Update on the Extracorporeal Life Support

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Extracorporeal life support (ECLS) is a type of cardiopulmonary bypass. It is an artificial means of supplying oxygen and removing CO₂ on behalf of damaged lungs while patients are recovering from underlying diseases. Recently, the use of ECLS is rapidly increasing as this machine becomes smaller, less invasive and easier to use. In addition, the improvement of clinicians’ technique and outcome is increasing their application to patients with acute respiratory distress. In this regard, the purpose of this review is to introduce the physiological principles, risk factors, and advantages of ECLS, clinical rationale for using ECLS, ventilatory strategy during ECLS, which are still causing different opinions, the weaning from ECLS, and the use of anticoagulant.

Keywords: Respiratory Distress Syndrome, Adult; Extracorporeal Membrane Oxygenation

What Is Extracorporeal Life Support?

Extracorporeal life support (ECLS), in particular, veno-venous (VV) extracorporeal membrane oxygenation (ECMO) is currently used as rescue therapy on patients with severe acute respiratory distress syndrome (ARDS) or severe hypoxia. Over the last five years, bridge therapy using ECLS has shown good clinical outcomes.

The basic principle of ECLS is that while a pump (from semi-occlusive roller-head device to centrifugal pump) drives blood flow through an oxygenator (from silicone membrane to polymethylpentene fibers) via the extracorporeal circuit, the blood interacts with constant flow of oxygen at a specific speed using sweep-gas flows (Table 1). Extracorporeal oxygenation and CO₂ removal are determined by three factors: extracorporeal blood flow rate controlled by the centrifugal-pump speed, sweep-gas flow rate controlled by a flow meters, and oxygen tension within the sweep gas controlled by a gas blender (Table 2).

The ECLS strategy which is mostly applied to ARDS patients is VV ECMO, but a switch to veno-arterial ECMO can be considered if reduced cardiac function is accompanied or hypoxia progresses even during the use of VV ECMO.

As extracorporeal CO₂ removal (ECCO₂R) requires low blood flow rates (1–2 L/min), small cannulas, and less anticoagulation to remove CO₂, it is more convenient to deal with than ECMO. Because of low blood flow rates, oxygen is supplied by a patient’s own lungs. As another type, the pumpless arteriovenous extracorporeal circuit is also used. Here, extracorporeal blood flows are caused by the native arteriovenous pressure gradient (≥60 mm Hg).

Considerations in Adult Patients with Respiratory Failure

There are no standardized criteria for the application of ECLS. However, it is mostly applied for rescue therapy on refractory hypoxia or hypercapnia or for ultra-protective ventilator strategies for the prevention of ventilator-induced lung injury (VILI). High ECMO flow rates (3–7 L/min) are required to improve oxygenation, and low flow rates (300–1,500 mL/min) are sufficient to remove CO₂ effectively. Indication of...
ECLS should be decided after considering the risk-benefit ratio by multidisciplinary discussions.

### 1. Extracorporeal membrane oxygenation

Factors deciding the application of ECLS in patients with respiratory failure are the oxygenation index, $\text{PaO}_2/\text{FiO}_2$, Murray score, and refractory hypercapnia with acidosis (Table 3).

In 2009 H1N1 influenza epidemic, many centers applied ECMO to patients with severe ARDS and refractory hypoxia. Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECOMO) Influenza Investigators reported a

| Table 1. ECMO vs. $\text{ECCO}_2\text{R}$ |
|---------------------------------------|
| **VV ECMO**                           | **ECCO$_2$R**                        |
| Blood drainage                        | From central vein (internal jugular vein, femoral vein, subclavian vein) | From central vein (internal jugular vein, femoral vein, subclavian vein) or femoral artery in arteriovenous configuration |
| Blood return                         | Into right atrium                    | Into central vein |
| Cannula dimension                    | 16–31 Fr (drainage cannula: 24–31 Fr, return cannula: 16–23 Fr) | 8–29 Fr |
| Cannula type                         | Two singular cannulas or dual-lumen cannula | Two singular cannulas or dual-lumen cannula |
| Pump                                 | Centrifugal                         | Centrifugal or peristaltic |
| Extracorporeal blood flow, L/min    | 2.0–7.0                             | 0.2–2.0 |
| CO$_2$ clearance                     | 100% VCO$_2$ dependent mainly on sweep gas flow | 10%–100% VCO$_2$ dependent mainly on sweep gas flow |
| Oxygen delivery capacity             | Dependent mainly on extracorporeal blood flow | Not significant |
| Anticoagulation target               | ACT 1.5–2.0 times normal, aPTT 1.2–1.8 times normal | ACT 1.5 times normal, aPTT 1.5 times normal |

