Extracorporeal Membrane Oxygenation in Cardiopulmonary Disease in Adults

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The use of extracorporeal membrane oxygenation (ECMO) for both respiratory and cardiac failure in adults is evolving rapidly. Advances in technology and accumulating data are spurring greater interest and explosive growth in ECMO worldwide. Expanding indications and novel strategies are being used. Yet the use of ECMO outpaces the data. The promise of a major paradigm shift for the treatment of respiratory and cardiac failure is tempered by a need for evidence to support many current and potential future uses. The authors review cannulation strategies, indications, and evidence for ECMO in respiratory and cardiac failure in adults as well as potential applications and the impact they may have on current treatment paradigms.   (J Am Coll Cardiol 2014;63:2769–78) © 2014 by the American College of Cardiology Foundation

Although extracorporeal membrane oxygenation (ECMO) has been in existence since the 1970s as a means of supporting respiratory or cardiac function, early application of this technology was plagued by high complication rates, with no proven survival advantage over conventional management (1,2). Major recent advances in extracorporeal technology have favorably altered its risk-benefit profile (3–6), and an expanding body of evidence and more extensive experience have generated renewed interest as well as a considerable rise in the use of ECMO for cardiopulmonary disease (7,8). In this review, we discuss the cannulation strategies, indications, and evidence for the initiation of ECMO in cardiopulmonary disease, along with potential future applications that could shift the paradigm in approaches to both respiratory and cardiac failure.

Configurations and Cannulation Strategies

ECMO involves an extracorporeal circuit that directly oxygenates and removes carbon dioxide from the blood using an oxygenator, a gas exchange device that uses a semipermeable membrane to separate a blood compartment from a gas compartment. Deoxygenated blood is withdrawn through a drainage cannula by an external pump, passes through the oxygenator, and is returned to the patient through a reinfusion cannula. When blood is drained from a central vein and returned to a central vein, a process known as venovenous ECMO, the device is providing gas exchange only. When blood is drained from the venous system and pumped into an artery, a process known as venoarterial ECMO, the circuit provides both respiratory and circulatory support. The amount of blood flow through the circuit, the fraction of oxygen delivered through the oxygenator, and the contribution of the native lungs are the main determinants of blood oxygenation for a given device, whereas the rate of gas flow through the oxygenator, known as the sweep gas flow rate, and the blood flow rate are the major determinants of carbon dioxide removal (9). Extracorporeal circuits are very efficient at removing carbon dioxide and can do so at blood flow rates much lower than what is needed to achieve adequate oxygenation (10,11). Therefore, when the goal is extracorporeal carbon dioxide removal ($ECCO_2R$), smaller cannulae can be used, which may be easier and safer to insert (12). $ECCO_2R$ may be used to address hypercapnic respiratory failure or to eliminate carbon dioxide in primarily hypoxemic respiratory failure to permit reduced ventilation strategies. An alternative configuration used primarily for carbon dioxide removal is arteriovenous $ECCO_2R$, in which the patient's native cardiac output generates blood flow through the circuit, without the need for an external pump (13).

Traditional venovenous ECMO configurations involve cannulation at 2 distinct venous access points for drainage and reinfusion of blood (9) (Fig. 1). This configuration,

with the drainage and infusion ports in close approximation, may lend itself to drawing reinfused, oxygenated blood back into the circuit, a phenomenon known as recirculation. Recirculated blood does not contribute to systemic oxygenation. Additionally, 2-site venovenous ECMO requires femoral access. With the advent of bicaval dual-lumen cannulae, the internal jugular vein can be used as the lone venous access site to provide venovenous extracorporeal support, avoiding femoral cannulation altogether (5,6) (Fig. 2). This approach requires the proper positioning of the cannula, with the reinfusion port oriented such that flow is directed across the tricuspid valve, minimizing the amount of recirculation (6). Placement is typically accomplished under fluoroscopic or transesophageal echocardiographic guidance (14). For patients in whom mobilization is anticipated, particularly those awaiting transplantation whose candidacy depends in part on their physical conditioning, a configuration that avoids femoral cannulation is preferred. Cannula size is based on the physiologic needs of the patient, and particular consideration should be given to the patient's estimated cardiac output. For a given extracorporeal blood flow, changes in cardiac output will alter the percent of the patient's blood volume passing through the oxygenator, which will affect systemic oxygenation.

