

# Extracorporeal life support for adults with severe acute respiratory failure

Lorenzo Del Sorbo, Marcelo Cypel, Eddy Fan



Extracorporeal life support (ECLS) is an artificial means of maintaining adequate oxygenation and carbon dioxide elimination to enable injured lungs to recover from underlying disease. Technological advances have made ECLS devices smaller, less invasive, and easier to use. ECLS might, therefore, represent an important step towards improved management and outcomes of patients with acute respiratory distress syndrome. Nevertheless, rigorous evidence of the ability of ECLS to improve short-term and long-term outcomes is needed before it can be widely implemented. Moreover, how to select patients and the timing and indications for ECLS in severe acute respiratory distress syndrome remain unclear. We describe the physiological principles, the putative risks and benefits, and the clinical evidence supporting the use of ECLS in patients with acute respiratory distress syndrome. Additionally, we discuss controversies and future directions, such as novel technologies and indications, mechanical ventilation of the native lung during ECLS, and ethics considerations.

## Introduction

Extracorporeal life support (ECLS) is an artificial means of providing oxygenation and carbon dioxide (CO<sub>2</sub>) elimination in patients who have acute respiratory failure. ECLS is not a cure, but can temporarily support heart and lung function, which might provide time for injured lungs to recover and enable treatment of underlying disease.<sup>1,2</sup> Advances in ECLS technology have reduced its complexity and increased its safety, which has led to a resurgence in its use.<sup>1,2</sup>

ECLS, particularly venovenous extracorporeal membrane oxygenation (ECMO), has been used as rescue therapy in patients with severe acute respiratory distress syndrome and refractory hypoxaemia,<sup>3-5</sup> but its efficacy remains uncertain.<sup>6</sup> The mortality associated with acute respiratory distress syndrome remains unacceptably high,<sup>7</sup> reaching 45% in patients with severe disease.<sup>3,8</sup> Despite sustained research to improve management,<sup>9</sup> no specific therapy has been developed. Thus, the cornerstone of treatment remains supportive care with mechanical ventilation. In the past 5 years, however, the use of ECLS in adult patients with severe acute respiratory distress syndrome has been associated with improved outcomes.<sup>4,10</sup>

In this Review we describe the physiological principles, the putative benefits, and the clinical evidence supporting the use of ECLS in patients with acute respiratory distress syndrome. Additionally, we discuss some current controversies and future directions for ECLS in patients with acute respiratory failure, such as novel technologies and indications, mechanical ventilation of the native lung, and ethics considerations.

## Extracorporeal life support

The ultimate goal of ECLS is to maintain adequate oxygen delivery and CO<sub>2</sub> elimination to partly or completely unload the cardiopulmonary system and enable recovery from underlying disease.<sup>2,11</sup> During ECLS, a pump drives blood flow through the extracorporeal circuit, which includes an oxygenator (eg, hollow-fibre

polymethylpentene). The blood interacts with a constant flow of oxygen (sweep-gas flow) across the hollow fibres, which enables gas exchange to take place (figure 1).<sup>12,13</sup> Extracorporeal oxygenation and CO<sub>2</sub> removal are controlled by three features: extracorporeal blood-flow rate, which depends on many different factors, but is controlled mainly by modification of the centrifugal-pump speed; sweep-gas flow rate, which is controlled by a flow meter; and fraction of delivered oxygen in the sweep gas, which is controlled by a gas blender. Alteration of these features achieves different outcomes (panel).<sup>14,15</sup>

The most frequently applied ECLS strategy in patients with severe acute respiratory distress syndrome is venovenous ECMO.<sup>4,10</sup> In this approach, venous blood is drained from the right atrium via a large vein (eg, the internal jugular or femoral vein), pumped through the oxygenator, and returned to the right atrium (figure 1).<sup>2</sup> In venoarterial ECMO, venous blood is drained from the right atrium, pumped through the oxygenator and delivered into the arterial circulation (eg, via the femoral

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Extracorporeal Life Support (ECLS) Program, University Health Network (L Del Sorbo MD, M Cypel MD, E Fan MD), Department of Surgery (M Cypel), and the Interdepartmental Division of Critical Care Medicine (L Del Sorbo, E Fan), University of Toronto, Toronto, ON, Canada

Correspondence to:  
Dr Eddy Fan, Critical Care Medicine, Toronto General Hospital, 585 University Avenue, 11C-1167, Toronto, ON, Canada M5G 2N2  
[eddy.fan@uhn.ca](mailto:eddy.fan@uhn.ca)

## Key messages

- Extracorporeal life support (ECLS) is not a treatment, but an artificial means of providing oxygenation and elimination of carbon dioxide (CO<sub>2</sub>) to enable recovery from and treatment of underlying lung disease
- Technological advances have led to reduced-size ECLS devices that are less invasive and easier to use than previous devices, and which might represent an important step towards improved management and outcome of patients with acute respiratory distress syndrome (ARDS)
- ECLS can be used in patients with ARDS in two distinct settings: for rescue from the harmful effect of refractory hypoxaemia, hypercapnia, or both; and for rescue from or prevention of injurious levels of mechanical ventilation
- Extracorporeal CO<sub>2</sub> removal, a less invasive and simpler ECLS configuration, might minimise ventilator-induced lung injury in patients with ARDS, but confirmatory clinical trials are needed
- Rigorous evidence regarding the optimum timing, selection of patients, and indications for ECLS in severe ARDS, and its ability to improve patients' short-term and long-term outcomes are needed before widespread adoption of this therapy

