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A Review of the Fundamental Principles and Evidence Base in the Use of Extracorporeal Membrane Oxygenation (ECMO) in Critically Ill Adult Patients

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Abstract

Extracorporeal membrane oxygenation (ECMO) comprises a commonly used method of extracorporeal life support. It has proven efficacy and is an accepted modality of care for isolated respiratory or cardiopulmonary failure in neonatal and pediatric populations. In adults, there are conflicting studies regarding its benefit, but it is possible that ECMO may be beneficial in certain adult populations beyond postcardiotomy heart failure. As such, all intensivists should be familiar with the evidence-base and principles of ECMO in adult population. The purpose of this article is to review the evidence and to describe the fundamental steps in initiating, adjusting, troubleshooting, and terminating ECMO so as to familiarize the intensivist with this modality.

Keywords

ECMO, adult, extracorporeal life support

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Introduction

Extracorporeal life support (ECLS) systems include a spectrum of technologies for temporary mechanical cardiopulmonary support (CPS). Modalities of ECLS include extracorporeal CO_2 removal ($ECCO_2R$), CPS, and extracorporeal membrane oxygenation (ECMO). Extracorporeal CO_2 removal, developed by Gattinoni, is used to remove partial pressure of carbon dioxide (P_{CO_2}) in states of isolated respiratory failure refractory to conventional mechanical ventilation.[1] Cardiopulmonary support can be used to support oxygenation and/or perfusion, but it can only be used for several hours due to the limited life span of the membrane oxygenator. Depending on its circuit configuration, ECMO can be used to provide oxygenation, carbon dioxide removal, and/or perfusion support for days to weeks. It has proven benefit in the neonatal population but may also be used in older children, adolescents, and adults.[2-4]

The ECMO circuit requires vascular access, connecting tubing, a blood pump, and a gas exchange device. Vascular access may be veno-venous or veno-arterial depending on the nature of physiologic support needed. In adults, it is generally used for severe, acute, and reversible cardiopulmonary collapse. Although it is frequently used as a last resort, the survival rate for adults has been reported to be over 50% in selected populations and at selected centers.[4,5]

Intensivists who care for adult patients may not be familiar with ECMO due to its lack of availability and limited indications. The purpose of this article is to review the evidence for use of ECMO in critically ill adult patients and to describe the fundamental steps in initiating, adjusting, and terminating ECMO support. This document is not meant to supplant the expertise and special training required to care for patients on ECMO. Rather, our goal is to familiarize the intensivist with this modality, what its use entails, and its possible benefits and complications. It is assumed that the reader has a sound understanding of cardiopulmonary physiology.

Principles of ECMO

Extracorporeal membrane oxygenation differs from traditional cardiopulmonary bypass (CPB) in several important ways. In

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CPB, the heart is stopped and systemic perfusion occurs at very low levels of blood flow (2 L/min). This necessitates total anticoagulation with heparin to prevent thrombus formation. Although systemic heparin may also be necessary with ECMO, the degree of anticoagulation needed is less due to the higher blood flow rates (>4 L/min) associated with ECMO, and systemic heparin exposure may be avoided altogether for short periods of time using heparin bonded circuits.[6] In addition, an ECMO circuit, based on the life of the membrane oxygenator, may last for weeks, whereas CPB is designed for use over the course of hours.

The main purpose of ECMO is to successfully exchange gas, both oxygen and CO_2. Oxygen exchange across the membrane oxygenator is dependent on the thickness of the blood film, membrane material, fraction of inspired oxygen (F_{IO_2}), and hemoglobin concentration. In addition, excessive volume and lack of uniform laminar flow can impair oxygen exchange by creating ventilation-perfusion mismatch in the oxygenator, similar to the process that occurs in the native lung.

As with the native lung, CO_2 exchange is much more efficient than O_2 exchange in the membrane oxygenator. Carbon dioxide elimination is primarily determined by total surface area, blood flow, and the "sweep gas" flow rate. The sweep flow is a measure of gas flow (liters/minute) across the membrane oxygenator. Although not commonly needed in adults, the efficiency of the membrane oxygenator for CO_2 exchange may necessitate adding CO_2 to the sweep gas to prevent excessive CO_2 removal and "respiratory" alkalosis.

There are 2 separate modes of access for ECMO, veno-venous (V-V) and veno-arterial (V-A). Veno-venous ECMO is used for isolated respiratory failure, whereas V-A ECMO is used for isolated cardiac failure or combined cardiopulmonary failure. A dialysis membrane can be added to either circuit to provide simultaneous continuous renal replacement therapy.[5]

Veno-venous ECMO results in the return of oxygenated blood to the venous circulation, resulting in increased oxygen content and lower CO_2 content in the right atrial blood. There is no net effect on central venous pressure. Systemic blood flow and pressure are the result of the native cardiac function unrelated to the extracorporeal flow. The arterial partial pressure of oxygen, arterial (Pa_{O_2}) and hemoglobin oxygen saturation are determined by the mixing effect of oxygenated blood returning from the ECMO circuit to the right heart and deoxygenated blood returning from the bronchial admixture, coronary sinus, and vena cava. Pulmonary recovery is measured as an improvement in the mixed venous oxygenation or systemic oxygen saturation with weaning of the ECMO circuit, thereby demonstrating the ability of the lung to augment gas exchange. The design of this circuit is described further below.

