Anticoagulation with VADs and ECMO: walking the tightrope

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The evolution of devices for mechanical circulatory support (MCS), including ventricular assist devices (VADs) for patients with heart failure and extracorporeal membrane oxygenation (ECMO) for patients with acute cardiac or respiratory failure, has improved survival for subsets of critically ill children and adults. The devices are intricate and complex, allowing blood to bypass the heart or lungs (or both). As blood flows through these artificial devices, normal hemostasis is disrupted, coagulation is promoted, and in the absence of anticoagulation, a thrombus may form in the device, resulting in device failure or embolic stroke. Therefore, anticoagulation is necessary to prevent thrombus formation and maintain device function. However, patients on MCS also have very high bleeding rates. Titrating anticoagulation to prevent hemorrhagic complications and thrombotic events can be a challenge, and hematologists may be consulted in complex cases. Substantial variability remains in the approach to anticoagulant and antiplatelet therapy for patients on MCS, largely because of the lack of high-quality data. Improvements in the design and manufacture of these devices, as well as in the individualized titration of antithrombotic intensity, are expected to enhance outcomes. Several factors pertaining to both the device and the patient (adult and children) should be considered when attempting to optimize this delicate balance.

Learning Objectives

- Recognize the common hemorrhagic and thrombotic complications associated with mechanical support devices
- Gain a general understanding of the principles that guide antithrombotic therapy in patients with a VAD or on ECMO
- Identify the limitations of coagulation assays used to monitor and adjust unfractionated heparin

Introduction

The number of children and adults with end-stage heart failure is increasing, although the etiologies are different.[1] Increasing demand, technologic advances, and growing expertise have expanded application of ventricular assist devices (VADs) in patients with heart failure when conventional approaches fail. Although heart transplantation remains the best option for many, there is a lack of suitable donors. The use of a VAD as a bridge to transplantation or recovery or, in the case of many adults, as "destination therapy" has improved survival and quality of life. Extracorporeal membrane oxygenation (ECMO), which can support both the heart and the lungs, offers short-term support for patients with cardiac and/or respiratory failure. Early ECMO success was demonstrated in neonates with respiratory failure and now extends to a much broader population with cardiac or respiratory failure.

Hemorrhagic and thrombotic events remain significant complications in patients receiving mechanical circulatory support (MCS) and are associated with increased morbidity and mortality. The approach to anticoagulation differs slightly in patients supported with a VAD compared with those on ECMO, although the principles are similar. Management and titration of anticoagulation in children, particularly neonates, offer additional challenges. Many of these issues are reviewed in the following sections.

VADs (adults)

Although VADs were first implanted successfully in 1966, their use to support the growing population of adults with heart failure has rapidly increased in the last 2 decades. Improved outcomes have led to more widespread adoption, and the use of VADs continues to expand. Since 2005, data from more than 15 000 patients have been entered into the Interagency Registry for Mechanically Assisted Circulatory Support.[2] Outcomes are generally quite good, with enhanced survival (1-year survival, 80%) and improved function and quality of life.[2] However, VADs are not without complications, including bleeding, infection, pump thrombosis, and stroke. The most common cause of death in people with a VAD is a neurologic event.[2]

The first generation of VADs relied on a pneumatic pulsatile flow; however, the field has transitioned to primarily continuous-flow devices, which are smaller, more durable, and more efficient. Two Food and Drug Administration (FDA)-approved VADs currently account for most use in the United States: the axial continuous-flow HeartMate II (Thoratec Corp., Pleasanton, CA) and the centrifugal continuous-flow HeartWare HVAD (HeartWare International, Framingham, MA). Additional devices are available, including the total artificial heart, but these are used less frequently and are not covered in this review.

In addition to the devices listed in the previous paragraph, the HeartMate 3 (Thoratec Corp.) is a small, bearingless, magnetic,

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Off-label drug use: antithrombin, argatroban, bivalirudin, enoxaparin.

centrifugal continuous-flow device that was engineered to improve hemocompatibility and reduce shear stress.[3] The HeartMate 3 is being compared with the HeartMate II in the MOMENTUM 3 trial, an ongoing randomized clinical study, with 6-month outcomes recently published.[4] The primary outcome in the trial, reoperation for pump thrombosis during the first 6 months, occurred less frequently in the HeartMate 3 than in the HeartMate II (0.7% vs 7.7%; $P = .002$).[4] There was no difference in stroke or bleeding between the groups. Long-term (24-month) outcomes are being investigated. This device is approved for use in the European Union and as of May 2017 is awaiting FDA approval in the United States.

