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Pediatric venoarterial and venovenous ECMO

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ABSTRACT

Extracorporeal membrane oxygenation (ECMO) is an invaluable resource in the treatment of critically ill children with cardiopulmonary failure. To date, over 36,000 children have been placed on ECMO and the utilization of this life saving treatment continues to expand with advances in ECMO technology. This article offers a review of pediatric ECMO including modes and sites of ECMO cannulation, indications and contraindications, and cannulation techniques. Furthermore, it summarizes the basic principles of pediatric ECMO including circuit maintenance, nutritional support, and clinical decision making regarding weaning pediatric ECMO and decannulation. Finally, it gives an overview of common pediatric ECMO complications including overall mortality and long-term outcomes of ECMO survivors. The goal of this article is to provide a comprehensive review for healthcare professionals providing care for pediatric ECMO patients.

1. Introduction and epidemiology

Extracorporeal membrane oxygenation (ECMO) was first introduced in 1972 for treatment of a critically ill adult patient with respiratory failure.[1] Since then, the application of ECMO has expanded to treat patients with either cardiac failure, respiratory failure or both. ECMO usage has expanded to include pediatric patients, with the first neonatal survivor in 1976.[2] The goal of ECMO is to provide adequate gas exchange, oxygenation, and perfusion in order to improve end organ dysfunction and allow time for the patient's underlying disease to be effectively treated. ECMO does not directly treat the underlying disease causing a patient's cardiopulmonary failure, but can be used as bridge to definitive treatments, such as recovery, or heart or lung transplant.

According to the Extracorporeal Life Support Organization (ELSO) registry that began collecting data in 1989, there have been 36,233 non-neonatal pediatric ECMO runs through the end of 2022, which includes patients aged 29 days to 17 years. Of these runs, 35.5% were for the treatment of pulmonary disease, 45.8% were for the treatment of cardiac disease, and 18.7% were to support cardiopulmonary resuscitation (eCPR).[3]

Pulmonary and cardiac support can be delivered individually or together by different modes, as well as, by different configurations of cannulas. Common modes include venovenous (VV), venoarterial (VA), and venovenoarterial (VVA). VV ECMO primarily provides pulmonary support and VA ECMO primarily provides both respiratory and cardiac support. Depending on the desired mode of support, ECMO cannulas may be placed into one or more major vessels. This article focuses on indications, cannulation sites and techniques, complications, and outcomes for VV and VA ECMO in pediatric patients. Of note, the term "pediatric" in this context does not include patients aged 28 days or younger.

2. Common ECMO modes

2.1. Venovenous (VV)

VV ECMO is primarily used for respiratory failure. Through this configuration deoxygenated blood is first extracted from the patient via a venous catheter, then oxygen is delivered and carbon dioxide removed in the ECMO membrane gas exchanger, and finally the blood is returned to the patient's venous system as oxygenated blood through a venous catheter. The VV ECMO circuit uses either a single-site dual lumen cannula or two separate venous cannulae configuration. One limitation of VV ECMO is that it does not provide a mechanism for hemodynamic support, requiring the patient's heart to serves as the primary "pump" for delivery of oxygenated blood to the body. VV ECMO offers lower amounts of oxygenation and ventilation support than VA ECMO because blood is returned to the patient's venous system and there is a component of mixing of the oxygenated blood from the circuit and deoxygenated blood from the body. Recirculation occurs when the oxygenated blood returns to the ECMO circuit instead of the patient. Recirculation is higher in patients with high circuit flow, low cardiac

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output, or dual lumen atrial catheter or single lumen catheters. The circuit operates in series with the heart and lungs and does not provide bypass of these organs. Of note, pediatric patients with hypotension and an anatomically normal heart may be supported by VV ECMO because this mode can improve hypotension by correcting severe hypoxia and hypercarbia.

2.2. Venoarterial (VA)

VA ECMO is utilized in patients who need both support of cardiac output and hemodynamics, in addition to providing improved oxygenation and ventilation. Similar to VV ECMO, deoxygenated venous blood is extracted from the patient via the venous catheter and oxygen delivery and carbon dioxide removal occur in the ECMO membrane gas exchanger. However, in VA ECMO, oxygenated blood is then returned to the patient through an arterial catheter. This mode operates in parallel to the heart and lungs and provides partial heart and lung bypass. It is the mode of choice for children who require high inotropic support or have underlying cardiac structural anomalies or impaired cardiac function. As previously noted, pediatric patients with hypotension and an anatomically normal heart do not necessarily require VA ECMO for treatment of severe hypoxia and hypercarbia. In these patients, VV ECMO may be the preferred mode.

VA ECMO provides a higher concentration of oxygen when compared to VV ECMO due to the minimal mixing of blood from the venous and arterial catheters. VA ECMO can result in an increased afterload on the left ventricle and cardiac stun, as well as left atrial hypertension and pulmonary edema. Afterload can be reduced with medications in mild and moderate circumstances or with an atrial septostomy to promote left-to-right shunting in severe circumstances. The use of transaortic ventricular assist devices, such as the Impella, during VA ECMO is described in adult ECMO literature.[4]

3. Indications and Contraindications for ECMO Cannulation in the Pediatric Population

3.1. Cardiac failure

VA ECMO is often utilized in children with cardiac failure who are unable to wean from cardiopulmonary bypass after congenital heart surgery and also can be used in a variety of other cardiac conditions. Congenital heart disease was the primary diagnosis in 52% of pediatric cardiac ECMO runs, which included hypoplastic left heart syndrome, left or right ventricular outflow tract obstruction, and septal defects. Additional primary diagnoses which required VA ECMO included the following: cardiac arrest, cardiogenic shock, cardiomyopathy, myocarditis, refractory arrythmias, severe pulmonary hypertension, massive pulmonary embolism, or cardiac trauma.[5] VA ECMO may also be used as a bridge to definitive treatment by heart transplantation or ventricular assist device implantation.

