Extracorporeal lung support

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Purpose of review
The applications for extracorporeal membrane oxygenation for lung support are constantly evolving. This review highlights fundamental concepts in extracorporeal lung support and describes directions for future research.

Recent findings
Since the 1950s, extracorporeal lung support has experienced continuous advancements in circuit design and safety in acute respiratory distress syndrome, chronic obstructive pulmonary disease exacerbations, as a bridge to transplantation, intraoperative cardiopulmonary support, and for transportation to referral centers. Patients on extracorporeal membrane oxygenation are now capable of being awake, extubated, and ambulatory for accelerated recovery or optimization for transplantation.

Summary
Extracorporeal lung support is a safe and an easily implemented intervention for refractory respiratory failure. Recent advances have extended its use beyond acute illnesses and the developments for chronic support will facilitate the development of durable devices and possible artificial lung development.

Keywords
acute respiratory distress syndrome, artificial lung, bridge to transplant, extracorporeal membrane oxygenation, hypercapnic respiratory failure

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is a modified form of cardiopulmonary bypass that provides tissue oxygen delivery in the setting of cardiac, pulmonary, or combined cardiopulmonary failure. In this review, we describe the evolution of ECMO, focusing primarily on extracorporeal lung support, its current applications, complications, and future directions.

ECMO traces its roots to the first heart-lung machine designed by John Gibbon in 1953, which laid the foundation for advances in cardiopulmonary bypass. However, the direct exposure of deoxygenated blood to oxygen in the original oxygenator caused high levels of hemolysis, often leading to multiorgan failure, death, or refractory circulatory shock if the device was used for more than an hour.

In 1965, Dr Robert Bartlett, a surgical resident working at the Boston Children's Hospital, was encouraged by Dr Robert E. Gross to develop a means of supporting children on extracorporeal circulatory support until their native hearts recovered. Supervised by Dr Francis Moore, and with the assistance of engineer Phil Drinker, Bartlett and Drinker developed a membrane lung capable of efficient gas exchange with limited blood damage [1]. By 1968, they were maintaining animals on extracorporeal circulation for as long as 4 days [2]. Shortly thereafter, Kolobow *et al.* [3] developed a silicon-based oxygenator that could provide prolonged support and would form the basis for one of the first commercially available oxygenators.

In the early 1970s, the three major research laboratories working on studying extracorporeal circulation were Bartlett at The University of California at Irvine, Kolobow at the NIH, and Don Hill at San Francisco Medical Center [4]. The first successful use of ECMO in an adult was in 1971 to treat a young man with acute respiratory distress syndrome (ARDS) after trauma [5]. After several more successful cases were reported, the National Institutes of Health sponsored a prospective randomized multicenter trial of ECMO for ARDS in adults [6]. The study was aborted for lack of efficacy after a 90%

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KEY POINTS

- ECMO in the form of lung support is a safe and reliable therapy for refractory respiratory failure.
- The applications of ECMO are continuing to expand from ARDS to hypercapnic respiratory failure, as a bridge to transplantation, and for pulmonary support in the operating room, among others.
- Patients on ECMO for lung support are now able to be awake, extubated, and ambulatory.
- ECMO transport is safe and reliable when performed by regional centers of excellence.
- Future patients requiring chronic support are anticipated to be on home ECMO or have paracorporeal artificial lungs implanted for destination therapy.

mortality rate was reported for both ECMO and control groups. Although this trial was criticized for its lack of protocol standardization and reliance on inexperienced centers, its publication effectively halted ECMO development for ARDS for nearly two decades. Fortunately, trials in newborn infants for neonatal respiratory failure demonstrated significant improvement in survival and encouraged the development of ECMO programs at most major children's hospitals by 1990.

