

ANESTHESIOLOGY

Extracorporeal Membrane Oxygenation for Respiratory Failure

Michael Quintel, M.D., Robert H. Bartlett, M.D.,
Michael P. W. Grocott, F.R.C.P.,
Alain Combes, M.D., Ph.D., Marco V. Ranieri, M.D.,
Massimo Baiocchi, M.D., Stefano Nava, M.D.,
Daniel Brodie, M.D., Luigi Camporota, M.D., Ph.D.,
Francesco Vasques, M.D., Mattia Busana, M.D.,
John J. Marini, M.D., Luciano Gattinoni, F.R.C.P.

ANESTHESIOLOGY 2020; XXX:00–00

The term *extracorporeal membrane oxygenation* is often used to refer to various extracorporeal procedures that support the lungs, the heart, or both. Whereas **cardiovascular support** requires a **veno-arterial** approach to temporarily relieve or even replace the heart function, lung support is mostly performed with veno-venous access. This review focuses on the use of **veno-venous** modes as **high-flow** or **low-flow** procedures as lung support, describing their indications, related physiology, and associated technical issues.

Historical Development

Cardiopulmonary bypass using a heart/lung machine, which enabled the entire field of cardiac surgery, was first performed by the surgeon John **Gibbon** in **1953** at the **Mayo** Clinic (Rochester, Minnesota). However, the original heart/lung machine caused lethal **damage to blood cells** after a few hours. This problem was solved in the **1960s** by the development of **artificial membrane lungs** (oxygenators). Extracorporeal support was first used outside the operating theater for respiratory support in 1971,¹ cardiac support in 1972,² and newborn and neonatal respiratory failure in 1975.³ From 1975 to 1985, prolonged extracorporeal circulation was **perfected** for **neonatal** respiratory failure. In this population its use grew

ABSTRACT

This review focuses on the use of **veno-venous extracorporeal membrane oxygenation** for respiratory failure across all blood flow ranges. Starting with a short overview of historical development, aspects of the physiology of gas exchange (*i.e.*, oxygenation and decarboxylation) during extracorporeal circulation are discussed. The mechanisms of phenomena such as recirculation and shunt playing an important role in daily clinical practice are explained.

Treatment of refractory and symptomatic hypoxemic respiratory failure (*e.g.*, acute respiratory distress syndrome [ARDS]) currently represents the main indication for **high-flow veno-venous**-extracorporeal membrane oxygenation. On the other hand, **lower-flow** extracorporeal **carbon dioxide removal** might potentially help to avoid or attenuate ventilator-induced lung injury by allowing reduction of the energy load (*i.e.*, driving pressure, mechanical power) transmitted to the lungs during mechanical ventilation or spontaneous ventilation. In the latter context, extracorporeal carbon dioxide removal plays an **emerging role in the treatment of chronic obstructive pulmonary disease** patients during acute exacerbations. Both applications of extracorporeal lung support raise important **ethical** considerations, such as **likelihood** of ultimate **futility** and **end-of-life** decision-making. The review concludes with a brief overview of potential technical developments and persistent challenges.

(ANESTHESIOLOGY 2020; XXX:00–00)

rapidly because with just a **few days** of **assistance** the changing physiologic conditions of the infant allowed outcomes in the most expert centers to change from **90% mortality** to **90% healthy survival**. The technique was called extracorporeal membrane oxygenation. During this development, most technical principles that addressed vascular access, physiology, anticoagulation, gas exchange, and patient management were established.⁴ By 1986, 715 cases from 18 centers were reported with an 81% survival rate.⁵ Based on prospective randomized trials,⁶ extracorporeal membrane oxygenation became the standard rescue intervention for infants with severe respiratory failure unresponsive to conventional care. The Extracorporeal Life Support Organization (ELSO; Ann Arbor, Michigan) was established in 1989 as a consortium of centers where extracorporeal membrane oxygenation was performed and studied.

After its successful application to neonates, the concept of extracorporeal membrane oxygenation was extended to children and adults with severe respiratory or cardiac

Submitted for publication January 29, 2019. Accepted for publication February 3, 2020. From the Department of Anesthesiology and Intensive Care Medicine, University of Göttingen Medical Center, Göttingen, Germany (M.Q., M.B., L.G.); University of Michigan, Ann Arbor, Michigan (R.H.B.); Perioperative Medicine and Critical Care Research Group, Southampton NIHR Biomedical Research Centre, University Hospital Southampton/University of Southampton, Southampton, United Kingdom (M.P.W.G.); Sorbonne Université, INSERM, UMRS_1166-ICAN, Institute of Cardiometabolism and Nutrition, Paris, France (A.C.); Service of Intensive Care, Institute of Cardiology, APHP Hôpital Pitié-Salpêtrière, Paris, France (A.C.); Alma Mater Studiorum – Department of Medical and Surgical Sciences, University of Bologna, Anesthesia and Intensive Care Medicine, Policlinico di Sant'Orsola, Bologna, Italy (M.V.R., M.B.); Department of Clinical, Integrated, and Experimental Medicine (DIMES), Respiratory and Critical Care, Sant'Orsola Malpighi Hospital, Bologna, Italy (S.N.); Department of Medicine, Columbia University College of Physicians and Surgeons, and New York Presbyterian Medical Center, New York, New York (D.B.); Department of Adult Critical Care, Guy's and St. Thomas' NHS Foundation Trust, King's Health Partners, and Division of Centre of Human Applied Physiological Sciences, King's College London, London, United Kingdom (L.C., F.V.); Department of Pulmonary and Critical Care Medicine, Regions Hospital and University of Minnesota, Minneapolis/St. Paul, Minnesota (J.J.M.).

Copyright © 2020, the American Society of Anesthesiologists, Inc. All Rights Reserved. Anesthesiology 2020; XXX:00–00. DOI: 10.1097/ALN.0000000000003221

failure. The changing patterns of the use of extracorporeal membrane oxygenation are seen in the ELSO registry report (<https://www.else.org/Registry/Statistics.aspx>; accessed February 18, 2020). In 1990, the most common indication for extracorporeal membrane oxygenation was neonatal respiratory failure. In 2018, most such cases were cardiac and lung support in children and adults, and fewer than 10% were neonatal respiratory failure (fig. 1). Further research on support by an artificial lung and pump led to the development of techniques such as extracorporeal carbon dioxide removal,⁷ extracorporeal cardiopulmonary resuscitation,⁸ and bridging to and from heart or lung transplantation. The first trial of the use of extracorporeal membrane oxygenation for severe respiratory failure⁹ failed to prove the expected clinical benefit, essentially sidelining this technology for adult patients. In 2008 through 2009, due to the H1N1 flu pandemic¹⁰ and the availability of safer and simpler devices, extracorporeal membrane oxygenation was rediscovered. In 2009 the first and so far only successful conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR) trial for ARDS¹¹ had been published. CESAR is just one of 13 prospective trials that have been conducted testing extracorporeal membrane oxygenation for respiratory failure. The most recent trial of extracorporeal membrane oxygenation in ARDS (ECMO [extracorporeal membrane oxygenation] to rescue Lung Injury in severe

ARDS (EOLIA)),¹² despite failing to prove statistically that extracorporeal membrane oxygenation used in ARDS reduced mortality, did demonstrate that this therapy can be applied safely and causes no additional harm. Additionally, the EOLIA results give the hint that extracorporeal membrane oxygenation might not offer just a rescue therapy; earlier use in the course of ARDS might be beneficial (table 1).

Yet, at the time of this writing, extracorporeal membrane oxygenation continues to represent the final step in the algorithm that defines management of severe respiratory failure for all age groups (fig. 2).

Technical Requirements

A veno-venous extracorporeal membrane oxygenation circuit consists of a vascular draining access to the inferior or superior vena cava, a blood pump, a membrane lung, a blood warmer, and a vascular access to return the oxygenated and decarboxylated blood into the venous circulation (inferior or superior vena cava, depending on the cannulation strategy used). In the context of conventional high-flow veno-venous extracorporeal membrane oxygenation, the most common cannulation configuration is femoro-jugular (drainage from the inferior vena cava, return to the superior vena cava), as the lower half of the body usually accommodates the majority of the cardiac output,¹³ easily allowing diversion of a broad range of extracorporeal blood flows. The size

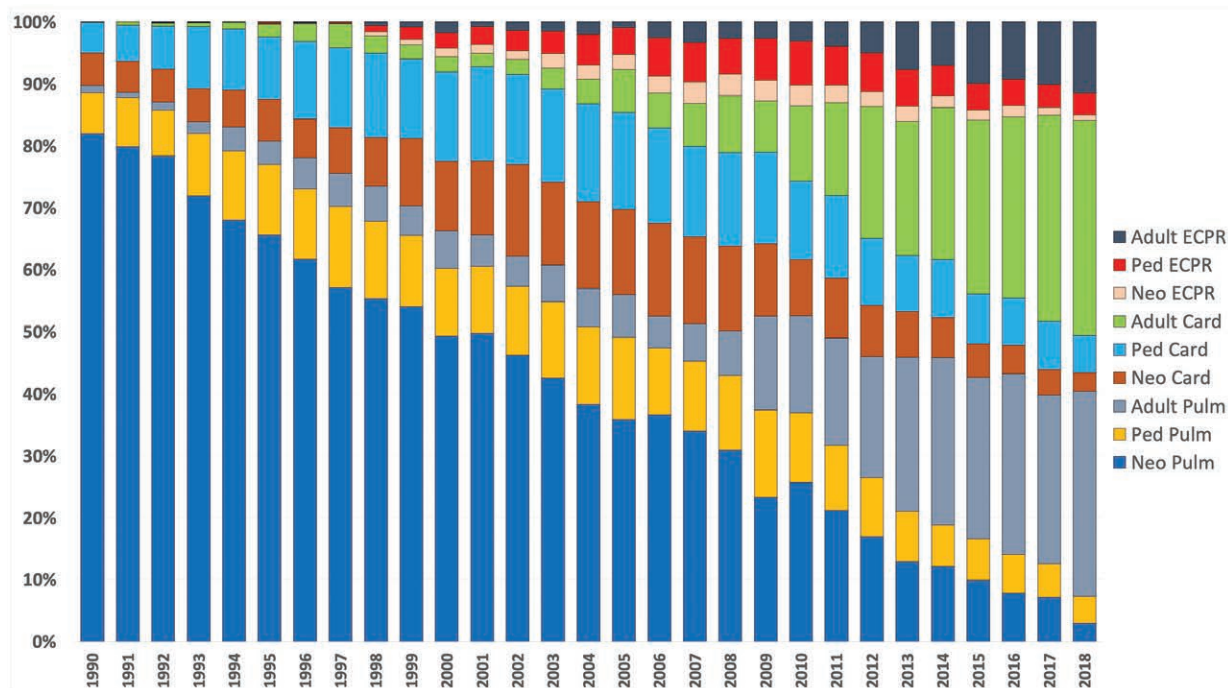


Fig. 1. Indications for extracorporeal membrane oxygenation from the Extracorporeal Life Support Organization (ELSO) Registry since 1990. EPCR, extracorporeal cardiopulmonary resuscitation.

Table 1. Summary Table of the Cornerstone Studies that Made the History of ECMO and ECCO₂R

Technology	Veno-venous ECMO				ECCO ₂ R		
Study	Zapol <i>et al.</i>	Davies <i>et al.</i>	Peek <i>et al.</i> (CESAR)	Combes <i>et al.</i> (EOLIA)	Gattinoni <i>et al.</i>	Morris <i>et al.</i>	Combes <i>et al.</i> (SUPERNOVA)
Journal	JAMA	JAMA	Lancet	NEJM	JAMA	Am J Respir Crit Care Med	Intensive Care Med
Year	1979	2009	2009	2018	1986	1994	2009
Patients, no.	150	201	180	240	43	40	95

Rationale	Treat a Life-threatening Hypoxemia				Lung Rest in ARDS		
Mortality ECMO vs. nonECMO	90.5% vs. 91.7%	23% vs. 9%	37% vs. 45%	37% vs. 47%	NA	66.7% vs. 57.9%	NA
Main finding	High mortality, young technology	H1N1 Influenza, it promoted an ECMO resurgence	First positive ECMO trial	Despite not significant, ECMO is safe	The lung can effectively be kept at rest	First ECCO ₂ R trial in ARDS, but a negative one	ECCO ₂ R in ARDS is possible, but still burdened by side effects

ARDS, acute respiratory distress syndrome; CESAR, conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure; ECCO₂R, extracorporeal carbon dioxide removal; ECMO, extracorporeal membrane oxygenation; EOLIA, ECMO to rescue Lung Injury in severe ARDS; SUPERNOVA, Strategy of Ultra-Protective Lung Ventilation with extracorporeal CO₂ removal for new-onset Moderate to severe ARDS.

