# Extracorporeal Gas Exchange The Expanding Role of Extracorporeal Support in Respiratory Failure 

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## KEYWORDS

- Extracorporeal membrane oxygenation (ECMO) • Extracorporeal gas exchange
- Extracorporeal life support • Respiratory failure • Mechanical ventilation
- Extracorporeal carbon dioxide removal


## KEY POINTS

- Extracorporeal support for respiratory failure is growing rapidly; critical care physicians will be required to make informed decisions about the application of extracorporeal gas exchange.
- Venovenous extracorporeal gas exchange for severe respiratory failure may be used to rescue patients with severe acute respiratory distress syndrome (ARDS) who are not responding to lung protective ventilation and optimal critical care therapies.
- Extracorporeal carbon dioxide removal is a promising emerging therapy that may be used as a preventive and even preemptive strategy in patients with non-ARDS respiratory failure.


## INTRODUCTION

Mechanical ventilation defines the modern intensive care unit, yet it is clear that positive pressure ventilation injures the lungs. ${ }^{1}$ Normal human inspiration is a negative pressure process, but positive pressure ventilation is necessary when gas exchanged is deranged due to lung injury. ${ }^{2}$ When positive pressure ventilation does not achieve adequate gas exchange, the application of more positive pressure in many different ways has been used over the last 50 years. Despite extensive and well-done clinical trials, the optimal method of supporting severely injured lungs remains unclear.

Solid evidence exists that lung protective ventilation improves outcomes in patients with
respiratory failure, yet for the patients who fail lung protective ventilation, any evidence for an alternative supportive therapy that improves survival remains in equipoise. ${ }^{3}$ Most ventilator support modes used after the failure of protective ventilation involve the use of higher pressures and/or volumes, which directly challenge the principles of lung protection.

Over the last decade, extracorporeal support has emerged as a promising supportive therapy for adults with respiratory failure. Similar to the microprocessor technology that informs mechanical ventilators, extracorporeal technology has evolved faster than the ability to examine it in randomized controlled trials (RCTs). This paucity of evidence has understandably engendered caution in the pulmonary critical care community regarding

[^0]extracorporeal support. The use of extracorporeal support, however, is expanding rapidly for adults with respiratory failure worldwide. Intensive care physicians will need to make prudent decisions about the application of extracorporeal support as they confront a significant paradigm shift in the care of patients with respiratory failure.

## EXTRACORPOREAL SUPPORT TERMINOLOGY

Extracorporeal membrane oxygenation (ECMO) is a temporary extracorporeal life support system (ECLS) to support a failing cardiopulmonary system in the setting of severe critical illness requiring mechanical ventilator support. ECMO may be implemented via venoarterial (VA-ECMO) or venovenous (VV-ECMO) approaches to exchange carbon dioxide $\left(\mathrm{CO}_{2}\right)$ and oxygen under high blood flow conditions (up to $7 \mathrm{~L} / \mathrm{min}$ ) requiring large canulas (20-31 Fr) ${ }^{4}$ (Table 1). Extracorporeal $\mathrm{CO}_{2}$ removal $\left(\mathrm{ECCO}_{2} \mathrm{R}\right)$ incorporates a device that removes $\mathrm{CO}_{2}$ at lower blood flow rates ( $<1.5 \mathrm{~L} / \mathrm{min}$ ) through smaller cannulas (14-23 Fr). ${ }^{5}$

Respiratory dialysis (RD) refers to the use of a hemofiltration system often in series with a gas exchange membrane and can decarboxylate blood at lower flow rates using smaller catheters. The term extracorporeal gas exchange refers to VV$\mathrm{ECMO}, \mathrm{ECCO}_{2} \mathrm{R}$, and RD techniques that facilitate ventilation. Although VA-ECMO can provide full cardiopulmonary support in patients with both severe cardiac and pulmonary failure, extracorporeal gas exchange supports intolerable hypoxia and/or hypercapnia and may facilitate lung protection strategies in severe cases of acute respiratory distress syndrome (ARDS). ${ }^{6}$ The acronym ECMO is linguistically incomplete, because ECMO regulates both oxygen and $\mathrm{CO}_{2}$, but the term has persisted despite some attempts in the ECMO community to use the more inclusive term ECLS. As the technology of the pump, oxygenator, circuit, and cannulas evolves, the indications for ECLS have expanded to include non-ARDS respiratory failure, hypercapnic failure, bridge-to-lung transplantation, pulmonary hypertension, and donor lung resuscitation (Box 1). ${ }^{7,8}$ ECMO and ECLS in

| Table 1 Terms |  |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: |
| Terms | Key Features | Support | $\begin{aligned} & \begin{array}{l} \text { Blood Flow } \\ (\mathrm{L} / \mathrm{min}) \end{array} \\ & \hline \end{aligned}$ | Cannula <br> Size | Priming Volume (mL) |
| VA-ECMO | Drains blood from the venous system and pumps it through a membrane oxygenator. Oxygenated blood is returned to the arterial system | Full cardiacpulmonary support | $\begin{aligned} & \text { High } \\ & 2-6 \end{aligned}$ | Large (17-31 Fr) | 500 |
| VV-ECMO | Drains blood from the venous system, pumps it through a membrane oxygenator, and returns it back to the venous system | Respiratory support | $\begin{aligned} & \text { High } \\ & 2-5 \end{aligned}$ | Large (20-30 Fr) | 500 |
| $\mathrm{ECCO}_{2} \mathrm{R}$ | Uses a venovenous (typically) or arteriovenous device to remove $\mathrm{CO}_{2}$ | Respiratory support | $\begin{aligned} & \hline \text { Low } \\ & 0.25-2 \end{aligned}$ | Smaller (14-20 Fr) | 300 |
| RD | Venovenous device based on modified hemofiltration system with a membrane in series | Respiratory support | $\begin{aligned} & \hline \text { Low } \\ & 0.25-0.55 \end{aligned}$ | Smaller (13-17 Fr) | 280 |
| Extra-corporeal gas exchange | Refers to VV-ECMO, $\mathrm{ECCO}_{2} \mathrm{R}$, and RD techniques | Respiratory support | High-low | Large-small | - |

## Box 1 <br> Expanding indications for the use of extracorporeal gas exchange

1. Hypercapnic failure (COPD, asthma, toxic overdose)
2. Bridge to lung transplantation
3. Pulmonary hypertension with right heart failure
4. Earlier use in less severe hypoxic respiratory failure
5. Resuscitation of donor lungs before transplantation
6. Bridge to early mobility
this review will refer to their use for extracorporeal gas exchange for respiratory failure. The rationale, indications, and practical implementation of extracorporeal gas exchange in clinical practice are addressed.

