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Extracorporeal Membrane Oxygenation (ECMO) for Lung Injury in Severe Acute Respiratory Distress Syndrome (ARDS): Review of the Literature

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Abstract

Despite advances in mechanical ventilation, severe acute respiratory distress syndrome (ARDS) is associated with high morbidity and mortality rates ranging from 26% to 58%. Extracorporeal membrane oxygenation (ECMO) is a modified cardiopulmonary bypass circuit that serves as an artificial membrane lung and blood pump to provide gas exchange and systemic perfusion for patients when their own heart and lungs are unable to function adequately. ECMO is a complex network that provides oxygenation and ventilation and allows the lungs to rest and recover from respiratory failure while minimizing iatrogenic ventilator-induced lung injury. In critical care settings, ECMO is proven to improve survival rates and outcomes in patients with severe ARDS. This review defines severe ARDS; describes the ECMO circuit; and discusses recent research, optimal use of the ECMO circuit, limitations of therapy including potential complications, economic impact, and logistical factors; and discusses future research considerations.

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Introduction

Extracorporeal membrane oxygenation (ECMO) is a rapidly evolving alternative treatment modality for lung injury in severe acute respiratory distress syndrome (ARDS; Park, Napolitano, & Bartlett, 2011). Per the Berlin definition, ARDS is defined as a ratio of arterial oxygen tension to fraction of inspired oxygen (PaO_2/FiO_2) ≤ 300 mm Hg with positive end-expiratory pressure (PEEP) ≥ 5 cm H_2O via mechanical ventilation. ARDS is classified as mild, moderate, or severe (Hansen-Flaschen & Siegel, 2015). ECMO is not recommended as the primary treatment for severe ARDS but is recommended as a rescue strategy when other treatment options have failed (Rosenberg et al., 2013). ARDS is associated with high morbidity and mortality rates despite conventional treatments such as alterations in mechanical ventilation settings, steroids, prone positioning, bronchoscopy, and inhaled nitric oxide. Patients who have undergone ECMO for treatment of severe ARDS show lower morbidity and mortality rates than those patients who were not considered for treatment by ECMO (Wallace, Milbrandt, & Boujoukos, 2010).

ARDS is an acute, diffuse, inflammatory lung injury that leads to increased pulmonary vascular permeability, increased lung weight, and a loss of aerated tissue. Diagnosis of ARDS is determined according to the Berlin definition and can be made once cardiogenic pulmonary edema and alternative causes of acute hypoxemic respiratory failure and bilateral infiltrates have been excluded. Criteria for diagnosis include new or worsening respiratory symptoms within 1 week, bilateral opacities consistent with pulmonary edema on chest radiograph or computed tomographic (CT) scan that cannot be explained by any other cause, absence of cardiac failure or fluid overload to explain respiratory failure, and a $PaO_2/FiO_2 \leq 300$ with a PEEP ≥5 cm H_2O (Hansen-Flaschen & Siegel, 2015). ARDS is classified as mild, moderate, or severe, with the severity of the hypoxia dictating the severity of the ARDS. According to Hansen-Flaschen and Siegel (2015), mild ARDS is defined as a PaO_2/FiO_2 between 200 and ≤300, moderate ARDS as a PaO_2/FiO_2 between 100 and ≤200, and severe as a $PaO_2/FiO_2 \leq 100$, all with a PEEP ≥ 5 cm H_2O via mechanical ventilation. An arterial blood gas (ABG) is obtained from the patient to determine the PaO_2/FiO_2 ratio. Mortality rates for ARDS range from

26% to 58% with the higher range of mortality rates attributable to severe ARDS (Hansen-Flaschen & Siegel, 2015). Goals of supportive therapy for mechanical ventilation in ARDS have switched in focus from maintaining normal physiological parameters to avoiding ventilator-induced lung injury (VILI) while providing acceptable oxygenation and carbon dioxide clearance (Silversides & Ferguson, 2013). Key strategies in reducing the risk of VILI in patients with severe ARDS include the use of low tidal volume ventilation to prevent volutrauma, the use of PEEP to reduce alveolar collapse, and minimization of exposure to potentially harmful oxygen concentrations. Low tidal volume ventilation strategies are considered lung protective despite resulting in higher carbon dioxide levels. Clinicians are now accepting that hypercapnia is harmless (or even potentially beneficial) in the absence of clear contraindications to hypercapnia (Silversides & Ferguson, 2013).