Veno-arterial ECMO may support the patient either partially or completely depending on the function of the native heart and lungs and the amount of flow provided by the ECMO circuit. Systemic flow, therefore, is a combination of that established by the extracorporeal circuit plus the amount of blood passing through the native heart and lungs. Systemic oxygen and CO_2 levels are determined by a mix of blood passing through the lungs and heart and oxygenated blood that is reinfused from the circuit into the arterial circulation. Assuming very poor pulmonary function, the oxygen content of the blood in the left ventricle will be nearly identical to the right atrial blood. Several scenarios may account for an increase in systemic Pa_{O_2}: (1) improved lung function at constant ECMO flow rates, (2) decreased native cardiac function at constant ECMO flow rates, and (3) increasing ECMO flow rates at constant native cardiac output. As noted below, most commonly in adults the aorta is perfused in a retrograde fashion by cannulation of the femoral artery. Thus, assuming poor pulmonary function, oxygen delivery to the aortic arch and cerebral vessels is hindered by the native heart function and optimized by maximizing ECMO flow. The best measure of cerebral oxygenation is to sample the arterial blood from the right upper extremity as the innominate artery is the last aortic arch vessel to receive blood from the ECMO circuit. Paradoxically, cardiopulmonary recovery is measured as a decrease in the mixed-venous oxygenation. This is because the partial pressure of oxygen will decrease as the percentage of cardiac output passing through the native heart and pulmonary circuit increases.[5]

The ventilator is set on minimal settings while the patient is on ECMO to minimize ventilator-induced lung injury using the concept of "lung rest" suggested by Gattinoni.[7] Although there are no studies describing the optimal ventilator settings, the authors set inspired oxygen fraction at less than 50% to minimize oxygen toxicity, the respiratory rate at 2 to 5 breaths/min, positive end expiratory pressure (PEEP) at 5 cm H_2O, tidal volume at 4 mL/kg, and keep the plateau pressure less than 30 cm H_2O. To minimize oxygen consumption, many centers pharmacologically paralyze and sedate patients on ECMO.[8-10]

Indications and Contraindications for the Use of ECMO

Indications for the initiation of ECMO can be divided into cardiac and respiratory failure. Table 1 lists suggested indications and contraindications for consideration of ECMO in this population based on criteria from selected prospective studies in adult populations. Importantly, one must take into account the likelihood of organ recovery. A time limit on ECMO should be determined *a priori* to give the providing team and family realistic expectations on probability of recovery.

The most common cardiac indication for ECMO is inability to successfully wean a patient from the CPB circuit following cardiac surgery. Other cardiac indications include primary graft failure following cardiac transplantation and cardiogenic shock from acute coronary syndrome, myocarditis, and decompensated cardiomyopathy. Patients with irreversible cardiac disease may still be candidates for ECMO due to the possibility of cardiac transplantation with or without the use of other ventricular assist devices (VADs) as a bridge to transplantation.

Indications for ECMO in respiratory failure include adult respiratory distress syndrome acute respiratory distress syndrome, primary graft failure after lung transplantation, and

Table 1. Indications and Contraindications for Initiation of ECMO[a]

Indication	Contraindication
Murray score[b] ≥ 3	Irreversible cardiac or pulmonary disease
Severe hypercapnea with pH < 7.20	Age >65 years
Pa_{O_2}:F_{IO_2} < 50-100 (mm Hg)	Metastatic malignancy
Alveolar−arterial oxygen gradient >600 mm Hg without cardiogenic pulmonary edema	Significant brain injury
Transpulmonary shunt >30%	Mechanical ventilation >5-10 days
	Multitrauma with high risk of bleeding

Abbreviations: ECMO, extracorporeal membrane oxygenation; Pa_{O_2}, pressure of oxygen, arterial; F_{IO_2}, fraction of inspired oxygen.
[a] These criteria have not been validated but were used to enroll adult patients in 3 recent prospective studies.[11-13]
[b] The Murray score is a measure of acute lung injury and takes into account the Pa_{O_2}:F_{IO_2}, extent of infiltration seen on a chest x-ray, applied PEEP, and pulmonary compliance.

trauma. Most institutions will not perform a lung transplant in patients on ECMO due to extremely poor outcomes. Therefore, the main end point in the use of ECMO with respiratory failure is recovery of pulmonary function. The use of ECMO as a bridge to lung transplantation remains controversial and must be done in partnership with the transplantation team.

There are several contraindications for the use of ECMO. These include the presence of widely spread malignancy, advanced age (often defined as greater than 65 years of age), necrotizing pneumonia, and prolonged mechanical ventilation which is generally variably defined as greater than 5 to 10 days of ventilator support. Although traditionally thought to be an absolute contraindication, ECMO has been used successfully in patients with severe traumatic brain injury [14,15] and the patients with multiple injuries. In these instances, heparin bonded circuits are used to forgo the need for systemic anticoagulation.[16,17]

Extracorporeal Membrane Oxygenation Equipment and Devices

An ECMO circuit is designed to pump and oxygenate blood and remove CO_2. The oxygenator and tubing are proinflammatory and result in activation of platelets and the complement cascade. The inflammatory reaction may be minimized by bonding the circuit with substances such as albumin or heparin.

One of the major limiting factors in providing adequate flow are the ECMO cannulae, which are sized in French units based on their external diameter. The largest possible cannulae should be placed to optimize flow. This is especially important in regard to the venous cannula because gravity and not the pump primarily determine venous outflow. Flow and resistance monitors in the circuit are used to determine whether impaired flow is due to impaired venous outflow or excessive resistance to blood return to the patient.

Pumps

The pump works both to push blood through the oxygenator and back to the patient and also to augment venous outflow to the circuit. Two types of pumps are used in the ECMO circuit, the centrifugal pump or the roller pump.

The centrifugal pump consists of a set of cones and a magnetic disc that rotate at an adjustable rate. As the disc spins, it forms a vortex and hence negative pressure at the pump head. This acts to pull the blood into the pump and directs it out at the top of the vortex. The flow is variable and is dependent on the blood volume from the patient, size of venous outflow cannulae, size of the disc head, and pump speed. The main advantages of the centrifugal pump are that it does not exert excessive negative pressure on the blood and creates less cavitation and therefore less hemolysis. Disadvantages of centrifugal pumps include the inability to maintain a set flow as described above. Factors such as a rise in patient systemic vascular resistance, air entrapment, or a kink in the ECMO circuit may lead to a dramatic decrease in pump flow or cause an immediate cessation of flow.