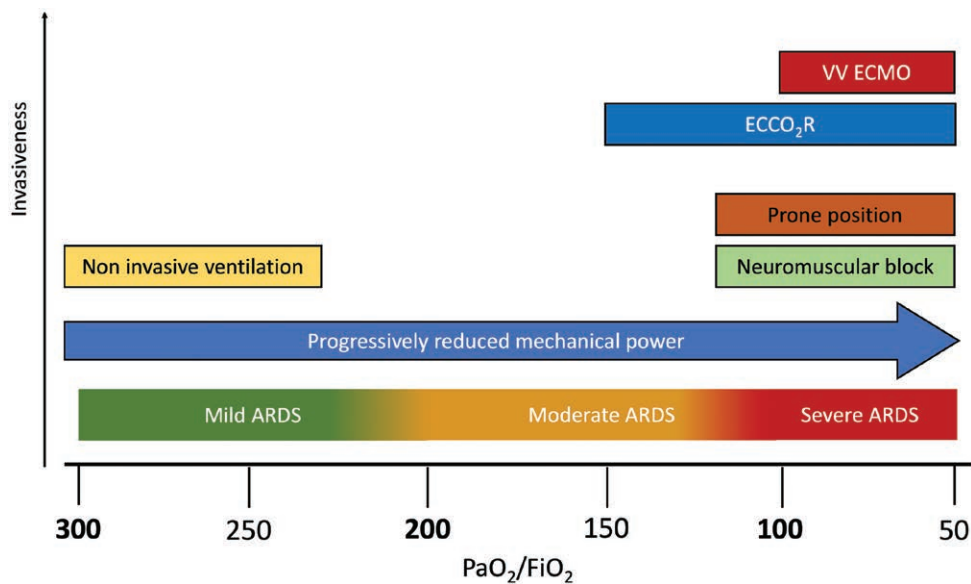


Fig. 2. Sequence of interventions in the course of acute respiratory distress syndrome (ARDS) in current clinical practice, according to the Berlin definition. ECCO₂R, extracorporeal carbon dioxide removal; VV ECMO, veno-venous extracorporeal membrane oxygenation.

of cannulas varies widely (from 16 to 32 Fr¹⁴), the choice depending on the required blood flow and the anatomy of the patient.¹⁵ Although the cannulas are placed femorally or jugularly, the draining port should be placed close the right atrium to take advantage of the higher flow of the systemic circulation. For this reason, cannulation should be guided by ultrasound (transthoracic echocardiography or transesophageal echocardiography) or fluoroscopy. In addition, a double lumen (so-called bicaval) cannula is available to perform

conventional high-flow veno-venous extracorporeal membrane oxygenation. These rather thick cannulas are placed in the internal jugular vein and positioned so that the two draining ports are located in the superior and inferior vena cava, whereas the outflow of the return port in the middle of this device ideally is directed toward the right atrium. In contrast, a single double lumen cannula designed on the model of renal replacement therapy catheters represents the access of choice¹⁶ for extracorporeal carbon dioxide removal, especially

for quite low blood flows (*i.e.*, 400 ml/min). A recent position paper from ELSO clearly states a uniform nomenclature for all the possible cannulation setups both for veno-venous and veno-arterial extracorporeal membrane oxygenation.¹⁷

Extracorporeal membrane oxygenation blood pumps are of either roller or centrifugal pump design. Roller pumps are simple and inexpensive, but impose the serious hazard of a potential vascular blowout if the outlet is occluded. Centrifugal pumps are more complex and expensive, and some reports suggest that they might cause more hemolysis.^{18,19} Moreover, a recent article highlighted the serious shear stress acting on the erythrocyte when the currently most widespread centrifugal pumps are used at low flow rates (less than 2 l/min).²⁰

Nonetheless, they are generally preferred because of their higher safety profile and demonstrated lower requirements for anticoagulation.¹⁵

Current membrane oxygenators have hollow fiber architecture. After being drained from the venous circulation, blood flows across a dense mat of small pipes (the hollow fibers) through which the sweep gas flows. The gas flow composition is regulated by a gas blender to achieve the desired inspired fraction of oxygen (FiO_2). Because the blood drained from the body has the tendency to disperse heat in the extracorporeal circulation, warming is required. Therefore, this device pushes warm water in separate, non permeable pipes into the membrane lung. To enhance efficacy of heat transfer and gas exchange, both water and sweep gas are directed countercurrently to blood flow. High efficiency heat exchange allows fine regulation of body temperature, an effect that in other settings can help manage hyperthermia or extreme hypothermia.²¹

Physiology of Extracorporeal Gas Exchange

Movement of gases within the membrane lung is based on diffusion: Oxygen moves from the fiber lumens into the blood, whereas the physically dissolved carbon dioxide in blood passes from the blood into the fibers where it is diluted and removed by the sweep gas.²²

Oxygenation

At the outlet of the membrane lung, the blood should have a PO_2 ranging between 100 and 500 mmHg, depending on the FiO_2 set at the gas blender. The net oxygen delivery provided by the extracorporeal circulation is described by the following mass transfer formula:

$$VO_{2ECMO} = ECBF \cdot (CaO_{2outlet} - CaO_{2inlet}) \quad (1)$$

Equation 1: VO_{2ECMO} is the oxygen transport of the extracorporeal circuit in ml/min. ECBF is extracorporeal blood flow. CaO_2 is the content of oxygen in ml per dl of whole blood.

Consequently, two ways to increase the oxygen provided by extracorporeal membrane oxygenation (VO_{2ECMO}) are as follows:

1. Increase the blood flow.
2. Increase the oxygen content difference between the inlet and the outlet of the membrane lung.

Whereas increasing the blood flow is simply a matter of turning a knob (given that a sufficient venous drainage flow is achievable), increasing the oxygen content difference across the membrane lung is not straightforward. At first, one might be tempted to raise the FiO_2 of the extracorporeal membrane oxygenation sweep gas. However, the solubility of oxygen in whole blood is limited by its binding capacity to hemoglobin. When hemoglobin is completely saturated, the increase in PO_2 that can be achieved (even by pure oxygen) leads only to a minor increase of oxygen delivery at the expense of alveolar nitrogen loss and consequent alveolar instability.²³ This constraint is reflected by the oxygen content equation:

$$C_aO_2 = 1.39 \cdot [Hb] \cdot Sat_{Hb} + (0.003 \cdot PO_2) \quad (2)$$

Equation 2: C_aO_2 is the content of oxygen in ml per dl of whole blood. $[Hb]$ is the concentration of hemoglobin in g/dl. Sat_{Hb} is saturation of the hemoglobin, in fraction (*i.e.*, 0.99). PO_2 is partial pressure of oxygen in mmHg.

In fact, raising blood PO_2 from 100 mmHg to 500 mmHg causes content to increase just 1.2 ml/dl.

A more rational approach would be to restore a more physiologic level of hemoglobin individualized on the specific patient's need. In fact, it makes little sense to cannulate a patient because of insufficient oxygen delivery when his innate oxygen carriage is far from the physiologic level, as it is often seen in extracorporeal membrane oxygenation patients.²⁴

After oxygenation in the membrane lung, the blood returns to the systemic circulation. In the right atrium, it mixes with the blood returning from the periphery that was not exposed to the extracorporeal circuit. Here the ratio between the extracorporeal membrane oxygenation blood flow and cardiac output ($ECBF/Q_c$) becomes important, as the mixed venous blood composition simply equals the average of the oxygen content of the blood returning from the membrane lung (high oxygen content) and from the periphery (low oxygen content), weighted for their respective flows. The sum of these equals the total cardiac output. The higher the flow from the extracorporeal membrane oxygenation circuit and the lower the flow from the periphery, the greater will be the saturation achieved in the mixed venous blood entering the pulmonary artery.

Blood flowing through the aerated "baby lung"^{25,26} (the remaining ventilable lung which, being not filled with edema/inflammatory infiltrates, can still participate in gas exchange) equilibrates with the alveolar PO_2 , depending on the FiO_2 at which the natural lung is ventilated. However, a higher oxygen saturation in the pulmonary artery blood

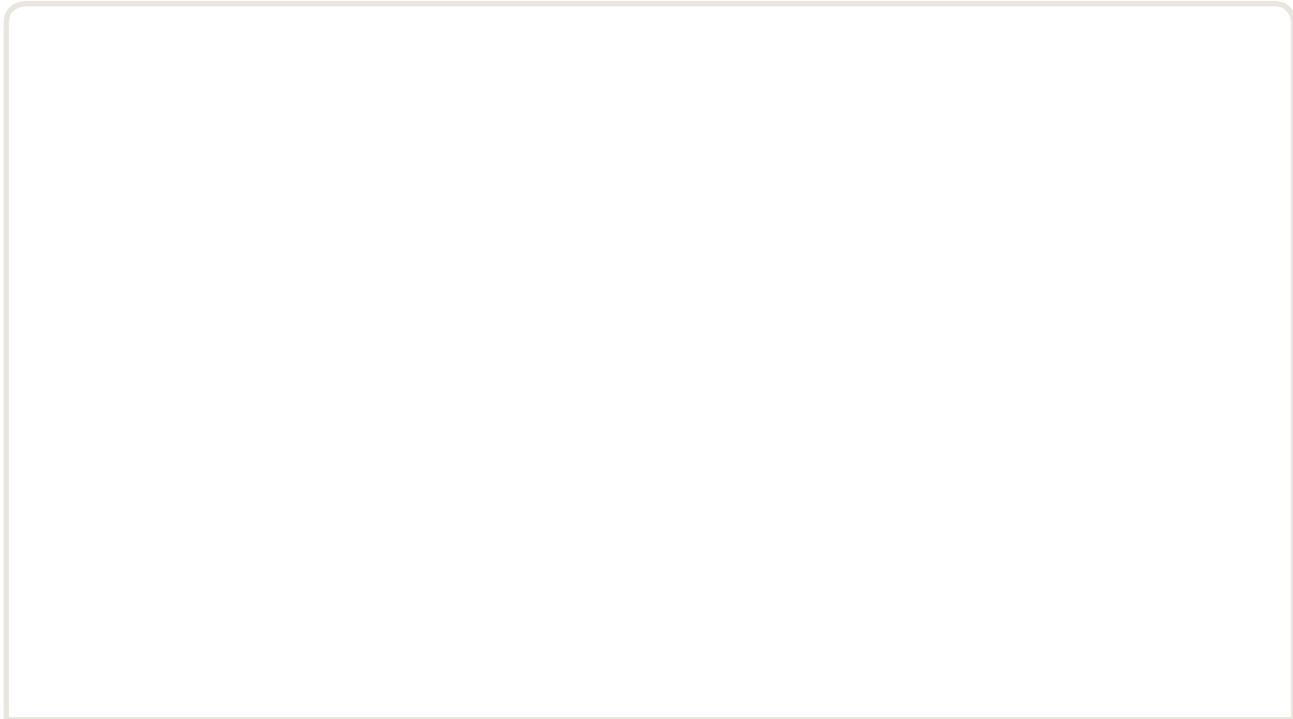


Fig. 3. Schematic view of the basic veno-venous extracorporeal membrane oxygenation circuit. Blood is drained from the vena cava (more often the inferior) and a centrifugal pump pushes it through an oxygenator. Inside the oxygenator, the blood is in contact with polymethylene hollow fibers, which are permeable only to gases. Gas flow, a mixture of medical air and oxygen (at a fraction decided by the clinician), flows into the hollow fibers, exchanging oxygen, which enters the blood, and carbon dioxide, which leaves the blood. The oxygenated and decarboxylated blood returns to the patient and, in absence of recirculation (see Recirculation section for more details), enters the right atrium and normally the systemic circulation.

leads to a lower \dot{V}_O_2 uptake across the baby lung. Therefore, the fraction of blood flowing through the shunted areas represents the major determinant of the \dot{V}_O_2 and consequently arterial P_{aO_2} increase that results from extracorporeal membrane oxygenation (Fig. 3). If the blood in the pulmonary artery were fully saturated, the arterial blood would also be fully saturated, even with at a shunt percentage of 100%. In reality, the increased saturation of the mixed venous blood reduces hypoxic vasoconstriction and increases the shunt fraction. This helps explain why, after an increase in extracorporeal membrane oxygenation blood flow, the arterial P_{aO_2} often does not increase as physics would suggest it should. In other words, as hypoxic pulmonary vasoconstriction decreases, the shunt increases and the arterial P_{aO_2} tends to increase only a little, despite a strong increase in oxygen delivery from the extracorporeal membrane oxygenation unit. Considering that impaired oxygenation represents the primary accepted indication for extracorporeal membrane oxygenation, two key points should be mentioned:

- A generally applicable rescue P_{aO_2} threshold does not exist. Mountain climbers, whales, and fetuses experience P_{aO_2} values as low as 19 mmHg. Although we do not suggest that those critically low levels should be accepted without intervention, this clearly highlights

that not the oxygenation level alone but the hemodynamic performance, the actual oxygen needs, as well as the general status of an individual decide on how critical a specific P_{aO_2} might be.

In most studies published to date, either extracorporeal membrane oxygenation only slightly increased or the P_{aO_2} observed in extracorporeal membrane oxygenation-treated patients was comparable with the P_{aO_2} of those conventionally treated without support.