According to the Extracorporeal Life Support Organization (ELSO), initiation of ECMO for severe hypoxic respiratory failure should be considered when the risk of mortality is 50% or greater, which is defined by a PaO_2/FiO_2 < 150 mm Hg on FiO_2 > 90% and/or a Murray score of 2 to 3 (Combes, Bacchetta, Brodie, Müller, & Pellegrino, 2012). Furthermore, ELSO suggests the use of ECMO when the risk of mortality exceeds 80%, which is defined by a PaO_2/FiO_2 < 80 on FiO_2 > 80% and/or a Murray score of 3 to 4 (Combes et al., 2012). Cognitive, psychological, and physical morbidity is common with ARDS survivors with slow resolution of symptoms that persist for up to 5 years following hospitalization (Siegel, 2015).

ECMO has emerged as an alternative to conventional therapies in patients with severe ARDS and is designed as supportive care and not as a primary treatment for ARDS. ECMO is a modified cardiopulmonary bypass circuit that serves as an artificial membrane lung and blood pump to provide gas exchange and systemic perfusion for patients when their own heart and lungs are unable to function adequately. ECMO is a complex and invasive network that provides oxygenation and ventilation that allows the lungs to rest and recover from respiratory failure while minimizing further iatrogenic VILI (Park et al., 2011). Venovenous (VV) ECMO is the primary method of ECMO used for acute lung injury in ARDS, compared with venoarterial (VA) ECMO (Combes et al., 2014). Both VA ECMO and VV ECMO provide respiratory support, but hemodynamic support is only provided with VA ECMO. VA ECMO drains deoxygenated blood from a central vein or the right atrium, pumps it through a membrane oxygenator, and returns oxygenated blood to the arterial circulation. It provides oxygenation while also providing cardiac support. It supports cardiac output in the form of flow through the circuit and is in addition to the patient's native cardiac output (Mid Carolina Internal Medicine Association, 2004). VV ECMO drains the blood from the venae

cavae and pumps it through a membrane oxygenator and returns it to the venous system. It can be implemented for full or partial extracorporeal pulmonary support. ECMO is a high risk, complex, costly, and resource-intensive system that requires trained and highly skilled professionals to provide close and frequent monitoring and management of the system (Combes et al., 2014). The average length of duration of ECMO in severe ARDS patients is 7 to 10 days, but respiratory failure patients with a prolonged length of duration of greater than 14 days report survival rates of 50% to 70% with native lung recovery. As the prevalence of ECMO trials continues to grow, new treatment guidelines are developed as to when and for whom to implement ECMO for the highest benefit-to-risk and benefit-to-cost ratios (Rosenberg et al., 2013). The purpose of this review is to discuss ECMO as an emerging form of treatment for acute lung injury and severe ARDS that is refractory to conventional forms of treatment. This review will discuss implementation guidelines to maximize the success of ECMO treatment in reducing morbidity and mortality in patients with severe ARDS.

Functional Outcome Measurements

Factors that contribute to the morbidity and mortality rates associated with severe ARDS are patient related, disease related, and treatment related. High mortality rates are reported in patients with severe ARDS and range from 26% to 58% (Siegel, 2015). Among survivors, serious morbidity still exists including physical, psychological, and cognitive morbidity. Siegel (2015) also reports the rates of dysfunction following ARDS on average range from 30% to 55% for cognitive dysfunction, 36% to 62% for psychiatric illnesses (including depression, anxiety, and post-traumatic stress disorder [PTSD]), and up to 66% for physical dysfunction. Other sequelae of ARDS include increased risk of death, poor quality of life, and high family stress (Siegel, 2015). According to Siegel's (2015) research, factors that influence the presence of long-term sequelae include duration of mechanical ventilation, lowest static thoracic compliance, mean pulmonary artery pressure, PEEP, initial intrapulmonary shunt fraction, and the requirement of an $FiO_2 > 60\%$ for longer than 24 hr. Improved functional outcomes at 1 year are associated with the absence of steroid treatment, absence of illness acquired during the patient's stay in the intensive care unit (ICU), and rapid resolution of multiple organ failure and lung injury (Siegel, 2015). Referral to an ECMO center for patients without contraindications is warranted as research shows that referral significantly improves recovery and survival from severe ARDS. Research by Haft and Bartlett (2015) shows that without ECMO implementation, there is an approximate recovery rate of 25% in patients with severe ARDS,