In patients with significantly impaired cardiac function, with or without impaired gas exchange, a venoarterial configuration is necessary to provide circulatory support. The traditional configuration for venoarterial ECMO involves femoral venous drainage and femoral arterial reinfusion. With this configuration, the reinfusion jet flows retrograde up the aorta and may meet resistance from antegrade flow generated by the left ventricle (Fig. 3). Depending on the amount of native cardiac function, the location of the interface between antegrade and retrograde flow will vary, and in circumstances in which there is impaired native gas exchange with a significant amount of poorly oxygenated blood ejected from the left ventricle, the oxygenated, reinfused blood may not reach the aortic arch from below, thereby rendering oxygen delivery to the cerebral and coronary vascular beds suboptimal. In such patients, an additional reinfusion cannula may be added to the configuration with a "Y" connection off of the femoral arterial reinfusion cannula, with insertion into an internal jugular vein. This configuration of venous drainage combined with both arterial and venous return (venoarterial-venous ECMO) may facilitate oxygenation of the cerebral and coronary circulation by returning oxygenated blood into the native
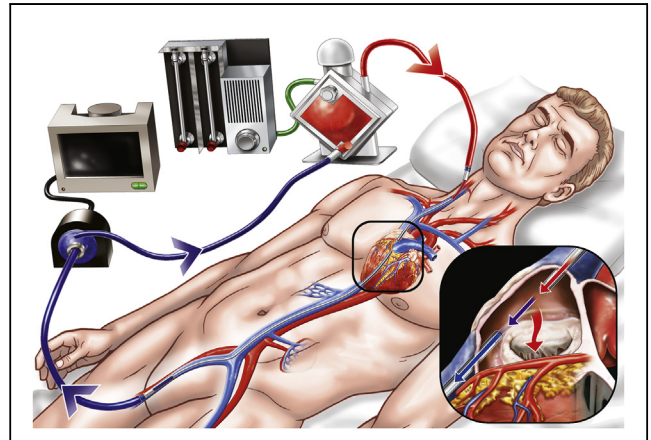
Figure 1 **Two-Site Venovenous Extracorporeal Membrane Oxygenation**

Venous blood is withdrawn from a central vein, pumped through an oxygenator, and reinfused into a central vein. **(Inset)** Drainage and reinfusion ports in close proximity may lead to oxygenated blood being drawn back into the circuit without having entered the systemic circulation, known as recirculation **(purple arrow)**.

cardiac circulation while providing circulatory support. In cases of severe left ventricular dysfunction, venoarterial ECMO may result in overdistention of the left ventricle and worsening pulmonary edema (15). Several approaches have been described to facilitate left ventricular decompression (16,17).

ECMO cannulation has traditionally been performed in the operating room by cardiothoracic surgeons, because they are best suited to perform cut-down procedures for cannulation and manage complications requiring surgical intervention (5,18). However, with a general trend toward percutaneous approaches, cannulation is being performed
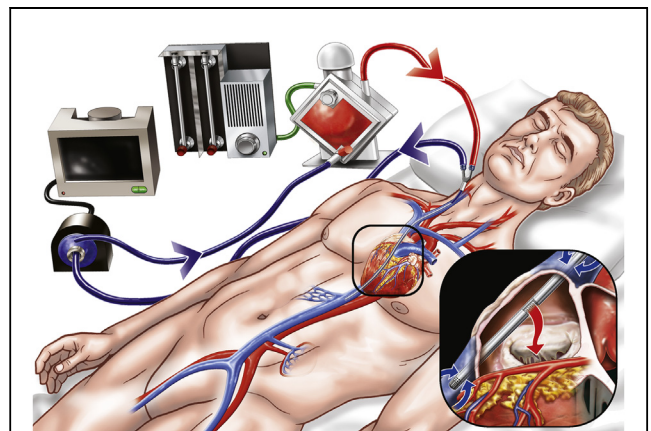
Figure 2 **Single-Site Venovenous Extracorporeal Membrane Oxygenation**

A dual-lumen cannula in the internal jugular vein permits both venous drainage and reinfusion without the need for femoral cannulation. **(Inset)** Deoxygenated blood is withdrawn through ports in the superior and inferior vena cavae. The reinfusion port is oriented such that oxygenated blood is directed toward the tricuspid valve.
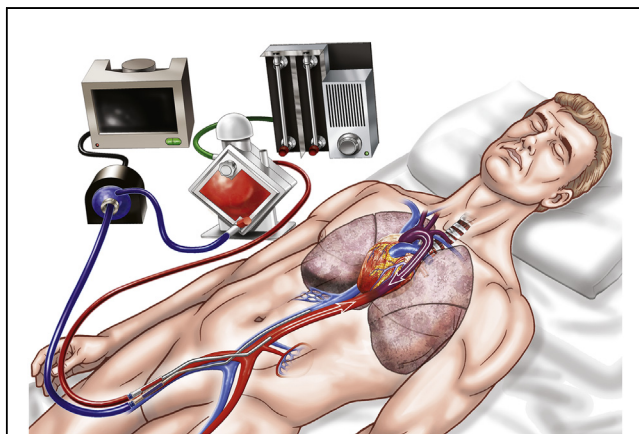
Figure 3   **Femoral Venoarterial ECMO**