Carbon Dioxide Removal

The partial pressure of carbon dioxide at the outlet of the membrane lung is the result of complex interactions among many factors, such as the partial pressure of carbon dioxide at the inlet, the blood flow, the functional surface of the membrane lung, the acid-base status on both sides of the unit and, above all, the sweep gas flow (Fig. 4). Critical for the understanding of carbon dioxide control through the extracorporeal circulation is that carbon dioxide is present in blood in three forms: bicarbonate, carbonic acid, and (to a relative small quantity) dissolved carbon dioxide. The partial pressure of carbon dioxide measured during a blood gas analysis reflects only the physically dissolved part, which is in equilibrium with the total carbon dioxide content. A membrane lung can only remove the gas that freely moves

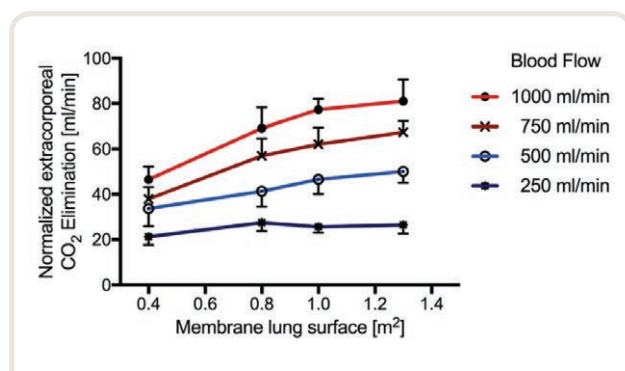


Fig. 4. Extracorporeal carbon dioxide removal (ml/min) at different blood flows and different membrane lung surfaces. It is clear that, at low blood flow (250 ml/min) and small surface (very often extracorporeal carbon dioxide removal–Continuous Renal Replacement Therapy combined systems), the decarboxylating capacity of the device is fairly low. Reprinted with permission from Karagiannidis *et al.*³⁴

through the hollow fibers. Therefore, the flow of carbon dioxide removed by the membrane lung in milliliters per minute is, to a large extent, controlled by the sweep gas flow, acting like alveolar ventilation in the natural lung. Increasing the blood flow through the membrane lung does also increase its carbon dioxide elimination, as more carbon dioxide passes through the gas exchanging surface per unit time, but the reduction in partial pressure of carbon dioxide that occurs between inlet and outlet of the exchanger is determined by the interaction of the two factors (sweep gas and blood flow; *i.e.*, the ventilation/perfusion ratio of the membrane lung).

Moreover, carbon dioxide removal strongly depends on equilibrium time, which is an inverse function of blood flow rate.³⁵ The first experiments using extracorporeal carbon dioxide removal demonstrated that removal of carbon dioxide increased with the logarithm of blood flow rates between 500 ml/min to more than 3 l/min. However, increasing the flow from 2 to 3 l or from 3 to 4 l/min only marginally increased carbon dioxide removal, as these rapid flow rates dramatically reduce equilibration time. In contrast, carbon dioxide removal increases linearly with blood flow at rates between 100 and 500 ml/min.

Based on these considerations, extracorporeal systems for respiratory support can be roughly assigned to two categories:

- High-flow systems with blood flows greater than 2 l/min that offer both oxygenation and decarboxylation. Oxygenation will mostly depend on blood flow, whereas sweep gas flow rate regulates partial pressure of carbon dioxide. The higher the ventilation/perfusion ratio of these units, the greater the drop in partial pressure of carbon dioxide across the membrane lung. Because the extracorporeal membrane oxygenation flow accounts

for a larger fraction of the cardiac output, the resulting mixed venous blood will largely resemble the one at the extracorporeal membrane oxygenation outlet. A high-flow system is theoretically capable of completely substituting for the native lungs.

- Low-flow systems with blood flows less than 2 l/min have limited the oxygenation capacity; at a flow of 400 ml/min it can be assumed that the system provides only decarboxylation. Because only a low fraction of the cardiac output passes the extracorporeal circuit, the resulting mixed venous blood composition will mostly reflect the influence of the large proportion of venous blood not perfusing the membrane lung. Therefore, if the goal is to remove as much carbon dioxide as possible at low blood flow rates, a membrane lung with large surface area is required (at similar blood and gas flow rates, the carbon dioxide removed by different artificial lungs [membrane lung V_{CO_2}] currently can vary between 23 ml/min to more than 100 ml/min). Outlet partial pressure of carbon dioxide values even lower than 10 mmHg may be reached, sometimes below the detection range of a standard blood gas analyzer. Although beneficial with regard to carbon dioxide removal, exiting blood pH may approach 8.0, dramatically increasing the risk of hemolysis.

The amount of carbon dioxide in 100 ml of blood typically ranges between 40 and 60 ml. This implies that of 400 ml of blood with a partial pressure of carbon dioxide between 45 to 70 mmHg has a content approximating the metabolic carbon dioxide production of the body over 1 min. Extracorporeal carbon dioxide removal reduces the amount of carbon dioxide eliminated through the natural lung^{36–39} during both spontaneous breathing and mechanical ventilation. In states of acute respiratory failure, this capability unloads the lungs, thereby offering the potential to reduce and/or avoid ventilation-induced lung injury^{40–42} (see Ventilating during Extracorporeal Membrane Oxygenation section).

While focusing on the veno-venous approach, the so-called hybrid approach deserves brief mention. In some cases, among which septic shock is the most common,⁴³ left ventricular dysfunction (*i.e.*, septic cardiomyopathy⁴⁴) occurs, creating a major challenge, as the respiratory failure is now associated with cardiogenic shock. A rational way to proceed may be to modify the extracorporeal veno-venous circuit by splitting the exchanger outflow into two parts: one directed to the venous circulation as usual during conventional veno-venous extracorporeal membrane oxygenation, while the remainder is directed into the arterial circulation. This arrangement constitutes the so-called veno-venoarterial extracorporeal membrane oxygenation approach for the simultaneous support of heart and lungs.^{45,46}

Recirculation

Recirculation is defined as the fraction of blood flow that is continuously drained directly from the return cannula.

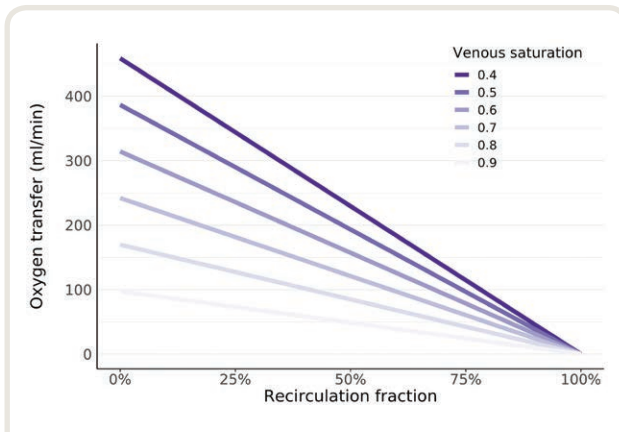


Fig. 5. Mathematical simulation of the oxygen transfer capability of the membrane lung as a function of increasing recirculation fraction. The greater the recirculation, the less the oxygen transfer. This capability is also a function of the oxygen content of the venous blood coming from the periphery (colored lines). Simulation done with 13 g/dl of hemoglobin, 4 l/min of blood flow, 40 mmHg of venous partial pressure of carbon dioxide, and 50% of F_{iO_2} of the membrane lung.

This blood, already decarboxylated and oxygenated, flows directly into the membrane lung without mixing with the blood from the systemic circulation.

Although the drained blood has a high oxygen saturation, oxygen delivery effectively decreases (fig. 5), because a substantial portion of the oxygenated and decarboxylated blood from the extracorporeal membrane oxygenation cartridge does not mix with the blood returning from the periphery. The consequent hypoxemia that might arise often prompts the decision to increase circuit blood flow, leading to unpredictable effects, as recirculation itself is function of the blood flow. Recirculation is a phenomenon determined primarily by the spatial proximity of the tips of draining and returning cannulae. Various strategies have been evolved to reduce recirculation (e.g., cannula repositioning, different cannula tip shapes and positions,⁴⁷ and bicaval double lumen cannulas intended to direct the return flow straight into the right atrium [Avalon, Getinge, Sweden]). The increase in recirculation fraction that accompanies increased circuit blood flow has been frequently reported.⁴⁸ Sensors positioned close to the membrane lung inlet to measure oxygen saturation might help to detect and monitor recirculation. However, ultrasound dilution⁴⁹ and the mixed venous oxygen saturation method⁵⁰ represent the only two ways to accurately measure its magnitude.

Membrane Lung Shunt

The shunt of the membrane lung is determined by the amount of blood flow passing the oxygenator without oxygenation and carbon dioxide removal. Clotting and protein adhesion impair gas transfer across the membrane, thus increasing shunt. A meaningful increase in membrane lung

shunt is a critical event. It reduces efficiency, increases the risk for embolism, and requires a change of the oxygenator that carries its own risks.

Shunt through the membrane lung can be determined by applying the formula used for calculating shunt through the natural lung.⁵¹

$$\frac{Q_s}{ECBF} = \frac{C_{oxy}O_2 - C_{outlet}O_2}{C_{oxy}O_2 - C_{inlet}O_2} \quad (3)$$

Equation 3: $Q_s/ECBF$ is fraction of membrane lung shunt on the global blood flow. $C_{oxy}O_2$ is content of oxygen in ml/dl ideally in equilibrium with the gas in the hollow fibers. $C_{outlet}O_2$ is content of oxygen in ml/dl at the outlet. $C_{inlet}O_2$ is content of oxygen in ml/dl at the inlet.

No shunt would lead to an outlet blood ($C_{outlet}O_2$) in equilibrium with the blood in direct contact with the hollow-fibers ($C_{oxy}O_2$). Ideally this blood is 100% saturated, with a P_{O_2} equal to the barometric pressure times the F_{iO_2} of the gas passing through the membrane lung, minus the partial pressure of carbon dioxide (assumed equal to the outlet partial pressure of carbon dioxide) divided by the respiratory quotient of the membrane lung (The ratio $\frac{V_{CO_2}}{V_{O_2}}$ a concept that can be easily adapted from the natural lung physiology). Any deviation from this ideal situation indicates the presence of shunt. A progressive decrease in the outlet P_{O_2} measured with a simple blood gas analysis is a quick bedside tool for detecting changes in membrane lung performance.

Anticoagulation

The coagulation cascade is activated when whole blood comes into contact with an artificial surface,⁵² and this undesired interaction intensifies when the blood flows slowly.⁵³ Therefore, running an extracorporeal circuit requires anticoagulation. The usual approach is the continuous infusion of unfractionated heparin, titrated to achieve an activated clotting time of 1.5 to 2 times above the normal value. Bivalirudin⁵⁴ or argatroban⁵⁵ are alternatives generally used in patients for whom heparin is contraindicated.

The real challenge is *how* to monitor anticoagulation. Activated clotting time is fast and inexpensive, but has been shown to correlate poorly with activated partial thromboplastin time.⁵⁶ Research efforts are currently directed to point-of-care viscoelastic coagulation tests, such as thromboelastography and rotational thromboelastometry, which hold promise to regulate effective anticoagulation while allowing reductions of infused heparin.⁵⁷

There are also ongoing endeavors to coat surfaces with anticoagulants or hydrophilic agents other than heparin, but so far additional systemic anticoagulation is still required.⁵⁸

Drug Pharmacology during Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation patients are mostly severely ill and complex. Many drugs are infused at the same time, ranging from sedation to antibiotics just to name some most common. Drug pharmacokinetics change during extracorporeal membrane oxygenation, as the circuit can be considered a separate pharmacokinetic compartment, especially for those molecules that are particularly likely to bind to the surface (lipophilic and highly protein-bound), thereby increasing the volume of distribution.^{59,60} Studies have highlighted the potential of the polyvinyl chloride tubing and of the membrane lung to absorb drugs,⁶¹ leading to a decreased plasma concentration. Furthermore, the circuit may itself release drugs previously bound to its surface.⁶⁰

It appears that extracorporeal membrane oxygenation patients often have higher sedation and analgesia requirements, probably owing to the extensive loss of drug in the extracorporeal circuit. In an *in vitro* study, the PVC coating, even in absence of the membrane lung, absorb 80% of fentanyl and 60% of morphine.⁶² Lemaitre *et al.*⁶³ showed in an *ex vivo* study that just after 30 min from the initiation of extracorporeal membrane oxygenation the plasma concentration of propofol dropped to almost 20%. Midazolam concentration dropped to about 40% after 30 min and further decreased over the following 48 h.

Regarding antimicrobial drugs, our understanding is still limited and specific studies are required for the single molecules. Studies have shown an increased volume of distribution for ceftriaxone,⁶⁴ whereas beta-lactams seem not to be so much affected.^{64,65} When using vancomycin, it seems reasonable to use a continuous infusion strategy instead of an intermittent administration.⁶⁶ Voriconazole has been shown to be heavily sequestered in the circuit,⁶⁷ whereas for the echinocandin caspofungin evidence is conflicting.^{68,69}

While keeping in mind that extracorporeal membrane oxygenation does not heal but buys time for healing, the effectiveness of the drugs administered, especially of those acting against the underlying cause for lung failure (antimicrobials, immunosuppressants, *etc.*), is of high importance.⁷⁰ Better knowledge in this field is needed. For the above-mentioned drugs it seems therefore useful to measure, when possible, the plasma concentration of the specific drugs. For an in-depth look at the topic for the pediatric population we suggest the recent review from Di Nardo and Wildschut.⁷¹

Indications for High-flow Venovenous Extracorporeal Membrane Oxygenation

Acute Refractory Hypoxemia

Acute, sustained, and refractory hypoxia represents the most common indication for high-flow extracorporeal membrane oxygenation. In 2009, venovenous extracorporeal

membrane oxygenation was successfully used in patients with extremely severe H1N1-associated ARDS.^{10,72,73} In the same year, the results of the CESAR trial in the United Kingdom were published. In that trial, 180 patients with severe ARDS were randomized to be either transferred to one single extracorporeal membrane oxygenation center or to remain for conventional treatment in the hospital where they already were receiving care (control patients).¹¹ The primary composite endpoint (death or severe disability at six months) occurred significantly less frequently in the extracorporeal membrane oxygenation group (37% *vs.* 53%, $P = 0.03$).