however, there is a 60% to 70% survival rate in patients who undergo ECMO. Thus, there is a demonstrated survival benefit from ECMO in severe ARDS, but it is still unclear whether the benefit is from ECMO itself or from the potential benefit of co-interventions present in ECMO centers (Haft & Bartlett, 2015). Although research continues to expand and evolve, there is a need for more high-level evidence from controlled clinical trials to demonstrate the definitive efficacy for ECMO in severe ARDS (Abrams, Brodie, & Combes, 2013).

Method

Searching biomedical databases for primary research material identified relevant research discussing the role of VV ECMO in treating lung injury in severe ARDS. Databases were searched for publications from 2004 through to the present (2016), with key articles obtained primarily from PubMed, UpToDate, Google Scholar, MEDLINE, life science journals, and online books. Search terms were entered broadly and included "critical care," "extracorporeal membrane oxygenation or ECMO," "severe acute respiratory distress syndrome or severe ARDS," "lung injury," "respiratory failure," and "extracorporeal life support." Studies were eligible for consideration in this review if the focus of the study was on ECMO, severe ARDS, or any combination of the two items. A comprehensive search was made of Internet resources nationally and internationally with the ELSO website and the International ECMO Network website as the primary reference sites.

Review of Supporting Evidence

A retrospective review of the ELSO registry included 1,473 adult patients who received ECMO for severe respiratory failure from 1986 to 2006 (Park et al., 2011). The median patient age was 34 years and the patients' median duration on ECMO was 6.4 days. The overall survival to hospital discharge was 50% and demonstrated that VV ECMO was associated with increased survival compared with VA ECMO. However, limitations of the study included that the patients were not randomized to specific ventilator protocols and reporting was completed on a voluntary basis. Complications incurred by some patients in this study included cerebral infarction, hemorrhage, and brain death (Park et al., 2011).

A randomized control trial (Conventional ventilation or ECMO for Severe Adult Respiratory failure, known as the CESAR trial) involved 180 adults aged 18 to 65 years with severe respiratory failure chosen for treatment by ECMO or instead for conventional management (Wallace et al., 2010).

Exclusion criteria for this study were high pressure (>30 cm H_2O of peak inspiratory pressure) or high FiO_2 (>80%) for longer than 7 days, intracranial bleeding, any contraindications to limited heparinization, or any contraindication to continuing active treatment. All patients chosen for the study had a Murray lung injury score ≥3.0 (indicates severe respiratory failure) or a pH < 7.20. For patients treated with ECMO, 63% of patients survived to 6 months without disability compared with 47% of the participants who only received conventional management (Wallace et al., 2010). The patients who were treated with ECMO gained 0.03 quality-adjusted life years (QALYs) at their 6-month follow-up. Based on this study, consideration for ECMO for severe, but potentially reversible respiratory failure, is both beneficial and cost-effective for patients with a Murray lung injury score >3.0 or a pH less than 7.20 on optimum conventional management (Wallace et al., 2010). However, this trial has been highly criticized for methodological limitations (Schmidt, Hodgson, & Combes, 2015).

The 2009 novel swine-origin influenza A (H1N1) virus was a worldwide pandemic that was responsible for an increase in severe pneumonia cases in young adults. An observational study of the 68 patients who experienced influenza A (H1N1)-associated ARDS and were treated with ECMO was conducted by Davies and colleagues (2009). The median age of these 68 patients was 34.4 years with a median PaO_2/FiO_2 ratio of 56, a PEEP of 18 cm, and the median duration of ECMO support was 10 days. Also, an examination of an additional 133 patients with influenza A in the same ICUs who received mechanical ventilation without ECMO was also performed. At the time of the published report, of the ECMO-treated patients, 48 (71%) patients survived to ICU discharge (Davies et al., 2009). At the end of the study period, the patients who received ECMO were often young adults with severe hypoxemia and had a mortality rate of 21%, despite the disease severity and intensity of treatment. Limitations of the study by Davies and colleagues (2009) included that data collection was only performed until September 7, 2009, due to the need to publish the data, but the report indicated that death after weaning from ECMO or following ICU discharge was uncommon. Long-term outcomes, based on the severity of pulmonary dysfunction and quality of life, were not reported. Despite the severity of the illness and the prolonged use of life support, the majority of patients who received treatment with ECMO for severe ARDS did survive (Davies et al., 2009).

