CLINICAL THERAPEUTICS

Extracorporeal Membrane Oxygenation for ARDS in Adults

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This Journal *feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the authors' clinical recommendations.*

A 41-year-old woman presents with severe community-acquired pneumococcal pneumonia. Chest radiography reveals diffuse bilateral infiltrates, and hypoxemic respiratory failure develops despite appropriate antibiotic therapy. She is intubated and mechanical ventilation is initiated with a volume- and pressure-limited approach for the acute respiratory distress syndrome (ARDS). Over the ensuing 24 hours, her partial pressure of arterial oxygen (Pa_{O_2}) decreases to 40 mm Hg, despite ventilatory support with a fraction of inspired oxygen (F_{IO_2}) of 1.0 and a positive end-expiratory pressure (PEEP) of 20 cm of water. She is placed in the prone position and a neuromuscular blocking agent is administered, without improvement in her Pa_{O_2}. An intensive care specialist recommends the initiation of extracorporeal membrane oxygenation (ECMO).

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THE CLINICAL PROBLEM

ARDS is characterized by the acute onset of hypoxemia and bilateral pulmonary infiltrates that are consistent with pulmonary edema but without evidence of left heart failure.[1] There are more than 140,000 cases of ARDS in the United States annually.[2] In clinical trials involving patients with acute lung injury and ARDS, mortality remains high (22 to 41%).[3-9]

There is no consensus definition of severe ARDS, so precise estimates of the mortality associated with more severe presentations of ARDS do not exist. However, the mortality is almost certainly higher with severe ARDS. Nearly 20% of all patients with ARDS ultimately die of refractory hypoxemia.[10] Oxygenation itself is not clearly predictive of poor outcomes,[11] although there is some evidence that a lower ratio of Pa_{O_2} to F_{IO_2} is predictive of death, especially over time.[5,7,12-18]

Many survivors of ARDS have a significantly diminished quality of life that may persist for at least 5 years.[19] Average annual medical costs for survivors are two to four times those for a healthy person.[20]

PATHOPHYSIOLOGY AND EFFECT OF THERAPY

The injury to the lungs in ARDS may be due to a direct pulmonary insult, such as pneumonia or aspiration, or one that is indirect, as in severe sepsis, trauma, or acute pancreatitis.[2,20] In the early exudative phase of ARDS, a complex interaction between inflammatory cells and cytokines causes injury to both the capillary endothelium and alveolar epithelium. Permeability increases, allowing the formation of protein-rich interstitial and alveolar edema. Surfactant production and function are impaired, promoting atelectasis.[5] Diffuse alveolar damage is the defining histopathological feature of ARDS and is characterized by acute inflammation, edema,

hyaline membrane formation, and hemorrhage. Clinically, there is abnormal gas exchange, with hypoxemia and impaired carbon dioxide excretion; lung compliance is decreased.[15,21,22]

The distribution of injury throughout the lungs is not uniform in ARDS, which accounts for the regional differences in compliance and gas exchange.[21] The use of positive-pressure ventilation, although potentially lifesaving in patients with ARDS, may cause ventilator-associated lung injury from overdistention of aerated areas of lung or from injurious forces generated during repeated collapsing and reopening of small bronchioles and alveoli.[21,23] The use of a high F_{IO_2} may also exacerbate lung injury.[23,24] Lung-protective ventilation strategies mitigate ventilator-associated lung injury and oxygen toxicity by using volume- and pressure-limited ventilation with permissive hypercapnia to avoid overdistention and PEEP to maintain alveolar patency, as well as by minimizing the use of supplemental inspired oxygen.[3,7,23,25-27] However, even with the use of these strategies, mortality from ARDS remains high.