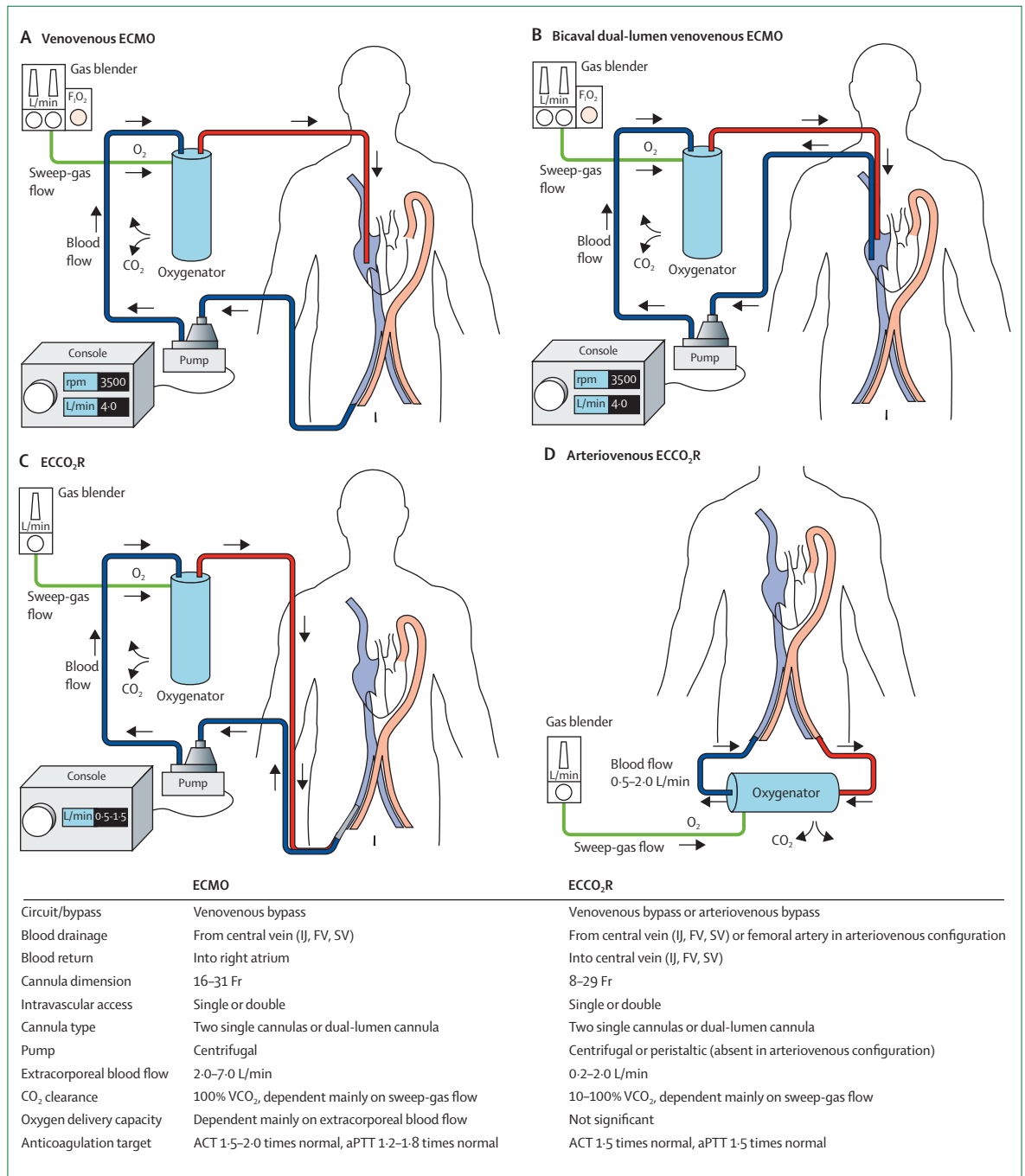
artery; figure 1).<sup>2</sup> In the latter configuration, the ECLS system can replace the lung and heart functions and, therefore, might be useful for patients with severe acute respiratory distress syndrome and associated severe cardiac dysfunction or in patients with refractory hypoxaemia undergoing venovenous ECMO.<sup>12</sup> Isolated right-ventricular dysfunction associated with acute respiratory distress syndrome is not necessarily a contraindication to venovenous ECMO because perfusion

of the lung with oxygenated blood might lead to vasodilation of the pulmonary circulation, which would decrease right-ventricular afterload and improve function.

Extracorporeal CO<sub>2</sub> removal requires low blood-flow rates (eg, 1–2 L/min) to clear the entire CO<sub>2</sub> volume metabolised by the body. Small cannulas and compact systems have been specifically developed, as they require less anticoagulation and are notably easier to manage than larger systems.<sup>16</sup> Blood is drained from a dual-

**Figure 1: Differences between ECMO and ECCO<sub>2</sub>R**

(A) Venovenous ECMO, in which venous blood is drained from the right atrium via a large vein (eg, the internal jugular or femoral vein), pumped through the oxygenator, and returned to the right atrium. (B) A bicaval dual-lumen cannula is inserted via the right internal jugular vein and drains blood from the superior and inferior vena cava through one lumen, and returns it into the right atrium through a second lumen. Only one upper-body cannulation site is required. (C) ECCO<sub>2</sub>R, in which blood is drained from a dual-lumen catheter inserted in the femoral or internal jugular vein, pumped through the oxygenator, and returned into the venous system. (D) ECCO<sub>2</sub>R configuration that relies on the native arteriovenous pressure gradient as driving force of extracorporeal blood flow. Blood is drained from an arterial access (eg, the femoral artery), run through the low-resistance membrane, and returned into the venous compartment (eg, via the femoral vein).  
ECMO=extracorporeal membrane oxygenation. F<sub>I</sub>O<sub>2</sub>=fraction of inspired oxygen. ECCO<sub>2</sub>R=extracorporeal CO<sub>2</sub> removal. IJ=internal jugular vein. FV=femoral vein. SV=subclavian vein. VCO<sub>2</sub>=metabolic CO<sub>2</sub> production. ACT=activated clotting time. aPTT=activated partial thromboplastin time.



### Panel: Characteristics of gas exchange and haemodynamic support during ECLS

#### Oxygenation in the artificial lung

Only a small amount of oxygen is required to maximise the arterial oxygen content of blood through the artificial lung.

Oxygenation in the ECLS circuit depends on:

- Volume of blood crossing the oxygenator over time (blood flow), rather than the sweep-gas flow
- Arterial oxygen saturation before crossing the artificial lung
- Haemoglobin concentration
- Fraction of delivered oxygen in the sweep gas
- Diffusion of oxygen through the oxygenator

#### CO<sub>2</sub> elimination

CO<sub>2</sub> is present in blood in dissolved form, dissociated into bicarbonates and hydrogen ions, and bound to haemoglobin.