3.2. Sepsis

Sepsis shock has become an increasingly common indication for the use of ECMO and accounts for up to 8% of pediatric patients who are on ECMO for respiratory support.[5] Refractory septic shock in children is defined as a combination of severe cardiovascular dysfunction, persistently high lactate despite resuscitation, and high vasopressor requirements.[6] Both the American College of Critical Care Medicine (ACCM) and international Society of Critical Care Medicine (SCCM) have identified ECMO as a potential therapy for children with septic shock.[7-9] ECMO allows cardiopulmonary support for children in distributive shock secondary to sepsis. The Surviving Sepsis Campaign indicates VA or VV ECMO should be used for refractory shock or oxygenation/ventilation failure after other causes of shock and respiratory failure are addressed. Specific recommendations suggest VV ECMO for sepsis-induced acute respiratory distress syndrome (ARDS) and VA ECMO as a rescue therapy for septic shock only if refractory to all other treatments. Both recommendations are noted to be weak due to being based on very low-quality evidence.[7]

A 2020 systematic review and meta-analysis evaluated 23 articles that reported on mortality in children aged 0 to 18 years with sepsis supported with ECMO. The cumulative survival based on 13 studies and nearly 2600 patients aged 0 to 18 years was estimated to be 59% (95% confidence interval [CI]: 51-67%). The subset of pediatric patients aged between 28 days and 18 years, based on 6 studies with 138 patients, had an overall pooled survival of 50% (95% CI: 41-59%). For all children aged 0-18 years, the median hospital stay was 28.8 days and median ECMO duration was 129 hours.[10]

A study based on ELSO registry data from 1990-2008 reported a 68% overall survival in pediatric patients aged 0-18 in which ECMO was used to treat sepsis, but survival decreased to 40% in children aged 1 month to 12 years and 32% in patients aged 13 to 18 years. VA ECMO was used 80% of the time for both age groups, but survival on VA ECMO was noted to be lower compared to VV ECMO. Selection bias was not controlled, and vasoactive drug support was higher in the VA group.[11]

Similarly, *Melnikov et al.* analyzed 31 patients (30 days to 18 years) with septic shock supported with peripheral ECMO cannulation and reported 71% survival from ECMO, 68% survival to discharge, and 60% long-term survival with median 6.5-year follow-up. Again, the patients on VV ECMO (n=10) had improved survival (82%) when compared to those on VA ECMO (n=21, 62% survival).[12]

In order to obtain survival benefit with ECMO for septic shock, high ECMO flow rates, notably greater than 150 mL/kg/min, have been recommended.[7,13] Larger children and adolescents may require central cannulation in order to achieve these high flows. Several small-volume studies have looked at survival with central cannulation and demonstrated survival rates between 61-75%.[14-16] In a study of 23 patients with a median age of 6 years, survival from ECMO with central cannulation and survival to discharge was 78% and 74%, respectively.[16]

3.3. Respiratory failure

Pediatric respiratory failure is a common indication for ECMO. Respiratory failure can be secondary to airway obstruction from a mediastinal mass, bronchiolitis, lung parenchymal disease such as pneumonias, pulmonary contusions, ARDS, or alveolar hemorrhage, hypercarbia and air trapping from refractory status asthmaticus, bronchopleural fistula, airway injury, or persistent air leaks, acute chest syndrome, drowning, or aspiration events. ARDS accounted for the largest proportion (22%) of primary diagnoses for pediatric respiratory support, followed by “other” diagnoses (21%), viral pneumonia (10%), bronchiolitis (10%), and bacterial pneumonia (8%).[5]

In 2015, the Pediatric Acute Lung Injury Consensus Conference Group provided recommendations regarding ECMO for the treatment of ARDS in children.[17] ECMO should be considered for severe ARDS when lung protective strategies result in inadequate gas exchange and when the cause of respiratory failure is believed to be reversible or the patient is suitable for lung transplantation. Based on current data there are no strict criteria regarding patients who will benefit from ECMO. In the absence of cardiac or circulatory dysfunction, VV ECMO is recommended. Specific indications for ECMO for respiratory disease in children include an oxygenation index >40, PaO2/FiO2 ratio of <60-80, high ventilatory pressures with mean arterial pressure (MAP) >20-25 on conventional ventilator or >30 on oscillator resulting in evidence of barotrauma, refractory hypercarbia defined as pH<7.2 or PCO2>100, or persistent air leak.[18-22]

A retrospective cohort study of patients between 2 weeks and 18 years old with respiratory failure demonstrated a significantly lower mortality (26.4% vs 47.2%, <0.01) in the ECMO-treated patients. Particular survival benefit was seen in those children who had a pediatric risk and mortality score predicting a 50-75% mortality. In this

subset, there was a 29% mortality in the ECMO group compared to a 71% mortality in the non-ECMO group.[23]

Although VV ECMO has recently become the preferred configuration in the management of pediatric respiratory failure, VA ECMO is also a viable option for centers that do not have VV ECMO resources or for patients who have significant concomitant cardiac failure independent of hypoxemia. A study of 103 pediatric patients (<18 years old) with respiratory failure on inotropes or vasopressors compared VA (n=57) versus VV ECMO (n=46). Although univariate analysis demonstrated an ECMO survival benefit with VV ECMO over VA ECMO (72% vs 44%), multivariable models controlling for severity of illness and cardiopulmonary resuscitation found no survival benefit. The VV ECMO group spent more days on ECMO (7 days vs 4.5 days), but both groups had no statistically significant difference in ICU days post-cannulation or disability at time of discharge.[24]

In approximately 5% of pediatric lung transplant cases, ECMO is used as bridge to lung transplant.[25] However, this area remains understudied and data from adult studies is not consistently applicable to the pediatric population. Pediatric lung transplant candidates remain on the waitlist longer and have higher waitlist mortality than adults. *Lancaster et al* noted in their review of adults that 1-year survival after pretransplant ECMO is 25%.[25]

3.4. Extracorporeal cardiopulmonary resuscitation (eCPR)

ECMO was first reported as a rescue therapy in pediatric patients with cardiac arrest in 1992 by de *Nido et al.*[26] Since then, many centers have begun to offer eCPR programs in which children are cannulated onto VA ECMO after cardiac arrest while CPR is in progress. The American Heart Association has added ECMO cannulation as a treatment option for cardiac arrest from an underlying reversible etiology to the Pediatric Advanced Life Support algorithm.

