Acute Respiratory Failure: ECLS
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Complications and Troubleshooting
Acute Respiratory Failure ECLS

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Acute Respiratory Failure

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Update Info
Learning Objectives

After studying this module on ExtraCorporeal Life Support (ECLS) in Acute Respiratory Distress Syndrome (ARDS) patients, you should be able to:

1. Describe the PHYSIOLOGY of ECLS
2. List the major INDICATIONS and associated CONFIGURATIONS of ECLS
3. Outline the role of ECLS for ARDS, Obstructive Lung Disease and a Bridge to Lung Transplant in terms of:
   1. Configurations and trouble shooting the circuit
   2. Clinical evidence
   3. Clinical management and controversies
4. List patient and circuit associated COMPLICATIONS

eModule Information

**Expiry date:** 10/2020

**COBATr!Ce competencies covered in this module:**

Competencies

- Recognises and manages the patient with acute respiratory failure and ARDS
- Describes the use of devices for circulatory or respiratory assist

**Faculty Disclosures:**
The authors of this module have not reported any disclosures.

**Duration:** 8 hours

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1. Introduction

Extracorporeal life support (ECLS) is a means to improving oxygenation, ventilation and hemodynamic support using an extracorporeal circuit comprised of an oxygenator and a centrifugal pump. Traditionally, its indications have spanned refractory hypoxemic or hypercapnic respiratory failure, and cardiogenic shock. Over the years, substantial advancements in the technology have resulted in an increase in safety and minimised the complexity associated with its use.

Recent evidence suggests possible favourable outcomes associated with the use of ECLS for severe acute respiratory failure; however, there are limited data from large, randomised controlled trials to confirm efficacy. Therefore, more evidence will be needed to guide clinicians on its role in patients with severe acute respiratory failure.

This module will focus primarily on ECLS for hypoxemic and hypercapnic respiratory failure.

Note

Potential applications for ECLS:
- Hypoxemia
- Hypercapnia
- Cardiogenic shock
- Significant technologic advancements have renewed enthusiasm for the role of ECLS in adults with respiratory failure
2. Physiology of gas exchange

2.1. The ECLS Circuit

Extracorporeal circuits use a centrifugal pump to aspirate or drain de-saturated venous blood from a large central vein (e.g. IVC via the femoral vein or SVC via the internal jugular vein). The venous blood is pumped to the oxygenator where gas exchange occurs. Modern oxygenators (also referred to as an artificial lung or gas exchange device) are composed of hollow fibres that separate the blood and gas phase. Blood flows around the hollow fibres while sweep gas (either 100% oxygen or air/oxygen mix) is delivered through the hollow fibres. Oxygen uptake and carbon dioxide removal occurs across the walls of these fibres. Oxygenated and de-carboxylated blood is then returned to the patient.

![Image](image.png)


2.2. Oxygenation

The single most important factor in oxygen uptake by the oxygenator is ECLS blood flow. This is a consequence of the unique mode of oxygen carriage by haemoglobin. Once haemoglobin is fully saturated, further oxygen uptake can only be achieved by
continued delivery of de-saturated haemoglobin to the oxygenator. Dissolved oxygen provides minimal contribution to overall oxygen uptake.

Diffusion of oxygen through the walls of the hollow fibres could be compromised in case of thrombus formation or excessive fibrin deposition. However, even in the presence of visible clot in the oxygenator, most contemporary oxygenators perform satisfactorily for many days.

Oxygen delivery is the product of cardiac output and oxygen content. Oxygen content is composed of haemoglobin, oxygen saturation, and a dissolved component of oxygen.

- Oxygen delivery = cardiac output x oxygen content
- Oxygen content = (Hb x SaO₂ x 1.34) + (0.003 x PaO₂)

The major factors in determining oxygen uptake via oxygenator include the following:

- **ECLS blood flow**
- Oxygen saturation of pre-oxygenator blood
- Haemoglobin concentration
- Diffusion of oxygen through hollow fibres

![Oxygen-Hemoglobin dissociation curve](image)


Illustration by Alberto Goffi

2. 3. Carbon Dioxide Removal
Carbon dioxide is dissolved in blood and its removal by the oxygenator is characterised by a linear and steep dissociation curve. The high solubility of carbon dioxide in blood allows for very efficient CO₂ removal by the oxygenator.

The major factors in determining blood CO₂ removal via ECLS include the following:

- Sweep Gas Flow
- Surface area of oxygenator
- Diffusibility through microfibers (could become compromised in the presence of clots or excessive fibrin deposition)
- Blood flow

![CO₂ dissociation curve](image)


Illustration by Alberto Goffi
3. Indications

![Diagram of indications for venovenous extracorporeal membrane oxygenation](image)


3.1. Indications: Hypoxemia

**ECLS** acts as an oxygenating shunt for hypoxemia refractory to conventional mechanical ventilation as a bridge to recovery. Causes of hypoxemia may include the following:

- Acute Respiratory Distress Syndrome (ARDS)
- Acute Pulmonary Embolism
- Other reversible causes of acute respiratory failure (e.g., acute eosinophilic pneumonia, alveolar haemorrhage)
- Primary Graft Dysfunction following Lung Transplant
Evidence-based thresholds to guide initiation ECLS for hypoxemia have not been established. Current indications suggested by the Extracorporeal Life Support Organization (2009) include the following:

- Consider if risk of mortality is 50% or greater (e.g., PaO₂/FiO₂ 90 mmHg and/or Murray Score 2-3)
- Indicated when risk of mortality is 80% or greater (e.g., PaO₂/FiO₂ 90 mmHg and a Murray Score 3-4)