Dissolved CO<sub>2</sub> is characterised by:

- A steep dissociation curve and high solubility in blood
- Elevated diffusion rate across the artificial lung

Clearance of CO<sub>2</sub> from the blood is efficient and mainly dependent on:

- Sweep-gas flow (artificial-lung ventilation), rather than the blood flow, through the artificial lung
- Total surface area of the artificial lung

#### Systemic oxygen delivery

##### Venovenous ECMO

Increases in arterial saturation and partial pressure of oxygen by increasing venous saturation of oxygen are dependent on:

- The ratio of ECLS blood flow to cardiac output: the higher the ratio, the higher the venous saturation of oxygen (ratios >60% generally result in saturation >90%)
- ECLS blood flow, influenced by the site and size of cannulation, efficiency of the pump, and cardiac output.
- Recirculation of blood in the ECLS circuit, influenced by the distance between the drainage and return cannulas, ECLS blood flow, and cardiac output

##### Venoarterial ECMO

Increases in arterial saturation and partial pressure of oxygen are dependent on:

- Ratio between ECLS blood flow and residual intrapulmonary blood flow
- ECLS blood flow
- Maximum oxygenation, influenced by site of ECLS cannulation (which results in anterograde direction when returned into the subclavian artery or retrograde direction when returned into the femoral artery), size of the cannula, efficiency of the ECLS pump, and cardiac preload
- Residual intrapulmonary blood flow: blood is generally deoxygenated due to the shunt present in the native lung which does not impair hypoxic vasoconstriction, and is roughly zero when the contractility of the heart is severely compromised

May decrease the intrapulmonary flow to virtually zero by bypassing cardiac output from the right atrium to the right aorta while maintaining systemic circulation with laminar flow

May result in the Harlequin syndrome if retrograde perfusion of the aorta is used by cannulation of the femoral artery, where the aortic arch is perfused partly by poorly oxygenated blood arriving from the heart and partly by the fully oxygenated blood provided by ECLS; the addition of a venous return cannula is a potential solution

Specific strategies to perfuse the limb undergoing arterial cannulation (eg, a distal-limb perfusion cannula) or to unload the left ventricle and avoid excessive ventricular dilation (eg, by intra-aortic balloon pump or atrial septostomy) might be required

##### Extracorporeal CO<sub>2</sub> removal

Provides insufficient oxygenation of the blood

#### Systemic CO<sub>2</sub> elimination

##### Venovenous or venoarterial ECMO

Potentially eliminates entire CO<sub>2</sub> production because the minimum ECLS blood flow is usually >1 L/min

Cause average arterial partial pressure of carbon dioxide to reach values >40 mm Hg only when the sweep gas flow is <6 L/min

##### Extracorporeal CO<sub>2</sub> removal

Usually needs high (>8 L/min) sweep-gas flow to efficiently remove CO<sub>2</sub>

In venovenous mode, CO<sub>2</sub> removal depends on ECLS blood flow, which is influenced by

- Size of cannula
- Recirculation of blood in the ECLS circuit
- Efficiency of the ECLS pump
- Total surface area of the artificial lung
- Cardiac preload

In arteriovenous mode, CO<sub>2</sub> removal also depends on ECLS blood flow, which is influenced by:

- Cardiac output
- Size of the cannula
- Total surface area of the artificial lung

#### Haemodynamic support

##### Venovenous ECMO

Does not provide haemodynamic support, but might indirectly improve haemodynamics secondary to improvement in oxygenation

##### Venoarterial ECMO

Might completely replace lung and heart function by bypassing the entire cardiac output from the right atrium to the aorta, maintaining systemic circulation with laminar flow

##### Extracorporeal CO<sub>2</sub> removal

Does not provide haemodynamic support

ECLS=extracorporeal life support. ECMO=extracorporeal membrane oxygenation.

	ELSO <sup>23</sup>	REVA <sup>5</sup>	ANZ ECMO <sup>4</sup>	ECMOnet <sup>24</sup>	CESAR <sup>10</sup>	EOLIA (NCT01470703)
Indications	Mortality >80%; PaO <sub>2</sub> /F <sub>0</sub> O <sub>2</sub> <80 with F <sub>0</sub> O <sub>2</sub> >90%; Murray score 3.0–4.0	PaO <sub>2</sub> /F <sub>0</sub> O <sub>2</sub> <50 despite PEEP 10–20 cm H <sub>2</sub> O and F <sub>0</sub> O <sub>2</sub> >80%; P <sub>plat</sub> >35 cm H <sub>2</sub> O, despite the attempt to reduce tidal volumes to less than 4 mL/kg PBW	PaO <sub>2</sub> /F <sub>0</sub> O <sub>2</sub> <60; PaCO <sub>2</sub> >100 mm Hg with PaO <sub>2</sub> /F <sub>0</sub> O <sub>2</sub> <100	Oxygenation index >30; PaO <sub>2</sub> /F <sub>0</sub> O <sub>2</sub> <70 with PEEP ≥15 cm H <sub>2</sub> O for patients already admitted to an ECMO centre; pH <7.25 for ≥2 h; haemodynamic instability	Potentially reversible respiratory failure; Murray score ≥3.0; pH <7.20 despite optimum conventional treatment	PaO <sub>2</sub> /F <sub>0</sub> O <sub>2</sub> ratio <50 with F <sub>0</sub> O <sub>2</sub> >80% for >3 h, despite optimum mechanical ventilation and adjunctive treatment; PaO <sub>2</sub> /F <sub>0</sub> O <sub>2</sub> ratio <80 with F <sub>0</sub> O <sub>2</sub> >80% for >6 h, despite optimum mechanical ventilation and adjunctive treatment; pH <7.25 for >6 h (respiratory rate increased to 35 breaths per min) with mechanical ventilation adjusted to keep P <sub>plat</sub> <32 cm H <sub>2</sub> O
Considerations	Mortality >50%; PaO <sub>2</sub> /F <sub>0</sub> O <sub>2</sub> <150 with F <sub>0</sub> O <sub>2</sub> >90%; Murray score 2.0–3.0	None	None	PaO <sub>2</sub> /F <sub>0</sub> O <sub>2</sub> <100 with PEEP ≥10 cm H <sub>2</sub> O for patients awaiting transfer to ECMO centre	Murray score ≥2.5	None
Contraindications	Pre-existing conditions preclude aggressive treatment (eg, CNS status, end-stage malignant disease, high risk of systemic bleeding with anticoagulation); age and size of patient; severe illness (eg, major immunosuppression, haemorrhagic stroke); have been undergoing conventional treatment for too long (mechanical ventilation >7 days) or have a fatal diagnosis	Presence of severe comorbidities and multiorgan failure (SOFA score >15)	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	Intracranial bleeding or other major contraindication to anticoagulation; previous severe disability; poor prognosis because of underlying disease; mechanical ventilation >7 days	PIP >30 cm H <sub>2</sub> O or F <sub>0</sub> O <sub>2</sub> >80%; mechanical ventilation >7 days; intracranial bleeding; contraindication to limited heparinisation; contraindication to continuation of active treatment	Mechanical ventilation ≥7 days; age <18 years; pregnancy; weight >1 kg/cm; BMI >45 kg/m <sup>2</sup> ; chronic respiratory insufficiency treated with 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

