

Control of Coagulation During Extracorporeal Membrane Oxygenation

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The use of extracorporeal membrane oxygenation (ECMO) requires maintaining a delicate balance between the prevention of thrombosis and the avoidance of hemorrhage. Anticoagulation is necessary to maintain circuit flow. It counteracts the activation of clotting mechanisms that occurs as a result of the interaction between circulating blood and the foreign surfaces of the ECMO equipment as well as endothelial damage within the vasculature. Heparin remains the anticoagulant of choice; however, the difficulty in adjusting dosages and the risk of developing heparin-induced thrombocytopenia have led to the use of alternative therapies such as argatroban and lepirudin. In addition, thrombolysis with alteplase is now being used in patients who develop clots despite anticoagulation. Aminocaproic acid has been used for more than a decade to manage or prevent hemorrhage in patients on ECMO, but a new report suggests that activated recombinant factor VII may also be useful as a hemostatic agent. Over the next decade, it is likely that the role of these newer agents will grow, making them important tools in the management of patients on ECMO.

KEYWORDS: anticoagulants, extracorporeal membrane oxygenation, hemostatics, pediatrics, thrombosis

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INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is a form of prolonged cardiopulmonary bypass used to support patients with life-threatening respiratory or cardiac failure. Since its introduction in the mid-1970s, ECMO has been used most often in neonates to treat severe respiratory failure associated with congenital diaphragmatic hernia, meconium aspiration syndrome, persistent pulmonary hypertension, severe respiratory distress syndrome, and sepsis. Although the use of ECMO

for these conditions has declined over the past decade as newer therapies such as high frequency mechanical ventilation and inhaled

ABBREVIATIONS: ACT, activated clotting time; APCC, activated prothrombin complex concentrates; aPTT, activated partial thromboplastin time; AT III, antithrombin III; DTI, direct thrombin inhibitors; EACA, Epsilon aminocaproic acid; ECMO, extracorporeal membrane oxygenation; ELSO, Extracorporeal Life Support Organization; HIT, immune-mediated heparin-induced thrombocytopenia; IV, intravenous; rFVIIa, Recombinant factor VIIa

nitric oxide have become available, there has been an increase in its use following surgical repair of congenital cardiac defects and in neonatal and pediatric cardiac transplantation.^{1,2} A wide variety of medications are necessary during ECMO; however, relatively little is known about their pharmacokinetic and phar-

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macodynamic properties in this setting. Among the most important medications are those used for controlling coagulation.

ANTICOAGULATION

The use of ECMO requires maintaining a delicate balance between the prevention of thrombosis and the avoidance of hemorrhage. Anticoagulation is necessary to maintain blood flow within the circuit during ECMO. It counteracts the activation of clotting mechanisms, which may occur as the result of the interaction between circulating blood and the foreign surfaces of the equipment as well as from damage to vascular endothelium.³ In spite of adequate anticoagulation, the risk for thrombosis remains high. In their January 2005 summary, the Extracorporeal Life Support Organization (ELSO) reported a 53% incidence of clots within the circuits of neonates on ECMO for respiratory illnesses and a 35% incidence in the circuits of neonates on ECMO for cardiac support.⁴

Heparin

Systemic anticoagulation during ECMO is currently achieved with the administration of intravenous (IV) heparin. Heparin binds to antithrombin III (AT III) to inactivate factor Xa, thus inactivating thrombin and many other components of the clotting cascade. The administration of heparin remains empirical, as relatively little has been published in the medical literature regarding its use in ECMO. A loading dose of 75 to 100 units/kg is typically administered at the time of cannulation, followed by an infusion of 25 to 40 units/kg/hr.^{1-3,5} Heparin is known to bind to the ECMO circuit components, resulting in altered pharmacokinetic parameters of heparin. In 1990, Green and colleagues found that the average clearance was 3.8 ± 1.9 mL/kg/min in five infants receiving ECMO.⁵ This was nearly the same clearance noted for the combined values from the patients after ECMO (1.6 ± 0.5 mL/kg/min) and the separated circuits (2.1 ± 0.8 mL/kg/min). The authors concluded that more than half of the heparin administered during ECMO was eliminated by the circuit. Heparin-coated circuit components are available which minimize binding of IV heparin to the lumen surface and

reduce platelet adhesion. Although the effectiveness of this technique is still being evaluated, these heparin-impregnated circuits may reduce the risk for hemorrhage, as well as decrease the need for systemic heparinization.^{3,6}

