Extracorporeal Life Support for Adults With Respiratory Failure and Related Indications
A Review

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Author Audio Interview

Supplemental content

IMPORTANCE The substantial growth over the last decade in the use of extracorporeal life support for adults with acute respiratory failure reveals an enthusiasm for the technology not always consistent with the evidence. However, recent high-quality data, primarily in patients with acute respiratory distress syndrome, have made extracorporeal life support more widely accepted in clinical practice.

OBSERVATIONS Clinical trials of extracorporeal life support for acute respiratory failure in adults in the 1970s and 1990s failed to demonstrate benefit, reducing use of the intervention for decades and relegating it to a small number of centers. Nonetheless, technological improvements in extracorporeal support made it safer to use. Interest in extracorporeal life support increased with the confluence of 2 events in 2009: (1) the publication of a randomized clinical trial of extracorporeal life support for acute respiratory failure and (2) the use of extracorporeal life support in patients with severe acute respiratory distress syndrome during the influenza A(H1N1) pandemic. In 2018, a randomized clinical trial in patients with very severe acute respiratory distress syndrome demonstrated a seemingly large decrease in mortality from 46% to 35%, but this difference was not statistically significant. However, a Bayesian post hoc analysis of this trial and a subsequent meta-analysis together suggested that extracorporeal life support was beneficial for patients with very severe acute respiratory distress syndrome. As the evidence supporting the use of extracorporeal life support increases, its indications are expanding to being a bridge to lung transplantation and the management of patients with pulmonary vascular disease who have right-sided heart failure. Extracorporeal life support is now an acceptable form of organ support in clinical practice.

CONCLUSIONS AND RELEVANCE The role of extracorporeal life support in the management of adults with acute respiratory failure is being redefined by advances in technology and increasing evidence of its effectiveness. Future developments in the field will result from technological advances, an increased understanding of the physiology and biology of extracorporeal support, and increased knowledge of how it might benefit the treatment of a variety of clinical conditions.

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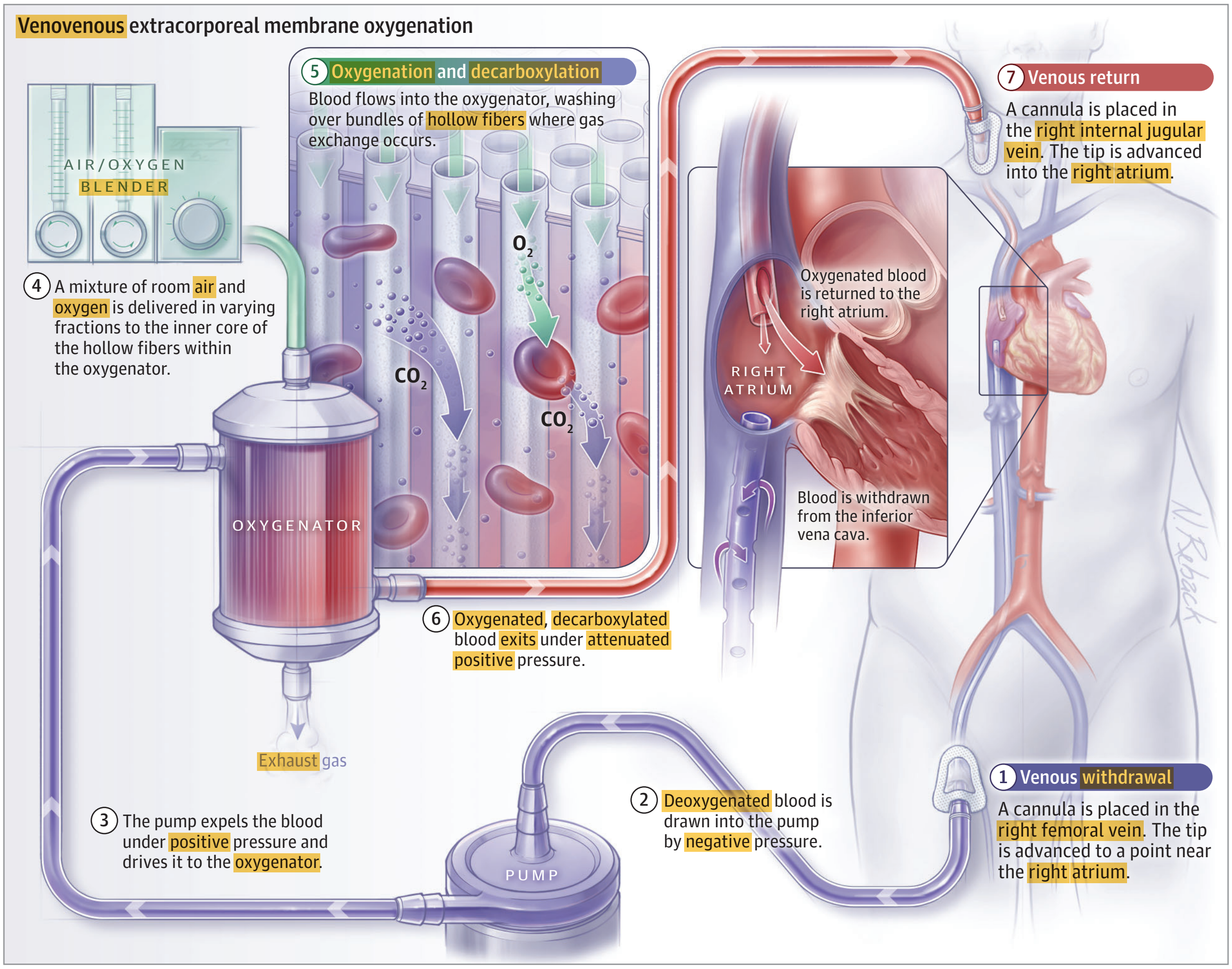
It is estimated that nearly 2 million people with acute respiratory failure are hospitalized annually in the United States at a cost exceeding $50 billion.[1] Approximately half require invasive mechanical ventilation, and in-hospital mortality exceeds 20% in these patients.[1] Mechanical ventilation has been the primary management tool for patients with acute respiratory failure since the 1950s' polio epidemic, yet it is associated with major complications that can increase mortality.[2] Consequently, there is a need for better ventilatory strategies, as well as alternative modes of respiratory support. In this setting, extracorporeal life support (ECLS), which provides gas exchange via an extracorporeal circuit, is increasingly being used to provide support to failing lungs, a failing heart, or both (**Figure 1**).

Rudimentary versions of ECLS developed in the 1970s were used for several decades but were largely abandoned because they lacked compelling evidence for their efficacy and resulted in major complications.[3,4] However, improvements in technology renewed interest in ECLS.[5] Over the last decade, use of ECLS has substantially increased (eFigure, A in the Supplement), at times, far outpacing the evidence justifying its use.[5-7] An increasing evidence base now supports greater use of ECLS for adult patients in respiratory failure.[8-11]

This review examines the reemergence of ECLS, discussing the physiologic rationale, current evidence, indications, and complications associated with its use in adult patients with respiratory failure and other related conditions. Importantly, ethical

Figure 1. How Extracorporeal Life Support Works



Schematic representation of a patient cannulated for venovenous extracorporeal membrane oxygenation (ECMO) with a typical 2-site set-up, with right femoral venous drainage and right internal jugular venous return. Deoxygenated blood is withdrawn from the patient and pumped through the membrane lung where layers of coated hollow fibers allow passage of gas (typically 100% oxygen), delivered from a blender, through the core of the fibers. Blood enters the membrane and washes over the fibers on its way through the gas exchange device. Carbon dioxide from the blood diffuses into the gas exchange fibers and exits the oxygenator; simultaneously, oxygen leaves the fibers to saturate the hemoglobin within the red cells during transit. A heat exchanger within the oxygenator allows control of body temperature. Oxygenated, decarboxylated blood is seen exiting the membrane lung under positive pressure (although a drop in pressure occurs across the membrane lung) and is reinfused into the patient through the internal jugular vein cannula.

considerations and the need for further research are highlighted, as is the potential future effect of the technology on patient outcomes. An overview of how ECLS provides circulatory support is presented in the eAppendix in the Supplement.

Methods

A literature search using PubMed was performed for literature published between January 1, 1960, and June 1, 2019. Search terms included *extracorporeal membrane oxygenation*, *extracorporeal carbon dioxide removal*, *extracorporeal life support*, *ECMO*, *ECLS*, and *ECCO$_2$R*. Non–English-language articles, and articles pertaining primarily to use in the neonatal or pediatric populations, were excluded. Specific articles for inclusion were selected based on their contribution to current practice or ongoing research questions. Priority was given to clinical trials, large longitudinal observational studies, and more recent articles.

Terminology

Extracorporeal support for respiratory and cardiac failure is referred to by many, often overlapping and imprecise terms. An international consensus statement recently clarified the nomenclature (**Box 1**).[12] *ECLS*, the overarching term, is divided into 2 modalities: extracorporeal membrane oxygenation (ECMO) and extracorporeal carbon dioxide removal (ECCO$_2$R). ECMO provides sufficient blood flow rates for either respiratory gas exchange support (venovenous ECMO) or circulatory support (venoarterial ECMO).

The goal of $ECCO_2R$ is to remove carbon dioxide (CO_2), which can be accomplished using comparatively lower blood flow rates, but which cannot provide substantial oxygenation. In retaining older terminology, these definitions represent a pragmatic compromise with a degree of lingering imprecision.

Basics of ECLS

ECLS encompasses many techniques to support the lungs or heart. Current uses of ECLS specifically for respiratory failure are shown in the **Table**. ECLS requires a vascular access cannula placed in a central vein, attached to a blood pump that withdraws blood under negative pressure, and delivers it to a gas exchange device, referred to as an oxygenator or membrane lung (Figure 1). Most membrane lungs are composed of bundles of hollow fibers with gas pumped through their hollow core and venous blood washing over the fibers. Analogous to gas exchange at the pulmonary alveolar-capillary membrane, CO_2 is removed by diffusion from the blood into the fibers and oxygen is delivered to the blood from the gas flowing through the fibers (known as sweep gas).

The fraction of delivered oxygen in the sweep gas (FDO_2) may be controlled by a blender, just as the fraction of inspired oxygen (FIO_2) is titrated in a mechanical ventilator. The faster the sweep gas is propelled through the membrane lung, the quicker the CO_2 is cleared from the gas compartment within the fibers and the greater the gradient that is created with the CO_2 in the blood, resulting in increased CO_2 clearance, up to a point. This is analogous to increasing minute ventilation (and, by extension, alveolar ventilation) with a mechanical ventilator. The exiting blood, typically fully saturated and with a lower CO_2 than when it entered, is then pumped back into the patient. If it is pumped into an artery, it is known as venoarterial, providing cardiocirculatory support and a degree of respiratory support. There are several devices for short-term cardiocirculatory support. These devices are not the focus of this review and are briefly summarized in the eAppendix in the Supplement. Venoarterial ECLS is not chosen for respiratory support unless there is concomitant right-sided or left-sided heart dysfunction. During venovenous support, which is used for respiratory failure, the blood may be returned to, or near, the right atrium via a second vascular cannula—or a second lumen of a dual-lumen cannula.[12,34]

Cannulation in ECLS is commonly percutaneous, using a modified Seldinger technique with imaging guidance, although surgical cut-down procedures may occasionally be used for better visualization of the vessels. Cannulation directly into major vessels, such as the aorta, or cardiac chambers may be used in patients requiring a high degree of cardiac support or postoperatively after cardiopulmonary bypass.[12]

The oxygen content of blood is limited by the amount of oxygen that can be dissolved or bound to hemoglobin requiring high blood flow rates to achieve adequate oxygenation with ECMO. Because the blood flow rate is in turn limited by cannula size, large bore cannulae are required. Because sufficient CO_2 may be removed at relatively low blood flow rates, $ECCO_2R$ can be achieved using smaller cannulae (or catheters), with less risk of vascular-related complications. At low blood flow rates, there is a greater risk for thrombosis requiring anticoagulation. The differences in the risk to benefit ratio between full-flow ECMO and $ECCO_2R$ are not entirely clear. A more detailed description of the physiology of ECLS may be found in the eAppendix in the Supplement.

