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Anesthetic Management of Patients on ECMO

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Abstract

The management of a patient placed on extracorporeal membrane oxygenation (ECMO) is a team effort. The anesthesiology team plays an integral part during cannulation and oftentimes as well during decannulation. In addition, the management of a patient taken to the operating room on ECMO requires a degree of expertise. This chapter will review monitors, echocardiography, medications, fluid and blood management protocols, and ventilation strategies to help the anesthesiology team provide best care for this patient population.

Keywords: anesthesia, monitoring, echocardiography, anticoagulation, ventilation

1. Introduction

The anesthetic management of patients on extracorporeal membrane oxygenation (ECMO) continues to evolve as the indication for ECMO use expands. The anesthesiology team has to care for these patients during the critical period prior to ECMO placement, during cannulation, for surgeries while on ECMO, and then finally during decannulation. A keen understanding of the physiology, pharmacokinetics, and pharmacodynamics of the patient on ECMO is needed in order to appropriately care for this delicate patient population.

2. Monitoring

2.1. Invasive blood pressure monitoring

Mean arterial pressure (MAP) should be monitored during ECMO with an invasive blood pressure catheter. End-organs typically require a MAP greater than 65 mmHg in order to

maintain an adequate perfusion pressure. Hypotension may be corrected by increasing ECMO flows and/or administering volume. If the hypotension is secondary to a decreased systemic vascular resistance, then vasopressor agents may be needed to increase MAP.

There should be a degree of pulsatility even while on higher levels of ECMO support. Lack of pulsatility may point toward stagnation, which can cause overdistension of the left ventricle (LV) and lead to thrombosis. LV decompression is imperative to prevent ventricular ischemia and allow ventricular recovery. In these cases, ECMO flow can be reduced, or a vasodilator may be administered to attempt afterload reduction or inotropic agents may be added [1]. If the LV is not adequately decompressed, a left-heart vent, a percutaneous left ventricular assist device (LVAD; Impella®, Abiomed Corp., USA), or a balloon atrial septostomy can be performed to decompress the LV [2, 3]. Decreased pulsatility may also be a sign of hypovolemia, a mechanical obstruction, right ventricular failure, and/or dysrhythmias [1].

2.2. Interpretation of arterial blood gases from different anatomical sites

The location of the arterial inflow cannula determines the best site for arterial blood sampling and/or monitoring of SpO_2. With axillary cannulation, radial artery catheters should be avoided on the ipsilateral side, as the values obtained are not reflective of the net gas exchange [1]. With femoral cannulation, the right radial artery should be monitored. If heart function is poor, then arterialized blood flow to the coronary and cerebral circulations will occur through retrograde flow in the aorta. As heart function begins to recover, the mixing point within the aorta travels distally, and perfusion will be provided by the native cardiac output. The degree of oxygenated perfusion will also be determined by lung function, with poor lung function in the setting of good cardiac output leading to poorly oxygenated blood being supplied to the coronary and upper body circulations. Placement of a radial artery catheter on the right will allow detection of this condition, referred to variably as Harlequin syndrome, North–South syndrome, or upper body hypoxemia [1].

If the patient is on venovenous (VV) ECMO, the infusion blood will mix with the systemic venous return blood. The typical ratio of infusion to deoxygenated blood is approximately 3:1. As a result, blood analysis will demonstrate approximately a PO_2 40, PCO_2 41, and saturation of 80% [4]. A minimum saturation of 80% is adequate to support systemic oxygen delivery as long as the hematocrit is greater than 40% and cardiac function is decent [4]. As the lung begins to recover, the saturation will increase over 80%.

If the patient is on veno-arterial (VA) ECMO, the infusion blood will mix with the blood in the aorta. This leads to a typical ratio of infusion to native blood of 8:1 [4]. If lung function is normal, then blood analysis will demonstrate approximately a PO_2 of 200, PCO_2 of 40, and saturation of 100% (on FiO_2 of 0.2) [4]. If there is no native lung function, then PO_2 will be approximately half at 100.

2.3. Mixed venous blood saturation and other hemodynamic monitors

An arterial oxygen saturation (SaO_2) greater than 80% may be sufficient to monitor appropriate systemic oxygen delivery during ECMO [5, 6]. SaO_2 alone, though, may not always be a suitable

monitor, as various variables including hemoglobin, degree of recirculation, membrane oxygenator function, extracorporeal blood flow to cardiac output ratio, and venous oxygen saturation contribute to systemic oxygen delivery (DO_2) and oxygen consumption (VO_2) [7]. Systemic perfusion is best measured by mixed venous blood saturation (SVO_2), with a goal to maintain it greater than 75% [4]. If mixed venous saturation is less than 75%, then pump flow may need to be increased or volume may need to be given in the form of blood and/or crystalloid solution.

Pulmonary artery catheters (PACs) can be difficult to place once ECMO has been initiated and may not be a valuable monitor. The minority of blood flows through the lungs while on ECMO, and SvO_2 from a PAC will probably not be accurate. SvO_2 can be estimated however by blood gas analysis or saturation probe at the level of the venous cannula leading to the membrane oxygenator [1]. Other markers of anaerobic metabolism such as lactate may be useful to monitor when SvO_2 appears to be inaccurate [8].

Central venous pressure (CVP) can be used as a trend monitor as ECMO flow also affects exact measurements of this monitor. A rising CVP pressure due to mechanical obstructive processes such as tension pneumothorax, tamponade, or abdominal compartment syndrome can be detected with a central venous catheter.

Newer flow-based hemodynamic monitoring devices such as the Flotrac™ and NICOM™ (Edward life sciences, USA) are currently being investigated in the ECMO patient population.

2.4. Cerebral oximetry

A high percentage of ECMO patients unfortunately suffer a neurological complication. These complications can run the gamut from seizure, intracranial hemorrhage, ischemic stroke to encephalopathy [9]. Neurological complications increase the rate of mortality [10]. Methods to monitor for neurological complications include electroencephalogram, transcranial Doppler, and cerebral oximetry.

Upper body hypoxemia can be detected by a decrease in cerebral oximetry values, either unilateral or bilateral. A differential cerebral desaturation may occur when the right brain becomes hypoxemic, but perfusion of the left brain is preserved because of retrograde oxygenated blood flow from the descending aorta [11]. Central aortic saturation may be improved by increasing venous drainage, increasing blood oxygen content, and/or placing additional outflow arterial cannulas.