A report published in 2013 presented a case of prolonged VV ECMO with native lung recovery (Rosenberg et al., 2013). Although the usual duration of ECMO in severe ARDS patients (defined by the Berlin definition) is 7 to 10 days, this patient showed unprecedented and unexpected native lung recovery after 56.13 days of VV ECMO. At the time of the report in 2013, the patient already returned to work full time, was ambulating without assistance,

driving independently, and only required supplemental oxygen with significant exertion. Based on the results of this case report, Rosenberg and colleagues (2013) recommended redefining the terms irreversible lung injury and futility in ECMO. Their research illustrated that the lung may have unexpected regenerative capacity with native lung recovery after prolonged mechanical support, which is similar to native renal recovery after acute kidney injury. The researchers advocated for not using duration of ECMO as the primary measure for declaring futility for a patient in single-organ system respiratory failure on VV ECMO for ARDS (Rosenberg et al., 2013).

A study known as the "University of Michigan experience" highlights 2,000 patients managed with ECMO from 1973 to 2010 (Gray et al., 2014). The patients were divided into groups subtyped as the "first 1,000 patients" and the "second 1,000 patients." The patients included in the study were from all age groups and had varying diagnoses warranting ECMO treatment. The group of the first 1,000 patients was predominantly newborns with respiratory failure with a low likelihood of irreversible respiratory failure and had a survival rate of 74% (Gray et al., 2014). The group of the second 1,000 patients was expanded to children and adults with cardiac and pulmonary failure. Of these patients, ECMO resulted in 70% to 80% survival in neonates and children, 50% in adults with respiratory failure, and 40% in patients with cardiac failure with an overall survival rate of 55% (Gray et al., 2014). The decrease in the survival rates between groups is attributable to the types of patients and the severity of illness of each group. Complications of therapy included nonintracranial bleeding (most common), renal failure, pump malfunction, air entry into the circuit, and intracranial bleeding or infarction. This study contained a large number of participants while demonstrating that ECMO decreases mortality rates in critically ill patients of all age groups with acute pulmonary and cardiac failure (Gray et al., 2014).

Facilitation of ECMO for the Patient With Severe ARDS

To fully optimize the implementation of ECMO for the patient with severe ARDS, recommendations and treatment strategies exist to best utilize the technology, improve patient outcomes, and conserve resources. ECMO is a high-risk and complex treatment modality and is, therefore, reserved for complex cases with clearly defined proposed clinical outcomes. Thus, ECMO initiation remains selective and relatively infrequent, and ECMO is only offered at high-volume, dedicated centers to minimize improper initiation of therapy that results in high hospital costs and potentially life-threatening patient risks (Combes et al., 2014). There is a set organization of ECMO centers regionally and nationally where case volume is demonstrated to

better ensure competence, trained skills, and strong institutional support that is able to handle the expense and risks of implementation of such a complex system. Research by Combes and colleagues (2014) has shown that the more cases a center performs, the better the outcomes, and studies have shown that ECMO centers caring for 20 to 25 cases per year have significantly better outcomes than centers with 10 to 20 cases and fewer than 10 cases per year. Other factors to consider when optimizing patient outcomes through the designation of specific ECMO centers include experience of the center over time, designation of an ECMO team, continuing medical education and training in ECMO, length of patient days on ECMO, and annual volume of cases per year. Research recommends that ECMO centers perform at least 20 cases of ECMO per year with at least 12 of the ECMO cases being for acute respiratory failure (Combes et al., 2014).