When extracorporeal membrane oxygenation (ECMO) is implemented via femoral venous drainage and femoral arterial return in patients with residual native cardiac function and impaired lung function, reinfused oxygenated blood **(red arrow)**, flowing retrograde through the aorta, may meet resistance from poorly oxygenated blood flowing antegrade from the left ventricle **(purple arrow)**. Depending on the amount of cardiac function, the location of the interface between antegrade and retrograde flow will vary, and the reinfused oxygenated blood may not reach the cerebral and coronary vascular beds.

more frequently by interventional cardiologists, anesthesiologists, and medical intensivists, among others. Regardless, management of the extracorporeal circuit requires a multidisciplinary team (19,20).

Indications and Evidence

ECMO for Respiratory Failure

Acute respiratory distress syndrome. The most extensively studied respiratory indication for ECMO is acute respiratory distress syndrome (ARDS) (9) (Table 1). In circumstances in which invasive mechanical ventilation is

necessary to support gas exchange, positive-pressure ventilation may potentiate lung injury (21). The only ventilation strategy proved to reduce mortality in ARDS is a volume- and pressure-limited ventilation strategy (22). ECMO has the potential to improve outcomes in patients with ARDS by providing adequate oxygenation while facilitating lung-protective ventilation by correcting unsustainable levels of hypercapnia and respiratory acidosis that may accompany low–tidal volume ventilation (23). Potential indications for ECMO in the setting of ARDS have been proposed (9).

Early randomized trials were unsuccessful in demonstrating a survival benefit from ECMO in patients with severe forms of ARDS (1,2). More recently, the impact of modern extracorporeal support on survival in patients with severe ARDS was evaluated in the Conventional Ventilation or ECMO for Severe Adult Respiratory Failure trial, in which 180 subjects with severe, potentially reversible respiratory failure were randomized to conventional mechanical ventilation or referral to a specialized center for consideration of ECMO (24). Compared with the conventionally managed group, those referred for consideration of ECMO had a significantly lower rate of death or severe disability at 6 months (37% vs. 53%; relative risk: 0.69; p = 0.03). However, a lung-protective ventilation strategy was not mandated for the control group, and only 70% of those patients received such a strategy at any time during the study. Additionally, only 76% of those referred for ECMO actually received it, making it difficult to evaluate the effect of ECMO alone on survival. Other nonrandomized observational studies, particularly during the influenza A (H1N1) pandemic in 2009, have shown conflicting results of the impact of ECMO on survival in severe ARDS (25). Results from propensity analyses in the United Kingdom suggested a mortality benefit from ECMO when ECMO-referred patients with severe influenza-related ARDS were compared with a similar cohort of patients in whom ECMO was not considered (24% vs. 47%; relative risk: 0.51; 95% confidence

Table 1	Indications and Highest Level of Evidence for ECMO in Cardiopulmonary Disease	
Respiratory		
	ARDS	Randomized controlled trials
	Hypercapnic respiratory failure	Prospective feasibility studies
	Bridge to lung transplantation	Cohort studies
	Primary graft dysfunction after lung transplantation	Cohort studies
Cardiac		
	Myocardial infarction–associated cardiogenic shock	Cohort studies
	Fulminant myocarditis	Cohort studies
	Sepsis-associated cardiomyopathy	Case series
	Pulmonary hypertension	Case series
	Extracorporeal cardiopulmonary resuscitation	Cohort studies with propensity analyses
	Post-cardiotomy cardiogenic shock	Cohort studies
	Primary graft failure after heart transplantation	Cohort studies
	Bridge to VAD implantation or heart transplantation	Cohort studies
	Prevention of acute right ventricular failure after LVAD implantation	Cohort studies

ARDS = acute respiratory distress syndrome; ECMO = extracorporeal membrane oxygenation; LVAD = left ventricular assist device; VAD = ventricular assist device.

interval: 0.31 to 0.84; p = 0.008) (26). However, a similar analysis in a distinct French cohort found no mortality benefit from ECMO (27). Additionally, compared with centers at which ECMO was used for H1N1-associated ARDS, a single-center study reported a comparably high rate of success with the use of conventional mechanical ventilation alone in patients with similar degrees of hypoxemia (28). Such discrepancies highlight the need for a prospective, randomized controlled trial evaluating the effect of ECMO on survival in severe ARDS. Such a trial is currently underway, (EOLIA [Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome]) (29). Mortality risk prediction models have been proposed to risk-stratify patients with severe ARDS receiving venovenous ECMO and may help identify those patients most appropriate for extracorporeal support (30,31). In addition to the evaluation of short-term outcomes, more data are needed to assess the long-term neurocognitive, psychiatric, and functional outcomes of those who recover from ARDS having received ECMO.