ECMO=extracorporeal membrane oxygenation. PaO<sub>2</sub>/F<sub>0</sub>O<sub>2</sub>=ratio of arterial partial pressure of oxygen to fraction of inspired oxygen ratio. F<sub>0</sub>O<sub>2</sub>=fraction of inspired oxygen. PEEP=positive end-expiratory pressure. PaCO<sub>2</sub>=arterial partial pressure of carbon dioxide. P<sub>plat</sub>=end-inspiratory plateau pressure. PBW=predicted bodyweight. PIP=peak inspiratory pressure. SOFA=sequential organ failure assessment score. BMI=body-mass index. SAPS II=simplified acute physiology score.

**Table 1: Findings for venovenous ECMO used as a rescue treatment in patients with acute respiratory distress syndrome**

lumen catheter inserted in the femoral or internal jugular vein, pumped through the oxygenator, and returned into the venous system (figure 1). Substantial oxygenation is not possible because of the low blood-flow rate,<sup>16–18</sup> and oxygen reaches the tissues only via the native lung. Another configuration of extracorporeal CO<sub>2</sub> removal uses a pumpless arteriovenous extracorporeal circuit.<sup>16,19,20</sup> This system relies on the native arteriovenous pressure gradient to drive extracorporeal blood flow through the artificial lung. Blood is drained from an arterial access (eg, via the femoral artery), run through the low-resistance membrane, and returned into the venous compartment (eg, via the femoral vein; figure 1).

**Considerations in adults**

Mechanical ventilation, although life-saving for patients with acute respiratory distress syndrome, is associated with ventilator-induced lung injury.<sup>21</sup> This complication has been attributed to two main mechanisms: cyclic overdistension, which can be caused by high airway pressures (barotrauma) and large tidal volumes (volutrauma), and cyclic collapse and reopening of airway units with each breath (atelectrauma).<sup>21</sup> Furthermore, lung-cell

distension, disruption, or necrosis after application of mechanical ventilation might increase the risk of a pulmonary and systemic inflammatory response (biotrauma).<sup>21</sup> ECLS might be ideal to avoid ventilator-induced lung injury in patients with severe acute respiratory distress syndrome because the ventilation settings are less injurious than other forms of mechanical ventilation, especially when respiratory-system compliance is very low.<sup>22</sup>

Despite renewed enthusiasm for ECLS, standardised criteria for its clinical application in patients with acute respiratory distress syndrome have not been established. Broadly speaking, ECLS can be used in these patients in two distinct settings: for rescue from the harmful effect of refractory hypoxaemia, hypercapnia, or both; or for rescue from or prevention of the harmful effects of injurious levels of mechanical ventilation.

**Rescue from refractory hypoxaemia or hypercapnia**

Venovenous ECMO is the ECLS technique most frequently applied in patients with severe acute respiratory distress syndrome and refractory hypoxaemia or hypercapnia, unless severe cardiac dysfunction prompts the use of venoarterial ECMO.

	ECLS technique	Mechanical ventilation strategy in ECLS group	Mechanical ventilation strategy in control group
Zimmermann et al, 2009 <sup>20</sup>	Pumpless interventional lung assist	Tidal volume $\leq 6$ mL/kg PBW, $P_{\text{plat}} \leq 30$ cm H <sub>2</sub> O, respiratory rate $\leq 25$ breaths per min, and high NHLBI ARDS Network PEEP/F <sub>i</sub> O <sub>2</sub> table	No control group
Terragni et al, 2009 <sup>27</sup>	Extracorporeal CO <sub>2</sub> removal	Tidal volume 4 mL/kg PBW and high NHLBI ARDS Network PEEP/F <sub>i</sub> O <sub>2</sub> table	Tidal volume 6 mL/kg PBW
Bein et al, 2013 <sup>19</sup>	Extracorporeal CO <sub>2</sub> removal	Tidal volume 3 mL/kg PBW	Tidal volume 6 mL/kg PBW (NHLBI ARDS Network)
EOLIA study (NCT01470703)	Venovenous ECMO	Volume-assist control mode, F <sub>i</sub> O <sub>2</sub> 30–60%, PEEP $\geq 10$ cm H <sub>2</sub> O, $P_{\text{plat}} < 25$ cm H <sub>2</sub> O, respiratory rate 10–30 breaths per min	Assist-controlled ventilatory mode, tidal volume 6 mL/kg PBW and PEEP set to keep $P_{\text{plat}} < 28$ –30 cm H <sub>2</sub> O
PARSA study (NCT01239966)	Extracorporeal CO <sub>2</sub> removal and renal-replacement therapy	Tidal volume 4 mL/kg PBW	No control group
ELP study (NCT01522599)	Extracorporeal CO <sub>2</sub> removal	Tidal volume 4 mL/kg PBW	Tidal volume 6 mL/kg PBW (NHLBI ARDS Network)

ECLS=extracorporeal life support. PBW=predicted bodyweight.  $P_{\text{plat}}$ =inspiratory plateau pressure. NHLBI ARDS Network=National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network. PEEP=positive end expiratory pressure. F<sub>i</sub>O<sub>2</sub>: fraction of inspired oxygen. ECMO=extracorporeal membrane oxygenation.

**Table 2: Clinical trials of ECLS to prevent ventilator-induced lung injury**

Theoretically, treatment with venovenous ECMO for refractory hypoxaemia or hypercapnia should be started in patients in whom the predicted benefit of ECLS (or hypoxaemia-related mortality) outweighs the risk of developing ECLS-related complications. Several professional organisations have published recommendations (table 1).