It would be nearly two decades before ECMO experienced a resurgence of interest in adults which was further bolstered in 2009, when the H1N1 influenza epidemic caused thousands of cases of respiratory failure and septic shock [7,8]. The Australian and New Zealand critical care research group reported that ECMO was one of the only interventions that improved survival with 79% survival in patients with severe ARDS [9]. Around this same time, there were major improvements made to the ECMO devices including more efficient oxygenators, less thrombotic centrifugal pumps, and improved percutaneous vascular access cannulas.

CIRCUITRY

A standard ECMO circuit is comprised of a mechanical pump, gas exchange device, a heat exchanger, tubing, and cannulae that are connected in various configurations depending upon the physiologic needs of the patient.

Configurations

The most common ECMO configurations are venovenous and venoarterial. In venovenous ECMO, blood is withdrawn from and returned to the central venous system after passing through a pump and oxygenator. This provides respiratory support but no direct hemodynamic support and can occur via either a dual-site or single-site configuration (Fig. 1). In contrast, venoarterial ECMO draws blood from a central vein and returns it to a peripheral or central artery, providing cardiopulmonary and direct hemodynamic support.

These configurations can be augmented with additional venous or arterial limbs depending on the evolving disease process and physiologic demands of the patient. Patients on venovenous ECMO who develop cardiogenic shock can be supported by splicing an arterial limb into the reinfusion line for hemodynamic support [venovenous-arterial (VVA) ECMO]. Likewise, patients receiving venoarterial ECMO can have additional venous reinfusion cannulas spliced into the circuit to deliver oxygenated blood into the jugular vein for improved oxygen delivery to the coronary and carotid circulations [venoarterial-venous (VAV) ECMO]. The relative

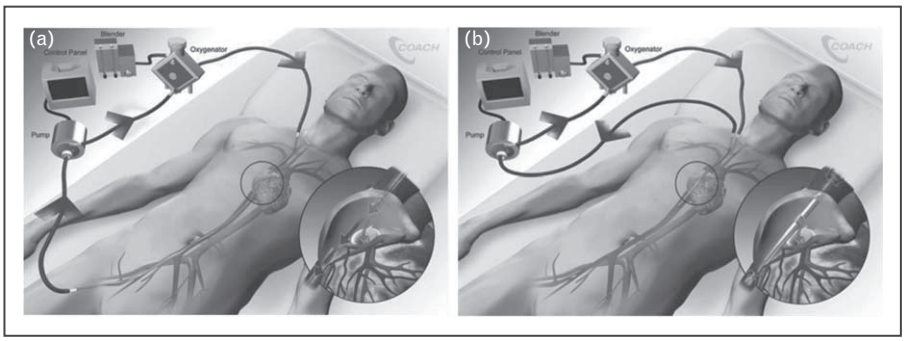

FIGURE 1. (a) Two-site venovenous extracorporeal membrane oxygenation (ECMO) cannulation. (b) Single-site approach to venovenous ECMO cannulation with double-lumen cannula. Venous blood is drained from ports in the drainage lumen from the superior and inferior vena cavae. Oxygenated blood returns through second lumen and directs flow across tricuspid valve. Reprinted with permission of collectmed.com.

	VV	VV with ASD	VA Femoral	VA Sport	VAV	PA-LA
DO_2	+++	+++	Low: ++++ Up: +	++++	+++	++++
mPAP	(-)	Marginal	++++	++++	++	+++
RV support	+	++	++++	++++	+++	+++
LV support	+	++	+ or (-)	+	++	++
Mobility	++++	++++	(-)	++++	Lower: (-) Up: ++++	+++
Simplicity	++++	++++	+++	+++	+++	+

FIGURE 2. Extracorporeal membrane oxygenation configuration characteristics. ASD, atrial septal defect; DO_2, delivery of oxygen; LV, left ventricle; mPAP, mean pulmonary artery pressure; PA-LA, pulmonary artery to left atrium; RV, right ventricle; VA, venoarterial; VAV, venoarterial-venous; VV, venovenous; +, minimal; ++, moderate; +++, good; ++++, excellent; (–), no advantage. Adapted from [10].

characteristics of each circuit configuration are presented in Fig. 2 [10].