The usual duration of ECMO in patients that meet the Berlin definition is usually 7 to 10 days, but individual cases have exceeded this average duration with native lung recovery (Rosenberg et al., 2013). Prior to initiation of a VV ECMO circuit, echocardiography should be performed to identify severe left ventricular dysfunction, which might warrant placement of a VA ECMO circuit instead (Combes et al., 2012). Combes and colleagues (2012) also recommend use of vascular ultrasound prior to peripheral cannulation for immediate confirmation of venous vessel access with cannulation strictly performed by the Seldinger technique. The Seldinger technique can be performed remotely by nonsurgical staff and without surgical equipment, requires no skin suturing, reduces bleeding, and allows for simple decannulation upon ECMO discontinuation. Catheter size and the number of drainage holes determine maximal flow of the circuit and are based on patient size, cardiac output, oxygen consumption, and lung shunt (Combes et al., 2012).

Once ECMO has been initiated, rapid stabilization of the patient is the goal, but intensive supportive ICU therapy is still required. Providers must continue to treat the patient's sepsis and reduce ventilator support as the ECMO support system permits (Park et al., 2011). Monitoring of the ECMO system should occur several times a day by the medical and nursing teams, and a perfusionist or other ECMO specialist should frequently and routinely monitor the circuit (Combes et al., 2012). Certain institutions are transitioning to a single care provider model through the use of ECMO nurse specialists. Per ELSO guidelines, ECMO nurse specialists are ICU nurses specifically trained in ECMO patient and circuit management. With the adoption of a single care provider model, the ICU nurse can primarily manage the ECMO patient. With the single care provider model, a registered nurse or respiratory therapist trained in ECMO meeting ELSO guidelines is able to independently manage the ECMO circuit with each individual institution's guidelines dictating if perfusion must remain within the hospital. An ECMO-trained

physician must provide 24-hr on-call coverage for the ECMO patient (ELSO Guidelines for ECMO Centers, 2014). Careful and proper observation of the cannula and circuit is intended to verify correct functioning of the device and to promptly identify any potential complications of the system including fibrin deposits, clots in the ECMO membrane, clots in the cannula or pump, bleeding, signs of inflammation or infection at the cannula insertion site, unexpected drops in ECMO outflow, and for clinical or biochemical signs of intravascular hemolysis (Combes et al., 2012).

Although a single ventilation strategy does not yet exist, research shows that volume- and pressure-limited ventilation are the only interventions with proven survival benefit in ARDS (Abrams et al., 2013). Other recommendations regarding management of mechanical ventilation include a limited respiratory rate (<22), tidal volume (<3 mL/kg), and peak inspiratory pressure (20-25 cm H_2O), maintenance of high levels of PEEP (≥10 cm H_2O), decrease ventilator FiO_2, and monitor transpulmonary pressure (Schmidt et al., 2014). Systemic anticoagulation is essential for preventing clotting of the ECMO circuit and patients often require multiple blood transfusions (Park et al., 2011). The threshold for red cell transfusion should be seven to eight g/dL and platelet transfusion should be discouraged except with severe thrombocytopenia accompanied by bleeding (Combes et al., 2012). Anticoagulation should be titrated to very low levels as current generation circuits and oxygenators are heparin coated or coated with a biocompatible material (Combes et al., 2012). The use of neuromuscular blocking agents can be used early after ECMO initiation with an SaO_2 less than 80% despite ECMO assistance. When not on neuromuscular blocking agents, sedation and analgesia should be titrated to the lowest possible dose to ensure patient comfort and prevent accidental dislodging of the ECMO cannula (Combes et al., 2012). Other treatment strategies include early tracheostomy placement for patients with anticipated prolonged respiratory support, early diuresis to dry weight (except when volume expansion is needed for management of sepsis), minimal doses of vasopressors, and initiation of continuous renal replacement therapy when indicated (Combes et al., 2012). Furthermore, early mobilization of the critically ill patient has been shown to improve patient outcomes. Abrams and colleagues (2013) have investigated the use of more compact ECMO circuits and strategies to avoid femoral cannulation as an opportunity for early mobilization and rehabilitation in patients receiving ECMO, particularly for the treatment of ARDS. Weaning of ECMO support should be considered once pulmonary function has improved, which is indicated by higher lung compliance, resolving lung infiltrates, and improvement in arterial PCO_2 and PO_2 with mechanical ventilation set to lung-protective levels of support (Combes et al., 2012). Removal of the system can occur once the patient remains stable and adequately ventilated after a few hours of

observation with confirmation via echocardiography showing no evidence of severe acute cor pulmonale.