Improved outcomes for eCPR have been documented after witnessed arrests, after short durations of high-quality standard CPR in which there are minimal disruptions, and for patients whose arrest is secondary to a cardiac condition.[21,27] Studies investigating eCPR for pediatric in-hospital cardiac arrest demonstrate survival to hospital discharge ranging from 33-55%, compared to 25-33% with non-eCPR treatment.[28-31] One single-center experience with 34 ECMO runs for patients 0 to 20 years old demonstrated 73% survival to hospital discharge with 82% of runs related to underlying cardiac disease and 9% for noncardiac etiologies.[32] The time from arrest to cannulation is essential to eCPR success. A study by *Bembea et al.* reported increased odds of death by 4% with every 5-minute delay in ECMO initiation.[33]

3.5. Toxin exposure

ECMO has been increasingly utilized in children for the treatment of toxin exposures and overdoses with resultant cardiopulmonary failure.[34] Although ECMO is not a specific treatment of toxin exposure, it provides time for organ recovery, administration of reversal agents, toxin and byproduct metabolization, and initiation of dialysis for toxin elimination while cardiac function recovers or transplantation is considered. Toxins leading to cardiopulmonary failure are often ingested or inhaled and may lead to shock, lethal arrhythmias, direct cardiac damage, or respiratory failure. Toxins include over ingestion of medications, particularly cardiac, seizure, and psychiatric medications, as well as, inhalation of chemical or environmental toxins. Inhalational exposure can specifically cause acute lung injury or pulmonary injury/fibrosis, which can result in acute hypoxia or hypercarbia refractory to medical management.[35]

ECMO outcomes for toxin exposures are excellent. An ELSO registry study of 28 patients between 30 days and 18 years old with toxin exposure from 2008 to 2017 reported 68% survival after ECMO. These patient had a variety of toxin exposures including hydrocarbons (9), gas inhalation (9), nonprescription analgesics (5), and antiepileptic drugs (3).[36] Another registry study included 86 pediatric patients treated with ECMO for toxin exposure from 2003 to 2019 and documented a 65% survival to discharge. ECMO support type (pulmonary, cardiac, and eCPR) and mode (VA and VV) were not statistically different between survivors and nonsurvivors.[34] Additionally, a study of 62 adult patients who had either cardiac arrest or severe shock due to drug intoxication reported survival of 86% for ECMO patients versus 48% treated without ECMO. Of the ECMO patients, those with refractory shock had greater survival than those who had eCPR for cardiac arrest.[37]

3.6. Burns

Several studies have demonstrated a survival benefit for pediatric burn patients with ECMO.[38-40] An ELSO registry study of 113 patients under 18 years old who were supported by ECMO for burn-associated respiratory or cardiopulmonary failure reported increased survival for those who were on ECMO for respiratory failure (56%) compared to those on ECMO for cardiac failure (33%) or ECPR (30%). Survival to discharge for the cohort was 52%. VA ECMO was used in 59% of the survivors and VV ECMO in 39% of survivors. [41]

Burns with greater total body surface area (TBSA) have increased morbidity and mortality in burn patients. Studies have demonstrated TBSA greater than 80% has near 100% mortality, while survival is approximately 70% when TBSA is less than 60%. A TBSA of 60% has been proposed as a cutoff for ECMO consideration in pediatric burns, though authors note that other diagnostic, social, and clinical data should be taken into consideration.[41,42]

3.7. Contraindications to ECMO

There are both relative and absolute contraindications to placing critically ill pediatric patients on ECMO (Table 1). Although many clinicians use a duration of 14 days of pre-ECLS ventilation as a cutoff,[21] ECMO mortality may increase after 7 days of pre-ECLS mechanical ventilation.[43,44] The pathophysiology of this finding is likely related to prolonged barotrauma or infectious complications caused by multiple days on high pressure mechanical ventilation. Though recent allogenic bone marrow transplant is considered a relative contraindication, bone marrow transplant recipients have been successfully supported on ECMO.[19,45,46]

Absolute contraindications should be evaluated in conjunction with the patient's overall clinical picture as ECMO can support a child in cardiopulmonary failure while the underlying cause of the patient's illness is treated and addressed. However, if the patient has an irreversible primary disease process and is not a candidate for organ transplantation or additional therapies, ECMO should not be considered. This decision can be made with the support of a multidisciplinary team of specialists knowledgeable about the patient's primary disease process.

Additionally, patients with chromosomal abnormalities should not be considered as a homogenous group. Mortality after ECMO for patients

Table 1
Contraindications to ECMO initiation in pediatric patients[20,21,49,50]

Relative Contraindications	Absolute Contraindications
• Mechanical ventilation >14 days • Pre-existing chronic illness with poor long-term prognosis • Recent allogenic bone marrow transplant recipients • Recent surgery or trauma with ongoing bleeding risk • Recent neurosurgical procedure or intracranial hemorrhage • Chromosomal Abnormalities (eg trisomy 13 or 18)	• Severe neurologic compromise • Incurable malignancy • Neurosurgical procedure with bleeding complication • Severe intracranial hemorrhage with mass effect • Severe coagulopathy • Irreversible primary disease process without bridge to transplant • Extreme prematurity

with trisomy 13 and 18 remains within the reported range for the general pediatric population.[47] Another recent study noted that variant, or non-classic, trisomy patients have improved survival and there has been a steady rise in survival to 1, 5, and 10 years.[48]

4. Cannulation sites and technique

Determination of cannula size and site for both VV and VA ECMO is based on vessel size and the ECMO flow rate required to support the patient's cardiopulmonary disease. Cannula size recommendations differ slightly by manufacturer. Table 2 outlines general cannula sizes for pediatric patients.

4.1. Cannulation sites

4.1.1. Central

Central cannulation is a technique initiated in most institutions by cardiothoracic surgeons via a sternotomy incision and more commonly in the postoperative cardiac patient. The benefit of central cannulation is that the large cannula sizes allow for excellent flow rates. This can be particularly useful in septic patients requiring flows greater than 150 mL/kg/min that cannot be obtained with peripheral cannulation, obese patients in whom high flows are difficult to obtain with peripheral cannulation, or patients whose vessels are too small, stenotic, or constricted for peripheral cannulation.

4.1.2. Neck

Neck cannulation is one of the mainstay access techniques in the pediatric population and includes the internal jugular veins and carotid arteries. In a survey of American Pediatric Surgical Association (APSA) members, 28.3% of respondents reported that they exclusively cannulate via the neck unless contraindicated.[51] By draining the right atrium (via the right internal jugular vein) and returning the blood distal to the aortic valve (via the right carotid), right heart strain is significantly reduced, allowing for cardiac recovery. This can be particularly beneficial in children with concomitant pulmonary hypertension.