Beyond facilitating gas exchange and adherence to lung-protective ventilation, ECMO may have the benefit of reducing lung injury even further by facilitating the application of very low tidal volumes and airway pressures, as well as a reduction in respiratory rate, an approach sometimes referred to as "lung rest" (32–34). Such an approach has been widely used in patients with severe ARDS receiving ECMO. However, future applications of very lung-protective ventilation strategies may extend to less severe cases of ARDS through the use of $ECCO_2R$, without the need for the higher blood flow rates of ECMO to provide oxygenation. Post-hoc analysis of a recent clinical trial comparing $ECCO_2R$-assisted very low tidal volume ventilation (approximately 3 ml/kg predicted body weight) with conventional low–tidal volume ventilation in patients with moderate to severe ARDS demonstrated more ventilator-free days for the very low tidal volume group (40.9 vs. 28.2; p = 0.033) among those with more severe hypoxemia (34). The role of ECMO or $ECCO_2R$ in patients with less severe ARDS, with hypercapnia and acidemia limiting the application of low–tidal volume ventilation, has yet to be defined and is the focus of a trial that is currently in the planning phases. Likewise, larger prospective studies are needed to better define the role of very lung-protective ventilation and whether such a strategy translates into reduced lung injury and improved clinical outcomes.

Hypercapnic respiratory failure. With an improved risk-benefit ratio, there is great potential to use $ECCO_2R$ to manage hypercapnic respiratory failure, thereby minimizing or even eliminating the need for a ventilator. In chronic obstructive pulmonary disease, invasive mechanical ventilation is associated with multiple complications, including dynamic hyperinflation and elevations in intrinsic positive end-expiratory pressure, ventilator-associated pneumonia, and impaired delivery of aerosolized medications (35,36). Several small case series have demonstrated the feasibility

of avoidance of or rapid weaning from invasive mechanical ventilation, with $ECCO_2R$ used to manage gas exchange (37–39). With correction of hypercapnia and respiratory acidosis, dyspnea and work of breathing rapidly improve, facilitating early mobilization (39). Although early mobilization has been described with invasive mechanical ventilation (40), it is more likely to be successful with the substitution of $ECCO_2R$ for mechanical ventilation because of the significant improvement in dyspnea that is seen with $ECCO_2R$ compared with mechanical ventilation in the hypercapnic population (39). The risks of $ECCO_2R$ must be weighed against the benefit of minimizing invasive mechanical ventilation, and additional studies are required to define the ideal patient population and the economic impact of such a strategy before it can be recommended for clinical use. Similarly, $ECCO_2R$ may be considered in other forms of hypercapnic respiratory failure, including refractory status asthmaticus, in which the ability to avoid invasive mechanical ventilation altogether is potentially advantageous (41,42).

Bridge to lung transplantation and post-transplantation primary graft dysfunction. Although ECMO has traditionally been considered a relative contraindication to lung transplantation because of poor perioperative outcomes (43), more recent studies have reported excellent post-transplantation survival, especially at centers with more extensive experience (44,45). With the potential for ECMO to provide sufficient gas exchange to supplant the ventilator, a nonintubated ECMO strategy may be considered for some transplantation candidates who would otherwise be ventilator dependent, a population with poor outcomes related to ventilator-associated complications (46). Outcomes may be further optimized when such a strategy is combined with active physical therapy and should be considered in patients who would otherwise be inactivated from the transplantation list because of deconditioning. This is particularly true for those patients in whom ECMO or $ECCO_2R$ alleviates dyspnea sufficiently to permit rehabilitation (45,47,48). A major limitation to the use of ECMO for end-stage respiratory failure is the lack of a destination device therapy, with ECMO remaining an intervention for which an intensive care unit is required.

In severe cases of primary graft dysfunction, a form of acute lung injury that is the leading cause of early death after lung transplantation (49), ECMO may be used to support gas exchange while the allograft recovers. Studies have described similar survival in cases of ECMO-supported severe primary graft dysfunction compared with those with less severe primary graft dysfunction without ECMO support, particularly when instituted early (50). However, ECMO has not been shown to affect long-term allograft function.