<table>
<thead>
<tr>
<th>Murray score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>CXR (quadrants with consolidation)</td>
<td>n. 0</td>
<td>n. 1</td>
<td>n. 2</td>
<td>n. 3</td>
<td>n. 4</td>
</tr>
<tr>
<td>Hypoxemia (PaO₂/FiO₂)(mmHg)</td>
<td>≥300</td>
<td>225-299</td>
<td>175-224</td>
<td>101-174</td>
<td>≤100</td>
</tr>
<tr>
<td>PEEP (cmH₂O)</td>
<td>&lt;5</td>
<td>6-8</td>
<td>9-11</td>
<td>12-14</td>
<td>&gt;15</td>
</tr>
<tr>
<td>Compliance (ml/cmH₂O)</td>
<td>&gt;80</td>
<td>60-79</td>
<td>40-59</td>
<td>20-39</td>
<td>&lt;19</td>
</tr>
</tbody>
</table>

The final score is calculated by the addition of the component parts divided by 4

These simply provide a framework for when to consider ECLS. Various organisations have established their own thresholds when to initiate or refer for ECLS. Indications for ECLS for ARDS from 3 recent studies are outlined below

<table>
<thead>
<tr>
<th>Peek 2009 (UK)1</th>
<th>ECMO net 2011 (Italy; H1N1)2</th>
<th>Pham 2013 (France; H1N1)3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 18-65 years old Severe but potentially reversible respiratory failure (Murray score ≥3.0 or pH &lt;7.2)</td>
<td>Oxygenation Index &gt;30 PaO₂/FiO₂ &lt;70 mmHg with PEEP &gt;15 cmH₂O at ECMO centre PaO₂/FiO₂ &lt;100 mmHg with PEEP &gt;10 cm H₂O awaiting transfer pH &lt;7.25 for at least 2 hours and haemodynamic instability</td>
<td>PaO₂/FiO₂ &lt;50mmHg, despite PEEP 10-20cmH₂O and FiO₂ &gt;0.80 or Plateau pressures &gt;35cmH₂O, despite attempts to reduce tidal volumes to &lt;4ml/kg</td>
</tr>
</tbody>
</table>

3. 2. Modalities: Hypoxemia
Veno-venous ExtraCorporeal Membrane Oxygenation (ECMO) is the configuration of choice for hypoxemic respiratory failure.

If concomitant shock exists and the shock is attributed to right ventricular dysfunction in the context of ARDS, haemodynamics may improve with the application of veno-venous ECMO given the rapid reversal of hypoxemic vasoconstriction and drop in pulmonary vascular resistance.

If vasodilatory shock complicates respiratory failure in the context of sepsis, veno-venous ECMO would remain the modality of choice with the employment of vasopressors for vasodilation.

When the origin of shock associated with respiratory failure is due to left ventricular or biventricular failure resulting in end organ hypoperfusion, veno-arterial or a hybrid veno-veno-arterial ECMO may be the modality of choice.

Refer to section on Configurations for more details.

3. 3. Indications: Hypercapnia

ECLS acts as a CO₂ removal circuit for hypercapnic respiratory failure refractory to conventional therapies or mechanical ventilation as a bridge to recovery. Causes of hypercapnia may include the following:

- Acute Respiratory Distress Syndrome (ARDS)
- Obstructive Airway Disease:
  - Chronic obstructive pulmonary disease (COPD)
  - Severe asthma/status asthmaticus
  - Bronchiolitis obliterans syndrome (BOS)
  - Cystic fibrosis

Definitive thresholds to guide initiation of ECLS for hypercapnia have not yet been established. Current indications suggested by the Extracorporeal Life Support Organization (2009) include the following:

- CO₂ retention due to asthma or permissive hypercapnia with a PaCO₂ >80 mmHg or inability to achieve safe inflation pressures (Pplat ≥ 30 cm H₂O)

3. 4. Modalities: Hypercapnia
A series of different ECLS configurations can be employed for hypercapnic respiratory failure:

Veno-venous ECMO: Veno-venous ECMO is useful if concomitant hypoxemia and hypercapnia are the indication for ECLS.

In the body CO$_2$ is produced at the rate of about 200-250 mL/min, and in normal conditions the venous blood (pH 7.38 and PaCO$_2$ 45 mmHg) contains about 500 mL/L of CO$_2$. Therefore, 0.5-1 L/min (low flow) ECMO blood flow through the artificial lung, provided with adequate sweep gas flow (> 6L/min), can theoretically remove the entire volume of CO$_2$ produced. In this setting, ECMO blood flow is low and therefore oxygen uptake is limited.

Low flow veno-venous extracorporeal carbon dioxide removal (VV ECCO$_2$R) is similar to VV EMO but uses smaller single or dual-lumen cannulae, a low resistance oxygenator and blood pump. The low ECLS blood flows achieved with these systems provide satisfactory CO2 removal but limited oxygen uptake. (see Physiology of Gas Exchange)

Arterio-venous extracorporeal CO$_2$ removal devices (pumpless or AV ECCO$_2$R) rely on the patient’s arterial pressure to drive blood flow through the oxygenator. The usual configuration of AV ECCO$_2$R is using small cannulae in the femoral artery and vein. Similar to VV ECCO$_2$R systems, the low extracorporeal blood flow achieved in AV ECCO$_2$R provides satisfactory CO$_2$ clearance with limited oxygen uptake.