4.1.3. Femoral

Femoral cannulation is a common ECMO site for older pediatric patients. When VA ECMO is established through femoral access, the venous cannula is often placed in the contralateral groin to minimize vascular compromise from impaired venous return and to allow more complete closure of the groin incision. The feasibility of femoral cannulation and maintenance of adequate flow is limited in patients less than 15 kg. Additionally, femoral artery catheterization in children under 5 years old has been shown to have an increased incidence of arterial occlusion or limb length discrepancy.[52] In the aforementioned APSA survey, 64% of respondents reported that they use age criteria and 8% use weight criteria when evaluating children for femoral ECMO cannulation.[51]

Complications specific to femoral cannulation include gastrointestinal bleeding, pseudoaneurysm, limb ischemia, and compartment syndrome.[53] If limb ischemia is observed, the etiology may be secondary to a low flow state from cannula obstruction or embolism/thrombus requiring removal of occlusive clot. Given the high morbidity associated with acute limb ischemia, several studies have argued that the smallest catheter possible should be used to obtain adequate flow rates. A study by *Garcia et al.* evaluated flow dynamics and complications associated with smaller cannulas (15-16F) versus larger cannulas (>21F). The authors found no significant difference in arterial flow rate between the catheter sizes but did find decreased incidence of complications with the smaller cannulas.[54]

For patients with small femoral vessels, a chimney graft can be utilized to minimize arterial cannula pressures and vascular compromise to the limb. During this procedure a polytetrafluoroethylene (PTFE) or Dacron graft is anastomosed to the femoral artery in an end-to-side fashion, and the arterial ECMO cannula is placed within the synthetic graft.

4.2. Special circumstances in cannulation

4.2.1. Reperfusion cannulas

Reperfusion cannulas are utilized to treat acute limb ischemia after femoral cannulation. Limb ischemia rates are higher in the pediatric population compared to adults, ranging from 29-54%.[55] There are two types of reperfusion catheter, one for antegrade flow and one for retrograde flow. For antegrade flow to the limb, a distal perfusion catheter (DPC) can be inserted in the superficial femoral artery. For retrograde flow to the limb, a perfusion catheter can be inserted in the dorsalis pedis or posterior tibial artery.

Table 2
Pediatric VA and VV cannula sizing by weight.

Venoarterial ECMO							**Venovenous ECMO**			
Weight	Neck		Femoral		Central		Neck	Groin		
	Venous	Arterial	Venous	Arterial	Venous	Arterial	Reinfusion	Drainage	Reinfusion	Dual Lumen
<2kg	8F	8F			12F	8F				
2-3kg	8-10F	8F			14F	8F				13F
3-4kg	10-12F	8F			14F	10F				13F
4-5kg	12F	10F			16F	10F				13F
5-6kg	12-14F	10F			16F	12F				16F
6-7kg	14F	12F			16F	12F				16F
7-8kg	14F	12F			18F	12F				16F
8-9kg	14F	14F			18F	12F				19F
9-10kg	14-15F	14F			18F	12F				19F
10-12kg	15F	14F	15F	14F	20F	12F		15F	12F	19F
13-14kg	15F	14F	17F	14F	20F	14F		15F	14F	19F
15-16kg	17F	14F	17F	14F	22F	14F		17F	14F	20F
17-18kg	19F	16F	19F	15F	22F	14F	15F	19F	15F	23F
19-25kg	19F	16F	19F	15F	22F	16F	15F	19F	15F	23F
26-35kg	21F	18F	21F	15F	24F	18F	15F	29F	15F	23F
36-40kg	21F	18F	23F	17F	24F	18F	17F	21F	17F	27F
41-45kg	23F	18F	25F	19F	29F	20F	19F	23F	19F	27F
46-50kg	23F	20F	25F	19F	29F	20F	19F	25F	19F	27F
51-60kg	25F	22F	27F	19F	29F	22F	19F	25F	19F	27F
61-65kg	27F	22F	27F	21F	29F	22F	21F	27F	21F	31F
66-70kg	27-29F	22F	27-29F	21F	32F	22F	21F	27F	21F	31F
>70kg	29F	24F	29F	23F	32F	24F	21F	27F	23F	31F

All reperfusion catheters carry risks of thrombosis, compartment syndrome, embolism, and bleeding, which can further exacerbate limb ischemia. In adult studies, prophylactic DPC placement has been shown to decrease ischemia-related limb complications.[56] In a study of 29 patients 4 to 22 years old who were cannulated by the common femoral artery for VA ECMO, 17 ECMO runs involved placement of a prophylactic DPC, while 14 ECMO runs involved reactive DPC placement after ischemic changes developed. The prophylactic group had decreased incidence of ischemia requiring surgical intervention (12%) compared to the reactive group (29%), but this was not statistically significant likely due to small sample size. Additionally, the authors found no survival benefit with prophylactic versus reactive DPC placement.[55] In another study involving 21 patients 2 to 22 years old, 11 patients (52%) developed limb ischemia and 9 had a resultant DPC placed.[56]

APSA survey respondents reported that 59% routinely insert reperfusion catheters after femoral arterial cannulation. Of these respondents, 44% reported they place a DPC prophylactically at the time of cannulation and 11% reported they place a DPC within 6 hours of cannulation. Thirty percent reported they would wait until the catheter is clinically needed.[51]

4.2.2. Harlequin syndrome/north-south syndrome

A unique complication of femoral cannulation is Harlequin syndrome, also known as North-South syndrome, which occurs in approximately 8% of patients.[57] This phenomenon results when the patient's cardiac output increases on femoral VA ECMO. Blood from the heart (which is relatively hypoxic from mixing of deoxygenated blood in the left ventricle with oxygenated blood from the distal aorta) is pumped preferentially to the patient's upper body and results in decreased oxygenation to the brain and coronary vessels. Meanwhile, the well-oxygenated blood from the arterial cannula perfuses the lower body. Patients with femoral cannulation can be monitored non-invasively for Harlequin syndrome with pulse oximeter placement on the right hand or ear and by using near infrared spectroscopy (NIRS) monitoring on the forehead.

Harlequin syndrome is treated by converting from VA to VVA ECMO. An additional venous reinfusion catheter is placed in a jugular vein to increase the mixed venous oxygenation content ejected by the heart. If cardiac recovery occurs prior to pulmonary recovery, affected patients can be converted from VVA to VV ECMO.