Approach and evolution of antithrombotic therapy

After device implantation and once bleeding has subsided, unfractionated heparin (UFH) is generally used in the postoperative period as a bridge to warfarin and aspirin to mitigate thrombotic risk. However, the rate of early postoperative bleeding requiring reoperation is ~30%, and this complication comes with substantial morbidity.[5] To reduce early bleeding, some centers eliminated the use of postoperative UFH. A 2010 retrospective analysis of patients who received the HeartMate II and were directly transitioned to warfarin and aspirin without the use of IV heparin did not demonstrate a short-term increase in thrombotic events.[6]

In addition, rates of gastrointestinal (GI) bleeding (discussed further in the next section) have increased, which led many centers to reduce the targeted warfarin international normalized ratio (INR) range to prevent GI bleeding. These practice changes (elimination of postoperative heparin and reduced intensity of outpatient anticoagulation) were temporally related to an increase in pump thrombosis. A multicenter study reported an increase in pump thrombosis at 3 months with the HeartMate II device (ie, from 2.2% in March 2011 to 8.4% by 2013),[7] and similar finding were reported in the Interagency Registry for Mechanically Assisted Circulatory Support.[8] The incidence and risk factors associated with pump thrombosis have gained tremendous attention over the past 5 years.

Pump thrombosis refers to a thrombus on any of the blood-contacting surfaces of the pump (the inflow cannula, pump itself, or outflow cannula) and is classified as either suspected or confirmed. When this complication occurs, patients are at risk of developing embolic stroke and/or experiencing device failure and have reduced survival.[2] Pump thrombosis may be suspected clinically when any 2 of the following conditions are present: abnormal pump parameters (pump power elevations), laboratory markers of hemolysis (rising lactate dehydrogenase or plasma-free hemoglobin level), or new heart failure symptoms not explained by structural disease.[9] Cases are confirmed when the device is changed and a thrombus is visualized. Most centers screen their patients with regular measurements of lactate dehydrogenase in addition to monitoring pump parameters and hemodynamics.

Pump thrombosis is a complex problem and may be related to nonmechanical or mechanical factors. Nonmechanical factors include intensity of anticoagulation and antiplatelet therapy, blood pressure management, and possibly the status of aortic valve opening after LVAD implantation.[9] Mechanical factors include the type of material used in the inflow cannula as well as surgical implantation techniques, such as the position and angulation of the inflow cannula.[9,10]

In a retrospective study of 382 patients who received the HeartWare HVAD device from August 2008 to November 2012, a total of 31 patients (8.1%) developed pump thromboses at a median time-to-event of 245 days. Most thromboses occurred in pumps of patients with subtherapeutic INRs on warfarin and with low-dose or no antiplatelet therapy, suggesting improved anticoagulation may reduce events.[11,12] In addition, modification of the inflow cannula (sintering), which began in 2011, appeared to reduce thrombotic events.[11]

The PREVENtion of HeartMate II Pump Thrombosis trial was a prospective, multicenter, single-arm study designed to evaluate the incidence of pump thrombosis using close adherence to a set of standardized clinical guidelines addressing (1) surgical technique during implantation, (2) anticoagulation and antiplatelet management, (3) pump speed management, and (4) blood pressure managment.[13] The overall rate of confirmed pump thrombosis was 2.9% at 3 months (primary end point) and 4.8% at 6 months, which compared favorably with historical reports of 8.4% at 3 months.[7] In patients with (1) full adherence to surgical recommendations, (2) postoperative heparin bridging followed by warfarin anticoagulation, and (3) pump speeds ≥9000 revolutions per minute, the risk of pump thrombosis was substantially lower than in patients who did not meet these 3 criteria (1.9% vs 8.9%; $P > .01$).[13] Anticoagulation and antiplatelet management in this study is summarized in Table 1. Among the findings, the overall incidence of bleeding was 45% at 6 months; in addition, 34% of patients had early bleeding (<30 days), and 21% experienced GI bleeding. Overall, 16% of patients required surgical intervention for bleeding. These bleeding rates are high but not dissimilar from those reported previously.[14] This study demonstrated the multifactorial nature of pump thrombosis and the importance of optimizing *both* mechanical and nonmechanical factors to improve outcomes.