3. Echocardiography for ECMO

In ECMO-supported patients, soft-tissue ultrasound for vascular access guidance, transthoracic (TTE) and transesophageal (TEE) cardiac ultrasound are complementary technologies that

can guide safe cannula placement, initiate therapy, monitor progress of therapy, detect complications, and help determine ultimate recovery and weaning strategies.

3.1. ECMO patient selection

A comprehensive TEE or TTE is important to help guide therapy in critically ill adults who may benefit from ECMO therapy. Patients may demonstrate refractory hypoxemia, despite maximal ventilator support or hemodynamic instability even with resuscitative efforts. Echocardiography can identify potentially reversible pathological states, which may account for the patient's hypoxic or hemodynamic condition. Findings may include tamponade, acute severe mitral or aortic insufficiency, severe pulmonary hypertension, intracardiac shunts, and/or severe right or left ventricular dysfunction. Alternative resuscitative maneuvers may be undertaken before ECMO is initiated to alleviate potentially reversible conditions. Significant conditions identified by echocardiography that may complicate VV or VA ECMO include a prominent patent foramen ovale, atrial septal defect (ASD), intra-atrial septal aneurysm, pacer and defibrillator leads, or tricuspid valvular disease. Echocardiography may also provide information regarding aortic dissections, which is a contraindication to VA ECMO. Finally, echocardiography allows prompt assessment of cardiac function to guide VV versus VA ECMO therapy.

3.2. Echocardiography for cannulation

Surface ultrasound guides the correct placement of guidewires and cannulas into vessels within the neck, thorax, axillary and/or femoral areas, and into their final correct positions within the right atrium (RA) and inferior vena cava (IVC) to allow proper flow and limit recirculation between cannulas [12–14]. TEE can be used to guide central versus peripheral arterial cannula placement. Prior to placement of the arterial cannula, echocardiography should exclude a preexisting aortic dissection, which is a contraindication to VA ECMO. After placement, echocardiography should evaluate the aorta for an iatrogenic dissection, which may be a complication of the cannulation and initiation sequence. All cannulas should be properly placed before initiating ECLS to optimize initiation time and eliminate repositioning, which introduces bleeding and infection risk.

Echocardiography also allows confirmation of proper positioning of the single Avalon Elite® Bi-Caval Dual Lumen catheter (Maquet Holding, Germany), which is inserted typically via the right internal jugular vein (IJ), but may be inserted via the left IJ if the right side is inaccessible [13]. The cannula body should span the RA and encompass both the superior vena cava (SVC) and IVC for drainage. The return lumen should be positioned in the center of the RA and directed to allow return flow of oxygenated blood to cross the tricuspid valve. Utilization of saline microbubble contrast through specific lumens of the dual lumen catheter may help guide correct placement and orientation within the RA in relation to the tricuspid valve [15]. Comparison of dual-lumen cannulation to conventional cannulation for VV ECMO demonstrated that dual-lumen cannulation required more materials, more technical and physician experience, and higher costs, but allowed better patient mobilization, including prone

positioning and potentially lighter sedation and shorter duration of mechanical ventilation [16].

Use of the Avalon Elite® bi-caval dual lumen catheter has also been described in adults with secundum ASDs and Eisenmenger's syndrome as a bridge to recovery or transplant. The right atrial infusion port is positioned echocardiographically to infuse oxygenated blood across the ASD as opposed to the traditional tricuspid valve position. Placement improves oxygenation, decreases pulmonary artery pressure, and unloads the right ventricle. Patients without an ASD who have pulmonary hypertension or Eisenmenger's syndrome requiring VV ECMO may benefit by having an atrial blade septostomy performed prior to bicaval cannula placement [17].

TTE can also be utilized to place and monitor the position of the Avalon Elite® using the subcostal sagittal plane view, which provides imaging of the RA and both venae cavae. All three of the catheter ports can be identified and confirmed in their correct anatomical locations using TTE. A survey demonstrated that TEE (67%) was utilized more frequently to place the Avalon Elite® catheter than TTE (25%) or fluoroscopy (4%) with a mean insertion and orientation time of 26 ± 13 min [18]. It is recommended during the initial provider training period that placement of the Avalon Elite® Bi-Caval dual-lumen catheter occurs under both fluoroscopy and TEE guidance. As proficiency with cannula placement improves, TEE alone provides excellent image guidance for correct placement and orientation [14].

3.3. ECMO maintenance

On VV ECMO, venous cannula malposition, with inflow and outflow cannula positioned in close proximity leads to recirculation of returned oxygenated blood back to the ECMO pump. Recirculation undermines effective treatment and occurs with both single-lumen and dual-lumen cannulas. Traditionally, two-dimensional (2D) and three-dimensional (3D) echocardiography with confirmation of proper venous cannula position were used to exclude significant recirculation. Research using dilution techniques with ultrasonic probes attached to the arterial inlet and venous outlet lines of the cannulas allows calculation of a recirculation percent. Surveillance TTE with serial quantification of the recirculation percent can help determine malposition and diagnose cannula migration [19].

On VA ECMO, echocardiography can be utilized to define myocardial contractility, left ventricular end diastolic volume (LVEDV), mitral regurgitation, aortic valve systolic excursion, and LV decompression. For patients supported with VV or VA ECMO, volume management is critical to prevent volume overload and worsening lung injury. A positive fluid balance on hospital day 3 has been shown to be an independent predictor of 90-day mortality in patients supported with either VA or VV ECMO [20]. In a study evaluating utilization of echocardiography to guide fluid therapy optimization, measurements of LV stroke volume using the aortic valve area and aortic velocity time integral were performed at baseline. Passive leg raise was then performed with elevation of the lower extremities to a 45-degree angle, while the trunk was lowered from a semirecumbent to a supine position. Repeat measurement of LV stroke volume was then performed, and an increase in 10% or greater of the passive leg raise stroke volume (PLRSV) from baseline predicted a greater than 15% increase in stroke volume after

volume expansion (500 ml saline administered over 15 min). This simple diagnostic procedure can reliably identify patients with ARDs supported with VV ECMO who may benefit from fluid loading [21].

3.4. Detection of extracorporeal life support complications

Patients supported by ECMO are at increased risk for complications due to their underlying critical illness and the complex support techniques being utilized. Complications that may occur during ECMO that can be diagnosed by echocardiography include thrombosis, cannula malposition, tamponade, SVC or IVC syndrome, RV overload, hepatic congestion, and/or cannula thrombus casting [2, 22].

