Chapter

34

Extracorporeal Membrane Oxygenation

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Case Scenario

A full-term infant boy weighing 3.5 kg with a prenatal diagnosis of left-sided congenital diaphragmatic hernia with bowels and stomach in the left chest was transferred on day of life 1 for escalation of care. A restrictive patent ductus arteriosus was suspected, so an alprostadil infusion at 0.01 mcg/kg/minute was initiated, along with inhaled nitric oxide at 20 parts per million. Persistent hypercapnia and hypoxemia prompted a transition from conventional ventilation to high-frequency oscillatory ventilation on day of life 3. Due to persistent hypotension and worsening ventricular function, epinephrine 0.05 mcg/kg/minute was started. With no clinical improvement noted the decision was made to initiate veno-arterial extracorporeal membrane oxygenation on day of life 5. Current infusions include fentanyl 1 mcg/kg/hour, midazolam 0.1 mg/kg/hour, dexmedetomidine 0.5 mcg/kg/hour, and heparin 28 units/kg/hour. An epinephrine infusion has been weaned to 0.03 mcg/kg/hour. Now, on day of life 10, after discussion among the multidisciplinary teams, the patient is scheduled for repair of his diaphragmatic hernia in the neonatal intensive care unit.

Echocardiography revealed the following:

- *Large patent ductus arteriosus*
- *Severely hypoplastic left pulmonary artery*
- *Right ventricular hypertrophy*
- *Normal biventricular function*

Key Objectives

- Discuss the intraoperative management of congenital diaphragmatic hernia repair.
- Review the main components of an extracorporeal membrane oxygenation circuit.
- Delineate the differences between veno-venous and veno-arterial extracorporeal membrane oxygenation.
- Identify the anesthetic considerations when caring for a patient on extracorporeal membrane oxygenation support.

Pathophysiology

What is a congenital diaphragmatic hernia and what are the physiologic implications? What are the prognostic indicators?

A congenital diaphragmatic hernia (CDH) is a rare birth defect that occurs in approximately 0.8–5 out of 10,000 births. It is characterized by a diaphragmatic defect allowing herniation of abdominal contents into the chest and subsequently impeding normal lung development. This results in structural and functional changes to lung structure, pulmonary circulation, and the heart. Classification of CDH is based on the location of the defect: posterolateral (Bochdalek), anterior (Morgagni), and central. Posterolateral hernias are by far the most common, with the majority occurring on the left side. The size of the defect can significantly affect the prognosis, as the severity of this condition is proportional to the severity of lung hypoplasia and pulmonary hypertension (PH). Vascular remodeling with hypertrophied muscular arterial extension more peripherally results in a "fixed, irreversible" component of PH, while an imbalance in vasoreactive mediators and autonomic innervation contribute to a "reversible" component. From a cardiac function perspective, PH results in right ventricular dysfunction that manifests after birth. Additionally, abnormalities of the left ventricle have been observed, especially in infants with left-sided CDH.

Several factors are associated with an adverse outcome, including the presence of associated anomalies, significant liver herniation into the thorax, severe pulmonary hypoplasia, and right-sided CDH. Additionally, liver herniation is predictive of the need for extracorporeal membrane oxygenation (ECMO)[1] and places the patient at a higher risk for mortality [2]. Gestational age at the time of diagnosis is significant, as an early diagnosis usually correlates with a large defect and possible complete absence of diaphragm.

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Do other anomalies frequently coexist with CDH?

Congenital diaphragmatic hernia occurs as an isolated defect in 50%–70% of cases. The remaining cases are associated with major structural abnormalities and/or chromosomal anomalies. Therefore, a diagnosis of CDH should trigger an evaluation for associated conditions. The most commonly affected organ system is the cardiovascular system, followed by the genitourinary, musculoskeletal, and central nervous systems. A postnatal echocardiogram is imperative to rule out associated congenital heart defects. Echocardiography is also helpful in evaluating biventricular function in the face of pulmonary hypertension, as well as flow direction across the patent ductus arteriosus (PDA) and patent foramen ovale.

