

Extracorporeal Membrane Oxygenation for Perinatal and Pediatric Patients

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Extracorporeal membrane oxygenation (ECMO) is a technique developed to ensure adequate tissue oxygen delivery in patients suffering cardiac and/or respiratory failure. ECMO can provide this delivery without causing the iatrogenic damage associated with high mechanical ventilation pressures, high fraction of inspired oxygen, or high doses of inotropic medications. Though practitioners use a multitude of other, more “conventional,” therapies for neonatal respiratory failure, only ECMO has been proven in a randomized, controlled, clinical trial to improve both mortality and morbidity among neonates. Though a randomized controlled trial of ECMO in the neonate has been published, to date no trial in the pediatric, adult, or cardiac population is complete. The Extracorporeal Life Support Organization registry provides data on the over 20,000 ECMO cases performed to date and serves as a resource to refine this supportive therapy. This support is not without complications, and it should be used in appropriate populations, with specific criteria for initiation.

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Introduction

Extracorporeal circulation is the technique of supporting the function of the heart or lungs, or both, with external artificial organs. Originally developed for use in the operating room during cardiac surgery, this support was limited to several hours duration. Intensivists and surgeons apply extracorporeal support in the intensive care unit in critically ill patients with pulmonary problems for periods of days and even weeks. In this setting, extracorporeal circulation enables the practitioner to minimize the ventilator's support, reduce the intrathoracic pressure, avoid iatrogenic damage, and allow the lungs and/or heart to heal. This form of support is called extracorporeal membrane oxygenation (ECMO). In the strictest sense ECMO is not a treatment but rather a therapeutic support and provides a means of ensuring adequate tissue oxygen delivery to support end-organ function while the (hopefully) reversible disease responds to treatment.

History of Extracorporeal Membrane Oxygenation

The technique known as ECMO evolved directly from the cardiopulmonary bypass procedure developed for cardiac surgery. During the 1950s several clinicians performed studies of extracorporeal gas exchange involving cross-circulation in animals, using biologic lungs for gas exchange. Lillehei et al were the first to perform cross-circulation in humans. In 1955 they reported a series of 8 pediatric patients in whom cardiac surgery was performed using the parent as the oxygenator.¹ The 8 patients and donors survived, and no long-lasting donor morbidity was noted.

In 1963 Kolobow et al developed a silicone membrane similar to the one commonly used today.² With this device the first extended bypass procedure was performed in animals and demonstrated minimal hematologic effect for up to 1 week.³ This development paved the way for the successful application of long-term extracorporeal support. Hill et al reported the first successful use of ECMO in 1972, with a 24-year-old man suffering from multiple trauma and respiratory failure.⁴ He received extracorporeal support for 75 hours, during which time his lung injury resolved.

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The National Institutes of Health sponsored a multicenter, randomized, prospective study of ECMO with adults suffering acute respiratory failure (ARF), and a collaborative study was published in 1979.⁵ Nine institutions randomized 90 adults suffering acute respiratory distress syndrome (ARDS) to either conventional mechanical ventilation or ECMO. The results were dismal, with only 8 survivors: 4 in the conventional mechanical ventilation group and 4 in the ECMO group. The authors concluded that, although ECMO could support gas exchange, it could not improve survival in ARDS. Despite these disappointing results, the search continued to identify a population with reversible lung disease that could benefit from ECMO.

In 1975 Bartlett and Harken at the University of California, Irvine, pioneered neonatal ECMO, developed the standard circuit, and successfully used ECMO in a neonate suffering meconium aspiration syndrome.⁶ Over the subsequent years; their success continued, and in 1982 Bartlett et al reported a 55% survival rate in a series of 45 neonates treated with ECMO.⁷

In the 1980s Bartlett et al⁸ and O'Rourke et al⁹ conducted prospective randomized trials comparing ECMO to conventional mechanical ventilation. Bartlett's study reported a 100% survival of the 11 patients receiving ECMO and 0% survival in the control group.⁸ This study was met with skepticism because there was only 1 patient in the control group. O'Rourke et al subsequently reported a 100% survival rate for 9 ECMO patients, compared with 33% survival among 6 newborns treated with conventional mechanical ventilation, but that study also encountered criticism for its design.⁹

In the 1990s ECMO became, for neonatal patients, a standard mode of therapy for ARF unresponsive to maximal medical therapy, despite the lack of a randomized, controlled, clinical trial proving ECMO's efficacy. In 1996 the United Kingdom Collaborative ECMO Trial Group answered the criticism that there existed no "real proof" of ECMO as an appropriate therapeutic intervention. They reported the results of a randomized, controlled, clinical trial to assess whether a policy of referral for ECMO improved outcomes for patients out to 1 year without severe disability, in comparison with conventional management. The board monitoring the trial stopped trial recruitment early (November 1995) because the data showed a clear advantage with ECMO. They enrolled 124 children. Overall, 81 (44%) infants died before leaving the hospital and 2 died later. Death rates differed between the 2 trial groups: 30 of 93 infants who received ECMO died, compared with 54 of 92 who received conventional care. The relative risk was 0.55 (95% confidence interval 0.39–0.77, $p = 0.0005$), which is equivalent to 1 extra survivor for every 3–4 infants treated with ECMO. The results, reported in 1996, leave little doubt that ECMO is an effective life-saving treatment for neonates suffering severe respiratory failure.¹⁰