ECMO is one of several terms used for an extracorporeal circuit that directly oxygenates and removes carbon dioxide from the blood (Fig. 1). In most approaches to ECMO in patients with ARDS, a cannula is placed in a central vein. Blood is withdrawn from the vein into an extracorporeal circuit by a mechanical pump before entering an oxygenator. Within the oxygenator, blood passes along one side of a membrane, which provides a blood–gas interface for diffusion of gases. The oxygenated extracorporeal blood may then be warmed or cooled as needed and is returned to a central vein. This specific technique is termed "veno-venous" ECMO, because blood is both withdrawn from and returned to the venous system.

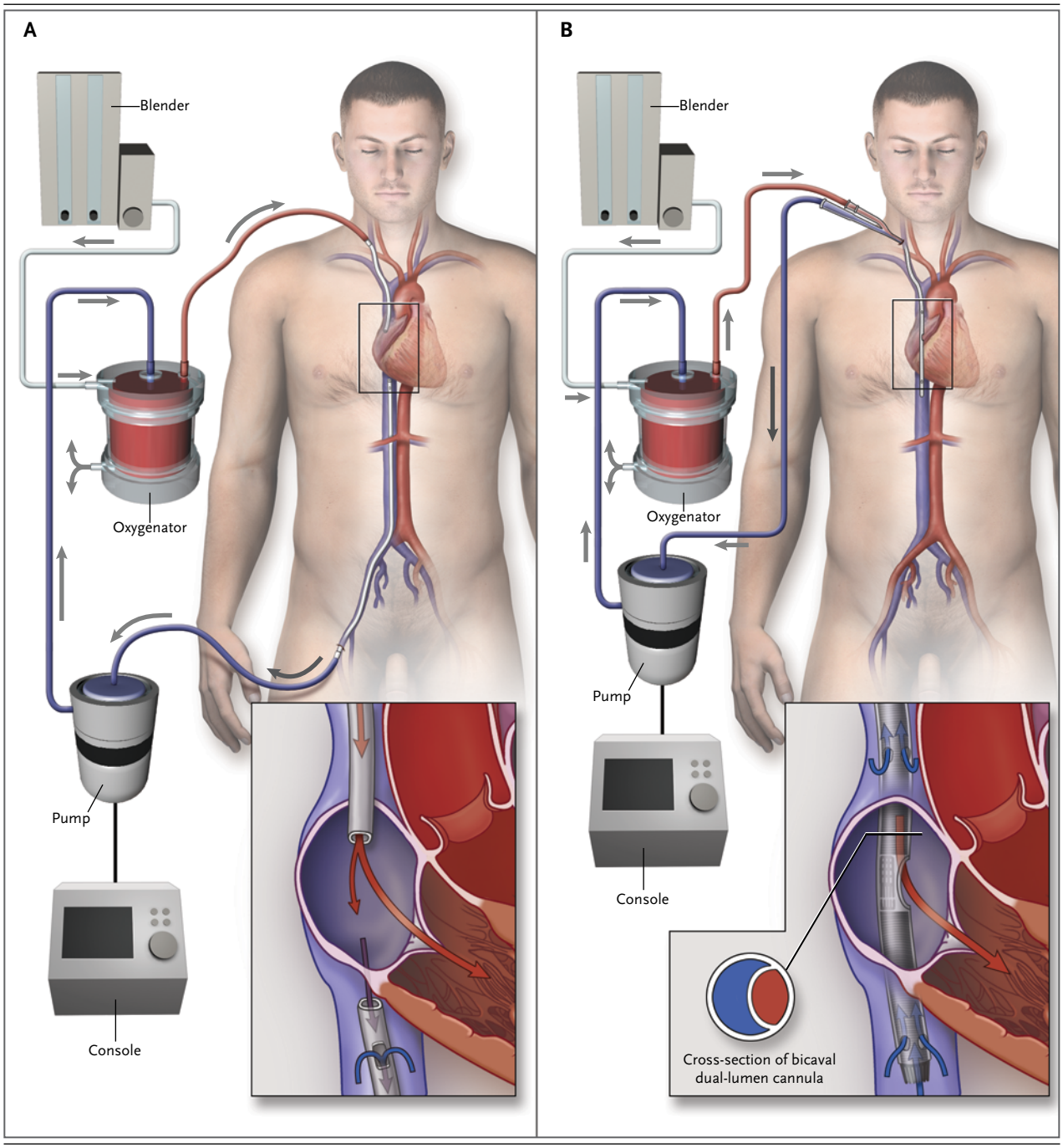
ECMO may be initiated as salvage therapy in patients with profound gas-exchange abnormalities when positive-pressure ventilation cannot maintain adequate oxygenation or carbon dioxide excretion to support life. However, ECMO may also be used in patients who can be sustained by positive-pressure ventilation, but only at the expense of excessively high inspiratory airway pressures, or in those who are unable to tolerate volume- and pressure-limited ventilation strategies because of the ensuing hypercapnia and acidemia. By directly removing carbon dioxide from the blood, ECMO facilitates the use of lung-protective ventilation. Furthermore, ECMO often allows for a strategy of lowering delivered volumes from the ventilator, the airway pressures required to deliver tidal breaths, and the F_{IO_2} to levels below those currently recommended. This strategy may improve outcomes by further mitigating ventilator-associated lung injury.[28-32] It is commonly used with ECMO for patients with ARDS and is often referred to imprecisely as "lung rest."[33-35] The value of lung rest remains unproved,[36] although a recent study suggests there may be a benefit from this approach.[37]