Management of a patient with suspected pump thrombosis can be medical or surgical. Optimal primary treatment has been debated, and the choice depends on patient presentation, predicted duration of the thrombus, surgical candidacy, and institutional philosophy.[9] Medical management may include aggressive IV heparin therapy with consideration of systemic thrombolysis; in some cases, glycoprotein IIb/IIIa inhibitors have been added.[9] Although medical therapy may be considered for hemodynamically stable patients, recent reports suggest success rates of only 23% to 50%, mortality rates of 17% to 52%, and bleeding complications in 65% of these patients.[9] A systematic review of medical management did not find a difference in thrombus resolution rates between thrombolytic and nonthrombolytic regimens, although the risk of major bleeding was higher in the thrombolytic group.[15]

GI bleeding

GI bleeding has emerged as a significant challenge that plagues the VAD field, occurring in ~20% to 30% of patients, and it has increased over time with the transition to continuous-flow devices.[16,17] It appears to be related to the development of acquired von Willebrand disease along with arteriovenous malformations (AVMs) in the intestinal mucosa, the mechanisms of which are poorly understood. Essentially all patients with continuous-flow left ventricular assist devices (LVADs) develop loss of high-molecular-weight (HMW) von Willebrand factor (VWF) multimers and may demonstrate reduced VWF function, as measured using the ristocetin cofactor or collagen binding, whereas levels of VWF antigen are generally increased.[16] These defects normalize when the device is removed.

The loss of HMW multimers, whose function is to support the interaction between subendothelial collagen and platelets at the site of injury, is thought to be related to increased rates of nonsurgical bleeding in patients on LVAD support. However, several observations suggest

Table 1. Anticoagulation and antiplatelet management in the PREVENtion of HeartMate II Pump Thrombosis study

- Within 48 h of device implantation and once bleeding has stopped, begin bridging with unfractionated heparin or low-molecular-weight heparin
  - o Goal PTT 40-45 s in first 48 h, followed by increase to PTT 50-60 s by 96 h
- Initiate warfarin within 48 h to obtain goal INR of 2.0-2.5 by postoperative day 5-7
- Discontinue heparin when INR is >2.0
- Initiate aspirin therapy (81-325 mg) 2-5 d postimplantation (if no bleeding)
- Maintain INR 2.0-2.5 and aspirin as long-term VAD support antithrombotic therapy

Adapted from Maltais et al.[13] PTT, partial thromboplastin time.

this is more complicated.[16] First, although all patients have loss of HMW multimers, not all patients experience bleeding. Second, loss of HMW multimers and reduced ristocetin activity are not associated with bleeding or the need for transfusion in patients on LVAD support.[16]

Loss of HMW multimers is related to the high shear rates created by continuous-flow LVADs, similar to what occurs in patients with aortic stenosis. However, the exact mechanisms of this loss have not been clearly demonstrated. Although many believe that increased shear forces alter the structure of VWF multimers to allow for enhanced cleavage by ADAMTS13, an increasing body of in vitro data suggests that shear- or oxidative stress−induced VWF binding to platelets may also play a role, perhaps causing a consumptive deficiency of VWF-like type IIB von Willebrand disease, which could be prothrombotic.[16] Clearly, this area deserves active investigation, as a better understanding of these alterations may lead to novel therapeutic targets designed to reduce bleeding and thrombotic complications.

Alterations in blood flow that exist in the presence of a continuous-flow device appear responsible for the development of AVMs in the gut and subsequent GI bleeding, although explanations differ regarding exactly why this occurs[16]. Recently, patients with VADs were found to have higher serum levels of an angiogenic factor, angiopoietin-2, which may contribute to AVM formation and bleeding.[18] Of note, the intensity of anticoagulation does not appear to play a major role in increasing the risk of GI bleeding.