Pumps

Mechanical blood pumps are necessary for ensuring controlled and reliable flow through the circuitry and the patient. The two most widely used types are roller pumps and centrifugal pumps.

Roller pumps

Roller pumps were the primary pump used for ECMO until the advent of centrifugal pumps. Although these pumps provide reliable flow, the tubing is subject to wear, which can result in spallation, whereby fragments of tubing slough off the luminal surface into the blood and act as potential microemboli [11]. Moreover, roller pumps are afterload insensitive, meaning that there is no limit to their infusion pressure even if there is an upstream occlusion. This significantly increases the risk of circuit blowout and rupture or harm to the patient.

Centrifugal pumps

Centrifugal pumps convert rotational energy from a spinning rotor into kinetic energy to generate flow and pressure. These pumps tend to be more durable, compact, and lightweight than roller pumps and are afterload sensitive, which makes circuit rupture extremely rare but can result in decreased flows in the setting of excessive systemic vascular resistance or mean arterial pressure in venoarterial-ECMO configurations.

Oxygenators

ECMO circuits employ oxygenators to provide gas exchange by adding O_2 and removing CO_2 from the blood. Blood and gas flow follow a countercurrent pathway to permit gas exchange via diffusion across a semi-permeable membrane. Initially made from silicone rubber, most modern oxygenators are made from hollow fibers of poylmethylpentene, which provide very efficient gas exchange and a low resistance to flow in a very compact surface area.

Vascular cannulas

The cannulas of the ECMO circuit come in two varieties, which permit providers to adopt a customized cannulation strategy for their patients. Single-lumen cannulas are used to provide multiple site access in venoarterial or venovenous ECMO, typically in the femoral veins and right internal jugular (venovenous) or the femoral vein and artery (peripheral venoarterial). Bicaval dual-lumen cannulas have been developed to provide venovenous support through a single jugular venous access site with placement facilitated by fluoroscopic or ultrasound guidance [12]. Blood is drained through one lumen and returned through another port located some distance away to limit recirculation within the ECMO circuit.

Circuit monitoring

One of the fundamental principles in an ECMO circuit is to limit the size of blood to artificial surface interface. The exposure of blood to a nonbiologic surface initiates a cascade of inflammatory and coagulation pathways. Although biocompatible linings are used to reduce bleeding and thrombosis, none have proven to eliminate these reactions completely. Most experienced centers minimize tubing length and connectors within the circuit to reduce thrombogenicity.

CURRENT APPLICATIONS

Pulmonary applications: extracorporeal lung support

Acute respiratory distress syndrome

One of the original and most studied applications of ECMO is for ARDS to ensure adequate tissue oxygenation during the recovery of native pulmonary function. Pivotal studies supporting the efficacy of ECMO for ARDS include the Australian and New Zealand group study that demonstrated greater than 70% survival to discharge in their H1N1-induced ARDS patients treated with ECMO [8]. Peek *et al.* [13] conducted a randomized control trial based in the UK called the CESAR trial, showing that patients with ARDS who were referred to an ECMO center had significantly improved survival 6 months from discharge than those who were not referred and treated with medical management alone. Notably, this trial was criticized for methodologic limitations as well as not including an ECMO transport service. The REVA study group published their results using ECMO for H1N1-associated ARDS and identified at 1 year post-ICU discharge that 83% of patients treated with ECMO had returned to work vs. 64% of non-ECMO treated patients [14]. Currently, an ongoing international multicenter randomized trial – the Extracorporeal Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA) – is underway to assess the efficacy of early venovenous-ECMO in patients with severe ARDS.