## HISTORICAL CONTEXT AND CURRENT EVIDENCE BASE FOR THE USE EXTRACORPOREAL GAS EXCHANGE

ECMO and $\mathrm{ECCO}_{2} \mathrm{R}$ advanced from bench-side experiments to clinical practice in the late 1960s and early 1970s. ${ }^{9,10}$ However, 4 decades of early trials implementing ECMO for critically ill adults showed a lack of benefit despite its theoretic intentions. ${ }^{11,12}$ Since these early trials, technology and the management of respiratory failure in intensive care units have evolved greatly. Critical care medicine now uses multidisciplinary teams, evidencebased protocols, efficient care bundles, lung protective ventilation strategies, paralysis, prone positioning, and minimization of fluids and sedation. Changes in intensive care medicine and significant technological advancement of cannulas, centrifugal pumps, biocompatible circuit components, and more efficient and durable membranes that optimize gas exchange while decreasing complications have led to rapid growth in the use of ECLS. ${ }^{13}$ As a result, VV-ECMO and $E C C O 2 R$ have seen a resurgence in the new millennium. ${ }^{7}$ Encouraging results from refractory H1N1 influenza-related ARDS cases, ${ }^{14-16}$ the Conventional ventilator support versus Extracorporeal membrane oxygenation for Severe Adult Respiratory Failure (CESAR) trial, ${ }^{17}$ and the Xtravent trial, which showed $\mathrm{ECCO}_{2} \mathrm{R}$ beneficence as an adjunct to lung protective ventilation, ${ }^{18}$ have all helped drive this resurgence.

## Evidence for Venovenous Extracorporeal Membrane Oxygenation

Recently Cochrane reviewed the evidence of ECLS in respiratory failure, including only RCTs, quasi-RCTs, and cluster-RCTs that compared adult ECLS versus conventional support. Between 1979 and 2015, only 4 RCTs met Cochrane's inclusion criteria (Table 2). Unfortunately, these trials are heterogeneous and prevent pooling of data.
The trials by Zapol and colleagues ${ }^{11}$ and Morris and colleagues ${ }^{12}$ are not applicable in 2016 due the changes in technology and critical care medicine. Even the CESAR trial (Peek and colleagues ${ }^{17}$ ) used roller pumps and a higher than usual use of liver dialysis or molecular adsorbents recirculating system, neither of which are used often in highvolume adult centers that report favorable outcomes. The CESAR trial essentially showed that if patients are sent to an experienced ECMO center, they have improved outcomes, independent of the application of ECMO support. Despite some of the methodological limitations of the CESAR trial, it has been influential in reviving interest and use of ECLS.

In addition to the trials included in the Cochrane review, in the last 15 years, there have been 16 published case control studies and case series involving 32 patients or more (Box 2). Another 16 case control studies and case series with 6 or more patients involving the use of ECMO in H1N1 influenza exist in the literature.

A multicenter international RCT is currently underway, named EOLIA (ECMO to rescue Lung Injury in severe ARDS). ${ }^{6}$ Experienced centers will use the most recent ECMO technology and will compare early initiation of VV ECMO to a control arm of mechanical ventilation using high positive end expiratory pressure (PEEP), plateau pressure less than 28 to $30 \mathrm{~cm} \mathrm{H}_{2} \mathrm{O}$, and tidal volume limited to $6 \mathrm{~mL} / \mathrm{kg}$ of ideal body weight. The control arm will follow the mechanical ventilation strategy in the EXPRESS trial, and it will also include prone positioning. ${ }^{19}$ The estimated patient enrollment is 331 and estimated primary completion date is February 2016.

## EVIDENCE FOR EXTRACORPOREAL CARBON DIOXIDE REMOVAL IN HYPOXIC AND HYPERCARBIC RESPIRATORY FAILURE Extracorporeal Carbon Dioxide Removal for Acute Respiratory Distress Syndrome

Much of the early work related to $\mathrm{ECCO}_{2} \mathrm{R}$ involved patients with ARDS. In general, most studies showed improvement in $\mathrm{PaCO}_{2}$ and accommodated low lung volume ventilation. A

| Table 2 <br> Selected randomized controlled trials of extracorporeal membrane oxygenation versus conventional treatment in acute respiratory distress syndrome |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: |
|  | Zapol et al, ${ }^{11} 1979$ | $\text { Morris et al, }{ }^{12}$ $1994$ | Peek et al, ${ }^{17} 2009$ | Bein et al, ${ }^{18} 2013$ |
| Intervention | VA-ECMO | $\mathrm{VV}-\mathrm{ECCO}_{2} \mathrm{R}$ | VV-ECMO | $\mathrm{AV}-\mathrm{ECCO}_{2} \mathrm{R}$ |
| All cause mortality (IG vs CG) | $\begin{gathered} \hline 38 / 42 \text { (91\%) vs } \\ 44 / 48 \text { (92\%) } \end{gathered}$ | $\begin{gathered} \hline \text { 14/21 (66\%) vs } \\ 11 / 19 \text { (57\%) } \end{gathered}$ | $\begin{gathered} \hline 33 / 90(37 \%) \text { vs } \\ 45 / 90(50 \%) \end{gathered}$ | $\begin{gathered} \hline 7 / 40(17.5 \%) \text { vs } \\ 6 / 39(15.4 \%) \end{gathered}$ |
| Relative risk | $\begin{aligned} & 0.99 \text { (0.97-1.12, } \\ & 95 \% \mathrm{CI}) \end{aligned}$ | $\begin{aligned} & 1.15(0.71-1.88, \\ & 95 \% \mathrm{CI}) \end{aligned}$ | $\begin{aligned} & 0.73 \text { (0.52-1.03, } \\ & 95 \% \mathrm{CI}) \end{aligned}$ | $\begin{aligned} & 1.14 \text { (0.42-3.08, } \\ & 95 \% \mathrm{CI}) \end{aligned}$ |
| Length of hospital stay in days (IG vs CG) | Not reported | 26.9 vs 28.8; not significant | 35 vs 17 | 46.7 vs 35.1 |
| Survival to discharge (IG vs CG) | Not reported | $\begin{aligned} & 7 / 21(33 \%) \text { vs } 8 / 19 \\ & \text { (42\%); not } \\ & \text { significant } \\ & \hline \end{aligned}$ | Not reported | $\begin{gathered} \hline 33 / 40(83 \%) \text { vs } \\ 33 / 39(85 \%) ; \\ \text { not significant } \end{gathered}$ |
| Disability as reported by study authors (IG vs CG) | Normal lung function: 7/8 vs 7/8; no limitations to daily activities for all survivors | Not reported | No severe disability at 6 mo: 57/90 (63\%) vs 41/87 (47\%); significant | Not reported |
| Statistically significant adverse outcomes | IG with lower blood platelets, lower WBC concentration, and increased blood and plasma transfusion | IG with increased non-brain hemorrhage events and transfusion requirements | IG with one death due to mechanical failure of oxygen supply during ambulation; one patient with vessel perforation during cannulation | IG with one patient with transient ischemia of the lower limb; 2 patients with "false aneurysm" from arterial cannulation |