In a patient with a VAD, diagnostic evaluation and management of GI bleeding should be performed in consultation with a gastroenterologist. When endoscopy or colonoscopy is unrevealing, a tagged red blood cell scan may be of use. In the absence of evident pump malfunction or concern for pump thrombosis, anticoagulant and antiplatelet therapies are often held in the presence of clinically significant bleeding.[16] Once bleeding has resolved, these agents can generally be resumed under careful monitoring. In some cases, octreotide, thalidomide, and danazol have been used off-label.[19,20] Patients with a history of GI bleeding are at increased risk for both pump thrombosis and recurrent bleeding, presumably because of adjustments in anticoagulation therapy in response to the clinical situation, posing a difficult challenge.[17]

VADs (pediatrics)

Use of VADs to support pediatric patients lags behind use to support adults, but experience is growing. Currently, the Berlin Heart EXCOR is the only pediatric-specific device approved by the FDA as a bridge to transplantation. Children with a body surface area of ~0.7 m^2 may be eligible to receive one of the continuous-flow devices approved for adults (although a body surface area >1.3 m^2 is recommended for the HeartMate II).[21] The EXCOR is a pulsatile flow VAD that can provide left ventricular, right ventricular, or biventricular support and is available in several sizes. The smallest pump size, which is 10 mL, has been used in very young infants (~3 kg).[22]

In the prospective, single-arm EXCOR Pediatric Investigational Device Exemption study, survival rates were significantly higher than those in historical control groups bridged with ECMO.[23] However, complication rates were high, including major bleeding in up to 50% of patients and stroke in 29%.[23] Comparison of historical cohorts of children receiving the EXCOR in Europe suggest that stroke rates were reduced by the addition of dual antiplatelet therapy with aspirin and dipyridamole compared with heparin alone.[24] The anticoagulation strategy used for the investigational device exemption trial is called the Edmonton Anticoagulation and Platelet Inhibition Protocol. This protocol was thoughtfully developed, taking into consideration prior pediatric VAD experience as well as developmental hemostasis (discussed subsequently in further detail).[25] In this protocol, coagulation assays included not only partial thromboplastin time (PTT) and/or anti-factor Xa (anti-Xa) level but also the use of thromboelastography (TEG) and TEG with platelet mapping (Haemonetics, Braintree, MA).[25] As a result of these additional assays, the protocol requires a fair amount of coagulation expertise to fully institute.

The primary differences between the pediatric protocol and the approach used in the adult PREVENtion of HeartMate II Pump Thrombosis trial include the following: (1) use of TEG to help adjust UFH; (2) initiation of dipyridamole at 48 hours as the first antiplatelet agent when the patient is not bleeding and meets specific laboratory parameters; (3) initiation of aspirin 1 mg/kg per day divided twice daily after chest tube removal when the patient is not bleeding and meets specific laboratory parameters; (4) titration of the aspirin dose using the TEG Platelet mapping assay to achieve >70% inhibition of arachidonic acid; and (5) transition to enoxaparin for goal anti-Xa level of 0.6 to 1.0 U/mL in patients <12 months of age or warfarin for goal INR of 2.7 to 3.7 in patients ≥12 months of age.[25] The intensification of anticoagulation in the Edmonton trial was likely due to the increased rates of thrombotic events in children compared with adults with continuous-flow devices.

It is important to emphasize the value of a standardized approach to antithrombotic therapy and well-defined clinical outcomes. These 2 factors are essential in identifying areas in which antithrombotic therapy may be refined for future study. Despite the fact that major bleeding occurred in up to 50% of subjects, only 24% of these events were adjudicated to be probably or definitely related to anticoagulation, and of the 29% of patients with stroke, only 9% were thought to be probably or definitely related to anticoagulation managment.[19,25] Interestingly, both bleeding and neurologic events occurred relatively early in the time course, demonstrating that this is a period worth further investigation. Overall, only 40% of coagulation monitoring assays for all agents were in the protocol-specified target ranges.[25] Whether this reflects intentional decisions that were made locally as a result of bleeding or rather the difficulty in maintaining the target range in children is not known. Also of note is the tremendous variability in medication dosing noted across patients at follow-up visits (eg, aspirin doses ranging from 0.5 to 30 mg/kg per day; enoxaparin

from 1 to 6 mg/kg per day).[25] Additional observations included the relationship between infection, inflammation, and thrombotic events, as patients with major infections were more likely to require subsequent pump change.[25]