Various research studies have discussed potential contraindications to therapy and different organizations offer different recommendations regarding contraindications to ECMO initiation. With the introduction of any life-saving, complex, and labor- and resource-intensive therapy comes risks and potential complications, and therefore contraindications to therapy are outlined to help reduce the risk of complications and optimization of patient outcomes. However, these contraindications are simply recommendations and not true exclusions from treatment. Some recommended contraindications include, significant preexisting comorbidities such as irreversible neurological condition, cirrhosis with ascites, encephalopathy or history of variceal bleeding, active and rapidly fatal malignancy, HIV infection, recent central nervous system (CNS) hemorrhage, major immunosuppression, and multiple organ failure, and are all associated with poor outcomes (Combes et al., 2012).

Limitations of Therapy

The contraindications to therapy discussed above are recommended as guidelines to reduce the risk of complications that are unavoidably present when operating such a high risk and complex system. Unfortunately, complications on ECMO are frequent and are associated with higher overall mortality (Park et al., 2011). The risks of potential complications must be evaluated prior to initiation of ECMO with the conceivable benefits outweighing those risks. Decreasing the length of duration of ECMO and identifying the circuit as a potential source of complications ultimately reduces all risks associated with treatment (Park et al., 2011).

The major concern for complications with ECMO initiation is centered on the coagulation cascade and the need for anticoagulation for optimal operation of the circuit. These complications include thrombosis in the circuit, intracranial hemorrhage/infarction, and bleeding (Gray et al., 2014). The most common complication during ECMO is hemorrhage and is treated by temporarily stopping anticoagulation, transfusing platelets and blood products, and occasionally the use of antifibrinolytics. Attempts to reduce the risk of complications related to systemic anticoagulation include bedside monitoring of activated clotting times (ACT), thromboelastography (TEG), activated partial thromboplastin time, and laboratory testing of coagulation factor levels (Park et al., 2011). Recommendations for systemic anticoagulation in ECMO patients who are not bleeding are in the range of 45 to 60 s for activated partial thromboplastin time (aPTT) and 0.2 to 0.3 IU/mL for heparinemia (Combes et al., 2012). Aspirin can be ordered at a platelet-antiaggregating dose when

the platelet count is greater than 100 g/L and in the absence of bleeding. Invasive procedures while the ECMO circuit is in place should be deferred whenever possible to reduce the chances of bleeding (Park et al., 2011).

Other potential complications with the implementation of ECMO that are not associated with bleeding include hemolysis due to problems in the circuit or with the patient and circuit infection in patients with active sepsis who are receiving ECMO (Park et al., 2011). Although VV ECMO is the primary mode used for severe ARDS, experience has shown that VA ECMO may accelerate pulmonary vascular thrombosis in the presence of severe lung injury (Schmidt et al., 2014). Also, it is possible that full-blown systemic inflammatory response syndrome (SIRS) may develop resulting in increased cytokine level, leukocyte activation, and multisystem organ dysfunction (Park et al., 2011). Other reported complications not related to bleeding include renal failure requiring dialysis, pump malfunction, infection, cardiac arrhythmia, and air entry into the circuit (Gray et al., 2014). Long-term psychological side effects of ECMO for ARDS survivors include PTSD, anxiety, and depressive symptoms (Schmidt et al., 2015). Schmidt et al. (2015) found that 6-month survivors report satisfactory mental health, but persistent physical and emotional-related difficulties, with anxiety (34% of survivors), depression (25% of survivors), or PTSD symptoms (16% of survivors). Other factors that influence the development of complications include patient characteristics such as age, number of ventilator days prior to ECMO initiation, initial PaO_2/FiO_2 ratio, pH prior to ECMO initiation, and gender (Park et al., 2011). Park and colleagues (2011) also found that the number of ventilator days prior to ECMO, decreasing patient weight, certain underlying causes of respiratory failure, and increased number of complications are also associated with increased mortality. Despite the potential complications, ECMO has proven to reduce morbidity and mortality rates for patients with severe ARDS.