A series of 23 adult and 8 pediatric VVA ECMO runs reported an overall survival of 71% and neurologic complication incidence of 29%, and the authors noted that there was no survival benefit or reduction in complications with VVA ECMO. Of these runs, 5 adult and 3 pediatric patients were converted from VA to VVA ECMO for Harlequin syndrome, and VVA ECMO was noted to be valuable in this circumstance.[58]

4.2.3. Additional/accessory cannula placement

Accessory venous catheters can be added to either a VA or VV ECMO circuit. The purpose of these additional catheters is to increase the volume of deoxygenated blood removed from the patient, which can then be oxygenated by the circuit and returned to the patient. These cannulas are particularly useful when flow is limited by small vessel size or in obese patients when the body surface area is disproportionally larger than the vasculature.

4.3. Cannulation technique

4.3.1. Venoarterial neck and femoral cannulation

VA neck cannulation is performed by placing the child supine with a shoulder roll and head turned to the left. The neck and chest are prepped to allow for sterile intraoperative echocardiography. A transverse incision is made one finger-breath above the clavicle and dissected down through the subcutaneous tissues and platysma. The sternocleidomastoid is separated at its bifurcation and the carotid artery and jugular veins are identified. The internal jugular vein is dissected laterally and carotid artery is dissected medially. Once the vessels have been isolated along their lengths, they are encircled with silk ties proximally and distally. Systemic heparin is administered and allowed to circulate for one minute. The vessels are each ligated and controlled with a vascular clamp prior to creating the venotomy and arteriotomy, respectively. Prolene sutures can be placed at the venotomy and arteriotomy sites to assist in passing the cannulas and to prevent intimal injuries. The cannulas are inserted under echocardiography guidance and secured with the pre-placed silk sutures over a vessel loop bumper. Final cannula position is demonstrated in on imaging with the arterial cannula tip in the ostium of the brachiocephalic trunk and venous cannula tip in the mid right atrium (Fig. 1). Cannula placement is verified with Echocardiography. The incision is then closed, and the cannulas are secured to the skin.

In femoral artery cannulation, the arterial cannula is advanced to the level of the external iliac artery with care not to advance too proximally into the aorta, which could compromise flow to the contralateral leg. The tip of the venous drainage cannula is placed at the inferior cavoatrial junction. If placement of a reperfusion catheter is warranted, the tip of this catheter should be in the common femoral artery or distal external iliac.[59]

4.3.2. Venovenous cannulation

VV cannulation can be performed percutaneously with ultrasound, fluoroscopy and echocardiography guidance, and cannulation in the operating room is preferable. If bedside cannulation is necessary due to patient instability, fluoroscopic guided cannula placement can be performed by transporting a fluoroscopy bed to the patient's location.

When placing percutaneous VV ECMO cannulas in children, the child should be positioned supine with a shoulder roll and head turned left. The neck and chest are prepped and draped to allow for sterile echocardiography. The right internal jugular can be accessed with a micropuncture kit in order to minimize trauma to the vessel. Once vascular access is obtained, exchange the micropuncture wire under live fluoroscopy for a guidewire and advance it into the distal inferior vena cava (IVC). Wire placement in the IVC can be confirmed with live echocardiography if needed. If it is difficult to advance the wire into the IVC, an ultra-stiff or Amplatz stiff wire can be used with an angled glide wire or an angled 4 French sheath. The wire should remain in the IVC and should not migrate into the hepatic vein, which is common in children.

Once the wire is in the IVC, a skin nick is made at the guidewire

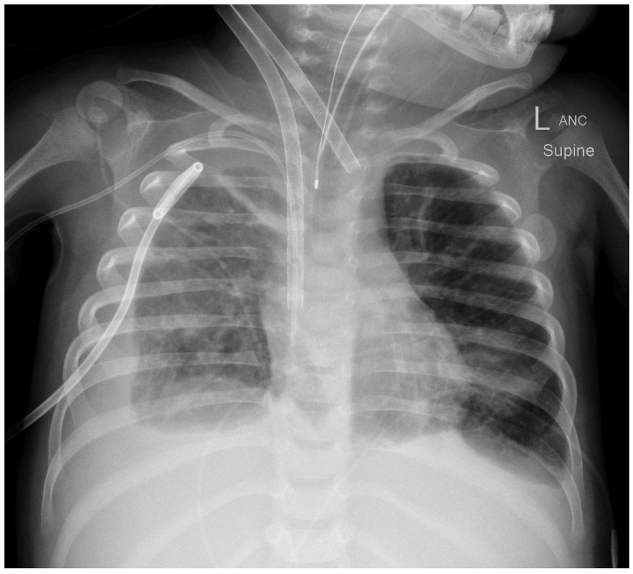

Fig. 1. VA ECMO cannula position Appropriate placement of VA ECMO cannula on chest Xray.

insertion site and the venotomy is serially dilated under fluoroscopic guidance to avoid cardiac or vascular injury. The guidewire should remain straight in the IVC and should not coil in the right atrium during dilations. Once the venotomy has been dilated to the size of the VV cannula, systemic heparin is administered and allowed to circulate for one minute. The cannula is inserted over the wire under live fluoroscopic guidance. The indicator dots on the cannula should be positioned in the mid right atrium with orientation of flow pointed towards the tricuspid valve. For single lumen and dual lumen atrial cannulas, the tip of the cannula should be situated in the mid atrium. For dual lumen bicaval cannulas, the tip should be situated in the retrohepatic IVC. Once fluoroscopic cannula position is confirmed, ECMO is initiated. Flow dynamics and positioning can be confirmed with real-time echocardiography, and the cannulas can be secured in place. Fig. 2 demonstrates fluoroscopic guidance of right atrial dual lumen VV ECMO cannula placement.

Bicaval VV cannulas drain blood from both the superior vena cava (SVC) and IVC, and blood returns through a separate port located in the right atrium at the level of the tricuspid valve. Fig. 3 demonstrates correct positioning of dual lumen bicaval and atrial VV ECMO cannulas. When utilizing single lumen catheters, femoral-jugular or femoral-femoral sites are appropriate.