In order to provide adequate anticoagulation without producing hemorrhage, the coagulation status of patients on ECMO must be closely monitored. Bedside monitoring of activated clotting time (ACT) is currently the most common approach, with a target range of 180 to 225 seconds in standard neonatal and pediatric cases.¹ The use of activated partial thromboplastin time (aPTT), while a more common test in settings other than ECMO, is often limited by the inability to conduct testing quickly and inexpensively at the bedside. Platelet counts are typically maintained at or near 100,000 cells/mm³.^{1,2}

While excessive bleeding is the primary adverse effect associated with heparin administration, patients can develop other complications, such as immune-mediated heparin-induced thrombocytopenia (HIT). With HIT there is an increase in thrombin generation, placing the patient at risk for arterial or venous thrombosis. There has been an increasing number of reports of HIT in children during the last decade, most of which have been associated with cardiac surgery.⁷ While there have been only a few case reports of HIT during ECMO, one case resulted in patient death.⁸ The low number of reports may be related to the difficulty in recognizing HIT since thrombocytopenia can be attributed to a number of other factors during ECMO. Clinicians should consider the possibility of HIT in any patient with significant thrombocytopenia. The management of HIT includes discontinuing heparin, which prevents the conformational changes on platelet factor 4 thereby allowing platelets to form antigenic sites to circulating immune globulin. Heparin must then be replaced with an alternative anticoagulant.⁷ Two direct thrombin inhibitors (DTIs), argatroban and lepirudin, have been used successfully in ECMO patients that developed HIT. A third DTI, bivalirudin, may also prove to be useful in this setting.

Argatroban

The first DTI used to maintain ECMO circulation was argatroban. It has been used suc-

cessfully in both adult and pediatric patients. Argatroban is a synthetic arginine derivative. Like the other DTIs, argatroban reversibly inhibits both free and clot-bound thrombin. In 2000, Kawada and colleagues described the use of argatroban during ECMO in two neonates.⁹ Continuous infusions of argatroban at doses of 0.5 to 10 mcg/kg/min were used to maintain ACT values of approximately 200 seconds for a period of 6 days in one patient and 78 days in the other. There was no evidence of intracranial hemorrhage, bleeding from the cannula site, or thrombosis requiring replacement of circuit components. Scanning electron microscopy of an oxygenator after 14 days of ECMO revealed only a few platelets adhering to the external surface of the polypropylene hollow fibers. Based on their observations, the authors suggested that argatroban may serve as a useful alternative anticoagulant during ECMO with less risk of systemic thromboembolization and hemorrhage.

Another successful case was reported in a 32-year-old adult on ECMO after acute rejection following cardiac transplantation.¹⁰ When the platelet count decreased from 278,000/mm³ to 28,000/mm³, HIT was suspected and the patient was switched from heparin to argatroban. Therapy was initiated with a bolus of 10 mg followed by an infusion of 2 mcg/kg/min. The dose was adjusted to maintain ACT values between 200 and 400 seconds and aPTT values of 80 to 90 seconds. Argatroban successfully maintained adequate anticoagulation for 6 days, without adverse effects.

A third account of argatroban usage involved a 2.6 kg newborn placed on a ventricular assist device for 3 days after a Norwood procedure for hypoplastic left heart syndrome.¹¹ During this period, heparin was infused at a rate of 16 to 32 units/kg/hr. The patient was weaned off the ventricular assist device on postoperative day 5. Two days later, the patient was placed on continuous veno-venous hemofiltration to mobilize fluids. Shortly after beginning hemofiltration, multiple clots developed and the platelet count dropped from 185,000 to 53,000/mm³. The diagnosis of HIT was made and the patient was converted to argatroban, with a 200 mcg/kg loading dose followed by an infusion of 3–7.5 mcg/kg/min titrated to maintain aPTT values between 60 and 80 seconds. Five days later,

the patient was placed back on the ventricular assist device. A 50-mcg dose of argatroban was added to the circuit prime, and the infusion was held for 4 hours to allow normalization of coagulation parameters. The infusion was restarted at 0.2 mcg/kg/min. Adequate anticoagulation was maintained; ACT values were 160 to 180 seconds. After 4 days, the ventricular assist device circuit was converted to ECMO. The argatroban infusion ranged from 0.05 to 1.8 mcg/kg/min to maintain ACT values between 200–220 seconds. A pulmonary biopsy revealed a venous clot which appeared to date from the period of heparin administration. Thrombolysis with alteplase was attempted but produced excessive bleeding. Support was withdrawn 2 days later.