The roller pump compresses the circuit tubing and pushes the blood through the raceway of the pump. This mechanism creates negative pressure that pulls blood from the venous cannula as well as positive pressure that moves the blood to the patient. The flow from the roller pump is dependent on the size of the tubing in the raceway, occlusion pressure of the rollers, pump speed, and blood volume. Different size roller pumps are required for neonates, pediatric, and adult patients, and occlusion must be set properly to ensure the proper volume is moving through the circuit with each revolution. The main advantage of roller pumps is the constant flow provided independent of circuit preload. Although there seems to be no reduction in hemolysis in adult patients due to the requirement for higher flows, there is a reported decrease in hemolysis at the lower flows used in neonates. Disadvantages include the fact that roller pumps continue to rotate independent of the available blood volume or entrapment of air and require servoregulation mechanisms to minimize these complications.

Gas Exchange Membranes

Two different devices have been developed for gas exchange in the ECMO circuit, the silicone membrane oxygenator and the hollow fiber oxygenator (HFO). Silicone membrane oxygenator is the more commonly used device in the United States. The oxygenator consists of a thin silicone sheath separated by a plastic screen spacer. The silicone sheet is wrapped around a polycarbonate core and housed in a silicone sleeve. Blood passes on one side of the membrane whereas sweep gas flows in the opposite direction on the other side of the membrane. This gas exchange device is very efficient and may require the reintroduction of CO_2 through the sweep gas to raise the circuit CO_2 to physiologic levels in neonates and some adults. The oxygenator varies by size and is selected based on patient size and approximated flow requirements.

Hollow fiber oxygenators are used in ECMO circuits outside the United States. These devices consist of capillary tubes that allow gas exchange via a countercurrent mechanism similar to that found in silicone membrane oxygenators. Advantages to HFO include ease and speed of circuit priming, a coating that reduces the risk of clot formation, a lesser surface area that reduces platelet activation and inflammation, and a lower pressure gradient across the membrane, which decreases shear stress on the red blood cell and hemolysis.

Membrane function is monitored by measuring pre- and post-membrane pressure differences and the ability to exchange gas. A rise in post-oxygenator resistance (eg, kink in arterial cannula, thrombus in the cannula, patient hypertension, or volume overload) will lead to an increase in both pre- and post-oxygenator pressures. Similarly, hypovolemia, hypotension, or a loss of pump occlusion may result in a decrease in both pressures. An increase in the transmembrane pressure is due to an increase in resistance within the oxygenator, and clot formation is the most common cause.

Heat Exchanger

A great deal of heat is lost while a patient is on ECMO. This is a direct result of the large extracorporeal surface area to which the patient's blood is exposed. To counteract this, heat exchangers are used on all ECMO circuits. The principle of the heat exchanger is countercurrent flow. The water is warmed to 37°C to 40°C to compensate for the heat loss in the remainder of the circuit, but the temperature must be kept less than 42°C to prevent complications such as hemolysis and formation of bubbles. The water should flow at low pressures to ensure that if there is a leak in the heat exchanger device the blood flows into the water bath and not the reverse.

Bridge

The bridge is a connection between the venous (drain) and arterial (return) components of the circuit. It functions as a bypass to allow the isolation of the patient from the circuit. This allows the circuit to continue to flow thereby reducing the risk of clot formation when weaning the patient off the circuit. This is discussed further in the section on decannulation.

In-Line Monitors

Monitors that continuously measure flow rate, pH, oxygen saturation, and P_{CO_2} have been built into the ECMO circuit, on both the venous and arterial sides. Examples of things that can be detected by these devices include oxygenator failure, disconnected sweep gas line, or increased metabolic demands of the patient.

Bubbles in the system are a critical problem, especially in V-A ECMO. If bubbles enter the V-A circuit, they may enter the arterial system and move directly to the cerebral circulation. Furthermore, large bubbles on the venous side can cause an airlock and cessation of flow in centrifugal pumps or at junction points in the tubing. In-line detectors detect bubbles as small as 300 to 600 μL.

Activated clotting time (ACT) analyzers are also built into the system to ensure that the proper clotting time is maintained. Unless contraindicated, the circuit is infused with heparin to prevent clot formation. There remains some controversy of the adequate ACT range, but commonly used parameters range from 180 to 220 seconds or 1.5 times the normal range.

Vascular Access for Cannulation

Proper vascular cannulation for ECMO is critical to maintain adequate flow which is typically 60 to 120 mL/kg per min, with the intention of generating a cardiac index $\geq$2.0 L/min per m^2. The exact technique used must take into account both the type of support needed and patient size. Cannulation may occur by surgical cutdown or percutaneous access. When possible, systemic heparin (100 units/kg) is administered at the time of cannula insertion.

Veno-Venous Cannulation

Venous drainage is mainly determined by gravity siphon; therefore, it is imperative to select a cannula with the largest internal diameter and shortest length to minimize resistance to flow. In the case of V-V ECMO, a smaller cannula (21-23F) may be used for venous return to the patient.[18] Most commonly, the femoral vein is used as the outflow tract to the ECMO circuit and oxygenated blood is returned to the right atrium via a right internal jugular catheter. Blood returning to the right heart via the superior vena cava remains deoxygenated relative to blood returning from the ECMO circuit.