Abbreviations: CG, control group; IG, intervention group.
Adapted from Tramm R, Ilic D, Davies AR, et al. Extracorporeal membrane oxygenation for critically ill adults. Cochrane Database Syst Rev 2015;1:CD010381; with permission.

## Box 2

Studies with more than 30 patients performed on adults using extracorporeal support for respiratory failure since 2000

- 3 case control studies
- 13 case series
- Mortality ranged from $13 \%$ to $57 \%$
- Multiple different technologies used
- Heterogeneous patient populations

Adapted from Schmidt M, Hodgson C, Combes A. Extracorporeal gas exchange for acute respiratory failure in adult patients: a systematic review. Crit Care 2015;19:99.
recent excellent review by Schmidt and colleagues ${ }^{13}$ provides a comprehensive review of $\mathrm{ECCO}_{2} \mathrm{R}$ for ARDS (Box 3). The concept of using extracorporeal support to facilitate $\mathrm{CO}_{2}$ removal as an adjunct to positive pressure ventilation was introduced and investigated as early as 1978 by Gattinoni and colleagues. ${ }^{20}$

The SUPERNOVA trial (A Strategy of Ultraprotective lung Ventilation with Extracorporeal $\mathrm{CO}_{2}$ Removal for New-Onset moderate to Severe ARDS) is currently enrolling patients in multiple international centers. ${ }^{21}$ Data from a pilot trial examining if $\mathrm{ECCO}_{2} \mathrm{R}$ can improve outcomes by enhancing lung protection will be used to develop clinical endpoints for a larger RCT. A 15.5- to 19-Fr


#### Abstract

Box 3 Studies involving use of extracorporeal carbon dioxide removal for hypoxic respiratory failure since the year 2000 - 1 randomized controlled study - 6 case series - All used a pumpless $\operatorname{AV} \mathrm{ECCO}_{2} \mathrm{R}$ configuration - Mortality ranged from $17 \%$ to $82 \%$ - Variable devices used - Heterogeneous patient populations

From Osborn E. Principle investigator: Comparison of Early Complete Rest versus Gradual Optimal Positive Airway Pressure for Ventilation in an Oleic Acid Porcine Lung Injury Model Supported by Venovenous Extracorporeal Support, in press.


venous double-lumen cannula will be used with a centrifugal pump and polymethylpentene (PMP) gas transfer membrane to achieve the primary outcome of a tidal volume reduction to $4 \mathrm{~mL} / \mathrm{kg}$ while maintaining a pH and $\mathrm{PaCO}_{2}$ within $20 \%$ of the baseline values obtained at a tidal volume of $6 \mathrm{~mL} / \mathrm{kg}$.

## Extracorporeal Carbon Dioxide Removal for Hypercapnic Respiratory Failure Without Acute Respiratory Distress Syndrome

Recently, literature has been accumulating for patients with hypercapnic respiratory failure without ARDS, particularly in patients with chronic obstructive pulmonary disease (COPD). Although there are no published RCTs, early retrospective studies and case studies suggest there may be an expanding role for $E \mathrm{ECO}_{2} \mathrm{R}$ as a minimally invasive tool to manage hypercapnic respiratory failure-related exacerbations and prevent intubations and/or prolonged mechanical ventilation. Table 3 provides a review of the English language studies of $\mathrm{ECCO}_{2} \mathrm{R}$ use related to non-ARDS hypercapnic respiratory failure. The positive results suggested in these small studies warrant further validation with prospective randomized trials.

## PERMISSIVE HYPERCAPNIA IN SEVERE RESPIRATORY FAILURE AND ITS PHYSIOLOGIC EFFECTS: RATIONALE FOR EXTRACORPOREAL CARBON DIOXIDE REMOVAL

The National Institutes of Health ARDS Network (ARDSnet) found that hypercapnic acidosis is something to tolerate for the mortality benefits from lung-protective ventilation using low-tidalvolume, low-pressure mechanical ventilation
strategies. ${ }^{22}$ Low-tidal-volume ventilation may result in decreased respiratory compliance resulting in hypercapnic acidosis. Although there have been suggestions that hypercapnia may mitigate lung injury and inflammation in ARDS, the evidence is conflicted, and there is a limit to the reduction in pH that patients will tolerate. In fact, excess and/or prolonged $\mathrm{CO}_{2}$ "costs" may include cardiovascular and cerebral depression, arrhythmias, gastric acidosis, and pulmonary vasoconstriction. In particular, hypoxic pulmonary vasoconstriction in ARDS has been shown to increase pulmonary artery pressure, which may exacerbate right ventricular failure. ${ }^{23,24}$ In addition, hypercapnia may also impair healing in the lung. Elevated $\mathrm{CO}_{2}$ levels cause mitochondrial dysfunction and lead to decreased oxygen consumption, decreased ATP production, and impaired cell proliferation. ${ }^{25}$ Proliferation and migration of alveolar epithelial type II pneumocytes are important for healing in lung injury. ${ }^{26}$

## EXTRACORPOREAL GAS EXCHANGE MAY FACILITATE LUNG PROTECTIVE VENTILATION; RATIONALE FOR CARBON DIOXIDE REMOVAL

Significant reductions in pH caused by hypercapnia may force intensivists to abandon low-tidalvolume ventilation strategies. ${ }^{27}$ Extracorporeal gas exchange offers the opportunity to continue low-tidal-volume ventilation and maintain pH , therefore enhancing lung protective ventilation and avoiding the complications of hypercapnia.