4.3.3. Image guidance

Ultrasound, fluoroscopy, and echocardiography all have a role in ECMO cannulation. Preoperatively, ultrasound can be used for planned VA or VV ECMO cannulation to estimate vessel size and to choose appropriate cannulas. The preferred method of ECMO cannulation in children is with the use of both radiography, preferably as live fluoroscopy, and echocardiography to ensure optimal cannula placement and to avoid injury. During cannula placement, image guidance by echocardiography ensures accuracy and safety. Blind cannulation can result in cardiac or vascular injury. The rate of cardiac complication and perforation in pediatric ECMO cannulation has been reported to be 5%, but studies have demonstrated decreased incidence due to heavy reliance of real-time fluoroscopy and echocardiography during placement. Cardiac injury is more common with use of dual lumen VV catheters.[60,61]

There is significant variability in the use of image guidance during cannulation. APSA survey respondents reported that during VA jugular cannulation 31% used echocardiography to guide cannulation and 56% used echocardiography to verify cannula placement. For VV cannulation, 50% and 80% of respondents reported using echocardiography during cannulations and for placement verification, respectively.[51]

5. ECMO run

5.1. Basic components

There are three major components of a ECMO circuit in addition to the vascular cannulas and tubing: the pump, the membrane oxygenator, and the heat exchanger. The pump moves blood through the circuit and provides the flow rate needed for hemodynamic support in VA ECMO. There are two types of pumps, roller and centrifugal, but roller pumps have largely fallen out of favor with advancements in ECMO technology. The membrane oxygenator provides gas exchange and is composed of hollow fibers which provide a large surface area for diffusion of carbon dioxide and oxygen. The heat exchanger ensures that blood stays at a preset temperature in order to avoid complications. Of note, this component does not allow the patient to exhibit clinical fevers, and a high index of suspicion is needed to identify potential infectious complications for pediatric patients on ECMO.

5.2. Circuit maintenance

During VA ECMO, the provided level of cardiopulmonary support

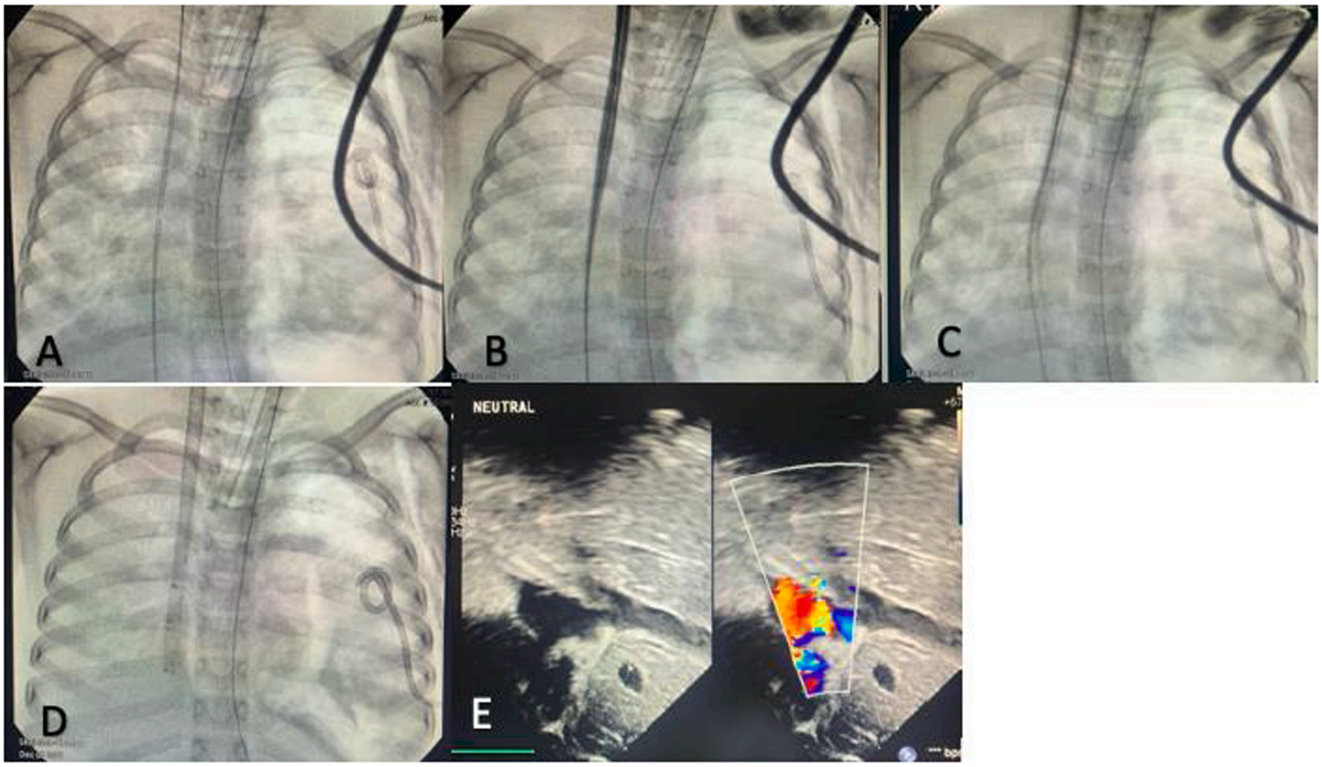

Fig. 2. Image guided VV ECMO dual lumen atrial ECMO cannulation (A) proper positioning of the EMCO guidewire in the IVC under fluoroscopic guidance. (B) Dilation of the venotomy with serial dilators. (C/D) Placement of the VV catheter under fluoroscopy. (E) Echocardiography demonstrating appropriate position and flow.

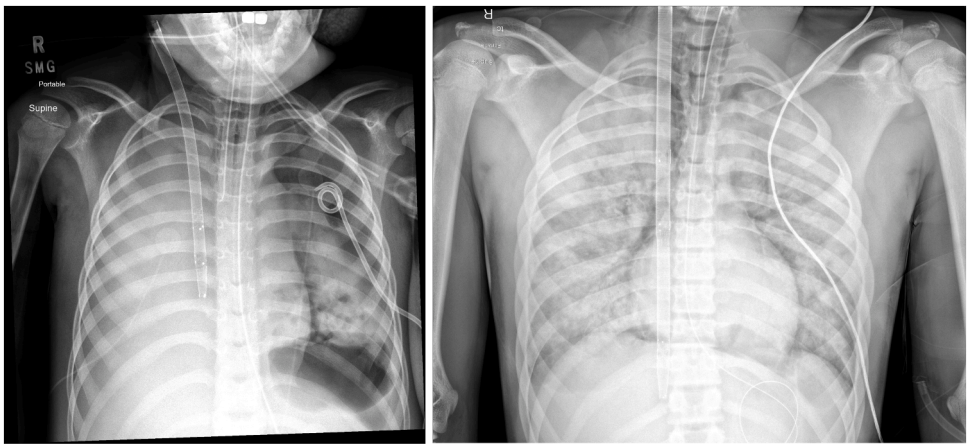

Fig. 3. VV ECMO cannula positioning on chest Xray (A) demonstrates correct placement of dual lumen atria (RA) cannula. (B) Demostrates correct placement of dual lumen bicaval cannula.