3.5. Recovery and weaning

Evaluating pulmonary and ventilator parameters help identify pulmonary recovery for patients on VV ECMO. Estimation of cardiac or cardiopulmonary recovery can be more complicated for VA ECMO. Historical metrics include a left ventricular ejection fraction (LVEF) of greater than 35–40%, right ventricular ejection fraction (RVEF) greater than 40% in the absence of moderate-to-severe tricuspid regurgitation, LV outflow tract velocity time integral greater than 10 cm, and/or the absence of LV dilatation with serial decreases in the ECMO flow rate. Multiple weaning protocols have been published, but ultimately ECMO flow is gradually decreased by set amounts, with periods of full support for recovery between trials. During the weaning phase, serial comprehensive echocardiographic examinations with a focus on qualitative and quantitative measures of RV and LV function can help guide the weaning process. Other more sophisticated applications of echocardiography to assess LV function during ECMO weaning include two-dimensional strain rate and Doppler tissue myocardial velocities [23].

TTE can be utilized to evaluate suitability for weaning, although contrast-enhanced TTE may be necessary to improve image quality. While contrast microspheres are hydrodynamically labile and demonstrate increased bubble destruction with passage through the ECMO circuit, the reduced signal persistence does not typically impair adequate image optimization with contrast-enhanced TTE [2].

Weaning protocols using a continuous hemodynamic TEE (hTEE®; Imacor, Garden City, NY) have been described to successfully manage separation of patients from ECMO in the ICU. The benefit of the hTEE® over conventional TEE or TTE is device placement and utilization in a continuous fashion over the 4–6 h weaning period, allowing multiple assessments and interventions over time. Timely determination of ventricular function recoverability is critical, secondary to the significant resources involved in caring for these complex, critically ill patients. Patients who demonstrate a low likelihood of ventricular recovery may have ECMO discontinued or transitioned to a longer term support solution, such as a LVAD or cardiac transplantation.

4. Drug administration

4.1. Pharmacokinetics and pharmacodynamics

The body's relationship between the drug dosage and the drug concentration over time is pharmacokinetics (PK). Pharmacodynamics (PD) is the relationship between drug concentration and the associated pharmacological response. PK and PD are linked via the dose–effect relationship. The goal of drug therapy is to maximize efficacy and minimize toxicity. Critical illness and ECMO alter the PK and PD of medications significantly, and therefore, the risk of therapeutic failure or toxicity is heightened in this patient population [24, 25]. Clearance of medications in critically ill patients is typically dependent upon renal or hepatic function, and clearance can increase or decrease depending upon the underlying disease process [26]. Complex changes in PK parameters occur with ECMO initiation and maintenance with an increased volume of distribution, altered clearance, and sequestration of drugs in the ECMO circuitry [27]. Failure to account for these alterations in PK can lead to therapeutic failure, and drug monitoring is critical for appropriate treatment outcomes when feasible.

ECMO alters the PK of sedative, analgesic, and antibiotic drugs, and their metabolites, independent of other associated patient and pathological factors. Drug molecular size, degree of ionization, lipophilicity, and plasma protein binding, all contribute significantly to adult, pediatric, and neonatal ECMO PK studies. Drugs with a high lipophilicity or protein binding have greater degradation or loss in the ECMO circuitry [25, 27–30]. Significant sequestration occurs primarily in the oxygenator due to its large surface area. The type and age of the components (oxygenator, pump, and tubing) also contribute to the degree of sequestration [25, 31].

4.2. Sedatives and analgesics

Sedatives and analgesics are necessary in the critically ill ECMO patients to provide optimal and safe care. A balance between light sedation and avoidance of muscle relaxants and the specific needs of the ECMO patient needs to be considered. Deeper sedation with muscle relaxants may be needed to optimize flows and ventilation strategies and minimize oxygen consumption. Adequate sedation minimizes catheter movement and dislodgements, and prevents patient coughing, which can create a "suck down" event and lowers ECMO flows and may cause hemolysis [25]. ECMO patients typically undergo total IV anesthesia during surgery with anesthetic agents including sedatives, hypnotics, analgesics, and muscle relaxants. Clinical teams with expertise in infusion therapy and total IV anesthetic techniques can be helpful to guide therapy and prevent underdosage or overdosage of medications. Significant and rapid increases in midazolam, morphine, and propofol doses immediately after ECMO initiation may be necessary to maintain pre-ECMO sedation levels. These "supranormal" elevations may be required for the entire ECMO support period and may warrant additional neuromonitoring to ensure adequate sedation levels [32, 33]. A survey of international ECMO centers identified that medications were used in the following frequencies: midazolam (79%), fentanyl (45%), morphine (43%), dexmedetomidine (41%), propofol (36%), and clonidine (25%) [33]. Muscle relaxants were used in only 35% of centers, and differences

in sedation and neuromuscular blocking agent use varied between experienced and less experienced centers. Critical care best practices can be extended to ECMO patients who should have consideration of daily cessation of sedation, analgesics, and avoidance of neuromuscular blockade.

Due to longer recognized indications for ECMO support in newborn patients compared to adults, most of the studies of PK exist in this patient population. Due to differences in physiology and circuit design between newborns and adults, translation of studies between patient populations may not be applicable [34]. Large PK studies in adult patients on ECMO focused upon antibiotics, antifungals, antivirals, sedatives, and analgesics are currently being performed [35, 36].

Variability in studies regarding drug sequestration in neonates exists for both morphine and fentanyl, and some advocate morphine use over fentanyl due to reduced drug withdrawal and length of stay in morphine-treated patients [25, 37, 38]. In vitro modeling has demonstrated that the tubing and membrane oxygenator of the ECMO circuit extract 67% of fentanyl over 48 h, but morphine demonstrated no extraction; therefore, higher fentanyl dosing but not morphine is needed to maintain adequate plasma levels [38]. Other in vitro studies examining morphine and fentanyl demonstrated significant sequestration of both agents by the ECMO circuit with 40% dose extraction by the PVC and membrane oxygenator [31, 39]. Some recommend using fentanyl for short-term pain relief and to avoid long-term fentanyl use in ECMO patients due to significant uptake by the tubing. Morphine may also be affected by uptake and may not be the best agent for long-term pain relief. IV acetaminophen, with lower lipophilicity and protein binding, may prove to bind less to the circuit components. An in vitro study of IV acetaminophen concentration over 6 h demonstrated relatively constant concentrations over time, irrespective of circuit age [40]. Based upon this study, use of IV acetaminophen in place of opioids may be preferable in patients requiring analgesia, undergoing ECMO therapy.