Most studies reporting the outcomes of venovenous extracorporeal membrane oxygenation-treated patients published since 2009 were retrospective,^{74,75} and often monocentric.^{76,77} Recently, however, the results of the multi-centric ECMO to rescue Lung Injury in severe ARDS (EOLIA) trial¹² were published. In this trial 249 patients with severe ARDS on mechanical ventilation for fewer than seven days were randomized either to early initiation of extracorporeal membrane oxygenation or conventional mechanical ventilation, allowing crossover to extracorporeal membrane oxygenation for refractory hypoxemia. Although terminated earlier for futility (failure to achieve the proposed 20% absolute reduction in 60-day mortality) the reduction of mortality was clinically relevant (11% absolute difference) but not statistically significant. The study also demonstrated significant benefits in secondary outcomes (cardiac failure, renal failure, need for dialysis) with early extracorporeal membrane oxygenation use. It is worth noting that extracorporeal membrane oxygenation-related adverse events were rare, with no significant difference between the two study groups in the incidence of hemorrhagic stroke. This trial illustrated the feasibility and the safety of the technique when employed in expert centers. As underlined by the editor of the *New England Journal of Medicine*,⁷⁸ “ECMO probably has some benefit in this context, despite the trial not being traditionally positive.”

Lastly, widespread adoption of proven conventional management approaches for severe ARDS, such as prone positioning,⁷⁹ should be more strongly promoted, because their use remained very low in the recent epidemiologic LUNG-SAFE⁸⁰ and LIFEGARD⁸¹ (ventilation, management of patients with extracorporeal membrane oxygenation for acute respiratory distress syndrome) studies. Ultimately, the results of EOLIA have created the need to reconsider the role of extracorporeal membrane oxygenation in managing severe ARDS. The question is no longer whether extracorporeal membrane oxygenation works, but by how much does extracorporeal membrane oxygenation work, in whom, and at what costs?⁸²

Bridge to Transplant

The shortage of organs destined for transplantation, especially lungs, poses major challenges in the management of patients who require a long term respiratory support. These patients often spend months waiting for a suitable organ, and their clinical condition may worsen to the point

at which extracorporeal membrane oxygenation is the last viable option to keep the patient alive while waiting for an organ. The average 12- to 24-month⁸³ waiting time renders these patients unsuitable for sustained conventional mechanical ventilation.

This scenario stimulated various strategies that incorporate extracorporeal assistance, such as total awareness and no sedation (awake extracorporeal membrane oxygenation⁸⁴) or even ambulating extracorporeal membrane oxygenation. Despite the lack of strong scientific evidence, published reports are promising and these approaches seem feasible for a restricted number of well-selected patients.⁸⁵

Indications for Low-flow Venovenous Technologies (Extracorporeal Carbon Dioxide Removal)

Avoidance or Reduction of Ventilation-induced Lung Injury

Mechanical ventilation assists or replaces spontaneous breathing to provide adequate gas exchange for all forms of acute respiratory failure. It was first described by Lassen⁸⁶ in a report of the 1952 poliomyelitis epidemic in Copenhagen leading to reduction of the mortality rate from 80 to 40%. The experience with these patients encouraged the perception that because higher pressures and larger volumes improve gas exchange, the worse the respiratory failure, the greater the need for greater volumes and pressures.^{87,88} It took almost 50 yr to realize the serious problems associated with this clinical approach. Ventilator-induced lung injury is an adverse consequence of aggressive mechanical ventilation.

Over the last decades, knowledge about ventilator-related interactions and consequences has markedly increased. The term *barotrauma* stressed the high airway pressure as the putative cause of ventilator-induced lung injury, whereas the term *volutrauma* stressed the importance of high volumes. More recently, in the 1990s, atelectrauma and biotrauma expanded the understanding of ventilator-induced lung injury pathophysiology. Quite recently a more comprehensive view of ventilator-induced lung injury causation—mechanical power—has gained favor as it incorporates not only tidal driving pressure and volumes but also frequency and flow and energy load.^{89–93} In theory, partial carbon dioxide removal allows the clinician to safely tailor mechanical ventilation to the varying requirements of the natural lung.

A minimally invasive carbon dioxide removal technique has been shown capable of removing up to 120 ml/min of carbon dioxide using a 13 Fr catheter directing a blood flow of 400 ml/min through a lung with a 1.8 m² surface.³⁵ This setup, which may allow implementation of a ventilatory strategy similar to the one used in the EOLIA trial,¹² extends the benefits of minimal invasive extracorporeal carbon dioxide removal to the acute respiratory failure setting as a practical tool to afford the lungs more rest.^{16,94}

A small number of recent studies have investigated the feasibility of ultra-protective ventilation facilitated by extracorporeal carbon dioxide removal. Two were single center studies with a small number of patients.^{96,97} Other multi-center observational^{98,99} or randomized¹⁰⁰ studies used only a single device and did not compare the feasibility and safety of different approaches to extracorporeal carbon dioxide removal. A survey of 239 French ICUs found that 15% of those centers had used extracorporeal carbon dioxide removal at least once on a total of 303 patients hospitalized between January 2010 and January 2015. The most frequent indication was ultra-protective ventilation for ARDS (54%).¹⁰¹

Although extracorporeal carbon dioxide removal definitely seems to be an appealing technology, the most recent evidence suggests a higher than expected incidence of adverse events. In a single-center study, Terragni *et al.*⁹⁶ reported adverse mechanical events in eight of their ten studied patients. Fanelli *et al.*⁹⁸ described a four-center study of 15 patients with seven incidents of bleeding, one of hemolysis, and one of catheter kinking. In a five-center study of 20 patients Schmidt *et al.*⁹⁹ reported bleeding in two patients and ten incidents of clotting in the membrane lung. A randomized clinical trial in 79 patients from eight sites using a pumpless arterial-venous extracorporeal carbon dioxide removal device reported the need for more blood transfusions in the extracorporeal carbon dioxide removal-group compared to control; however, the incidence of extracorporeal carbon dioxide removal-related adverse events was low.¹⁰⁰

The SUPERNOVA trial¹⁰² (Strategy of Ultra-Protective Lung Ventilation with extracorporeal CO₂ removal for new-onset Moderate to severe ARDS; Clinicaltrials.gov: NCT02282657) is the most recent, international, multi-center, prospective, observational study of patients with ARDS that assessed the feasibility and safety of extracorporeal carbon dioxide removal as a component of ultra-protective ventilation (tidal volume 3–4 ml/kg and plateau pressure at or above 25 cm H₂O). This study provided clear evidence that protective ventilation aided by extracorporeal carbon dioxide removal is feasible in the context of ARDS, but highlighted again a relatively high incidence of adverse events such as circuit clotting (14%), hemolysis (12%), and bleeding (14%).

Extracorporeal Carbon Dioxide Removal in Patients with Chronic Obstructive Pulmonary Disease

Patients with chronic obstructive pulmonary disease (COPD) often experience acute hypercapnic respiratory failure during exacerbation episodes. During such events, worsening expiratory flow results in dynamic hyperinflation that increases end-expiratory and residual lung volumes,¹⁰³ accompanied by decreases of inspiratory capacity and reserve volumes. Consequently, because tidal breathing approaches total lung capacity, the respiratory muscles must

exert greater effort to maintain satisfactory tidal volumes. In addition, progressively reduced expiratory time promotes gas trapping and intrinsic positive end-expiratory pressure that increases the work of breathing.¹⁰³ Dyspnea invariably results and patients with COPD are often unable to sustain spontaneous breathing because their respiratory muscles cannot generate the required pressure needed during these acute exacerbations without carbon dioxide retention.

Noninvasive ventilation remains the first-line treatment for these patients,¹⁰⁴ but although noninvasive ventilation is quite effective, a significant proportion of patients, especially those with severe acidosis, will require intubation.¹⁰⁵ Such patients have a poor prognosis and higher mortality risk.¹⁰⁶

Extracorporeal carbon dioxide removal has been proposed as an alternative to invasive mechanical ventilation for the treatment of acute COPD exacerbations. The rationale is to improve alveolar ventilation with noninvasive ventilation while relieving the workload of the respiratory muscles by removing carbon dioxide directly from the blood. Extracorporeal carbon dioxide removal can accelerate weaning from endotracheal intubation^{107,108} by reducing inspiratory work and preventing ineffective shallow-breathing patterns even as it maintains stable PaCO_2 levels that avoid respiratory acidosis.¹⁰⁹ Although extracorporeal low blood flow devices eliminate carbon dioxide very efficiently (especially at high inlet partial pressure of carbon dioxide), scientific evidence from patients with COPD is still limited. The majority of available data derive from case reports and observational studies¹⁰⁹; no randomized, controlled studies have been conducted so far.

A systematic review of ten publications comprising a total 85 patients¹¹⁰ concluded that intubation could usually be avoided using extracorporeal carbon dioxide removal assistance. Three case-control studies have been published to date. In a retrospective study using pumpless extracorporeal lung-assist, 21 patients were matched with controls based on age, Simplified Acute Physiology Score II, and pH before extracorporeal carbon dioxide removal or intubation. Nineteen (90%) patients treated with the extracorporeal treatment did not require intubation.¹¹¹ Twenty-five patients considered at risk of failing noninvasive ventilation were treated with noninvasive ventilation plus extracorporeal carbon dioxide removal by Del Sorbo *et al.*¹¹² Adding extracorporeal carbon dioxide removal to noninvasive ventilation acutely lowered carbon dioxide levels, thereby reducing the relative risk of intubation by 73%. Despite this promising result, relevant extracorporeal carbon dioxide removal-associated adverse events were observed in 13 patients (52%). Another recent multicenter case-control study (ECLAIR; 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) showed that intubation was avoided in 14 of 25 extracorporeal carbon dioxide removal-assisted

patients (56%).¹¹³ Unfortunately, clinically relevant extracorporeal carbon dioxide removal-associated adverse events were observed in more than one-third of the patients.

In conclusion, extracorporeal carbon dioxide removal potentially offers an attractive and clinically viable option for several stages in the course of exacerbated COPD. The data currently available provide the basis for conducting the randomized clinical trials needed to definitively assess the risk-benefit balance of extracorporeal carbon dioxide removal assistance in these settings.

Ethical Considerations

Numerous ethical considerations arise with the use of extracorporeal membrane oxygenation in respiratory failure, because this procedure represents a complex and resource-consuming intervention with its own risks. The most basic questions concerning the everyday practice of extracorporeal membrane oxygenation are: *Who should receive extracorporeal membrane oxygenation and who should not?* Those decisions must be based on a careful consideration of the potential risks and benefits. However, given the constraints imposed by the current level of evidence, we often struggle to find a reassuring balance.^{114–116}

When extracorporeal membrane oxygenation has been implemented, whether as bridge to recovery or to transplantation, and when recovery appears impossible and transplantation is not an option, how do we then proceed?^{117–119} If the device can sustain the failing lungs, and no other organ system failure is poised to end life, the patient is bound to a device for an uncertain but often prolonged period of time, unable to live outside an intensive care unit (ICU) and on the so-called bridge to nowhere. With no possibility of an acceptable outcome, withdrawal of extracorporeal membrane oxygenation would seem a reasonable option. However, this is easier said than done,¹¹⁹ especially in the context of lung transplantation. Imagine a patient awake, endotracheally extubated, and without obvious discomfort. Do we recommend withdrawal of extracorporeal membrane oxygenation to the patient? What if the patient declines, choosing instead to cling to life at all costs? Could we then withdraw against the patient's stated wishes? This would appear to violate the key guiding principle of patient autonomy.¹¹⁷ In such circumstances, there appears to be no clear path to follow.¹¹⁸

This conundrum highlights the importance of offering extracorporeal membrane oxygenation only to patients who might benefit. As an example, if recovery from an acute exacerbation of end-stage lung disease is not possible, extracorporeal membrane oxygenation is an option only when it is deemed likely to bridge the patient successfully to transplantation. If the patient is not a candidate for transplantation, extracorporeal membrane oxygenation is contraindicated.¹²⁰

We must also consider the costs imposed by the use of sophisticated life-sustaining technologies.¹²¹ Without careful

selection of patients for extracorporeal membrane oxygenation, both viable and nonviable patients could rapidly fill our ICU beds and consume our health care resources. Even more beds would be filled if surrogate decision-makers were allowed to demand extracorporeal membrane oxygenation for those who cannot possibly benefit, if only to extend life. The end result would be nonviable extracorporeal membrane oxygenation patients crowding out others who might benefit from access to the ICU and extracorporeal membrane oxygenation^{118,122}—clearly an unacceptable situation. The issue of resource scarcity has similarly been framed as equality *versus* equity—equal treatment for all patients in having access to extracorporeal membrane oxygenation or providing the individual patient with whatever she or he needs to survive.¹¹⁴ When do we as a society decide that the costs incurred by widely applying an expensive, labor-intensive technology outweigh the gains? Core principles of ethical decision-making and a humane approach to the patient remain unchanged in the context of extracorporeal membrane oxygenation. It is the complexity of applying these technologies that brings additional challenges.¹²³ This is further complicated by the different policy that every country has toward the reimbursement of the extracorporeal membrane oxygenation related costs. Especially for borderline indications, economic reasoning, also more and more ruling healthcare, seems deeply unethical.