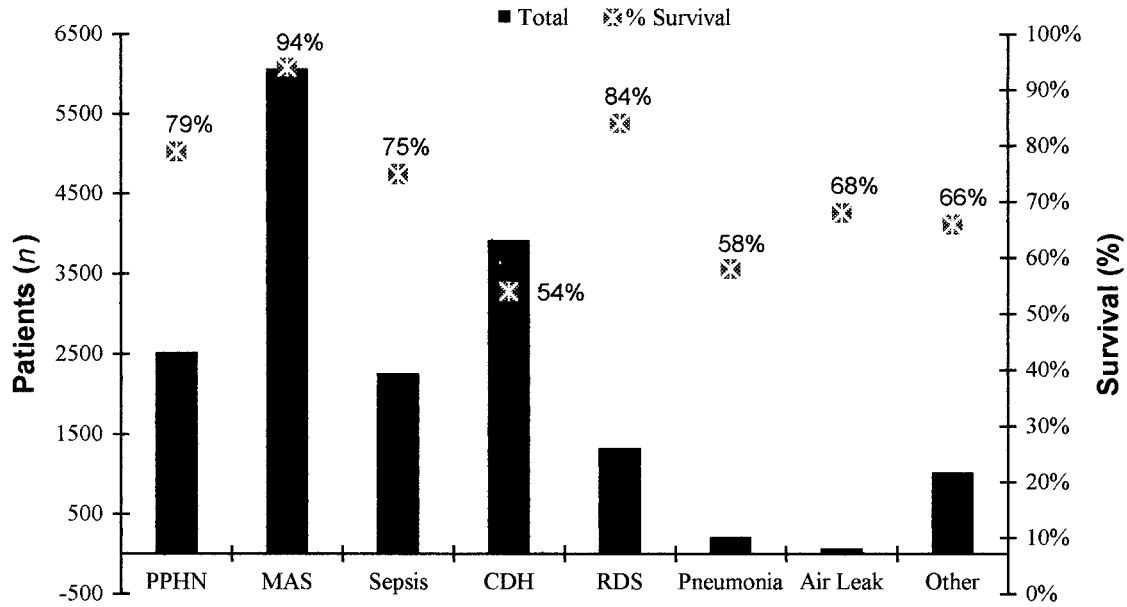


Fig. 1. Neonatal survival, by diagnosis. CDH = congenital diaphragmatic hernia. MAS = meconium aspiration syndrome. PPHN = persistent pulmonary hypertension of the newborn. RDS = respiratory distress syndrome. (From Reference 14, with permission.)

I reviewed The Cochrane Library, which is a regularly updated collection of evidence-based medicine databases, including The Cochrane Database of Systematic Reviews. A search for other commonly used therapies for neonatal ARF (ie, high-frequency oscillatory ventilation, surfactant, inhaled nitric oxide) revealed that no other therapeutic intervention has the positive impact on mortality and morbidity that ECMO does. Finer and Barrington's Cochrane Review concluded, "Inhaled nitric oxide appears to improve outcome in hypoxemic term and near-term infants by reducing the incidence of the combined end point of death or need for ECMO. The reduction seems to be entirely a reduction in need for ECMO; mortality is not reduced."¹¹

For patients receiving surfactant therapy, 2 randomized, controlled trials indicate a significantly lower risk of requiring ECMO; however, no difference was found in overall mortality.¹²

Finally, though high-frequency oscillatory ventilation has become a mainstay in the neonatal intensive care unit, there is no evidence of lower mortality at 28 days or of less failed therapy on the assigned mode of ventilation requiring cross-over to the other mode. There were no significant differences in the numbers of patients requiring ECMO, days on a ventilator, days on oxygen, or days in the hospital.¹³

Since Bartlett's first reported success with ECMO in neonates,⁷ the number of ECMO centers has continued to grow, with 114 active ECMO centers reported in 2000. In 1989 the ECMO centers formed a national organization, the Extracorporeal Life Support Organization (ELSO).

ELSO's purpose is to coordinate clinical research on extracorporeal support, develop ECMO guidelines, and maintain the ELSO National Registry, which is a data bank of all reported ECMO cases from the active ELSO centers and contains information on more than 22,500 neonatal, pediatric, and adult cases to date.¹⁴

Neonatal Extracorporeal Membrane Oxygenation

The majority of the reported ECMO cases (78%) are neonates, and the highest reported rates of survival occur in the neonatal population. The neonate with ARF rarely has a "chronic" disease. This makes the neonatal patient an ideal candidate for ECMO support. Figure 1 summarizes the survival rates for the neonatal diseases treated with ECMO.¹⁴

Persistent Pulmonary Hypertension of the Newborn

Persistent pulmonary hypertension of the newborn (PPHN), also known as persistent fetal circulation, is major pathophysiologic condition supported with ECMO.¹⁵

In utero, pulmonary vascular resistance (PVR) is greater than systemic vascular resistance, resulting in higher pressures in the right atrium than in the left atrium. With the infant's first breath there is an immediate reduction in PVR, resulting from the effects of mechanical lung expansion and the increase in oxygenation. This leads to an increase in pulmonary blood flow and a reversal in atrial pressures, resulting in the transition to the postnatal circulatory pattern. Should a hypoxic state occur following birth,

an increase in PVR can result, which, in turn, promotes the reinstatement of right-to-left shunting at both the atrial and ductal levels, sustaining or reestablishing the fetal circulation.

PPHN can result from any underlying neonatal condition leading to hypoxia.¹⁶ Most commonly, it is associated with meconium aspiration syndrome, perinatal asphyxia, congenital diaphragmatic hernia, sepsis, and respiratory distress syndrome. The presentation and clinical course depends on the primary disease.¹⁷ The majority of these neonates can be managed with pharmacologic and ventilatory support.^{18,19} A small percentage are unresponsive to conventional therapy, however, and prior to the advent of ECMO they would have died. Institution of ECMO interrupts the cycle of pulmonary hypertension, minimizes the need for escalating mechanical ventilation, and avoids barotrauma while the underlying condition resolves.

Meconium Aspiration Syndrome

Using ECMO to treat neonates with meconium aspiration syndrome (of all of the neonatal diseases commonly treated), has resulted in the highest survival rate. Meconium is a sterile, dark green substance that is normally present in the fetus's colon. Meconium staining of amniotic fluid is common in 10% of all deliveries but is rare in neonates < 37 weeks gestation.²⁰ Premature passage of the meconium into the amniotic fluid may occur under several conditions; most commonly in fetal hypoxia.²⁰ Therefore, presence of meconium-stained fluid may indicate fetal distress.

The diagnosis of meconium aspiration syndrome is made if the infant has a history of meconium-stained fluid, the presence of meconium in the trachea at birth, and a variable radiographic pattern of patchy infiltrates with hyperinflation to consolidation.²¹ The infant may suffer mild to severe respiratory distress. The resulting hypoxia and acidosis can increase PVR, leading to right-to-left shunting and further hypoxia.

Sepsis

The most common organism to cause sepsis in the neonate is group B streptococcus. The bacterium is found primarily in the intestinal tract, with colonization occurring in the mother's vagina.²² Although sepsis is associated more commonly with early rupture of membranes, the fetus can still become infected even if the membranes are intact. This bacterial infection can be serious in the immediate neonatal period, with mortality approaching 45%.²³ Sepsis can present as either pneumonia or overwhelming vascular collapse, referred to as septic shock. Other organisms, such as *Escherichia coli* and *Listeria*, can follow the same clinical course as Group B *Streptococcus*. The over-

all survival rate in this group is lower than in the group with meconium aspiration syndrome because cardiovascular instability and difficulties in coagulation management lead to a more complicated and prolonged course of ECMO.

Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia occurs in approximately 1 in 2,200 births.²⁴ It is characterized by the incomplete formation of the fetal diaphragm and usually occurs on the left side. The most common diaphragmatic hernia is the posterolateral type known as a Bochdalek hernia. This defect allows herniation of the abdominal contents into the thoracic cavity, affecting fetal lung development. It compresses the lung on the affected side but also shifts the mediastinum to the opposite side and compresses the contralateral lung, resulting in various degrees of bilateral pulmonary hypoplasia. Infants who are symptomatic within the first 6 hours of life have the highest mortality rate.²⁵ The distressed newborn has a scaphoid abdomen and diminished or absent breath sounds on one side and has a chest radiograph that demonstrates gastrointestinal structures in the thorax.

Congenital diaphragmatic hernia continues to have the lowest cure rate of all common neonatal diseases treated with ECMO. Before the advent of ECMO, identifying the infant who had severe pulmonary hypoplasia incompatible with survival was an elusive goal.²⁶

Since the introduction of ECMO many predictors of mortality have been proposed; however, because of differences in clinical management, none has been reproducible from institution to institution.²⁷

Recent data reported by Kays et al reveal that infants maintained with "gentle ventilation" methods, including permissive hypercapnia, moderate hypoxemia, minimal use of sedatives, and minimal stimulation, are less likely to require ECMO and have significantly better survival.²⁸

Neonatal Extracorporeal Membrane Oxygenation Selection Criteria

The success of neonatal ECMO depends on the disease process. Most neonatal respiratory failure results in PPHN, which is completely reversible. However, the escalating ventilator pressures and fraction of inspired oxygen (F_{IO_2}) used to treat PPHN can lead to secondary lung injury. Knowing the correct time to cease exposing the neonate's lungs to these iatrogenic complications becomes a concern for ensuring long-term survival and limiting morbidity. One guideline for determining when conventional management is failing is the oxygenation index (OI), which is a calculation based on mean airway pressure, F_{IO_2} , and arterial oxygenation (P_{aO_2}):²⁹

Table 1. Neonatal Inclusion/Exclusion Criteria

Oxygen index ≥ 40
No major cardiac defect
No fatal chromosomal abnormality
Reversible lung or cardiac disease
Gestational age > 33 wk
Intraventricular hemorrhage \leq Grade II
No serious bleeding or untreatable coagulopathy

$$OI = [(\bar{P}_{aw} \times F_{IO_2}) / P_{aO_2}] \times 100$$

A number of centers performed retrospective chart reviews and found that when the OI exceeded 40, then mortality exceeded 80%. OI is currently the most widely accepted predictor of mortality in neonates suffering respiratory failure on conventional ventilators. However, as experience with neonatal resuscitation improves, and as more institutions employ high-frequency ventilation as rescue therapy prior to ECMO, the value of OI and other guidelines will require constant reassessment.

In addition to statistical indicators for employing ECMO, practitioners consider other criteria with ECMO candidates. All neonatal candidates should have a cranial ultrasound prior to initiation of ECMO, unless the delay would increase the risk of mortality. Bleeding is the major complication of ECMO; therefore, active bleeding or uncorrectable coagulopathies are relative contraindications.

Ultimately, the patient's pulmonary disease should be reversible; therefore, prior mechanical ventilation for > 14 days is a relative contraindication for ECMO because of the potential iatrogenic lung injury. Performing an echocardiogram should rule out a cyanotic cardiac defect. Surgical intervention (correction or palliation) should be the first option. If lung disease prevents surgical correction, stabilization on ECMO prior to surgery for pulmonary

resolution is a valuable consideration. Other congenital and medical conditions associated with poor prognosis may be contraindications for ECMO. Table 1 summarizes current selection criteria.

Pediatric Extracorporeal Membrane Oxygenation

Beyond infancy there is no pulmonary condition as completely reversible as PPHN. In older children most conditions leading to respiratory failure involve pulmonary parenchymal injury, including post-traumatic respiratory failure, viral or bacterial pneumonia, and blood, gastric acid, and foreign substance aspiration. These conditions all present a picture more closely related to ARDS than to PPHN. In the mid-1970s the mortality rate from ARDS among children was 80%.³⁰ It continued to remain equally high in the late 1980s, despite changes in ventilator strategies.³¹

Centers that elect to provide ECMO in the pediatric population must consider the additional supplies required as well as the potential for longer, more complex cases. Table 2 reveals the lower survival rates as well as the higher run times associated with the pediatric diseases commonly supported with ECMO.

A recent publication by Swaniker et al, from the University of Michigan, evaluated data from 128 pediatric ARF patients and revealed an overall survival-to-discharge of 71%.³²

As it is impossible to provide specific recommendations for the institution of ECMO in older patients, most centers provide ECMO to these patients when they recognize the current maximal medical management is not working. At that point, unless the patient has specific exclusion criteria similar to those in the neonatal population (non-reversible disease, uncontrolled bleeding, moribund), ECMO is offered to the patient.

Table 2. Pediatric Respiratory Runs by Diagnosis*

Diagnosis	Total Runs	Survived (%)	Average Run Time	Longest Run Time
Viral pneumonia	615	61	322	1,372
Bacterial pneumonia	221	52	286	1,332
Pneumocystis pneumonia	17	41	352	1,144
Aspiration pneumonia	160	64	284	2,437
ARDS	278	53	285	999
ARF	558	48	249	1,483
Other	331	54	189	833

*Run time in hours. Survived = survival to discharge or transfer, based on number of runs

ARDS = acute respiratory distress syndrome

ARF = acute respiratory failure

Data are from the ELSO Registry, July 2002¹⁴

Venoarterial Extracorporeal Physiology

Oxygen delivery in ECMO is provided by a combination of blood flow from the ECMO circuit and blood flow from the patient's own cardiopulmonary system.³³ Oxygen delivery is a function of both the oxygen content of the blood and the cardiac output. Both variables (oxygenation and cardiac function) can be controlled by the venoarterial (VA) ECMO route. In VA ECMO a venous cannula, inserted via the right internal jugular vein, drains blood from the right atrium. An arterial cannula, inserted into the right common carotid artery, reinfuses the oxygenated blood into the aortic arch. The greater the ECMO pump flow, the greater the oxygen delivery.

In ECMO the specialist controls the P_{aCO_2} by controlling the minute ventilation across the artificial lung. Once adjusted, however, the P_{aCO_2} remains relatively stable on ECMO, responding only slightly to large changes in pulmonary blood flow and carbon dioxide production.

The right internal jugular vein and right common carotid artery are the preferred vessels for cannulation, especially in the neonate. This cannula orientation provides both pulmonary and cardiac support, a major advantage of this ECMO route.