Extracorporeal CO$_2$ removal (ECCO$_2$R) devices: ECCO$_2$R, similar to haemodialysis, employs a single venous dual-lumen catheter and low extracorporeal blood flow through the gas exchanger. Similar to the arterio-venous interventional lung assist, it does not provide significant oxygenation due to the low blood flow rates. (Refer to section on Configurations for more details)

3. 5. Contraindications

Absolute contraindications:

- Any critical co-morbid conditions preventing bridge to meaningful recovery (e.g., metastatic cancer, catastrophic neurologic injury)

Potential relative contraindications include the following:

- Any significant contraindication to heparinisation (e.g., central nervous system haemorrhage, heparin induced thrombocytopenia, major bleeding not amenable to treatment/reversal)
- Prolonged exposure to injurious mechanical ventilation (>7-10 days), given the high likelihood of ventilator-associated lung injury
- An irreversible cause of respiratory failure and not a candidate for lung transplant

The nature (absolute or relative) of these contraindications may vary from centre to centre
4. Configurations

![Diagram](image)


4.1. Veno-venous Extracorporeal Membrane Oxygenation

For veno-venous ECMO, venous blood is drained from a large central vein (inferior vena cava via the femoral vein or superior vena cava via the internal jugular vein). Blood is pumped through the oxygenator and returned to the superior vena cava/right atrium via the internal jugular or inferior vena cava via femoral vein.

Femoral-femoral, femoral-internal jugular or the bicaval dual-lumen internal jugular catheter are possible veno-venous ECMO configurations.

Figure 7: Illustration by Alberto Goffi

Figure 8: Illustration by Alberto Goffi
4. 2. Veno-arterial Extracorporeal Membrane Oxygenation

In the setting of respiratory failure with concomitant cardiogenic shock, veno-arterial ECMO, may be the configuration of choice. Venous blood is drained from a large central vein (often the inferior vena cava via the femoral vein). Blood is pumped through the oxygenator and returned to the arterial circulation via the contra-lateral femoral artery.

However, during this form of peripheral VA ECMO, fully oxygenated blood from the ECMO circuit is delivered retrograde to the distal aorta via the femoral artery and in the presence of continued native lung dysfunction, de-oxygenated blood maybe ejected into the proximal aorta from the left ventricle (LV) and pulmonary circulation. The level in the aorta at which these two sources of blood mix is determined by extent of left ventricular dysfunction. When LV function is minimal, fully oxygenated blood from the ECMO circuit is pumped back up to the level of the aortic valve. If LV ejection is preserved, poorly oxygenated blood from the dysfunctional native lungs may be delivered to the proximal aorta (coronary and cerebral circulation).

In these circumstances, veno-arterial-venous (VA-V) ECMO may alleviate this problem. In VA-V configuration, de-saturated venous blood is drained from the IVC via the femoral vein and oxygenated blood is returned to two sites, the contra-lateral femoral artery and to the SVC. Oxygenated blood is delivered to the distal aorta but also to the pulmonary circulation to improve oxygenation of blood ejected into the proximal aorta. If LV function remains stable, consideration should be given to changing from VA-V to VV ECMO for continued native lung dysfunction.

4. 3. Extracorporeal CO Removal

The three modalities available for isolated CO₂ removal:

Extracorporeal CO₂ removal devices employ a single venous dual-lumen catheter (internal jugular or femoral vein) and low flow extracorporeal blood flow that is pumped through a gas exchanger.

Low flow VV ECCO₂R uses a single dual-lumen cannula in the internal jugular vein. Low blood flow is maintained through the oxygenator using a low capacity centrifugal pump. This configuration has been used to facilitate mobilisation/ambulation of the patient.
Low flow veno-venous ECMO is similar to veno-venous ECMO with the exception of the employment of smaller cannula leading to a limited amount of flow through the ECMO circuit.

Low flow VV ECCO₂R uses a small single-lumen cannula in each femoral vein. Low blood flow is maintained through the oxygenator using a low capacity centrifugal pump.

Arterio-venous interventional lung assist is a pumpless form of ECMO that relies on the arterio-venous pressure difference to facilitate flow through a gas exchanger. It employs smaller cannula and can easily facilitate CO₂ removal.

Arterio-venous ECCO₂R uses a small femoral arterial and venous cannula. The patient’s arterial-venous pressure difference pumps blood through the gas exchanger.
4.4. PA to LA pumpless device

This configuration has been described in small case series of patients with primary pulmonary hypertension awaiting lung transplantation but who develops life threatening failure of the right ventricle (RV). After sternotomy, a surgically placed cannula in the pulmonary artery trunk is connected to a left atrial cannula using the same low resistance gas exchange device employed in peripherally placed AV ECCO$_2$R system (see above). The extracorporeal shunt immediately decompresses the failing RV. Gas exchange is achieved by a combination of extracorporeal CO$_2$ elimination and continued perfusion/ventilation of native lungs.

![Illustration](image)


<p>| <strong>Table 3:</strong> depicts the configurations and settings of the different ECLS modalities available |
|---------------------------------|---------------------------------|---------------------------------|
| <strong>VV-ECMO</strong>                      | <strong>ECCO$_2$R</strong>                    | <strong>ECCO$_2$R</strong>                   |
| Veno-venous by pass, in series with pulmonary circulation | Veno-venous by pass, in series with pulmonary circulation | Veno-venous by pass, in series with pulmonary circulation |
| from central vein (IJ, FV, SV)   | Blood drainage                  | from central vein (IJ, FV, SV) or Fem artery in AV configuration |
| into right atrium                | Blood return                    | into central vein (IJ, FV, SV)  |
| 16 -31 Fr                       | Cannula                         | 8-29 Fr                        |
| Single or Double                 | Intravascular                   | Single or Double                |
| Two single cannulas or dual-lumen cannula | Cannula type                  | Two single cannulas or dual-lumen cannula |
| Centrifugal                      | Pump                            | Centrifugal or peristaltic      |</p>
<table>
<thead>
<tr>
<th>2-7 L/min</th>
<th>Extracorporeal Blood Flow</th>
<th>0.2-2.0 L/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>100% VCO₂</td>
<td>CO₂ clearance</td>
<td>10-100% VCO₂ dependent mainly on sweep gas flow</td>
</tr>
<tr>
<td>dependent</td>
<td>Oxygen delivery capacity</td>
<td>not significant</td>
</tr>
</tbody>
</table>