Hypercapnic respiratory failure

Chronic obstructive pulmonary disease (COPD) is the third most common cause of adult death in the USA. Acute exacerbations can result in hypercapnic respiratory failure necessitating intubation and mechanical ventilation. Although noninvasive ventilation remains a viable alternative, a significant number of patients fail this intervention with unacceptably high morbidity and mortality [15]. In 2009, Dr Zwischenberger's group successfully used venovenous-ECMO for carbon dioxide removal ($ECCO_2R$) in a hypercarbic patient with COPD [16]. In 2013, the Columbia University group used $ECCO_2R$ to facilitate extubation in five patients with COPD, all of whom had failed to wean from the ventilator. These patients were extubated in a median time of 4 h and most were ambulatory within 24 h of venovenous ECMO initiation [17]. Since that time, there have been multiple reports supporting the efficacy of venovenous ECMO in treating hypercapnic respiratory failure in COPD and reducing intubation time or preventing it altogether [18▪,19,20].

Bridge to transplant

ECMO is being used more frequently as a bridge to lung transplantation (BTT) for patients who are failing optimal medical management in the wake of increasing lung allocation scores without a concomitant rise in suitable donor organs. Although early endeavours at BTT were not very successful, multiple high-volume centers have shown that BTT has comparable outcomes with patients not requiring support [21–24].

Our institution employs a multidisciplinary ECMO team approach for BTT decision-making. Factors used in deciding whether patients will benefit from BTT are age, functional status on admission, underlying disease, infection or other organ system dysfunction, and anticipated waitlist time. We developed a clinical decision-making algorithm to optimize ECMO configurations and cannulation strategies based on the patient's pathophysiology (Fig. 3) [10].

One of the primary goals of using ECMO as a BTT is to optimize transplant candidates before transplantation to improve postprocedural outcomes. A cornerstone to this philosophy is ambulation, which depends on optimal cannulation configurations and early physiotherapy, with patients being mobilized as early as ECMO day 1 (Fig. 4) [25▪▪]. We also aim to cannulate patients without intubation or general anesthesia whenever possible. This form of 'awake ECMO' with spontaneously breathing patients has been shown to be a safe and effective approach to BTT [26,27,28▪].

Intraoperative extracorporeal membrane oxygenation

ECMO is increasingly being used for intraoperative cardiopulmonary support. Although the use of cardiopulmonary bypass has long been a component of cardiothoracic surgery, ECMO has been found to reduce perioperative blood transfusion requirements, possibly reduce the incidence of primary graft dysfunction, and shorten overall hospital length of stay in lung transplantation [29▪▪,30,31]. Many lung transplant teams have shifted from cardiopulmonary bypass to the use of ECMO for cardiopulmonary support during lung transplantation because of these benefits. Careful anesthesia management must be employed in these cases because of the effects of the oxygenator on anesthetic agents and concerns for air entrainment through central lines into venoarterial ECMO circuits.

ECMO has also found utility in other forms of thoracic surgery. There have been several studies [32–35] demonstrating ECMO as a safe and useful approach to complex tracheobronchial surgery in