Is there a preferred ventilation strategy for a CDH patient?

Ventilation strategies have evolved from historically aggressive (to reduce pulmonary hypertension via hypocapnia and alkalosis) to gentler ventilation, attempting to protect already damaged lung parenchyma from further injury related to mechanical ventilation. The CDH EURO Consortium has published recommendations on ventilator parameters should the patient require mechanical ventilation after birth: target $PaCO_2$ between 50 and 70 mm Hg, peak inspiratory pressures (PIP) <25 cm H_2O, and positive end-expiratory pressure (PEEP) limited to 3–5 cm H_2O [3]. This "gentle ventilation" strategy should target a preductal oxygen saturation between 80% and 95% and a postductal oxygen saturation >70%. Unfortunately, in the most severe cases of CDH, conventional ventilation is not sufficient to prevent hypoxia and severe hypercapnea. High-frequency oscillatory ventilation can be used as a rescue strategy but has not been shown to decrease mortality.

What is the role of extracorporeal membrane oxygenation in the management of CDH patients?

Extracorporeal membrane oxygenation is considered a last resort, life-preserving option for neonates with CDH who have failed all other medical therapies. Support of infants with CDH is the most common indication for neonatal ECMO utilization, but prognosis is guarded, as survival rates remain only 50% in this high-risk population. Most agree that ECMO does confer a survival advantage in the most severe cases of CDH, meaning those patients with a predicted mortality >80%.

Selection criteria for ECMO use in CDH patients varies among institutions, but according to the CDH EURO Consortium Consensus, ECMO should be considered in the following circumstances [3]:

- Inability to maintain preductal saturation >85% or postductal saturation >70%
- Increased $PaCO_2$ and respiratory acidosis with pH <7.15 despite optimal ventilator management
- Peak inspiratory pressure >28 cm H_2O or mean airway pressure >17 cm H_2O to achieve SpO_2 >85%
- Inadequate oxygen delivery with metabolic acidosis as measured by elevated lactate ≥5 mmol/L and pH <7.15
- Systemic hypotension resistant to fluid and pressor therapy, resulting in decreased urine output <0.5 mL/kg/hour for 12–24 hours
- Oxygenation index ≥40 for at least 3 hours

Should repair be delayed until the patient is weaned off ECMO?

The surgical repair of a CDH is not an emergency. The patient should meet the following criteria set by the CDH EURO Consortium: (1) appropriate mean arterial pressure for gestational age; (2) appropriate preductal saturations with FiO_2 <50%; and (3) adequate organ perfusion with lactate <3 mmol/L and urine output >1 mL/kg/hour [3].

Provided the patient has shown signs of stabilization since ECMO was initiated, repair would generally not be delayed until after the patient was weaned from ECMO. The increased risk of bleeding when performing surgery while on ECMO must be taken into account, however. The timing of surgery for an ECMO-dependent patient remains controversial, as studies provide conflicting results. Three approaches have been described: early repair <72 hours after ECMO initiation, delayed repair as a last resort operation when patient has been unable to wean from ECMO, and after decannulation. While some studies have shown improved outcomes if the surgery occurs after decannulation from ECMO [4], others have found a higher likelihood of survival and shorter duration on ECMO if the CDH is repaired within 72 hours of initiation of ECMO [5, 6].

What is ECMO and how does it work?

Extracorporeal membrane oxygenation is essentially a modified cardiopulmonary bypass (CPB) system, providing support when the cardiac and/or pulmonary systems are failing. Venous blood is drained from the patient and passed through a lung membrane for gas exchange and oxygenation. It is then returned to the patient via a large vein (veno-venous ECMO) or artery (veno-arterial ECMO).

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What are the components of an ECMO circuit?