given to a child is dependent on the flow rate, hemoglobin level, native cardiac output and systemic vascular resistance. Throughout the ECMO run, the child's perfusion can be monitored using mixed venous saturation, urine output, lactates, and NIRS among other clinical markers. Flow rate can be increased to improve hemodynamics and oxygenation but is associated with greater risk of hemolysis. As perfusion and oxygenation improve, pressors can be weaned and the ventilator de-escalated to rest settings. Hyperoxia should be avoided as it is associated with increased mortality on ECMO.[20]

During VV ECMO, recirculation results in decreased systemic arterial saturations compared to VA ECMO, but as the lung recovers, native pulmonary function will contribute to increased oxygenation and arterial saturations will improve. Hypercarbia should be correctly slowly (over 4 hours) by titrating the sweep gas flow in order to avoid changes in cerebral blood flow. Permissive hypercarbia may be appropriate in patients with chronic lung disease. Because VV ECMO does not provide cardiac support, vasoactive medications may be needed; however, hypotension will often improve as systemic and coronary hypoxia improves.

For all ECMO patients, fluid overload and anemia should be avoided while maintaining adequate anticoagulation. Sedation should be titrated for comfort, but many emerging studies have demonstrated feasibility of awake ECMO and early mobilization and rehabilitation in pediatric patients.[62,63]

5.3. Nutrition

Adequate nutrition is imperative for the critically ill child and their recovery. Pediatric ECMO patients may be hypermetabolic during their ECMO run and for three weeks post-decannulation.[64] Enteral nutrition is the preferred route of nutrition because of its improved absorption, positive impact on intestinal health, decreased impact on liver function, and reduced rates of bacteremia and septic complications. Despite this, *Demarais et al.* reported that only 84% of pediatric ECMO centers utilize enteral nutrition for ECMO patients. Additionally, 71% of these centers state they often or always use enteral nutrition for VV ECMO patients, and 54% of centers use enteral nutrition often or always for VA ECMO patients.[65] Enteral nutrition can be started at 10-20 mL/kg/day and slowly titrated to full feeds with monitoring for tolerance. The most common cause of feeding intolerance in ECMO patients is delayed gastric emptying. Contraindications to enteral feeding include significant pressor requirements or evidence of clinical evidence of impaired perfusion, unrepaired congenital diaphragmatic hernia, and ileus or abdominal pathology such as colitis or enteritis. *Ong et al.* found that enteral nutrition was associated with lower mortality in pediatric ECMO patients.[66] As a result, ELSO has developed a guideline for nutritional support of pediatric ECMO patients (Table 4).[67]

ELSO Guidelines for Nutritional Support of Pediatric ECMO Patients[67]

1) ECMO patients should undergo a nutritional assessment for ECMO patients using a Nutrition Focused Physical Exam.
2) ECMO patients should be evaluated by the same methods for estimation of nutritional needs as other critically ill pediatric patients.
3) ECMO patients should have a minimum of 1.5 gm/kg/day protein with a gradual increase to 3 gm/kg/day as needed to meet protein requirements.
4) Nutritional delivery should be initiated within 48 hours of ECMO support or as soon as clinically stable.
5) ECMO patients should have early initiation and slow advancement of enteral nutrition as the method of choice for nutritional support with the goal of two-thirds nutrient goal in the first week. If nutrient delivery goal cannot be achieved by enteral nutrition alone, parenteral nutrition with lipids should be started within 3–5 days for malnourished children and within 5–7 days for well-nourished children.
6) ECMO patients should be monitoring for feeding intolerance. If feeding intolerance develops, consider changing the route of enteral nutrition delivery, reducing volume while maintaining protein goal, using a hydrolyzed formula, or initiating a prokinetic agent.
7) A stepwise nutrition support algorithm should be utilized to determine the feasibility of early enteral nutrition versus the need for parenteral nutrition.

5.4. Weaning ECMO

Once a pediatric patient demonstrates evidence of sufficient cardiopulmonary recovery, ECMO support can be weaned prior to decannulation. For VV ECMO, the ventilator is transitioned off rest settings and the ECMO sweep and FiO2 are titrated down to minimal settings. ECMO flow rates do not need to be changed for a VV ECMO weaning trials because the flow does not provide hemodynamic support; in addition, lower flow rates may lead to unnecessary thrombotic complications within the ECMO circuit. In contrast, when weaning VA ECMO, in addition to titrating down FiO2 and sweep gas, the patient's ECMO flow rate must be decreased in order to determine if cardiac recovery is sufficient to support decannulation. Once the patient has tolerated low flow trials, the circuit can be clamped to the patient for several minutes to determine if ECMO support is still warranted. During low flow states, the bridge can be opened to decrease stasis in the circuit. Echocardiography, arterial blood gases, and clinical exams are used during weaning to determine patient tolerance.

5.5. Decannulation

When a pediatric patient no longer requires ECMO support,

decannulation can be performed at the bedside or in the operating room. Decannulation for VA or VV ECMO through an open incision involves opening the cannulation incision, isolating the vessels in which the cannulas were placed, and either repairing or ligating the vessels. When a percutaneous approach is used for VV ECMO cannulation, a purse-string suture can be placed around the cannula insertion site. The cannula can then simply be removed similar to a central line removal and pressure held over the venotomy site after decannulation. An open exploration and ligation is rarely indicated.