Batchinsky and colleagues ${ }^{28}$ have professed the role of extracorporeal gas exchange as a form of "respiratory dialysis" to facilitate lung protective ventilation. Terragni and colleagues ${ }^{29}$ clinically showed that low tidal volumes at $4 \mathrm{~mL} / \mathrm{kg}$ with $\mathrm{ECCO}_{2} \mathrm{R}$ resulted in more tolerable permissive hypercapnia with reductions in plateau pressures and inflammatory cytokines. Bein and colleagues ${ }^{18}$ used "ultralow" tidal volumes of $3 \mathrm{~mL} / \mathrm{kg}$ with $\mathrm{ECCO}_{2} \mathrm{R}$ to show feasibility and lack of harm compared with more conventional protective ventilation at $6 \mathrm{~mL} / \mathrm{kg}$ in patients with ARDS. This study was not powered to assess mortality, but there were higher ventilator-free days at 1 and 2 months and reduction in the amount of sedation and analgesia during mechanical ventilation in the $\mathrm{ECCO}_{2} \mathrm{R}$ group versus "conventional" control group.

## INDICATIONS FOR EXTRACORPOREAL LIFE SUPPORT IN RESPIRATORY FAILURE AND PATIENT SELECTION

Indications and patient selection for use of VV ECMO or $\mathrm{ECCO}_{2} \mathrm{R}$ are developed by each

| Table 3 <br> English language studies of extracorporeal carbon dioxide removal for non-acute respiratory distress syndrome hypercapnic respiratory failure |  |  |  |
| :---: | :---: | :---: | :---: |
| Author | Trial Design | Study Population (No.) | Key Outcomes |
| Cardenas et al, ${ }^{40} 2009$ | Case study | COPD/asthma (1) | $\mathrm{VV}-\mathrm{ECCO}_{2} \mathrm{R}$ used successful for treating AECOPD |
| $\begin{aligned} & \text { Kluge et al, }{ }^{41} \\ & 2012 \end{aligned}$ | Multicenter retrospective RCT | Hypercapneic respiratory failure failing $\mathrm{NIV}^{\text {a }}$ (21) | $\mathrm{AV}-\mathrm{ECCO}_{2} \mathrm{R}$ group avoided intubation: IG $2 / 21$ ( $10 \%$ ) vs CG 21/21 ( $100 \%$ ). <br> Compared with conventional invasive ventilation, short- and long-term survivals and length of hospital stay were similar. Statistically significant return to baseline arterial pH and $\mathrm{PCO}_{2}$ and respiratory rate within first 24 h in IG |
| $\begin{aligned} & \text { Burki et al, }{ }^{42} \\ & 2013 \end{aligned}$ | Single-center prospective pilot study | COPD (20) | Single-catheter, low-flow $\mathrm{ECCO}_{2} \mathrm{R}$ system provided clinically useful levels of $\mathrm{CO}_{2}$ removal in these patients with COPD |
| $\begin{aligned} & \text { Abrams et al, }{ }^{43} \\ & 2013 \end{aligned}$ | Single-center prospective pilot study | COPD (5) | $\mathrm{ECCO}_{2} \mathrm{R}$ facilitates early extubation and ambulation in AECOPD requiring invasive mechanical ventilation |
| $\begin{aligned} & \text { Bonin et al, }{ }^{44} \\ & 2013 \end{aligned}$ | Case study | COPD patient failing NIV with a persistent pneumothorax (1) | $\mathrm{ECCO}_{2} \mathrm{R}$ prevented intubation |
| $\begin{aligned} & \text { Brenner et al, }{ }_{2013} \\ & 25 \end{aligned}$ | Case study | Status asthmaticus (2) | $\mathrm{ECCO}_{2} \mathrm{R}$ corrected the respiratory acidosis and allowed for reductions in respiratory rate and tidal volume, which reversed dynamic hyperinflation in both cases |
| $\begin{aligned} & \hline \text { Del Sorbo } \\ & \text { et } \mathrm{al}^{46} 2013 \end{aligned}$ | Multicenter matched cohort study with historical control | Hypercapneic respiratory failure (46) | Risk of being intubated was $3 \times$ higher in patients treated with noninvasive ventilation-only than in patients treated with noninvasive ventilation-plusextracorporeal $\mathrm{CO}_{2}$ removal |
| $\begin{aligned} & \text { Cole et al, }{ }^{47} \\ & 2014 \end{aligned}$ | Case study | AECOPD patient unresponsive to NIV (1) | Initiation of $\mathrm{ECCO}_{2} \mathrm{R}$ was used effectively to prevent endotracheal intubation |

Abbreviations: AECOPD, acute exacerbation of COPD; CG, control group; IG, intervention group; NIV, noninvasive ventilation.
${ }^{\text {a }}$ In Kluge's study, 14/21 were COPD; the remainder were patients with cystic fibrosis (2/21), pulmonary graft-vs-host disease (2/21), pulmonary fibrosis (1/21), and bronchial asthma (1/21). Of note, $9 / 21$ patients in the $E C C O_{2} R$ group were on the lung transplant list compared with $0 / 21$ in the matched control group.
institution and variation exists. The Extracorporeal Life Support Organization (ELSO) has published expert guidelines informed by available evidence, which are listed in Box 4.

Once the indications for extracorporeal support have been met, patient selection may be further guided by the list in Box 5 .