We should make use of adjuvant techniques, such as shared decision-making and time-limited trials,¹²² engage spiritual support, seek palliative care and ethics consultations when appropriate,^{123,124} and recognize the differences in acceptable ethical practices that exist across the world with regard to, for instance, withdrawal of life-sustaining therapies. As we continue to gather more evidence to guide us in the use of extracorporeal membrane oxygenation, the technology will continue to advance and to challenge our notion of what is possible and what is ethical.

Extracorporeal Membrane Oxygenation, *Quo Vadis?*¹²⁵

Over the past decade the use of extracorporeal membrane oxygenation has expanded exponentially, and its indications have become less restrictive. Some patients may require long-term ventilation, and some may be candidates for lung transplantation. Because extracorporeal membrane oxygenation is occasionally performed in nonventilated awake patients, the need and desirability of even less invasive devices is abundantly clear.^{126,127}

Implantable artificial lungs, so-called *para-corporeal* devices,^{128–130} are still in preclinical development. They are low-resistance oxygenators (pumped or pumpless) implanted either in series (pulmonary artery-to-pulmonary artery) or in parallel (pulmonary artery to left ventricle). Their advantage is their portability, making them suitable for extra-hospital use, even in ambulatory patients.^{131,132} Regarding conventional extracorporeal membrane

oxygenation or extracorporeal carbon dioxide removal, it seems likely that many recent innovations will gradually enter everyday practice, rendering extracorporeal therapy more effective and safe for the patient.

Improvements in Circuit Technology

Resistance

For artificial lungs, the membrane resistance should be reduced from the current range of 4.5–5 mmHg · l⁻¹ · min⁻¹ to a resistance approximating that of the normal lung (approximately 1 mmHg · l⁻¹ · min⁻¹).¹³³ Systems with resistances of 0.5 to 1.8 mmHg · l⁻¹ · min⁻¹ are currently undergoing preclinical testing.^{134,135}

Thrombogenicity

Reducing the risk of clot formation while minimizing the need for anticoagulation are major goals in the development of durable, portable systems and success will require changes in oxygenator design. Current efforts are focused on developing materials with low nonspecific protein adsorption, as well as smart antibacterial surfaces with antithrombotic and anti-fouling properties.¹³⁶ Candidate approaches include using heparin-mimetic polymers, albumin-coated, blood-compatible hydrogels, elastin-inspired surfaces, endothelial/autologous cell-coated surfaces,^{137,138} zwitterionic polymers, submicron-patterned surfaces, nanoparticles, *etc.*¹³⁹ Combinations of such options with the addition of surface-modifying additives are also being tested. Polymeric materials have been developed that generate and release low concentrations of nitric oxide with local (*i.e.*, nonsystemic) antiplatelet, antithrombogenic, and antibacterial properties.^{137,140} In addition, factor XII blockers could reduce thrombogenicity without increasing the risk of bleeding.^{141–143}

Low-flow Extracorporeal Carbon Dioxide Removal Devices: Maximizing Carbon Dioxide Removal

Systems for selectively removing carbon dioxide function at lower blood flows than full-blown extracorporeal membrane oxygenation (generally 0.5–1.5 l/min) and use smaller cannulas. Future developments will focus on systems that maximize carbon dioxide removal with blood flows in the range of 200 to 250 ml/min.^{144,145}

Quite efficient devices (50–80 ml CO₂/min) accomplish carbon dioxide removal by using bicarbonate dialysis while restoring normal blood pH with nonbicarbonate buffers, or by increasing the partial pressure of carbon dioxide gradient between premembrane blood and sweep gas.^{145–149} The latter can be achieved, for example, by blood acidification^{145,150,151} with lactate or citrate,¹⁵² by carbonic anhydrase immobilized in a gas-liquid membrane^{139,153–155} (or, more commonly, on hollow fibers), or by respiratory electro dialysis.¹⁵⁶

Carbonic Anhydrase-enhanced Membranes

Immobilized carbonic anhydrase converts bicarbonate to carbon dioxide and improves the efficiency of carbon dioxide transfer by as much as 60%. Acidifying the sweep gas with sulphur dioxide further promotes carbon dioxide elimination.¹⁵⁷

Respiratory Electrodialysis

Respiratory electrodialysis achieves regional blood acidification using an electrodialysis unit interposed between a hemofilter and the membrane lung. Acidic hemofiltrate liberates carbon dioxide into the premembrane blood, thereby enhancing carbon dioxide removal. The section of the electrodialysis cell that produces alkaline hemofiltrate is then reinfused postmembrane to restore the venous blood pH and electrolytes.¹⁵⁶

Challenges and Perspectives for Extracorporeal Gas Exchange in Respiratory Failure

Ventilating during Extracorporeal Membrane Oxygenation

One of the major challenges is to decide on how to treat the injured lungs to keep alive and to promote the healing. The potential options range from complete lung rest¹⁵⁸ to the total open-lung approach,¹⁵⁹ and anything in between.¹⁶⁰

Ideally, the natural lung should be ventilated with low mechanical power to reduce or even avoid the risk of ventilator-induced lung injury. In this context, extracorporeal membrane oxygenation offers a tool allowing to protect the lungs by reducing the mechanical power delivered (fig. 6). Extracorporeal carbon dioxide removal by definition dissociates oxygenation and decarboxylation,¹⁶¹ allowing to reduce the invasiveness of the intervention ventilation. The recently published LIFEGARD study examined how patients are currently ventilated during extracorporeal membrane oxygenation.⁸¹ The results demonstrated a marked reduction in driving pressure and mechanical power during extracorporeal respiratory support, thus raising even more urgently the question on how to find the best balance between lung rest and ventilatory load.⁹⁵ A definitive answer will come from both preclinical and clinical studies that aim to elucidate which strategy ensures best conditions for lung healing and repair. In a recent study¹⁶² a near apneic ventilation (10 cmH₂O of positive end-expiratory pressure, 10 cmH₂O driving pressure, five breaths per minute) resulted in markedly superior results when compared with conventional strategy of ventilation in an animal study with pigs, decreasing fibroproliferation and promoting lung healing. We also know that some degree of alveolar cyclic inflation promotes lung growth and differentiation. Already during the prenatal life, a certain degree of cyclic lung stretch promotes lung growth and differentiation.¹⁶³ In the near future, the Rest Or Moderate MEchanical ventilation in ECMO (ROME) trial that will be performed mostly

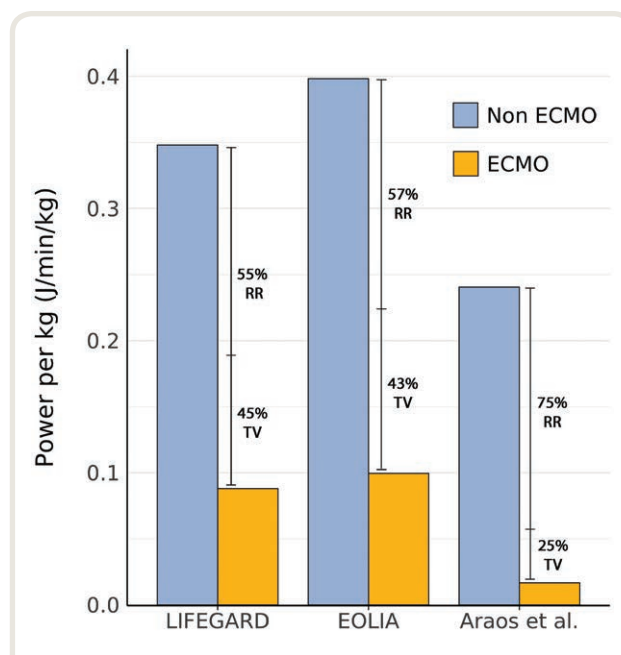


Fig. 6. Reduction in mechanical power that was possible to achieve in the EOLIA (ECMO to rescue Lung Injury in severe ARDS) trial, in the LIFEGARDS survey, and in the study from Araos *et al.*¹⁶² after the extracorporeal membrane oxygenation initiation. ECMO, extracorporeal membrane oxygenation. Reprinted with permission from Quintel *et al.*⁹⁵

in the United Kingdom will provide insights into this topic and will hopefully signal whether lung rest is superior to conventional treatment in promoting healing and increasing ventilation-free days and survival.

Weaning from Extracorporeal Membrane Oxygenation

Objective criteria defining extracorporeal membrane oxygenation dependency and reliable guidelines for weaning from extracorporeal membrane oxygenation are currently lacking. Such criteria are relevant both for clinicians treating patients and for researchers comparing trials in which duration of extracorporeal membrane oxygenation is relevant. The most important questions include: Which criteria identify patients ready to be weaned? How does one monitor an extracorporeal membrane oxygenation weaning trial? What defines weaning success or failure? How does one quantify the interaction artificial and native lung during weaning?

Extracorporeal membrane oxygenation can be terminated when the native lung can maintain gas exchange with acceptable ventilator settings and patient comfort. The most relevant determining factors are the carbon dioxide removal (ml/min) of the native lung relative to total carbon dioxide production, and the carbon dioxide response curve that determines respiratory drive in spontaneously breathing patients. Surprisingly, these parameters, as well as esophageal

pressure, are rarely closely monitored. In most cases, weaning is an empirical process based on arbitrary reductions of extracorporeal support. Carefully analyzing such extracorporeal membrane oxygenation–patient interactions should eventually lead to reliable guidelines for weaning.

Outcome

The mortality of patients receiving extracorporeal membrane oxygenation has decreased but still remains relatively high. Patient selection based on the reversibility of lung disease, a timely, deliberate implementation of extracorporeal membrane oxygenation, and an efficient patient referral–retrieval system have proved effective in further increasing survival during and after extracorporeal membrane oxygenation. Establishing extracorporeal membrane oxygenation programs in specialized extracorporeal membrane oxygenation centers will promote the development of expertise and of dedicated clinical protocols, which favor resource use and outcome optimization.¹⁶⁴

Developing sophisticated extracorporeal membrane oxygenation programs will not only improve outcome, but the associated studies will provide basic data for improving extracorporeal membrane oxygenation management. Although extracorporeal membrane oxygenation allows a drastic reduction of ventilation that minimizes the risk of ventilator-induced lung injury, the optimal ventilatory strategy for this situation is still not conclusively defined. Lung rest with low-to-moderate positive end-expiratory pressure and low minute ventilation (and low mechanical power) might allow a better outcome than other ventilation strategies. Simultaneously, care must be taken to avoid the promotion of diaphragmatic atrophy.

Resolving these uncertainties is an important challenge for the near future, because successful resolution may not just reduce the risk of ventilator-induced lung injury but also even promote lung healing.

Conclusions

Extracorporeal membrane oxygenation and extracorporeal carbon dioxide removal are complex, expensive, and delicate devices that require a thorough physiologic and technical understanding to be effectively and safely used. These technologies will certainly play more important and better established role in the therapeutic armamentarium than past decades. However, there are challenging steps to be taken to increase their effectiveness, feasibility, and safety.

Acknowledgments

The authors dedicate this review from their hearts to Brian Kavanagh, who gave the first impetus for it. They will always honor his memory and have lost a brilliant, sharp-minded physician and researcher, but most importantly a reliable friend. The authors also kindly thank Mr. Marco Busana for his valuable contribution in drawing figure 3.

Research Support

Supported in part by the National Institutes of Health (Bethesda, Maryland).

Competing Interests

Dr. Grocott has financial relationships with Sphere Medical, Ltd. (Cambridge, United Kingdom) and Pharamcosmos, Ltd. (Reading, United Kingdom). Dr. Brodie has financial relationships with ALung Technologies (Pittsburgh, Pennsylvania), Baxter (Deerfield, Illinois), and BREETHE and medical advisory boards for Hemovent (unpaid; Aachen, Germany) and Xenios (Heilbronn, Germany). The other authors declare no competing interests.