Pharmacokinetic and dynamic studies of midazolam in newborns supported with ECMO demonstrate an increase in the volume of distribution and an increased clearance of midazolam and its active metabolite 1-hydroxymidazolam. Over time, the active 1-hydroxymidazolam accumulates and may contribute to a greater proportion of the sedative effects seen clinically. The clinical significance of the active metabolite is unclear, because typically after 5–7 days of ECMO, infusion rates of midazolam need to be increased substantially to maintain sedation levels despite accumulation of the active metabolite. Others are concerned that 1-hydromidazolam accumulates and must be accounted for when the infusion is discontinued and the sedative effect remains. Careful titration based upon sedation scores are recommended to guide sedative therapy [41]. In vitro experiments demonstrate that sequestration is higher in older circuits than newer circuits and suggest that sequestration may be a time-dependent process. This phenomenon, in conjunction with increased clearance, contributes to the need to increase drug doses over time [25]. Benzodiazepines, as a class, demonstrate sequestration with 46–89% of midazolam and 50–59% of a dose of lorazepam being extracted by the PVC tubing and membrane oxygenator in a time-dependent fashion [31, 38, 39, 42].

Dexmedetomidine has demonstrated decreases in concentrations over time during in vitro ECMO analysis related to PVC circuit adsorption, and dosing adjustments to maintain appropriate serum concentrations are recommended [43]. Use of propofol in patients on ECMO has been debated over concerns of propofol damaging the ECMO circuit or membrane oxygenator. For cardiac surgical cases, it is not recommended to administer propofol directly into the cardiopulmonary bypass circuit with a membrane oxygenator due to poor blood mixing and propofol separation in the reservoir [44]. Administration is recommended via a dedicated peripheral intravenous line as opposed to a central line to prevent prompt venous cannula uptake and direct routing to the pump. Despite theoretical concerns, injection of propofol into the pump does not cause alteration in gas exchange nor oxygenation to patients on cardiopulmonary bypass [45]. Use of propofol in patients on ECMO has been debated. Propofol, a highly lipophilic medication, demonstrates significant sequestration with up to 98% concentration loss due to tubing binding, which limits drug efficacy [46]. Propofol-induced hypertriglyceridemia with associated hemolysis has been reported in ECMO patients [47]. Surveys indicate that propofol use for sedation is not common and may stem from concerns regarding poor mixing and poor gas exchange from the oxygenator, despite these findings not having been found specifically in ECMO patients [33]. Propofol may be utilized in patients on ECMO, but concerns regarding extremely high dose requirements, limited effect, propofol infusion syndrome, hypertriglyceridemia, and hemolysis exist.

4.3. Antibiotics

Antibiotics are commonly given to patients on ECMO for surgical prophylaxis and/or to treat the underlying pathology of the respiratory failure or associated infection occurring during the critical illness. Bloodstream infections are common in ECMO patients, occurring in 14.4% of patients supported for greater than 48 h, with Gram-negative bacilli being the most frequent pathogen [48]. The success of ECMO may rely on the success of the antibiotic therapy, and therapeutic failure secondary to inadequate drug concentrations must be avoided. PK features and dosing requirements of vancomycin, cephalosporins, and carbapenems are unclear with some studies suggesting significant sequestration with resultant lower concentrations, while others suggesting no change in concentration in ECMO patients [31, 42, 49, 50]. Antifungal agents, caspofungin and voriconazole, have been studied, with caspofungin demonstrating maintained peak and trough levels but voriconazole being significantly sequestrated. Limited data exist for antivirals; there is no significant change in concentration across the oxygenator for oseltamivir given for influenza A infections to ECMO patients [51]. For patients with H1N1 disease, standard dosing of enteral oseltamivir in ECMO patients is recommended and produces concentrations necessary to inhibit the neuraminidase activity of the H1N1 virus [52]. Therapeutic drug monitoring is recommended for all antibiotics, antifungals, and antivirals when available, and is critical to guide therapy to optimize outcomes [25].

4.4. Inotropes and vasopressors

ECMO is initiated for a variety of life-threatening respiratory or cardiac issues, and can be used to support patients and organ recovery for extended periods of time. Many patients are

critically ill when ECMO is initiated and are supported with cardiovascular adjuncts (96.2%) prior to ECMO support, including inotropes (95.8%), vasopressors (83.5%), IABP (40.1%), cardiopulmonary resuscitation/defibrillation (31.1%), and ventricular assist devices (9.0%) [9]. Patients who were on cardiovascular adjuncts at the initiation of ECMO have a worse outcome than patients not supported on these agents [9]. Pharmacological agents are typically required to provide support to recovering organs during the weaning and separation phases, as these organs are still recovering from recent intervention and/or injury. Weaning of ECMO occurs commonly in the intensive care unit or the operating room and requires collaboration of a team of professionals. Hemodynamic instability in the separation phase may be secondary to vasodilation, RV or LV dysfunction, left ventricular outflow tract obstruction, pulmonary hypertension, respiratory failure, and/or acidosis. Specific therapy should be initiated prior to separation to improve weaning and separation success rates, as failed weaning is associated with organ injury or failure [53]. Predictors of successful weaning are improved pulse pressure, decreased inotropic score, and improved LVEF and RVEF.

5. Anticoagulation

5.1. Heparin

Initiation of ECMO requires the consideration of anticoagulation and associated risk of bleeding versus thrombosis due to blood exposure to nonnatural surfaces. Exposure of blood to the artificial surfaces of the ECMO circuits initiates a complex inflammatory response and the coagulation pathway. Multiple biochemical pathways are activated, which lead to procoagulant activity as well as fibrinolytic activity, which can lead to circuit thrombosis and patient hemorrhage. Unfractionated heparin is the most widely used anticoagulant and works via two endogenous anticoagulants—antithrombin (AT) and tissue factor pathway inhibitor (TFPI). A survey of 121 ECMO centers determined that unfractionated heparin is the preferred anticoagulant for most cases and that alternative anticoagulants are used only 8% of the time [54].