The major disadvantage of the VA approach is the need to ligate the right common carotid artery and internal jugular vein. Some patients have had the carotid artery reconstructed after ECMO, but the efficacy of this procedure is also unknown.³⁴

Additional disadvantages arise from the efficiency of VA ECMO at diverting native flow. The ECMO circuit is nonpulsatile. Diverting blood away from the native cardiopulmonary system results in less pulsatile flow to the body's organs and disruption of the normal blood flow pattern.³⁵ The combination of the orientation of the reinfusion cannula (distal aortic arch) and poorly oxygenated blood leaving the left ventricle may potentiate a lower oxygen delivery to the coronary arteries.³⁶ Another potential disadvantage to VA ECMO is that any particle or bubble in the circuit may be directly infused into the arterial circulation, leading to emboli formation.

Venovenous Extracorporeal Physiology

In venovenous (VV) ECMO, blood is drained and reinfused back into the venous circulation, thereby providing only pulmonary support. The oxygenated perfusate mixes with the venous blood in the right atrium, raising the oxygen content and lowering the carbon dioxide content. Because both the drainage and reinfusion cannulae are in the venous system, some of the perfusate blood returns to the circuit. This phenomenon, known as recirculation, decreases the efficiency of gas transfer between circuit and patient. Currently, the degree of recirculation is monitored

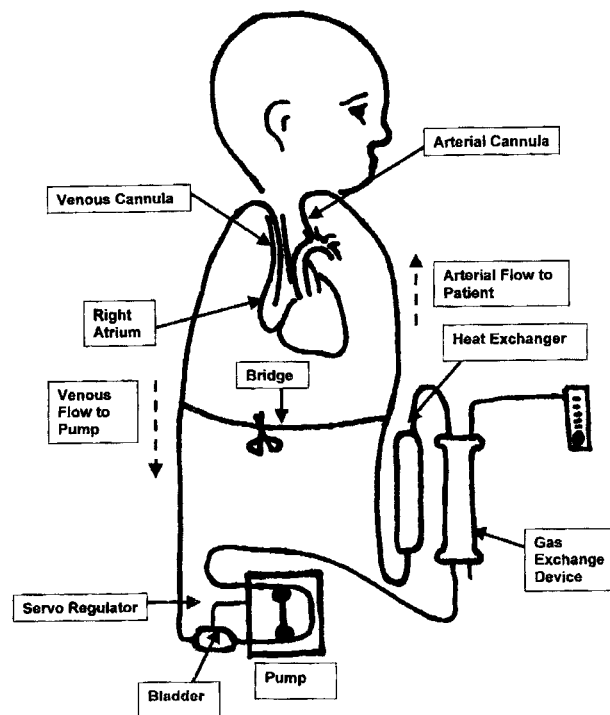


Fig. 2. A typical extracorporeal membrane oxygenation circuit.

by comparing the oxygen saturation of the venous drainage (S_{vO_2}) with the arterial saturation (S_{aO_2}).³⁷ Should the S_{vO_2} be greater than the S_{aO_2} , the recirculation is excessive and either the blood flow rate or cannula placement requires adjustment.

Since VV ECMO is less efficient than VA ECMO, the maximum S_{aO_2} achievable may be as low as 80–85%. As lung function improves, the S_{aO_2} increases. Because VV ECMO is essentially operating in series with the native circulation, alterations in cardiac output will not have a substantial effect on oxygenation. Since the volume of blood removed is equal to the volume reinfused, there is also no effect on the patient's hemodynamics.

The advantages of VV ECMO are that the carotid artery is spared, full pulsatile flow is maintained, and potential emboli from the circuit are trapped in the pulmonary vascular bed.³⁷ The major disadvantage is lack of cardiovascular support. The presence of mild to moderate myocardial dysfunction, however, should not discourage one from using the VV approach. The usual cause of myocardial dysfunction in the neonate is respiratory failure. Hypoxia, combined with the increased mean intrathoracic pressures from the ventilatory strategies used to maintain oxygenation and ventilation, decreases cardiac output and tissue oxygen delivery. The improved oxygenation and lower airway pressures achieved with implementation of ECMO often improve cardiac output substantially.

Extracorporeal Membrane Oxygenation Circuit

The ECMO circuit is composed of several disposable and nondisposable components. The disposable components are the tubing and various connectors, bladder, membrane, heat exchanger, and cannulae. Pre-assembled sterile tubing packs simplify the set-up of the circuit. The nondisposable components include the pump, venous servo-regulation system, water bath, coagulating timer, oxygen and carbon dioxide flow meters, and portable ECMO cart.

Blood flow through a typical circuit follows the path presented in Figure 2. Blood is drained by gravity from the venous cannula to a small venous reservoir. From there, the blood is pumped through an oxygenator and the heat exchanger before it is reinfused via the arterial cannula. The bridge is located near the cannula section of the circuit. It allows the patient to be isolated from the circuit while a blood flow is maintained to prevent stagnation. A complete description of the components of the ECMO circuit is beyond the scope of this article; however, detail is available in ELSO's publication known as "The Red Book."³⁸

Cannulation

Once the patient meets ECMO criteria, the team obtains consent and orders blood products. It is critical that the team moves quickly, because ECMO candidates are by definition critically ill. The patient's head is rotated to the left, and the right side of the neck and the chest are prepared in a sterile manner and draped. A small incision is made at the base of the neck, and the right common carotid artery and internal jugular vein are mobilized. The patient is given 30–100 units/kg of heparin; when this has been circulating for several minutes, cannulation is begun. The appropriate cannulae are selected for the patient size and anticipated flow rates. The surgeon places the venous cannula into the right atrium via the jugular vein and the arterial cannula into the distal aortic arch via the right carotid artery. The surgeon secures both cannulae to vessels and to the patient's skin to avoid accidental decannulation. At this point the cannulae are connected to the ECMO circuit, avoiding any air bubbles in the system. Once connected, the pump flow is slowly increased while the ventilator settings are concomitantly decreased. This usually results in immediate stabilization of the patient's vital signs. Note that with VV ECMO via the double-lumen cannula, only the internal jugular vein is cannulated; this is often performed using a "semi-percutaneous" technique that obviates ligating the vessel.

Management During Extracorporeal Membrane Oxygenation

Cardiovascular System

The main goal of ECMO is to provide adequate oxygen delivery to prevent tissue hypoxia. The oxygen saturation of the circuit venous blood reflects our success or failure in achieving that goal. Most practitioners consider a circuit S_{vO_2} of 75% acceptable on VA ECMO. On VV ECMO the S_{vO_2} also reflects the recirculation and is less reliable indicator of oxygen delivery. Pulse oximetry provides continuous assessment of the patient's S_{aO_2} , especially on VV ECMO, with $\geq 85\%$ being acceptable. With full VA ECMO, however, the pulse pressure is narrow and the oximeter may be inaccurate or a signal unobtainable.