The Pumps for Kids, Infants, and Neonates program, which is funded by the National Heart, Lung, and Blood Institute, was developed in response to the lack of devices small enough for children with congenital heart disease or heart failure and the lack of market incentive to drive product development. This program led to development of the Jarvik 2015, a fully implantable continuous-flow VAD (15 mm wide) in which blood flow can be adjusted as the child grows.[26] A randomized clinical trial comparing this device with the EXCOR VAD was expected to start enrolling patients in the spring of 2017.[26] The antithrombotic guidelines for this protocol have not been published but are expected to be modified on the basis of experience and results from the EXCOR study.

ECMO

ECMO, which offers temporary MCS, gained early success in neonates with respiratory failure. Its use has progressed to include pediatric cardiac patients (as a bridge to transplantation or an adjunct to cardiopulmonary resuscitation) and older children and adults with acute respiratory or cardiac failure. In contrast to VADs, ECMO includes oxygenation of the blood provided through an artificial lung (membrane oxygenator) with return to the circulation via the vein (venovenous) or artery (venoarterial). In venovenous mode, the artificial lung is in series with the native lungs and replaces lung function. In venoarterial mode, the artificial lung is in parallel with the native lungs and replaces both heart and lung functions.

Exposure of blood to the large surface of the ECMO circuit initiates the contact factor pathway, activates platelets, and induces an inflammatory response. To prevent the circuit from clotting, anticoagulation is necessary. Generally, this is achieved using UFH. However, titrating the intensity of anticoagulation to prevent the ECMO circuit from clotting and prevent bleeding in the patient remains a major challenge. As with VADs, hemorrhagic and thrombotic complications, including intracranial hemorrhage (particularly in neonates), embolic stroke, surgical bleeding, and circuit thrombosis, are common and occur in up to 50% of patients.[27] These complications have a significant impact on morbidity and mortality.

Of note, the correlation between intensity of anticoagulation and clinical outcomes has not been clearly demonstrated. In an autopsy series of 29 pediatric patients on ECMO, thrombosis and/or hemorrhage was observed in 86% of patients, whereas 31% of patients had both.[28] There was no correlation between laboratory studies (PTT or activated clotting time [ACT]) or heparin dose and hemorrhage or thrombosis.[28] A large retrospective study suggested increased heparin doses were associated with increased survival, independent of other variables including ACT.[29]

Developmental hemostasis

The coagulation system in neonates and young children differs from that of older children and adults. Although the basic pathways are maintained, the concentrations of many of the coagulation factors differ.[30] The consequences of developmental hemostasis for young children include (1) reduced thrombin generation compared with that of adults, (2) a greater risk of imbalances in hemostasis with subsequent thrombotic or hemorrhagic complication, and (3) a need for higher weight-based doses of anticoagulants to reach the same target level, particularly with UFH or low-molecular-weight heparin, which require antithrombin (AT) to exert anticoagulant effects. AT levels are markedly reduced in neonates compared with adults.[30]

Approach to anticoagulation in ECMO

UFH remains the primary anticoagulant used in ECMO. Benefits of UFH include clinician familiarity, short half-life, and reversibility, although it is a challenging drug to titrate, particularly in critically ill children and neonates. There is considerable interpatient variation, in part related to the nonspecific binding of heparin to various plasma proteins. This nonspecific protein binding can cause heparin resistance, which refers to lack of an anticoagulant effect despite high doses of heparin. Low levels of AT, which are common in young children, also contribute to heparin resistance.

Most patients receive a bolus of UFH (50-100 U/kg) at the time of ECMO cannulation, although this may be withheld or reduced in patients with recent surgery or bleeding. This is followed by a continuous infusion of UFH for the duration of ECMO therapy. The use of antiplatelet therapy in neonates and children on ECMO is uncommon, whereas there is more variability in practice in adults on ECMO. Antiplatelet agents may be continued in adult patients on ECMO who have additional indications for antiplatelet therapy.[31]

