REVIEW

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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 CO_2 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[1,2].

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)[3]. Extracorporeal oxygenation and CO_2 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)[3].

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[4].

As extracorporeal CO_2 removal ($ECCO_2R$) requires low blood flow rates (1–2 L/min), small cannulas, and less anticoagulation to remove CO_2, it is more convenient to deal with than ECMO[5]. 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)[6].

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 (500–1,500 mL/min) are sufficient to remove CO_2 effectively. Indication of

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Table 1. ECMO vs. $ECCO_2R$

	VV ECMO	$ECCO_2R$
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; $ECCO_2R$: 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
	Hemoglobin concentration
	Fraction of delivered oxygen in the sweep gas
	Diffusion of oxygen through the oxygenator
Clearance of CO_2	Sweep-gas flow
	Total surface area of the artificial lung
Systemic oxygen delivery	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
	Extracorporeal CO_2 removal: provides insufficient oxygenation of the blood
Systemic CO_2 elimination	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
Hemodynamic support	VV ECMO and extracorporeal CO_2 removal: no
	VA ECMO: might replace lung and heart function by bypassing the cardiac out

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ECLS: extracorporeal life support; VV ECMO: veno-venous extracorporeal membrane oxygenation; VA: veno-arterial.

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, PaO_2/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[1] reported a

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

	Indication	Contraindication
REVA[9]	PaO_2/FiO_2 <50 despite PEEP 10–20 cm H_2O and FiO_2 >80%; P_{plat} >35 cm H_2O despite the attempt to reduce TV <4 mL/kg PBW	Presence of severe comorbidities and multiorgan failure (SOFA score >15)
ANZ ECMO[1]	PaO_2/FiO_2 <60; $PaCO_2$ >100 mm Hg with PaO_2/FiO_2 <100	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
ECMOnet[7]	Oxygenation index >30; PaO_2/FiO_2 <70 with PEEP ≥15 cm H_2O for patients already admitted to an ECMO center; pH <7.25 for ≥2 hr; hemodynamic instability	Intracranial bleeding or other major contraindication to anticoagulation; previous severe disability; poor prognosis because of underlying disease; mechanical ventilation >7 days
CESAR[2]	Potentially reversible respiratory failure; Murray score ≥3; pH <7.2 despite optimum conventional treatment	PIP >30 cm H_2O or FiO_2 >80%; mechanical ventilation >7 days; intracranial bleeding; contraindication to limited heparinization; contraindication to continuation of active treatment
EOLIA (NCT01470703)	PaO_2/FiO_2 <50 with FiO_2>80% for 3 hr, despite optimum mechanical ventilation and adjunctive treatment; PaO_2/FiO_2 <80 with FiO_2 >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 P_{plat} <32 cm H_2O	Mechanical ventilation ≥7 days; age <18 yr; pregnancy; weight >1 kg/cm; BMI >45 kg/m^2; 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

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VV ECMO: veno-venous extracorporeal membrane oxygenation; PaO_2: arterial partial pressure of O_2; FiO_2: 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[3]

	ECLS technique	Mechanical ventilation strategy	
		ECLS group	Control group
Zimmermann et al.[6]	Pumpless interventional lung assist	Tidal volume ≤6 mL/kg PBW, P_{plat} ≤30 cm H_2O, RR ≤25/min, and high NHLBI ARDS network PEEP/FiO_2 table	No control group
Terragni et al.[11]	Extracorporeal CO_2 removal	Tidal volume ≤4 mL/kg PBW, and high NHLBI ARDS network PEEP/FiO_2 table	Tidal volume 6 mL/kg PBW
Bein et al.[10]	Extracorporeal CO_2 removal	Tidal volume 3 mL/kg PBW	Tidal volume 6 mL/kg PBW
PARSA study (NCT01239966)	Extracorporeal CO_2 removal and renal replacement therapy	Tidal volume 4 mL/kg PBW	No control group
ELP study (NCT 01522599)	Extracorporeal CO_2 removal	Tidal volume 4 mL/kg PBW	Tidal volume 6 mL/kg PBW

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ECLS: extracorporeal life support; PBW: predicted bodyweight; P_{plat}: inspiratory plateau pressure; RR: respiratory rate; NHLBI: National Heart, Lung, and Blood Institute; ARDS: acute respiratory distress syndrome; PEEP: positive end-expiratory pressure; FiO_2: 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[7]. 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)[8]. In the CESAR trial, severe ARDS patients also showed the higher survival rate in the ECMO treatment group (63% vs. 47%, p=0.03)[2].