A standard ECMO circuit consists of a venous access cannula draining blood from the patient to a mechanical blood pump that moves blood through an oxygenator and a heat exchanger before returning blood to the patient through either the arterial (VA) or venous (VV) infusion cannula. Variability in the circuit arises from the number of monitors and circuit access points and presence of a bridge between venous access and arterial infusion limbs. Circuit pressures are monitored at different points on the circuit to identify complications: pressure difference across the oxygenator, inlet/suction pressure applied to the patient, and outlet/line pressure delivering flow to the patient. Flow monitors use ultrasound technology to estimate flow within the circuit and are commonly located at the pump outlet to measure flow generated by the pump and beyond the oxygenator to determine the flow actually delivered to the patient.

The goal of an ECMO pump is to provide appropriate blood flow for the patient at a safe pressure that avoids hemolysis. There are two main types of ECMO pumps. For decades, the ***roller pump*** has been the standard of care. It consists of a positive displacement pump that uses a roller head to sequentially compress the tubing, thereby displacing the column of blood forward. A collapsible bladder exists on the venous line to prevent direct suction on the venous catheter, which could lead to suction on the right atrium at low filling pressures. Disadvantages of a roller pump include the need for a large and heavy motor, possible wear or rupture of the tubing in the pump head, and risk of blowout from high infusion pressures. More centers currently use a ***centrifugal pump***, where a spinning rotor generates flow and pressure. The inflow to the pump can connect directly to the venous cannula. Disadvantages of a centrifugal pump include possible thrombus formation at low flows or with occlusion of the outlet line. Occlusion of the venous inlet line can lead to cavitation and hemolysis.

The gas exchange device or "lung" in the ECMO circuit is a ***membrane oxygenator***. Gas and blood flow in countercurrent directions on opposite sides of the membrane, and gas exchange occurs via diffusion. The gas flow or "sweep" rate via an oxygen/nitrogen blender can be adjusted to maintain the desired arterial PaO_2 and $PaCO_2$. The ***heat exchanger*** warms the blood to the appropriate temperature before it is returned to the patient. Commonly used hollow-fiber oxygenators incorporate a heat exchanger into the oxygenator.

The ***vascular access cannulas*** used for ECMO are made of biocompatible polyurethane material and come in a variety of sizes with different features. The body is wire reinforced in most cannulas to prevent collapse and internally coated to prevent thrombus formation. Various cannula tip configurations are available; examples include single-end-hole, multifenestrated flexible tip, and short fenestrated tip. Single-lumen cannulas are used for venous and arterial access for patients on veno-arterial (VA) ECMO or multiple site venous access for veno-venous (VV) ECMO patients. Dual-lumen cannulas can provide VV-ECMO via a single jugular venous access site, as blood is removed from the patient through one lumen and returned to the patient by the smaller lumen. (See Figure 34.1.)

What is the difference between veno-venous and veno-arterial ECMO?

Veno-venous ECMO provides respiratory support in a patient with stable cardiac function. Pulmonary blood flow is maintained, and an advantage is that with oxygenated flow through the pulmonary circulation, there is a decrease in hypoxia-induced vasoconstriction. Adequate support is defined as arterial saturation >80%. Neonatal and pediatric patients are most commonly cannulated in the right internal jugular vein, using a multiport double-lumen cannula that has outflow ports situated in the superior vena cava (SVC) and inferior vena cava (IVC) positions and the return port for oxygenated blood in the right atrium. Optimal positioning of the ports is crucial for proper functioning. Malposition of cannulae in VV-ECMO can cause significant recirculation of oxygenated blood resulting in inefficient oxygenation. Examples of situations where only respiratory support might be required include acute respiratory distress syndrome, status asthmaticus, pulmonary hemorrhage, congenital diaphragmatic hernia with good cardiac function, and situations in which the lungs need to "rest" such as pulmonary contusion or smoke inhalation.