Different perspectives exist regarding the definition of failure of optimal treatment. The inability to achieve lung protective ventilation for a period of 6 to 12 hours, depending on the severity of the patient's gas exchange abnormalities, for example, acidosis compromising perfusion, may favor
earlier ECLS initiation. In addition to lung protective ventilation, the other 2 interventions that have been shown to improve survival in severe hypoxic respiratory failure, neuromuscular blockade and prone positioning, are often used before ECLS initiation. Different perspectives may exist about the use of paralytics and prone positioning, but both interventions confer lower risk and cost for the patient when compared with ECLS. ${ }^{30,31}$
Once a patient is identified as a potential candidate for extracorporeal support, an additional clinic tool called the RESP score can be helpful

## Box 4 <br> Suggested indications for extracorporeal gas exchange in respiratory failure

- Severe hypoxic respiratory failure with $\mathrm{Pao}_{2} / \mathrm{Fio}_{2}$ ration less than 100 on greater than $90 \%$ and/or Murray score of 3 to 4 despite optimal care for 6 to 12 hours
- Concurrent respiratory failure and mild-to-moderate cardiac failure unresponsive to optimal care
- Severe air leak syndromes
- Potential bridge to lung transplantation
- $\mathrm{CO}_{2}$ retention on mechanical ventilation despite optimal mechanical ventilation in the setting of high plateau pressures greater than $30 \mathrm{~mm} \mathrm{Hg}\left(\mathrm{ECCO}_{2} \mathrm{R}\right.$ may be a viable alternative)

There are few absolute contraindications to VV - ECMO or $\mathrm{ECCO}_{2} \mathrm{R}$ and risks versus benefits must be weighed for each individual patient.
Adapted from ELSO adult respiratory failure guidelines. Available at: http://www.elso.org/Portals/0/IGD/Archive/ FileManager/989d4d4d14cusersshyerdocumentselsoguidelinesforadultrespiratoryfailure1.3.pdf. Accessed January 17, 2016.
in predicting survival after ECLS in ARDS. ${ }^{32}$ The RESP score stands for the Respiratory Extracorporeal membrane oxygenation Survival Prediction score and was developed by analyzing 12 preECMO variables in 2355 international patients. The variables are listed in Box 6, and an online calculator exists at www.respscore.com. The RESP score was externally validated by comparing it with the PRESERVE score, another prognostication model developed from 140 ECMO-treated patients in 3 French intensive care units. ${ }^{33}$
Each variable in the RESP score is assigned a number, from -7 for central nervous system (CNS) dysfunction to 11 for asthma, for example, and a total score from -22 to 15 is calculated. The total score places patients in a risk class from I to V that predicts hospital survival, where a higher score confers a higher survival percentage. CNS dysfunction includes neurotrauma, stroke, encephalopathy, cerebral embolism, and seizure. An immunocompromised status is defined by a hematologic malignancy, solid tumor, solid organ transplant, human immunodeficiency virus, and cirrhosis.

## Box 5 <br> Patient selection for extracorporeal support

1. Failure of optimal evidence-based treatment and support
2. Reversible process exists
3. Ability to tolerate anticoagulation
4. Good neurologic outcome is possible
5. Good functional status before current illness and lack of chronic organ dysfunction in patients who are not transplant candidates

## TECHNICAL ASPECTS: CANNULA, CIRCUIT, PUMP, GAS EXCHANGE MEMBRANE

An extracorporeal system requires at least 4 components: a cannula or cannulas, tubing for the circuit, usually a pump, and a gas exchange device. Additional components include a heater/cooler, pressure monitor, continuous blood gas analyzer, and flow meter. Some of the newer devices have pressure, temperature, blood gas analyzers, and flow meters included into their system already.

## Cannulation

Most extracorporeal gas exchange strategies will involve VV-ECMO. Venovenous access is usually

## Box 6 <br> RESP score to predict survival for extracorporeal membrane oxygenation patients

1. Age
2. Immunocompromised status
3. Duration of mechanical ventilation before ECMO
4. Acute respiratory distress diagnosis group
5. Central nervous system dysfunction
6. Acute associated (nonpulmonary) infection
7. Neuromuscular blockage agents before ECMO
8. Nitric oxide use before ECMO
9. Bicarbonate infusion before ECMO
10. Cardiac arrest before ECMO
11. $\mathrm{PaCO}_{2}>75 \mathrm{~mm} \mathrm{Hg}$
12. Peak inspiratory pressure $>42 \mathrm{~cm} \mathrm{H}_{2} \mathrm{O}$
obtained via a double-lumen catheter (DLC) in relatively stable patients. With the DLC, blood is drained from the vena cavae, enters the ECLS circuit and oxygenator, and is returned in the right atrium. Percutaneous placement of a large DLC using the Seldinger technique into the internal jugular vein is safely done using fluoroscopy to ensure the guide wire remains in the inferior vena cava and to allow visualization of the radiotranslucent portion of the DLC in the right atrium. Transthoracic and transesophageal ultrasound are also used to assist with placement of the outflow port in the right atrium. Doppler views are used once flow has been initiated to confirm that the return jet of oxygenated blood is traversing the tricuspid valve. Fig. 1 shows a picture of a $31-\mathrm{Fr}$ DLC in a patient. Fig. 2 shows a graphic of a DLC.

In circumstances where fluoroscopy or ultrasound is not readily available and in unstable patients where immediate bedside access must be accomplished, 2-catheter venovenous access may be used. In this technique, the femoral vein is drained, enters into ECMO circuit and oxygenator, and then is returned to the superior vena cava via the internal jugular vein. Ambulation is limited with femoral access and may eventually be replaced with a single DLC.
$E C C O_{2} \mathrm{R}$ cannulation usually involves smaller catheters and can be either in a venovenous configuration going to a single large vein or via an often pumpless arteriovenous shunt. Venovenous access use is increasingly used in $\mathrm{ECCO}_{2} \mathrm{R}$ due to the greater risks involved with arterial cannulation. Most of the initial studies for $\mathrm{ECCO}_{2} \mathrm{R}$ for hypoxic respiratory failure involved a pumpless arteriovenous shunt. As the pumps, gas exchange membranes, and cannulas have advanced, however, practice patterns and clinical trials are increasingly applying a venovenous strategy for


Fig. 1. A 31-French double-lumen cannula, drains inferior vena cava (IVC) and superior vena cava (SVC), returns to right atrium and is placed under fluoroscopy and/or with ultrasound.