### Rescue or prevention of ventilator-induced lung injury

In a landmark study by the National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (NHLBI ARDS) Network, mechanical ventilation with low tidal volumes (6 mL/kg of predicted bodyweight) and plateau pressure (lower than 30 cm H<sub>2</sub>O) resulted in improved survival in patients with acute respiratory distress syndrome.<sup>25</sup> Moreover, a patient-level meta-analysis of three large randomised trials suggested that high positive end-expiratory pressure is associated with a significant reduction of deaths in hospital among patients with severe acute respiratory distress syndrome,<sup>26</sup> although the optimum positive end-expiratory pressure level has not been identified.

Whether further reducing tidal volume, plateau pressure, or both, would improve survival in patients with acute respiratory distress syndrome is unclear. Terragni and colleagues<sup>27</sup> showed that a third of patients with severe acute respiratory distress syndrome ventilated according to the NHLBI ARDS Network protocol had radiographic evidence of alveolar overdistension. These data were consistent with those from a secondary analysis, which showed that there is no safe threshold for plateau pressure in patients with acute respiratory distress syndrome and that further reductions might be more lung protective.<sup>28</sup> Ideally, injured lungs should not undergo any mechanical stress or strain.

Further reductions in tidal volume and plateau pressure might result in decreased minute ventilation and alveolar derecruitment, which could make adequate gas exchange difficult to achieve while keeping ventilator-induced lung injury to a minimum. Venovenous ECMO or

extracorporeal CO<sub>2</sub> removal are suitable approaches,<sup>29</sup> but the application of the latter might be less invasive and easier to manage while achieving similar efficiency in CO<sub>2</sub> clearance (figure 1). No definitive clinical criteria have been created for the use of ECLS for rescue or prevention of ventilator-induced lung injury. Nevertheless, several studies have shown significantly reduced tidal volumes by removal of a portion of CO<sub>2</sub>, for which only a low blood-flow rate through ECLS is necessary (table 2).

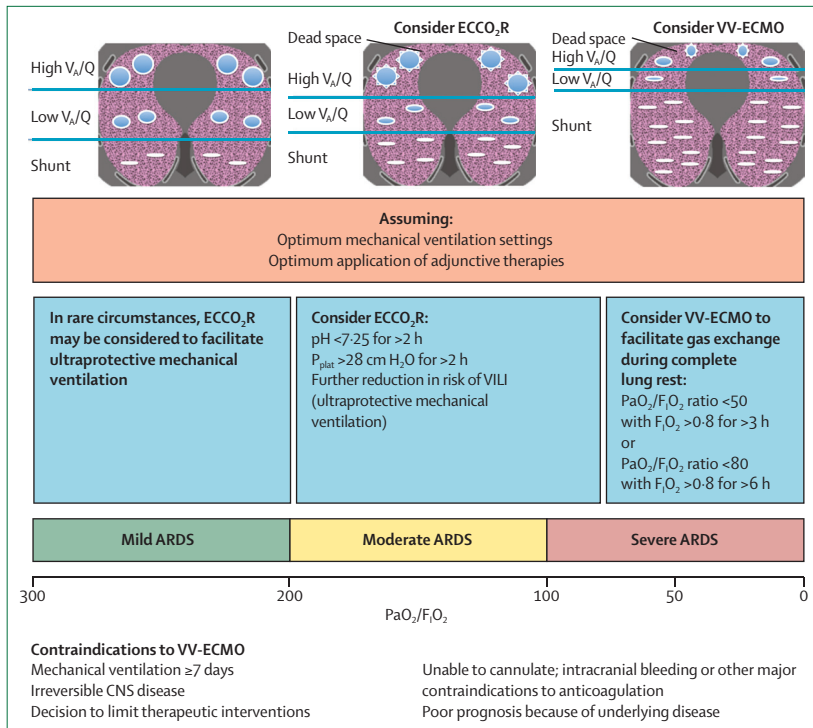
ECLS might be suitable for use in patients with early acute respiratory distress syndrome who would otherwise require injurious levels of mechanical ventilation to maintain adequate gas exchange. The lowering of plateau pressure, tidal volume, or both,<sup>28,30</sup> has been associated with decreased mortality, which led to the hypothesis that ultrprotective mechanical ventilation with ECLS could further improve outcomes in patients with acute respiratory distress syndrome.<sup>16</sup> Thus, ECLS might prove to be an alternative to mechanical ventilation altogether in the treatment of acute respiratory distress syndrome (figure 2).<sup>31,32</sup>

Mild acute respiratory distress syndrome might not justify the use of extracorporeal CO<sub>2</sub> removal, but it could be considered for patients with very high distending (transpulmonary) pressure, in whom the goal is to substantially reduce the tidal volume (eg, to less than 4 mL/kg of predicted bodyweight). To reach these goals, extracorporeal CO<sub>2</sub> removal might rarely be required in patients with mild acute respiratory distress syndrome, although the potential benefits of this strategy are not yet confirmed.

### Extracorporeal membrane oxygenation

Since the first successful clinical application of ECLS in a patient with post-traumatic acute respiratory distress syndrome in 1972,<sup>33</sup> more than 30 000 patients worldwide have been supported with this approach.<sup>34</sup> Although most studies have investigated the role of ECLS as a rescue treatment in patients with refractory hypoxaemia, some investigation has been done of its role in the prevention





**Figure 2: Possible clinical and pathophysiological criteria for extracorporeal gas exchange in patients with acute respiratory distress syndrome**

ECCO<sub>2</sub>R may be used to reduce VILI or to deliver an ultraprotective strategy of mechanical ventilation. VV-ECMO may be considered in patients with severe ARDS and refractory, life-threatening hypoxaemia. ECCO<sub>2</sub>R=extracorporeal CO<sub>2</sub> removal. VV-ECMO=venovenous extracorporeal membrane oxygenation. V<sub>A</sub>/Q=alveolar ventilation to perfusion ratio. P<sub>plat</sub>=end-inspiratory plateau pressure. VILI=ventilator-induced lung injury. F<sub>i</sub>O<sub>2</sub>=fraction of inspired oxygen. PaO<sub>2</sub>/F<sub>i</sub>O<sub>2</sub>=ratio of partial pressure of arterial oxygen to fraction of inspired oxygen. ARDS=acute respiratory distress syndrome.