Once the surgeon connects the cannulae to the circuit, the pump's flow rate is slowly increased, to a goal of 100–120 mL/kg/min or until the S_{vO_2} is 75%. This approximates 70–80% of total cardiac output and is usually sufficient to support gas exchange. Once adequate flow and S_{vO_2} are established, the practitioner may lower the ventilator settings. Altering the flow rate of the sweep gas alters the P_{aCO_2} .

The mean blood pressure range for neonates on ECMO is 40–65 mm Hg. If inotropic support was required during cannulation, it is often rapidly weaned or discontinued. Occasionally, hypertension will occur, requiring antihypertensive administration to maintain a mean blood pressure of < 65 mm Hg. This is an essential precaution taken to reduce the incidence of intraventricular hemorrhage (IVH).

Anticoagulation

Clotting will occur within the ECMO circuit unless the blood is anticoagulated. When blood is exposed to a foreign surface, several changes take place. A layer of protein adheres to the foreign surface instantly. Some of these proteins "pacify" the surface, whereas others activate platelets and the clotting and complement cascades, resulting in clot formation.

Heparin prevents or delays thrombus formation during ECMO. The effect of heparin is immediate and produces no adverse effects. It has no direct anticoagulant effect on the blood by itself, but combines with a cofactor, antithrombin III, to prevent thrombi from forming. This stops the conversion of fibrinogen to fibrin and ultimately prevents blood from clotting. A deficiency in antithrombin III can cause heparin to be ineffective, resulting in excessive heparin use.

Activated clotting times are monitored to assess heparin administration with a simple whole blood test performed at the bedside. Generally, a continuous infusion of 20–60

units/kg/h is required to sustain the activated clotting time at 180–200 seconds (normal being 90–120 s). Once the activated clotting times are stable, they are measured at least hourly.

The amount of heparin required can be influenced by several factors. Since heparin binds to platelets, higher doses of heparin are required with platelet transfusions. Conversely, less heparin is needed when thrombocytopenia exists. Heparin is excreted in the urine, so a higher dose may be required during substantial diuresis.

Hematologic System

Of all the blood components, platelets are most affected by ECMO. They are continuously consumed during ECMO and are generally administered in concentrated form on a daily basis.^{39,40} They attach themselves to areas in which fibrinogen is present, become activated, and attract more platelets. These platelet aggregates are continuously formed while the patient receives ECMO. Because platelets adhere to the silicone membrane, they are administered directly to the patient or into the circuit after the membrane. Other blood products also adhere to the circuit but the effect is less.⁴⁰

Although protocols differ among institutions, platelets are generally administered when the count is < 100,000/mL, accompanied by additional heparin. The hematocrit, prothrombin time, and fibrinogen are also monitored, and appropriate blood products are administered as needed.

Neurologic System

The use of paralysis drugs is usually avoided during ECMO, except during cannulation and decannulation procedures. The patient is sedated while on ECMO to prevent accidental decannulation or hypertension secondary to agitation, and to provide comfort. Fentanyl, midazolam, and lorazepam are commonly used. Fentanyl continues to bind to the membrane during ECMO, and increasing amounts are usually required.⁴¹ Narcotic withdrawal can delay recovery following ECMO.⁴²

Head ultrasound is performed to rule out IVH. If IVH does occur, the mean blood pressure is decreased, the range of activated clotting times is lowered, coagulation values are optimized, and an antifibrinolytic drug may be given to avoid extension of the bleed. As with any complication, the risks and benefits of continuing ECMO should be carefully considered.

Because of the ligation of the internal jugular vein and the right common carotid artery, the head is maintained in the midline position to assure adequate cerebral drainage and perfusion. Some institutions also insert an additional cannula into the cephalad segment of the right jugular vein to avoid venous obstruction and to enhance drainage.⁴³

Pulmonary System

After the initiation of VA ECMO, the ventilation settings are generally reduced to $F_{I_{O_2}}$ of 0.21–0.4, peak inspiratory pressure of 20–25 cm H₂O, positive end-expiratory pressure of 4–10 cm H₂O, and respiratory rate of 5–10 breaths/min. These resting ventilator settings strive to maintain functional residual capacity while avoiding iatrogenic damage. Pulmonary care should include chest vibrations, manual ventilation with an inspiratory hold, and suctioning. Chest radiographs are taken daily and often exhibit a generalized opacification within the first 24 hours.⁴⁴ This phenomenon has been attributed to an abrupt decrease in airway pressure and to the release of inflammatory mediators from the blood-circuit interface. Patients who continue to have persistent pulmonary air leaks while receiving ECMO may require low-level continuous positive airway pressure for the lungs to heal. Kessler et al have shown accelerated lung recovery with positive end-expiratory pressure of 12–14 cm H₂O.⁴⁵ They found less opacification on chest radiographs and a shorter duration of ECMO. In general, lung recovery usually occurs over 3–4 days and can be quantified by improvements in the chest radiograph, lung compliance, and gas exchange.⁴⁶

Fluid Balance

Many patients receiving ECMO are quite edematous because of fluid resuscitation prior to ECMO. This edematous state can further compromise the lungs and retard lung recovery. Once capillary leak ceases, the goal of fluid management is to promote diuresis while maintaining adequate perfusion. Accordingly, fluid intake and output should be monitored for the duration of ECMO. Insensible water loss from the patient and the membrane cannot be measured but should not be forgotten. Although renal function is usually normal during ECMO, it is common to see a decrease in urine output early in the run, especially if the patient sustained a prolonged period of hypoxia or hypotension prior to cannulation. If oliguria or anuria occurs, ultrafiltration can be added to enhance output and manage fluid overload.⁴⁷ This is accomplished by connecting a hemofilter to the ECMO circuit, which allows a fraction of plasma water and dissolved solutes to pass through the filter's pores, while maintaining the cellular components and proteins. Nutrition is usually started on the third day of life; hyperalimentation and an intralipid infusion are usually initiated. However, transpyloric feeding can also be considered. In addition, most patients require calcium and potassium replacement while receiving ECMO.