Veno-Arterial Cannulation

In adults, the femoral artery is the most common site of arterial cannulation. However, if the diameter of the cannula is too large, it may diminish flow distally and cause lower extremity ischemia. A distally placed perfusion catheter will help prevent this complication. The cannula should be situated in the mid-descending thoracic aorta. In this configuration, blood is siphoned from the right internal jugular vein/right atrium and/or the femoral vein/inferior vena cava. Depending on the sites and efficiency of venous outflow to the circuit, a variable degree of venous return to the heart will remain and contribute to native cardiac output. Mediastinal cannulation may be necessary in certain situations including those who have failed to wean from CPB or who have undergone aggressive resuscitation after sternotomy. In these situations, direct cannulation of the arterial and venous systems are achieved using standard techniques for CPB.[18]

Infusion of oxygenated blood via the femoral artery relies on retrograde perfusion of the aorta and the aortic arch. It is most effective in instances where the ECMO circuit overtakes nearly all of the cardiac output. Significant residual venous return and cardiac function can hinder adequate perfusion to the aortic arch due to the ejection of desaturated blood from the left ventricle due to poor pulmonary function. This problem can

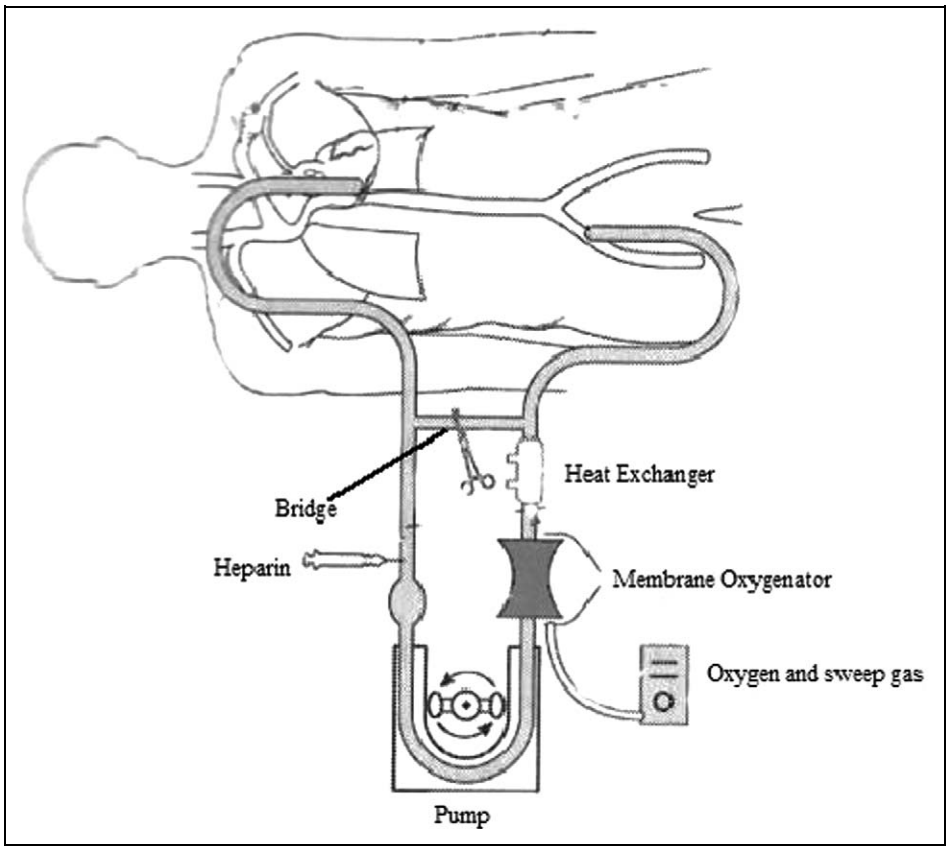

Figure 1. A veno-venous ECMO circuit using a roller pump. The sites of cannulation in this figure are the right atrium (blood returning to the patient) and the right femoral vein (blood leaving the patient). More commonly, the right internal jugular vein is used in place of the right atrium. A similar circuit can be used for veno-arterial ECMO with blood returning to the patient via the femoral artery (retrograde flow to the heart) and blood leaving the patient via the femoral vein and the internal jugular vein as needed.[107]

be identified as (1) excessive resistance against the arterial cannula which is not due to kinking, air lock, or too narrow cannula selection, (2) low Pa_{O_2} in the right upper extremity, or (3) inability to augment ECMO flow. This problem may be circumvented by the use of an additional venous cannula which results in veno-arterio-venous (VAV) bypass. In this method, an additional venous cannula is placed in the jugular or femoral vein to allow the right ventricle to also receive oxygenated blood from the ECMO circuit. Assuming reasonable cardiac function, a benefit of VAV bypass is that oxygenated blood received by the heart is ejected by the left ventricle thereby allowing the upper body to receive oxygenated blood as in V-V bypass while also providing the hemodynamic support of V-A bypass.[18,19] Other solutions to resolve the problem of excessive native cardiac output include diuresis to decrease venous return to heart or placement of an additional venous cannula in the internal jugular vein/superior vena cava to augment venous drainage to the ECMO circuit.

Weaning From ECMO

Weaning from ECMO begins by determining that cardiac and/or pulmonary function has improved. As has been discussed, in V-V ECMO, pulmonary recovery is noted as ability to maintain adequate oxygenation and CO_2 exchange with decreasing ECMO and sweep flow. Paradoxically, in V-A ECMO, the mixed-venous oxygenation saturation will decrease as the patient recovers. This occurs because the native heart and lungs will increasingly generate cardiac output and determine systemic oxygenation. Echocardiography is useful to determine cardiac recovery.

Once the decision to wean ECMO has been made, the flow rate is slowly decreased and arterial and mixed venous blood gases are monitored as the ventilator is placed on full support settings. Although there is no standard, once the ECMO flow rate is 1 L/min or less, the bridge is opened and flow to the patient is bypassed. This ''idle'' mode allows a chance to confirm that the patient is ready for decannulation without the need to dismantle and stop the ECMO circuit. If the patient manifests signs of deterioration, the bridge is clamped and flow is re-directed to the patient as before.

