer cryoprecipitate/fibrinogen concentrate *Usually associated with a prolonged R time, so treat prolonged R time with FFP first, and if the angle is still low, then administer cryoprecipitate as above.
EPL >15% or LY30 >7.5% and CI ≤1 CLI30 <85%	Consider treatment with antifibrinolytic for primary fibrinolysis

and underlying pathophysiology should dictate adjustments of laboratory determinations and blood product administration. Laboratory testing can be decreased and blood product transfusion reduced in patients who have reached a stable clinical status. Blood product transfusion carries with it infectious and non-infectious risks and will be covered in Chapter 8

Hemorrhagic and Thrombotic Complications

Hemorrhagic complications produce significant morbidity and mortality among ECLS patients. Their prevention requires correcting coagulopathy and thrombocytopenia, careful titration of anticoagulation therapy, and repair of surgical sources of bleeding.

The ELSO Registry defines a significant clotting complication as requiring a change in a portion of the circuit or entire circuit. In the July 2015 ELSO International Registry Report across all age groups and indications, circuit clots have been reported in nearly 40% of all ECLS runs, with the oxygenator being the site with the greatest number of reported clots.[52] Inadequate anticoagulation, low flow states, and patient hypercoagulability lead to increased risk of thrombosis. Areas of stasis or turbulence in the ECLS circuit are prone to clot formation. Even when thrombotic complications are not evident during an ECLS run, thrombosis is commonly observed during postmortem examinations of ECLS patients. A single center report of postmortem examinations of pediatric ECLS patients revealed significant thrombosis in 69% of patients overall and 85% of patients with a history of congenital heart disease.[53] In a report of autopsy findings of postcardiotomy adult ECLS patients, over 70% had previously unrecognized thromboembolic complications.[54]

Conclusions

The number and complexity of patients supported with ECLS continues to increase. With this growth comes an even greater need for improved surfaces for blood-circuit interaction, safer anticoagulation, and enhanced anticoagulation monitoring. Consultation with hematology specialists and laboratory medicine should be considered for managing complex issues regarding anticoagulation for ECLS or for any ECLS patient with unexplained hemorrhagic or thrombotic complications.

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