Figure 1 (facing page). Approaches to Venovenous Extracorporeal Membrane Oxygenation (ECMO).

Panel A shows a two-site approach to venovenous ECMO cannulation. Cannulae are inserted into the internal jugular vein (extending into the right atrium) and the femoral vein (extending into the inferior vena cava). When the ECMO circuit is connected, venous blood is withdrawn through the femoral venous drainage cannula into the pump. It then passes through the oxygenator, where gas exchange takes place, and it is reinfused into the venous system through the internal jugular venous cannula. With the two-site approach, a portion of the oxygenated blood returning through the internal jugular venous cannula (inset) can be drawn directly back into the femoral venous cannula without passing through the systemic circulation. Blood that is recirculated in this fashion does not contribute to systemic oxygenation. Panel B shows a single-site approach to venovenous ECMO cannulation. A dual-lumen cannula is inserted into the internal jugular vein (extending through the right atrium and into the inferior vena cava). Venous blood is withdrawn through the drainage lumen with ports in both the superior and inferior venae cavae. Reinfusion of oxygenated blood occurs through the second lumen with a port situated in the right atrium. The two ports of the drainage lumen (inset) are situated in the superior and inferior venae cavae, at a distance from the reinfusion port. The reinfusion port is positioned so that oxygenated blood is directed across the tricuspid valve and directly into the right ventricle. This arrangement substantially reduces recirculation of blood when the cannula is properly positioned.

CLINICAL EVIDENCE

The results of two early randomized, controlled trials (published in 1979 and 1994) did not show improved survival with ECMO or extracorporeal carbon dioxide removal (a related technique) in patients with ARDS.[38,39] Subsequent observational studies of the two techniques have suggested a benefit in severe cases of ARDS, with survival rates of 47 to 66% among selected patients.[34,40-47] Recent experience with ECMO for severe cases of ARDS during the 2009 influenza A



(H1N1) pandemic generated widespread interest in these techniques.[48-52] However, similar cases in which ECMO was not used also had favorable outcomes.[53] Therefore, conclusions that may be drawn from these observational studies are necessarily limited.[11,54]

Conventional Ventilation or ECMO for Severe Adult Respiratory Failure (CESAR; Current Controlled Trials number, ISRCTN47279827)[33] was the only controlled clinical trial using modern ECMO technology. In this trial, 180 adults with severe but potentially reversible respiratory failure were randomly assigned to continued conventional management at designated treatment centers or referral to a specialized center with a standardized management protocol that included consideration for