Troubleshooting Complications on ECMO

Complications of ECMO are classified as mechanical or patient-related (Table 2). The most dangerous patient-related complication involves stroke, most commonly hemorrhagic due to the need for systemic heparin therapy. Preventing and treating

Table 2. Troubleshooting the ECMO Circuit

Complication	Sign	Action
Large thrombus formation	Dark or white areas on oxygenator/tubing connectors, increase pressure gradient across oxygenator	Change oxygenator or circuit, increase heparin infusion
Cannulae complication		
Venous cannulae too close to one another (V-V ECMO)	No color difference between venous and arterial cannulae	X-ray confirmation. Pullback cannula
Arterial cannula in ascending aorta	Aortic valve insufficiency, left ventricular failure	X-ray and echocardiographic confirmation. Pullback cannula
Hypovolemia, pneumothorax, pericardial tamponade	"Chatter" (shaking) of cannulae	Hypovolemia: Administer Fluids, decrease ECMO flow; pneumothorax: thoracostomy tube; pericardiac tamponade: pericardiocentesis and/or pericardial window
Air embolism (large)		
Venous	Lack of blood flow (airlock)	Stop ECMO flow. Change circuit or oxygenator.
Arterial	Stroke, hypotension	Stop ECMO flow. Trendelenburg position
Oxygenator failure	Increase gas or pressure gradient across the membrane, thrombocytopenia, hemolysis	Replace oxygenator
Pump failure	Decrease blood flow/pump speed	Manually hand crank the pump and replace pump or power source
Hemorrhagic stroke	Little clinical evidence. Brain CT scan needed	Prevent hypertension and excessive anticoagulation
Lower extremity ischemia (with V-A ECMO)	Cool, pale extremity, signs of compartment syndrome (late), rhabdomyolysis (late)	Use smaller bore femoral arterial cannula, place shunt from the arterial cannula directed to distal femoral artery

Abbreviations: CT, computed tomography; ECMO, extracorporeal membrane oxygenation; V-V ECMO, veno-venous ECMO; V-A ECMO, veno-arterial ECMO.

hypertension and maintaining a platelet count greater than 100 000 cells/μL may minimize this risk. Other complications include hemorrhage, renal failure, extremity ischemia (with V-A ECMO using the femoral artery as a cannulation site), and bacteremia. Bacteremia, in particular, may be difficult to detect due to inability to mount a fever owing to the heat loss previously described and altered ability to mount a leukocytosis due to the altered inflammatory response which results from exposure of the blood to the tubing and oxygenator. Because of this, many centers use routine surveillance blood cultures but recommend against prophylactic antibiotics during ECMO.

Mechanical Complications

Formation of thrombus within the circuit. The most common mechanical complication is clot formation. These thrombi tend to occur in areas of turbulence such as in the membrane oxygenator and tubing connection points. Development of small clots in the circuit are very common and are of no consequence to the patient. Large clots, however, may lead to failure of the oxygenator, result in platelet consumption, or may travel to the pulmonary or systemic circulation. Regular inspection of the entire circuit is mandatory to identify thrombus formation early. These appear as dark or occasionally white areas around the ends of the gas exchange device and at the tubing connection sites. Because catastrophic thrombus formation in the oxygenator is more likely in instances where pharmacologic anticoagulation is contraindicated, a parallel circuit with a separate oxygenator may be created to allow for immediate oxygenator exchange.

Problems with the cannulae. Cannula placement must be performed with care to prevent injury to the vessels, specifically venous tear, which may result in significant, uncontrollable hemorrhage. The venous cannula placement is critical for successful pump function and X-ray evaluation of cannula placement may be beneficial if venous flow is not sufficient. As noted previously, venous flow is determined mainly by gravity with some contribution by the pump, and both the size and location of the cannula and pump function should also be assessed if venous outflow is limited.

Arterial cannula position is also critical. If the cannula is placed into the ascending aorta, there may be increased ventricular afterload which may exacerbate left ventricular failure. The cannula may also be placed through the aortic valve and against the left ventricular wall. This will not only result in aortic insufficiency but also potential ventricular perforation. If the arterial cannula is too distal in the descending thoracic aorta, coronary artery, and cerebral blood flow may be

compromised. As with the venous cannula, x-ray evaluation of the arterial cannula is beneficial to ensure adequate placement.

In V-V ECMO, it is possible to place the 2 venous cannulae too close to one another. This will result in circulation of the blood mainly from one cannula to the other, with little flow through the heart to the systemic circulation. A visual check can be used to determine that there is a color difference between the blood flowing through the venous drainage cannula (deoxygenated blue) and the arterial return cannula.

Extracorporeal membrane oxygenation flow is very volume dependent and will drop with hypovolemia, cannula malposition, pneumothorax, and pericardial tamponade. This usually manifests as shaking or "chatter" of the tubing caused by excessive negative pressure (created by the pump in the venous system) as well as a drop in pump output. Management includes increasing intravascular volume, exclusion of abdominal hypertension, cardiac tamponade, or pneumothorax. If this does not work, a slight reduction in flows may be helpful or an additional venous cannula can be inserted to augment venous drainage and flow to the pump.

Air embolism. Air within the ECMO circuit makes up approximately 4% of the reported complications.[20] Air within the circuit may arise from a number of other sources. First, cavitation can serve as a source for air. In this case, gas is pulled out of solution if the venous side of the circuit is clamped or kinked during priming and the pump creates significant negative pressure. Second, a small tear within the wall of the membrane oxygenator may lead to a significant air embolus. Least commonly, super saturation of the blood with oxygen may result in the oxygen being forced out of solution.[21] Air emboli into the arterial cannula can travel to the cerebral circulation, and air emboli into the venous cannula can create an airlock. Venous airlock is a catastrophic complication that requires that the patient come off the ECMO circuit with removal of the air from the current circuit or replacement of the entire circuit.