**Abbreviations:**
- FV = femoral vein
- IJ = internal jugular vein
- SV = subclavian vein
- Fr = French
5. Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome

References found in this Chapter


References

• 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., 2009, PMID:19741487
• Del Sorbo L, Cypel M, Fan E., Extracorporeal life support for adults with severe acute respiratory failure., 2014, PMID:24503270

5. 1. Indications and Rationale
ECMO facilitates oxygenation and ventilation via an oxygenating shunt as opposed to relying on the ventilator to use the non-compliant, injured lung beyond lung protective limits in an attempt to achieve adequate oxygenation and ventilation. This strategy of off-loading the lungs helps facilitate “lung rest and recovery” and minimises ventilator-associated lung injury (VALI).

VALI is characterised by volutrauma and barotrauma (volume and pressure overload leading to over distension), atelectrauma (cyclic recruitment and derecruitment) and biotrauma (lung inflammation that develops as a consequence of the mechanical forces above). Strategies to protect against VALI include minimising tidal volumes to 6 mL/kg PBW and plateau pressures to <30 cmH₂O. Despite strict adherence to optimal lung protective ventilation, some patients with severe ARDS may still experience tidal hyperinflation, VALI and develop life threatening progressive hypoxia and hypercapnia. ECMO provides sufficient stability with gas exchange to facilitate lung protection or even “ultra” lung protective mechanical ventilation.

ECMO provides an ideal environment to facilitate lung protective or even “ultra”-lung protective ventilation by offloading the lungs, in part, through an oxygenating and ventilating shunt.

5. 2. Veno-Venous ECMO For ARDS

Veno-venous ECMO is the most common configuration for severe hypoxaemia and hypercapnia in patients with ARDS:

- Femoral (drainage) - internal jugular (return)
- Bicaval dual lumen cannula (superior and inferior vena cava drainage and right atrium return)
- Femoral (drainage) - contralateral femoral (return)

In the presence of cardiogenic shock, veno-arterial (VA) or veno-veno-arterial (VA-V) ECMO are the modalities of choice.

Highly oxygenated blood delivered to the pulmonary circulation from the ECMO circuit reverses hypoxemic pulmonary vasoconstriction, increasing perfusion to poorly ventilated lung units. At the initiation of ECMO, the contribution of the native lungs to systemic gas exchange may be minimal. With some improvement in native lung function, lower ECMO blood flow rates can be tolerated, so that a greater proportion of blood flowing through the pulmonary artery is poorly oxygenated, potentially allowing improved V/Q matching and a greater contribution of native lungs to systemic oxygenation.

During the early phase of ECMO for ARDS, a high ECMO blood flow is required to maintain oxygenation, and as the native lungs recover, a lower ECMO blood flow rate
can be tolerated. When initiating ECMO in a hypoxic but severely hypercapnic patient, a low sweep gas flow is used to prevent too rapid a correction of pH and PaCO₂ by the highly efficient ECMO gas exchange device.

5. 3. ECCOR For ARDS

An alternative indication for ECLS in the setting of ARDS is to facilitate “ultra” lung protective ventilation using an ECCO₂R device. In patients with satisfactory oxygenation but severe hypercapnia, ECCO₂R may allow tidal volumes of 3-4 mls/kg predicted body weight and plateau pressures of <25 cmH₂O to be used.

ECCO₂R may be useful when a patient with ARDS has severely non-compliant lungs that prevent the delivery of lung protective ventilation (i.e., tidal volumes of 6 mL/kg PBW or plateau pressures <30 cmH₂O), or as a rescue from injurious levels of mechanical ventilation. Hypothetically, ECCO₂R may allow an “ultra”-lung protective ventilatory strategy to be used aiming for tidal volumes of 3-4 cc/kg and plateau pressures of <25 cmH₂O.

5. 4. Configurations of ECLS for ARDS

![Diagram of Venovenous extracorporeal membrane oxygenation for acute respiratory failure](image)

5. 5. Clinical Evidence

There has been significant improvement in survival rates associated with ECLS use in patients with ARDS, with the earliest trials in the 1970’s demonstrating extremely poor survival rates (10%) to survival rates exceeding 70% in some recent publications.

Earlier trials were characterised by the continued use of injurious ventilation, use of the veno-arterial (VA) rather than VV ECMO, late initiation of ECMO, high dose anticoagulation and high transfusion requirements.

Advancements in ECLS circuit technology, improved knowledge of ventilator-associated lung injury, less intensive anti-coagulation and earlier initiation of ECLS have contributed to more favourable outcomes over the past two decades, renewing enthusiasm for the role of ECLS for severe ARDS.

A randomised controlled trial from the United Kingdom in 2009 randomised patients with severe ARDS to transfer to a specialist centre for consideration of ECMO as compared to continued conventional therapy in the referral hospital. The patients transferred for consideration of ECMO had a significant reduction in 6-month mortality without disability (RR 0.69; 95% CI 0.05-0.97, p = 0.03).