Table 1. Indications and Contraindications for ECMO in Severe Cases of ARDS.*

Indications
Severe hypoxemia (e.g., ratio of Pao_2 to Fio_2 <80, despite the application of high levels of PEEP [typically 15–20 cm of water]) for at least 6 hr in patients with potentially reversible respiratory failure†
Uncompensated hypercapnia with acidemia (pH <7.15) despite the best accepted standard of care for management with a ventilator
Excessively high end-inspiratory plateau pressure (>35–45 cm of water, according to the patient's body size) despite the best accepted standard of care for management with a ventilator
Relative contraindications
High-pressure ventilation (end-inspiratory plateau pressure >30 cm of water) for >7 days
High Fio_2 requirements (>0.8) for >7 days
Limited vascular access
Any condition or organ dysfunction that would limit the likelihood of overall benefit from ECMO, such as severe, irreversible brain injury or untreatable metastatic cancer
Absolute contraindication
Any condition that precludes the use of anticoagulation therapy‡

* ARDS denotes the acute respiratory distress syndrome, ECMO extracorporeal membrane oxygenation, Fio_2 fraction of inspired oxygen, Pao_2 partial pressure of arterial oxygen, and PEEP positive end-expiratory pressure.
† ECMO may be considered after a shorter interval if the ratio of Pao_2 to Fio_2 is less than 50. The threshold for the initiation of ECMO varies considerably across studies and guidelines.[33,34,45,51,57-59]
‡ In patients with severe bleeding, anticoagulation may be withheld for limited periods of time.

treatment with ECMO; 76% of these patients ultimately underwent ECMO. These patients also underwent mechanical ventilation with a strategy of volume- and pressure-limited lung rest. A lung-protective ventilation strategy was not mandated in the conventional-management group, and only 70% of patients in that group were treated with such a strategy at any time during the study. The primary outcome, death or severe disability at 6 months, occurred in 37% of the patients referred for consideration for ECMO, as compared with 53% of those assigned to conventional management (relative risk, 0.69; 95% confidence interval, 0.05 to 0.97; P=0.03).[33] This recent trial provides support for a strategy of transferring patients with severe ARDS to a center that is capable of providing ECMO. However, this study was not a randomized trial of ECMO as compared with standard-of-care mechanical ventilation. Substantial differences in overall care between the study groups may account for the beneficial effect that was associated with referral for consideration for ECMO.[11,33,55,56]

CLINICAL USE

The cornerstone of the management of ARDS is treatment of the precipitating illness and application of a low-volume, low-pressure ventilation strategy.[11] The use of a conservative fluid-management strategy is also recommended,[6] and the administration of neuromuscular blocking agents may be associated with decreased mortality when they are used early in the course of severe ARDS.[8] In patients with refractory gas-exchange abnormalities despite these measures, other so-called unproven therapies should be considered.[56] These include glucocorticoids, inhaled vasodilators, lung-recruitment maneuvers, high levels of PEEP, prone positioning, and high-frequency oscillatory ventilation. The decision to use such therapies, including ECMO, and the order in which they are used depend on the clinician's preference and the availability of resources, including access to referral centers, since evidence-based algorithms are not available.

The indications for ECMO in patients with ARDS are one or more of the following: severe hypoxemia, uncompensated hypercapnia, and the presence of excessively high end-inspiratory plateau pressures, despite the best accepted standard of care for management with a ventilator (Table 1). Patients requiring mechanical ventilation with a high end-inspiratory plateau pressure or a high Fio_2 for more than 7 days may be less likely to benefit from ECMO. Earlier initiation has been associated with better outcomes in some, but not all, observational studies.[42,44,45,51,60]

ECMO should be performed at centers with high case volumes, established protocols, and clinicians who are experienced in its use. Traditionally, in

most cases, ECMO for ARDS has been managed in surgical intensive care units. We use a different approach, treating patients with ARDS and other medical conditions requiring ECMO in our medical intensive care unit ("medical ECMO") and treating postoperative patients in the cardiothoracic unit ("surgical ECMO"). This approach shifts the emphasis of care from device management to disease management.