Correspondence

Address correspondence to Dr. Quintel: University of Göttingen Medical Center, Department of Anesthesiology and Intensive Care Medicine, Robert Koch Strasse 40, 37075 Göttingen, Germany. mquintel@med.uni-goettingen.de. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

References

- Hill JD, O'Brien TG, Murray JJ, Dontigny L, Bramson ML, Osborn JJ, Gerbode F: Prolonged extracorporeal oxygenation for acute post-traumatic respiratory failure (shock-lung syndrome). *Use of the Bramson membrane lung.* *N Engl J Med* 1972; 286:629–34
- Bartlett RH, Gazzaniga AB, Fong SW, Burns NE: Prolonged extracorporeal cardiopulmonary support in man. *J Thorac Cardiovasc Surg* 1974; 68:918–32
- Bartlett RH, Gazzaniga AB, Jefferies MR, Huxtable RF, Haiduc NJ, Fong SW: Extracorporeal membrane oxygenation (ECMO) cardiopulmonary support in infancy. *Trans Am Soc Artif Intern Organs* 1976; 22:80–93
- Bartlett RH: Esperanza: The first neonatal ECMO patient. *ASAIO J* 2017; 63:832–43
- Toomasian JM, Snedecor SM, Cornell RG, Cilley RE, Bartlett RH: National experience with extracorporeal membrane oxygenation for newborn respiratory failure. Data from 715 cases. *ASAIO Trans* 1988; 34:140–7
- Bartlett RH: Clinical research in acute fatal illness: Lessons from extracorporeal membrane oxygenation. *J Intensive Care Med* 2016; 31:456–65
- Gattinoni L, Kolobow T, Tomlinson T, White D, Pierce J: Control of intermittent positive pressure breathing (IPPB) by extracorporeal removal of carbon dioxide. *Br J Anaesth* 1978; 50:753–8

8. Kennedy JH: The role of assisted circulation in cardiac resuscitation. *JAMA* 1966; 197:615–8
9. Zapol WM, Snider MT, Hill JD, Fallat RJ, Bartlett RH, Edmunds LH, Morris AH, Peirce EC 2nd, Thomas AN, Proctor HJ, Drinker PA, Pratt PC, Bagniewski A, Miller RG Jr: Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study. *JAMA* 1979; 242:2193–6
10. Davies A, Jones D, Bailey M, Beca J, Bellomo R, Blackwell N, Forrest P, Gattas D, Granger E, Herkes R, Jackson A, McGuinness S, Nair P, Pellegrino V, Pettilä V, Plunkett B, Pye R, Torzillo P, Webb S, Wilson M, Ziegenfuss M; 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; 302:1888–95
11. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, Hibbert CL, Truesdale A, Clemens F, Cooper N, Firmin RK, Elbourne D; 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; 374:1351–63
12. Combes A, Hajage D, Capellier G, Demoule A, Lavoué S, Guervilly C, Da Silva D, Zafrani L, Tirot P, Veber B, Maury E, Levy B, Cohen Y, Richard C, Kalfon P, Bouadma L, Mehdaoui H, Beduneau G, Lebreton G, Brochard L, Ferguson ND, Fan E, Slutsky AS, Brodie D, Mercat A; EOLIA Trial Group, REVA, and ECMONet: Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med* 2018; 378:1965–75
13. Greenway CV, Lawson AE: The effects of adrenaline and noradrenaline on venous return and regional blood flows in the anaesthetized cat with special reference to intestinal blood flow. *J Physiol* 1966; 186:579–95
14. Kohler K, Valchanov K, Nias G, Vuylsteke A: ECMO cannula review. *Perfusion* 2013; 28:114–24
15. Extracorporeal Life Support Organization: The physiology of extracorporeal life support, Extracorporeal Life Support: The ELSO Red Book, 5th edition. Edited by Brogan TV, Lequier L, Lorusso R, MacLaren G., Peek, G. 2017, pp 31–47
16. Camporota L, Barrett N: Current applications for the use of extracorporeal carbon dioxide removal in critically ill patients. *Biomed Res Int* 2016; 2016:9781695
17. Broman LM, Taccone FS, Lorusso R, Malfertheiner MV, Pappalardo F, Di Nardo M, Belliato M, Bembea MM, Barbaro RP, Diaz R, Grazioli L, Pellegrino V, Mendonca MH, Brodie D, Fan E, Bartlett RH, McMullan MM, Conrad SA: The ELSO Maastricht Treaty for ECLS Nomenclature: Abbreviations for cannulation configuration in extracorporeal life support – A position paper of the Extracorporeal Life Support Organization. *Crit Care* 2019; 23:36
18. Barrett CS, Jagers JJ, Cook EF, Graham DA, Rajagopal SK, Almond CS, Seeger JD, Rycus PT, Thiagarajan RR: Outcomes of neonates undergoing extracorporeal membrane oxygenation support using centrifugal *versus* roller blood pumps. *Ann Thorac Surg* 2012; 94:1635–41
19. Halaweish I, Cole A, Cooley E, Lynch WR, Haft JW: Roller and centrifugal pumps: A retrospective comparison of bleeding complications in extracorporeal membrane oxygenation. *ASAIO J* 2015; 61:496–501
20. Gross-Hardt S, Hesselmann F, Arens J, Steinseifer U, Vercaemst L, Windisch W, Brodie D, Karagiannidis C: Low-flow assessment of current ECMO/ECCO2R rotary blood pumps and the potential effect on hemocompatibility. *Crit Care* 2019; 23:348
21. Hilmo J, Naesheim T, Gilbert M: “Nobody is dead until warm and dead”: Prolonged resuscitation is warranted in arrested hypothermic victims also in remote areas—a retrospective study from northern Norway. *Resuscitation* 2014; 85:1204–11
22. Moerer O, Vasques F, Duscio E, Cipulli F, Romitti F, Gattinoni L, Quintel M: Extracorporeal gas exchange. *Crit Care Clin* 2018; 34:413–22
23. Dantzker DR, Wagner PD, West JB: Proceedings: Instability of poorly ventilated lung units during oxygen breathing. *J Physiol* 1974; 242:72P
24. Martucci G, Grasselli G, Tanaka K, Tuzzolino F, Panarello G, Schmidt M, Bellani G, Arcadipane A: Hemoglobin trigger and approach to red blood cell transfusions during veno-venous extracorporeal membrane oxygenation: The international TRAIN-ECMO survey. *Perfusion* 2019; 34(1_suppl):39–48
25. Gattinoni L, Pesenti A, Avalli L, Rossi F, Bombino M: Pressure-volume curve of total respiratory system in acute respiratory failure. Computed tomographic scan study. *Am Rev Respir Dis* 1987; 136:730–6
26. Gattinoni L, Pesenti A: The concept of “baby lung.” *Intensive Care Med* 2005; 31:776–84
27. Marshall BE, Marshall C: A model for hypoxic constriction of the pulmonary circulation. *J Appl Physiol* (1985) 1988; 64:68–77
28. Bishop MJ, Cheney FW: Effects of pulmonary blood flow and mixed venous O₂ tension on gas exchange in dogs. *ANESTHESIOLOGY* 1983; 58:130–5
29. Domino KB, Wetstein L, Glasser SA, Lindgren L, Marshall C, Harken A, Marshall BE: Influence of mixed venous oxygen tension (PVO₂) on blood flow to atelectatic lung. *ANESTHESIOLOGY* 1983; 59:428–34
30. Cressoni M, Caironi P, Polli F, Carlesso E, Chiumello D, Cadringer P, Quintel M, Ranieri VM, Bugego G, Gattinoni L: Anatomical and functional intrapulmonary shunt in acute respiratory distress syndrome. *Crit Care Med* 2008; 36:669–75

31. Grocott MP, Martin DS, Levett DZ, McMorrow R, Windsor J, Montgomery HE; Caudwell Xtreme Everest Research Group: Arterial blood gases and oxygen content in climbers on Mount Everest. *N Engl J Med* 2009; 360:140–9
32. Shaffer SA, Costa DP, Williams TM, Ridgway SH: Diving and swimming performance of white whales, *Delphinapterus leucas*: An assessment of plasma lactate and blood gas levels and respiratory rates. *J Exp Biol* 1997; 200(Pt 24):3091–9
33. Rychik J: Fetal cardiovascular physiology. *Pediatr Cardiol* 2004; 25:201–9
34. Karagiannidis C, Strassmann S, Brodie D, Ritter P, Larsson A, Borchardt R, Windisch W: Impact of membrane lung surface area and blood flow on extracorporeal CO₂ removal during severe respiratory acidosis. *Intensive Care Med Exp* 2017; 5:34
35. Duscio E, Cipulli F, Vasques F, Collino F, Rapetti F, Romitti F, Behnemann T, Niewenhuis J, Tonetti T, Pasticci I, Vassalli F, Reupke V, Moerer O, Quintel M, Gattinoni L: Extracorporeal CO₂ removal: The minimally invasive approach, theory, and practice. *Crit Care Med* 2019; 47:33–40
36. Kolobow T, Gattinoni L, Tomlinson TA, Pierce JE: Control of breathing using an extracorporeal membrane lung. *ANESTHESIOLOGY* 1977; 46:138–41
37. Kolobow T, Gattinoni L, Tomlinson T, White D, Pierce J, Iapichino G: The carbon dioxide membrane lung (CDML): A new concept. *Trans Am Soc Artif Intern Organs* 1977; 23:17–21
38. Gattinoni L, Kolobow T, Damia G, Agostoni A, Pesenti A: Extracorporeal carbon dioxide removal (ECCO2R): A new form of respiratory assistance. *Int J Artif Organs* 1979; 2:183–5
39. Gattinoni L, Iapichino G, Kolobow T: Hemodynamic, mechanical and renal effects during “apneic oxygenation” with extracorporeal carbon dioxide removal, at different levels of intrapulmonary pressure in lambs. *Int J Artif Organs* 1979; 2:249–53
40. Gattinoni L, Kolobow T, Agostoni A, Damia G, Pelizzola A, Rossi GP, Langer M, Solca M, Citterio R, Pesenti A, Fox U, Uziel L: Clinical application of low frequency positive pressure ventilation with extracorporeal CO₂ removal (LFPPV-ECCO₂R) in treatment of adult respiratory distress syndrome (ARDS). *Int J Artif Organs* 1979; 2:282–3
41. Hilty MP, Riva T, Cottini SR, Kleinert EM, Maggiorini A, Maggiorini M: Patient selection for extracorporeal CO₂ removal: A task as challenging as for ECMO therapy. *Minerva Anestesiol* 2018; 84:410–1
42. Crotti S, Bottino N, Ruggeri GM, Spinelli E, Tubiolo D, Lissoni A, Protti A, Gattinoni L: Spontaneous breathing during extracorporeal membrane oxygenation in acute respiratory failure. *ANESTHESIOLOGY* 2017; 126:678–87
43. Küstermann J, Gehrmann A, Kredel M, Wurmb T, Roewer N, Muellenbach RM: [Acute respiratory distress syndrome and septic cardiomyopathy: Successful application of veno-venoarterial extracorporeal membrane oxygenation]. *Anaesthesist* 2013; 62:639–43
44. Rudiger A, Singer M: Mechanisms of sepsis-induced cardiac dysfunction. *Crit Care Med* 2007; 35:1599–608
45. Belliato M, Caneva L, Aina A, Degani A, Mongodi S, Prah Wittberg L, Pellegrini C, Broman LM, Iotti GA: An experimental model of veno-venous arterial extracorporeal membrane oxygenation. *Int J Artif Organs* 2019; 39:1398819882024
46. Ius F, Sommer W, Tudorache I, Avsar M, Siemeni T, Salman J, Puntigam J, Optenhoefel J, Greer M, Welte T, Wiesner O, Haverich A, Hoepfer M, Kuehn C, Warnecke G: Veno-veno-arterial extracorporeal membrane oxygenation for respiratory failure with severe haemodynamic impairment: technique and early outcomes. *Interact Cardiovasc Thorac Surg* 2015; 20:761–7
47. Palmér O, Palmér K, Hultman J, Broman M: Cannula design and recirculation during venovenous extracorporeal membrane oxygenation. *ASAIO J* 2016; 62:737–42
48. Abrams D, Bacchetta M, Brodie D: Recirculation in venovenous extracorporeal membrane oxygenation. *ASAIO J* 2015; 61:115–21
49. Krivitski NM: Theory and validation of access flow measurement by dilution technique during hemodialysis. *Kidney Int* 1995; 48:244–50
50. van Heijst AF, van der Staak FH, de Haan AF, Liem KD, Festen C, Geven WB, van de Bor M: Recirculation in double lumen catheter veno-venous extracorporeal membrane oxygenation measured by an ultrasound dilution technique. *ASAIO J* 2001; 47:372–6
51. Riley RL, Cournand A: Ideal alveolar air and the analysis of ventilation-perfusion relationships in the lungs. *J Appl Physiol* 1949; 1:825–47
52. Urlesberger B, Zobel G, Zenz W, Kuttinig-Haim M, Maurer U, Reiterer F, Riccabona M, Dacar D, Gallisti S, Leschnik B, Muntean W: Activation of the clotting system during extracorporeal membrane oxygenation in term newborn infants. *J Pediatr* 1996; 129:264–8
53. Anning ST: The historical aspects of venous thrombosis. *Med Hist* 1957; 1:28–37
54. Sanfilippo F, Asmussen S, Maybauer DM, Santonocito C, Fraser JF, Erdoes G, Maybauer MO: Bivalirudin for alternative anticoagulation in extracorporeal membrane oxygenation: A systematic review. *J Intensive Care Med* 2017; 32:312–9
55. Menk M, Briem P, Weiss B, Gassner M, Schwaiberger D, Goldmann A, Pille C, Weber-Carstens S: Efficacy and safety of argatroban in patients with acute respiratory distress syndrome and extracorporeal lung support. *Ann Intensive Care* 2017; 7:82