Monitoring heparin

Several coagulation assays can be used to monitor and titrate UFH. The differences between these assays are listed in Table 2. Traditionally, the ACT has been used in patients on ECMO. More recently, in an attempt to reduce high complication rates, many pediatric ECMO centers have incorporated additional coagulation assays, including PTT, heparin anti-Xa level, AT activity, and TEG, in their routing monitoring. Most centers have developed their own guidelines for managing anticoagulation, but there is significant practice variation.[32] General guidelines for managing anticoagulation in ECMO have been summarized and published by the Extracorporeal Life Support Organization.[33]

Several studies have demonstrated the poor correlation of ACT with both anti-Xa level and PTT in neonates and children on ECMO.[34,35] A retrospective study that compared ACT with PTT in pediatric ECMO patients suggested that management of patients using PTT resulted in fewer bleeding complications and a reduction in mortality, although more circuit changes were required with this approach.[35] In a prospective study of 34 neonates and children, Bembea et al[34] evaluated the correlation between ACT, anti-Xa level, and PTT. The rate of heparin was adjusted on the basis of ACT, with a goal of 180 to 220 seconds. ACT and anti-Xa correlated poorly; PTT correlated weakly with anti-Xa.[34]

Because these assays correlate so poorly and no high-quality evidence has demonstrated that any single assay is best, it is unlikely that ACT can be completely replaced by either the PTT or anti-Xa assay. The primary value of the anti-Xa level is that it provides a direct measurement of the anticoagulant effect, whereas the PTT (with heparinase) may be helpful in assessing coagulopathy, especially when there are discrepant results. However, the ACT remains the only readily available point-of-care assay. The PTT and anti-Xa level can provide additional information; when used in conjunction with the heparin dose, other laboratory values (platelet count, fibrinogen level, prothrombin time, AT), and the clinical status of the circuit and patient, they may help guide therapy, including blood product replacement and heparin titration. However, because these

Table 2. Assays used to monitor heparin

Assay	Assay details	Advantages	Disadvantages	Comments
ACT	Fresh whole blood + activator; initiates coagulation via the contact factor pathway	Rapid, point-of-care test	Nonspecific to heparin	Typical range for ECMO is 180-220 s
		Most useful at very high concentrations of heparin when PTT is unmeasurable (cardiopulmonary bypass)	Prolonged ACT may be due to heparin; hypothermia; low concentrations of factor XII, XI, X, IX, V, II, or fibrinogen; thrombocytopenia; or platelet dysfunction	The type of activator influences the results
PTT	Citrated plasma + activator; initiates coagulation via contact factor pathway	Used for decades to measure anticoagulant effect of heparin in patients with deep vein thrombosis	Nonspecific to heparin	Therapeutic PTT range for adults with DVT is 1.5-2.5 times midpoint of normal PTT range
		Widely available	Prolonged PTT may be due to heparin; low concentrations of factor XII, XI, X, IX, V, II, or fibrinogen; or lupus anticoagulant	
			PTT may be shortened because of elevated factor VIII or fibrinogen	
Anti-Xa	Citrated plasma is added to a known amount of excess FXa	Direct measure of heparin effect	Some assays are affected by hyperlipidemia and hyperbilirubinemia	Some assays add exogenous AT, others do not; this can influence the results
	The heparin in the sample binds to AT and inhibits Xa Residual Xa cleaves a chromogenic substrate that is measured	Not influenced by coagulopathy, thrombocytopenia, or dilution	May not be always available	Therapeutic range for adults with DVT: 0.3-0.7 U/mL

DVT, deep vein thrombosis; FXa, factor Xa.

assays are often discrepant and interpretation is not always straightforward, the level of coagulation expertise required to manage patients is far greater than that required with the ACT alone.

TEG

TEG has gained recognition in some pediatric centers over the last decade because of its role in monitoring antiplatelet therapy in children on the EXCOR VAD. The utility of TEG in monitoring the coagulation status of patients receiving ECMO has not been well established. Ideally, samples should be split and evaluated with and without the addition of heparinase to evaluate both the baseline coagulation status and the heparin effect. In a bleeding patient, TEG may be useful in assessing the overall coagulation status and may help distinguish clotting factor deficiency from platelet dysfunction or hyperfibrinolysis.

AT replacement

AT concentrates are available and approved for use in patients with inherited AT deficiency. Several studies have suggested that AT may be of benefit in adults undergoing cardiopulmonary bypass who are resistant to heparin.[36] The use of AT in this setting improves the likelihood of achieving a therapeutic ACT, but it has not been shown to alter overall clinical outcomes.