of ventilator-induced lung injury.<sup>17,19,20</sup>

In a randomised, controlled trial of ECLS for patients with acute respiratory distress syndrome and severe hypoxaemia (partial pressure of arterial oxygen in the blood lower than 50 mm Hg for longer than 2 h, fraction of inspired oxygen 100%, and positive end-expiratory pressure higher than 5 cm H<sub>2</sub>O) 90 patients were assigned to conventional mechanical ventilation or to ECMO.<sup>34</sup> Survival did not differ between the two groups, but several important issues characterise the results. First, the mortality rate was very high (90%) in both groups, which suggests that the respiratory failure was too advanced, and the intervention was applied too late, for patients to respond to any therapy; many of the patients had developed severe acute respiratory distress syndrome from influenza. Second, venoarterial ECMO was applied via the femoral vein and artery, which might have led to reduced oxygen delivery to the brain and increased the risk of pulmonary thrombosis because of reduced pulmonary blood flow. Third, patients treated with ECMO required blood transfusions of up to 2.5 L plasma and blood daily because of bleeding episodes related to treatment. Last, the ventilation strategy used in both groups would be deemed injurious in practice (the rough

incidence of pneumothorax in each group was 45%). In a prospective study that used positive end-expiratory pressure up to 25 cm H<sub>2</sub>O and a low respiratory rate of 3–5 breaths per min coupled with extracorporeal CO<sub>2</sub> removal to keep the lung at rest and avoid ventilator-induced lung injury, a much lower rate of mortality (49%) was seen.<sup>22</sup> Owing to the lack of a control group, however, these data should be interpreted with caution.

On the basis of these encouraging results, a randomised, controlled trial was done to compare pressure-controlled inverse-ratio ventilation alone with that in association with extracorporeal CO<sub>2</sub> removal in patients with acute respiratory distress syndrome.<sup>35</sup> Survival did not differ between groups (33% vs 42%, p=0.8). Importantly, the rates of bleeding complications and transfusion requirements were high in the extracorporeal CO<sub>2</sub> removal group. Moreover, the authors had limited experience with the technology for this treatment, and the mechanical ventilation strategy was changed after enrolment of half of the patients because of difficulties in maintaining tidal volumes higher than 100 mL with the original pressure-controlled strategy (peak-pressure limit 45 cm H<sub>2</sub>O).<sup>35</sup>

The multicentre CESAR trial<sup>10</sup> randomised 180 patients who had severe acute respiratory distress syndrome to transfer to a specialist centre for possible ECMO or usual care. Despite only 68 (75%) of 90 patients in the intervention group actually receiving ECMO, survival was significantly higher than with usual care (63% vs 47%, p=0.03). The study might not be conclusive on the clinical efficacy of ECMO compared with conventional mechanical ventilation, but the findings strongly suggest that referral of patients to centres with proven expertise is helpful.

The H1N1 influenza epidemic in 2009 led a substantial number of people to develop severe acute respiratory distress syndrome and refractory hypoxaemia, and ECMO was used as rescue oxygenation therapy. The Australia and New Zealand Extracorporeal Membrane Oxygenation Influenza Investigators reported an observational trial involving 68 patients with severe H1N1-associated acute respiratory distress syndrome treated with ECMO;<sup>4</sup> the survival rate was 75%. Similarly, the Italian ECMO Network,<sup>24</sup> which includes 14 ECMO centres, treated 153 patients with severe acute respiratory distress syndrome, of whom 60 (39%) received ECMO. Survival to discharge was 68%, which increased to 77% when those who received ECMO within 7 days of the beginning of mechanical ventilation were included. In the Swine Flu Triage (SWiFT) study, done in the UK,<sup>36</sup> patients who were and were not referred for ECMO were compared. In-hospital mortality was significantly lower among referred patients (24% vs 53%, p=0.006). In a French Réseau Européen de Recherche en Ventilation Artificielle (REVA) Network study,<sup>5</sup> the overall observed mortality rate among 123 patients with H1N1-associated acute respiratory distress syndrome was 36% and did

not differ between patients who did or did not receive ECMO (50% vs 40%,  $p=0.32$ ). The lack of a centralised ECMO strategy in this study, which was done in more than 30 centres, might have contributed to the difference in results from those in previous studies. Overall mortality, however, was similar across the most experienced centres and those that cared for few ECMO patients.<sup>5</sup> A multivariate analysis showed that age, lactation, and plateau pressure under ECMO were most strongly associated with mortality, which suggests that protective mechanical ventilation during ECMO improves outcome.

The above results, however, must be considered alongside those of an observational study of 30 patients with H1N1-associated severe acute respiratory distress syndrome (baseline ratio of partial pressure of arterial oxygen to fraction of inspired oxygen 61 and positive end-expiratory pressure 22 cm H<sub>2</sub>O) treated with mechanical ventilation (ie, usual care).<sup>37</sup> Survival was 73%, which is similar to that in the ECMO-treated patients in the other cohorts. Therefore, definitive clinical evidence of a survival advantage with the use of ECMO in patients with severe acute respiratory distress syndrome remains elusive. The results of a multicentre randomized clinical trial, the Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome trial (NCT01470703), should help to define the clinical efficacy of venovenous ECMO in patients with severe acute respiratory distress syndrome. The trial will compare patients treated with early venovenous ECMO and lung rest with a control group treated with lung-protective ventilation.

### Extracorporeal CO<sub>2</sub> removal

An increasing number of clinical studies of extracorporeal CO<sub>2</sub> removal in patients with acute respiratory distress syndrome have included ultraprotective strategies of mechanical ventilation that apply minimally invasive ECLS techniques. These approaches, however, do not provide clinically sufficient oxygenation support.<sup>11</sup>

Zimmermann and colleagues<sup>20</sup> used pumpless arteriovenous ECLS in 51 patients with acute respiratory distress syndrome characterised by ratios of partial pressure of arterial oxygen to fraction of inspired oxygen of 70–200 mm Hg, with positive end-expiratory pressure higher than 10 cm H<sub>2</sub>O, arterial pH lower than 7.25 because of respiratory acidosis, or both. ECLS removed a substantial amount of CO<sub>2</sub>, which enabled maintenance of protective levels of mechanical ventilation with tidal volumes lower than 6 mL/kg predicted bodyweight. Half of the patients survived and only three (6%) had ECLS-related complications (eg, leg ischaemia with arterial cannulation).