Box 1. Nomenclature and Definitions[a]

Extracorporeal life support (ECLS): Overarching term for extracorporeal support, intended to support either the failing heart or lungs, for short- or long-term use. Encompasses venovenous and venoarterial ECMO as well as $ECCO_2R$.

Extracorporeal membrane oxygenation (ECMO): Used by some as an overarching term for all forms of support, now assigned to extracorporeal support with a blood pump, artificial lung, and vascular access cannulae, capable of providing circulatory support or generating blood flow rates adequate to support blood oxygenation (in addition to carbon dioxide removal).

Venovenous ECMO: Describes the support modality used when extracorporeal gas exchange is provided to blood withdrawn from the venous system, which is then reinfused to the venous system (typically at flow rates of 3-7 L/min). This mode supports respiratory gas exchange only.

Venoarterial ECMO: Gas exchange is provided to blood that is withdrawn from the venous system and then infused directly into the arterial system to provide partial or complete circulatory or cardiac support. The degree of respiratory support is variable.

Extracorporeal carbon dioxide removal ($ECCO_2R$): Gas exchange support via an extracorporeal circuit at relatively low blood flow rates (typically <1500 mL/min), which may be adequate for meaningful carbon dioxide removal, but not for oxygenation.

Membrane lung or oxygenator: The component of the extracorporeal life support device containing a gas chamber and a blood chamber separated by a semipermeable membrane that exchanges oxygen and carbon dioxide with venous blood flowing through the device.

Vascular cannulation: The placement of a cannula (a large bore catheter) into the vascular system for drainage or reinfusion of blood.

Single-lumen cannula: One lumen for either drainage or reinfusion of blood.

Double-lumen cannula: A single cannula with 2 internal lumens, one of which is used to drain venous blood and the other to reinfuse venous blood.

Sweep gas: The gas delivered to the membrane lung, typically oxygen or a blend of oxygen and air (rarely carbon dioxide may be blended in).

Fraction of delivered oxygen (FDO_2): The fraction of oxygen delivered through the sweep gas by blending oxygen and air.

[a] Additional variants of the terminology described may be used for more complex configurations of extracorporeal support.[12]

Complications

ECLS is a resource-intense, complex, interprofessional undertaking with many potentially serious complications[35-37] (**Figure 2**). Such complications arise either directly as a result of the device or its insertion or indirectly through the use of anticoagulation or the

Table. Current Clinical and Research Uses of Respiratory Extracorporeal Life Support (ECLS) for Respiratory Failure and Related Indications

Application	Clinical or Research Indication	Highest Level of Evidence	Basic Type of ECLS Used
Very severe ARDS	Clinical	Randomized clinical trial[8,9,13]	Venovenous ECMO
Moderate ARDS	Research	Randomized clinical trial[4,14,15]	Venovenous $ECCO_2R$
Bridge to lung transplantation[a,b]	Clinical	Matching study[16-19]	Venovenous or venoarterial ECMO or $ECCO_2R$
Primary graft dysfunction after lung transplantation	Clinical	Cohort studies[20]	Venovenous ECMO
COPD, acute exacerbation[b]	Research	Matching studies[21-23]	Venovenous $ECCO_2R$
Asthma, status asthmaticus[b]	Clinical	Case series[24]	Venovenous $ECCO_2R$
Pulmonary embolism, acute massive	Clinical	Case series[25-29]	Venoarterial ECMO with or without adjunctive therapies[c,d]
Pulmonary hypertension, acute decompensation	Clinical	Case series[17,30-33]	Venoarterial ECMO

Abbreviations: ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; $ECCO_2R$, extracorporeal carbon dioxide removal; ECMO, extracorporeal membrane oxygenation

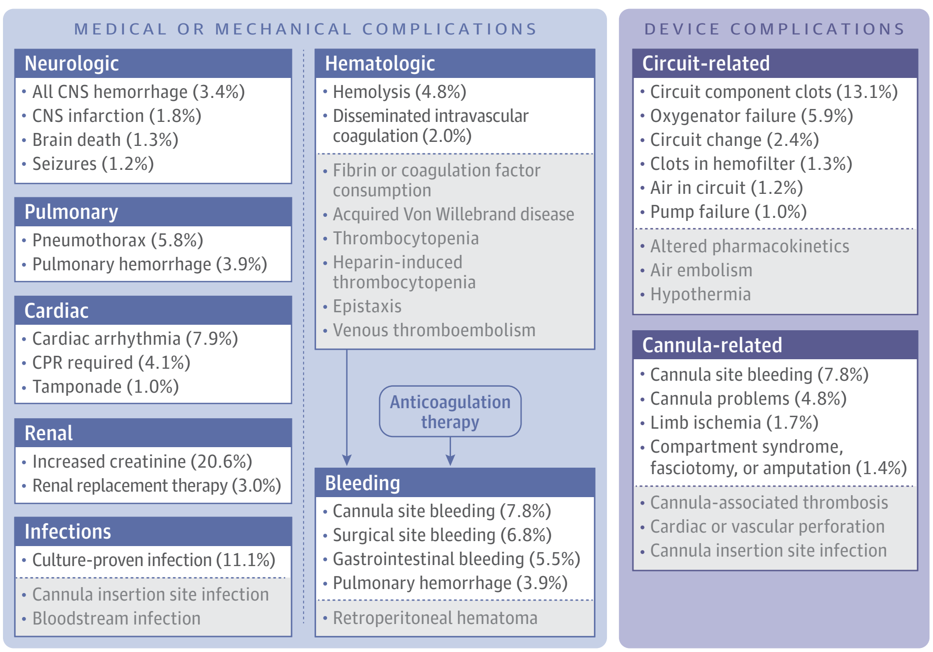
[a] Short-term for physiologic support; long-term or anticipated long-term support with minimal sedation and physical rehabilitation, with or without endotracheal extubation.

[b] Best potential candidates for minimizing sedation, endotracheal extubation, and physical rehabilitation.

[c] Adjunctive therapies may include catheter-directed thrombolysis or embolectomy, surgical embolectomy, or anticoagulation alone.

[d] Typical candidates failed intravenous thrombolysis or were not candidates for this therapy.

Figure 2. Selected Complications Associated With Adult Respiratory Extracorporeal Membrane Oxygenation (ECMO)



Selected major complications reported in at least 1% of patients in the Extracorporeal Life Support Organization (ELSO) Registry from 2014 to present (data abstracted from the ELSO International Summary, January 2019) are listed with percentages. Overlapping categories are combined, where appropriate. Additional complications, not specifically tracked in the ELSO Registry, are listed in the gray shaded areas. Precise rates of occurrence for these complications are difficult to determine from the literature, given that they are not uniformly tracked and definitions vary across studies. In addition, some complications may not be caused directly by ECMO, but may represent associations related, at least in part, to the patients' underlying illnesses. Bleeding complications are common during ECMO and may arise from procedures, such as cannula insertion, or occur spontaneously. Bleeding may also be precipitated or exacerbated by some of the hematologic complications listed in the figure (eg, thrombocytopenia or coagulation factor consumption), as well as by anticoagulation therapy, which is typically used to prevent circuit thrombosis. CNS indicates central nervous system; CPR, cardiopulmonary resuscitation.

effects of ECLS on distal organs,[38] what may be termed *ECLS-induced injury*. Precise complication rates are difficult to ascertain given the heterogeneity of definitions used across studies and the inconsistent reporting of some complications. The most comprehensive data on complications come from the registry of ECLS cases maintained by the Extracorporeal Life Support Organization (http://www.elso.org). Such adverse events range from trivial to devastating. Among the most common complications, rates seen in the registry were bleeding (24%), infection (11%), and circuit-related complications (25%), while cardiac arrhythmias were reported in 7.9% of patients and central nervous system hemorrhage or infarction in 5.2% (Figure 2).[7]

Historical Perspective

ECLS originated from operating room cardiopulmonary bypass and evolved into a tool for supporting heart or lung failure in the intensive care unit (ICU). First successfully deployed in a patient with acute respiratory distress syndrome (ARDS) in 1971,[39] early enthusiasm for ECLS in acute respiratory failure was dampened by 2 negative randomized clinical trials (RCTs) in 1979 and 1994.[3,4] The earlier of these 2 trials compared venoarterial (rather than venovenous) ECMO plus invasive mechanical ventilation, with mechanical ventilation alone in patients with severe acute respiratory failure (including patients with pulmonary embolism).[3] The study was stopped early due to difficulty with recruitment. Ninety patients were randomized (42 to the ECMO arm). Notably, 30-day survival was similarly poor in both groups at less than 10%, in part reflecting the severity of illness of the patients. While ECMO could theoretically have benefited these patients, any potential benefits may have been offset by the crude technology of that era, which led to serious complications, such as bleeding, and that several enrolling centers had little to no experience with the device. In addition, the concept of ventilator-induced lung injury (VILI) was not as well appreciated at the time, and hence the intensity of the mechanical ventilation strategy was not appreciably decreased in the ECMO group. This is in marked contrast to the recent Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA) Trial, which will be discussed here.

In 1994, Morris et al[4] randomized 40 patients with severe ARDS to 2 interventions: pressure-controlled inverse ratio ventilation followed by venovenous $ECCO_2R$ (n = 21; 19 received both interventions) or to conventional mechanical ventilation (n = 19). The trial was stopped early for futility, with no significant survival difference between groups (42% in controls and 33% in the intervention arm, $P = .8$). There was a major problem with increased bleeding in the extracorporeal group, with marked differences in requirements for blood products related in part to the aggressive anticoagulation required for the intensely thrombogenic circuit surfaces used at that time.

Subsequently, ECMO for adult respiratory failure was relegated to a few centers and largely to the publication of case series.[6] Nonetheless, the technology—primarily used during that time for cardiopulmonary bypass, as well as neonatal and pediatric ECLS—advanced considerably with improvements in pumps, membrane lungs, biocompatible coated surfaces, and cannulae.[6]

An inflection point in the use of ECMO occurred around 2009 due to the confluence of 2 events: the publication of the CESAR trial,[13] and the widespread use of ECMO for patients with influenza A(H1N1)–associated ARDS during that year's pandemic.[40-42] CESAR was a pragmatic trial of 180 adults with severe acute respiratory failure randomized to conventional management at any of 68 hospitals in the United Kingdom or to transfer to a single ECMO center where patients received a management protocol including ECMO, if needed. The trial was not designed to directly compare ECMO vs no ECMO; only 76% of patients in the ECMO group received ECMO. It was also a pragmatic trial in which patients in the control group were not mandated to receive low-volume, low-pressure ventilation, and only 70% did at any point during their course. Not providing standard ventilation for all patients in the control group biased the results in favor of the intervention group, making the 16% absolute reduction in the primary end point of death or severe disability at 6 months, reported as survival to 6 months without disability (63% vs 47%; relative risk [RR], 0.69 [95% CI, 0.05-0.97]; $P = .03$) difficult to interpret.