However, only 76% of patients randomised for consideration of ECMO actually received ECMO. The other important consideration is that only 70% of the control arm patients (compared to 93% of the intervention arm) received lung protective ventilation. Thus, the survival benefit conferred was more likely related to being at a “centre of excellence” where ECMO might have been part of the management strategy as opposed to the direct benefit of ECMO alone. The following table outlines studies over the years for ECMO in ARDS

### Evidence:

<table>
<thead>
<tr>
<th>Table 4: Pivotal Studies of ECMO for ARDS</th>
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<tbody>
<tr>
<td>Indication</td>
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<tr>
<td>-------------</td>
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<tr>
<td>Study</td>
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<td>------------------------------</td>
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<tr>
<td>ZAPOL, 19794</td>
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<tr>
<td>PEEK, 20091 (CESAR TRIAL)</td>
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<td>NOAH, 20105</td>
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<td>PHAM, 20123</td>
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5.6. Evidence: ECCOR
Bein et al, recently published the first randomised controlled trial evaluating the impact of an “ultra”-lung protective strategy (using 3 mL/kg PBW tidal volumes) facilitated by ECCO₂R for ARDS.

The primary endpoint was ventilator-free days at 28 days. While the overall population did not demonstrate a statistically significant increase in ventilator-free days, a post hoc analysis of patients in the more severe ARDS subgroup (PaO₂/FiO₂ <150 mmHg) demonstrated a significant improvement in ventilator free days. A larger trial is pending to further explore this association.

5. 7. Future Research:

While a strong physiological rationale for employing ECLS may exist, current research does not support its routine application for severe ARDS.

A multi-centre, international randomised controlled trial is currently underway to evaluate the clinical efficacy of VV-ECMO for ARDS. The Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA) trial (ClinicalTrials.gov NCT01470703) is evaluating the early initiation of VV ECMO for severe ARDS combined with a lung rest strategy as compared to a standardised lung protective ventilation control group.

Risk factors associated with a poor prognosis and increased mortality in ARDS patients treated with ECMO have been evaluated in different cohorts. More research is needed to further validate these variables.

Two studies, listed below, based upon observational data, have identified the following variables associated with a poor prognosis:

| Table 5: Risk Factors Associated with Poor Prognosis in ARDS patients treated with ECLS |
|-----------------------------------------------|-------------------------------------------|
| Variable                        | ECMO NET SCORE (H1N1)                     |
| Immunocompromised               | Hospital length of stay prior to ECLS    |
| Older age (>55 years old)       | Total bilirubin                           |
| High                               | Creatinine                               |
| Sequential Organ Failure         | Hematocrit                                |
| Assessment Score (>12)           | Mean arterial pressure                    |
| Duration of mechanical          |                                          |
| ventilation (>7 days)            |                                          |
| No prone positioning            |                                          |
| pre-ECMO PEEP <10 cmH₂O         |                                          |
| Plateau pressures >30           |                                          |
| cmH₂O                           |                                          |
| BMI >30 (protective)            |                                          |
5. 8. Clinical Management and Controversies

**Mechanical Ventilation**
Optimal or ‘rest’ mechanical ventilation settings while on ECLS is an area of much debate. Most agree on a strategy of maximising the support provided by the ECLS circuit at the outset with a gradual transition to greater dependence upon mechanical ventilation once native lung recovery is evident.

**Tidal Volume**
Some patients with severe ARDS may experience tidal hyperinflation despite using a lung protective strategy, including 6 mL/kg predicted body weight (PBW). Perhaps in severe ARDS, 6 mL/kg PBW may not be sufficiently conservative to protect the “baby lung” and lower tidal volumes are needed. How low the tidal volume should be is not clear and there are currently no data to support a particular tidal volume or strategy, although 2 proof-of-concept studies have safely lowered tidal volume to 3-4 mL/kg PBW.

**Plateau Pressures**
Higher plateau pressures during ventilation with ARDS have been associated with a worse outcome. Extrapolating from this, lowering plateau pressure while on ECLS may lead to improved outcomes.

**Positive End Expiratory Pressure (PEEP):**
The optimal level of PEEP during ECLS is also unclear. Some would argue that PEEP related alveolar recruitment is no longer necessary given the oxygenation from ECMO. However, opening lung units and preventing atelectasis may have an impact on alveolar healing. Others investigators have demonstrated that when previously atelectatic lung units are opened, it may lead to an increased metabolic activity in those lung units and a release of inflammatory mediators.

**Oxygen Thresholds**
It remains unclear what the optimal PaO₂ threshold should be while on ECMO. While somewhat controversial, recent evidence post cardiac arrest suggests a possible deleterious impact of hyperoxia post arrest presumably due to ischemia-reperfusion and the presence of oxygen free radicals. On the contrary, a post hoc analysis of the ARDSNet trial demonstrated a higher incidence of neurocognitive impairment in the subgroup with a lower PaO₂ threshold. Given the uncertainty of the risk of hyperoxia and the suggestion of harm with severe hypoxemia, we recommend targeting modest oxygenation targets similar to those from ARDSnet (i.e., SpO₂ 88-93%) until further evidence is available.

**Carbon Dioxide Thresholds**
It is unclear whether permissive hypercapnia should be tolerated or targeted in ARDS patients. While we know that permissive hypercapnia can be safely tolerated, CO₂
removal with ECMO may lead to rapid normocapnia in patients with ARDS. We recommend targeting modest pH goals similar to those from the ARDSnet trial (i.e., pH 7.25-7.45) until further evidence is available.

**Weaning**
When evidence of clinical improvement occurs (e.g., improved respiratory mechanics, tidal volumes on similar ventilator settings, gas exchange), this may be an indication that the patient is ready to be weaned from ECMO.