A significant degree of vigilance is necessary to minimize the risk of air embolus. Measures to reduce this risk include keeping the post-membrane P_{O_2} from exceeding 600 mm Hg and ensuring all connections are airtight and sealed. Additionally, clamps must not be placed on the circuit unless flow is diverted through the bridge.

Should a bolus of air be noted, the arterial cannula should be clamped near the patient to prevent air entry to the patient. Flow through the ECMO circuit should be stopped. Additionally, in the case that air has entered the patient, the patient's head should be lowered to divert any air from the cerebral circulation. Air may be aspirated from the right heart by placing a central line and aspirating from the distal port.

Membrane oxygenator failure. Failure of the membrane oxygenator/gas exchange device is the second most common mechanical complication reported in the literature, with an estimated incidence of 18% in the adult ECMO population.[21,22] Failure of the membrane oxygenator is often defined as impaired exchange of O_2 or CO_2 and is most readily diagnosed by serially measuring both the pre- and post-oxygenator blood gas. Other frequently used parameters to describe oxygenator failure include increased trans-oxygenator pressure gradients, presence of plasma-free hemoglobin or a decrease in haptoglobin, and the elevation in fibrin split product concentration. Platelet consumption may also be exacerbated by a failing gas exchange device. One technique that allows in-line replacement of the oxygenator as needed uses 2 connectors in the pre- and post-oxygenator, thereby allowing one to swap oxygenators without interrupting ECMO flow.[21]

Pump failure. In the case of pump failure due to either motor malfunction or power outage, the pump can be operated with a manual hand crank. Another cause of pump failure is inadequate venous return. Causes of poor venous return include hypovolemia, kinks or obstructions in the circuit, or (rarely) cardiac tamponade.

Replacement of Equipment on the ECMO Circuit

Isolating the patient emergently from the ECMO circuit must be carried out in an orderly fashion. Tubing clamps are used to first clamp the venous line, followed by unclamping the bridge and finally clamping the arterial line. A simple mnemonic for the order in which the cannulae should be clamped and unclamped is Very (Vein), Bad (Bridge), Accident (Artery). The case of air embolism is the only instance in which the arterial cannula should be clamped first as described previously to prevent air from entering the patient's body.

Evidence-Based Approach to ECMO

Although a review of the literature reveals a plethora of reports on ECMO, very few clinical trials have been performed in the adult population, and the majority of reports consist of single-institution experiences. The heterogeneity between these studies in terms of indications for, patient populations enrolled, techniques of ECMO, and the lack of randomized clinical trials leave basic questions about which adult populations may benefit from ECMO largely unanswered. Furthermore, reports on the use of ECMO in adults are limited by small sample sizes, retrospective design, or either a historical or no control population. For the purpose of this review, studies in the pediatric population or those consisting of less than 5 patients have been excluded except where historically relevant. Tables 3 and 4 list the most relevant and reliable studies published.

Cardiogenic Shock

In addition to pharmacologic and mechanical support, initiation of ECMO has emerged as an adjunctive modality for the treatment of cardiac arrest and cardiogenic shock (Table 3).[4,23-54] In 2006, Nichol et al performed a systematic review of the published case series in which ECMO was used for cardiogenic shock or cardiac arrest from 1966 to 2005.[27] An analysis of 84 studies demonstrated a 50% survival when ECMO was initiated

Table 3. ECMO for Cardiac Failure in Adults

Evidence Level	Year	Study Design	Indications	Patient (#)	Survival	Reference
Nichol	2006	SR	Cardiac arrest			40
Kennedy	1966	CS, SC	Cardiac arrest	9	17%	32
Lande	1970	CS, SC	Cardiac arrest	18	0%	34
Baird	1972	CS, SC	Cardiac arrest	25	20%	24
Wakabayashi	1974	CS, SC	Cardiogenic shock, mixed etiologies	6	67%	52
Winton	1983	CS, SC	Postcardiotomy cardiogenic shock	15	48%	55
Pennington	1984	CS, SC	Cardiogenic shock, mixed etiologies	14	27%	42
Raithel	1989	CS, SC	Cardiogenic shock, mixed etiologies	24	13%	56
Shawl	1989	CS, SC	Cardiac arrest	8	88%	49
Hartz	1990	CS, SC	Cardiac arrest	32	13%	29
Reichman	1990	CS, SC	Cardiogenic shock, mixed etiologies	38	16%	44
Shawl	1990	CS, SC	Cardiogenic shock, mixed etiologies	7	57%	50
Frazier	1990	CS, SC	Cardiac arrest	7	60%	27
Wampler	1991	CS, SC	Cardiogenic shock, mixed etiologies	53	32%	57
Mooney	1991	CS, SC	Cardiogenic shock, mixed etiologies	11	64%	39
Hill	1992	CS, MC	Cardiac arrest	169	31%	58
Rees	1992	CS, SC	Cardiac arrest	9	44%	43
Martens	1993	CS, SC	Cardiac arrest	16	13%	36
Anderson	1993	CS, SC	Cardiogenic shock, mixed etiologies	10	40%	23
Grambow	1994	CS, SC	Cardiac arrest	30	20%	28
Kurose	1994	CS, SC	Cardiac arrest	9	22%	33
Kawahito	1994	CS, SC	Postcardiotomy cardiogenic shock	13	39%	59
Monties	1995	CS, SC	Cardiogenic shock, mixed etiologies	10	40%	60
Matsuwaka	1996	CS, SC	Postcardiotomy cardiogenic shock	16	19%	61
Sasako	1996	CS, SC	Cardiogenic shock, mixed etiologies	16	32%	47
Wang	1996	CS, SC	Postcardiotomy cardiogenic shock	18	33%	62
Reiss	1996	CS, SC	Acute myocarditis	5	40%	63
Mair	1996	CS, SC	Cardiac arrest	7	43%	35
Muehrke	1996	CS, SC	Postcardiotomy cardiogenic shock	23	52%	64
Willms	1997	CS, SC	Cardiac arrest	81	25%	53
Wittenmyer	1997	CS, SC	Cardiac arrest	104	31%	54
Martin	1998	CS, SC	Cardiac arrest	10	0%	54
Orime	1998	CS, SC	Postcardiotomy cardiogenic shock	20	35%	65
Obo	1998	CS, SC	Cardiac arrest	21	43%	41
Kawahito	1998	CS, SC	Acute myocarditis	6	83%	66
Mitsui	1999	CS, SC	Cardiac arrest	8	25%	67
Kitamura	1999	CS, SC	Postcardiotomy cardiogenic shock	30	27%	68
Magovern	1999	CS, SC	Postcardiotomy cardiogenic shock	82	36%	69
Jaski	1999	CS, SC	Cardiac arrest	10	40%	61
Pagani	1999	CS, SC	Cardiogenic shock, bridge to transplant	32	43%	70
Sasaki	1999	CS, SC	Postcardiotomy cardiogenic shock	9	56%	46
Kato	1999	CS, SC	Acute myocarditis	9	78%	71
Hata	2000	CS, SC	Cardiogenic shock, mixed etiologies	30	43%	30
Bartlett	2000	RC, SC	Cardiogenic shock, mixed etiologies	136	44%	4
Hayashi	2000	CS, SC	Postcardiotomy cardiogenic shock	6	67%	72
Bowen	2001	CS, SC	Cardiogenic shock, bridge to transplant	9	78%	73
Aiaba	2001	CS, SC	Cardiac arrest after AMI	26	19%	74
Smith	2001	CS, SC	Cardiogenic shock, mixed etiologies	17	41%	75
Bowen	2001	CS, SC	Postcardiotomy cardiogenic shock	23	43%	73
Ko	2002	CS, SC	Postcardiotomy cardiogenic shock	76	26%	76
Schwarz	2003	CS, SC	Cardiac arrest	46	28%	48
Chen	2003	RC, SC	Cardiac arrest	57	32%	77
Tanaka	2004	CS, SC	Cardiogenic shock, mixed etiologies	17	24%	51
Doll	2004	RC, SC	Postcardiotomy cardiogenic shock	219	24%	78
Murashita	2004	CS, SC	Postcardiotomy cardiogenic shock	23	52%	79
Ohata	2004	CS, SC	Cardiogenic shock, mixed etiologies	8	63%	80
Leprince	2005	CS, SC	Cardiogenic shock after cardiac transplant	14	57%	81
Asuami	2005	CS, SC	Acute myocarditis	13	71%	82