Table 3. Complications Reported to the Extracorporeal Life Support Organization Registry: July 2002

Neonatal complications	Oxy Failure	Oxy Clots	Cannula Problems	Hemolysis	IVH
Reported (%)	5.7	18.6	11	13	4.9
Pediatric complications	Oxy Failure	Oxy Clots	Clots in Bladder	Hemolysis	IVH
Reported (%)	15	5.7	14.7	8.8	3.5

Oxy failure = oxygenator failed and was unable to provide adequate gas exchange
Oxy clots = oxygenator suffered enough clotting that it had to be replaced
IVH = intraventricular hemorrhage
Data are from the ELSO Registry, July 2002.¹⁴

Weaning from Extracorporeal Membrane Oxygenation

The amount of time a patient requires ECMO depends on the diagnosis. The average duration for a neonate is 4–6 days, though runs of > 4 weeks are possible. There are 2 philosophies in weaning patients from VA ECMO. In the first, as lung function improves, ECMO is slowly withdrawn as ventilator support is slowly increased. This is usually carried out over a period of several days. Once the flow rate is decreased to 20 mL/kg/min, the patient is usually ready for decannulation.

In the second approach, the patient is maintained on full flows of 100 mL/kg/min and minimal ventilator settings. At varying intervals, the patient is weaned from the ECMO circuit over a few minutes while the ventilator settings are increased. The patient circuit is then clamped off and blood gases are obtained to assess pulmonary function. The rationale for the second approach is that the longer period of low ventilator support maximizes the (resting) time for the lungs to heal. Both methods are widely used and neither has been clearly shown to have any advantage over the other.

Weaning from VV ECMO is slightly different from, and much easier than, weaning from VA ECMO. After the ventilator settings are increased, both of the membrane's gas ports are isolated from the ambient air. Eventually, the blood entering and exiting the membrane is in equilibrium and reflects typical venous values. This eliminates any issues associated with clamping of the cannulae, particularly thrombus formation, which allows a longer trial without any pulmonary support.

Decannulation

When the patient is ready to be removed from ECMO, the decannulation is performed at the bedside. Sedative and paralytic agents are administered, and all infusions are switched to a peripheral site. Heparin is discontinued; however, its anticoagulation effect is not pharmacologically reversed. In a mirror-image reversal of the original can-

nulation procedure, the cannulae are removed and the vessels are either reconstructed or ligated. After the patient recovers from the paralysis, weaning from the ventilator can proceed. Before the patient is discharged from the hospital, it is essential that he or she be referred to a follow-up program within the hospital for further and future evaluations. Again, when the "semi-percutaneous" method of cannulation is used, the cannula is simply pulled out and direct pressure held against the site until the bleeding stops and a small dressing is applied.

Complications

Complications of ECMO are divided into patient and mechanical issues. All patient complications are potentially due to 2 physiologic alterations: alterations in the blood-surface interaction, and changes in the blood flow pattern. Both of these variables can have adverse effects on all the organ systems. As already stated, when blood is exposed to a foreign surface, a chain of events occurs that results in thrombus formation and platelet consumption. This necessitates the use of heparin and consequently contributes to the bleeding complications of ECMO. Systemic heparinization makes IVH the primary risk of ECMO. The central nervous system, therefore, becomes the major area of concern. The risk of IVH is compounded by blood flow changes from the ligation of both the right internal jugular vein and right common carotid artery. The effect of this perfusion and drainage interruption to the right side of the brain has been documented by Schumacher et al, who reported several occurrences of right-sided brain lesions following ECMO.⁴⁸ Stolar et al, in reviewing the experience of the Neonatal ECMO Registry, reported that neurologic complications were predominant, with a 24% occurrence.⁴⁹ The incidence of IVH among neonates receiving ECMO is approximately 14%. In early ECMO studies Cilley et al reported on a series of 8 infants < 35 weeks gestational age, all of whom experienced IVH while receiving ECMO.⁵⁰ This led to the recommendation that ECMO should not be offered to infants < 36 weeks ges-

tational age or until anticoagulation is minimized or eliminated.

Wilson et al recently reported a different approach to this issue.⁵¹ They successfully employed an antifibrinolytic drug, aminocaproic acid, in infants considered at high risk for IVH and other types of hemorrhage. They reported a decrease in IVH, from 18% to 0%, with the use of aminocaproic acid, along with a decrease in all postoperative bleeding. Circuit thrombotic complications appeared to be greater with its use.

Venoarterial ECMO alters the blood flow pattern throughout the body, especially the cerebral and pulmonary perfusion. Diverting blood flow through a nonpulsatile pump contributes to the diminished pulse pressure. Cardiac stun, a term used to describe a dramatic decrease in the cardiac function of a patient receiving ECMO, is characterized by a minimum pulse pressure (< 5 mm Hg).⁵² This minimum pulse pressure infers nearly absent ventricular contribution, resulting in a P_{aO_2} almost equalizing the postmembrane P_{O_2} . Cardiac stun is transient and occurs infrequently. The exact mechanism of its occurrence is unknown; however, a higher mortality rate is associated with it.

The ELSO registry contains information from more than 17,000 cases and includes every reported occurrence of both physiologic and mechanical complications. Table 3 lists some of the most common patient and mechanical complications reported in the registry.¹⁴

Summary

When Zapol et al⁵ published the results of the National Institutes of Health-sponsored Adult ECMO Trial, many believed that the use of prolonged ECMO for cardiac and respiratory failure would stop. The early pioneers of this intervention, Bartlett, Short, O'Rourke, Stolar, and their students and (for want of a better term) disciples could not have imagined the impact of their persistence in refining this form of therapy. Now, over 2 decades later, ECMO is considered by many the accepted standard for treating respiratory failure in term neonates not responsive to conventional management. Challenges for the future include continued refinement of criteria for initiating ECMO in the pediatric, cardiac, and adult populations. Currently those patients are managed by practitioners who, much the same as the early pioneers of neonatal ECMO, believe that ECMO positively impacts outcomes. A physician I know states that when asked about providing ECMO as a therapeutic intervention, even without strong evidence that it will ensure survival, "most families, when given the choice between a slim chance and no chance at all, will choose slim." This attitude, coupled with the ongoing data collected in the ELSO Registry, will continue the long tradition of supporting the critically ill patient with the ultimate

mechanical ventilator. The tenets of medicine dictate that we continue this philosophy; most would agree that a 30% survival is still better than 0% survival. As ECMO practitioners continue to refine their art, we will continue to improve the outcomes of those patients not responsive to maximal medical therapy.

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Discussion

Cheifetz: Doug, thank you for an excellent summary of ECMO. My question concerns a subject you did not mention, probably intentionally, and that is the use of ECMO as a rapid response for children in full cardiorespiratory arrest. The preliminary data I have seen from ongoing studies show that the short-term survival rate is better with ECMO, but the neurologic outcome may be concerning. Do you have any views on this issue, and are you aware of any new data?