Cannulation for venovenous ECMO may involve two sites or a single site. In the two-site approach, blood is typically withdrawn from the inferior vena cava through a drainage cannula in the femoral vein, and oxygenated blood is reinfused into the right atrium through a cannula in the internal jugular vein (Fig. 1A). This approach can result in recirculation of blood, which occurs when reinfused blood is drawn back into the circuit in a closed loop (Fig. 1A, inset). Recirculated blood does not contribute to systemic oxygenation.

The recent introduction of a bicaval dual-lumen cannula allows single-site cannulation of the internal jugular vein. Venous blood is withdrawn through one lumen with ports in both the superior and inferior vena cava. Reinfusion of blood occurs through the second lumen and is directed across the tricuspid valve (Fig. 1B). The advantages of the single-site approach include avoidance of the femoral access site, improved patient mobility, and considerably reduced recirculation when the cannula is properly positioned.[61]

Alternatives to venovenous ECMO include venoarterial ECMO, in which the pump returns blood to the arterial system, thus providing hemodynamic support when needed, in addition to some respiratory support; extracorporeal carbon dioxide removal, which involves a smaller cannula, with blood flows adequate to remove carbon dioxide, but, as compared with ECMO, is less well suited to oxygenation; and arteriovenous carbon dioxide removal, which involves a pumpless circuit, with flows driven by the patient's own arterial pressure. Although carbon dioxide removal may be used to facilitate lung-protective ventilation,[37,39,47,62-64] the use of these three techniques in severe cases of ARDS is limited.

Once cannulation has been accomplished and the ECMO circuit set up (Fig. 2), fresh gas, known as sweep gas, is delivered to the gas side of the oxygenator membrane to allow for exchange of oxygen and carbon dioxide with the extracorporeal blood. The composition of the gas is determined by adjustment of a blender, a device that mixes ambient air with oxygen for delivery into the oxygenator. The fraction of delivered oxygen (FDO_2) (the term FIO_2 should be avoided, since the gas is not, in fact, inspired) is selected directly from the blender. Elimination of carbon dioxide is controlled principally by adjusting the flow rate of sweep gas. The greater the flow, the more carbon dioxide is eliminated. The partial pressure of arterial carbon dioxide ($PaCO_2$) is usually targeted to avoid or ameliorate acidemia.

Oxygenation is modulated primarily by altering the amount of blood flowing through the ECMO circuit, which is mainly limited by the size of the drainage cannula. The higher the blood flow, the greater the percentage of cardiac output that is oxygenated and the higher the PaO_2. We aim for an arterial oxygen saturation of 88% or more whenever possible.

Systemic anticoagulation with unfractionated heparin is required during ECMO to avoid thrombus formation in the circuit. An initial bolus is given before cannulation. We then target an activated partial-thromboplastin time of 40 to 60 seconds to minimize the risk of bleeding complications; the target range varies considerably according to the center.

The most appropriate ventilator settings for patients with severe ARDS who are undergoing ECMO are unknown. We frequently apply initial ventilator settings that are similar to those used in the CESAR trial[33]: pressure-controlled ventilation for a peak inspiratory pressure of 20 to 25 cm of water, a set rate of 10 breaths per minute, a PEEP of 10 to 15 cm of water, and an FIO_2 of 0.3. However, we consider multiple approaches to ventilation acceptable. Whenever possible, we aim for limitation of pressure and set respiratory rates that are at least as restrictive as those described above, along with tidal volumes that are typically maintained below 4 ml per kilogram of predicted body weight, to minimize the potential for ventilator-associated lung injury. Whatever the approach, applying adequate PEEP is important to maintain airway patency at the low lung volumes attained with these settings. As the patient's condition improves, the pressure-support mode of ventilation may be preferred when appropriate.