Another minimally invasive device for extracorporeal CO<sub>2</sub> removal that uses small dual-lumen catheters and low blood flow (5–10% of cardiac output) has been studied in patients with severe acute respiratory distress syndrome.<sup>17</sup> This system significantly reduced mean tidal

volume (from 6.3 [SD 0.2] to 4.2 [0.2] mL/kg predicted bodyweight) while maintaining normocapnia. Lung hyperinflation on CT and concentrations of inflammatory mediators in the lungs were significantly reduced.

Finally, a randomised, controlled trial was done in 79 patients with acute respiratory distress syndrome to compare an ultraprotective mechanical ventilation strategy (3 mL/kg predicted bodyweight combined with pumpless arteriovenous ECLS) with a ventilation strategy with a low tidal volume (6 mL/kg predicted bodyweight) without ECLS. Survival was improved with the ultraprotective approach in patients with a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen were lower than 200.<sup>19</sup> The two groups did not differ for in-hospital mortality (18% vs 15%,  $p=1.0$ ) or number of ventilator-free days (33 vs 29,  $p=0.47$ ), but a reduction in inflammatory response was seen in the ultraprotective group. Nevertheless, the study was underpowered to detect small differences in mortality because of the small sample size. Rather, the findings represent proof of concept and require confirmation in large randomised trials.

More definitive evidence on the efficacy of ventilation strategies with very low tidal volumes during extracorporeal CO<sub>2</sub> removal in patients with acute respiratory distress syndrome may be provided by a multicentre randomised, controlled trial, that is assessing tidal volumes of 4 mL/kg and 6 mL/kg predicted bodyweight as protection from ventilator-induced lung injury (NCT01522599).

### Controversies and future directions

As the role of ECLS in the management of acute respiratory distress syndrome has evolved, several areas of concern have arisen that deserve consideration.

#### Mechanical ventilation strategies

The optimum ventilatory strategy for ECLS in patients with severe acute respiratory distress syndrome is unclear. Although the ventilator settings for venovenous ECMO should be as low as possible to keep ventilator-induced lung injury to a minimum,<sup>5</sup> no data indicate specific limits. For instance, positive end-expiratory pressure higher than 10 cm H<sub>2</sub>O to keep the lungs open and prevent atelectasis has been suggested,<sup>24</sup> but strategies without any positive end-expiratory pressure (ie, extubated patients) are also supported by the data. In the CESAR trial,<sup>10</sup> ventilator settings were gradually reduced to enable lung rest by limitation of the peak inspiratory pressure to 20 cm H<sub>2</sub>O with positive end-expiratory pressure 10 cm H<sub>2</sub>O, respiratory rate 10 breaths per min, and fraction of inspired oxygen 30%. Because the injured (native) lung contributes little to gas exchange, tidal volume can be very low (potentially near zero). Although alveolar recruitment induced by positive end-expiratory pressure is no longer required to improve oxygenation or to reduce the effect of regional alveolar stress and strain in patients

supported on ECLS, it might accelerate lung healing or optimise cardiopulmonary function.<sup>38,39</sup> The atelectasis-induced local impairment of lung-tissue oxygen tension might lead to an increase in pulmonary vascular leakage<sup>40</sup> and induce lung inflammation through macrophage activation.<sup>41</sup> Therefore, if the lung is continuously distended and aerated, the chances of healing might be increased compared with that of a collapsed lung. Atelectatic parenchyma, however, can completely recover in patients with lobar pneumonia who do not undergo mechanical ventilation.

Among patients with acute respiratory distress syndrome who are supported with ECLS, controlled mechanical ventilation is often applied in the first few days. After the acute phase of the illness, mechanical ventilation with spontaneous breathing should be considered because it might improve diaphragmatic function and reduce the need for sedation.<sup>42,43</sup>

During assisted mechanical ventilation, the risks of patient-ventilator asynchrony leading to diaphragmatic impairment and long-term weaning are high, particularly in patients with very low respiratory system static compliance, such as those requiring ECLS, which can contribute to difficulty in weaning patients off ventilation.<sup>44,45</sup> In one study patients underwent venovenous ECMO ventilation either with pressure-support ventilation or neurally adjusted ventilatory assist. Neurally adjusted ventilatory assist is a mode of ventilation in which the delivered assistance is proportional to measured diaphragm electrical activity, and was associated with significantly fewer asynchronies than pressure support ventilation, although the incidence with both methods was notably high.<sup>46</sup> Further studies are needed to elucidate the optimum modes of mechanical ventilation in ECLS.

### Tracheostomy

Patients with severe acute respiratory distress syndrome supported with ECLS might benefit from early tracheostomy because they need to be mechanically ventilated for a prolonged period of time. When compared with oral-tracheal intubation, tracheostomy provided patients with less discomfort, decreased rates of orolabial ulcerations, and improved oral care and airway security.<sup>47</sup> Moreover, critically ill patients who have undergone tracheostomy require less sedation, are less agitated, and are more likely to be mobilised earlier than those who do not have a tracheostomy.<sup>47</sup> Nonetheless, the use of anticoagulants during ECLS could represent an important barrier to tracheostomy. In a retrospective observational study that assessed the safety of percutaneous dilatational tracheostomy in 118 patients undergoing ECMO with a short interruption of the anticoagulation infusion, only 25 (21%) needed plasma or platelet transfusion before the intervention to correct potentially hazardous coagulopathy.<sup>48</sup> Furthermore, only a few patients experienced procedure-related complications, such as major bleeding (n=2), minor

bleeding (n=37), hypotension (n=1), and pneumothorax (n=2). More importantly, no deaths were related to complications of tracheostomy.<sup>48</sup> These data suggest that tracheostomy with the percutaneous dilatational technique is safe if performed by experienced physicians and with a brief interruption of anticoagulation.