Hansell: I haven't seen any new data, Ira. I do know that a lot of centers that provide rapid-response ECMO and extracorporeal CPR [ECPR] are evaluating that service, especially in the adult population. At our institution, we're talking about whether we should provide ECPR. I think the key is to make sure that ECPR is controlled by the appropriate people. If the fellow or the resident on the general care floor or emergency department can initiate that process, then a lot of inappropriate candidates are going to be placed on ECMO. On the other hand, initiating rapid-response ECMO or ECPR in patients who are in the intensive unit care or evaluated by the ECPR team in the emergency department may be perfectly acceptable and a good way to improve outcomes. The ELSO registry data indicate that CPR before the initiation of ECMO does not have a negative impact on outcome. So the ability to rapidly initiate ECMO *after* CPR may be a good thing.

Nevertheless, I think we have to be careful about saying ECMO is simply an extension of CPR and use it out in the general care area or emergency department. The University of Michigan had substantial experience with that, and it was so poorly controlled they stopped providing ECPR in that manner.

Rotta: You mentioned that your ECMO numbers are thriving. In our institution, and I think this is representative of many institutions around the country, we've seen a substantial decrease in the number of neonatal ECMOs. ECMO used to be a "happy event" when we were dealing with straightforward meconium aspiration syndrome and we had 4-day ECMOs with 95% survival. We just don't see those cases anymore. ECMO has become a very complicated proposition, generally involving the most severe ARDS or cardiac patients, with 50–60% survival at best.

After Tom Wiswell's presentation we talked about whether to resuscitate newborns with room air, 40% oxygen, or 100% oxygen, and here we are talking about VV ECMO as something that will maybe bring highly oxygenated blood through the pulmonary vasculature, and we don't think twice about that. We published a study a few years ago about oxidative damage, comparing VV ECMO and VA ECMO in the laboratory and showed substantial lipid peroxidation in the lungs subjected to VV ECMO, which was directly proportional to the P_{aO_2} .¹ Do you have any data on oxidative damage with VV ECMO versus VA ECMO in nonexperimental ECMO?

Also, you mentioned that VA ECMO provided "terrible left ventricle support." I see VA ECMO as a modality that can unload the left ventricle and that any increased afterload translates into well-oxygenated coronary perfusion.² You also mentioned that the advantage of VV ECMO is that the left ventricle is receiving oxygenated blood that will ultimately go to the coronaries. Does the left ventricle know the difference whether the oxygenated blood is coming through the left atrium (VV ECMO) or through the arterial cannula (VA ECMO)?

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Hansell: The first question had to do with concerns about VV ECMO exposing the lung to highly oxygenated blood and the potential for oxidative damage. We don't have a strong concern with that. At optimal ECMO flow, you're pumping blood with a P_{O_2} of about 500 mm Hg into the blood that's returning from the systemic circulation, which has a P_{O_2} of 40 mm Hg. By the time the blood from those 2 sources mixes, we're looking at blood exiting the right ventricle with oxygen saturation of somewhere in the 85–90% range. I wouldn't question the fact that you saw oxidative pulmonary damage in those animal models, but I'm not exactly sure how that would happen in humans, since the pulmonary artery oxygen saturation is only about 85–90%.

The second question was about the fact that VA ECMO provides poor left ventricular support. Patients who require VA ECMO probably already have some or degree of left ventricular and right ventricular insufficiency, which may be due to hypoxia. Additionally, a child coming out of the operating room may have left ventricular dysfunction and had a long cross-clamp time or multiple re-initiations of cardiopulmonary bypass. That patient already has a less than optimally functioning left ventricle. As you increase ECMO pump flow, you reduce the amount of blood entering the right side of the heart; that is, you decrease preload. However, the left ventricle eventually fills with blood from the coronary sinus and bronchial veins. Any volume in the left ventricle must be pumped against the pressure in the aorta generated by the ECMO flow; that is, you have increased afterload. Finally, the blood ejected from the left ventricle is, in essence, venous blood;

that blood fills the coronary arteries during diastole.

In summary, early in the VA ECMO run the functionally impaired left ventricle is supplied with poorly oxygenated blood *and* must pump against an elevated afterload. Devn Cornish did a wonderful study of oxygen transport into the coronary arteries and found that oxygen delivery in coronary arteries, was better in VV ECMO, especially early in a run than it was in VA ECMO.¹ You're absolutely correct that as the ECMO run progresses, and as venous oxygen saturation on VA ECMO gets up into the 80–90% range, there's probably no real difference in oxygen being supplied through the coronary arteries. We've seen it time and again with VA ECMO, where kids with poor left ventricular function get put on VA ECMO and end up with increased left ventricular dysfunction. We attribute that to either the poor oxygen delivery or the increased afterload.

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Rotta: Wouldn't you be reluctant to place a patient suffering respiratory failure and marginal cardiac function on VV ECMO with the expectation that VV ECMO would actually improve things? Do you have a high conversion rate?

Hansell: Actually, we have an extraordinarily low conversion rate. We've done 175 total patients in our institution.¹ We reported our data at the Children's National Medical Center ECMO meeting 2 years ago, and we had done 75 consecutive VV ECMO patients with widely variable and some very high levels (15 or 20 μ g) of dopamine or dobutamine (some of the patients were on norepineph-

rine), and none of those patients were converted to VA ECMO for hemodynamic instability. Once we got oxygen to the coronaries, their cardiac function got better. We've had 1 neonatal conversion to VA ECMO. That was a patient who developed severe sepsis after he'd gone on VV ECMO and developed myocardial dysfunction. I can't think of any adults that we've had to convert.

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Cheifetz: Based on all your expertise with VV ECMO, would you review the pros and cons of cephalad venous drainage with VV ECMO? I have heard much controversy over whether it is a clinically beneficial technique.

Hansell: I have yet to see any really good reason to expose the patient to an additional cannula and a prolonged surgical process. Now I know there are centers (Children's Health Care of Atlanta is one of the primary users that I'm aware of) that wouldn't dream of initiating VV or VA ECMO without a cephalad drain, the idea being that you improve venous outflow from the cerebral vasculature. They also use it as an indicator of the overall adequacy of oxygen delivery to the patient. I don't know that that gains them a lot in the overall management of the patient. They report that they're able to get a good amount of venous drainage from that cephalad drain. They also report, I believe, about a 10–15% incidence of that cannula clotting off.

Again, I'll refer to my own experience. Of all the ECMO cases I did at Duke and all of the ECMO cases that I've done at Wake Forest we've never inserted a cephalad drain. I don't know that that has impaired our ability to adequately monitor or get enough venous return.