Hemodynamics are managed in the same fashion as they are in patients who do not receive venovenous ECMO support. In our experience, the requirement for vasopressors in patients with shock frequently decreases after the initiation of ECMO

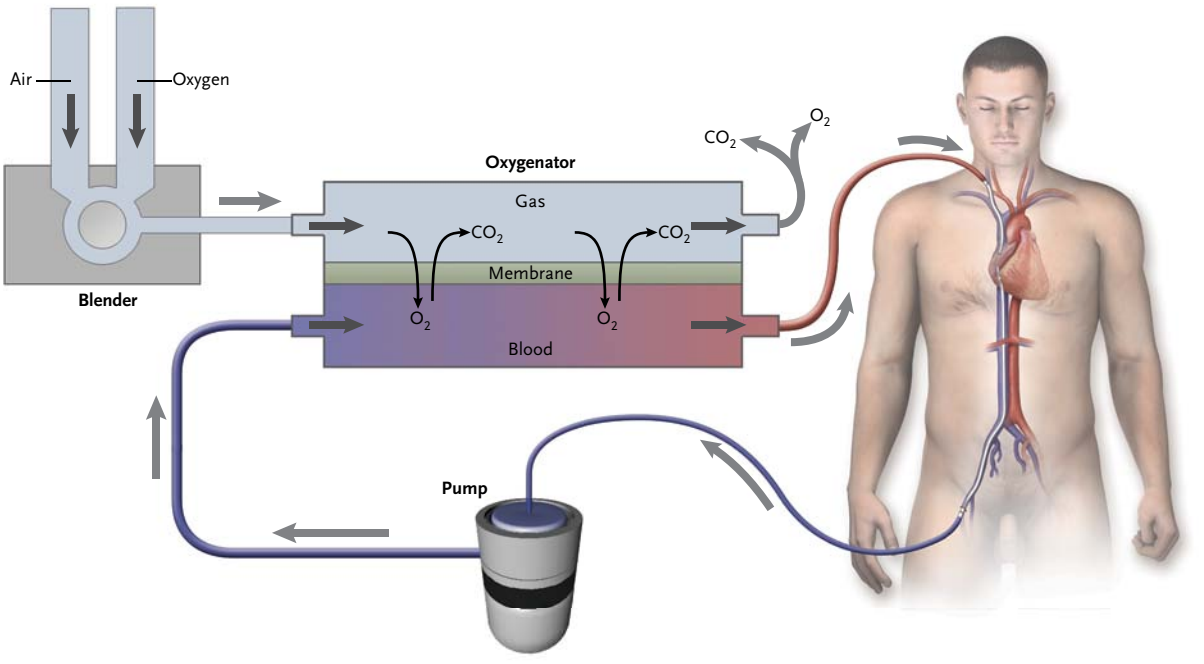


Figure 2. The Oxygenator in Venovenous ECMO.

The extracorporeal membrane oxygenation pump delivers venous blood to the oxygenator. This device is divided into two chambers by a semipermeable membrane. The venous blood enters the oxygenator and travels along one side of the membrane (the blood side), while fresh gas, known as sweep gas, is delivered to the other side (the gas side). Gas exchange (oxygen uptake and carbon dioxide elimination) takes place across the membrane. The oxygenated blood is then reinfused into the patient's venous system. The composition of the gas on the gas side of the oxygenator membrane is determined by adjustment of a blender that mixes room air with oxygen for delivery into the oxygenator.

and lung rest. Although some centers use venoarterial ECMO in patients with vasodilatory shock, we do not typically find this to be necessary.

Aggressive diuresis is attempted whenever possible, or, if necessary, ultrafiltration is implemented to facilitate a conservative fluid-management strategy. If extracorporeal blood flow is compromised by depletion of intravascular volume, temporarily decreasing the output of the pump rather than administering intravenous fluid is our preferred approach when possible. This approach may require briefly increasing the F_{IO_2} from the ventilator to maintain oxygenation in the face of lower blood flows. These changes can be reversed once intravascular volume is restored from the extravascular space.

We favor deep sedation during the initial period of ECMO for ARDS. However, as the patient's condition improves, it may be possible to reduce the level of sedation or even keep the patient awake.