Fig. 2. Graphic of double lumen cannula. Drains from IVC and SVC, returns to right atrium with return jet across tricuspid valve.
$\mathrm{CO}_{2}$ removal. Pumpless circuits depend on the patient's own forward flow to propel blood across the membrane, and higher rates of bleeding and limb ischemia attend arterial cannulation. Fig. 3 diagrams the various strategies involved in extracorporeal gas exchange strategies.

## Pumps, Membranes, and Circuits

Pumps have evolved with features that emphasize automation and servoregulation in order to adjust to a variety of transient patient conditions (eg, blood loss, coughing spasm) or exercise. Centrifugal pumps that are driven by a rotating impeller are used more frequently at present in adults. Fig. 4 shows a photo of a centrifugal pump. They have largely replaced roller pumps, where flow is generated by compressing the circuit tubing. Centrifugal pumps generate less shear stress on the blood and less hemolysis. Roller pumps are still commonly used in neonatal ECMO, where lower flows and a smaller circuit volume are necessary.

With Respiratory Dialysis, the dialysis system pump drives blood through the gas exchange membrane. Importantly, some arteriovenous (AV) $\mathrm{ECCO}_{2} \mathrm{R}$ systems can operate without a pump using only the patient's arterial pressure to drive flow.

The newer oxygenators achieve more efficient gas exchange, are more durable and less prone to malfunction, and can function for long periods with lower levels of systemic anticoagulation. Most gas exchange membranes in use for ECLS today are made from PMP, a hollow fiber technology where gas flows within the tube and blood flows outside the membrane tube, thus allowing for exchange through diffusion without a direct blood-to-gas interface. Although many current devices are rectangular or square, due to the

B
Bicaval dual-lumen venovenous ECMO

C $\mathrm{ECCO}_{2} \mathrm{R}$
D Arteriovenous $\mathrm{ECCO}_{2} \mathrm{R}$


|  | ECMO |
| :--- | :--- |
| Circuit/bypass | Venovenous bypass |
| Blood drainage | From central vein (IJ, FV, SV) |
| Blood return | Into right atrium |
| Cannula dimension | $16-31 \mathrm{Fr}$ |
| Intravascular access | Single or double |
| Cannula type | Two single cannulas or dual-lumen cannula |
| Pump | Centrifugal |
| Extracorporeal blood flow | $2.0-7.0 \mathrm{~L} /$ /min |
| $\mathrm{CO}_{2}$ clearance | $100 \% \mathrm{VCO}_{2}$, dependent mainly on sweep-gas flow |
| Oxygen delivery capacity | Dependent mainly on extracorporeal blood flow |
| Anticoagulation target | ACT 1.5-2.0 times normal, aPTT 1.2-1.8 times normal |

$E \mathrm{ECO}_{2} \mathrm{R}$
Venovenous bypass or arteriovenous bypass
From central vein (IJ, FV, SV) or femoral artery in arteriovenous configuration Into central vein (IJ, FV, SV)
$8-29 \mathrm{Fr}$
Single or double
Two single cannulas or dual-lumen cannula
Centrifugal or peristaltic (absent in arteriovenous configuration) $0.2-2.0 \mathrm{~L} / \mathrm{min}$
$10-100 \% \mathrm{VCO}_{2}$, dependent mainly on sweep-gas flow
Not significant
ACT 1.5 times normal, aPTT 1.5 times normal

Fig. 3. Cannulation and strategies for VV ECMO and $\mathrm{ECCO}_{2} \mathrm{R}$. (A) Venovenous ECMO with a femoral vein drain and a right internal jugular return. ( $B$ ) shows a double lumen cannula, that drains from the inferior and superior venacava and returns to the right atrium. (C) shows a femoral venous catheter that drains and returns to the femoral vein. (D) shows a femoral venous drain with a femoral arterial return. (From Del Sorbo L, Cypel M, Fan E. Extracorporeal life support for adults with severe acute respiratory failure. Lancet Respir Med 2014;2(2):157; with permission.)
increased risk of clot formation in areas where there is relative stasis, some newer devices are round to minimize thrombosis. Circuit tubing is often coated with heparin mixed with various proprietary blends to help enhance biocompatibility and decrease inflammation and thrombus formation.
An interesting adjunct to enhance $\mathrm{CO}_{2}$ removal during $\mathrm{ECCO}_{2} \mathrm{R}$ or RD is "electrodialysis." This
technique, uses an electrodialysis cell that regionally modulates blood electrolyte concentration to convert bicarbonate to $\mathrm{CO}_{2}$ before entering the membrane lung, enhancing membrane lung $\mathrm{CO}_{2}$ extraction. At present, this device has only been used in animals. ${ }^{34}$ Blood modification that increases the $\mathrm{CO}_{2}$ removal coefficient allows for lower blood flows and smaller cannulas, which renders the intervention less invasive for patients.


Fig. 4. Centrifugal pump. Magnetically levitated impeller rotates to create preload and afterload dependent nonpulsatile flow.

## Choosing Devices for Extracorporeal Gas Exchange

Most patients with severe respiratory failure and an indication for extracorporeal life support will be supported with VV-ECMO, which relies on the patient's own hemodynamics. It is important to consider the logistical and the increased risks associated with larger cannula sizes in ECMO compared with $\mathrm{ECCO}_{2} \mathrm{R}$, when extracorporeal support is used to facilitate ventilation in the setting of hypercarbic respiratory failure. Tables

4 and 5 list available devices for VV-ECMO and $\mathrm{ECCO}_{2} \mathrm{R}$, respectively, although many of them may be used for both and some can be configured to provide full or partial cardiopulmonary support. It is important to note that not all devices are currently approved in the United States by the US Food and Drug Administration (FDA).