Salzer: All the survival data and the ELSO data you showed are aggregated; there's no display of the data over time. Haven't overall ECMO survival numbers gone down some since the use of nitric oxide became more widespread, because patients going on ECMO are now sicker and some of the less ill patients are being taken out of the equation?

Hansell: I believe you are absolutely correct. If you look at survival data by year¹ since the introduction of high-frequency ventilation, surfactant, and inhaled nitric oxide therapy, I don't think there's any question that there has been some delay in the initiation of ECMO. That underscores the struggle about initiating ECMO versus using those other adjunct therapies. I don't discount those therapies; they have an important place in how we treat patients.

ECMO is not without risk, although in some centers the risk is fairly small, and I think the ability to provide ECMO with a dual-lumen venovenous cannula, as opposed to ligating the carotid artery and internal jugular vein, make VV ECMO very appealing for treating respiratory failure in the term neonate, so *our* neonatologists don't struggle very long with thinking, "Oh boy, we kept that kid off ECMO." I think our people are much more prone to saying, "You know, I could keep trying non-ECMO treatments for a little while longer, but I don't know that that's any better an option than putting him on ECMO for 3–5 days." Those patients are often off of the ventilator in 6–8 days, as opposed to doing something that may have them on a ventilator for 2 weeks.

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Donn: Let me amplify that a little bit, because I think there are a couple of things that we probably didn't address. First, the derivation of the criteria for going on ECMO (such as oxygenation index and alveolar-arterial oxygen difference) were all retrospective analyses based, at least in our center, on mortality data generated from a 10-year period before we started ECMO, before the modern era of mechanical ventilation for newborns. They've never been updated, never been looked at prospectively, and to say that an oxygenation index of 40 in a baby in the year 2002 is equivalent to what an oxygenation index of 40 indicated in 1982 is not only "apples and oranges," it's probably "coconuts and sequoias." It's so much different than the babies that we dealt with 20 years ago that it's almost nonsensical.

Second, most of the indices used to select patients for neonatal ECMO are manipulatable, though I say that kind of tongue-in-cheek. If you use the oxygenation index and you want to put a baby on ECMO, all you have to do is increase your peak inspiratory pressure, because sooner or later you're going to ventilate dead space, and all you're going to do is raise the mean airway pressure and not raise the P_{O_2} . If you use the alveolar-arterial oxygen difference, and you're a believer in hyperventilation, and you successfully hyperventilate a baby and get the P_{CO_2} down into the mid-20s, then the alveolar-arterial oxygen difference (which is nothing more than an arithmetic expression) is going to go up and qualify that baby for ECMO.

Neither of those are particularly conducive to determining which babies really need ECMO. I think there are other mitigating circumstances right now that we may see, such as Doug Hansell observed in his center. We're studying this right now and it appears it's cheaper to treat a baby for 3 or 4 days of ECMO than it is to put him on nitric oxide. The other confounding variable is that as the ECMO experience declines and fewer centers

begin to offer ECMO, referrals may go up to centers that continue to do it. It's going to be very hard to interpret all those numbers and look at things sequentially over a period of 10 years, because things have changed so dramatically.

Salyer: I think that's why I have doubts, at least from what I've seen in my experience with children going on ECMO. Is this really now a group of patients that universally has an 80% mortality? If so, then we can make these kinds of comparisons about their survival and feel really great about it. Another thing you didn't discuss was neurological sequelae—the percentage of children who have ligated carotid arteries and what is their developmental status at 3 and 5 years.

Hansell: The best data out there have been accumulated by Penny Glass at Children's National Medical Center in Washington D.C. Penny has been updating this data for (I'm guessing) more than 15 years now and has data on kids who are now in their teens. To roughly summarize the outcome data for those kids who underwent ECMO (and a lot of them are still at Children's National Medical Center), we're studying kids who underwent VA ECMO and had the carotid artery ligated. The neurologic sequelae of those kids is, in essence, statistically the same as infants who were extraordinarily sick and would have qualified for ECMO. So the fact that we put the kid on ECMO did not contribute to any additional neurologic sequelae, unless you want to argue that in all probability the child wouldn't have survived. But they certainly aren't any worse than any other critically ill children at that time.

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Wiswell: Devn Cornish was my partner for 2 years and he had a wonderful saying: "You can either consider ECMO to be a 4-letter-word or a religious experience." ECMO was used as a bad outcome for all the nitric oxide trials. Is ECMO a bad outcome? It's never really been adequately compared using it at lower oxygenation indexes. For the major trials, the NINOS [Neonatal Inhaled Nitric Oxide Study Group]¹ and Ohmeda trials² of inhaled nitric oxide, the kids who entered the trials all met the criteria for ECMO and had oxygenation indexes > 40, so it is no surprise that if a patient randomizes not to be on nitric oxide, he's highly likely to go on ECMO. The only significant differences in the trials were more kids going on ECMO.

The follow-up period in the NINOS and the Ohmeda nitric oxide studies was only for a year or a year and a half. In the nitric oxide group there was a substantial trend to more neurodevelopmental problems. This is something that is generally not recognized among neonatologists, nor is it being commented on. So I don't know if what you're practicing at Wake Forest—putting kids on VV ECMO for 3 days—is that much better than nitric oxide and getting them off the ventilator at 6 days rather than 15 days. Is that better? Maybe so. There may be hazards.

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Hansell: I very much appreciate the commentary because, again, I think Devn Cornish's point is very poignant and really reflects a lot of what we're talking about as people who do ECMO. When you consider that for the first 15 or so years, in spite of a lot of people saying that ECMO is bad, the number of ECMO centers in this country continued to go up, and people were jumping on the bandwagon because they realized that, especially at a ter-

tiary referral center, this is what folks wanted to be able to do, and there was at least some feeling that these kids were doing pretty well, and at least surviving and not going home with horribly damaged lungs.

I think that belief still continues regarding pediatric respiratory failure and respiratory syncytial virus or post-trauma adults. We've still got 40–50% survival in the patient population about which our trauma surgeons are saying,

"I give up. I don't know what else to do. They're going to die." If you say they're going to die and we don't do anything, that's 100% mortality, but I'm going to give you at least 45–55% mortality. Even if you can't do that out in a randomized, controlled trial, which it would be nice to do, I still think it's quite valid to at least try the therapy, though knowing that half the time it's not going to work. At least we know that there's an option out there.



Morning Rounds: Children's Ward, Bellevue Hospital, NY, Jane Hodson.
 Book illustration in *How to Become Trained Nurse*, [c 1897], W Abbatt.
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