Standard anticoagulation protocols for VV and VA ECMO include a bolus of unfractionated heparin (2500–5000 IU) administered intravenously during guidewire placement immediately prior to cannulation. After ECMO institution, heparin is administered via a central line by continuous infusion to maintain an ACT between 180 and 220 s. Small case series, however, suggest that lower goal ACT values between 140 and 160 s lead to less major bleeding and bleeding-induced death and transfusions without an increase in oxygenator changeovers or thrombotic events [55].

Studies have investigated ECMO patients supported without anticoagulation in order to minimize bleeding complications. In one study of 32 patients (24 post cardiotomy, 8 eCPR) on VA ECMO without anticoagulation during maintenance of ECMO, no neurologic or hemorrhagic complications occurred [56]. In certain high-risk patients for hemorrhagic complications supported on ECMO, it may be reasonable to withhold systemic anticoagulation during VA ECMO. VV ECMO patients may also tolerate no anticoagulation, as a case report described a

successful 32-day heparin-free VV ECMO support period for a patient who suffered a retroperitoneal hematoma during initial cannulation [57]. Another case report described a weaning strategy in a patient on VV ECMO who required cessation of heparin therapy due to persistent thoracic and mediastinal bleeding by maintaining a normal blood flow (62.5 ml/kg/min) and weaning the gas flows only [58]. Based upon these small series of studies, interruption or cessation of systemic anticoagulation may be considered if necessary to manage bleeding risk.

Bleeding is a common complication in ECMO patients, occurring in up to 22–32% of patients [59]. In the presence of hemorrhage, or traumatic bleeding, heparin may be held temporarily to control bleeding sources. Patients with traumatic brain injury have historically been a relative contraindication due to concerns about anticoagulation and intracranial bleeding. Two published case reports indicate that these patients may be managed successfully on ECMO with low-dose anticoagulation (heparin 2000 unit bolus at initiation) and goal aPTT of 40–60 s [60]. Although studies are small, historical contraindications such as severe septic shock, traumatic brain injury, polytrauma patients, pregnancy, and patients requiring frequent surgical intervention are now being treated with ECMO without full-dose anticoagulation and broadening the indications for ECMO significantly [61–65].

Patients on ECMO may require surgery, with tracheostomy, extremity, and vascular and abdominal exploration being the most common procedures performed. Heparin infusions may be held during the surgical procedure and immediately resumed postoperatively. Postoperatively, ECMO patients requiring noncardiac surgery have been shown to have statistically significant higher blood transfusion requirements (73.3 vs. 25.5%), higher average number of units transfused (2.8 vs. 0.8%), and higher perioperative mortality (46.7 vs. 6.4%) in comparison to LVAD patients undergoing similar noncardiac surgical procedures [66]. The use of blood products increases mortality in both ECMO and LVAD patients undergoing noncardiac surgery, and meticulous surgical technique, interrupting anticoagulation, and minimizing blood transfusions may improve overall mortality. Mortality may be decreased if 81 mg of aspirin is continued preoperatively in both ECMO and LVAD patients undergoing noncardiac surgery.

5.2. Direct thrombin inhibitors

Bivalirudin (Angiomax®, The Medicines Company, USA) has been proposed as an alternative anticoagulant to heparin for patients on ECMO. According to guidelines, ECMO patients with heparin-induced thrombocytopenia (HIT) should be anticoagulated with direct thrombin inhibitors (DTIs) such as bivalirudin or argatroban [67]. Dosing of bivalirudin for ECMO patients ranges from 0.025 to 0.5 mg/kg/h, although no standard dose exists due to limited use. Monitoring of the anticoagulation effect for patients on DTIs is difficult, with ACT, aPTT, and ecarin clotting time all being recommended [68]. A retrospective study of 21 patients (12 adults and 9 children) undergoing postcardiotomy ECMO receiving heparin versus bivalirudin demonstrated a better coagulation profile, less bleeding and less transfusions, and overall lower costs in the bivalirudin group [69]. In this study, bivalirudin-treated patients had significantly longer ACT, aPTT, and TEG®r times at different specific time intervals. A study

comparing aPTT in patients receiving heparin versus bivalirudin on VV and VA ECMO demonstrated more frequent aPTT variations greater than 20% of the previous value in the heparin-treated group [70]. Based upon these variations, the number of drug dose corrections was higher in the heparin-treated group. Although not statistically significant, both major and minor bleeding were higher in the heparin group. Bivalirudin may be superior to heparin due to more consistent aPTT levels with less drug dose alterations.

Avoidance of blood stagnation with bivalirudin anticoagulation is critical due to a short half-life and rapid cleavage of bivalirudin by proteolytic enzymes. This may lead to inadequate anticoagulation and increased risk of thrombosis, especially in stagnant flow areas. Cardiac chambers can become natural reservoirs for stagnant flow on ECMO when chambers are enlarged, and poor cardiac function limits forward cardiac flow. In bivalirudin-anticoagulated patients, echocardiography findings of a dilated atrium, poor ventricular function, and/or no aortic valve opening are concerning and increase the risk of thrombosis. If present, partial ECMO, institution of improved drainage, venting, or inotropic support should be performed urgently. If unsuccessful, conversion to a different anticoagulant should occur [71].

Argatroban (Argatroban, GlaxoSmithKline, USA), a DTI, is also indicated as an anticoagulant for prophylaxis or treatment of thrombosis in patients with HIT. In vitro analysis of circuits primed with argatroban suggests that thrombin generation may be lower [72]. Utilization in patients undergoing VV ECMO was studied in nine patients with the suspicion of HIT, eight of which were also on renal replacement therapy [73]. The first patient received argatroban infusion of 2 mcg/kg/min as recommended in the product information. Significant bleeding requiring transfusion occurred in this patient, and the subsequent eight patients received 0.2 mcg/kg/min continuous infusions to minimize bleeding. This dosing was sufficient to increase the aPTT and thrombin time (TT) to goal within 4 h in the majority of the patients. In this small study, the maintenance dose of argatroban was 0.15 mcg/kg/min, and no adjustment in dosing was necessary for patients in renal failure. It is recommended that dosages of argatroban should be decreased in the critically ill patients, patients with hepatic dysfunction, and ECMO patients. Several successful case reports using full-dose argatroban dosing in patients with HIT exist, but adequacy of standard anticoagulation monitoring remains a concern [74–76]. DTIs can be used safely in patients on ECMO, but limited experience and concern over a consistent monitor of adequacy of anticoagulation limit widespread acceptance of these agents for all ECMO patients. Currently, DTIs are typically reserved for patients with severe AT-III deficiency or HIT.