56. Cunningham D, Besser MW, Giraud K, Gerrard C, Vuylsteke A: Agreement between ACT and aPTT during extracorporeal membrane oxygenation shows intra- and inter-individual variation. *Perfusion* 2016; 31:503–7
57. Panigada M, Iapichino GE, Brioni M, Panarello G, Protti A, Grasselli G, Occhipinti G, Novembrino C, Consonni D, Arcadipane A, Gattinoni L, Pesenti A: Thromboelastography-based anticoagulation management during extracorporeal membrane oxygenation: A safety and feasibility pilot study. *Ann Intensive Care* 2018; 8: 7
58. Coughlin MA, Bartlett RH: Anticoagulation for extracorporeal life support: Direct Thrombin inhibitors and heparin. *ASAIO J* 2015; 61:652–5
59. Cheng V, Abdul-Aziz MH, Roberts JA, Shekar K: Optimising drug dosing in patients receiving extracorporeal membrane oxygenation. *J Thorac Dis* 2018; 10(Suppl 5):629–41
60. Dzierba AL, Abrams D, Brodie D: Medicating patients during extracorporeal membrane oxygenation: the evidence is building. *Crit Care* 2017; 21:66
61. Shekar K, Fraser JF, Smith MT, Roberts JA: Pharmacokinetic changes in patients receiving extracorporeal membrane oxygenation. *J Crit Care* 2012; 27:741.e9–18
62. Preston TJ, Hodge AB, Riley JB, Leib-Sargel C, Nicol KK: *In vitro* drug adsorption and plasma free hemoglobin levels associated with hollow fiber oxygenators in the extracorporeal life support (ECLS) circuit. *J Extra Corpor Technol* 2007; 39:234–7
63. Lemaitre F, Hasni N, Leprince P, Corvol E, Belhabib G, Fillâtre P, Luyt CE, Leven C, Farinotti R, Fernandez C, Combes A: Propofol, midazolam, vancomycin and cyclosporine therapeutic drug monitoring in extracorporeal membrane oxygenation circuits primed with whole human blood. *Crit Care* 2015; 19:40
64. Shekar K, Roberts JA, Ghassabian S, Mullany DV, Wallis SC, Smith MT, Fraser JF: Altered antibiotic pharmacokinetics during extracorporeal membrane oxygenation: Cause for concern? *J Antimicrob Chemother* 2013; 68:726–7
65. Roberts JA, Kumar A, Lipman J: Right dose, right now: Customized drug dosing in the critically ill. *Crit Care Med* 2017; 45:331–6
66. Donadello K, Roberts JA, Cristallini S, Beumier M, Shekar K, Jacobs F, Belhaj A, Vincent JL, de Backer D, Taccone FS: Vancomycin population pharmacokinetics during extracorporeal membrane oxygenation therapy: A matched cohort study. *Crit Care* 2014; 18:632
67. Mehta NM, Halwick DR, Dodson BL, Thompson JE, Arnold JH: Potential drug sequestration during extracorporeal membrane oxygenation: Results from an *ex vivo* experiment. *Intensive Care Med* 2007; 33:1018–24
68. Spriet I, Annaert P, Meersseman P, Hermans G, Meersseman W, Verbesselt R, Willems L: Pharmacokinetics of caspofungin and voriconazole in critically ill patients during extracorporeal membrane oxygenation. *J Antimicrob Chemother* 2009; 63:767–70
69. Ruiz S, Papy E, Da Silva D, Nataf P, Massias L, Wolff M, Bouadma L: Potential voriconazole and caspofungin sequestration during extracorporeal membrane oxygenation. *Intensive Care Med* 2009; 35:183–4
70. Zapol WM, Kitz RJ: Buying time with artificial lungs. *N Engl J Med* 1972; 286:657–8
71. Di Nardo M, Wildschut ED: Drugs pharmacokinetics during veno-venous extracorporeal membrane oxygenation in pediatrics. *J Thorac Dis* 2018; 10(Suppl 5):642–52
72. Noah MA, Peek GJ, Finney SJ, Griffiths MJ, Harrison DA, Grieve R, Sadique MZ, Sekhon JS, McAuley DF, Firmin RK, Harvey C, Cordingley JJ, Price S, Vuylsteke A, Jenkins DP, Noble DW, Bloomfield R, Walsh TS, Perkins GD, Menon D, Taylor BL, Rowan KM: Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1). *JAMA* 2011; 306:1659–68
73. Pham T, Combes A, Rozé H, Chevret S, Mercat A, Roch A, Mourvillier B, Ara-Somohano C, Bastien O, Zogheib E, Clavel M, Constan A, Marie Richard JC, Brun-Buisson C, Brochard L; 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; 187:276–85
74. Schmidt M, Bailey M, Sheldrake J, Hodgson C, Aubron C, Rycus PT, Scheinkestel C, Cooper DJ, Brodie D, Pellegrino V, Combes A, Pilcher D: 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; 189:1374–82
75. Schmidt M, Zogheib E, Rozé H, Repesse X, Lebreton G, Luyt CE, Trouillet JL, Bréchet N, Nieszkowska A, Dupont H, Ouattara A, Leprince P, Chastre J, Combes A: 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; 39:1704–13
76. Enger T, Philipp A, Videm V, Lubnow M, Wahba A, Fischer M, Schmid C, Bein T, Müller T: Prediction of mortality in adult patients with severe acute lung failure receiving veno-venous extracorporeal membrane oxygenation: A prospective observational study. *Crit Care* 2014; 18:R67

77. Roch A, Lepaul-Ercole R, Grisoli D, Bessereau J, Brissy O, Castanier M, Dizier S, Forel JM, Guervilly C, Gariboldi V, Collart F, Michelet P, Perrin G, Charrel R, Papazian L: Extracorporeal membrane oxygenation for severe influenza A (H1N1) acute respiratory distress syndrome: A prospective observational comparative study. *Intensive Care Med* 2010; 36:1899–905
78. Harrington D, Drazen JM: Learning from a trial stopped by a data and safety monitoring board. *N Engl J Med* 2018; 378:2031–2
79. Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, Mercier E, Badet M, Mercat A, Baudin O, Clavel M, Chatellier D, Jaber S, Rosselli S, Mancebo J, Sirodot M, Hilbert G, Bengler C, Richecoeur J, Gannier M, Bayle F, Bourdin G, Leray V, Girard R, Baboi L, Ayzac L; PROSEVA Study Group: Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013; 368:2159–68
80. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, Gattinoni L, van Haren F, Larsson A, McAuley DF, Ranieri M, Rubenfeld G, Thompson BT, Wrigge H, Slutsky AS, Pesenti A; 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; 315:788–800
81. Schmidt M, Pham T, Arcadipane A, Agerstrand C, Ohshimo S, Pellegrino V, Vuylsteke A, Guervilly C, McGuinness S, Pierard S, Breeding J, Stewart C, Ching SSW, Camuso JM, Stephens RS, King B, Herr D, Schultz MJ, Neuville M, Zogheib E, Mira JP, Roze H, Pierrot M, Tobin A, Hodgson C, Chevret S, Brodie D, Combes A, International EN, the LSG: Mechanical ventilation management during ECMO for ARDS: An international multicenter prospective cohort. *Am J Respir Crit Care Med* 2019
82. 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; 320:2208–10
83. Javidfar J, Bacchetta M: Bridge to lung transplantation with extracorporeal membrane oxygenation support. *Curr Opin Organ Transplant* 2012; 17:496–502
84. Langer T, Santini A, Bottino N, Crotti S, Batchinsky AI, Pesenti A, Gattinoni L: “Awake” extracorporeal membrane oxygenation (ECMO): pathophysiology, technical considerations, and clinical pioneering. *Crit Care* 2016; 20:150
85. Biscotti M, Sonett J, Bacchetta M: ECMO as bridge to lung transplant. *Thorac Surg Clin* 2015; 25:17–25
86. Lassen HC: A preliminary report on the 1952 epidemic of poliomyelitis in Copenhagen with special reference to the treatment of acute respiratory insufficiency. *Lancet* 1953; 1: 37–41
87. Bendixen HH, Hedley-Whyte J, Laver MB: Impaired oxygenation in surgical patients during general anesthesia with controlled ventilation. A concept of atelectasis. *N Engl J Med* 1963; 269:991–6
88. Pontoppidan H, Hedley-Whyte J, Bendixen HH, Laver MB, Radford EP Jr: Ventilation and oxygen requirements during prolonged artificial ventilation in patients with respiratory failure. *N Engl J Med* 1965; 273:401–9
89. Gattinoni L, Tonetti T, Cressoni M, Cadringer P, Herrmann P, Moerer O, Protti A, Gotti M, Chiurazzi C, Carlesso E, Chiumello D, Quintel M: Ventilator-related causes of lung injury: The mechanical power. *Intensive Care Med* 2016; 42:1567–75
90. Gattinoni L, Marini JJ, Collino F, Maiolo G, Rapetti F, Tonetti T, Vasques F, Quintel M: The future of mechanical ventilation: Lessons from the present and the past. *Crit Care* 2017; 21:183
91. Collino F, Rapetti F, Vasques F, Maiolo G, Tonetti T, Romitti F, Niewenhuys J, Behnemann T, Camporota L, Hahn G, Reupke V, Holke K, Herrmann P, Duscio E, Cipulli F, Moerer O, Marini JJ, Quintel M, Gattinoni L: Positive end-expiratory pressure and mechanical power. *ANESTHESIOLOGY* 2019; 130:119–30
92. Protti A, Maraffi T, Milesi M, Votta E, Santini A, Pugini P, Andreis DT, Nicosia F, Zannin E, Gatti S, Vaira V, Ferrero S, Gattinoni L: Role of strain rate in the pathogenesis of ventilator-induced lung edema. *Crit Care Med* 2016; 44:e838–45
93. Cressoni M, Gotti M, Chiurazzi C, Massari D, Algieri I, Amini M, Cammaroto A, Brioni M, Montaruli C, Nikolla K, Guanzioli M, Dondossola D, Gatti S, Valerio V, Vergani GL, Pugini P, Cadringer P, Gagliano N, Gattinoni L: Mechanical power and development of ventilator-induced lung injury. *ANESTHESIOLOGY* 2016; 124:1100–8
94. Alessandri F, Pugliese F, Mascia L, Ranieri MV: Intermittent extracorporeal CO₂ removal in chronic obstructive pulmonary disease patients: A fiction or an option. *Curr Opin Crit Care* 2018; 24:29–34
95. Quintel M, Busana M, Gattinoni L: Breathing and ventilation during extracorporeal membrane oxygenation: How to find the balance between rest and load. *Am J Respir Crit Care Med* 2019; 200:954–6
96. Terragni PP, Del Sorbo L, Mascia L, Urbino R, Martin EL, Birocco A, Faggiano C, Quintel M, Gattinoni L, Ranieri VM: Tidal volume lower than 6 ml/kg enhances lung protection: role of extracorporeal carbon dioxide removal. *ANESTHESIOLOGY* 2009; 111:826–35
97. Winiszewski H, Aptel F, Belon F, Belin N, Chaignat C, Patry C, Clermont C, David E, Navellou JC, Labro G, Piton G, Capellier G: Daily use of extracorporeal CO₂ removal in a critical care unit: indications and results. *J Intensive Care* 2018; 6:36

98. Fanelli V, Ranieri MV, Mancebo J, Moerer O, Quintel M, Morley S, Moran I, Parrilla F, Costamagna A, Gaudiosi M, Combes A: Feasibility and safety of low-flow extracorporeal carbon dioxide removal to facilitate ultra-protective ventilation in patients with moderate acute respiratory distress syndrome. *Crit Care* 2016; 20:36
99. Schmidt M, Jaber S, Zogheib E, Godet T, Capellier G, Combes A: Feasibility and safety of low-flow extracorporeal CO₂ removal managed with a renal replacement platform to enhance lung-protective ventilation of patients with mild-to-moderate ARDS. *Crit Care* 2018; 22:122
100. Bein T, Weber-Carstens S, Goldmann A, Müller T, Staudinger T, Brederlau J, Muellenbach R, Dembinski R, Graf BM, Wewalka M, Philipp A, Wernecke KD, Lubnow M, Slutsky AS: 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; 39:847–56
101. Deniau B, Ricard JD, Messika J, Dreyfuss D, Gaudry S: Use of extracorporeal carbon dioxide removal (ECCO₂R) in 239 intensive care units: Results from a French national survey. *Intensive Care Med* 2016; 42:624–5
102. 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 CO₂ removal to enhance protective ventilation in acute respiratory distress syndrome: The SUPERNOVA study. *Intensive Care Med* 2019; 45:592–600
103. O'Donnell DE, Parker CM: COPD exacerbations. 3: Pathophysiology. *Thorax* 2006; 61:354–61
104. Rochweg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, Navalesi P, Antonelli M, Brozek J, Conti G, Ferrer M, Guntupalli K, Jaber S, Keenan S, Mancebo J, Mehta S, Raouf S: Official ERS/ATS clinical practice guidelines: Noninvasive ventilation for acute respiratory failure. *Eur Respir J* 2017; 50
105. Lindenauer PK, Stefan MS, Shieh MS, Pekow PS, Rothberg MB, Hill NS: Outcomes associated with invasive and noninvasive ventilation among patients hospitalized with exacerbations of chronic obstructive pulmonary disease. *JAMA Intern Med* 2014; 174:1982–93
106. Chandra D, Stamm JA, Taylor B, Ramos RM, Satterwhite L, Krishnan JA, Mannino D, Sciruba FC, Holguín F: Outcomes of noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease in the United States, 1998–2008. *Am J Respir Crit Care Med* 2012; 185:152–9
107. Pisani L, Fasano L, Corcione N, Comellini V, Guerrieri A, Ranieri MV, Nava S: Effects of extracorporeal CO₂ removal on inspiratory effort and respiratory pattern in patients who fail weaning from mechanical ventilation. *Am J Respir Crit Care Med* 2015; 192:1392–4
108. Abrams DC, Brenner K, Burkart KM, Agerstrand CL, Thomashow BM, Bacchetta M, Brodie D: Pilot study of extracorporeal carbon dioxide removal to facilitate extubation and ambulation in exacerbations of chronic obstructive pulmonary disease. *Ann Am Thorac Soc* 2013; 10:307–14
109. Burki NK, Mani RK, Herth FJF, Schmidt W, Teschler H, Bonin F, Becker H, Randerath WJ, Stieglitz S, Hagemeyer L, Priegnitz C, Pfeifer M, Blaas SH, Putensen C, Theuerkauf N, Quintel M, Moerer O: A novel extracorporeal CO(2) removal system: Results of a pilot study of hypercapnic respiratory failure in patients with COPD. *Chest* 2013; 143:678–86
110. Sklar MC, Beloncle F, Katsios CM, Brochard L, Friedrich JO: Extracorporeal carbon dioxide removal in patients with chronic obstructive pulmonary disease: A systematic review. *Intensive Care Med* 2015; 41:1752–62
111. Kluge S, Braune SA, Engel M, Nierhaus A, Frings D, Ebel H, Uhrig A, Metschke M, Wegscheider K, Suttorp N, Rousseau S: Avoiding invasive mechanical ventilation by extracorporeal carbon dioxide removal in patients failing noninvasive ventilation. *Intensive Care Med* 2012; 38:1632–9
112. Del Sorbo L, Pisani L, Filippini C, Fanelli V, Fasano L, Terragni P, Dell'Amore A, Urbino R, Mascia L, Evangelista A, Antro C, D'Amato R, Sucre MJ, Simonetti U, Persico P, Nava S, Ranieri VM: Extracorporeal CO₂ removal in hypercapnic patients at risk of noninvasive ventilation failure: A matched cohort study with historical control. *Crit Care Med* 2015; 43:120–7
113. Braune S, Sieweke A, Brettner F, Staudinger T, Joannidis M, Verbrugge S, Frings D, Nierhaus A, Wegscheider K, Kluge S: 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; 42:1437–44
114. Machado FR: All in a day's work - Equity vs. equality at a public ICU in Brazil. *N Engl J Med* 2016; 375:2420–1
115. Quintel M, Gattinoni L, Weber-Carstens S: The German ECMO inflation: When things other than health and care begin to rule medicine. *Intensive Care Med* 2016; 42:1264–6