VV ECMO is weaned primarily by reducing sweep gas flow while maintaining ECMO blood flow and anti-coagulation. Mechanical ventilation settings should be increased to compensate for lower ECMO support. Once the patient can tolerate zero sweep gas flow with modest mechanical ventilator settings (e.g. tidal volume < 6 ml/kg of predicted body weight, plateau pressure < 30 cmH2O, PEEP < 12 cmH2O, FiO2 < 0.6), decannulation should be considered.

**Anticoagulation Management**
Most modern ECLS circuits are heparin coated and engineered with biocompatible materials leading. This leads to a lower requirements for systemic heparin anticoagulation as well as less haemolysis and platelet consumption by the circuit.

Despite these advancements; however, systemic anticoagulation is still required, most often in the form of unfractionated heparin. Factors that impact anticoagulation targets depends upon three major factors: ECLS technique (VA vs. VV vs. ECCO2R), blood flow rate (lower flows higher risk of thrombus formation), and the presence of bleeding.

Typical anticoagulation targets include: Activated clotting time (ACT) 1.5 times normal, activated partial thromboplastin time (aPTT) 1.2-2.8 times normal, anti-Xa activity 0.2-0.3 IU/ml., Thromboelastography may also be considered.

If heparin requirements are noted to increase substantially on ECLS (e.g., > 50 units/kg/hr), screening for anti-thrombin deficiency may be.

**Blood Transfusion Thresholds**
Optimal transfusion thresholds have not be rigorously evaluated for patients on ECMO. While the Extracorporeal Life Support Organization suggest targeting normal values of haemoglobin (>10g/dl) in attempt to optimize tissue oxygen delivery, some centres target a more conservative threshold of 7 g/dl, given the risks associated with transfusions. More research is needed to understand what the optimal haemoglobin threshold is while on ECMO.
6. ECLS for Obstructive Lung Diseases

References found in this Chapter


References

- Abrams D, Brodie D., Emerging indications for extracorporeal membrane oxygenation in adults with respiratory failure., 2013, PMID:23952860
- O'Donnell DE, Parker CM., COPD exacerbations . 3: Pathophysiology., 2006, PMID:16565268
- McFadden ER Jr, Acute severe asthma., 2003, PMID:14522812
- Braune SA, Kluge S, Extracorporeal lung support in patients with chronic obstructive pulmonary disease., 2013, PMID:23698548

6. 1. Rationale and Evidence

The main pathophysiological characteristic of obstructive lung disease exacerbation is the expiratory flow limitation caused by the increased resistance of the small airways. The development of dynamic alveolar hyperinflation and intrinsic PEEP increase the work of breathing in these patients, leading to respiratory muscle fatigue and rapid shallow breathing. The reduction of alveolar ventilation and rise in PaCO₂ further increases the ventilatory demand, creating a vicious loop.

In this setting, non-invasive ventilation (NIV) reduces the work of breathing and increases alveolar ventilation, but may not be sufficient in severe cases. Invasive mechanical ventilation (IMV) can normalise gas exchange and reduce the work of breathing, but is associated with adverse effects, such as ventilator-associated pneumonia, ICU-acquired weakness, and ventilator-induced diaphragmatic dysfunction.

ECCO₂R reduces the volume of alveolar ventilation required to eliminate CO₂ production. The consequent reduction of tidal volume and respiratory rate is associated with increased expiratory time, facilitating the resolution of the dynamic hyperinflation. Therefore, the work of breathing decreases despite persistent airflow limitation.
Given this strong pathophysiological rationale, the application of ECCO₂R, has been described in several case reports of patients with obstructive lung diseases. However, until there are randomised trials providing definitive proof of its efficacy, we cannot recommend the routine use of ECCO₂R in these patients.

6. 2. Configurations


6. 3. Indications and Goals Reported in the Literature

Potential Indications:

1. Invasive mechanical ventilation for COPD exacerbation with failed two or more weaning attempts
2. Failing treatment with NIV:
   1. NIV for at least 1 -2 hours with signs of respiratory distress (i.e., respiratory rate ≥30 breaths/min and use of accessory muscles or paradoxical abdominal movements), and
   2. PaCO₂ > 55 mmHg and pH < 7.25, or
   3. pH < 7.30 and PaCO₂ > 55 mm Hg, with PaCO₂ decrease < 5 mmHg from baseline
Clinical goals:

- Prevention of endotracheal intubation
- Facilitation of weaning from invasive mechanical ventilation
- Early mobilisation and physiotherapy
### 7. ECLS for COPD Exacerbation

#### Table 6: Selected Case Series of ECLS for COPD Exacerbations

<table>
<thead>
<tr>
<th>Modality</th>
<th>No. of treated patients and outcome</th>
<th>Complications</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pesenti A, 1990 First description of ECLS for COPD exacerbation</td>
<td>ECCO₂R and IMV</td>
<td>1 patient, survived</td>
<td>None</td>
</tr>
<tr>
<td>Abrams DC, 2013 ECLS to facilitate weaning from IMV</td>
<td>ECCO₂R and IMV</td>
<td>5 patients; age 73 ± 8.7 years All weaned from IMV Duration of IMV post ECCO₂R: 4 hours (1.5–21.5) Duration of ECCO₂R: 193.0 ± 76.5 hours Time to ambulation after ECCO₂R initiation: 29.4 ± 12.6 hours</td>
<td>Minor bleeding in 2/5 patients</td>
</tr>
<tr>
<td>Authors</td>
<td>Year</td>
<td>Conditions</td>
<td>Patients</td>
</tr>
<tr>
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</tr>
<tr>
<td>Kluge S, 2012 ECLS during NIV to prevent IMV</td>
<td>Pumpless arterio-venous ECCO2R and NIV</td>
<td>21 patients with hypercapnia, 14 with COPD age 58 (27-80) years</td>
<td>Gas exchange parameters before ECLS: pH 7.28 (7.10–7.41) PaCO₂ 84.0 (54.2–131.0) mmHg PaO₂/FiO₂ ratio 208 (153–396)</td>
</tr>
<tr>
<td>Burki NK, 2013 ECLS during NIV to prevent IMV, and during IMV to facilitate weaning</td>
<td>ECCO2R</td>
<td>20 patients with COPD: 9 on NIV, 11 on IMV age 49-78 years</td>
<td>Duration of ECCO₂R: 0.2-192 hours none of the patients on NIV was intubated 3/11 patients on IMV were successfully weaned</td>
</tr>
</tbody>
</table>