5.3. Heparin-induced thrombocytopenia

HIT is a complication of heparin therapy with a mortality of 10–30%. Antibodies bind to a complex of heparin and platelet factor 4 and cause thrombocytopenia and thrombosis. Within 4–5 days of heparin exposure, platelet counts fall but symptoms may present sooner in patients who have been previously exposed to heparin. If HIT is suspected, discontinuation of heparin should occur, and continuation of anticoagulation with an alternative agent should be considered to prevent thrombosis. As thrombocytopenia is common in critically ill patients due to a variety of other illnesses, HIT should be ruled out by lab testing with PF4 ELISA

analysis [73]. A study of 119 patients supported on ECMO demonstrated that by day 4, 60% of the patients had a 50% or greater decrease in platelet counts [77]. In patients suspected of having HIT (19%), a reduction of platelet count by 71% was present with a median platelet count of 43×10^9/l. One patient had laboratory-confirmed HIT; yet, all patients suspected of having HIT, warranting a change in anticoagulation therapy, demonstrated a higher hospital mortality rate (61 vs. 32%).

Once HIT is suspected, unfractionated heparin should be stopped and conversion to a nonheparin anticoagulant should be considered. Warfarin should be avoided until thrombocytopenia resolves, and prophylactic platelet transfusions should not be administered. DTIs or factor Xa inhibitors should be used for anticoagulation. Bivalirudin is the recommended agent for patients with HIT requiring urgent cardiac surgery and ECMO [67, 78]. Recommended dosing for ECMO is 0.5 mg/kg/h IV, which is closer to the thrombosis prophylaxis dose of 0.25 mg/kg/h versus the bypass-dosing regimen (1.75–2.5 mg/kg/h). A short half-life and absence of renal or hepatic clearance make bivalirudin a preferred alternative to other DTIs for ECMO patients [79, 80].

5.4. Monitoring of anticoagulation

Activated coagulation time (ACT) is the most commonly used measure of anticoagulation for patients maintained on ECMO. Experiences extrapolated from the cardiac operating room form the decision to use this technology for patients on ECMO. ACT is a simple, quick, and crude measure of anticoagulation for patients on high-dose heparin therapy (300 units/kg), but is less reliable at standard rates of heparin infusion (<50 U/kg/h). ACT levels do not correlate with either activated partial thromboplastin time (aPTT) or with anti-Xa activity, especially at lower levels of heparin dosing with ECMO [78]. Despite these limitations, ACT can be used for patients on ECMO with goal values between 150 and 220.

Antifactor Xa assay can be used to monitor and manage unfractionated and low molecular weight heparin therapy. Antifactor Xa levels between 0.3 and 0.7 IU/ml reflect a heparin effect; yet, some ECMO centers advocate higher target ranges between 0.7 and 1.1 IU/ml. ACT and antifactor Xa measure two distinct components of the coagulation process. ACT measures whole blood clotting and is therefore affected by heparin, thrombocytopenia, and inflammation. Antifactor Xa assay measures heparin effect or heparin concentration. Antifactor Xa assay is specific to the anticoagulant effect of unfractionated heparin and is unaffected by coagulopathy, thrombocytopenia, or dilution. aPTT is unreliable in the initial management of ECMO patients. Once ECMO is established, aPTT can be used as a measure of anticoagulation, with goal aPTTs between 1.5 and 2.5 times normal [81]. When comparing therapeutic ACT values to therapeutic aPTT levels, a poor correlation exists between ACT and aPTT, and ACT testing alone may not be enough to optimize heparin dosing [82]. Despite these limitations in ACT monitoring, a survey of ECMO centers reported the preferred method of anticoagulation monitoring was ACT, as reported by 97% of the respondents [54]. Most respondents reported using more than one test to guide therapeutic decisions, with 82% utilizing AT testing, 65% anti-factor Xa testing, and 43% thromboelastography monitoring. Utilization of ACT to manage ECMO patients can be complicated by limitations intrinsic to the ACT test. ACT values

are affected by heparin therapy as well as patient characteristics, including coagulopathy, platelet dysfunction, hypothermia, AT level, and hemodilution [78]. The use of ACT alone to monitor the degree of anticoagulation on ECMO is too insensitive, and therefore, the addition of other coagulation tests may prove beneficial to the patient [83]. Limited studies have been performed with heparin concentration (Hepcon® HMS Plus, Medtronic, USA) management in ECMO patients, and therefore target heparin concentration levels for ECMO patients are undetermined [84]. Thrombosis and clot formation within circuits, membrane oxygenators, and patients is a significant complication of ECMO therapy and can occur despite full anticoagulation with heparin. Clot formation in the oxygenator is reported to occur in 13–19%, and reported rates of serious patient complications include GI bleeding (4%), cardiac tamponade (10%), neurological events (3.5–11%), and surgical bleeding (21–24%) [78, 85].

6. Fluid management

Goals of fluid management include maintaining a normal blood volume while achieving an adequate hematocrit and keeping a normal body weight. Blood volume should be maintained at a level needed to maintain right atrial pressure between 5 and 10 mmHg [4]. A net negative fluid balance should be achieved, and volume overload should be avoided as this in itself can lead to further heart or lung injury. This balance can be difficult to achieve in patients with capillary leakage and inflammation. Pharmacological diuretics or continuous hemofiltration in patients with renal failure may be needed to achieve a fluid balance.

"Chattering" of the cannulas may be an indicator of intravascular volume depletion. Administration of fluid and/or blood is indicated when this occurs. Similarly, a fluctuating flow rate of the centrifugal pump may be due to hypovolemia, but may also occur due to excessive pump speed or malposition of the cannulas [86].

Fluid management is also of critical importance when weaning and decannulating from ECMO. Due to the change in the volume of distribution, fluid overload and right ventricular failure may occur during this period [8].