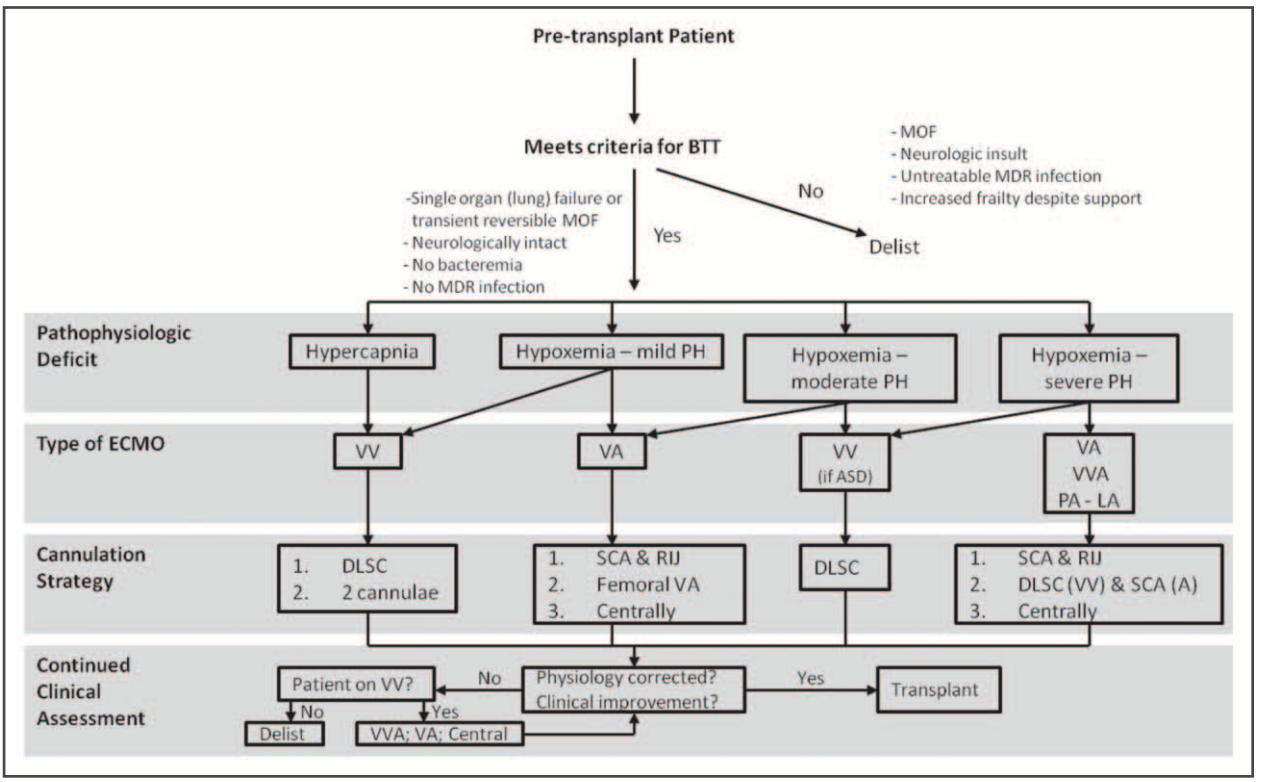

FIGURE 3. Decision algorithm. ASD, atrial septal defect; BTT, bridge to lung transplantation; DLSC, dual-lumen, single cannula; ECMO, extracorporeal membrane oxygenation; MDR, multidrug resistant; MOF, multiorgan failure; PA-LA, pulmonary artery to left atrium; PH, pulmonary hypertension; RIJ, right internal jugular vein; SCA, subclavian artery; VA, venoarterial; VV, venovenous; VVA, venovenous-arterial. Adapted from [10].

neonates and adults as well as in patients with central airway obstruction. Intraoperative ECMO has been employed in pneumonectomy cases to permit early extubation and thereby prevent positive-pressure ventilation associated pneumonia, stump breakdown, or bronchoplueral fistula post lung resection [36,37].

FIGURE 4. Patient with 'Sport Model' as BTT during ambulation. Reproduced by courtesy of New York Presbyterian/Columbia University Medical Center, New York, NY. BTT, bridge to lung transplantation.

Novel applications

The applications of ECMO for respiratory failure have substantially broadened. ECMO has been used successfully for bridge to recovery (BTR) and BTT for pulmonary arterial hypertension (PAH) patients with decompensated right heart failure – a patient population who often suffer from long waitlist times and were previously thought to be incapable of weaning off ECMO in BTR [38]. Columbia University reported the largest series on the use of ECMO during pregnancy and for postpartum complications of various etiologies with favorable maternal and fetal outcomes [39▪]. Finally, the transport of critically ill patients on ECMO to tertiary care centers for advanced cardiopulmonary failure management has been demonstrated to be both feasible and safe with dedicated teams and management protocols [40▪,41]. Most institutions employ a hub-and-spoke model in which local hospitals can transport critically ill patients for tertiary levels of care to a regional center of excellence. However, a select few centers perform complex, long-distance transports, including trans-continental flights. Our