- IMV = Invasive Mechanical Ventilation
8. ECLS for Near Fatal Asthma Exacerbation

8. 1. Indications and Configurations

Severe dynamic lung hyperinflation with consequent refractory hypercapnia characterise near fatal episodes of asthma exacerbation.

ECLS has been used as rescue strategy in these patients as an adjunct to mechanical ventilation. ECLS can correct gas exchange, thereby prolonging the duration of the expiratory time and thus facilitating the reduction of dynamic lung hyperinflation, while providing time for the resolution of bronchospasm.

Low flow ECCO$_2$R, by correcting respiratory acidosis, may accomplish the goal of facilitating the resolution of dynamic lung hyperinflation. However, the most severe cases of asthma exacerbation can be characterised by hypoxemia and hemodynamic decompensation. In these conditions, VV-ECMO or VA-ECMO provides a more adequate means of support, especially in case of rescue conditions.

8. 2. Evidence

<table>
<thead>
<tr>
<th>Table 7: Selected Case Series of ECLS for Near Fatal Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Modality</strong></td>
</tr>
<tr>
<td>Study</td>
</tr>
<tr>
<td>------------------------------</td>
</tr>
<tr>
<td>Hebbar KB, 2009 ELSO report</td>
</tr>
<tr>
<td>Mikkelsen ME, 2009 ELSO</td>
</tr>
<tr>
<td>Brenner K, 2014</td>
</tr>
</tbody>
</table>

- IMV = Invasive Mechanical Ventilation
9. ECLS as a bridge to lung transplant

References found in this Chapter


- Cypel M, Keshavjee S., Extracorporeal life support as a bridge to lung transplantation., 2011, PMID:21511087
- Strueber M, Bridges to lung transplantation., 2011, PMID:21897243
- Diaz-Guzman E, Hoopes CW, Zwischenberger JB., The evolution of extracorporeal life support as a bridge to lung transplantation., 2013, PMID:23271390

9. 1. Definition

“Bridge to lung transplant” defines strategies to utilise artificial support to manage the acute decompensation of patients with chronic respiratory failure awaiting a suitable organ. Clinical advancements in this field are particularly required, as the mortality rate of patients on the lung transplant waiting list is still very high (14.1% in North America in 2009) and higher than those of other solid organs transplant.

The goal of bridge strategies to lung transplant should be preferably to improve the critical condition of patients with end stage respiratory failure, preventing multi-organ dysfunction and restoring physiological homeostasis in order to increase the chances of a successful transplant. Ideally, bridge to lung transplant should not be applied with the sole intent of prolonging the pre-transplant life expectancy of patients. This approach, in fact, would raise ethical issues by potentially selecting for transplantation very ill patients for lung transplantation with long-term outcomes that are likely to be poor.
9. 2. Rationale and Evidence

Invasive mechanical ventilation (IMV) may be considered a bridging strategy to lung transplantation as it improves gas exchange and decreases the work of breathing, but it is associated with several injurious side effects. Indeed, patients with end stage lung diseases are particularly susceptible to ventilator-associated lung injury and pneumonia. Moreover, the application of IMV often requires patients to be sedated and bed-bound, reducing their ability to undergo adequate physiotherapy. These events lead to severe deconditioning of these critically ill patients and may compromise their suitability for transplant.

The increased efficiency of the ECLS systems in maintaining adequate gas exchange with fewer complications has resulted in the possibility to remarkably reduce the need for IMV.

The use of a single, bi-caval dual-lumen cannula in the internal jugular vein for ECLS represents an important technological advancement for these patients. By accessing only one vessel, preferably in the upper body, it becomes possible to deliver more intensive physical therapy and rehabilitation in the pre-transplant period while on ECLS. This innovative strategy may result in shorter duration of post-transplant mechanical ventilation and hospital stay, with less morbidity and mortality.

9. 3. Indications

There are no evidence-based Indications and contraindications to ECLS as a bridge to transplant, but there is general consensus that young age, absence of multiple-organ dysfunction and good potential for rehabilitation are criteria for ECLS as a bridge to transplant. Septic shock, multi-organ dysfunction, severe arterial occlusive disease, heparin-induced thrombocytopenia, long duration of mechanical ventilation, and advanced age are considered at least relative contraindications. The appropriate selection of patients and ECLS mode and configuration has been crucial in obtaining progressively better outcomes.

Several recent case series and observational studies have shown that the post-transplant mortality rate of selected patients bridged to transplant with ECLS is comparable to that of patients transplanted without pre-transplant ECLS.