In addition to these cases, Tcheng and colleagues published an abstract describing their experience with six pediatric patients who received argatroban after developing HIT.¹² Four of the children (ages 15 months to 16 years) were receiving ECMO. Argatroban was initiated at 0.5 to 2 mcg/kg/min and titrated up to a maximum of 3.5 mcg/kg/min in these patients. The duration of therapy ranged from 1 to 39 days. In three of the cases, argatroban was terminated when ECMO was discontinued. In the remaining case, the patient resumed heparin therapy after HIT had been ruled out. All cases were considered to be adequately anticoagulated, and no complications were noted.

Argatroban may also be useful in patients with low levels of AT III.^{9,13} The efficacy of heparin is dependent on the presence of AT III, and the reduction in AT III observed during ECMO may explain, in part, the difficulties in maintaining adequate anticoagulation. Unlike heparin, DTIs do not require AT III as a cofactor and, therefore, may provide a more consistent level of anticoagulation during ECMO. In 2002, Yonekawa and colleagues conducted an *in vitro* assessment of five ECMO circuits: one primed with 500 units heparin, one primed with 1 mg argatroban and one with the combination of the two anticoagulants.¹³ The circuits were then primed according to standard procedures. The authors found equivalent ACT values in all three circuits throughout the 6-hour evaluation period. Additional measurements of clotting function, D-dimer, thrombin-antithrombin complex, and

prothrombin fragment 1+2 were also similar. The authors concluded that argatroban may provide a similar degree of anticoagulation to heparin and recommended that clinical trials be conducted to compare the two agents.

While these initial reports suggest that argatroban can be successfully used to maintain anticoagulation during ECMO, an abstract presented at the 2004 meeting of the Pediatric Academic Societies describing 45 courses of argatroban in pediatrics patients with HIT included one patient on ECMO who developed thrombi in the circuit oxygenator.¹⁴ Controlled clinical trials with argatroban are needed to better define an optimal dosing strategy and to establish the relative risk for thrombosis. Until these trials are available, argatroban should be reserved for patients with HIT or other contraindications to heparin.

Lepirudin

Deitcher and colleagues reported the first use of lepirudin, another DTI, in a patient receiving ECMO in 2002.¹⁵ A 4-year-old patient with dilated cardiomyopathy and worsening cardiac failure developed HIT while on heparin awaiting cardiac transplantation. After the diagnosis, anticoagulation was switched to lepirudin, with an infusion starting at 0.15 mg/kg/hr and titrated to maintain an aPTT 1.5 to 2.5 times the normal value. After three days, the patient developed pulmonary failure and was placed on ECMO. Lepirudin was discontinued and heparin was begun. Within 24 hours, the platelet count again dropped, a clot was noted in the ECMO circuit and heparin was discontinued. The patient was given a 0.4 mg/kg loading dose of lepirudin and the circuit was primed with 0.4 mg of lepirudin for every 75 mL blood volume and an unspecified dose of lepirudin as an infusion was resumed. Therapy was continued for another 13 days. No hemorrhagic or thrombotic complications were noted; however, the patient expired 5 hours after cardiac transplantation from excessive postoperative blood loss.

In 2004, Dager and colleagues reported the use of lepirudin in a 17-year-old patient on ECMO.¹⁶ The patient was receiving ECMO, with heparin as the anticoagulant, after developing sepsis and progressive pulmonary failure following a motor vehicle accident. The patient's platelet count after initiation of

ECMO was 116,000/mm³, but gradually declined to 44,000/mm³ over the next five days. An enzyme-linked immunosorbent assay was highly positive for HIT antibodies. The heparin infusion was discontinued and lepirudin was initiated with a bolus dose of 0.1 mg/kg followed by an infusion of 0.12 mg/kg/hr. The lepirudin infusion was titrated in 0.01 to 0.02 mg/kg/hr increments and reached 0.23 mg/kg/hr at its highest. Although no significant hemorrhage or thrombosis occurred, there was some minor bleeding when the aPTT ratio was greater than 2. After reducing the lepirudin dose, the patient's aPTT ratio was maintained at two times control. Management of anticoagulation was complicated by the use of a heparin-coated circuit, but the authors believed a change to a non-coated circuit would pose an additional risk to the patient. After 6 days, ECMO was discontinued because of continued pulmonary failure and the patient expired.