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**ECMO:** extracorporeal membrane oxygenation; **ECCO$_2$R:** extracorporeal CO$_2$ removal; **VV:** veno-venous; **VCO$_2$:** CO$_2$ production; **ACT:** activated clotting time; **aPTT:** activated partial thromboplastin time.

| Table 2. Characteristics of gas exchange and hemodynamic support during ECLS |
|-----------------------------------------------------------------------------|
| **Factors determining the oxygenation in the ECLS circuit**                | **Volume of blood crossing the oxygenator over time (blood flow)** |
| Arterial oxygen saturation before crossing the artificial lung             | Arterial oxygen saturation before crossing the artificial lung |
| Hemoglobin concentration                                                   | Hemoglobin concentration |
| Fraction of delivered oxygen in the sweep gas                              | Fraction of delivered oxygen in the sweep gas |
| Diffusion of oxygen through the oxygenator                                  | Diffusion of oxygen through the oxygenator |
| Clearance of CO$_2$                                                        | Clearance of CO$_2$ |
| Sweep-gas flow                                                             | Sweep-gas flow |
| Total surface area of the artificial lung                                   | Total surface area of the artificial lung |
| Systemic oxygen delivery                                                   | Systemic oxygen delivery |
| VV ECMO: ratio of ECLS blood flow to cardiac output, ECLS blood flow, recirculation of blood in ECLS circuit | VV ECMO: ratio of ECLS blood flow to cardiac output, ECLS blood flow, recirculation of blood in ECLS circuit |
| VA ECMO: ratio between ECLS blood flow and residual intrapulmonary blood flow, ECLS blood flow, maximum oxygenation, residual intrapulmonary blood flow | VA ECMO: ratio between ECLS blood flow and residual intrapulmonary blood flow, ECLS blood flow, maximum oxygenation, residual intrapulmonary blood flow |
| Extracorporeal CO$_2$ removal: provides insufficient oxygenation of the blood | Extracorporeal CO$_2$ removal: provides insufficient oxygenation of the blood |
| Systemic CO$_2$ elimination                                                | Systemic CO$_2$ elimination |
| VV or VA ECMO: potentially eliminates entire CO$_2$ production because the ECLS blood flow is enough | VV or VA ECMO: potentially eliminates entire CO$_2$ production because the ECLS blood flow is enough |
| Extracorporeal CO$_2$ removal: usually needs high (>8 L/min) sweep-gas flow to remove CO$_2$ | Extracorporeal CO$_2$ removal: usually needs high (>8 L/min) sweep-gas flow to remove CO$_2$ |
| Hemodynamic support                                                        | Hemodynamic support |
| VV ECMO and extracorporeal CO$_2$ removal: no                              | VV ECMO and extracorporeal CO$_2$ removal: no |
| VA ECMO: might replace lung and heart function by bypassing the cardiac out | VA ECMO: might replace lung and heart function by bypassing the cardiac out |

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**Table 3. VV ECMO for rescue treatment in patients with acute respiratory distress syndrome**