ECMO for Cardiac Failure

Cardiogenic shock. Cardiogenic shock, defined as myocardial contractile dysfunction, low cardiac output, and

tissue hypoperfusion, may be the consequence of an acute ischemic event or a nonischemic process, with or without underlying chronic heart failure. Medical therapies, consisting primarily of inotropic agents and vasopressors, may improve cardiac output at the expense of increased myocardial oxygen demand, myocardial ischemia, arrhythmogenicity, and compromise of tissue microcirculation and may be associated with increased risk for mortality (51). Mechanical circulatory support systems, with venoarterial ECMO being one of several percutaneous approaches, have the potential to attenuate the inflammatory response by improving tissue perfusion without the adverse consequences of medical therapies, creating the opportunity to reduce the high mortality rates currently associated with conventionally managed cardiogenic shock. The advantage of ECMO over other percutaneous devices—intra-aortic balloon counterpulsation devices, the TandemHeart left ventricular assist device (LVAD) (CardiacAssist, Inc., Pittsburgh, Pennsylvania), and Impella devices (Abiomed, Danvers, Massachusetts)—accrues from the rapidity of insertion; the ability to support right ventricular, left ventricular, or biventricular failure at high blood flow rates; and the potential to support patients with concomitant lung injury when needed (52).

Cardiogenic shock complicating acute myocardial infarction. There are no randomized controlled trials comparing ECMO with other mechanical support systems in myocardial infarction–associated cardiogenic shock, but several nonrandomized studies suggest a survival advantage from the early use of ECMO in such circumstances (53,54). In an observational study of patients with ST-segment elevation myocardial infarction–related cardiogenic shock undergoing percutaneous coronary intervention (PCI) with and without ECMO support, those receiving ECMO had significantly lower 30-day mortality (39.1% vs. 72%; p = 0.008) (54). Interpretation of these data is limited by the fact that cohorts were enrolled over different time frames (1993 to 2002 for the non-ECMO cohort vs. 2002 to 2009 for the ECMO cohort), potentially leading to discrepancies in treatment between groups, especially given that coronary stents were unavailable at the study center before 1998. Higher rates of Thrombolysis In Myocardial Infarction flow grade 3 achieved in the ECMO group may reflect improved hemodynamic stability in the catheterization laboratory or, alternatively, may be a consequence of improved PCI technique over time. Ultimately, randomized controlled trials are needed to determine the true benefit, if any, of ECMO in myocardial infarction–associated cardiogenic shock.

Fulminant myocarditis. ECMO use has been investigated as a modality to support nonischemic cardiogenic shock, including fulminant myocarditis (55–58). Patients with fulminant myocarditis who are successfully bridged with ECMO to recovery may have long-term prognoses comparable with those of hemodynamically stable patients with acute myocarditis (55). In 1 cohort of patients who received either a biventricular assist device (n = 6) or ECMO (n = 35) for fulminant myocarditis with refractory cardiogenic shock, overall intensive care unit survival was 68%, with higher severity of illness and elevated cardiac biomarkers serving as independent predictors of mortality and an inability to wean from ECMO (57). ECMO may be as efficacious as a ventricular assist device (VAD) while having the advantage of being less invasive. In a study comparing ECMO with biventricular assist devices for fulminant myocarditis, those receiving ECMO had comparable rates of weaning from device therapy and survival to hospital discharge without the need for transplantation (83% vs. 80%) and more rapid improvement in renal and hepatic laboratory profiles, despite having a higher severity of illness and worse left ventricular function before device implantation (58).

Sepsis-associated cardiomyopathy. Myocardial depression is a well-recognized consequence of severe septic shock (59). There are emerging data suggesting that ECMO may have a role in supporting patients who develop refractory cardiac failure in this setting (60,61). Larger studies are needed to determine whether the benefit of ECMO outweighs the risk, especially in cases in which septic shock is complicated by marked disturbances in coagulation.

Pulmonary hypertension. ECMO is an emerging management option in patients with decompensated pulmonary hypertension with concomitant right ventricular failure, particularly when there is an acutely reversible process, medical management has not been optimized, or lung transplantation is a consideration (62). ECMO for this indication typically requires a femoral venoarterial configuration to bypass the high resistance of the pulmonary vasculature and decompress the right ventricle. However, 3 configurations have been used to avoid femoral cannulation. Internal jugular venous drainage may be combined with subclavian arterial reinfusion (18) (Fig. 4). In patients with pre-existing intra-atrial defects, a dual-lumen cannula may be oriented with the reinfusion jet directed across the defect (rather than across the tricuspid valve), effectively providing an oxygenated right-to-left shunt while decompressing the right ventricle (63,64). Additionally, arteriovenous ECMO can be inserted between the main pulmonary artery and the left atrium, though this typically requires a sternotomy (65). When ECMO is initiated as a bridge to recovery, pulmonary vasodilators may be optimized while the underlying acute process is treated (62). When the goal of ECMO is to bridge to transplantation, pulmonary vasodilators may be down-titrated to preferentially shunt blood through the extracorporeal circuit and away from the high-resistance pulmonary vasculature, thereby optimizing systemic oxygenation (66). Reducing the dosage of intravenous pulmonary vasodilators will also minimize the degree of systemic vasodilation that may occur as the medications pass through the ECMO circuit and into the arterial circulation.
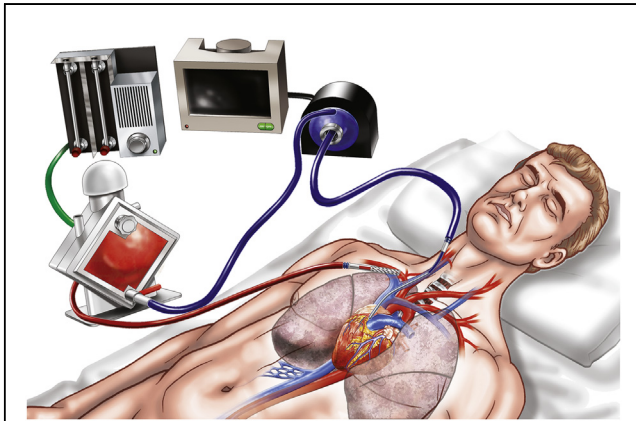
| Figure 4 | Venoarterial ECMO With Internal Jugular Venous Drainage and Subclavian Arterial Reinfusion |