116. Bein T, Weber-Carstens S, Herridge M: Extracorporeal life support, ethics, and questions at the bedside: How does the end of the pathway look? *Intensive Care Med* 2015; 41:1714–5
117. Abrams DC, Prager K, Blinderman CD, Burkart KM, Brodie D: Ethical dilemmas encountered with the use of extracorporeal membrane oxygenation in adults. *Chest* 2014; 145:876–82
118. Truog RD, Thiagarajan RR, Harrison CH: Ethical dilemmas with the use of ECMO as a bridge to transplantation. *Lancet Respir Med* 2015; 3:597–8
119. Ramanathan K, Cove ME, Caleb MG, Teoh KL, Maclaren G: Ethical dilemmas of adult ECMO: Emerging conceptual challenges. *J Cardiothorac Vasc Anesth* 2015; 29:229–33
120. Abrams D, Brodie D: Extracorporeal membrane oxygenation for adult respiratory failure: 2017 update. *Chest* 2017; 152:639–49
121. Abrams DC, Prager K, Blinderman CD, Burkart KM, Brodie D: The appropriate use of increasingly sophisticated life-sustaining technology. *Virtual Mentor* 2013; 15:1050–5
122. Brodie D, Curtis JR, Vincent JL, Bakker J, Brown CE, Creteur J, Papazian L, Sladen RN, Ranieri VM; participants in the Round Table Conference: Treatment limitations in the era of ECMO. *Lancet Respir Med* 2017; 5:769–70
123. Bein T, Brodie D: Understanding ethical decisions for patients on extracorporeal life support. *Intensive Care Med* 2017; 43:1510–1
124. Courtwright AM, Robinson EM, Feins K, Carr-Loveland J, Donahue V, Roy N, McCannon J: Ethics committee consultation and extracorporeal membrane oxygenation. *Ann Am Thorac Soc* 2016; 13:1553–8
125. Kolobow T, Cereda M, Sparacino ME, Trawoger R: Acute respiratory failure, mechanical ventilation, and ECMO/ECCO2R: *Quo vadis?* *Int J Artif Organs* 1997; 20:301–3
126. Chacko CJ, Goyal S, Yusuff H: Awake extracorporeal membrane oxygenation patients expanding the horizons. *J Thorac Dis* 2018; 10(Suppl 18):2215–6
127. Biscotti M, Gannon WD, Agerstrand C, Abrams D, Sonett J, Brodie D, Bacchetta M: Awake extracorporeal membrane oxygenation as bridge to lung transplantation: A 9-year experience. *Ann Thorac Surg* 2017; 104:412–9
128. Strueber M, Hoepfer MM, Fischer S, Cypel M, Warnecke G, Gottlieb J, Pierre A, Welte T, Haverich A, Simon AR, Keshavjee S: Bridge to thoracic organ transplantation in patients with pulmonary arterial hypertension using a pumpless lung assist device. *Am J Transplant* 2009; 9:853–7
129. Schmid C, Philipp A, Hilker M, Arlt M, Trabold B, Pfeiffer M, Schmid FX: Bridge to lung transplantation through a pulmonary artery to left atrial oxygenator circuit. *Ann Thorac Surg* 2008; 85:1202–5
130. Camboni D, Philipp A, Arlt M, Pfeiffer M, Hilker M, Schmid C: First experience with a paracorporeal artificial lung in humans. *ASAIO J* 2009; 55:304–6
131. Zwischenberger BA, Clemson LA, Zwischenberger JB: Artificial lung: Progress and prototypes. *Expert Rev Med Devices* 2006; 3:485–97
132. Maul TM, Nelson JS, Wearden PD: Paracorporeal lung devices: Thinking outside the box. *Front Pediatr* 2018; 6:243
133. Naito N, Cook K, Toyoda Y, Shigemura N: Artificial lungs for lung failure: JACC technology corner. *J Am Coll Cardiol* 2018; 72:1640–52
134. Skoog DJ, Pohlmann JR, Demos DS, Scipione CN, Iyengar A, Schewe RE, Suhaib AB, Koch KL, Cook KE: Fourteen day *in vivo* testing of a compliant thoracic artificial lung. *ASAIO J* 2017; 63:644–9
135. Sato H, Hall CM, Lafayette NG, Pohlmann JR, Padiyar N, Toomasian JM, Haft JW, Cook KE: Thirty-day in-parallel artificial lung testing in sheep. *Ann Thorac Surg* 2007; 84:1136–43; discussion 1143
136. Amoako KA, Sundaram HS, Suhaib A, Jiang S, Cook KE: Multimodal, biomaterial-focused anticoagulation via superlow fouling zwitterionic functional groups coupled with anti-platelet nitric oxide release. *Advanced Materials Interfaces* 2016; 3: 1500646
137. Wiegmann B, von Seggern H, Höffler K, Korossis S, Dipresa D, Pflaum M, Schmeckebier S, Seume J, Haverich A: Developing a biohybrid lung - Sufficient endothelialization of poly-4-methyl-1-pentene gas exchange hollow-fiber membranes. *J Mech Behav Biomed Mater* 2016; 60:301–11
138. Pflaum M, Kühn-Kauffeldt M, Schmeckebier S, Dipresa D, Chauhan K, Wiegmann B, Haug RJ, Schein J, Haverich A, Korossis S: Endothelialization and characterization of titanium dioxide-coated gas-exchange membranes for application in the bioartificial lung. *Acta Biomater* 2017; 50:510–21
139. Salley SO, Song JY, Whittlesey GC, Klein MD: Immobilized carbonic anhydrase in a membrane lung for enhanced CO₂ removal. *ASAIO Trans* 1990; 36:M486–90
140. Tevaearai HT, Mueller XM, Tepic S, Cotting J, Boone Y, Montavon PM, von Segesser LK: Nitric oxide added to the sweep gas infusion reduces local clotting formation in adult blood oxygenators. *ASAIO J* 2000; 46:719–22
141. Weitz JI: Factor XI and factor XII as targets for new anticoagulants. *Thromb Res* 2016; 141 Suppl 2:S40–5
142. Kenne E, Nickel KF, Long AT, Fuchs TA, Stavrou EX, Stahl FR, Renné T: Factor XII: a novel target for safe prevention of thrombosis and inflammation. *J Intern Med* 2015; 278:571–85

143. Maul TM, Massicotte MP, Wearden PD: ECMO Biocompatibility: Surface Coatings, Anticoagulation, and Coagulation Monitoring, Extracorporeal Membrane Oxygenation Edited by Fistenberg MS, 2016
144. Barrett NA, Camporota L: The evolving role and practical application of extracorporeal carbon dioxide removal in critical care. *Crit Care Resusc* 2017; 19(Suppl 1):62–7
145. Manap HH, Abdul Wahab AK: Extracorporeal carbon dioxide removal (ECCO2R) in respiratory deficiency and current investigations on its improvement: A review. *J Artif Organs* 2017; 20:8–17
146. Tapia P, Lillo F, Soto D, Escobar L, Simon F, Hernández K, Alegría L, Bruhn A: Liquid extracorporeal carbon dioxide removal: use of THAM (tris-hydroxymethyl aminomethane) coupled to hemofiltration to control hypercapnic acidosis in a porcine model of protective mechanical ventilation. *Am J Transl Res* 2016; 8:3493–502
147. May AG, Sen A, Cove ME, Kellum JA, Federspiel WJ: Extracorporeal CO₂ removal by hemodialysis: *In vitro* model and feasibility. *Intensive Care Med Exp* 2017; 5:20
148. Gille JP, Saunier C, Schrijen F, Hartemann D, Tousseul B: Metabolic CO₂ removal by dialysis: THAM vs NaOH infusion. *Int J Artif Organs* 1989; 12:720–7
149. Chang BS, Garella S: Complete extracorporeal removal of metabolic carbon dioxide by alkali administration and dialysis in apnea. *Int J Artif Organs* 1983; 6:295–8
150. Zanella A, Patroniti N, Isgro S, Albertini M, Costanzi M, Pirrone F, Scaravilli V, Vergnano B, Pesenti A: Blood acidification enhances carbon dioxide removal of membrane lung: an experimental study. *Intensive Care Med* 2009; 35:1484–7
151. Zanella A, Mangili P, Redaelli S, Scaravilli V, Giani M, Ferlicca D, Scaccabarozzi D, Pirrone F, Albertini M, Patroniti N, Pesenti A: Regional blood acidification enhances extracorporeal carbon dioxide removal: A 48-hour animal study. *ANESTHESIOLOGY* 2014; 120:416–24
152. Scaravilli V, Di Girolamo L, Scotti E, Busana M, Biancolilli O, Leonardi P, Carlin A, Lonati C, Panigada M, Pesenti A, Zanella A: Effects of sodium citrate, citric acid and lactic acid on human blood coagulation. *Perfusion* 2018; 33:577–83
153. Kimmel JD, Arazawa DT, Ye SH, Shankarraman V, Wagner WR, Federspiel WJ: Carbonic anhydrase immobilized on hollow fiber membranes using glutaraldehyde activated chitosan for artificial lung applications. *J Mater Sci Mater Med* 2013; 24:2611–21
154. Kaar JL, Oh HI, Russell AJ, Federspiel WJ: Towards improved artificial lungs through biocatalysis. *Biomaterials* 2007; 28:3131–9
155. Arazawa DT, Oh HI, Ye SH, Johnson CA Jr, Woolley JR, Wagner WR, Federspiel WJ: Immobilized carbonic anhydrase on hollow fiber membranes accelerates CO(2) removal from blood. *J Memb Sci* 2012; 404-404:25–31
156. Zanella A, Castagna L, Salerno D, Scaravilli V, Abd El Aziz El Sayed Deab S, Magni F, Giani M, Mazzola S, Albertini M, Patroniti N, Mantegazza F, Pesenti A: Respiratory electro dialysis: A novel, highly efficient extracorporeal CO₂ removal technique. *Am J Respir Crit Care Med* 2015; 192:719–26
157. Arazawa DT, Kimmel JD, Finn MC, Federspiel WJ: Acidic sweep gas with carbonic anhydrase coated hollow fiber membranes synergistically accelerates CO₂ removal from blood. *Acta Biomater* 2015; 25:143–9
158. Pelosi P, Rocco PRM, Gama de Abreu M: Close down the lungs and keep them resting to minimize ventilator-induced lung injury. *Crit Care* 2018; 22:72
159. Lachmann B: Open up the lung and keep the lung open. *Intensive Care Med* 1992; 18:319–21
160. Del Sorbo L, Tonetti T, Ranieri VM: Alveolar recruitment in acute respiratory distress syndrome: Should we open the lung (no matter what) or may accept (part of) the lung closed? *Intensive Care Med* 2019; 45:1436–9
161. Gattinoni L, Pesenti A, Mascheroni D, Marcolin R, Fumagalli R, Rossi F, Iapichino G, Romagnoli G, Uziel L, Agostoni A: Low-frequency positive-pressure ventilation with extracorporeal CO₂ removal in severe acute respiratory failure. *JAMA* 1986; 256:881–6
162. Araos J, Alegria L, Garcia P, Cruces P, Soto D, Erranz B, Amthauer M, Salomon T, Medina T, Rodriguez F, Ayala P, Borzone GR, Meneses M, Damiani F, Retamal J, Cornejo R, Bugedo G, Bruhn A: 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; 199:603–12
163. Hooper SB, Wallace MJ: Role of the physicochemical environment in lung development. *Clin Exp Pharmacol Physiol* 2006; 33:273–9
164. Barbaro RP, Odetola FO, Kidwell KM, Paden ML, Bartlett RH, Davis MM, Annich GM: 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; 191:894–901