Early mobilization is attempted as the situation allows. The doses of some medications may need to be adjusted because of altered pharmacokinetics resulting from the ECMO circuit.

Many centers recommend transfusion in patients with ARDS who are receiving ECMO until their hematocrit levels are in the normal range, ostensibly to maintain adequate oxygen delivery.[59,65,66] This approach has been associated with the transfusion of multiple units of blood products each day.[35,46,67] The theoretical benefit of enhanced oxygen delivery must be weighed against the potential harm of transfusion.[68,69] Transfusion may worsen outcomes, including an increased risk of death, if the blood has been stored for prolonged periods of time before transfusion.[70] We recommend the use of the same transfusion thresholds as those used in the care of patients with ARDS who are not being treated with ECMO.[71] Our practice, which is not based on high-level evidence, is to maintain the platelet count above 20,000 per cubic millimeter, or above 50,000 per cubic millimeter if there is active bleeding.

Weaning from ECMO may begin when improvement is noted in lung compliance, arterial oxygenation, or the findings on chest radiography. Ventilator settings are adjusted to standard lung-protective settings or pressure-support ventilation, and the flow rate of sweep gas is lowered to compensate for any increase in lung ventilation. Extracorporeal support is gradually decreased over a period of hours by reducing the rate of blood flow (or the F_{DO_2}). The goal is to discontinue ECMO when the patient can tolerate ventilator settings that are considerably less injurious than those at the initiation of ECMO. If, for example, the patient's ventilator settings can be maintained with end-inspiratory plateau pressures of less than 30 cm of water and an F_{IO_2} of 0.6 or less without considerable extracorporeal support, then discontinuation of ECMO may be appropriate. If complications such as severe bleeding arise, weaning from ECMO may be necessary at an earlier time. In our experience, patients with ARDS typically require extracorporeal support for a week to 10 days. However, patients can be successfully supported with ECMO for longer periods if necessary, although the risk of complications increases with time.

ECMO is costly and labor-intensive. In the CESAR trial, mean costs per patient in the group that could receive ECMO were more than twice as high as in the control group, at a mean of £73,979 ($116,502) over a period of 6 months.[33,72]

Table 2. Adverse Events Associated with ECMO in Adults with Respiratory Failure.*

Event	Rate
	%
Directly related to the ECMO circuit	
Oxygenator failure	17.5
Blood clots	
Oxygenator	12.2
Other circuit	17.8
Cannula-related problems	8.4
Other mechanical complications	7.9
Not directly related to the ECMO circuit†	
Bleeding	
Surgical-site bleeding	19.0
Cannulation-site bleeding	17.1
Pulmonary hemorrhage	8.1
Gastrointestinal hemorrhage	5.1
Intracranial hemorrhage	3.8
Hemolysis	6.9
Disseminated intravascular coagulation	3.7
Culture-confirmed infection at any site (related or unrelated to ECMO)‡	21.3

* Data are from the Extracorporeal Life Support Organization (ELSO).[73] Rates of adverse events reported by ELSO include events associated with the use of both modern and outdated ECMO technology as well as events occurring at centers with and those without experience in ECMO. These data are inclusive of all adult patients with respiratory failure, not just ARDS alone.

† Adverse events not related to the ECMO circuit are restricted to those that are most clinically significant and potentially related to the use of ECMO.

‡ The event rate for culture-confirmed infection includes infection at the ECMO cannula site and all other infections. The rate of infection at the ECMO cannula site was 10% in one observational study.[48]

ADVERSE EFFECTS

A database used by many ECMO centers, hosted by the Extracorporeal Life Support Organization (ELSO),[73] includes rates of adverse events associated with the use of ECMO. Event rates associated with the ECMO circuit and those not associated with the ECMO circuit are shown in Table 2.