Regardless of vessel approach after decannulation, serial neurovascular checks should be conducted. Carotid artery decannulation may result in carotid stenosis or stroke, while femoral artery decannulation may result in thrombosis, embolism, or dissection that can lead to limb ischemia. Multiple studies evaluating carotid reconstruction demonstrate excellent vascular patency rates.[68-73] However, a few studies have shown severe postoperative stenosis or complete occlusion after carotid repair.[74-77] Studies evaluating internal jugular vein patency after repair have reported patency ranging from 78 to 100%.[78-80] Most recently, a systematic review analyzed 18 manuscripts written on carotid artery vascular reconstruction after ECMO cannulation in children. It found an overall arterial patency rate of 78.6% and no major thromboembolic events documented in the literature. That being said, although vascular reconstruction after ECMO cannulation did not appear to have significant short term morbidity, the review failed to show a relationship between vascular reconstruction of the carotid artery and improved neurologic outcomes in pediatric ECMO survivors (in terms of neuroimaging or functional outcomes).[81]

APSA survey respondents reported that after decannulation 7% always attempt repair of the carotid artery, 11% selectively repaired the artery, and 83% never repaired the artery.[51] For femoral cannulation, 39% of respondents indicated that they repair the femoral vessels, and of these respondents 13% reported they use a vein patch for repair and 41% indicated that they request vascular or cardiac surgery assistance for repair.[51]

5.6. Complications

Although ECMO can be a lifesaving intervention in critically ill children, ECMO runs can be complicated by various issues, including mechanical circuit issues, hemorrhage due to anticoagulation, infection, hypertension, kidney injury, and stroke.

Mechanical circuit issues may be due to cannula malpositioning, air in the circuit, pump thrombosis, circuit rupture, or oxygenator failure. Recommendations for avoiding mechanical circuit issues have specifically commented on team training and organization. It is imperative that all personnel directly caring for a patient on ECMO should understand the circuit and its physiologic interactions with the patient as this can promote early identification of mechanical problems.

Hemorrhagic complications are due to anticoagulation and hematologic derangements, sometimes in combination with technical issues. These complications include surgical site bleeding, gastrointestinal bleeding, venotomy or arteriotomy site bleeding, and intracranial hemorrhage. If bleeding persists and coagulopathy worsens, the patient may develop disseminated intravascular coagulation. Bleeding complications are reported to occur in 2-30% of patients during ECMO.[21] Hemolysis can also occur during ECMO runs and may lead to renal injury, pump thrombosis, hyperbilirubinemia, and increased mortality on ECMO. Hemolysis should be monitored using free plasma hemoglobin levels with levels greater than 50 mg/dL warranting intervention. Hemolysis can be minimized by decreasing revolutions per minute, decreasing negative venous pressures, and maintaining hemoglobin less than 13 mg/dL.[21]

Nosocomial infections are thought to arise from the need for multiple procedures during ECMO.[82] Current data does not support daily or surveillance blood cultures or prophylactic antibiotics. Infections occur in approximately 16% of ECMO runs and are most commonly caused by bacteria. Respiratory infections account for 11% of nosocomial infections, followed by bacteremia (4%) and urinary tract infections (4%).[82] Line infections and bacteremia in the circuit occur in approximately 17% and 11% of patients on pulmonary and cardiac support, respectively.[21] Interestingly, *Cashen et al.* did not find an association between nosocomial infections and increased mortality.[77]

Hypertension is a common complication of ECMO that has been reported to occur in as high as 87% of children on VV ECMO support. Of children with hypertension while on ECMO, 70% of cases were controlled with a single antihypertensive agent and 33% were discharged on an antihypertensive medication.[83] Hypertension on ECMO is likely multifactorial, but may occur as a result of decreased cardiac filling pressures. When choosing medications to treat hypertension on ECMO, vasodilators are not considered for initial management as they may further exacerbate hypertension by decreasing preload. In addition, altered renal perfusion can cause volume overload, changes in renal hormone levels, and sodium-water dysregulation. Additionally, inadequate sedation, catecholamine response, and corticosteroids may exacerbate hypertension.

Renal injury can be caused by toxins, hypoxia, or hypoperfusion, or hemolysis. The resultant fluid overload can be treated by either slow continuous ultrafiltration (SCUF) or continuous renal replacement (CRRT). CRRT is preferred because it allows for solute clearance, correction of electrolytes, and correction of acid base disturbances, in addition to fluid removal. Unfortunately, CRRT is associated with higher rates of hemolysis and thrombocytopenia. In the pediatric ECMO population, 33% of respiratory failure patients and 26% of cardiac failure patients have required dialysis due to ECMO-related renal injury.[21]

Lastly, the incidence of stroke in ECMO patients is approximately 10%.[84] Mortality is higher in patients who suffered strokes. A study by *Carpenter et al.* reported that neurologic complications were higher in VA ECMO patients compared to VV ECMO patients (36% vs 19%, p=0.0033). There has long been debate whether neurologic complications are more common with carotid cannulation. A 2018 study examined 30,282 pediatric ECMO runs in which 64% utilized the carotid artery for cannulation, 4% the femoral artery, and 32% central cannulation. Although carotid cannulation was reported to be associated with more strokes and neurologic complications on univariate analysis, there was no difference in neurologic complications (18.4% vs 19.5%) or stroke (4.35% vs 4.5%) after controlling for age, weight, race, severity of illness, and previous ECMO runs.[53] In contrast, a study by *Teele et al.* demonstrated carotid cannulation in children was associated with increased odds of neurologic complications across all age groups.[85]

6. Outcomes

6.1. Survivorship/follow-up

According to the ELSO registry, survival to discharge for pediatric ECMO is 61% for respiratory ECMO, 55% for cardiac ECMO, and 41% for eCPR, but it is slightly lower in patients with significant medical comorbidities such as cancer.[3,21] Studies have demonstrated a survival benefit in children treated at high-volume centers, defined as greater than 30 annual pediatric cannulations. Additionally, designated pediatric ECMO centers have significantly lower mortality rates than high-volume non-pediatric ECMO centers (17.4% vs 38.2%).[86] Pediatric ECMO patients have a high rate of readmission with approximately 3-5% mortality during subsequent readmissions after ECMO admission.[87,88]

All pediatric ECMO survivors should be followed regularly to evaluate for evidence of chronic lung disease, kidney injury, and neurodevelopmental abnormalities, including behavioral abnormalities or abnormal school performance. Survivors of pediatric ECMO have been shown to have mild disability in 27% of cases, moderate disability in 9% of cases and severe disability in 9% of cases based on pediatric cerebral performance scores.[21] Studies have demonstrated a 16% prevalence of

seizure disorders in former ECMO patients.[89]

7. Conclusion

Pediatric ECMO has evolved greatly over the past 5 decades. Cannulation strategies, circuit arrangements and new technology has allowed the most critically ill and complicated patients a second chance at life. Advances in circuit maintenance, nutritional support, and clinical decision making have mitigated many of the complications once thought insurmountable.

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