Despite these promising results, the application of ECLS as a bridge to transplant remains controversial and better quality data on its putative risks and benefits are needed before routine adoption in clinical practice can take place.
9. 4. Configurations

![Diagram of venovenous extracorporeal membrane oxygenation for acute respiratory failure](image)


9. 5. Evidence

Table 8: Selected Case Series of ECLS as a Bridge to Lung Transplant

<table>
<thead>
<tr>
<th>Modality</th>
<th>No. of treated patients and outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veith FJ, 1977</td>
<td>First successful ECLS as bridge to lung transplant</td>
<td>ECMO and IMV1 patient survived pre-transplant died post transplant</td>
</tr>
<tr>
<td>Bermudez CA, 2011</td>
<td>VV or VA-ECMO and IMV</td>
<td>17 patients with COPD, idiopathic pulmonary fibrosis, cystic fibrosis, graft failure; age: 40 ± 14 year Duration of ECLS: 1-49 days Mortality rate pre transplant: 0% Survival rate: 74% at 1 year</td>
</tr>
<tr>
<td>De Perrot M, 2011</td>
<td>VA-ECMO or Pumppless pulmonary artery-left atrium circuit</td>
<td>6 patients with idiopathic pulmonary hypertension Duration of ECLS: 1-69 days 4 patients required IMV Mortality rate pre transplant: 0% Survival rate post transplant: 66%</td>
</tr>
<tr>
<td>------------------</td>
<td>----------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Fuehner T, 2012</td>
<td>Awake ECMO</td>
<td>26 patients with pulmonary fibrosis, cystic fibrosis, graft failure, pulmonary hypertension; age: 44 (23-62) years 7 patients required IMV Duration of ECLS: 9 (1-45) days Mortality rate pre transplant: 23% Survival rate post transplant: 80% at 6 months</td>
</tr>
<tr>
<td>Lafarge M, 2013</td>
<td>VV or VA-ECMO</td>
<td>36 patients with pulmonary fibrosis (20), cystic fibrosis (11), others (5); age: 30.8 (22.4–47.7) years 33 patients with IMV before ECLS Duration of ECLS pre transplant: 3.5 (0-11) days Mortality rate pre transplant: 16.7% Survival rate post transplant: 47% at 17 months</td>
</tr>
</tbody>
</table>

- IMV = Invasive Mechanical Ventilation
10. Complications and Troubleshooting

<table>
<thead>
<tr>
<th>CIRCUIT/OXYGENATOR</th>
<th>CANNULA</th>
<th>ANTICOAGULATION</th>
<th>PATIENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air In Circuit</td>
<td>Limb ischemia</td>
<td>Bleeding</td>
<td>Line Seizure</td>
</tr>
<tr>
<td>Minor Air: Release air from oxygenator and look for cause (cracked line, air entranced through other venous access)</td>
<td>May occur with femoral arterial cannula obstructing distal flow to limb. Can address by adding a distal perfusion catheter, increasing flows, or decreasing vasopressors</td>
<td>Identify whether the bleeding is related to surgical procedure (post operative patient) or degree of anticoagulation. May benefit from decreasing anticoagulation threshold, stopping anticoagulation temporarily or anti-fibrinolytic/clotting agents (tranexamic acid/recombinant factor VIIa depending upon severity) or surgical/procedural exploration of the bleed depending upon source.</td>
<td>Use sterile technique for all central and ECMO cannulation sites. Avoid unnecessary central line insertion in order to minimize risk of catheter-related blood stream infection. ECMO cannulae and associated Pneumothorax</td>
</tr>
<tr>
<td>Clot or Thrombus Formation</td>
<td>Low flow or No Flow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Identify cause (insufficient ECLS blood flow, insufficient anti-coagulation, platelet activation/aggregation, underlying hypercoagulable state i.e. heparin induced thrombocytopenia)</td>
<td>If no flow after insertion, assess for kinking, thrombus formation and depth of insertion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemolysis</td>
<td>Deep Vein Thrombosis</td>
<td>Heparin-induced thrombocytopenia</td>
<td>Respiratory Muscle Weakness</td>
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<tr>
<td>High flows inducing sheering of cells/hemolysis, look for alternative patient-associated causes of hemolysis (transfusion reaction etc). May benefit from decreasing flows. Less of a problem with contemporary ECLS equipment.</td>
<td>Large venous cannula could lead to the development of DVTs if the cannula is sufficiently large that it induces stasis proximal to its insertion. Ensure cannula size is not too big for vessel</td>
<td>Identify whether heparin induced thrombocytopenia is present, if confirmed, employ use of alternative anticoagulation agents (ie. Argatroban, bivalirudin)</td>
<td>Minimizing use of sedation and using spontaneous ventilation may reduce respiratory muscle weakness</td>
</tr>
<tr>
<td>Thrombocytopenia, platelet dysfunction</td>
<td>Vessel Dissection</td>
<td></td>
<td>Delirium</td>
</tr>
<tr>
<td>Platelets adhere to surface of circuit and become activated, platelet aggregation, consumption and further activation of coagulation system may result. May require platelet transfusions</td>
<td>Vessel dissection could be induced by insertion. Monitoring of distal perfusion is essential and if there is concern, consult vascular surgery</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Table 10: Troubleshooting Hypoxemia*
<table>
<thead>
<tr>
<th><strong>ECMO RELATED STRATEGIES or ETIOLOGIES</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PATIENT RELATED ISSUES. Insufficient oxygen delivery?</strong></td>
</tr>
<tr>
<td><strong>Increase in oxygen consumption?</strong></td>
</tr>
<tr>
<td><strong>CIRCUIT RELATED ISSUES. Recirculation</strong></td>
</tr>
<tr>
<td><strong>Cannula</strong></td>
</tr>
<tr>
<td><strong>Chatter</strong></td>
</tr>
<tr>
<td><strong>Oxygenator compromise</strong></td>
</tr>
<tr>
<td><strong>If native lungs were contributing to systemic oxygenation, need to evaluate cause for worsening hypoxaemia</strong></td>
</tr>
</tbody>
</table>