Only 2 serious adverse events were reported, both in the ECMO group, in which 1 patient died prior to undergoing ECMO cannulation due to failure of the oxygen supply in the ambulance during transport and 1 died as a consequence of cannulation. Bleeding, stroke, and infection were not reported. While the CESAR trial was an important trial and demonstrated relative safety, if not effectiveness, it could be interpreted in different ways depending on one's prior beliefs about the efficacy of ECMO—a Rorschach test of sorts, reflecting a range of such beliefs from strongly skeptical to strongly enthusiastic.[43,44]

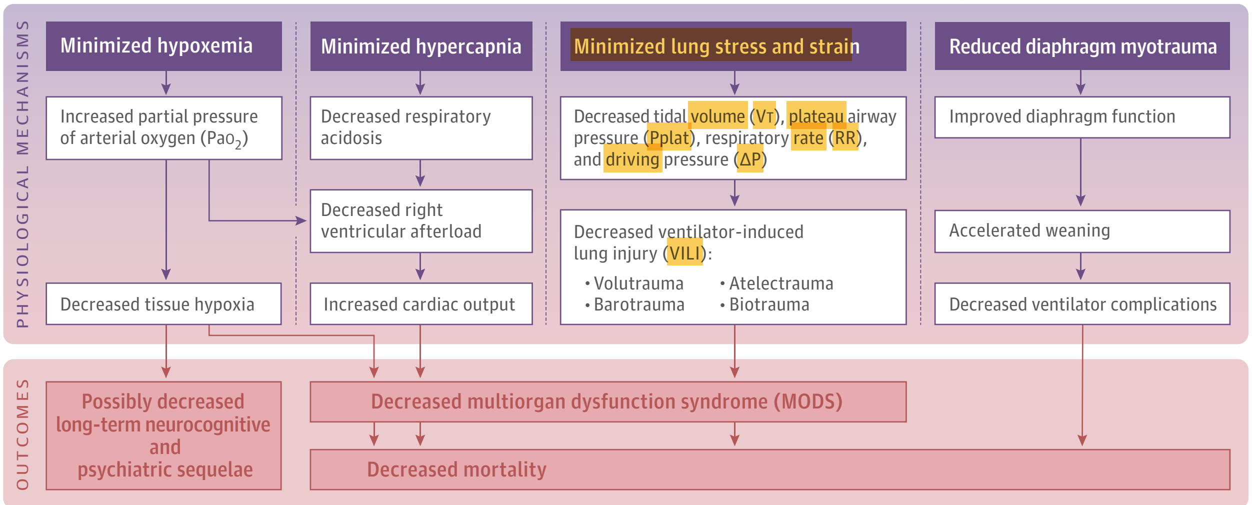
The first major nonrandomized study of ECMO in patients with H1N1-associated ARDS suggested outstanding outcomes with ECMO, greatly increasing interest in its use.[40] However, a subsequent series that included similar patients, none of whom were treated with ECMO, demonstrated nearly identical outcomes.[45] Further studies of ECMO in H1N1-associated ARDS, with matched controls, yielded inconsistent results.[41,42] Despite this contradictory evidence, use of ECMO in adults increased substantially worldwide over the last decade (eFigure, A in the Supplement),[7,46] as did the number of ECLS-related publications (eFigure, B in the Supplement).

Goals of ECLS

In the past, the major goal of ECMO for respiratory failure was to maintain adequate oxygenation. The hypothesis was that patients with severe hypoxemia were dying of tissue hypoxia; hence, increasing arterial oxygenation using ECMO would improve survival. However, over the past few decades, it has become clear that a major cause of mortality in patients with severe respiratory failure is iatrogenic injury due to the ventilatory support itself, referred to as VILI.[2] ECMO, by providing adequate gas exchange, allows the clinician to decrease the intensity of mechanical ventilation, in turn decreasing VILI. Based on a large body of evidence from patients with ARDS, this decrease in VILI is thought to be more important to clinical outcomes in most patients with ARDS receiving ECMO, as compared with the effect of ECMO on hypoxemia[2] (**Figure 3**).

Other key goals during ECLS might be to minimize sedation, liberate patients expeditiously from mechanical ventilation, and mobilize patients. This may be advantageous, in general, in appropriate critically ill patients,[47] and is a theoretically attractive strategy in patients receiving ECLS. Without invasive mechanical ventilation, for instance, there can be no ventilator-associated pneumonia and no VILI. Importantly, however, no VILI does not equate to no additional lung injury because patient respiratory effort may lead to further lung injury even in the absence of mechanical ventilation, so-called patient self-inflicted lung injury.[48] While the strategy of keeping ECLS patients awake, extubated, and ambulatory has been shown to be feasible and safe when undertaken in a methodical, interprofessional fashion,[49,50] it is unclear whether it should be

Figure 3. Potential Physiologic Mechanisms of Benefit of Extracorporeal Life Support (ECLS) for Respiratory Failure



routinely encouraged in patients with ARDS given the inherent risks, including additional lung injury,[48] even though it may be possible to mitigate the risk of further lung injury.[51,52] However, there is clearly a role for a strategy of keeping patients awake and ambulatory in those who require ECLS as a bridge to lung transplantation (as described here) and a potential role in other indications.[16,21,24]

Indications and Potential Indications for ECMO and $ECCO_2R$

There are several current and potential indications for ECMO and $ECCO_2R$ (Table).

Very Severe ARDS

The EOLIA trial[8] was a multicenter, international RCT in patients with very severe ARDS. Patients were randomized to standard of care, including protocolized mechanical ventilation (n = 125) or to ECMO (n = 124) with ventilator pressures, volumes, and respiratory rates set lower than the current standard; 90% of controls and 66% of ECMO patients underwent prone positioning. Crossover from control to "rescue" ECMO for failure of conventional management was allowed based on strict criteria. All enrolling centers were expert in the management of patients with acute respiratory failure.

The trial was terminated early for futility. There was, however, a nonstatistically significant, yet large reduction in mortality with ECMO (35% vs 46%; RR, 0.76 [95% CI, 0.55-1.04]; *P* = .09). There were 2 deaths attributed to ECMO. Although bleeding leading to transfusion occurred more frequently in the ECMO group (46% vs 28%) as did severe thrombocytopenia (27% vs 16%), the overall rate of complications in the ECMO group was reassuringly low, most notably, there was no statistically significant difference between groups in ischemic or hemorrhagic strokes. Overall, there were 3 strokes in the ECMO group and 8 in the control group.

Given that EOLIA was reported as a negative study but with a large absolute reduction in mortality, is an additional RCT necessary? Another trial seems unlikely given that EOLIA took 5.5 years to enroll 249 patients, and there was a 28% crossover to ECMO, demonstrating a lack of clinical equipoise.[53] This lack of equipoise at ECMO centers would be even greater today given the mortality difference seen in EOLIA. With another similar trial unlikely, how should these results be interpreted? Two analyses following the publication of EOLIA help in this regard.

Goligher et al[9] published a post hoc Bayesian analysis of EOLIA. Bayesian analyses take into account prior beliefs and knowledge (known as *priors*), and combine them with data from the new trial, yielding a *posterior probability*, defined as the probability of benefit based on what is now known from the combination of the priors and the new trial data. Given that the Goligher et al[9] study was undertaken after the publication of EOLIA, unbiased prior beliefs could not be ascertained.[9] As such, a range of priors was chosen, from strongly skeptical to strongly enthusiastic, as well as a meta-analysis of prior ECMO studies. Readers of the study may choose which prior beliefs and what weighting of the earlier studies best reflect their priors and draw conclusions about EOLIA based on the corresponding posterior probabilities. Overall, based on the Bayesian analysis, the probability of a mortality benefit at 60 days (RR<1) was high, ranging from 88% to 99%. The probability of an absolute risk reduction of 2% or more ranged from 78% to 98%, depending on the chosen priors.

This analysis strongly suggests that there is a mortality benefit to ECMO in very severe ARDS as defined by the EOLIA entry criteria (**Box 2**). As the editorialists wrote, it is no longer a question of "'Does ECMO work?' because that question appears to be answered. Instead the key question…is 'By how much does ECMO work, in whom, and at what cost?'"[54]

A formal meta-analysis by Munshi et al[10] came to a similar conclusion. This group analyzed 5 studies (2 RCTs and 3 observational studies; 773 patients). Based on the 2 RCTs (429 patients), 60-day mortality was significantly lower in the ECMO group compared with the control group (RR, 0.73 [95% CI, 0.58-0.92]; *P* = .008), with a moderate GRADE level. A similar conclusion, but with a slightly lower RR, was obtained when all 5 studies were combined (RR, 0.69 [95% CI, 0.50-0.95]).[10] Due to inconsistent reporting, adverse events were not pooled. Among the studies reporting bleeding complications (n = 251 in the 3 studies), 19% of patients experienced a major hemorrhage, 6% with intracranial bleeding. Only 2% of patients had circuit- or cannula-associated major complications in the 4 studies reporting these complications (n = 341). The conclusion from these studies fundamentally alters the algorithm for the treatment of patients with very severe ARDS, with ECMO becoming a standard strategy in experienced ECMO centers for patients meeting EOLIA criteria (Box 2).[11,55]

What are the potential mechanisms of benefit of ECMO in very severe ARDS? Clearly, for patients dying of profound hypoxemia, the ability to improve systemic oxygenation is important. However, patients who were enrolled in EOLIA due to severe respiratory acidosis (arterial pH <7.25 with arterial partial pressure of CO_2 [$Paco_2$] ≥60 mm Hg for >6 hours), rather than solely hypoxemia, appeared to benefit most.[8] This suggests that a major mechanism of benefit was the decrease in VILI due to the ventilation strategy that lowered pressures and volumes below standard values (Figure 3). Given the mechanism of action, the use of ECMO in the setting of very severe ARDS may be appropriate across a wide range of patient populations, including but not limited to pneumonia, sepsis, trauma, aspiration, near drowning, and transfusion-associated acute lung injury.

Understanding the long-term outcomes after ECMO for patients with very severe ARDS helps clinicians provide prognostic information. Survival prediction models offer some information in this regard.[56,57] However, further work is needed before such models are fully integrated into clinical care.

Box 2. ECMO for Severe ARDS: Entry Criteria for EOLIA[a,b]

Eligibility for EOLIA Was Defined by:

Fulfilling the American-European consensus definition for ARDS

Receiving invasive mechanical ventilation for <7 days

Meeting 1 of the following 3 criteria despite optimization of mechanical ventilation (Fio_2 ≥0.80, tidal volume of 6 mL/kg predicted body weight, PEEP ≥10 cm H_2O):

- Pao_2:Fio_2 <50 mm Hg for >3 hours, or
- Pao_2:Fio_2 <80 mm Hg for >6 hours, or
- pH <7.25 with $Paco_2$ ≥60 mm Hg for >6 hours with a respiratory rate increased to 35 breaths per minute, adjusted for plateau pressure ≤32 cm H_2O.

[a] Physicians were encouraged to use neuromuscular blocking agents and prone positioning before randomization.

[b] Criteria adapted from Combes et al.[8]

Abbreviations: ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; EOLIA, the Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome Trial; Fio_2, fraction of inspired oxygen; $Paco_2$, partial pressure of arterial carbon dioxide; Pao_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.

Moderate to Severe ARDS

Given that very severe ARDS constitutes a small percentage of patients with ARDS,[58] a key question is whether ECLS has a role for patients with less severe ARDS. In such cases, although the hypoxemia is not as severe, there is a rationale for lowering ventilation volumes and pressures beyond standard values to further reduce VILI.[59-64] However, in the absence of ECLS, this approach may lead to hypercapnic acidosis. A typical strategy of *permissive hypercapnia* trades the potential downsides of hypercapnia[65-67] for lower lung injury. Yet there is a limit, after which it may become *impermissible hypercapnia*, reaching levels of pH and $Paco_2$ that are intolerable. In these situations, there is a rationale for using $ECCO_2R$, which provides direct CO_2 removal from blood, albeit with little appreciable increase in oxygenation.

With $ECCO_2R$ or ECMO, it is possible to decrease $Paco_2$, allowing a lower intensity of mechanical ventilation, potentially reducing VILI and mortality. While the 1994 RCT showed no benefit of $ECCO_2R$ in ARDS,[4] it was performed with older technology and the complication rate was notably high. A more recent small RCT of $ECCO_2R$ using more modern ECMO technology was completed in patients with moderate to severe ARDS.[14] Patients were randomized to tidal volumes of 6 mL/kg predicted body weight vs approximately 3 mL/kg, with $Paco_2$ controlled by arteriovenous $ECCO_2R$ (a pumpless form of $ECCO_2R$ using systemic arterial pressure as the pump). Although the trial failed to meet its ventilator-free days primary end point, a post hoc subgroup analysis demonstrated a significant reduction in ventilator-free days at 60 days in patients with Pao_2:Fio_2 ratios of 150 or less. In this trial, transfusion to day 10 was higher in the $ECCO_2R$ group (mean [SD], 3.7 [2.4] units vs 1.5 [1.3] units; $P < .05$), and $ECCO_2R$-related adverse events occurred in 7.5% of patients.