Bivalirudin

A third DTI, bivalirudin, has also been suggested as an anticoagulant for patients receiving ECMO. Although no case reports have yet been published, an *in vitro* study produced favorable results.¹⁷ Yonekawa and colleagues prepared three ECMO circuits according to standard procedures at their institution. One circuit was primed with 500 units of heparin, a second with 5 mg bivalirudin, and a third with 50 mg bivalirudin. As in their previous work with argatroban, all three circuits showed adequate anticoagulation. Thrombin generation was also similar among the three circuits. Levels of thrombin-antithrombin complexes and prothrombin fragment 1+2 were higher at the 6-hour observation period in both bivalirudin groups. The authors speculated that this increase was a reflection of the short half-life of the bivalirudin. Based on their results, the authors concluded that bivalirudin may be useful as another alternative to heparin in maintaining anticoagulation during ECMO.

THROMBOLYSIS

Alteplase

Despite adequate anticoagulation, a significant number of patients on ECMO still develop thromboses. Alteplase, a recombinant tissue

plasminogen activator, has been used in the neonatal and pediatric population to promote clot lysis. Unlike urokinase or streptokinase, alteplase has a specific affinity for binding to fibrin within a thrombus. The alteplase-fibrin complex promotes the binding of plasminogen to fibrin, generating plasmin at the site of the thrombus without producing significant effects on circulating plasminogen. In addition to its specificity, alteplase also offers the advantage of a short elimination half-life (3 to 9 minutes). In the event of a hemorrhagic complication, discontinuation of therapy will result in a rapid return to normal levels of plasminogen.¹⁸

Three case reports described the use of alteplase in neonates on ECMO.¹⁹⁻²¹ Glover et al. reported using alteplase to resolve an occlusion of the left arm distal to the brachial artery.¹⁹ The patient, a 2-day-old female with sepsis, developed clinical symptoms consistent with thrombus formation after 21 hours on ECMO. Alteplase was initiated with a bolus dose of 0.48 mg/kg followed by an infusion of 0.27 mg/kg/hr for 3 hours. When ultrasound failed to show significant improvement after the initial infusion, alteplase was continued for another 3 hours. At the end of the second infusion, perfusion had improved and a palpable pulse was present. A head ultrasound performed at that time revealed a grade I hemorrhage on the right. A day later, ECMO was discontinued and a subsequent head ultrasound showed almost complete resolution of the bleed. It is uncertain whether the intracranial hemorrhage was associated with the use of ECMO, alteplase, or the combination of the two therapies. The patient had no other complications potentially related to alteplase administration.

A second case described a term infant with a left-sided congenital diaphragmatic hernia who was placed on ECMO for respiratory support.²⁰ On the third day of ECMO, bleeding was noted from the urinary catheter and the infant became anuric. An ultrasound revealed a large clot in the bladder. The patient's coagulation status on ECMO was considered to be stable. Over the next four days, repeated doses of 0.5 or 1 mg alteplase (0.17 to 0.34 mg/kg) were diluted with normal saline and instilled into the bladder. After each dose, the catheter was clamped for one hour and then allowed to drain. Two days after apparent resolution of the bladder

clot, an aortic clot was identified in the arterial cannula. In addition to adjustment of the heparin infusion, a loading dose of 0.5 mg/kg alteplase was administered and was followed by an infusion of 0.17 mg/kg/hr for 3 hours. The dose was then decreased to 0.03 mg/kg/hr for a total duration of 48 hours. Following resolution of the aortic clot, an ultrasound revealed clot retention again in the bladder. Alteplase (1 mg) was again administered intravesically and repeated 8 hours later. The patient had no further complications and ECMO was discontinued on day 15.

Alteplase was also used in the lysis of an aortic and renal artery thrombus in a neonate on ECMO.²¹ The patient was a female with a left-sided congenital diaphragmatic hernia. On the seventh day of ECMO, ultrasound revealed a thrombus in the abdominal aorta from the level of the diaphragm down to the bifurcation. Both kidneys showed signs of ischemic injury. The umbilical artery catheter was removed and hemodialysis was initiated. On day 12, alteplase was initiated with a dose of 0.5 mg/kg/hr and continued for 12 hours. Follow-up ultrasound revealed resolution of the aortic clot and improvement in renal blood flow. There was no evidence of adverse effects. The patient's respiratory condition, however, continued to deteriorate and support was withdrawn after 18 days of ECMO.