hospital utilizes a multidisciplinary team approach to evaluate the patients, choose the ideal ECMO transport cannulation configuration, and select the safest mode of transport. ECMO transport indications are inclusive of standard ECMO indications and range from primary acute respiratory failure such as ARDS to complex cardiac and cardiopulmonary diseases in which patients may require ventricular assist devices or transplant evaluations. In our institution, we developed standardized protocols for the pre-initiation process, transport equipment, ventilator management, and team structure.

COMPLICATIONS

The most commonly cited complication of ECMO is nonintracranial bleeding associated with cannula insertion sites, followed by renal failure warranting dialysis or hemofiltration. In Gray *et al.*'s [42▪▪] 2015 review of the 2000 patients at the University of Michigan, the incidence of these complications were 39 and 31%, respectively. Mechanical complications are relatively rare in ECMO, and in the aforementioned series – the largest published single center series – the least common complications were pump malfunction (2%) and air entry into the circuit (8%) [42▪▪]. Other centers have reported significantly lower complication rates, which may reflect improvements in device technology and management protocols [43▪].

FUTURE DIRECTIONS

ECMO has experienced major advancements since its infancy in the early 1970s. No longer are patients required to be intubated, sedated, and immobilized in bed. Well-selected patients are extubated, awake, and can be ambulatory. The concept of 'irreversible' lung failure is being redefined as patients are now capable of remaining on ECMO for lung recovery for months instead of days. We anticipate further improvements in the use of ECMO as technological improvements come to market.

Circuits/anticoagulation

Current circuits have a heparin-based nonthrombogenic coating that minimizes, but does not eliminate the need for anticoagulation. One solution in development is the use of nitric oxide eluting materials to inhibit coagulation at the level of initial platelet adhesion [44–46]. In the meantime, there have been reports advocating for a shift from unfractionated heparin for anticoagulation during ECMO to direct thrombin inhibitors due to their rapid on/offset and superior safety profiles [47]. The Regensberg group also reported on their concomitant use of aspirin for ECMO [48].

Patient management

With more reliable devices, it is likely that many ECMO patients will not require ICU level care. Managing these patients in stepdown units may engender the development of ECMO units for patients on chronic ECMO – similar to those used in advanced heart failure patients.

Artificial lungs

Unlike patients who receive left ventricular assist devices for long-term hemodynamic support, patients requiring long-term ECMO cannot leave the hospital. The concept of an artificial lung, with conduits attached to the native circulation and a paracorporeal membrane oxygenator would permit patients to go home on ECMO and create the option of destination therapy for end-stage lung disease patients who are not transplant candidates. Groups have used devices to manage patients with pulmonary hypertension by inserting an oxygenator between a pulmonary artery to left atrium conduit [49▪], which conceptually works as a paracorporeal lung.

CONCLUSION

ECMO is a resource-intensive form of lung support that requires significant institutional commitment and well-trained physicians, nurses, and ancillary staff to ensure good outcomes. Despite the high level of infrastructure required, there are clear benefits to its use in patients with acute respiratory illness such as ARDS from pneumonia, complex intraoperative support requirements, BTR for chronic lung disease patients with acute exacerbations such as COPD or PAH, and BTT for decompensated lung transplant candidates. With the rise of multidisciplinary teams and improvements in the reliability of ECMO equipment, regional centers have developed robust ECMO transport systems to extend care to patients who otherwise would not be stable enough to transport to tertiary care centers. With the pace of recent innovations, it is possible to imagine ECMO technology laying the groundwork for outpatient chronic ECMO management and artificial lungs for destination therapy.

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Conflicts of interest

There are no conflicts of interest.

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