An alternative approach to femoral venoarterial extracorporeal membrane oxygenation (ECMO) is drainage from the internal jugular vein and reinfusion into the subclavian artery through an end-to-side graft. The graft and arterial cannula are oriented such that reinfused blood is directed toward the aorta. In contrast to femoral venoarterial ECMO, this configuration ensures the delivery of oxygenated blood to the aortic arch and, consequently, the cerebral and coronary vasculature.

Pulmonary embolism. Massive pulmonary embolism may likewise benefit from ECMO. A retrospective single-center review of ECMO for massive pulmonary embolism, including patients in active cardiac arrest, demonstrated 62% overall survival when combined with anticoagulation or surgical embolectomy (67). The combination of ECMO, thrombolysis, and catheter-directed thrombectomy or embolus fragmentation has also been reported, with 30-day survival of 70% (68).

Extracorporeal cardiopulmonary resuscitation. "Extracorporeal cardiopulmonary resuscitation" (ECPR) is the term used to describe the institution of extracorporeal support to restore circulation during cardiac arrest. Although there are no randomized controlled trials investigating the efficacy of ECPR for cardiac arrest, its use has been steadily increasing (69–72). In a prospective, observational study of witnessed in-hospital cardiac arrests, propensity analysis matching 46 subjects who received conventional cardiopulmonary resuscitation (CPR) with 46 subjects who received ECPR demonstrated significantly higher survival at discharge in the ECPR group (32.6% vs. 17.4%; p < 0.0001) and at 1 year (hazard ratio: 0.53; p = 0.006) (69), with a trend toward improved neurological outcomes. In multivariate analysis, an initial rhythm of ventricular fibrillation or ventricular tachycardia and use of ECPR were positively associated with survival to discharge. A more recent propensity analysis of patients who experienced in-hospital cardiac arrest demonstrated significantly higher 2-year survival with minimal neurological impairment in those treated with ECPR compared with conventional CPR (20% vs. 5%; p = 0.002). Independent predictors associated with minimal neurological impairment included age <65 years, CPR

duration <35 min, and subsequent cardiovascular intervention (71). Regarding out-of-hospital cardiac arrests, a recent matched propensity analysis demonstrated significantly higher neurologically intact survival at 3 months in those who received ECPR compared with conventional CPR (29.2% vs. 8.3%; p = 0.018) (72).

With the ability of ECMO to both maintain systemic circulation during cardiac arrest and increase coronary perfusion pressure, the combination of ECPR and intra-arrest PCI may greatly improve the likelihood of successful defibrillation and recovery in cardiac arrest due to an acute coronary syndrome. A multicenter nonrandomized study demonstrated the feasibility of combining ECMO and emergency coronary angiography in 81 subjects, 61 of whom received intra-arrest PCI (73). Compared with those who received ECMO and coronary angiography without PCI, those receiving PCI achieved higher rates of resumption of spontaneous beating (100% vs. 60%; p < 0.001), weaning from ECMO (59% vs. 28%; p = 0.009), 30-day survival (36% vs. 12%; p = 0.03), and favorable neurological outcomes (33% vs. 4%; p = 0.005). In-hospital (vs. out-of-hospital) cardiac arrest and shorter duration from collapse to initiation of ECMO were correlated with 30-day survival.

Although observational trials suggest a possible survival advantage of ECPR over conventional CPR, overall survival remains relatively low. More research is needed to define the patient population that would derive the greatest benefit from extracorporeal resuscitation, with an emphasis on survival with minimal neurological impairment.