(continued)

Table 3 (continued)

Evidence Level	Year	Study Design	Indications	Patient (#)	Survival	Reference
Chen	2005	CS, SC	Acute myocarditis	15	73%	77
Rhee	2006	CS, SC	Cardiac arrest	30	47%	45
Hoefer	2006	CS, SC	Cardiogenic shock, bridge to transplant	28	50%	83
Megarbane	2007	CS, SC	Cardiogenic shock, mixed etiologies	17	18%	38
Saito	2007	CS, SC	Cardiogenic shock	91	41%	84
Bahktiary	2008	CS, SC	Postcardiotomy cardiogenic shock	45	29%	85
Brunet	2008	CS, SC	Cardiac arrest	10	40%	25
Combes	2008	CS, SC	Cardiogenic shock, mixed etiologies	81	42%	86
Arpesella	2008	CS, SC	Shock after cardiac transplant	11	91%	87

Abbreviations: ECMO, Extracorporeal Membrane Oxygenation; RCT, randomized controlled trial; RC, retrospective cohort; SR, systematic review; CS, case series; SC, single center; MC, multicenter; AMI, acute myocardial infarction; PCCS, postcardiotomy cardiogenic shock.

Table 4. ECMO for Respiratory Failure in Adults

Evidence Level	Year	Study Design	Indications	Patient (#)	ECLS Survival	Control Survival	*P* Value	Reference
Zapol	1978	RCT, MC	ECMO vs CM	42	10%	10%	NS	96
Morris	1994	RCT	$ECCO_2R$ vs CM	21	33%	42%	NS	97
Peek	2009	RCT	ECMO vs CM	90	63%	47%	.03	13
Gatinoni	1986	PC, SC	ARDS	43	49%	[a]	[a]	1
Egan	1988	CS, SC	Respiratory failure	17	18%	[a]	[a]	98
Bindsley	1991	CS, SC	ARDS	14	43%	[a]	[a]	99
Hill	1992	CS, MC	Respiratory failure	9	31%	[a]	[a]	58
Anderson	1994	CS, SC	Respiratory failure	30	47%	[a]	[a]	9
Macha	1996	CS, SC	Respiratory failure	33	39%	[a]	[a]	100
Kolla	1997	CS, SC	Respiratory failure	100	54%	[a]	[a]	6
Lewandowski	1997	PC, SC	ARDS	49	55%	[a]	[a]	12
Peek	1997	CS, SC	ARDS	50	66%	[a]	[a]	16
Masaikos	1999	CS, SC	ARDS, nonneonatal	34	53%	[a]	[a]	101
Michaels	1999	CS, SC	Posttraumatic respiratory failure	30	50%	[a]	[a]	8
Bartlett	2000	CS, SC	ARDS, pneumonia	146	56%	[a]	[a]	2
Mols	2000	RC, SC	ARDS	62	55%	[a]	[a]	102
Hemmila	2004	CS, SC	ARDS	255	52%	[a]	[a]	11
Maggio	2007	CS, SC	Pulmonary embolism	21	62%	[a]	[a]	103
Beiderlinden	2006	CS, SC	ARDS	32	47%	[a]	[a]	104

Abbreviations: ECLS, extracorporeal life support; RCT, randomized controlled trial; MC, multicenter; SC, single center; CS, case series; PC, prospective cohort; RC, retrospective cohort; ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; $ECCO_2R$, extracorporeal CO_2 removal; CM, conventional management; "a" not performed.

for cardiogenic shock and 44% when ECMO was initiated following cardiac arrest. However, statistically significant heterogeneity was found within each patient group, and funnel plot analysis suggested the presence of publication bias.