A pilot study demonstrating the safety and feasibility of $ECCO_2R$ in moderate to severe ARDS using 3 different devices was recently completed,[15] with planning under way for a multicenter RCT using a form of personalized medicine with a predictive enrichment strategy for choosing the patients most likely to benefit from $ECCO_2R$.[68] An RCT of $ECCO_2R$ in patients with acute hypoxemic respiratory failure (Pao_2:Fio_2 ratio ≤150) with an intended enrollment of more than 1100 patients is ongoing in the United Kingdom (NCT02654327).[69] The move toward treating patients with moderate ARDS may foreshadow the eventual use of $ECCO_2R$ in mild ARDS or even patients at high risk for ARDS. However, this remains speculative at this time.

Bridge to Lung Transplantation

Traditionally, outcomes after lung transplantation were poor if the patient required pretransplant ECMO,[16,70] reflecting the severity of the patients' pretransplant condition, with further deconditioning occurring while the patient was receiving ECMO. A strategy using ECMO in conjunction with minimal sedation, liberation from mechanical ventilation, and early mobilization allows patients to maintain—or even improve—physical conditioning and nutritional status while waiting for an organ donor when wait times are prolonged.[16-19]

It is important to recognize that lungs are a scarce resource. It is not enough to bridge patients successfully to transplant; these patients should also have long-term outcomes comparable with or better than transplanted patients who never required ECMO prior to transplant. In the largest series to date using this strategy, Tipograf and colleagues[16] reported a 3-year survival of 83%, which was not significantly different when compared with transplanted, propensity-matched, non–ECMO-treated patients, despite much higher lung allocation scores in the ECMO group. This suggests that ECMO as a bridge to lung transplantation is a viable and potentially beneficial strategy.[16]

Acute Exacerbations of Chronic Obstructive Pulmonary Disease

$ECCO_2R$ is most compelling physiologically for patients with hypercapnic respiratory failure, such as those with acute exacerbations of chronic obstructive pulmonary disease (COPD) who are either failing noninvasive ventilation to avoid endotracheal intubation[22,23] or who are already intubated and might be liberated earlier from invasive mechanical ventilation.[21] The control of respiratory drive by $ECCO_2R$, when used in hypercapnic patients,[51] minimizes pulmonary hyperinflation by reducing minute ventilation and facilitates avoiding sedation and invasive mechanical ventilation, which in turn decreases the risk of ventilator-associated pneumonia. It might also help with delivery of inhaled bronchodilators and nutrition, as well as improve rehabilitation by decreasing dyspnea.[21]

Currently, the use of $ECCO_2R$ in acute exacerbations of COPD should be limited to research studies given the high rates of device-related complications seen in some series.[22,23] The risk to benefit ratio of this strategy should be tested in RCTs before widespread adoption.[71]

Right-Sided Heart Failure With or Without Respiratory Failure

Acute Pulmonary Embolism | Low-grade evidence and good physiologic rationale support the use of venoarterial (and, less commonly, venovenous) ECMO in massive pulmonary embolism with or without adjunctive therapeutic procedures (catheter-directed thrombolysis or embolectomy or surgical embolectomy) or with anticoagulation alone.[25-29]

Acute Decompensation of Pulmonary Hypertension | Venoarterial ECMO has been successfully used in patients with decompensated pulmonary hypertension with right-sided heart failure as both a bridge to transplant and a bridge to recovery using multiple cannula configurations.[17,30-33] Case selection is crucial in bridge to recovery, which should only be attempted when a potentially reversible process is identified, and centers should have expertise in both ECMO and pulmonary hypertension.

Other Applications of ECLS for Respiratory Failure | Other potential indications supported only by case series, yet having a compelling underlying physiologic rationale, include primary graft dysfunction after lung transplantation[20] and status asthmaticus[24] (Table). Given that large trials are unlikely in these populations, ECMO or $ECCO_2R$ may be considered in centers experienced in both ECLS and management of the underlying condition. For asthma, extending the use of $ECCO_2R$ to less severe exacerbations, especially in those not requiring invasive mechanical ventilation, should be considered a research indication, given the potentially higher risk to benefit ratio in these patients.

Contraindications

The only absolute contraindication to the use of ECLS for respiratory failure is an irreversible underlying process when the patient is not a candidate for lung transplantation. Proposed relative contraindications, such as moribund state, devastating neurologic injury, or untreatable metastatic cancer, are mostly common sense and relate to poor overall prognosis. Difficult vascular access can rarely preclude the use of ECLS.

Regionalization at Expert Centers and Mobile ECLS

As with other complex techniques in medicine, a volume-outcome relationship has been suggested in ECLS.[72,73] Although the literature is not entirely consistent on this point,[74,75] consensus statements have proposed minimum case volumes for ECLS centers,[76,77] and both CESAR and EOLIA may be taken as arguments in favor of concentrating ECLS cases in expert centers. Importantly, centers should be expert in the care of acute respiratory failure and the underlying patient conditions, with ECLS being just one tool available as part of a larger management algorithm.[11,55]

ECLS is often provided to desperately ill patients. Concentrating such patients in expert centers requires the ability to transport them safely, often over considerable distances. In the largest experience with ECLS transport reported to date, of 908 transports, 20% experienced a severe complication. However, such complications were not associated with increased mortality and only 2 patients died during transport.[78] Overall, mobile ECLS transport has been shown to be safe when performed by experienced teams using detailed transport protocols.[78-82]

The regionalization of ECLS services, however, should not be taken as an absolute.[83] Higher volumes do not guarantee better outcomes and there may be a role for low-volume, high-quality centers in areas with sparse populations or during pandemics, when larger centers are unable to accommodate an unusually high volume of patients. Although such centers may be able to keep up some of their team's skills through high-fidelity simulation,[84] the issues of which centers should be performing ECLS and the optimal annual case volume required to maintain competency remain open questions.

Financial and Ethical Implications

ECLS is expensive, with the costs varying according to geographic region. Because of this, there is a need for data reflecting real-world costs of performing ECLS to inform policy makers, governments, and health care institutions. Issues have been raised about whether financial incentives for providing ECLS are a major driver of utilization in some countries, as opposed to the clinical imperative.[46] With the use of ECLS spreading worldwide, there are also issues of both equity and equality that need to be addressed.[85,86]

Most of the ethical challenges arising during ECLS are not unique to the technology, but are often magnified by the severity of the patients' illness and the intensity of the clinical scenarios in which they occur.[87,88] Key ethical issues include determining when it is appropriate to withhold ECLS[89] and whether to withdraw ECLS when the goals of care can no longer be met.[90,91] Other scenarios, such as ECLS in a patient who is awake and bridging to lung transplantation but no longer a candidate for transplantation (the so-called "bridge to nowhere" scenario), also require further exploration.[87,92] In general, careful consideration of the ethical, palliative, and spiritual needs of these patients is of paramount importance.[93,94]

Current and Future Research Priorities

Despite the growth in ECLS, standardization is lacking across centers and regions, and the optimal approach to management is frequently unknown. For instance, membrane lungs, pumps, and cannulae vary considerably in their basic design properties, making comparisons across patients and centers difficult. There is no widespread agreement on the most appropriate approach for delivering and measuring anticoagulation during ECLS, and there is an incomplete understanding of the effect of the circuit on pharmacokinetics. Furthermore, the appropriate levels of blood flow and sweep gas flow rates are unknown, in part because ideal targets for oxygenation and ventilation are ill-defined. Optimal management of the ventilator during ECMO[95-97] and weaning from ECMO are other key areas of uncertainty.

As a technology-centered field, whose application is limited to a relatively modest number of patients for any given indication, research in ECLS is challenging.[98] The severity of illness of the patients, the heterogeneity of practice, low case volumes at any one center, and the resources needed to perform ECLS create considerable barriers to research. Technical advances make research findings a moving target, requiring frequent reassessment. Given this, a coordinated effort among stakeholders to study ECLS through organizations such as the Extracorporeal Life Support Organization, which maintains the largest international registry of ECLS patients, and research networks, such as the International ECMO Network (http://www.internationalecmonetwork.org) are essential. Further high-quality research is needed to better understand the indications, risks, and potential benefits of this technology, and ideally all ECLS-treated patients should be entered into registries.

Importantly, the evolution of the evidence in the field should not be seen as an invitation to unlimited use of the technology. While the role of ECLS is clearly increasing, caution must be taken not to let enthusiasm fill the gaps in the current evidence.

The Future of Extracorporeal Support

Advances in technology will no doubt transform the landscape of extracorporeal support in the coming decades. The emergence of a true artificial lung that may allow patients with acute respiratory failure to be treated outside the ICU and patients with chronic respiratory failure to be treated at home without mechanical ventilation is possible in the not-too-distant future.[99] Chronic COPD might be treated with intermittent respiratory dialysis, the removal of CO_2 in sessions conceptually similar to renal dialysis.[99] Such advances could one day make mechanical ventilation obsolete for some indications. The current conception of the ICU is built, in large part, around the mechanical ventilator. Perhaps extracorporeal technologies could one day disrupt the prevailing ICU model.

Expanding on the understanding of the crosstalk between native organs, a novel concept is emerging of extracorporeal organ support (ECOS), representing support for the lungs, heart, liver, kidneys, and perhaps other organs.[99] And with this, one can envision integrated ECOS platforms capable of providing support in a coordinated fashion to multiple organs simultaneously.[38,99]

Conclusions

ECLS (ECMO and $ECCO_2R$) for acute respiratory failure has evolved rapidly in recent years from a niche technology on the fringes of medicine to a mainstream modality of respiratory and right heart support. While the development of new ECLS technologies holds the promise of changing the approach to treatment for respiratory failure, and while the role of ECLS will no doubt continue to grow, the need for high-quality research to guide this growth has never been greater.

ARTICLE INFORMATION

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Edward Livingston, MD, at Edward.livingston@jamanetwork.org or Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

REFERENCES

1. Stefan MS, Shieh MS, Pekow PS, et al. Epidemiology and outcomes of acute respiratory failure in the United States, 2001 to 2009: a national survey. *J Hosp Med*. 2013;8(2):76-82. doi:10.1002/jhm.2004

2. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. *N Engl J Med*. 2013;369(22):2126-2136. doi:10.1056/NEJMra1208707

3. Zapol WM, Snider MT, Hill JD, et al. Extracorporeal membrane oxygenation in severe acute respiratory failure: a randomized prospective study. *JAMA*. 1979;242(20):2193-2196. doi:10.1001/jama.1979.03300200023016

4. Morris AH, Wallace CJ, Menlove RL, et al. Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO2 removal for adult respiratory distress syndrome. *Am J Respir Crit Care Med*. 1994;149(2, pt 1):295-305. doi:10.1164/ajrccm.149.2.8306022

5. Brodie D. The evolution of extracorporeal membrane oxygenation for adult respiratory failure. *Ann Am Thorac Soc*. 2018;15(supplement_1):S57-S60. doi:10.1513/AnnalsATS.201705-386KV

6. Brodie D, Bacchetta M. Extracorporeal membrane oxygenation for ARDS in adults. *N Engl J Med*. 2011;365(20):1905-1914. doi:10.1056/NEJMct1103720

7. Extracorporeal Life Support Organization. *ECLS Registry Report, International Summary*. Ann Arbor, MI: Extracorporeal Life Support Organization; January 2019.