## CHALLENGES AND ADVERSE EFFECTS OF EXTRACORPOREAL GAS EXCHANGE

Successful implementation of extracorporeal gas exchange in critically ill patients requires a specialized multidisciplinary team. A facility with appropriate resources and experience with ECLS is recommended. In addition, staff must be experienced and trained in both the insertion and the setup of devices and in recognizing and managing complications. Finally, quality assurance and improvement policies should be implemented. The coordination of care and institutional requirements for implementing ECLS are described in the position paper. ${ }^{35}$
Table 6 describes adverse events grouped by percentages when ECLS was indicated for respiratory failure. Of note, adverse events are selfreported in most trials. The most common adverse events reported ( $10 \%-20 \%$ ) included cannula and

| Table 4 |  |  |
| :---: | :---: | :---: |
| Device | Company (Country) | Key Features |
| Cardiohelp (Fig. 5) | Maquet (Germany) | - Small and easier to transport; weighs 10 kg <br> - Can provide partial to full support <br> - Built-in monitoring for pressure, blood flow, blood gas analysis <br> - Pump is coupled to oxygenator |
| Deltastream DP3 (Fig. 6) | Medos (Germany) | - Small and easier to transport; weighs 5 kg <br> - Axial rotation pump with diagonal impeller <br> - Optional pulsatile flow <br> - Pump and oxygenator separate |
| ILa Active Interventional Lung assist (Fig. 7) | Novalung (Germany) | - Uses a small portable diagonal pump and operational console <br> - Can run at low or high flow rates <br> - Can provide partial to full lung support <br> - Not approved in United States |
| Rotoflow (Figs. 8 and 9) | Maquet (Germany) | - Predecessor to the Cardiohelp <br> - Separate oxygenator and pump <br> - Requires separate monitoring equipment |
| Centrimag | Thoratec (CA, USA) | - Centrifugal pump with magnetically levitated impeller <br> - Requires separate oxygenator and monitoring equipment <br> - Higher flow rates possible <br> - Approved for use up to 30 d |

Most devices approved for 6 hours of use, but often used off label for long periods of time.

| Table 5 <br> Available devices for extracorporeal carbon dioxide removal |  |  |
| :---: | :---: | :---: |
| Device | Company (Country) | Key Features |
| Cardiohelp Pump- <br> Assisted Lung <br> Protection (PALP) <br> (Fig. 10) | Maquet (Germany) | - Portable; adaptation of Cardiohelp unit <br> - Can provide partial to full lung support <br> - Pending approval in United States <br> - Centrifugal pump head connects to membrane |
| iLA Active Interventional Lung assist (Fig. 11) | Novalung (Germany) | - Uses a small portable diagonal pump and operational console <br> - Can run at low- or high-flow rates <br> - Can provide partial to full lung support <br> - Not approved in United States |
| Alung-Hemolung <br> (Fig. 12) | Alung Technologies (PA, USA) | - Only system specifically designed for $\mathrm{CO}_{2}$ removal and targeting $\mathrm{CO}_{2}$ retention <br> - Integrates blood pump and gas exchange membrane into a single unit <br> - Blood flows centrally into a rotating core and is gradually pumped through a stationary annular fiber bundle and returns to the patient via an outlet port |
| Abylcap (Fig. 13) | Bellco (Italy) | - Hemofiltration system in series with oxygenator for $\mathrm{CO}_{2}$ removal <br> - Lilliput2 oxygenator (Sorin/Livanova, UK) <br> - Not available in United States <br> - Clinical trial enrolling patients |
| Decap (Fig. 14) | Hemodec (Italy) | - Membrane lung connected in series with a hemodialysis filter and roller pump <br> - Ultrafiltrate from the filter is returned to the bloodstream before the membrane lung inflow, allowing additional $\mathrm{CO}_{2}$ removal <br> - Smaller membrane lung can be used with lower flow rates <br> - Useful for patients requiring both pulmonary and renal support |

Adapted from Morimont P, Batchinsky A, Lambermont A. Updated on the role of extracorporeal $\mathrm{CO}_{2}$ removal as an adjunct to mechanical ventilation in ARDS. Crit Care 2015;19:117; with permission.
surgical site hemorrhage, pneumothorax, and culture-proven catheter-related infection.

Bleeding remains the most common side effect, and optimal management of anticoagulation to


Fig. 5. Cardiohelp (Maquet) used for VV ECMO.


Fig. 6. Deltastream DP3 (Medos) pump and oxygenator, capable of pulsatile flow up to 7 L .


Fig. 7. Interventional lung assist, Active (Novalung). Not approved in the United States. Capable of VV ECMO and $\mathrm{ECCO}_{2} \mathrm{R}$.
prevent thrombus formation requires welldesigned protocols.

Artificial surfaces serve as a nidus for platelet adhesion and ultimately clot formation. Most commercially available devices have heparinbased nonthrombotic coatings. Nitric oxide-


Fig. 9. Rotoflow (Maquet). Drive console that powers pump.
eluting surfaces are currently being developed that may further prevent clot formation. ${ }^{36}$

The ELSO published general anticoagulation guidelines in 2014, which may help centers develop their own institutionally specific guidelines. ${ }^{37}$ Many high-volume adult centers reporting good outcomes are using increasingly lower levels of systemic heparinization. Possible goals for anticoagulation are listed in Table 7.


Fig. 8. Rotoflow (Maquet). Oxygenator and centrifugal pump.


Fig. 10. Cardiohelp PALP (Maquet). For use with Cardiohelp in $\mathrm{ECCO}_{2} \mathrm{R}$ at lower flows. Pending FDA approval in the United States.


Fig. 11. Interventional lung assist (Maquet). AV configuration for pumpless $\mathrm{CO}_{2}$ removal; not approved in the United States.

The optimal strategy for mechanical ventilation during ECLS remains unclear. An international survey of 283 ELSO-registered ECMO centers analyzed 141 responses to the survey. ${ }^{38}$ Ventilation methods varied across the centers, but 77\% of respondents stated that lung rest was the primary goal. A tidal volume of $6 \mathrm{~mL} / \mathrm{kg}$ or less was


Fig. 12. Hemolung (ALung). For $\mathrm{ECCO}_{2} \mathrm{R}$.