Neonates are born with low concentrations of AT, and critically ill children have AT levels that are 50% less than those of age-matched controls.[37] Monitoring of AT levels in children during ECMO has increased in an effort to improve anticoagulation management, and the off-label use of AT replacement has drastically increased in ECMO patients across US children's hospitals over the last 10 years.[32,38] The hypothesis driving this empiric therapy is that AT replacement in patients with low AT levels will improve the anticoagulant effect of heparin and reduce thrombotic complications. There are conflicting data regarding the effect of AT supplementation to enhance the effect of heparin in children on ECMO.[34,39]

The largest risk of AT supplementation may be hemorrhage, although several uncontrolled series have not reported increased hemorrhage in this setting. A Cochrane review of 20 randomized clinical trials of AT supplementation in critically ill patients (including 267 children) concluded that there was no decrease in mortality and that AT supplementation was associated with a 1.5-fold increase in bleeding.[40] Although it is theoretically possible that AT supplementation can improve anticoagulation and reduce thrombotic complications, it is equally possible that it may be of no clear benefit or may be associated with increased bleeding. Thus, it is paramount that AT therapy be evaluated in a vigorous, controlled, multicenter study with clinically important outcomes. In the meantime, it seems prudent to restrict routine use of AT to patients who demonstrate significant heparin resistance with low levels of AT until well-designed studies can be completed.

Alternative anticoagulants

In patients with presumed heparin-induced thrombocytopenia, heparin alternatives are necessary. Argatroban and bivalirudin are parenteral direct thrombin inhibitors (DTIs) that have been used successfully in patients with VADs and on ECMO. Increasingly, pediatric centers have reported good experience in small studies with bivalirudin, in both the EXCOR device and ECMO in patients who had "failed" heparin.[41-43] These drugs are not reversible but have

a short half-life. Unlike heparin, bivalirudin can inhibit clot-bound thrombin. This drug can be monitored using PTT, titrating 1.5 to 2 times the normal value, although the response is not linear and the PTT often "levels off" despite increases in bivalirudin dose. When there is venous stasis, bivalirudin is metabolized by proteolytic degradation, reducing its anticoagulant effect, which could be a concern in patients with poor cardiac function.[44]

In addition, because MCS involves foreign surface and contact factor activation, one should pause when considering the rationale for using a DTI, given findings in a randomized clinical trial of dabigatran (oral DTI) compared with warfarin to prevent stroke in patients with heart valves.[45] In this trial, both stroke and bleeding events were increased with dabigatran; this is hypothesized to be attributable to the fact that unlike warfarin (or heparin), the DTIs do not inhibit the contact pathway. Nonetheless, UFH is such a challenging drug in children that alternatives may possibly provide better anticoagulation. However, it is important that they be studied systematically using standardized protocols with well-defined outcomes.

Summary

The use of VADs and ECMO, both lifesaving technologies, continues to grow. Bleeding and thrombosis remain common causes of morbidity and mortality, and increasing attention has focused on the management of antithrombotic therapy. Although meticulous titration of anticoagulation intensity is important, it is clear that both bleeding and thrombotic complications are multifactorial, and each factor must be optimizing to improve outcomes. In addition to anticoagulation, these factors include device design and hemocompatibility, surgical considerations, flow parameters, blood pressure, inflammation, and infection.

Further technologic advances in VAD design, potentially with the HeartMate 3 and Jarvik 2015, offer hope of reducing complications. Novel approaches for anticoagulation are also warranted, and several potential strategies may offer hope. Both factor XI and factor XII may be good targets for inhibition, reducing thrombin formation with less bleeding risk, and several strategies are in development.[46] The use of antibodies that inhibit factor XII has prolonged ECMO circuits in a porcine model without risk of bleeding.[47]

A "one-size-fits-all" approach to anticoagulation management in patients on MCS is problematic because of interpatient variability as well as subtle differences between devices. Rather, a team of dedicated and experienced providers must take multiple factors into consideration and adjust therapy accordingly. It is useful to have a standardized starting point for antithrombotic therapy so that patients can be evaluated systematically and with a consistent approach.

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