On the other hand, ***veno-arterial ECMO*** bypasses both the heart and the lungs and provides complete cardiac and pulmonary support. The venous cannula takes blood from the right atrium or vena cavae and the arterial cannula returns the oxygenated blood to a peripheral or central artery; there is no recirculation. Veno-arterial support provides the most oxygen delivery to the patient. Typically neonatal cannulas are surgically placed in the right internal jugular vein and right carotid artery. (See Figure 34.2.) Patients must be larger for their femoral vessels to be of adequate size to accommodate ECMO cannulas. Central cannulation is used when patients are unable to wean from CPB intraoperatively. Other indications for VA-ECMO include cardiogenic shock, bridge therapy for chronic cardiomyopathy, and intraoperative use in high-risk percutaneous cardiac interventions.

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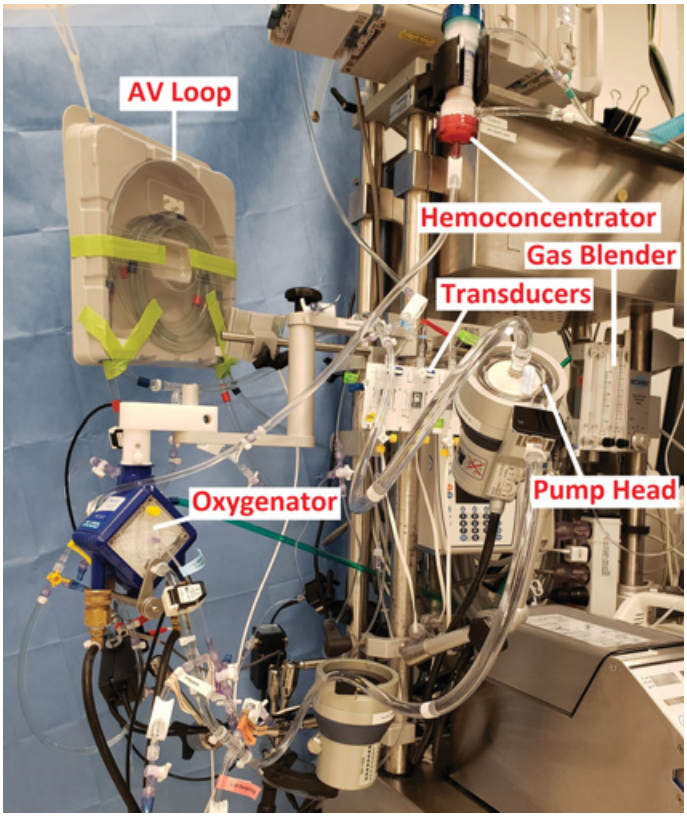

Figure 34.1 **Extracorporeal membrane oxygenation pump.** Courtesy of Mr. James Reagor.

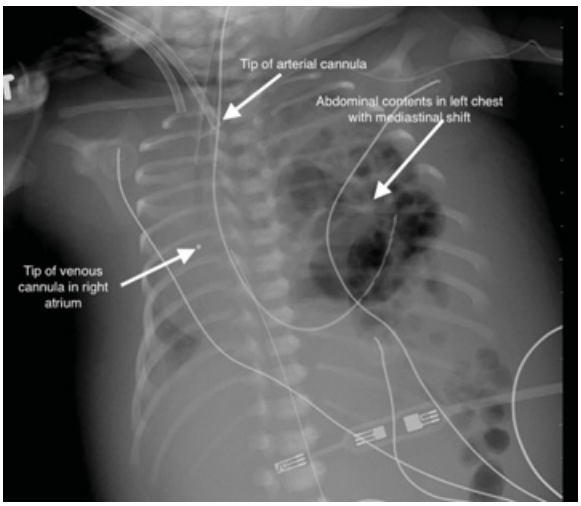

Figure 34.2 **Neonate with a large left congenital diaphragmatic hernia on VA-ECMO, cannulated through the right neck**. The distal part of the venous cannula is radiolucent except the tip.