PREVENTION OR TREATMENT OF EXCESSIVE BLEEDING

While avoiding thrombosis is a major concern during ECMO therapy, the prolonged maintenance of systemic anticoagulation is not without risk. Hemorrhage is one of the most serious complications of ECMO. In their most recent report, the Extracorporeal Life Support Organization (ELSO) documented a 15% incidence of bleeding at surgical and cannula sites in neonates on ECMO for respiratory or cardiac causes. In addition, there was a 5.8% incidence of intracranial hemorrhage in the neonatal respiratory ECMO population and a 9.4% incidence in neonates receiving ECMO after cardiac surgery.⁴ Hemorrhage during ECMO may result from excessive administration of anticoagulants, surgical blood loss, or coagulopathy related to hemodilution, thrombocyto-

penia and impaired platelet function, deficiency of clotting factors, and hyperfibrinolysis.¹

Epsilon Aminocaproic Acid

Epsilon aminocaproic acid (EACA) is a synthetic lysine analog that suppresses fibrinolytic activity by fitting into the lysine-binding site of plasminogen and preventing the binding of plasminogen to fibrin. In addition, EACA prevents plasmin-mediated degradation of platelet glycoprotein Ib receptors, preserving platelet function.^{22,23} It has recently been suggested that EACA also promotes release of endogenous α_2 -antiplasmin, which exerts an additional antifibrinolytic effect through neutralization of free plasmin.^{24,25} For more than a decade, EACA has been used to decrease the bleeding complications associated with ECMO.²⁶⁻²⁸ In 1993, Wilson and colleagues published their early experience with EACA in 42 infants on ECMO, comparing them to a group of 68 historical controls.²⁶ The group receiving EACA were given a bolus dose of 100 mg/kg IV at the time of cannulation, followed by an infusion of 30 mg/kg/hr until decannulation. Patients receiving EACA had significantly less bleeding while on ECMO ($P = .03$) and required fewer exogenous blood products ($P = .01$). The difference between EACA treatment and control was greatest in the congenital diaphragmatic hernia and cardiac patients, and was not significantly different in the patients with meconium aspiration syndrome. The incidence of intracranial hemorrhage was also significantly different ($P = .007$), with none of the EACA patients developing bleeds compared to 12% of the controls. There was a trend towards more thrombotic complications in the EACA group, but the difference was not statistically or clinically significant. In order to reduce the risk for thrombosis, the authors recommended using EACA only when the circuit flow is at least 100 mL/kg/min. Based on this early report, many institutions have implemented EACA protocols for their ECMO patients at high risk for bleeding.

In 1998, Horwitz and colleagues attempted to replicate these results in a prospective study.²⁷ They conducted a multicenter, randomized, placebo-controlled study of EACA in 29 infants on ECMO. Thirteen neonates were randomized to receive EACA as a 100 mg/kg IV bolus followed

by a 25 mg/kg/hr infusion for 72 hours, and 16 received placebo. Although the results were not statistically different, there was a higher incidence of intracranial hemorrhage in the patients receiving EACA (23% versus 12.5% in controls). Thrombotic complications developed in only two patients, both in the placebo group. The authors concluded that EACA did not appear to decrease the risk of intracranial hemorrhage during ECMO.

In 2003, Wilson's group published a ten-year retrospective review of their cumulative experience with EACA in high risk neonates on ECMO.²⁸ During the period from 1991 to 2001, 431 neonates were placed on ECMO. Of those, 298 patients (69%) were given EACA. The most frequent reason for use was the need to perform surgical procedures during ECMO. Comparing the results of their EACA patients to cumulative patient data from the ELSO registry, the authors found no significant difference in the rate of intracranial hemorrhage, but there was a significant reduction in blood loss associated with surgical procedures (10% in the EACA patients versus an average of 30% in the ELSO registry data). The rates of thrombotic complications were no different between the EACA patients and controls, with a 4% rate of cerebral infarction in EACA patients versus 5% in controls and a 3% rate of vessel thrombosis versus 1% in controls. The EACA patients required more frequent circuit changes and were on ECMO for a significantly longer period of time. The authors concluded that although EACA did not reduce intracranial hemorrhage, it was effective in reducing surgical blood loss. They suggested that EACA may be most beneficial in patients who have had cardiac surgery and are at greater risk for surgical site bleeding.