The economic impact of initiating a highly complex, resource-intensive, labor-intensive circuit requiring an extensive interdisciplinary team undoubtedly must be considered prior to initiation despite its proven ability to lower patient morbidity and mortality rates. The initial costs of ECMO include circuit components, intensive care time, and personnel time. Patients treated with ECMO have higher median days of mechanical ventilation, longer lengths of ICU stay, and higher ICU mortality, all of which incur higher costs (Park et al., 2011). To evaluate the full economic impact of implementing ECMO, the researcher must consider the immediate and long-term financial expenses; however, there is limited research that fully assesses the long-term expenditures related to operation of the circuit.

Park and colleagues (2011) reported that the incremental cost per disability-free life year gained was well below willingness-to-pay levels, and an economic analysis showed that the average cost per patient for

ECMO referral was more than double the cost of treatment with conventional management. Their data also suggested that the lifetime predicted cost-usefulness was approximately US$31,000 per QALY and that ECMO is likely to prove more efficient than conventional management (Park et al., 2011). Wallace et al. (2010) developed the "CESAR trial," which determined that referral for consideration for treatment by ECMO led to a gain of 0.03 QALYs at 6-month follow-up. The CESAR trial found that a lifetime model predicted the cost per QALY of ECMO to be £19, 252 (approximately US$26,707.34) at a discount rate of 3.5% (Wallace et al., 2010). With this financial evaluation, the CESAR trial recommends only referring adult patients with ARDS for referral to ECMO if their Murray score exceeds 3.0 or if they have a pH of less than 7.20 on optimum conventional management (Wallace et al., 2010). Their research indicated this screening tool was most cost-effective and would significantly improve patient survival without severe disability compared with conventional mechanical ventilation techniques. In summary, despite high costs of operation, when implemented based on the recommended criteria, ECMO is shown to decrease severe disability and improve survival.

Other limitations of ECMO therapy include the logistical factors associated with its initiation and management. The ECMO circuit requires a comprehensive, organized, interdisciplinary team that is trained and skilled in optimizing its therapeutic effects. Factors related to effective coordination are centered on ensuring availability of ECMO centers and teams, and use of circuits that are equipped to handle such complex and time-sensitive situations without causing major complication or death (Combes et al., 2012). Currently, different countries have varied ECMO activation protocols and supervisory roles for initiation and management of the system (Park et al., 2011). Strategies aimed at improving the initiation process are focused on universalization and optimization of ECMO protocols while minimizing the risk of complications or patient harm and promotion of efficient utilization of health care resources.

Future Research and Implications

Research and experience has greatly enhanced the current operation of ECMO from initiation to conclusion, and the goal of future trials is to continue to improve on these strategies. Considerable gains have been made in terms of conception and composition of ECMO circuits that allow for simpler and safer constructions that require less anticoagulation and therefore less risk of bleeding complications (Combes et al., 2012). It is expected that data will continue to expand for simpler, safer, and more automatic designs that will also require less anticoagulation (Gray et al., 2014). There is great

promise in this as researchers are currently investigating nonthrombogenic surfaces to remove the need for anticoagulation (Gray et al., 2014). The International ECMO Network is committed to expanding the growth of ECMO-proficient centers and educated professionals, and is driven by high quality, high impact research in this field (Combes et al., 2014).

Future research is also focused on the development of standard-of-care mechanical ventilation strategies for patients with severe ARDS requiring ECMO, and evaluates the need for earlier transportation for ECMO intervention (Combes et al., 2012). The goal of the Extracorporeal Membrane Oxygenation to Rescue Lung Injury in ARDS (EOLIA) trial is to test the efficacy of early VV ECMO in ARDS and to address some of the criticism associated with the CESAR trial by using specified ventilator management protocols and early ECMO transport from referral centers without cannulation capacity (Park et al., 2011). The EOLIA trial is an international, multicenter, randomized trial that will test the efficacy of early VV ECMO in ARDS with strict control of mechanical ventilation in the control group, initiation of ECMO prior to transportation to ECMO centers, and the use of ECMO in every patient randomly assigned to receive it (Combes et al., 2012). As the use of ECMO expands rapidly and internationally, the EOLIA trial will provide more much-needed evidence regarding the impact of ECMO in severe respiratory failure allowing for more widespread adoption of the technique.