The 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care do not recommend the routine use of ECPR for cardiac arrest. However, ECPR may be considered when the time without spontaneous circulation is short, resuscitation attempts are adequate, and the cause of cardiac arrest is potentially reversible (74). The guidelines emphasize that ECPR use should be restricted to centers at which it is readily available and that its initiation and management require highly trained personnel and specialized equipment.

Post-operative cardiogenic shock and post-transplant primary graft failure. Post-cardiotomy cardiogenic shock is an uncommon but highly lethal complication of cardiac surgery. ECMO may be considered as temporary support post-operatively, particularly when unable to wean from cardiopulmonary bypass in the operating room (75). Mortality in patients requiring this level of support remains high (76).

Primary graft failure (PGF) is a well-recognized complication of heart transplantation associated with a high mortality, for which ECMO has been used as temporary support (77,78). As expected, overall survival for patients with PGF requiring ECMO is worse than in those who do not develop PGF. However, patients with ECMO-supported PGF who survive beyond the early post-transplantation period have comparable long-term survival with non-PGF transplant recipients (78,79).

Bridge to VAD implantation or heart transplantation. VADs may be used as a bridging therapy to heart transplantation in appropriately selected patients with severe cardiac dysfunction (51), with the advantage of being able to function as destination devices if transplantation is not feasible. ECMO has also been reported as a bridging therapy to heart transplantation or VAD implantation or as a bridge to decision when prognosis is uncertain (80–82). However, the duration of support that can be provided is shorter than for VADs, making transplantation or transition to VAD of greater urgency, and patients receiving ECMO support must remain within an intensive care unit (82). Success of ECMO bridging varies greatly and depends in large part on pre-ECMO patient characteristics and organ availability in the cases in which transplantation is the goal. In a retrospective review of 70 patients in whom ECMO was used as a bridge to heart transplantation, 31 (44%) were bridged to either heart transplantation (n = 15) or VAD implantation (n = 16), though only 11 (73%) and 8 (50%) of the heart transplant and VAD recipients, respectively, survived to hospital discharge, highlighting the limitations of bridging therapy in this highly morbid patient population (80). Age > 50 years, CPR before ECMO initiation, and high sequential organ failure assessment score were independent predictors of unsuccessful bridging. Pre-implantation CPR as a predictor of poor outcomes was corroborated in a more recent single-center study of 90 patients who received mechanical circulatory support (VAD or ECMO) for refractory cardiogenic shock (83). Forty-nine percent received short-term VAD support as a bridge to decision, and 51% received ECMO when neurological status was uncertain or there was complete hemodynamic collapse or severe coagulopathy. Overall survival was 49%, with 26% of patients transitioned to implantable VADs, 18% recovering sufficient native cardiac function, and 11% bridged to transplantation. CPR at the time of implantation was an independent predictor of in-hospital mortality (odds ratio: 5.79; p = 0.022). These studies highlight the need for careful consideration of relative and absolute contraindications to mechanical circulatory support. In particular, ECMO for cardiogenic shock superimposed on chronic cardiomyopathy may be associated with particularly poor outcomes (84).

ECMO to prevent acute right ventricular failure after LVAD implantation. Both femoral venoarterial ECMO and percutaneous venous-to-pulmonary arterial ECMO have been successfully used to provide right ventricular support in patients with biventricular dysfunction undergoing LVAD implantation (85,86). In this setting, ECMO can allow time for the already compromised right ventricle to get accustomed to the increasing preload, thereby avoiding distension and right ventricular failure leading to poor filling of the LVAD.