The most serious complication of EACA use in surgical patients is thrombosis, with resultant infarction, stroke, or pulmonary embolism. Fatal thrombosis has been reported in both children and adults.²⁹ Hocker and Saving reported fatal aortic thrombosis in a neonate receiving EACA during ECMO for congenital diaphragmatic hernia.³⁰ The patient underwent surgical repair on day of life 5 (hour 58 of the ECMO course). Because of the risk for postoperative bleeding, the patient was given EACA, with a 100 mg/kg loading dose followed

by an infusion of 30 mg/kg/hr. At ECMO hour 79, the patient had stiffness and blanching of the extremities, and small thrombi were noted in the arterial cannula. The patient was taken off ECMO and placed on conventional mechanical ventilation; EACA was discontinued. An echocardiogram revealed a large aortic thrombus. The heparin infusion was increased and the patient was given urokinase, but went on to develop severe metabolic acidosis, anuria, hypotension, and bradycardia. The patient expired shortly after withdrawal of mechanical ventilation. Although the reasons for the extensive thrombosis were not clear, the authors suggested that the clot may have formed during a period when the ACT values were below the target range and the flow rate was less than 100 mL/kg/min.

Recombinant Factor VIIa

Recombinant factor VIIa (rFVIIa) is a vitamin-K dependent glycoprotein structurally similar to human factor VII. In pharmacologic doses, rFVIIa promotes hemostasis at the site of injury without significant systemic activation of the clotting cascade. This local effect is initiated when cell-bound tissue factor is exposed during vessel injury. Under normal circumstances, factor VII in the circulating blood volume binds with tissue factor and is activated. The resulting complex stimulates clot formation. Administration of rFVIIa results in formation of a similar complex with tissue factor, resulting in the activation of factors IX and X. It also interacts with factor V to convert prothrombin to thrombin. The thrombin produced at the site of injury not only stabilizes the clot, but also triggers further local response by stimulating surrounding platelet surfaces to activate and release additional clotting factors.^{31,32}

At this time, the only indication for rFVIIa approved by the Food and Drug Administration is the treatment of bleeding in patients with hemophilia A or B and inhibitors to factors VIII or IX.³¹ In clinical practice, rFVIIa has been shown to be useful in patients with coagulation disorders resulting from acquired hemophilia, thrombocytopenia, hepatic dysfunction, and oral anticoagulant overdose.³² In addition, rFVIIa has recently been found to be beneficial in the management of bleeding associated with trauma or surgery.³²⁻³⁴ Although the specific

mechanism by which rFVIIa benefits patients without underlying hemophilia is not yet well understood, it has been suggested that increasing the total concentration of activated factor VII may compensate for low circulating levels of factors V, VIII, and IX and prothrombin occurring in the face of significant blood loss. Administration of rFVIIa may also compensate for the loss of or damage to platelets that is known to occur during surgery and cardiopulmonary bypass.^{32,34}

There are currently three reports of using rFVIIa during ECMO.³⁵⁻³⁷ In 2004, Verrijckt and colleagues described the successful use of rFVIIa in a neonate on ECMO.³⁵ The patient was a term, 3.2 kg male with d-transposition of the great arteries. Following repair of his congenital cardiac defect, the patient exhibited persistent left ventricular failure. After failing to wean from cardiopulmonary support, he was transitioned to ECMO. During the first two postoperative days, the patient had severe bleeding from his chest tubes, despite repeated administration of blood products. Surgical re-exploration failed to reveal a source. Aminocaproic acid (100 mg/kg IV) was administered without improvement. The authors then elected to administer rFVIIa at a dose of 30 mcg/kg IV. The patient exhibited a sharp decline in bleeding without evidence of excessive thrombosis. Chest tube bleeding declined from 9.1 to 3.5 mL/kg/hr after rFVIIa administration, while the platelet count increased from 8,999/mm³ to 125,000/mm³. The patient was weaned from ECMO on postoperative day 5, but expired six days later due to continued left ventricular failure.

Although successful in that report, the administration of rFVIIa together with activated prothrombin complex concentrates (APCC) resulted in fatal thrombosis in an adult patient on ECMO after lung retransplantation.³⁶ In an effort to stem postoperative blood loss, the patient was given two 90 mcg/kg doses of rFVIIa without incident. Subsequent administration of APCC, however, resulted in massive fatal thrombosis. Based on the length of time between rFVIIa doses and the development of thrombosis (approximately 6 hours) and the relatively short elimination half-life of rFVIIa (2 to 3 hours), the authors concluded that the thrombosis was more likely the result of APCC

use rather than factor VII replacement.

A third report describes two cases, an 11-year-old on ECMO after heart transplantation and a 13-year-old on ECMO for cardiopulmonary failure resulting from necrotizing staphylococcal pneumonia.³⁷ The first patient received three doses of rFVIIa (90 mcg/kg/dose) and the second patient was given 10 doses. Hemostasis was achieved in both patients, with no evidence of thrombus formation in their ECMO circuits. While rFVIIa may become a useful tool to reduce bleeding in ECMO in the future, more research is clearly needed to establish a safe and effective dosing regimen and to define the potential for adverse effects.