8. Combes A, Hajage D, Capellier G, et al; EOLIA Trial Group, REVA, and ECMONet. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med*. 2018; 378(21):1965-1975. doi:10.1056/NEJMoa1800385

9. Goligher EC, Tomlinson G, Hajage D, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome and posterior probability of mortality benefit in a post hoc Bayesian analysis of a randomized clinical trial. *JAMA*. 2018;320(21):2251-2259. doi:10.1001/jama.2018.14276

10. Munshi L, Walkey A, Goligher E, Pham T, Uleryk EM, Fan E. Venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: a systematic review and meta-analysis. *Lancet Respir Med*. 2019;7(2):163-172. doi:10.1016/S2213-2600(18)30452-1

11. Abrams D, Ferguson ND, Brochard L, et al. ECMO for ARDS: from salvage to standard of care? *Lancet Respir Med*. 2019;7(2):108-110. doi:10.1016/S2213-2600(18)30506-X

12. Conrad SA, Broman LM, Taccone FS, et al. The Extracorporeal Life Support Organization Maastricht Treaty for Nomenclature in Extracorporeal Life Support: a position paper of the Extracorporeal Life Support Organization. *Am J Respir Crit Care Med*. 2018;198(4):447-451. doi:10.1164/rccm.201710-2130CP

13. Peek GJ, Mugford M, Tiruvoipati R, et al; CESAR trial collaboration. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet*. 2009;374(9698):1351-1363. doi:10.1016/S0140-6736(09)61069-2

14. Bein T, Weber-Carstens S, Goldmann A, et al. Lower tidal volume strategy (≈3 ml/kg) combined with extracorporeal CO2 removal versus 'conventional' protective ventilation (6 ml/kg) in severe ARDS: the prospective randomized Xtravent-study. *Intensive Care Med*. 2013;39(5): 847-856. doi:10.1007/s00134-012-2787-6

15. Combes A, Fanelli V, Pham T, Ranieri VM; European Society of Intensive Care Medicine Trials Group and the "Strategy of Ultra-Protective lung ventilation with Extracorporeal CO2 Removal for New-Onset moderate to severe ARDS" (SUPERNOVA) investigators. Feasibility and safety of extracorporeal CO_2 removal to enhance protective ventilation in acute respiratory distress syndrome: the SUPERNOVA study. *Intensive Care Med*. 2019;45(5):592-600. doi:10.1007/s00134-019-05567-4

16. Tipograf Y, Salna M, Minko E, et al. Outcomes of extracorporeal membrane oxygenation as a bridge to lung transplantation. *Ann Thorac Surg*. 2019; 107(5):1456-1463. doi:10.1016/j.athoracsur.2019.01.032

17. de Perrot M, Granton JT, McRae K, et al. Impact of extracorporeal life support on outcome in patients with idiopathic pulmonary arterial hypertension awaiting lung transplantation. *J Heart Lung Transplant*. 2011;30(9):997-1002. doi:10.1016/j.healun.2011.03.002

18. Benazzo A, Schwarz S, Frommlet F, et al; Vienna ECLS Program. Twenty-year experience with extracorporeal life support as bridge to lung transplantation. *J Thorac Cardiovasc Surg*. 2019; S0022-5223(19)30488-X.

19. Chicotka S, Pedroso FE, Agerstrand CL, et al. Increasing opportunity for lung transplant in interstitial lung disease with pulmonary hypertension. *Ann Thorac Surg*. 2018;106(6):1812-1819. doi:10.1016/j.athoracsur.2018.04.068

20. Hartwig MG, Walczak R, Lin SS, Davis RD. Improved survival but marginal allograft function in patients treated with extracorporeal membrane oxygenation after lung transplantation. *Ann Thorac Surg*. 2012;93(2):366-371. doi:10.1016/j.athoracsur.2011.05.017

21. Abrams DC, Brenner K, Burkart KM, et al. Pilot study of extracorporeal carbon dioxide removal to facilitate extubation and ambulation in exacerbations of chronic obstructive pulmonary disease. *Ann Am Thorac Soc*. 2013;10(4):307-314. doi:10.1513/AnnalsATS.201301-021OC

22. Del Sorbo L, Pisani L, Filippini C, et al. Extracorporeal Co2 removal in hypercapnic patients at risk of noninvasive ventilation failure: a matched cohort study with historical control. *Crit Care Med*. 2015;43(1):120-127. doi:10.1097/CCM.0000000000000607

23. Braune S, Sieweke A, Brettner F, et al. The feasibility and safety of extracorporeal carbon dioxide removal to avoid intubation in patients with COPD unresponsive to noninvasive ventilation for acute hypercapnic respiratory failure (ECLAIR study): multicentre case-control study. *Intensive Care Med*. 2016;42(9):1437-1444. doi:10.1007/s00134-016-4452-y

24. Brenner K, Abrams DC, Agerstrand CL, Brodie D. Extracorporeal carbon dioxide removal for refractory status asthmaticus: experience in distinct exacerbation phenotypes. *Perfusion*. 2014; 29(1):26-28. doi:10.1177/0267659113494964

25. Meneveau N, Guillon B, Planquette B, et al. Outcomes after extracorporeal membrane oxygenation for the treatment of high-risk pulmonary embolism: a multicentre series of 52 cases. *Eur Heart J*. 2018;39(47):4196-4204. doi:10.1093/eurheartj/ehy464

26. Kmiec L, Philipp A, Floerchinger B, et al. Extracorporeal membrane oxygenation for massive pulmonary embolism as bridge to therapy. *ASAIO J*. 2019. doi:10.1097/MAT.0000000000000953

27. Corsi F, Lebreton G, Bréchot N, et al. Life-threatening massive pulmonary embolism rescued by venoarterial-extracorporeal membrane oxygenation. *Crit Care*. 2017;21(1):76. doi:10.1186/s13054-017-1655-8

28. Pasrija C, Kronfli A, George P, et al. Utilization of veno-arterial extracorporeal membrane oxygenation for massive pulmonary embolism. *Ann Thorac Surg*. 2018;105(2):498-504. doi:10.1016/j.athoracsur.2017.08.033

29. Munakata R, Yamamoto T, Hosokawa Y, et al. Massive pulmonary embolism requiring extracorporeal life support treated with catheter-based interventions. *Int Heart J*. 2012;53(6):370-374. doi:10.1536/ihj.53.370

30. Rosenzweig EB, Brodie D, Abrams DC, Agerstrand CL, Bacchetta M. Extracorporeal membrane oxygenation as a novel bridging strategy for acute right heart failure in group 1 pulmonary arterial hypertension. *ASAIO J*. 2014;60(1):129-133. doi:10.1097/MAT.0000000000000021

31. Abrams DC, Brodie D, Rosenzweig EB, Burkart KM, Agerstrand CL, Bacchetta MD. Upper-body extracorporeal membrane oxygenation as a strategy in decompensated pulmonary arterial hypertension. *Pulm Circ*. 2013;3(2):432-435. doi:10.4103/2045-8932.113178

32. Javidfar J, Brodie D, Sonett J, Bacchetta M. Venovenous extracorporeal membrane oxygenation using a single cannula in patients with pulmonary hypertension and atrial septal defects. *J Thorac Cardiovasc Surg*. 2012;143(4):982-984. doi:10.1016/j.jtcvs.2011.10.061

33. Chicotka S, Rosenzweig EB, Brodie D, Bacchetta M. The "Central Sport Model": extracorporeal membrane oxygenation using the innominate artery for smaller patients as bridge to lung transplantation. *ASAIO J*. 2017;63(4):e39-e44. doi:10.1097/MAT.0000000000000427

34. Biscotti M, Lee A, Basner RC, et al. Hybrid configurations via percutaneous access for extracorporeal membrane oxygenation: a single-center experience. *ASAIO J*. 2014;60(6): 635-642. doi:10.1097/MAT.0000000000000139

35. Luyt CE, Bréchot N, Demondion P, et al. Brain injury during venovenous extracorporeal membrane oxygenation. *Intensive Care Med*. 2016; 42(5):897-907. doi:10.1007/s00134-016-4318-3

36. Lorusso R, Gelsomino S, Parise O, et al. Neurologic injury in adults supported with veno-venous extracorporeal membrane oxygenation for respiratory failure: findings from the Extracorporeal Life Support Organization database. *Crit Care Med*. 2017;45(8):1389-1397. doi:10.1097/CCM.0000000000002502

37. Na SJ, Chung CR, Choi HJ, et al. The effect of multidisciplinary extracorporeal membrane oxygenation team on clinical outcomes in patients with severe acute respiratory failure. *Ann Intensive Care*. 2018;8(1):31. doi:10.1186/s13613-018-0375-9

38. Husain-Syed F, Ricci Z, Brodie D, et al. Extracorporeal organ support (ECOS) in critical illness and acute kidney injury: from native to artificial organ crosstalk. *Intensive Care Med*. 2018; 44(9):1447-1459. doi:10.1007/s00134-018-5329-z

39. Hill JD, O'Brien TG, Murray JJ, et al. Prolonged extracorporeal oxygenation for acute post-traumatic respiratory failure (shock-lung syndrome): use of the Bramson membrane lung. *N Engl J Med*. 1972;286(12):629-634. doi:10.1056/NEJM197203232861204

40. Davies A, Jones D, Bailey M, et al; Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators. Extracorporeal membrane oxygenation for 2009 influenza A(H1N1) acute respiratory distress syndrome. *JAMA*. 2009;302(17):1888-1895. doi:10.1001/jama.2009.1535

41. Noah MA, Peek GJ, Finney SJ, et al. Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1). *JAMA*. 2011;306(15):1659-1668. doi:10.1001/jama.2011.1471

42. Pham T, Combes A, Rozé H, et al; REVA Research Network. Extracorporeal membrane oxygenation for pandemic influenza A(H1N1)-induced acute respiratory distress

syndrome: a cohort study and propensity-matched analysis. *Am J Respir Crit Care Med*. 2013;187(3):276-285. doi:10.1164/rccm.201205-0815OC

43. Dalton HJ, MacLaren G. Extracorporeal membrane oxygenation in pandemic flu: insufficient evidence or worth the effort? *Crit Care Med*. 2010;38(6):1484-1485. doi:10.1097/CCM.0b013e3181e08fff

44. Pellegrino VA, Davies AR. CESAR: deliverance or just the beginning? *Crit Care Resusc*. 2010;12(2):75-77.

45. Miller RR III, Markewitz BA, Rolfs RT, et al. Clinical findings and demographic factors associated with ICU admission in Utah due to novel 2009 influenza A(H1N1) infection. *Chest*. 2010;137(4):752-758. doi:10.1378/chest.09-2517

46. Karagiannidis C, Brodie D, Strassmann S, et al. Extracorporeal membrane oxygenation: evolving epidemiology and mortality. *Intensive Care Med*. 2016;42(5):889-896. doi:10.1007/s00134-016-4273-z

47. Pun BT, Balas MC, Barnes-Daly MA, et al. Caring for critically ill patients with the ABCDEF bundle: results of the ICU Liberation Collaborative in over 15,000 adults. *Crit Care Med*. 2019;47(1):3-14. doi:10.1097/CCM.0000000000003482

48. Brochard L, Slutsky A, Pesenti A. Mechanical ventilation to minimize progression of lung injury in acute respiratory failure. *Am J Respir Crit Care Med*. 2017;195(4):438-442. doi:10.1164/rccm.201605-1081CP

49. Abrams D, Javidfar J, Farrand E, et al. Early mobilization of patients receiving extracorporeal membrane oxygenation: a retrospective cohort study. *Crit Care*. 2014;18(1):R38. doi:10.1186/cc13746

50. Kurihara C, Walter JM, Singer BD, et al. Extracorporeal membrane oxygenation can successfully support patients with severe acute respiratory distress syndrome in lieu of mechanical ventilation. *Crit Care Med*. 2018;46(11):e1070-e1073. doi:10.1097/CCM.0000000000003354

51. Crotti S, Bottino N, Ruggeri GM, et al. Spontaneous breathing during extracorporeal membrane oxygenation in acute respiratory failure. *Anesthesiology*. 2017;126(4):678-687. doi:10.1097/ALN.0000000000001546

52. Mauri T, Grasselli G, Suriano G, et al. Control of respiratory drive and effort in extracorporeal membrane oxygenation patients recovering from severe acute respiratory distress syndrome. *Anesthesiology*. 2016;125(1):159-167. doi:10.1097/ALN.0000000000001103

53. London AJ. Equipoise in research: integrating ethics and science in human research. *JAMA*. 2017;317(5):525-526. doi:10.1001/jama.2017.0016

54. Lewis RJ, Angus DC. Time for clinicians to embrace their inner Bayesian? reanalysis of results of a clinical trial of extracorporeal membrane oxygenation. *JAMA*. 2018;320(21):2208-2210. doi:10.1001/jama.2018.16916

55. Fan E, Brodie D, Slutsky AS. Acute respiratory distress syndrome: advances in diagnosis and treatment. *JAMA*. 2018;319(7):698-710.