| Indication                                                                 | Contraindication                                                                                                                                 |
|----------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| **REVA**⁹                                                                  | Presence of severe comorbidities and multiorgan failure (SOFA score >15)                                                                                           |
| PaO₂/FiO₂ <50 despite PEEP 10–20 cm H₂O and FiO₂ >80%; Pplat >35 cm H₂O despite the attempt to reduce TV <4 mL/kg PBW |                                                                                                                                                    |
| **ANZ ECMO¹                                                                | Irreversible CNS condition; cirrhosis with ascites, encephalopathy, or history of variceal bleeding; active and rapidly fatal malignant disease; HIV infection; weight >120 kg; pulmonary hypertension; cardiac arrest |
| PaO₂/FiO₂ <60; PaCO₂ >100 mm Hg with PaO₂/FiO₂ <100                         |                                                                                                                                                   |
| **ECMOnet²                                                                 | Intracranial bleeding or other major contraindication to anticoagulation; previous severe disability; poor prognosis because of underlying disease; mechanical ventilation >7 days |
| Oxygenation index >30; PaO₂/FiO₂ <70 with PEEP ≥15 cm H₂O for patients already admitted to an ECMO center; pH <7.25 for ≥2 hr; hemodynamic instability |                                                                                                                                                    |
| **CESAR²                                                                  | Mechanical ventilation ≥7 days; age <18 yr; pregnancy; weight >1 kg/cm; BMI >45 kg/m²; chronic respiratory insufficiency treated oxygen therapy of long duration and/or long-term respiratory assistance; history of heparin-induced thrombocytopenia; malignant disease with 5-year fatal prognosis; patient moribund; SAPS II >90; non-drug-induced coma following cardiac arrest; irreversible CNS pathology; decision to limit therapeutic interventions; unable to cannulate |
| Potentially reversible respiratory failure; Murray score ≥3; pH <7.2 despite optimum conventional treatment |                                                                                                                                                    |
| **EOLIA (NCT01470703)**                                                   |                                                                                                                                                   |
| PaO₂/FiO₂ <50 with FiO₂ >80% for 3 hr, despite optimum mechanical ventilation and adjunctive treatment; PaO₂/FiO₂ <80 with FiO₂ >80% for 6 hr, despite optimum mechanical ventilation and adjunctive treatment; pH <7.25 for 6 hr (RR increased to 35 beats per minute) with mechanical ventilation adjusted to keep Pplat <32 cm H₂O |                                                                                                                                                    |

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VV ECMO: veno-venous extracorporeal membrane oxygenation; PaO₂: arterial partial pressure of O₂; FiO₂: fraction of inspired oxygen; PEEP: positive end-expiratory pressure; TV: tidal volume; PBW: predicted body weight; SOFA: sequential organ failure assessment score; CNS: central nervous system; HIV: human immunodeficiency virus; RR: respiratory rate; BMI: body mass index; SAPS II: Simplified Acute Physiology Score.

**Table 4. Clinical studies of ECLS to prevent ventilator-induced lung injury**

| ECLS technique                          | Mechanical ventilation strategy                                                                 |
|-----------------------------------------|------------------------------------------------------------------------------------------------|
| **Zimmermann et al.⁶**                  | Tidal volume ≤6 mL/kg PBW, Pplat ≤30 cm H₂O, RR ≤25/min, and high NHLBI ARDS network PEEP/FiO₂ table |
| Pumpless interventional lung assist      | No control group                                                                                   |
| **Terragni et al.¹¹**                   | Tidal volume ≤4 mL/kg PBW, and high NHLBI ARDS network PEEP/FiO₂ table                             |
| Extracorporeal CO₂ removal              | Tidal volume 4 mL/kg PBW                                                                           |
| **Bein et al.¹⁰**                       | Tidal volume 3 mL/kg PBW                                                                           |
| Extracorporeal CO₂ removal              | Tidal volume 6 mL/kg PBW                                                                           |
| **PARSA study (NCT01239966)**           | Tidal volume 4 mL/kg PBW                                                                           |
| Extracorporeal CO₂ removal and renal replacement therapy | No control group                                                                                   |
| **ELP study (NCT 01522599)**            | Tidal volume 4 mL/kg PBW                                                                           |
| Extracorporeal CO₂ removal              | Tidal volume 6 mL/kg PBW                                                                           |

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ECLS: extracorporeal life support; PBW: predicted body weight; Pplat: inspiratory plateau pressure; RR: respiratory rate; NHLBI: National Heart, Lung, and Blood Institute; ARDS: acute respiratory distress syndrome; PEEP: positive end-expiratory pressure; FiO₂: fraction of inspired oxygen.
survival rate of 75% in the ECMO treatment group. The Italian ECMO Network also showed a survival rate of 68% in the ECMO treatment group. The Swine Flu Triage (SWiFT) study, done in the UK showed the lower in-hospital mortality in the ECMO treatment group (24% vs. 53%, p=0.006). In the CESAR trial, severe ARDS patients also showed the higher survival rate in the ECMO treatment group (63% vs. 47%, p=0.03).