SUMMARY

Optimizing the degree of anticoagulation during ECMO requires maintenance of a careful balance between prevention of thrombosis and avoidance of hemorrhage. Heparin remains the anticoagulant of choice, but DTIs, such as argatroban, lepirudin, or bivalirudin, may play a significant role in ECMO in the future. At the present time, these agents are considered only as alternative therapies for patients with heparin-related adverse effects, but may become first-line agents as experience with their use in ECMO grows. The management of excessive bleeding is also expanding to include new agents, such as rFVIIa, in addition to the standard use of aminocaproic acid. Over the next decade, it is likely that these newer agents will become important tools in the management of patients on ECMO.

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REFERENCES

- Rais-Bahrami K, Short BL. The current status of neonatal extracorporeal membrane oxygenation. *Sem Perinatol* 2000;24:406-17.
- Buck ML. Pharmacokinetic changes during extracorporeal membrane oxygenation: implications for drug therapy of neonates. *Clin Pharmacokinet* 2003;42:403-17.
- Muntean W. Coagulation and anticoagulation in extracorporeal membrane oxygenation. *Artif Organs* 1999;23:979-83.
- ECLS Registry Report, International Summary. Extracorporeal Life Support Organization (ELSO), Ann Arbor, MI. January 2005.
- Green TP, Isham-Schopf B, Irmiter RJ, Smith C, Uden DL, Steinhorn RH. Inactivation of heparin during extracorporeal circulation in infants. *Clin Pharmacol Ther* 1990;48:148-54.
- von Segesser LK. Heparin-bonded surfaces in extracorporeal membrane oxygenation for cardiac support. *Ann Thorac Surg* 1996;61:330-5.
- Ranze O, Ranze P, Magnani HN, Greinacher A. Heparin-induced thrombocytopenia in pediatric patients—a review of the literature and a new case treated with danaparoid sodium. *Eur J Pediatr* 1999;158(Suppl 3):S130-3.
- Butler TJ, Sodoma LJ, Doski JJ, Cheu WH, Berg ST, Stokes GN, et al. Heparin-associated thrombocytopenia and thrombosis as the cause of a fatal thrombus on extracorporeal membrane oxygenation. *J Pediatr Surg* 1997;32:768-71.
- Kawada T, Kitagawa H, Hoson M, Okada Y, Shiomura J. Clinical application of argatroban as an alternative anticoagulant for extracorporeal circulation. *Hematol Oncol Clin North Am* 2000;14:445-57.
- Johnston N, Wait M, Huber L. Argatroban in adult extracorporeal membrane oxygenation. *J Extra Corpor Technol* 2002;34:281-4.
- Mejak B, Giacomuzzi C, Heller E, You X, Ungerleider R, Shen I, et al. Argatroban usage for anticoagulation for ECMO on a post-cardiac patient with heparin-induced thrombocytopenia. *J Extra Corpor Technol* 2004;36:178-81.
- Tcheng WY, Wong W. Successful use of argatroban in pediatric patients requiring anticoagulant alternatives to heparin. [abstract] *Blood* 2004;104 (Part 2):107b-8b.
- Yonekawa KE, Nagakawa PA, Nugent DJ, Young G. Argatroban is as effective as heparin at preventing thrombin generation in extracorporeal membrane oxygenation circuits. [abstract] *Blood* 2002;100:127b.