Fig. 13. Abylcap (Bellco). Hemofiltration system in series with oxygenator for $\mathrm{CO}_{2}$ removal; not approved in the United States.
targeted by $76 \%$ of respondents, with $58 \%$ targeting a PEEP of 6 to $10 \mathrm{~cm} \mathrm{H}_{2} \mathrm{O}$. In addition, most of the centers attempted to remove extracorporeal support before extubation. Animal studies comparing complete rest (tidal volume $4 \mathrm{~mL} / \mathrm{kg}$ and PEEP of $4 \mathrm{~cm} \mathrm{H}_{2} \mathrm{O}$, respiratory rate of 6 within 35 minutes) versus optimal positive airway pressure (gradual decrease to tidal volume of 4 mL kg and PEEP between 8 and 12 and titrated to compliance over 12 hours) suggest that a more gradual decrease to an ultraprotective ventilation strategy attenuates lung injury. ${ }^{39}$ Box 7 describes general recommendations for the management of mechanical ventilation and extubation for patients with extracorporeal life support. Table 8 describes an overview of a possible approach to severe respiratory failure.


Fig. 14. Decap (Hemodec). Extracorporeal $\mathrm{CO}_{2}$ removal system in series with membrane lung for $\mathrm{CO}_{2}$ removal; not approved in the United States.

| Table 6 <br> Adverse events grouped percentages related to extracorporeal life support system indicated for respiratory failure |  |  |  |
| :---: | :---: | :---: | :---: |
| 10\%-20\% | 5\%-10\% | 1\%-5\% | <1\% |
| - Cannula site hemorrhage <br> - Surgical site hemorrhage <br> - Pneumothorax requiring treatment <br> - Culture-proven catheter related infection | - Pulmonary hemorrhage <br> - Gastrointestinal hemorrhage <br> - Hemolysis | - CNS bleed <br> - Disseminated intravascular coagulation | - Limb ischemia <br> - Compartment syndrome <br> - Pseudoaneurysm <br> - Heparin-induced thrombocytopenia |

Adapted from Osborn E, Principle investigator: Comparison of Early Complete Rest versus Gradual Optimal Positive Airway Pressure for Ventilation in an Oleic Acid Porcine Lung Injury Model Supported by Venovenous Extracorporeal Support, in press.

## SUMMARY

The revival of extracorporeal support over the last decade suggests an impending paradigm shift in the management of adult respiratory failure. If the EOLIA trial reports a survival benefit for ECMO, the use of ECMO will continue to expand in severe ARDS. Several RCTs examining the use of $\mathrm{ECCO}_{2} \mathrm{R}$ in non-ARDS respiratory failure are in progress. Based on the epidemiology of respiratory failure and the possible use of extracorporeal support in a preventative and preemptive fashion, the use of extracorporeal gas exchange may expand exponentially if the controlled studies mirror the findings of the current uncontrolled trials.

| Table 7 <br> Possible goals for anticoagulation |  |
| :--- | :--- |
| PTT | Anticoagulation in ECLS |
| Xa | $0.2-0.6 \mathrm{lU} / \mathrm{mL}$ <br> Antithrombin III <br> May replace if low and high <br> heparin doses required <br> TEG and ROTEMMay help diagnose nature <br> of bleeding and direct <br> blood product <br> replacement |
| Tranexamic acid | Surgical site bleeding |
| Prothrombin | Surgical site bleeding and <br> bleeding not responding <br> to lower anticoagulation <br> levels |
| Factor VII | Life-threatening bleeding, <br> intracerebral <br> hemorrhage |

Abbreviations: Factor VII, recombinant, activated factor VII; PTT, activated partial thromboplastin time; ROTEM, thromboelastometry; TEG, thromboelastography; Xa, antifactor Xa activity levels.

As technology and the understanding continue to advance, extracorporeal support is likely to evolve into low-flow and high-flow ECLS, with devices capable of both poised to provide partial,

## Box 7 <br> Recommendations for mechanical ventilation for patients with extracorporeal life support

Mechanical Ventilation Recommendations

- VV access can supply all metabolic oxygen requirements but measured arterial saturations may be $75 \%$ to $85 \%\left(\mathrm{PaO}_{2} 45-55 \mathrm{~mm} \mathrm{Hg}\right)$ while on VV-ECMO. Avoid the temptation to turn up the ventilator settings or $\mathrm{Fio}_{2}$ above rest settings during VV support.
- For selective $\mathrm{CO}_{2}$ removal, blood flow can be as low as $1 \mathrm{~L} / \mathrm{min}$ and sweep gas can be up to $15 \mathrm{~L} / \mathrm{min}$, titrated to maintain $\mathrm{PaCO}_{2}$ at 40 mm Hg


## Extubation Recommendations

- Assess if patient's clinical condition is appropriate for attempting to decrease the level of respiratory support
- Patient must be awake enough to protect airway, cooperative enough not to be at significant risk for dislodgment of cannulas or catheters, and secretions must be manageable
- The patient should have an acceptable arterial blood gas on minimal ventilator settings, for example, $\mathrm{Fio}_{2} 0.4$, PEEP 5
- Goal $\mathrm{Pao}_{2}$ greater than 80 on $\mathrm{Fio}_{2}$ of $40 \%$
- Goal $\mathrm{pH}>7.35$ with minute ventilation less than $10 \mathrm{~L} / \mathrm{min}$ while receiving a sweep gas flow less than $6 \mathrm{~L} / \mathrm{min}$

Adapted from ELSO adult respiratory failure guidelines. Available at: http://www.elso.org/Portals/0/IGD/ Archive/FileManager/989d4d4d14cusersshyerdocuments elsoguidelinesforadultrespiratoryfailure1.3.pdf. Accessed January 17, 2016.

| Table 8 |
| :--- |
| Overview of a possible approach to severe |
| respiratory failure |


| Severe hypoxic  <br> respiratory <br> failure Lung protective ventilation <br> ○ Early paralysis <br> o Early prone positioning <br> o Diuresis if possible |
| :--- | :--- |


| Failure to <br> improve <br> after 6-12 h h | - Is patient candidate for VV <br> - ECMO? <br> Buffer therapy and/or vaso- <br> dilator therapy to lengthen <br> bridge to decision |
| :---: | :--- |
| Initiation of <br> VV ECMO | - Does VV ECMO expertise <br> exist at your institution? <br> - Contact mobile VV ECMO <br> team to discuss initiation at |
|  | home institution followed |
| by transport to ECMO center |  |
| - Consent family |  |

full, preventative, and/or rescue support. Strong data does not exist at present, however, so it remains essential to ensure that optimal, evidencebased therapy is maximized before initiation of extracorporeal support.

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