Complications

The benefits of ECMO must be weighed against its inherent risks. Hemorrhagic complications are among the most commonly reported adverse events (8). The use of lower levels of anticoagulation mitigates the extent of bleeding, with some centers targeting activated partial thromboplastin times as low as 40 to 60 s (3). There are, however, no universally accepted anticoagulation protocols, and anticoagulation needs to be adjusted to the specific needs of the individual patient. Thromboses, either within the circuit or related to the indwelling portions of the cannulae, pose an embolic risk to the patient, which, in the case of venoarterial ECMO or venovenous ECMO in the presence of interatrial defect, may result in stroke. Infectious complications have been reported to varying degrees, with some reports indicating longer durations of mechanical ventilation, ECMO support, and hospital stays associated with infection (8,87). Limb ischemia and compartment syndrome are of concern in venoarterial ECMO. The insertion of a distal reperfusion cannula into the superficial femoral artery or the use of an end-to-side graft may be considered to optimize blood flow to the extremity (18,88,89). Other complications that have been associated with ECMO include hemolysis, thrombocytopenia, acquired von Willebrand syndrome, disseminated intravascular coagulopathy, and air embolism (8,90). In a recent meta-analysis incorporating 1,866 patients from 20 studies of ECMO for cardiogenic shock or cardiac arrest between 2000 and 2012, complication rates were reported as follows: lower extremity ischemia, 16.9%; fasciotomy or compartment syndrome, 10.3%; lower extremity amputation, 4.7%; stroke, 5.9%; major or significant bleeding, 40.8%; rethoracotomy for post-cardiotomy bleeding or tamponade, 41.9%; and significant infection, 30.4% (91). Cardiac or major vascular perforation is a rare but potentially lethal complication of cannulation, the frequency of which depends on the type of cannula used (92). Ultimately, complication rates will vary according to institutional experience and patient selection.
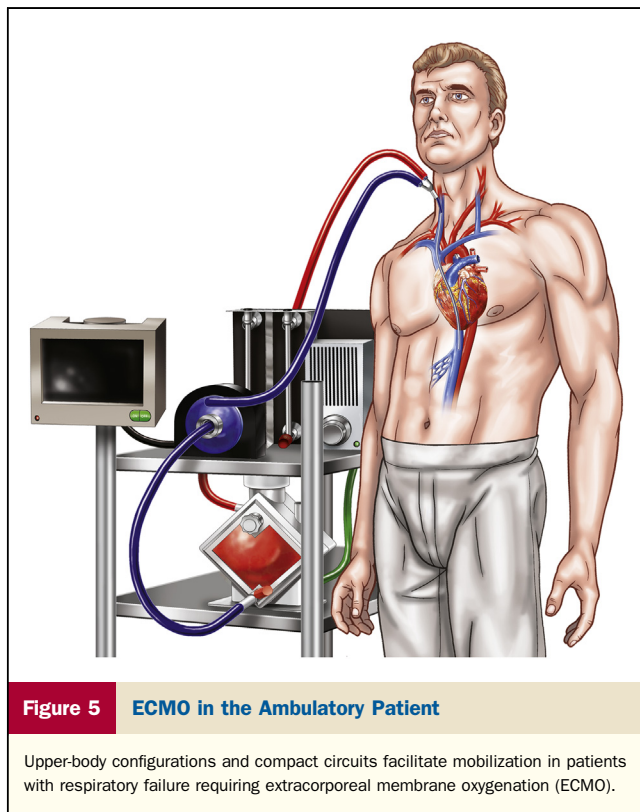
Future Directions

Early Mobilization

Physical therapy in critically ill patients is increasingly being recognized not only as safe but also as a significant determinant of important clinical outcomes (40,93). As ECMO circuits become more compact, femoral cannulation is avoided, and invasive mechanical ventilatory support is minimized or eliminated, active rehabilitation, including ambulation, becomes more feasible (39,45,62,94–96) (Fig. 5). Physical therapy is particularly important in pre-transplantation patients to prevent deconditioning and maintain transplant candidacy.

ECMO as Destination Therapy for Respiratory Failure

Although ECMO may serve as bridging therapy to recovery, VAD implantation, or transplantation in cardiac failure, it can currently serve only as bridging therapy to recovery or transplantation in respiratory failure, without any existing destination device. Advances in ECMO technology,

Figure 5   ECMO in the Ambulatory Patient

Upper-body configurations and compact circuits facilitate mobilization in patients with respiratory failure requiring extracorporeal membrane oxygenation (ECMO).

including smaller circuit components and more efficient gas exchange membranes, are moving the field toward the development of a portable extracorporeal gas exchange device, effectively an artificial lung, with the potential to create a true paradigm shift in the management of respiratory failure.

Need for Additional Studies

Despite the increasing popularity of ECMO in cardiopulmonary disease, many questions remain about the optimal patient populations in which it should be deployed. The most robust evidence for ECMO in respiratory failure is a randomized controlled trial with significant limitations in interpretation inherent in the study design. In cardiac disease, the highest level of evidence is limited to cohort studies with propensity analyses (Table 1). Larger, randomized controlled trials, such as Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome, are necessary to best evaluate many of the uses of this technology and compare them with existing therapeutic options for cardiopulmonary failure (97). These studies should ideally incorporate cost-benefit analyses to best understand the economic impact of such a resource-intensive intervention. In the absence of higher-quality evidence, ECMO has not been incorporated into the major cardiac and pulmonary practice guidelines. General practice guidelines for the use and management of ECMO in cardiopulmonary disease are provided by the Extracorporeal Life Support Organization (98).

Conclusions

Significant advances in extracorporeal technology have led to more widespread use of ECMO for severe respiratory or cardiac failure. More data are ultimately needed to understand the appropriate role of ECMO for its various potential indications. Likewise, the use of ECMO may introduce numerous ethical dilemmas to practice (99,100). As additional technological advances are made, ECMO has the potential to significantly alter current management paradigms for severe cardiac and respiratory disease.

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