In our experience, advances in component technology and the techniques used to perform ECMO have significantly reduced the rates of adverse events from those reported in the ELSO database. This view is corroborated by the report of only one serious adverse event related to ECMO in the CESAR trial (a death related to vessel perforation during cannulation).[33] Similarly, recent studies of the bicaval dual-lumen cannula showed a low rate of complications.[74-77] Nevertheless, complications of ECMO such as bleeding remain a clinically significant issue.[48,52,77] Vigilance in setting up and maintaining the circuit, cannulation performed by an expert, and adherence to management protocols are advised to minimize adverse events.

AREAS OF UNCERTAINTY

The role and proper use of ECMO for patients with ARDS have not been definitively established. The continued evolution of ECMO technology also limits the conclusions that may be drawn from recent studies. The role of extracorporeal carbon dioxide removal in ARDS, although potentially promising, remains to be defined.

Although the CESAR trial[33] provides some guidance for the use of ECMO, it is not clear which patients with ARDS are the best candidates for this treatment. The most favorable timing for the initiation of ECMO has not been established, and it is not clear whether patients who have required

more than 7 days of high-pressure or high-FIO_2 ventilation should be excluded from receiving ECMO. Various strategies to achieve lung rest and their effects on the inflammatory process have not been compared, nor have any such strategies been shown to be superior to standard-of-care lung-protective ventilation[3] during ECMO. The most appropriate strategy for weaning patients with ARDS from ECMO is also unknown. Whether there will be a role for removing the endotracheal tube and mechanical ventilation from some patients with ARDS who are receiving ECMO will require careful study.

Transfusion thresholds should be studied prospectively and correlated with outcomes. Our experience suggests that the degree of anticoagulation needed to prevent thrombosis within newer circuits is lower than that which was previously required. However, the ideal level balanced against the need to avoid cannula-site thrombosis remains uncertain. Accurate dosing for many classes of medications is unknown and will require careful study.

The long-term effects of ECMO, especially potential neuropsychiatric effects, require further investigation. Finally, more detailed information about the cost of expanding the use of this therapy is clearly needed to aid policymakers and health care providers.

GUIDELINES

The most comprehensive guidelines on ECMO are published by ELSO.[59] These guidelines address personnel, training, resources, the use of ECMO, and quality assurance. According to the ELSO guidelines, the use of ECMO should be considered when the ratio of PaO_2 to FIO_2 is less than 150, and ECMO is indicated when the ratio is less than 80. A $PaCO_2$ greater than 80 mm Hg or an end-inspiratory plateau pressure greater than 30 cm of water is also considered an indication for ECMO in patients with ARDS.

As the authors note, the ELSO guidelines are not intended to represent a standard of care and do not always represent a consensus. They do, however, reflect the views of a substantial number of experts in the field. Our practice, like that in other centers, differs from these guidelines in several areas.

RECOMMENDATIONS

The patient in the vignette has refractory hypoxemia despite standard therapy and aggressive additional measures. She is an appropriate candidate for venovenous ECMO. This recommendation, and the potential risks of ECMO, should be discussed with the patient's legal surrogate.

After initiation of systemic anticoagulation, we would insert a bicaval dual-lumen cannula in the right internal jugular vein, using fluoroscopic or transesophageal echocardiographic guidance, and connect it to a circuit primed with blood. The maximum blood-flow rate permitted by the cannula would be attained, improvement in oxygenation would be confirmed, and the flow rate of sweep gas would be adjusted for the targeted level of $PaCO_2$ and pH. The ventilator would be set to one of our accepted rest settings, and we would aim for a goal of an activated partial-thromboplastin time of 40 to 60 seconds. We would also recommend continued appropriate antibiotic therapy, aggressive volume removal as tolerated, and maximal supportive care.

Dr. Brodie reports receiving consulting fees and travel expenses from Maquet Cardiovascular, being a member of its cardiovascular advisory board, and anticipating possible receipt of grant support from Maquet Cardiovascular. Dr. Bacchetta reports receiving consulting fees and travel expenses from Maquet Cardiovascular, anticipating possible receipt of grant support from Maquet Cardiovascular, and discussing with Avalon Laboratories a possible instructional video for which he would not be paid. No other potential conflict of interest relevant to the article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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