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 CO_2 removal

Recent studies reported that the application of $ECCO_2R$ in ARDS patients can reduce the lung injury as it enables the ultraprotective strategies of mechanical ventilation (Table 4). Zimmermann et al.[6] 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 CO_2, 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[10]. At present, studies on the efficacy of very low tidal volumes ventilation strategies during $ECCO_2R$ are working in progress.

Controversies

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 H_2O 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[12,13].

In the CESAR trial, lung rest was induced by limitation of the peak inspiratory pressure to 20 cm H_2O with PEEP 10 cm H_2O, 10 breaths per minute, and FiO_2 of 30%. Another study also showed positive outcomes in patients who maintained a mean plateau pressure of 25 cm H_2O[9].

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[14,15].

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,

Table 5. Weaning from ECMO

	Weaning trial	Criteria for ECMO weaning
VV ECMO	$F_{EC}O_2$=21%	P_{plat} <25 to 30 cm H_2O with TV around 6 mL/kg and PEEP <12 cmH_2O
	Sweep gas flow 1 L/min or stopped	And PaO_2 > 70 mm Hg on FiO_2 <60% or PaO_2/FiO_2 >200 mm Hg
	Duration: several hours	And pH>7.3 with PCO_2 <50 mmHg
		And no acute cor pulmonale
VA ECMO	$F_{EC}O_2$=21%	P_{plat} <25 to 30 cm H_2O with TV around 6 mL/kg and PEEP <12 cm H_2O
	Sweep gas flow 1 L/min	And PaO_2 >70 mm Hg on FiO_2 <60% or PaO_2/FiO_2 >200 mm Hg
	Reduce pump blood flow by steps of 0.5 L/min	And pH >7.3 with PCO_2 <50 mm Hg
	Duration: several hours	And no acute cor pulmonale
		Without left ventricular failure:
		Left ventricular ejection fraction >25% to 30%
		Velocity-time integral >12 cm

Adopted from Richard C et al. Ann Intensive Care 2014;4:15, according to the Creative Commons License[17].
ECMO: extracorporeal membrane oxygenation; VV: veno-venous; $F_{EC}O_2$: oxygen fraction delivered by the extracorporeal circuit; P_{plat}: plateau pressure; TV: tidal volume; PEEP: positive end-expiratory pressure; PaO_2: arterial partial pressure of O_2; FiO_2: fraction of inspired oxygen; PCO_2: partial pressure of CO_2; VA: venous-arterial.

no major complications such as death were observed[16].

3. Weaning from ECLS (Table 5)[17]

When mechanical ventilation settings is acceptable (tidal volume <6 mL/Kg PBW, plateau pressure <30 cm H_2O, PEEP <12 cm H_2O, FiO_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[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[20-23]. 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[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[25].

6. Anticoagulantion 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-

Table 6. RESP score

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
$PaCO_2$, mm Hg	
<75	0
≥75	−1
Peak inspiratory pressure, cm H_2O	
<42	0
≥42	−1
Total score	−22 to 15
Hospital survival by risk class	
Risk class/Total RESP score	
I (≥6)	92%*
II (3 to 5)	76%*
III (−1 to 2)	57%*
IV (−5 to −2)	33%*
V (≤−6)	18%*

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*Survival (%).
RESP: Respiratory ECMO Survival Prediction; ECMO: extracorporeal membrane oxygenation; $PaCO_2$:partial pressure of carbon dioxide.

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atroban or bivalirudin can be used as alternatives[26].

The guidelines of the Extracorporeal Life Support Organization (ELSO) recommend maintaining normal hemoglobin concentration for tissue oxygenation. However, some centers is 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 (Table 6)[27].

Conflicts of Interest

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

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