7. Blood management

7.1. Transfusion thresholds

Surgical procedures in the United States account for 15 million units of packed red blood cells (pRBCs) being transfused annually, with cardiac surgery consuming 10–15% of the U.S. blood supply [67]. Studies in ECMO patients demonstrate even higher utilization of blood products, most likely secondary to critical illness and alterations in hemostasis. Current transfusion practices for cardiac surgery support transfusion when hemoglobin (Hgb) is less than 7 g/dl. A study of 158 patients on VV and VA ECMO established that 97% of patients received transfusions, and bleeding occurred in 17% of VV ECMO patients and 33% of VA ECMO

patients [48]. Patients on VA ECMO received more transfused units of pRBCs than patients on VV ECMO, and transfusion rates were higher in patients who subsequently died [48, 87, 88]. Platelet volume requirement was an independent risk factor of mortality for VV ECMO patients, while the volume of blood transfused was an independent risk factor for mortality on VA ECMO [48].

7.2. Red blood cells

Volume of pRBC transfused varies in ECMO patients based upon underlying indications for support with the greatest volume transfused in cardiac patients, intermediate for eCPR patients, and least for noncardiac indications. Volume of RBCs transfused remains an independent predictor of in-hospital mortality among ECMO patients for noncardiac indications and postcardiotomy patients [89]. A retrospective study of 38 patients on VA, VV, or VAV ECMO, utilizing a transfusion trigger of 7 g/dl, a low dose anticoagulation strategy with a targeted aPTT of 40–60 s and autotransfusion following decannulation demonstrated an overall transfusion rate of 63.2% [90]. Median hemoglobin was 8.2 g/dl, and a median of 1 unit was transfused over a median duration of 9 days. Bleeding occurred in 26.3% of patients, with severe bleeding in 5.3%. Survival to hospital discharge occurred in 73.7%. This study suggests a restrictive transfusion practice in critically ill patients with ARDs supported with ECMO with a favorable and comparable outcome to studies using a higher transfusion trigger. A study of 18 patients on VV ECMO maintained with a hemoglobin concentration between 7 and 9 g/dl and transfused when Hgb was less than 7 g/dl demonstrated no increase in mortality (38.9%) [91]. A restrictive transfusion approach, which is well supported in the critically ill, may also be applicable to patients on ECMO, but large randomized control trials have not been conducted to compare restrictive versus liberal transfusion practices.

7.3. Platelets

Initiation of ECMO causes profound changes in coagulation parameters. Platelet counts, factor XIII, and fibrinogen all fall within the first 5 days of ECMO support, while thrombin–AT complex, D-dimer, and AT levels rise [92, 93]. Platelet counts typically fall during ECMO, and remain low and only recover after cessation of ECMO therapy [92]. Platelet transfusions remain a frequent occurrence on ECMO due to both patient factors and extracorporeal circuit factors. Severe thrombocytopenia occurs with ECMO initiation, especially in neonates and infants. Adults placed on ECMO post cardiotomy may have underlying thrombocytopenia and platelet dysfunction due to recent bypass support. Some experts recommend maintaining platelet counts between 45 and 65 × 10^9/l, with mandatory transfusion recommended when platelet counts are less than 20 × 10^9/l [84, 93]. Thromboelastometry can help define platelet function, and transfusion of platelets may be necessary despite a normal platelet count due to platelet dysfunction.

7.4. Fresh frozen plasma and fibrinogen

Transfusion of clotting factors also occurs frequently to support coagulation in ECMO patients. Maintenance of an INR less than or equal to 1.3 is recommended by transfusion guidelines.

While FFP contains most of the clotting factors, concentrations of specific components vary widely per unit of FFP transfused. Fibrinogen levels should be checked, and maintenance of fibrinogen levels greater than 100 mg/dl is recommended. When supplementing fibrinogen with cryoprecipitate, concomitant administration with platelets may increase the risk of thrombus and thromboembolic complications. Fibrinolysis, documented by thromboelastography, may be treated with antifibrinolytic therapy. Treatment should be undertaken cautiously as case reports exist of fatal thrombosis associated with antifibrinolytic therapy in ECMO patients.

7.5. AT-III levels

Unfractionated heparin binds with AT, and this complex increases the efficacy of AT. AT levels affect heparin PD, and measurements of AT levels can be helpful, especially in patients with elevated unfractionated heparin requirements. Acquired AT-III deficiency occurs commonly during ECMO, especially in pediatric patients and can create anticoagulation issues. Supplementation of AT is currently available from three sources, if AT levels fall below 0.5–0.7 U/ml: FFP, concentrated pooled human AT (Thrombate III®, Grifols Therapeutics, USA), and/or recombinant AT (ATryn®, rEVO Biologics, USA). Use of Thrombate III® has been shown to be safe in pediatric patients on ECMO without increasing bleeding complications or pRBC transfusions [94]. Recombinant AT (rAT) has the greatest concentration among the three products and has also been used successfully to elevate AT levels in pediatric ECMO patients. Frequent monitoring of AT levels is recommended due to prolonged rAT pharmacokinetics in ECMO-supported patients [95]. In conjunction with AT supplementation, heparin dosing should be decreased by 25% to prevent over anticoagulation. Recombinant AT is preferred over FFP for AT supplementation in ECMO patients due to low levels of AT in FFP and unpredictable responses to replacement with FFP. Conversion from heparin to a DTI has been used successfully in patients with low AT-III and concerns over supplementation with AT-III or FFP [68].

7.6. Recombinant factor VIIa

Concern exists for using recombinant factor VIIa (rFVIIa) on ECMO patients, despite successful case reports for bleeding cessation, due to overwhelming patient or circuit thrombosis. A study of 30 VA and VV ECMO patients who received recombinant factor VIIa (rFVIIa) for refractory bleeding demonstrated an efficacy rate of 93.3% in stopping bleeding, but a patient thrombotic rate of 3.3% and a circuit thrombotic rate of 16.7%, which were not statistically significant when compared to controls [96]. Recombinant FVIIa should only be considered as a "last resort" to stop bleeding in ECMO patients [67, 78, 84, 96].

7.7. Transfusion protocols

Utilization of a comprehensive ECMO anticoagulation monitoring protocol in children can result in fewer bleeding complications, reduced blood product usage, and increased circuit life [97]. In a small study of 10 patients using a proposed transfusion algorithm incorporating thromboelastometry and platelet function assays, less than 20% of the

transfusions corresponded to the algorithm, and transfusions were noted to be in excess of those recommended [98]. This finding suggests poor adherence to algorithm-based transfusion practices. Consensus guidelines for blood component therapy in ECMO patients suggest transfusing to ensure adequate oxygen carrying capacity, normal AT-III activity (80–120% control), fibrinogen levels of 250–300 mg/dl, and a platelet count greater than 80,000/μl [67].