56. Schmidt M, Bailey M, Sheldrake J, et al. Predicting survival after extracorporeal membrane oxygenation for severe acute respiratory failure: the Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score. *Am J Respir Crit Care Med*. 2014;189(11):1374-1382. doi:10.1164/rccm.201311-2023OC

57. Schmidt M, Zogheib E, Rozé H, et al. The PRESERVE mortality risk score and analysis of long-term outcomes after extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *Intensive Care Med*. 2013;39(10):1704-1713. doi:10.1007/s00134-013-3037-2

58. Bellani G, Laffey JG, Pham T, et al; LUNG SAFE Investigators; ESICM Trials Group. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA*. 2016;315(8):788-800. doi:10.1001/jama.2016.0291

59. Gattinoni L, Tonetti T, Cressoni M, et al. Ventilator-related causes of lung injury: the mechanical power. *Intensive Care Med*. 2016;42(10):1567-1575. doi:10.1007/s00134-016-4505-2

60. Frank JA, Gutierrez JA, Jones KD, Allen L, Dobbs L, Matthay MA. Low tidal volume reduces epithelial and endothelial injury in acid-injured rat lungs. *Am J Respir Crit Care Med*. 2002;165(2):242-249. doi:10.1164/ajrccm.165.2.2108087

61. Grasso S, Stripoli T, Mazzone P, et al. Low respiratory rate plus minimally invasive extracorporeal Co2 removal decreases systemic and pulmonary inflammatory mediators in experimental acute respiratory distress syndrome. *Crit Care Med*. 2014;42(6):e451-e460. doi:10.1097/CCM.0000000000000312

62. Araos J, Alegria L, Garcia P, et al. Near-apneic ventilation decreases lung injury and fibroproliferation in an acute respiratory distress syndrome model with extracorporeal membrane oxygenation. *Am J Respir Crit Care Med*. 2019;199(5):603-612. doi:10.1164/rccm.201805-0869OC

63. Hager DN, Krishnan JA, Hayden DL, Brower RG; ARDS Clinical Trials Network. Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. *Am J Respir Crit Care Med*. 2005;172(10):1241-1245. doi:10.1164/rccm.200501-048CP

64. Needham DM, Colantuoni E, Mendez-Tellez PA, et al. Lung protective mechanical ventilation and two year survival in patients with acute lung injury: prospective cohort study. *BMJ*. 2012;344:e2124. doi:10.1136/bmj.e2124

65. Casalino-Matsuda SM, Nair A, Beitel GJ, Gates KL, Sporn PH. Hypercapnia inhibits autophagy and bacterial killing in human macrophages by increasing expression of Bcl-2 and Bcl-xL. *J Immunol*. 2015;194(11):5388-5396. doi:10.4049/jimmunol.1500150

66. Reis Miranda D, van Thiel R, Brodie D, Bakker J. Right ventricular unloading after initiation of venovenous extracorporeal membrane oxygenation. *Am J Respir Crit Care Med*. 2015;191(3):346-348. doi:10.1164/rccm.201408-1404LE

67. Nin N, Muriel A, Peñuelas O, et al; VENTILA Group. Severe hypercapnia and outcome of mechanically ventilated patients with moderate or severe acute respiratory distress syndrome. *Intensive Care Med*. 2017;43(2):200-208. doi:10.1007/s00134-016-4611-1

68. Goligher EC, Amato MBP, Slutsky AS. Applying precision medicine to trial design using physiology: extracorporeal CO_2 removal for acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2017;196(5):558-568. doi:10.1164/rccm.201701-0248CP

69. McNamee JJ, Gillies MA, Barrett NA, et al. pRotective vEntilation with veno-venouS lung assisT in respiratory failure: a protocol for a multicentre randomised controlled trial of extracorporeal carbon dioxide removal in patients with acute hypoxaemic respiratory failure. *J Intensive Care Soc*. 2017;18(2):159-169. doi:10.1177/1751143716681035

70. Mason DP, Thuita L, Nowicki ER, Murthy SC, Pettersson GB, Blackstone EH. Should lung transplantation be performed for patients on mechanical respiratory support? the US experience. *J Thorac Cardiovasc Surg*. 2010;139(3):765-773.e1. doi:10.1016/j.jtcvs.2009.09.031

71. Boyle AJ, Sklar MC, McNamee JJ, et al; International ECMO Network (ECMONet). Extracorporeal carbon dioxide removal for lowering the risk of mechanical ventilation: research questions and clinical potential for the future. *Lancet Respir Med*. 2018;6(11):874-884. doi:10.1016/S2213-2600(18)30326-6

72. Barbaro RP, Odetola FO, Kidwell KM, et al. Association of hospital-level volume of extracorporeal membrane oxygenation cases and mortality: analysis of the extracorporeal life support organization registry. *Am J Respir Crit Care Med*. 2015;191(8):894-901. doi:10.1164/rccm.201409-1634OC

73. Hayes D Jr, Tobias JD, Tumin D. Center volume and extracorporeal membrane oxygenation support at lung transplantation in the lung allocation score era. *Am J Respir Crit Care Med*. 2016;194(3):317-326. doi:10.1164/rccm.201511-2222OC

74. Bailey KL, Downey P, Sanaiha Y, et al. National trends in volume-outcome relationships for extracorporeal membrane oxygenation. *J Surg Res*. 2018;231:421-427. doi:10.1016/j.jss.2018.07.012

75. McCarthy FH, McDermott KM, Spragan D, et al. Unconventional volume-outcome associations in adult extracorporeal membrane oxygenation in the United States. *Ann Thorac Surg*. 2016;102(2):489-495. doi:10.1016/j.athoracsur.2016.02.009

76. Combes A, Brodie D, Bartlett R, et al; International ECMO Network (ECMONet). Position paper for the organization of extracorporeal membrane oxygenation programs for acute respiratory failure in adult patients. *Am J Respir Crit Care Med*. 2014;190(5):488-496. doi:10.1164/rccm.201404-0630CP

77. Abrams D, Garan AR, Abdelbary A, et al; International ECMO Network (ECMONet) and The Extracorporeal Life Support Organization (ELSO). Position paper for the organization of ECMO programs for cardiac failure in adults. *Intensive Care Med*. 2018;44(6):717-729. doi:10.1007/s00134-018-5064-5

78. Fletcher-Sandersjoo A, Frenckner B, Broman M. A single-center experience of 900 interhospital transports on extracorporeal membrane oxygenation. *Ann Thorac Surg*. 2019;107(1):119-127.

79. Salna M, Chicotka S, Biscotti M III, et al. Management of surge in extracorporeal membrane oxygenation transport. *Ann Thorac Surg*. 2018;105(2):528-534. doi:10.1016/j.athoracsur.2017.07.019

80. Bréchot N, Mastroianni C, Schmidt M, et al. Retrieval of severe acute respiratory failure patients on extracorporeal membrane oxygenation: any impact on their outcomes? *J Thorac Cardiovasc Surg*. 2018;155(4):1621-1629.e2. doi:10.1016/j.jtcvs.2017.10.084

81. Gillon SA, Rowland K, Shankar-Hari M, et al. Acceptance and transfer to a regional severe respiratory failure and veno-venous extracorporeal membrane oxygenation (ECMO) service: predictors and outcomes. *Anaesthesia*. 2018;73(2):177-186. doi:10.1111/anae.14083

82. Tipograf Y, Liou P, Oommen R, et al. A decade of interfacility extracorporeal membrane oxygenation transport. *J Thorac Cardiovasc Surg*. 2019;157(4):1696-1706. doi:10.1016/j.jtcvs.2018.09.139

83. Fan E, Brodie D. Higher volumes, better outcomes: the end or just the beginning of the story for extracorporeal membrane oxygenation? *Am J Respir Crit Care Med*. 2015;191(8):864-866. doi:10.1164/rccm.201503-0459ED

84. Zakhary BM, Kam LM, Kaufman BS, Felner KJ. The utility of high-fidelity simulation for training critical care fellows in the management of extracorporeal membrane oxygenation emergencies: a randomized controlled trial. *Crit Care Med*. 2017;45(8):1367-1373. doi:10.1097/CCM.0000000000002437

85. Machado FR. All in a day's work: equity vs equality at a public ICU in Brazil. *N Engl J Med*. 2016;375(25):2420-2421. doi:10.1056/NEJMp1610059

86. Phua J, Joynt GM, Nishimura M, et al; ACME Study Investigators; Asian Critical Care Clinical Trials Group. Withholding and withdrawal of life-sustaining treatments in low-middle-income versus high-income Asian countries and regions. *Intensive Care Med*. 2016;42(7):1118-1127. doi:10.1007/s00134-016-4347-y

87. Abrams DC, Prager K, Blinderman CD, Burkart KM, Brodie D. Ethical dilemmas encountered with the use of extracorporeal membrane oxygenation in adults. *Chest*. 2014;145(4):876-882. doi:10.1378/chest.13-1138

88. Brodie D, Curtis JR, Vincent JL, et al; participants in the Round Table Conference. Treatment limitations in the era of ECMO. *Lancet Respir Med*. 2017;5(10):769-770. doi:10.1016/S2213-2600(17)30263-1

89. Abrams DC, Prager K, Blinderman CD, Burkart KM, Brodie D. The appropriate use of increasingly sophisticated life-sustaining technology. *Virtual Mentor*. 2013;15(12):1050-1055. doi:10.1001/virtualmentor.2013.15.12.stas2-1312

90. DeMartino ES, Braus NA, Sulmasy DP, et al. Decisions to withdraw extracorporeal membrane oxygenation support: patient characteristics and ethical considerations. *Mayo Clin Proc*. 2019;94(4):620-627. doi:10.1016/j.mayocp.2018.09.020

91. Ramanathan K, Cove ME, Caleb MG, Teoh KL, Maclaren G. Ethical dilemmas of adult ECMO: emerging conceptual challenges. *J Cardiothorac Vasc Anesth*. 2015;29(1):229-233. doi:10.1053/j.jvca.2014.07.015

92. Truog RD, Thiagarajan RR, Harrison CH. Ethical dilemmas with the use of ECMO as a bridge to transplantation. *Lancet Respir Med*. 2015;3(8):597-598. doi:10.1016/S2213-2600(15)00233-7

93. Bein T, Brodie D. Understanding ethical decisions for patients on extracorporeal life support. *Intensive Care Med*. 2017;43(10):1510-1511. doi:10.1007/s00134-017-4781-5

94. Courtwright AM, Robinson EM, Feins K, et al. Ethics committee consultation and extracorporeal membrane oxygenation. *Ann Am Thorac Soc*. 2016;13(9):1553-1558. doi:10.1513/AnnalsATS.201511-757OC

95. Schmidt M, Pham T, Arcadipane A, et al; International ECMO Network (ECMONet), and the LIFEGARDS Study Group. Mechanical ventilation management during ECMO for ARDS: an international multicenter prospective cohort. *Am J Respir Crit Care Med*. 2019. doi:10.1164/rccm.201806-1094OC

96. Zakhary B, Fan E, Slutsky A. Pro: should patients with acute respiratory distress syndrome on veno-venous extracorporeal membrane oxygenation have ventilatory support reduced to the lowest tolerable settings? *Crit Care Med*. 2019. doi:10.1097/CCM.0000000000003835

97. Shekar K, Brodie D. Should Patients With Acute Respiratory Distress Syndrome on Venovenous Extracorporeal Membrane Oxygenation Have Ventilatory Support Reduced to the Lowest Tolerable Settings? No. *Crit Care Med*. 2019. doi:10.1097/CCM.0000000000003865

98. Brodie D, Vincent JL, Brochard LJ, et al; International ECMO Network (ECMONet). Research in extracorporeal life support: a call to action. *Chest*. 2018;153(4):788-791. doi:10.1016/j.chest.2017.12.024

99. Ranieri VM, Brodie D, Vincent JL. Extracorporeal organ support: from technological tool to clinical strategy supporting severe organ failure. *JAMA*. 2017;318(12):1105-1106. doi:10.1001/jama.2017.10108

Supplementary Online Content

Brodie D, Slutsky AS, Combes A. Extracorporeal life support for adults with respiratory failure and related indications: a narrative review. *JAMA*.
doi:10.1001/jama.2019.9302

eAppendix
eReferences
eFigure. ELSO Case and ECLS Publication Volume Trends

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix

The Physiology of Respiratory ECLS

Gas Exchange in Venovenous ECMO

Carbon dioxide removal

When providing venovenous ECMO support for a patient with respiratory failure, the device may be providing partial support to supplement the failing lungs or may even replace the gas exchange function of the lungs entirely. As with native lung gas exchange, CO_2 readily diffuses out of the blood traversing the device, and removal of CO_2 may be accomplished at relatively lower blood flow rates than what is required to oxygenate the blood. This is especially true when the partial pressure of arterial CO_2 is high, creating a stronger gradient for diffusion out of the membrane.