As expected, research continues to expand regarding the impact of ECMO on survival rates compared with conventional ventilator management protocols (Abrams et al., 2013). Schmidt and colleagues (2014) have also suggested directing future research toward evaluating the possibility of eliminating invasive mechanical ventilation with ECMO entirely. Invasive mechanical ventilation presents risks to the patient such as VILI and ventilator-associated pneumonia (VAP), which can further perpetuate existing lung damage (Schmidt et al., 2014). Thus, as ongoing research continues, future cases of severe ARDS could potentially avoid invasive mechanical ventilation through the use of ECMO. Other areas for research involving the use of mechanical ventilation includes evaluation of the impact of ultra-protective lung ventilation strategies with ECMO for ARDS, ECMO as a bridge to lung transplantation without invasive ventilation, monitoring and adjustment of mechanical ventilation settings prior to and during ECMO, and the development of enhanced patient monitoring devices such as end-tidal CO_2 and electrical impedance tomography to assess regional lung mechanics (Schmidt et al., 2014).

Other potential areas of exploration for patients with severe ARDS include extracorporeal carbon dioxide removal ($ECCO_2R$) for ARDS, low tidal volume versus very low tidal volume ventilation, assessment of long-term

neurocognitive and psychiatric outcomes, effect of early mobilization on functional outcomes, how to improve cost-effectiveness, and the effect of ECMO on pharmokinetics of medications (Abrams et al., 2013). Other topics for consideration include determining which patients are best candidates for ECMO, timing of ECMO initiation in terms of early versus late stages of ARDS, how to minimize ECMO-associated inflammatory responses, optimal "lung rest" strategies regarding cardiopulmonary bypass, long-term functional outcomes of patients and how to improve recovery in ICUs, safer and more effective composition of ECMO teams, competencies and resources to best deliver safe care, and possible regionalization of ECMO centers (Park et al., 2011). Research continues to grow on cases of prolonged ECMO duration as current recommendations for patients with severe ARDS are investigated and established (Rosenberg et al., 2013). Rosenberg and colleagues (2013) recommend redefining irreversible lung injury and futility in ECMO in the context of an organized evidence-based data collection. Furthermore, the development of prediction models to help risk stratify patients prior to ECMO initiation would help select the most appropriate candidates to achieve the best cost-to-benefit ratio (Abrams et al., 2013). For example, a prediction model regarding the assessment of extrapulmonary organ dysfunction may assist in risk stratification prior to beginning ECMO (Abrams et al., 2013).

As future research focuses on enhanced screening protocols for ECMO candidates, universalization of ECMO practices, and strategies aimed at reducing the risk of complications, the recommendation at the current time is that health care providers should attempt to optimize conventional treatments prior to consideration of ECMO for severe ARDS (Combes et al., 2014). Long-term prognosis after ECMO for ARDS requires further evaluation (Schmidt et al., 2015). The results of long-term outcome studies on patients evaluating their level of pulmonary dysfunction and quality of life are still forthcoming (Davies et al., 2009). Combes and colleagues (2014) recommend a follow-up program for patients receiving ECMO with establishment of customized, patient-centered, rehabilitation programs that might help improve long-term outcomes. The goal of all research and development is aimed at reducing patient morbidity and mortality in the most cost-effective means possible.

Conclusion

Severe ARDS is associated with high morbidity and mortality rates for patients on mechanical ventilation in critical care units. ECMO for the critically ill patient receiving mechanical ventilation has been suggested as a modified cardiopulmonary bypass circuit to provide gas exchange and systemic perfusion when a patient's own heart and lungs are unable to meet the

demands of the body. There is evidence that initiation of ECMO, via a specially trained team of experts, allows the lungs to rest and recover from respiratory failure while minimizing further lung injury to the patient and is effective at lowering patient morbidity and mortality rates. However, ECMO is a highly complex and costly medical intervention that does not operate without risks. This approach to treating severe lung injury in ARDS patients is a proven strategy to improving patient morbidity and mortality rates. Future research is focused on optimization and universalization of ECMO protocols to reduce potential complications, lessening the economic strain of the technology, and improving morbidity and mortality rates using this technology. Long-term data continue to evolve on extended functionality and quality of life measures for patients treated with ECMO for severe ARDS but show great promise as research has already demonstrated a substantial decrease in morbidity and mortality in treated patients.

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