14. Panicker N, Liedel JL, Kahana MD. Argatroban for anticoagulation in children with heparin-induced platelet antibodies. [abstract] *Pediatr Res* 2004;55(4 Pt 2):287A.
15. Deitcher SR, Topoulos AP, Bartholomew JR, Kichuk-Chrisant MR. Lepirudin anticoagulation for heparin-induced thrombocytopenia. *J Pediatr* 2002;140:264-6.
16. Dager WE, Gosselin RC, Yoshikawa R, Owings JT. Lepirudin in heparin-induced thrombocytopenia and extracorporeal membrane oxygenation. *Ann Pharmacother* 2004;38:598-601.
17. Yonekawa KE, Nugent DJ, Young G. Use of bivalirudin for anticoagulation of a neonatal extracorporeal membranous oxygenation (ECMO) circuit. [abstract] *Blood* 2002;100:129b.
18. Smets K, Vanhaesebrouck P, Voet D, Schelstraete P, Govaert P. Use of tissue type plasminogen activator in neonates: case reports and review of the literature. *Am J Perinatol* 1996;13:217-22.
19. Glover ML, Camacho MT, Wolfsdorf J. The use of alteplase in a newborn receiving extracorporeal membrane oxygenation. *Ann Pharmacother* 1999;33:416-9.
20. Olarte JL, Glover ML, Totapally BR. The use of alteplase for the resolution of an intravesical clot in a neonate receiving extracorporeal membrane oxygenation. *ASAIO Journal* 2001;47:565-8.
21. Gunnarsson B, Heard CMB, Martin DJ, Brecher ML, Steinhorn RH. Successful lysis of an obstructive aortic and renal artery thrombus in a neonate on extracorporeal membrane oxygenation. *J Perinatol* 2000;20:555-7.
22. Wells PS. Safety and efficacy of methods for reducing postoperative allogeneic transfusion: a critical review of the literature. *Am J Ther* 2002;9:377-88.
23. Laupacis A, Fergusson D, for the International Study of Peri-operative Transfusion (ISPOT) Investigators. Drugs to minimize perioperative blood loss in cardiac surgery: meta-analyses using postoperative blood transfusion as the outcome. *Anesth Analg* 1997;85:1258-67.
24. Ray MJ, Hales M, Marsh N. Epsilon-aminocaproic acid promotes the release of alpha₂-antiplasmin during and after cardiopulmonary bypass. *Blood Coagul Fibrinolysis* 2001;12:129-35.
25. Royston D. Aprotinin versus lysine analogues: the debate continues. *Ann Thorac Surg* 1998;65:S9-S19.
26. Wilson JM, Bower LK, Fackler JC, Beals DA, Bergus BO, Levy SV. Aminocaproic acid decreases the incidence of intracranial hemorrhage and other hemorrhagic complications of ECMO. *J Pediatr Surg* 1993;28:536-41.
27. Horwitz JR, Cofer BR, Warner BW, Cheu HW, Lally KP. A multicenter trial of 6-aminocaproic acid (Amicar) in the prevention of bleeding in infants on ECMO. *J Pediatr Surg* 1998;33:1610-3.
28. Downard CD, Betit P, Chang RW, Garza JJ, Arnold JH, Wilson JM. Amicar on hemorrhagic complications of ECMO: a ten-year review. *J Pediatr Surg* 2003;38:1212-6.
29. Fanashawe MP, Shore-Lesserson L, Reich DL. Two cases of fatal thrombosis after aminocaproic acid therapy and deep hypothermic circulatory arrest. *Anesthesiology* 2001;95:1525-7.
30. Hocker JR, Saving KL. Fatal aortic thrombosis in a neonate during infusion of epsilon-aminocaproic acid. *J Pediatr Surg* 1995;30:1490-2.
31. Hedner U. Recombinant factor VIIa (NovoSeven[®]) as a hemostatic agent. *Dis Mon* 2000;49:39-48.
32. Allen GA, Hoffman M, Roberts HR, Monroe DM. Recombinant activated factor VII: its mechanism of action and role in the control of hemorrhage. *Can J Anesth* 2002;49 (Suppl.):S7-S14.
33. Martinowitz U, Kenet G, Segal E, Luboshitz J, Lubetsky A, Ingerslev J, et al. Recombinant activated factor VII for adjunctive hemorrhage control in trauma. *J Trauma* 2001;51:431-9.
34. Pychynska-Pokorska M, Moll JJ, Krajewski W, Jarosik P. The use of recombinant coagulation factor VIIa in uncontrolled postoperative bleeding in children undergoing cardiac surgery with cardiopulmonary bypass. *Pediatr Crit Care Med* 2004;5:246-50.

35. Verrijckt A, Proulx F, Morneau S, Vobecky S. Activated recombinant factor VII for refractory bleeding during extracorporeal membrane oxygenation. *J Thorac Cardiovasc Surg* 2004;127:1812-3.
36. Bui JD, Despotis GD, Trulock EP, Patterson GA, Goodnough LT. Fatal thrombosis after administration of activated prothrombin complex concentrates in a patient supported by extracorporeal membrane oxygenation who had received activated recombinant factor VII. *J Thorac Cardiovasc Surg* 2002;124:852-4.
37. Dominguez TE, Mitchell M, Friess SH, Huh JW, Manno CS, Ravishankar MC, et al. Use of recombinant factor VIIa for refractory hemorrhage during extracorporeal membrane oxygenation. *Pediatr Crit Care Med* 2005;6:348-51.