7.8. Bloodless ECMO

Refusal of blood products by patients should not contraindicate ECMO support as a case report describes a successful 44-day period of ECMO support in a patient with hemoglobins between 4.5 and 6.0 g/dl who refused transfusion on religious ground [99]. A multimodal approach to stimulate erythropoiesis and minimize blood loss was utilized to manage the anemia. Another case report described a successful 15 days of bloodless VV ECMO support in a 17-year Jehovah's Witness patient [100]. Experience with bloodless cardiac surgery including circuit miniaturization, reduction from the standard ECMO lab sampling protocol, retrograde priming the ECMO circuit following cannulation, erythropoietin administration, hemostasis, and cell saver reinfusion during decannulation and separation was performed.

7.9. Thromboelastometry

Thromboelastometry [(ROTEM®, TEM/Pentapharma, Germany)(TEG®, Haemonetics, USA)] are point of care testing devices to examine the viscoelastic properties of whole blood. Different activators and inhibitors are utilized to examine clotting via the different pathways and components of the coagulation cascade. These devices evaluate from initiation of clot formation to clot lysis and can diagnose factor deficiencies, fibrinogen deficiencies, clot strength, heparin effect, platelet function and fibrinolysis. Interpretable information is provided within 10 minutes with a full analysis of clot formation and lysis within 60 minutes. Thromboelastography is however a poor guide to monitor and manage heparin anticoagulation in ECMO patients. A 5-year retrospective study of 20 heparinized patients on ECMO investigated the correlation between ACT, aPTT, and thromboelastography [101]. Analysis demonstrated poor correlation between aPTT, ACT and INTEM clotting time with unfractionated heparin infusion rates. Approximately 50% of patients in this study demonstrated normal INTEM tracings despite an elevated aPTT, questioning the sensitivity of INTEM clotting time to heparin dosing. Reliance on INTEM clotting times only for heparin dosing could lead to heparin overdosing due to the association of normal INTEM clotting times despite therapeutic aPTT in heparinized ECMO patients. Thromboelastography has a role in ECMO patients, not for heparin dose management, but to evaluate the hemostatic balance in these complex patients. Transfusion algorithms exist for cardiac surgery patients based upon thromboelastography patterns, and these algorithms can be extrapolated to ECMO patients to guide medication and transfusion therapies [98].

8. Ventilation strategies

Prior to initiation of ECMO, lung strategies that may be undertaken beyond lung protective ventilation include use of neuromuscular blockade [102] and/or prone positioning [103]. Another rescue therapy for patients with severe acute respiratory distress syndrome (ARDS) and refractory hypoxemia includes high levels of positive end-expiratory pressure (PEEP) [104].

Whether on VV or VA ECMO, the patient's lungs should be allowed to rest and hence the ventilator should be managed at low settings. Ventilator-induced lung injury (VILI) also needs to be minimized [105]. In order to reduce VILI, alveolar strain, atelectrauma, and oxygen lung toxicity have to be prevented, and this can be achieved with ECMO [106]. According to Extracorporeal Life Support Organization Guidelines [4], standard rest settings consist of a low rate with a long inspiratory time, low plateau inspiratory pressure (under 25 cm H_2O), low FiO_2 (under 30%), and PEEP between 5 and 15 cm H_2O. For patients with VV ECMO, especially those with ARDS, tidal volume should be targeted to less than 4 ml/kg predicted body weight, and plateau pressures should be kept ≤25 cm H_2O, a concept referred to as ultraprotective ventilation [106]. This ventilation strategy is associated with the use of high PEEP levels and extracorporeal carbon dioxide removal ($ECCO_2R$) [107–109]. Higher PEEP is needed in order to prevent ventilation/perfusion mismatch [110]. High PEEP should not be used however in patients with low lung recruitability, as this may increase alveolar strain and impair hemodynamics [111].

Manipulating ventilator settings to improve oxygenation is not recommended. Unfortunately, the best mode of ventilation for patients on both VA and VV ECMO have yet to be determined. Only 27% of ELSO-registered centers have a mechanical ventilation protocol for ECMO patients [112]. About 77% of these centers report "lung rest" to be the primary goal for ventilation. Pressure-controlled ventilation is the most popular mode for patients with ARDS, and airway pressure release ventilation (APRV) is being used more in recent clinical trials [106, 113]. Specific large randomized trials that focus on mechanical ventilation with ECMO are needed.

Monitoring the lung during ECMO can be challenging. Daily monitoring of plateau pressure, compliance, and tidal volume may offer valuable information [106]. Transpulmonary pressure can be estimated by an esophageal balloon in order to titrate PEEP [114].

The ventilator should be turned off in cases of interstitial emphysema or severe air leak syndromes [4]. This will result in atelectasis, and aggressive lung recruitment will be needed when resuming mechanical ventilation.

If the patient develops a pneumothorax during ECMO, a significant risk/benefit analysis should be undertaken in order to decide on best management. If it is a small pneumothorax (<20%) without hemodynamic compromise, then it is best to treat conservatively [4]. An enlarging pneumothorax or one causing hemodynamic compromise will require external drainage. Caution should be made in placing a chest tube, as this may lead to significant bleeding potentially requiring a thoracotomy. A small catheter should alternatively be placed.

The timing of tracheostomy on mechanical ventilation is controversial, with most centers performing early tracheostomies, even though evidence has demonstrated that there is no benefit in performing this procedure in the first 10 days on ECMO [115, 116].

Certain patients can be extubated while on ECMO and allowed to breathe spontaneously. Awake ECMO is recommended, if possible, for patients awaiting lung transplants or suffering from hypercapnic respiratory failure [117–119]. Also, if the patient is on VA ECMO for cardiac support and the lungs are adequate, these patients may be extubated and managed awake.

As the patient begins to recover, lung recruitment maneuvers consisting of sustained inflation at 25–30 cm H_2O should be undertaken. In addition, sedation should be titrated to allow spontaneous breathing while adjusting the sweep gas to maintain a PCO_2 between 40 and 45 mmHg [4]. Additional lung recovery strategies include diuresis, pleural drainage, therapeutic bronchoscopy, and positional therapy [8].

9. Conclusions

The usage of ECMO continues to evolve faster than the literature can support. Large randomized trials need to be undertaken in order to support clinical practice and define best anesthetic management. Until then, literature from other specialties such as emergency medicine and critical care should be carefully evaluated in order to guide management of this unique patient population.

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