Clinical Pearl

Veno-venous ECMO provides only respiratory support, while veno-arterial ECMO provides both respiratory and cardiac support. Cannulation in the neonatal and pediatric population up to 15 kg or approximately 2 years of age is exclusively through neck vessels (right internal jugular vein and right carotid artery) or centrally in cases of post-CPB heart failure.

How does ECMO differ from a ventricular assist device?

Extracorporeal membrane oxygenation differs from a ventricular assist device (VAD) in that it has an oxygenator and can therefore provide pulmonary support. By contrast, a VAD can only support cardiac function, and can be oriented to support either right ventricle, left ventricle, or both ventricles. (See Chapters 35 and 36.)

What ventilator settings are recommended for a patient on ECMO?

Utilization of ECMO should allow damaged lungs to recover, so ventilator settings should avoid inducing further injury. Minimal "rest" settings focus on tidal volumes <6 mL/kg with long inspiratory time, low plateau pressure <25 cm H_2O, FiO_2 <30%, and PEEP <10 cm H_2O. Some advocate a low respiratory rate of 3–5 breaths

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per minute to minimize movement of the lungs. Inspired oxygen is maintained at 0.21–0.3. It is essential to remember that during VV-ECMO, a significant amount of blood still circulates through the native lung. Therefore, the lungs need to be adequately ventilated, as complete collapse of the lungs would actually delay recovery.

Clinical Pearl

Issues with gas exchange and oxygenation are addressed through adjustments of ECMO settings and optimizing patient hemoglobin level and not by ventilator management.

Anesthetic Implications

What ECMO-related factors should be considered during preoperative assessment?

The anesthesiologist should have a clear idea of the current ECMO settings and flow rates. An assessment of coagulation status is necessary and should include both a review of laboratory values and evaluation of any clinical evidence of either bleeding or thrombosis. This includes a review of neuroimaging studies (cranial ultrasound and/or portable head computed tomography follow-up scans of abnormal head ultrasounds), evaluation of cannulation sites, and determination of whether gastrointestinal bleeding is present. The ECMO circuit should similarly be inspected for the presence of thrombus. If possible, the heparin infusion should be decreased or even stopped to minimize surgical bleeding; this decision, however, must be made jointly by the multidisciplinary team, given the risk of circuit thrombosis. The patient's hemoglobin level, platelet count, and fibrinogen levels should be optimized. Blood products should be crossmatched and available at bedside. Resting ventilator settings should be reviewed and continued.

How should an ECMO patient be monitored intraoperatively?

A patient on ECMO will likely have all necessary lines and monitors for a surgical procedure, as they are requisite for patient stabilization, initiation of ECMO, and ongoing monitoring. Arrhythmia monitoring by continuous electrocardiogram (ECG) is especially important for VV-ECMO patients who are dependent on their native cardiac function. Central venous access is typically present, as most of these patients will have required inotropic support prior to initiation of ECMO. Similarly, peripheral vascular access is often already in place. An arterial line is mandatory for following the mean arterial pressure (MAP) as well as blood gas monitoring. Mixed venous saturation is the best measurement of systemic perfusion, with a venous saturation >65% indicative of adequate systemic oxygen delivery. Urine output is another surrogate indicator of perfusion and should be monitored closely. Measurement of lactate levels at regular intervals can also signal possible organ hypoperfusion. Echocardiographic evaluation is useful should issues with cannula positioning arise.

Ideally, the anesthesiologist should have a dedicated vascular line for administration of anesthetic medications. Use of a dedicated line prevents inadvertent boluses of anticoagulants or vasoactive agents currently being administered. Medications and volume can also be delivered by the perfusionist directly into the ECMO circuit.