Oxygenation

The main limiting factor in providing adequate oxygenation is the blood flow rate through the device.[1] The reason is that, regardless of the amount of oxygen added to the blood by the membrane lung, the oxygen saturation exiting the membrane cannot exceed 100%. Further increasing the partial pressure of oxygen in the blood leaving the membrane lung, essentially increases only the amount of dissolved oxygen, which contributes relatively little to oxygen content. The exact oxygen content will depend on hemoglobin concentration, oxygen saturation (which should be near 100%, unless the membrane lung is not functioning optimally) and the amount of dissolved oxygen. When the well-saturated blood is reinfused into the patient, it encounters "native" venous deoxygenated blood returning to the heart. As the two streams mix, the essentially fully oxygenated blood coming from the device will combine with mixed venous "native" desaturated blood. The systemic oxygenation will depend on the ratio of the oxygen content delivered by these two sources. If the blood flowing from the extracorporeal circuit is a small fraction of the overall cardiac output, then the reinfused oxygenated blood will be overwhelmed by native deoxygenated blood and the impact on systemic oxygenation will be minimal. The key point is that it is the extracorporeal blood flow-to-systemic blood flow ratio (Q_E:Q_S) that determines oxygenation and a ratio of 0.6 or higher typically yields an arterial oxygen saturation of at least 90%.[1] It is important to note that this ratio is highly dynamic and dependent on the patient's cardiac output from moment to moment, just as it is dependent on changes made to the speed of the ECMO pump. If a patient becomes agitated or develops sepsis, for instance, and the cardiac output increases, the Q_E:Q_S ratio will decrease and, along with it, the arterial oxygen saturation. This is a key physiologic principle of venovenous ECMO. Venoarterial ECMO is more complex in this regard.

Typical venovenous ECMO blood flow rates range from 3-7 liters per minute. The amount of flow is determined by the speed of the ECMO pump (in rotations per minute) and limited by the size of the cannulae used. To withdraw blood from the patient requires negative drainage pressures. As this pressure becomes more negative, there is a greater potential for hemolysis. Because the positive pressures generated when reinfusing blood are less prone to creating hemolysis, the size of the drainage cannula is typically the limiting factor for the rate of blood flow that is possible while minimizing the potential for hemolysis.

Another factor in determining the ability of the device to provide oxygenation is the degree of recirculation.[2] A portion of the reinfused, oxygenated blood entering the right atrium may be inadvertently withdrawn back into the circuit due to the negative pressure within the venous drainage cannula; this is known as recirculation. The proportion of blood that is recirculating is not contributing to systemic oxygenation and thereby decreases the effective blood flow rate through the circuit. Attempts to minimize recirculation by, for instance, lowering the speed of the blood pump so as to decrease the negative pressure, drawing less reinfused blood back into the circuit; or by manipulating the position of the cannula, may be crucial in providing effective oxygenation to the patient. Other factors that may affect oxygenation include the size and functioning of the membrane lung, the set fraction of delivered oxygen from the device (FDO_2), the contribution of the native lung to gas exchange, and the patient's metabolic rate.

What is $ECCO_2R$?

ECMO utilizes high blood flow rates and requires relatively large membrane lungs to oxygenate blood and remove CO_2. Using an ECMO device at high blood flows, one could opt to decrease the FDO_2 to 21% such that the degree of oxygenation from the device is relatively lower, yet CO_2 removal would remain high. In other words, oxygenation can be virtually divorced from decarboxylation at high blood flow rates. Conversely, at lower and lower blood flow rates, the contribution to oxygenation begins to wane (lower Q_E:Q_S) and oxygenation is very sensitive to changes in blood flow rate. Whereas CO_2 removal is impervious to changes in blood flow rate at the range typically used in ECMO (3-7 liters per minute) and only begins to drop off at blood flow rates below this range. Putting numbers to these rates is complex because the rate of CO_2 removal varies according to the PCO_2 entering the membrane lung, the size and efficiency of the membrane lung, and the sweep gas flow rate.[3] Typical extracorporeal blood flow rates used when the goal is primarily CO_2 removal range from 200-1500 ml/min,[4] and devices which can provide only this range of blood flows are thought of as $ECCO_2R$ (not ECMO) devices. These devices may also frequently use smaller membrane lungs than are used in ECMO. However, since CO_2 removal may likewise be accomplished at high blood flow rates, it is not the blood flow rate that defines $ECCO_2R$, and neither is it the size of the cannula used (often referred to as a "catheter" when smaller sizes are used for lower blood flow rates with $ECCO_2R$). $ECCO_2R$ is primarily defined by the intention of the clinician. It's more a matter of the physiologic goal of extracorporeal support. If initiating support for hypercapnic respiratory failure without substantial need for extracorporeal oxygenation, for instance, or for moderate ARDS only to decrease the $PaCO_2$, without an intention to provide significant oxygenation, then the clinician is providing $ECCO_2R$.

Venoarterial ECMO in the Context of Mechanical Circulatory Support

Short-term Mechanical Circulatory Support for cardiogenic shock

Temporary circulatory support (TCS) with short-term mechanical circulatory support (MCS) devices, which includes venoarterial ECMO, has become the cornerstone of the management of patients with severe or refractory cardiogenic shock, although their use only received a Class IIb recommendation from the European Society of Cardiology.[5] Accepted medical indications for MCS may be classified as follows: acute myocardial infarction complicated by cardiogenic shock, acute decompensated heart failure with refractory cardiogenic shock, post-cardiac surgery cardiogenic shock, fulminant myocarditis, cardiotoxic drug intoxication, stress-induced cardiomyopathy, cardiac arrest (extracorporeal cardiopulmonary resuscitation, known as ECPR), post-cardiac arrest resuscitation syndrome, decompensated pulmonary vascular disease, or massive pulmonary embolism.[6-9] Many of these patients receive a device as salvage therapy after having already developed signs of refractory cardiogenic shock with multi-organ failure. In these situations, mechanical assistance is used as a bridge to decision-making if the patient survives the first days of support. In patients with potentially reversible etiologies of heart failure (e.g. myocarditis, myocardial stunning post-myocardial infarction), a short-term device may also be used as a bridge to cardiac function recovery.[10-12] Earlier intervention with MCS devices, prior to the onset of multi-organ failure is preferred.

The use of the intra-aortic balloon pump (IABP), which had been the only MCS device widely available for almost five decades, has markedly decreased recently following the publication of the IABP-SHOCK II trial. In this study conducted in patients with cardiogenic shock complicating acute myocardial infarction, there was no difference in 30-day mortality between patients randomized to IABP versus conventional treatment.[13] The utility of IABP in other cardiogenic shock populations remains unclear.

In the last decade, venoarterial ECMO has been increasingly used for cardiogenic shock since it provides both respiratory and cardiac support, is easy to insert at the bedside using percutaneous peripheral vascular cannulation[14], provides stable flow rates, and is associated with less organ failure after implantation compared to large biventricular assist-devices that require open-heart surgery. Other short-term MCS devices include short-term ventricular assist devices (VADs), such as the Impella (ABIOMED Inc., Danvers, MA, USA), a catheter-based axial pump positioned in a retrograde fashion across the aortic valve into the left ventricle, and the TandemHeart (LivaNova, London, UK), an extracorporeal centrifugal pump which drains blood from the left atrium using a trans-septal approach, that is, a cannula introduced via the femoral vein and extending across the inter-atrial septum, pumping the blood back into the femoral artery. Compared to venoarterial ECMO, these systems are more expensive, do not provide respiratory support and are not easily adapted to patients with severe biventricular failure. Long-term VAD support and total artificial heart devices are also available for support outside the ICU or hospital.

Venoarterial ECMO: the Basics

The use of venoarterial ECMO in adults is also growing rapidly, including when used as extracorporeal cardiopulmonary resuscitation, known as ECPR (eFigure, A).[15] Venoarterial ECMO is typically achieved with a femoral venous drainage cannula and a return cannula in the contralateral or ipsilateral femoral artery (although several other configurations may be used). In this configuration, the oxygenated reinfused blood travels retrograde up the aorta toward the heart. When there is little or no native cardiac function, the retrograde reinfused blood reaches the aortic arch and perfuses all the organs of the body along the way. If, however, there is a degree of native cardiac function (or native function is recovering), then the retrograde flow *competes* directly with this native flow and the degree to which the reinfused blood extends up the aorta depends on the relative force of the two competing streams of blood.

Competitive Flow in Venoarterial ECMO

This competitive flow in peripheral venoarterial ECMO results in a *mixing point*, the point at which the two flows meet. The mixing point itself is quite dynamic, varying with the relative strength of the native cardiac and ECMO flows as well as the distribution of systemic vascular resistance. Native flow depends on cardiac contractility, pre-load (which is lowered by the act of draining blood into the ECMO circuit and reinfusing it directly into the arterial circulation), and afterload, which is increased by directing a jet of blood back toward the aortic valve. Medications (e.g. inotropes) and the addition of other mechanical circulatory support (MCS) devices may modulate the native cardiac flow. The ECMO blood flow is, of course, dependent on the amount of blood drained and reinfused and may be modulated by the pump (and limited by the size of the cannulae, especially the drainage cannula).

The concept of competitive flow is important for understanding the afterload imposed on a failing or recovering heart with venoarterial ECMO. When the heart is weak or non-functioning, it explains how the unopposed ECMO blood flow can shut the aortic valve resulting in stasis and potentially clot formation within the left ventricle or other cardiac chambers (a devastating complication). However, the concept takes on added significance when native gas exchange through the patient's lungs is compromised sufficiently such that native cardiac output is deoxygenated. This may occur if there is intrinsic lung disease or if the added afterload results in frank pulmonary edema, for instance. In such a case, residual native cardiac output delivers deoxygenated blood to the mixing point and, most importantly, will include the coronary and carotid arteries if the mixing point is far enough from the heart, resulting in poor oxygen delivery to the heart and brain, respectively, despite the delivery of oxygenated blood from the ECMO device into the aorta on the other side of the mixing point. This split in oxygenation between the upper and lower circulations has been termed differential hypoxia[16] and the Harlequin Syndrome, among other terms.

Competitive flow is not eliminated by reinfusion into an axillary, subclavian or innominate artery. Reinfusing in a physiologic direction by directing blood into a cardiac chamber, such as the left atrium, or to the proximal aorta, will effectively eliminate this issue.

The Convergence of Venovenous and Venoarterial ECMO

Numerous other more complex configurations exist to support a wide range of physiologic needs. Venovenous-arterial ECMO, for instance, drains venous blood in the same fashion as venovenous ECMO, but splits the reinfused blood, sending it into two separate cannulae connected by a Y-connector, so that a portion of the blood enters the arterial system to provide circulatory (mean arterial blood pressure) support and the remainder enters the venous system through a separate cannula to provide a degree of pulmonary (oxygenation and ventilation) support, if both are needed. Venovenous-arterial ECMO is another strategy to overcome the issue of competitive flow when native lung gas exchange is sufficiently impaired.