The above results suggested that the implementation of protective mechanical ventilation during ECMO can improve the prognosis.

EOLIA (NCT01470703) should help to define the clinical efficacy of VV ECMO in severe ARDS patients.

2. Extracorporeal CO₂ removal

Recent studies reported that the application of ECCO₂R in ARDS patients can reduce the lung injury as it enables the ultra-protective strategies of mechanical ventilation (Table 4). Zimmermann et al. reported that when pumpless AV ECLS was applied to 51 patients with ARDS, low tidal volume ventilation could be maintained along with the continuous removal of CO₂, and the survival rate was 50%.

A randomized, controlled study was done to compare an ultra-protective mechanical ventilation (3 mL/kg predicted body weight [PBW] with Pumpless AV ECLS) with low tidal volume ventilation (6 mL/kg PBW) strategies in 79 patients with ARDS. While the two groups did not differ for in-hospital mortality, within the patient group with PF ratio <200, the ultra-protective group showed an improved survival. At present, studies on the efficacy of very low tidal volumes ventilation strategies during ECCO₂R are working in progress.

1. Mechanical ventilation strategies

For minimizing VILI, the ventilator settings during VV ECMO should be maintained at low levels to enable the prevention of atelectasis while keeping the alveoli open. However, there are no specific recommendations other than the maintenance of positive end-expiratory pressure (PEEP) at 10 cm H₂O or above. As the injured lungs contribute little to oxygenation, lung recruitment using PEEP while maintaining minimal tidal volumes might accelerate lung healing or optimise cardiopulmonary function

In the CESAR trial, lung rest was induced by limitation of the peak inspiratory pressure to 20 cm H₂O with PEEP 10 cm H₂O, 10 breaths per minute, and FiO₂ of 30%. Another study also showed positive outcomes in patients who maintained a mean plateau pressure of 25 cm H₂O.

After the acute phase of the illness, mechanical ventilation with spontaneous breathing should be considered to reduce the use of sedatives and to improve the diaphragmatic function.

2. Tracheostomy

In the case of applying ECLS due to severe ARDS, mechanical ventilation for a long period of time is predicted. Therefore, the early tracheostomy might be considered. The use of anticoagulants during ECLS is not the contraindication for tracheostomy. In a recent study, a tracheostomy with the percutaneous dilatational technique done by experienced physician is safe with a brief interruption of anticoagulation. In this study, the use of sedatives and to improve the diaphragmatic function.

Table 5. Weaning from ECMO

| Weaning trial | Criteria for ECMO weaning |
|---------------|--------------------------|
| VV ECMO  FinsO₂=21% | Pplat <25 to 30 cm H₂O with TV around 6 mL/kg and PEEP <12 cmH₂O |
| Sweep gas flow 1 L/min or stopped | And PaO₂ > 70 mm Hg on FiO₂ <60% or PaO₂/FiO₂ >200 mm Hg |
| Duration: several hours | And pH >7.3 with PCO₂ <50 mmHg |
| VA ECMO  FinsO₂=21% | Pplat <25 to 30 cm H₂O with TV around 6 mL/kg and PEEP <12 cm H₂O |
| Sweep gas flow 1 L/min | And PaO₂ > 70 mm Hg on FiO₂ <60% or PaO₂/FiO₂ >200 mm Hg |
| Reduce pump blood flow by steps of 0.5 L/min | And pH >7.3 with PCO₂ <50 mmHg |
| Duration: several hours | And no acute cor pulmonale |
| | Without left ventricular failure: |
| | Left ventricular ejection fraction >25% to 30% |
| | Velocity-time integral >12 cm |

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no major complications such as death were observed\textsuperscript{16}.