Clinical Pearl

Patients on ECMO support typically already have necessary monitors and lines in place, including ECG monitoring, arterial line, central venous line for inotropic medication infusion, peripheral vascular access, Foley catheter, and temperature monitor. Dedicate a vascular line for anesthetic medications to avoid bolusing anticoagulants or vasoactive agents.

What is an appropriate anesthetic plan for this patient?

A total intravenous anesthetic (TIVA) based primarily on narcotics and benzodiazepines is the most practical method of anesthetizing a patient on ECMO. All preoperative sedative infusions should be continued. Depending on the level of current sedation and the planned procedure, the patient may require only a small amount of additional anesthetic. The bedside nurse can provide information on the patient's sedation status and whether he has required any intermittent bolus dosing in addition to his fentanyl, midazolam and dexmedetomidine infusions. Prior to incision, an additional bolus of fentanyl along with neuromuscular blocking agent can be administered. The limitation with TIVA is drug sequestration by the ECMO circuit, especially for lipophilic drugs, and medications should therefore be titrated to effect.

Clinical Pearl

A narcotic- and benzodiazepine-based intravenous anesthetic is most reliable in ECMO-dependent patients. However, dose requirements may be increased due to medication sequestration by ECMO circuitry.

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How should coagulopathy, bleeding, and anticoagulation be managed in the perioperative period?

Exposure of blood to the artificial, nonnatural surfaces of the ECMO circuit triggers an inflammatory response and the coagulation pathway, leading to both procoagulant activity and fibrinolysis. The balance between preventing circuit thrombosis and patient hemorrhage is challenging. When a patient is dependent on ECMO for survival, a clot in the circuit due to inadequate anticoagulation can be devastating, as it can lead to inadequate oxygenation, consumption coagulopathy, and emboli throughout the body. *Unfractionated heparin is the most commonly used anticoagulant in ECMO patients.* A bolus dose is typically given during ECMO cannulation, and levels are then maintained at therapeutic levels with a continuous infusion. Neonates may require higher infusion rates due to low plasma antithrombin III (ATIII) levels. Low ATIII levels can contribute to heparin resistance, which can be treated with either fresh frozen plasma or recombinant ATIII. While heparin-induced thrombocytopenia is extremely rare in neonates, possible alternatives to the use of heparin include the direct thrombin inhibitors bivalirudin and argatroban.

Activated coagulation time (ACT) is the most commonly used measure of anticoagulation for ECMO patients, as it is a simple and quick test that can be performed at the bedside, making it ideal for intraoperative monitoring. The goal ACT for ECMO patients generally ranges from 180 to 220 and should be checked every 1–2 hours (depending on hospital protocol) and as needed. In addition to ACT monitoring, the ECMO team often uses an expanded array of coagulation parameters including anti-Xa assay, partial thromboplastin time, fibrinogen, prothrombin time, thromboelastography, and ATIII levels to monitor coagulation status and guide therapeutic decision-making.

The benefit of withholding systemic anticoagulation preoperatively is to reduce the risk of perioperative bleeding. This may not be possible in patients who are known to have clot burden in their circuit or have other ongoing thrombotic complications. For CDH repair, there are institution-specific perioperative protocols that reduce the systemic anticoagulation goal ACT to 140–160 (compared to the aforementioned 180–220) in combination with the use of aminocaproic acid, but bleeding complications remain significant in this population [5, 6]. Although cannula site bleeding, surgical site bleeding, and gastrointestinal hemorrhage can all occur, cerebral hemorrhage is perhaps the most feared complication. Neonates are at higher risk for intracranial bleeding. Seizures may be a presenting symptom, although some patients present with subclinical findings determined only by electroencephalogram.