Venting the Left Ventricle

The afterload imposed on the left ventricle by retrograde venoarterial ECMO blood flow may result in increased left ventricle pressures, left ventricular distension and frank pulmonary edema. It may increase myocardial oxygen demand and, as previously mentioned, it can close the aortic valve.[17] Unloading the left ventricle, known as venting, in patients at risk for such complications, is of paramount importance in affected patients. The first strategy should aim at decreasing left ventricular afterload by decreasing the

ECMO blood flow and promoting left ventricular ejection with or without inotropes. Combining an IABP with venoarterial ECMO, which decreases afterload when it deflates, has also been shown to decrease left ventricular pressures and associated pulmonary edema.[18-21] Direct venting of left-sided cardiac chambers or the pulmonary artery is a more common means of venting than, for instance, percutaneous balloon atrial septostomy to open a left-to-right atrial shunt. Perhaps the most potent form of venting may be accomplished with the use of a second MCS device in conjunction with venoarterial ECMO, in particular the Impella.[22,23]

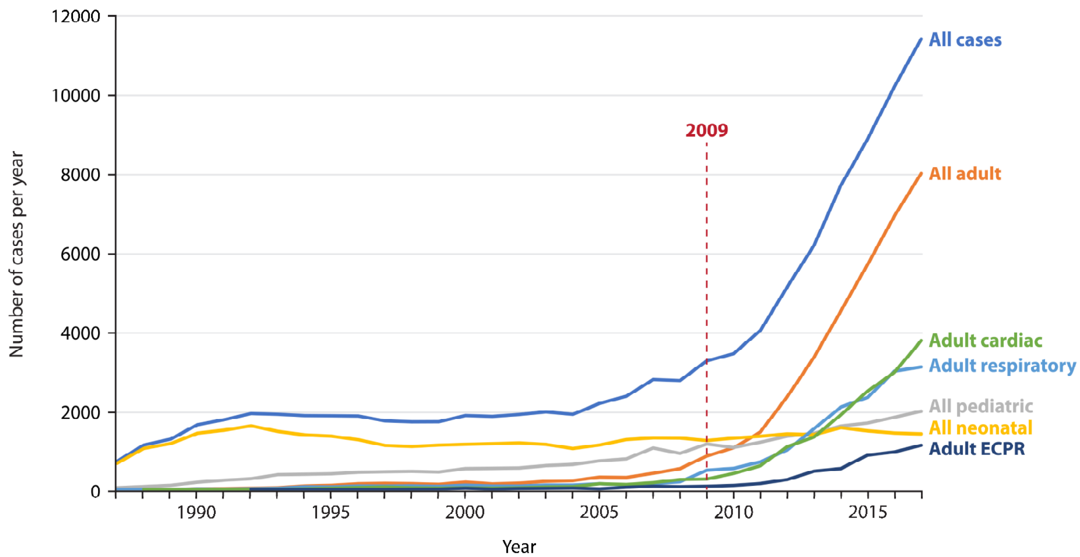
eReferences

1. Schmidt M, Tachon G, Devilliers C, et al. Blood oxygenation and decarboxylation determinants during venovenous ECMO for respiratory failure in adults. *Intensive Care Med.* 2013;39(5):838-846.
2. Abrams D, Bacchetta M, Brodie D. Recirculation in venovenous extracorporeal membrane oxygenation. *ASAIO J.* 2015;61(2):115-121.
3. Strassmann S, Merten M, Schafer S, et al. Impact of sweep gas flow on extracorporeal CO2 removal (ECCO2R). *Intensive care medicine experimental.* 2019;7(1):17.
4. Boyle AJ, Sklar MC, McNamee JJ, et al. Extracorporeal carbon dioxide removal for lowering the risk of mechanical ventilation: research questions and clinical potential for the future. *The Lancet Respiratory medicine.* 2018;6(11):874-884.
5. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J.* 2016;37(27):2129-2200.
6. Ouweneel DM, Eriksen E, Sjauw KD, et al. Percutaneous Mechanical Circulatory Support Versus Intra-Aortic Balloon Pump in Cardiogenic Shock After Acute Myocardial Infarction. *J Am Coll Cardiol.* 2017;69(3):278-287.
7. Stretch R, Sauer CM, Yuh DD, Bonde P. National trends in the utilization of short-term mechanical circulatory support: incidence, outcomes, and cost analysis. *J Am Coll Cardiol.* 2014;64(14):1407-1415.
8. Maekawa K, Tanno K, Hase M, Mori K, Asai Y. Extracorporeal cardiopulmonary resuscitation for patients with out-of-hospital cardiac arrest of cardiac origin: a propensity-matched study and predictor analysis. *Crit Care Med.* 2013;41(5):1186-1196.
9. Sheu JJ, Tsai TH, Lee FY, et al. Early extracorporeal membrane oxygenator-assisted primary percutaneous coronary intervention improved 30-day clinical outcomes in patients with ST-segment elevation myocardial infarction complicated with profound cardiogenic shock. *Crit Care Med.* 2010;38(9):1810-1817.
10. Brechot N, Luyt CE, Schmidt M, et al. Venoarterial extracorporeal membrane oxygenation support for refractory cardiovascular dysfunction during severe bacterial septic shock. *Crit Care Med.* 2013;41(7):1616-1626.
11. Mirabel M, Luyt CE, Leprince P, et al. Outcomes, long-term quality of life, and psychologic assessment of fulminant myocarditis patients rescued by mechanical circulatory support. *Crit Care Med.* 2011;39(5):1029-1035.
12. Muller G, Flecher E, Lebreton G, et al. The ENCOURAGE mortality risk score and analysis of long-term outcomes after VA-ECMO for acute myocardial infarction with cardiogenic shock. *Intensive Care Med.* 2016;42(3):370-378.
13. Thiele H, Zeymer U, Neumann FJ, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med.* 2012;367(14):1287-1296.
14. Danial P, Hajage D, Nguyen LS, et al. Percutaneous versus surgical femoro-femoral veno-arterial ECMO: a propensity score matched study. *Intensive Care Med.* 2018;44(12):2153-2161.
15. Extracorporeal Life Support Organization. ECLS registry report, international summary. January 2019.
16. Hou X, Yang X, Du Z, et al. Superior vena cava drainage improves upper body oxygenation during veno-arterial extracorporeal membrane oxygenation in sheep. *Crit Care.* 2015;19:68.
17. Meani P, Gelsomino S, Natour E, et al. Modalities and Effects of Left Ventricle Unloading on Extracorporeal Life support: a Review of the Current Literature. *Eur J Heart Fail.* 2017;19 Suppl 2:84-91.
18. Aso S, Matsui H, Fushimi K, Yasunaga H. The Effect of Intraaortic Balloon Pumping Under Venoarterial Extracorporeal Membrane Oxygenation on Mortality of Cardiogenic Patients: An Analysis Using a Nationwide Inpatient Database. *Crit Care Med.* 2016;44(11):1974-1979.

19. Petroni T, Harrois A, Amour J, et al. Intra-aortic balloon pump effects on macrocirculation and microcirculation in cardiogenic shock patients supported by venoarterial extracorporeal membrane oxygenation*. *Crit Care Med.* 2014;42(9):2075-2082.
20. Brechot N, Demondion P, Santi F, et al. Intra-aortic balloon pump protects against hydrostatic pulmonary oedema during peripheral venoarterial-extracorporeal membrane oxygenation. *European heart journal Acute cardiovascular care.* 2018;7(1):62-69.
21. Russo JJ, Aleksova N, Pitcher I, et al. Left Ventricular Unloading During Extracorporeal Membrane Oxygenation in Patients With Cardiogenic Shock. *J Am Coll Cardiol.* 2019;73(6):654-662.
22. Schrage B, Burkhoff D, Rubsamen N, et al. Unloading of the Left Ventricle During Venoarterial Extracorporeal Membrane Oxygenation Therapy in Cardiogenic Shock. *JACC Heart failure.* 2018;6(12):1035-1043.
23. Pappalardo F, Schulte C, Pieri M, et al. Concomitant implantation of Impella((R)) on top of veno-arterial extracorporeal membrane oxygenation may improve survival of patients with cardiogenic shock. *Eur J Heart Fail.* 2017;19(3):404-412.

eFigure. ELSO Case and ECLS Publication Volume Trends

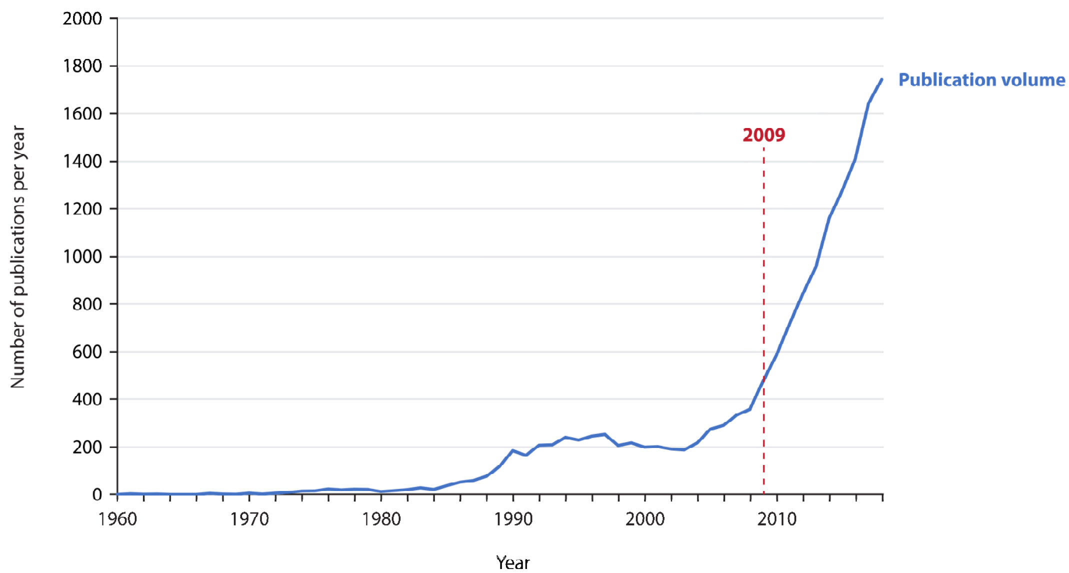
eFigure A: ELSO case volume trends: 1987 - 2017



eFigure A: Extracorporeal life support (ECLS) case volume trends: 1987-2017

Data obtained from Extracorporeal Life Support Organization (ELSO) International Summary, January 2019. Trends are shown for all cases of ECLS in the registry by year (blue line), including adult, pediatric and neonatal age groups and all respiratory, cardiac and ECPR cases; all adult ECLS cases (orange line), including respiratory, cardiac and ECPR; all pediatric ECLS cases (grey line); all neonatal ECLS cases (yellow line); and a breakdown of adult cases into respiratory (light blue), cardiac (green) and ECPR (dark blue). Data collection for the registry is best characterized since 1987. Data reflect those cases voluntarily entered into the ELSO registry by member centers and do not represent all cases performed worldwide. An inflection point is noted soon after 2009, with subsequent volume rising most rapidly for adult respiratory and cardiac ECLS, with less pronounced increases in adult ECPR and in pediatric ECLS, whereas neonatal ECLS volume remained stable during this period of time. Because the International Summary in January 2019 was incomplete for 2018 cases, 2018 is not included. However, the overall trend for 2018 continues to show an increase in the use of ECLS.

eFigure B: Number of ECLS publications by year: 1960 - 2018



eFigure B: Number of extracorporeal life support (ECLS) publications by year: 1960-2018

Number of publications regarding ECLS, by year, for all indications and all age groups. Derived by searching PubMed, according to the following search terms: *extracorporeal membrane oxygenation, extracorporeal carbon dioxide removal, extracorporeal life support, extracorporeal cardiopulmonary resuscitation, ECMO,* $ECCO_2R$*, ECLS and ECPR*. Search terms were each separated by "OR". PubMed Publication Dates Custom search was used, by year (January 1st through December 31st of each year) 1960 through 2018. Search date January 27, 2019.