3. Weaning from ECLS (Table 5)\textsuperscript{17}

When mechanical ventilation settings is acceptable (tidal volume <6 mL/Kg PBW, plateau pressure <30 cm H\textsubscript{2}O, PEEP <12 cm H\textsubscript{2}O, FiO\textsubscript{2} <60\%) and respiratory mechanics, gas exchanges, and radiographic findings are improved, weaning from ECLS can be considered. Before weaning, the existence of acute cor pulmonale should be identified. Two main strategies of weaning can be used: reducing sweep-gas flow rates or reducing extracorporeal blood-flow rates. Alternatively, weaning of mechanical ventilation may be considered earlier than weaning from ECLS\textsuperscript{18,19}.

4. Sedation

While deep sedation and neuromuscular blockade might be required in the initial stages to relieve symptoms and reduce oxygen consumption, patients should be kept awake to actively participate in rehabilitation therapy during ECLS. In addition, early mobilization could suppress the progression of weakness and reduce the incidence of delirium.

The indication for the use of awake ECMO, instead of invasive mechanical ventilation is not confirmed in patients with ARDS refractory to non-invasive ventilation. However, the use of awake ECMO as a bridge before lung transplantation has shown promising results\textsuperscript{20-25}. Mechanical ventilation and sedation might worsen outcomes before and after the transplantation. Awake ECMO enables patients to communicate, eat, and walk and improves physical and physiological conditions.

5. Technological advances

The first technological advances in this field may be the production of bicaval dual-lumen cannulas\textsuperscript{24}. This cannula is inserted via the right internal jugular vein, and then drains blood from the superior and inferior vena cava through one lumen and returns blood into the right atrium through a second lumen. Only one cannulation enables patients to receive intensive physiotherapy more conveniently. Second, reduction in the size of ECLS equipment has enabled patients receiving ECLS to transfer and mobilise\textsuperscript{25}.

6. Anticoagulant and transfusion

Although the ECLS circuits are engineered with biocompatible materials, the systemic anticoagulants are still required to prevent thrombotic complication. Unfractionated heparin is most commonly used and monitoring is performed using activated partial thromboplastin time (1.2–1.5 times control), anti-Xa activity (0.2–0.4 IU/mL), or the activated clotting time. When heparin-induced thrombocytopenia is suspected, arg-

| Parameter | Score or Survival (%) |
|-----------|-----------------------|
| Age, yr   |                       |
| 18–49     | 0                     |
| 50–59     | –2                    |
| ≥60       | –3                    |
| Immunocompromised status | –2                  |
| Mechanical ventilation prior to initiation of ECMO | |
| <48 hr    | 3                     |
| 48 hr–7 days | 1                   |
| >7 days   | 0                     |
| Acute respiratory diagnosis group (select only one) | |
| Viral pneumonia | 3                  |
| Bacterial pneumonia | 3              |
| Asthma    | 11                    |
| Trauma and burn | 3                   |
| Aspiration pneumonitis | 5                  |
| Other acute respiratory diagnoses | 1                  |
| Nonrespiratory and chronic respiratory diagnoses | 0               |
| Central nervous system dysfunction | –7                |
| Acute associated (nonpulmonary) infection | –3                |
| Neuromuscular blockade agents before ECMO | 1                  |
| Nitric oxide use before ECMO | –1                |
| Bicarbonate infusion before ECMO | –2                 |
| Cardiac arrest before ECMO | –2                 |
| PaCO\textsubscript{2}, mm Hg | |
| <75       | 0                     |
| ≥75       | –1                    |
| Peak inspiratory pressure, cm H\textsubscript{2}O | |
| <42       | 0                     |
| ≥42       | –1                    |
| Total score | –22 to 15            |

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*Survival (%).
RESP: Respiratory ECMO Survival Prediction; ECMO: extracorporeal membrane oxygenation; PaCO\textsubscript{2}: partial pressure of carbon dioxide.
atroban or bivalirudin can be used as alternatives. 

The guidelines of the Extracorporeal Life Support Organization (ELSO) recommend maintaining normal hemoglobin concentration for tissue oxygenation. However, some centers are more restrictive to transfusion thresholds in critically ill patients (Hb <7 g/dL).

7. Evaluation of prognosis

ELSO has recently announced the Respiratory ECMO Survival Prediction (RESP) score using data extracted from the ELSO international registry. This score can be a good tool to predict survival for patients receiving ECMO for respiratory failure (Table 6).

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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