In light of the bleeding risk, ample blood products should be available to optimize conditions. Patients should be transfused to maintain platelet levels ≥100,000, recognizing that even though the platelet level may be above the transfusion threshold, platelet function may still be impaired. The fibrinogen level should be maintained within the normal range of >150 mg/dL by transfusion of cryoprecipitate if necessary. Packed red blood cells should be given to maintain at least a hematocrit ≥30%, although ELSO Guidelines for Neonatal Respiratory Failure suggest maintaining a hemoglobin level of 13–14 g/dL to optimize oxygen carrying capacity [7].

Clinical Pearl

Bleeding risk is significant in ECMO-dependent surgical patients. Decisions regarding decreasing or withholding anticoagulant infusions should be made by a multidisciplinary team. Hemoglobin, platelet, and fibrinogen levels should be optimized preoperatively. Monitoring of anticoagulation status should be continued intraoperatively. Adequate blood products should be available to replace intraoperative losses.

Aside from balancing hemorrhage and thrombosis, what other ECMO-related complications can arise?

Mechanical pump malfunction is uncommon but possible. An integrated battery exists as backup support during transport or electrical failure, with an audible alert signaling loss of power and transition to battery power. Additionally, a hand pump system exists as a secondary backup. Oxygenator failure can present over time as a result of clot buildup in the membrane lung; an inability to oxygenate and exchange CO_2 and a widening pressure gradient across the oxygenator with increased resistance to flow would be noted. Tubing rupture is less common in the era of centrifugal pumps. Air in the circuit, especially post-oxygenator, can enter the patient and requires immediate response. Accidental decannulation is life threatening and is more likely during patient transport and positioning.

How should intraoperative hemodynamic instability be managed in a VA-ECMO–dependent patient?

Unlike the VV-ECMO patient who is solely dependent on his native cardiac function, the VA-ECMO patient's

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hemodynamics are driven by blood flow generated by both the pump and native cardiac output as well as vascular resistance. An appropriate MAP for this neonate would be 40–50 mm Hg. Hypotension intraoperatively is commonly due to inadequate circulating volume. The ECMO personnel may notice "chattering" of the venous cannula and fluctuating flow rates. Intravascular volume depletion can be managed with fluid and/or blood administration. Vasopressor infusions may be needed in cases of vasodilatation from infection. In the setting of septic shock, higher ECMO flow rates may be also necessary. Hypertensive episodes impede perfusion, so high systemic vascular resistance should be avoided and promptly treated. Once certain that the patient is adequately anesthetized, judicious use of a vasodilator may be considered if signs of high systemic vascular resistance persist. If any acute changes in pressure occur, circuit factors (pump issues, oxygenator failure, tubing kink, or malpositioned/obstructed cannulas) should be eliminated from the differential.

Who should manage ECMO circuitry and transfusion of blood products?

During the surgery, there should be dedicated personnel to monitor the ECMO machine, its parameters and function; often this is a perfusionist or specially trained ECMO nurse who manages ECMO during the day under the supervision of the intensivist. Any changes in the ECMO system should be communicated to the anesthesiologist immediately. Closed-loop communication is essential. Intraoperative transfusion will ultimately be at the discretion of the anesthesiologist; however, input from the surgeon and intensivist may be helpful to delineate surgical bleeding and ongoing medical bleeding or thrombotic concerns. Products can be directly infused directly into the ECMO circuit or through other available vascular access.

What considerations are important when surgical cases are performed in the intensive care unit?

The primary benefit of doing this particular case at bedside is the avoidance of transporting an ECMO-dependent neonate through the hospital. Physical space constraints can exist at the bedside however, given the abundance of equipment necessary to maintain a patient on ECMO. The anesthesiologist must ensure unfettered access to the patient, in particular the airway, infusion pumps, and vascular access sites. Availability of all required medications and equipment should be verified for both anesthesia and surgical services. Personnel to manage less familiar equipment, such as the ICU ventilator, should be immediately available. The bedside nurse or a surrogate should remain on the unit as an extra resource person. The physical room or space should be decluttered by removal of nonessential equipment and furniture and the pod should be closed to visitors.

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