Postcardiotomy cardiogenic shock (PCCS) has an incidence of 3% to 5%.[88] In most cases, a combination of intra-aortic balloon pump placement and inotropic support will allow weaning from CPB.[64] However, approximately 1% of patients cannot be weaned from CPB leaving initiation of ECMO or placement of a VAD as the only alternatives to withdrawal of support. In a series of 219 PCCS patients who received ECMO, Doll found a 24% 30-day survival rate.[78] Morbidity, however, was high with 62% of patients requiring reoperation for bleeding, 58% developing acute renal failure, and 13% manifesting lower extremity ischemia related to femoral arterial cannulation. In another series of 82 patients with PCCS who received ECLS, Ko et al found that 37 patients (45%) were ultimately weaned off ECMO. Of this group, 20 patients (54%) survived to hospital discharge, but 47% required reoperation for bleeding. Overall, survival after ECLS for PCCS ranges from 19% to 67%,[59,61,68,69,72,73,76,78,85] with irreversible cardiac failure and multiple organ failure being the most common causes of death.[64,76,78]

Although a meta-analysis on the use of ECMO for various etiologies of cardiogenic shock has not been performed, survival seems to be best when it is performed early for a potentially reversible indication such as fulminant myocarditis.[63,66,71,77,82] Indeed, several reports have documented survival rates of 71% to 83%, when ECMO is used to treat cardiogenic shock secondary to acute viral myocarditis.[66] A review of 295 cases of ECMO implemented as an adjunct to CPR found that a pre-ECMO diagnosis of acute myocarditis was associated with improved survival

compared to other diagnoses (odds ratio: 0.18; 95% confidence interval: 0.05-0.69).[89] These results must be interpreted with caution, however, as there is a lack of a standardized definition of fulminant myocarditis. In addition, the natural history of this clinical entity is not well defined with 1 study reporting a 93% survival rate in a group of 15 patients without the use of ECMO.[90]

When cardiogenic shock persists despite maximal pharmacologic and mechanical support, cardiac transplantation may be considered. To this end, ECMO has been used for short-term circulatory support (bridge to transplant).[73,81,83,87] In a situation where a suitable graft will not be available in the near future, the use of ECMO as a bridge to a more long-term cardiac support device, such as a VAD, has also been described. Hoefer et al reported outcomes on 28 patients who were implanted with a VAD following initial ECMO support. A total of 14 patients died prior to transplantation, 11 patients underwent successful cardiac transplantation, and 3 recovered without the need for transplantation.[83] Pagani et al examined the outcomes of 33 patients initiated on ECLS with intent for more long-term support. They found that 10 patients survived to VAD placement, 1 was transplanted, 5 were weaned off ECMO, and 16 died while on ECLS. Of the 10 patients who survived to VADs, 6 underwent cardiac transplant and 1 year actuarial survival was 80%.[91]

After cardiac transplantation, early cardiac graft dysfunction carries a high mortality and morbidity. Even in refractory cases of cardiogenic shock, retransplantation is not recommended.[92] With medical therapy, graft recovery often occurs and ECMO has been used as a technique to allow time for this to happen. In a series of 11 patients placed on ECMO for cardiogenic shock due to early graft dysfunction, Arpesella et al found that 10 patients were weaned off successfully from ECMO and 1 patient died of cerebral hemorrhage.[87] Another series found that 9 of 14 patients were able to wean off from ECMO, with 7 long-term survivors.[81] In a retrospective review of 28 patients with early cardiac graft dysfunction, Taghavi et al found that use of ECMO was associated with a higher weaning rate and lower need for retransplantation when compared to VAD support.[93] Although data are limited to retrospective studies, the use of ECMO appears to allow recovery after early cardiac graft dysfunction.

Respiratory Failure

Although the use of ECMO to support pediatric patients (especially neonates) with respiratory failure has been well established since the 1980s,[3,94,95] proof of efficacy in adults has been more difficult to establish (Table 4). The first report on the use of ECMO for adult respiratory failure was published in 1972, in a patient with posttraumatic acute respiratory distress syndrome (ARDS).[105] Zapol et al published the first randomized controlled trial of ECMO in adults with ARDS in 1979.[96] In this study, 20 patients were randomized to receive either conventional mechanical ventilation or ECMO for ARDS. Survival rates in both arms of the study were only 10%.

Since Zapol's study, improvements in the membrane oxygenator and the development of circuits with heparin-bonded surfaces led many to hypothesize that ECMO may be beneficial for respiratory failure refractory to conventional therapy.[2] Also during this time, a host of small studies reported significantly better survival rates following the use of ECMO for respiratory failure in adults.[1,6,8,11,12,16,17,58,98-106] The recently published Conventional ventilation or ECMO for Severe Adult Respiratory failure (CESAR) trial,[13] which sought to compare ECMO to conventional ventilation in patients with severe ARDS, found that patients who received ECMO had a higher survival without severe disability rate at 6 months. The biggest limitation of this study was that all patients who were randomized to ECMO were transferred to a single highly specialized center and may have undergone more aggressive medical management, thus raising the possibility of treatment bias. Although we still do not know whether ECMO is superior or even equal to conventional ventilation for severe ARDS, it remains a modality that can be used for patients with respiratory failure that is refractory to conventional mechanical ventilation.

Conclusion

Although controversial, ECMO may be of benefit in selected adult patients with cardiopulmonary failure. Due to its complexity, patients requiring ECMO are best served in centers which use this technique regularly. However, all intensivists should be familiar with the principles and methods of ECMO both to optimize its use and also to facilitate education for staff, patients, and families.

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