### Weaning from extracorporeal life support

Weaning patients with acute respiratory distress syndrome from ECLS is relatively simple and should be considered when the reason for starting ECLS is substantially improved or resolved. Specifically, improvement must be seen in the respiratory mechanics, gas exchange, and radiological findings with moderate mechanical ventilation (eg, tidal volume less than 6 mL/kg predicted bodyweight, plateau pressure lower than 30 cm H<sub>2</sub>O, positive end-expiratory pressure lower than 12 cm H<sub>2</sub>O, and fraction of inspired oxygen less than 60%) before starting the ECLS weaning process. When these conditions are met, two main strategies are used:<sup>1,2</sup> decrease of the sweep-gas flow rate or the extracorporeal blood-flow rate. The work of breathing is transferred from ECLS to the patient in a progressive or sudden manner, respectively. ECLS can be removed if the patient tolerates this challenge consistently for several hours.

Alternatively, patients may be weaned from mechanical ventilation and extubated while remaining on ECLS until lung injury resolves. Mechanical ventilation might be injurious even at minimum settings, but extubated patients are not at risk of developing ventilator-induced lung injury. Along these lines, and in view of mechanical ventilation and ECLS both being able to support gas exchange in patients with resolving acute respiratory distress syndrome, assessment of whether weaning from mechanical ventilation should precede rather than follow weaning from ECLS might be useful.

### Sedation

Patients with severe acute respiratory distress syndrome receiving ECLS have very low static lung compliance and, therefore, in the first few days of mechanical ventilation they require deep sedation and often neuromuscular blockade to lessen symptoms and reduce oxygen consumption. The respiratory distress in these patients depends not only on altered oxygenation or ventilation, but also on the artificial improvement in gas exchange that might shorten the need for sedation, and which significantly improves clinical outcome in critical illness.<sup>49,50</sup>

Patients receiving ECLS, irrespective of the severity of the acute respiratory distress syndrome, should be awake and alert enough to actively participate in physical rehabilitation. ECMO might improve outcomes in patients with acute respiratory distress syndrome by promoting early mobilisation, lessening the degree of weakness and decreasing the incidence of delirium through improvement in oxygenation and keeping



ventilator-induced lung injury to a minimum. If ECLS were used as an alternative to invasive mechanical ventilation (termed awake ECMO), the negative effects of sedation and ventilator-induced lung injury should be abolished. This hypothesis was tested in single-centre uncontrolled trial.<sup>30</sup> Six patients with acute respiratory distress syndrome received venovenous ECMO while awake, non-intubated, and spontaneously breathing. Three patients subsequently required invasive mechanical ventilation, two of whom died. These data suggest that awake ECMO can be useful in selected patients with acute respiratory distress syndrome refractory to non-invasive ventilation, but the selection criteria need to be confirmed in large studies. Awake ECMO has been more extensively studied as a bridge to lung transplantation with very promising results.<sup>51–54</sup> In such patients there is a strong rationale to minimise side-effects of mechanical ventilation and sedation that might worsen outcomes before and after transplantation.<sup>55,56</sup> Awake ECMO enables patients to communicate, eat, drink, and have some mobility, which improves physical and physiological conditions.<sup>54</sup> In a large case series, awake ECMO was assessed in 26 patients awaiting lung transplant. 6-month survival after transplantation was improved in those receiving awake ECMO compared with that of historical controls who received ECMO (80% vs 50%,  $p=0.02$ ).<sup>51</sup> In another case series, five patients awaiting lung transplant were treated with active rehabilitation plus awake ECMO and were compared with four patients who received ECMO with mechanical ventilation and sedation.<sup>52</sup> The awake ECMO group was weaned faster from mechanical ventilation and the mean hospital stay was shorter after transplantation than in the mechanical ventilation group. Additionally, none of the patients in the awake ECMO group had post-transplant weakness associated with intensive care, compared with three of four patients in the mechanical ventilation and ECMO group.<sup>52</sup>

These studies strongly suggest that ECLS can reduce or remove the risk of ventilator-induced lung injury and enable more active rehabilitation. Clinical studies are needed to confirm these hypotheses for patients with acute respiratory distress syndrome.

### Novel technology

The technological advances made in ECLS have substantially contributed to the renewed clinical interest in this intervention. Improvements in size, safety, and simplicity of the equipment mean that ECLS is being used in an increasing number of intensive-care units.

One important advance has been the production of the bicaval dual-lumen cannula (figure 1).<sup>57</sup> This cannula, inserted via the right internal jugular vein, drains blood from the superior and inferior vena cava through one lumen and returns it into the right atrium through a second lumen. The requirement for only one upper-body cannulation site means the patient can receive more

intensive physiotherapy and possibly walk, which might help to lessen long-term functional morbidity in survivors.<sup>51,53</sup>

The notable reduction of the size of ECLS equipment has made it possible to transfer and mobilise patients receiving ECLS.<sup>58</sup> Patients therefore have access to more diagnostic testing than previously (eg, CT) and increased access to ECLS in hospitals that do not own equipment. The latter aspect might improve health-system organisation by facilitating regionalisation of this scarce resource in expert centres.

### Anticoagulation management and transfusion thresholds

Although modern ECLS circuits are mainly engineered with biocompatible materials, patients still need systemic anticoagulation to prevent thrombotic complications. Infusion of unfractionated heparin is currently the most frequently used anticoagulation strategy during ECLS. The anticoagulation target might vary according to several factors, such as ECLS technique, extracorporeal blood-flow rate, and presence of active bleeding. Anticoagulation adequacy can be monitored by assessment of several features (eg, activated partial thromboplastin time, anti-Xa activity, activated clotting time). The lower limits of anticoagulation needed to minimise the risk of thrombotic or bleeding complications and the most accurate and reliable characteristic for monitoring, however, remain unclear. In patients with heparin-induced thrombocytopenia, alternative agents, such as argatroban or bivalirudin, have been used.<sup>59</sup>

The haemoglobin threshold for blood transfusion is another important issue. The guidelines of the Extracorporeal Life Support Organization recommend maintaining normal haematocrit value and haemoglobin concentrations (more than 100 g/L) to optimise tissue oxygen delivery and efficacy of ECLS.<sup>13</sup> Practice, however, is highly variable with some centres adhering to more restrictive transfusion thresholds in critically ill patients (eg, haemoglobin less than 70 g/L) and taking into account the risks of transfusion-related complications and further lung injury.<sup>60</sup> Studies are needed to establish evidence-based guidelines.

### Ethics

Although the average time spent on ECLS by patients recovering from acute respiratory distress syndrome is a few weeks, how to determine whether and when underlying lung injury has become irreversible remains uncertain. Full recovery might take months, and protracted support with ECLS in a few cases has been described.<sup>61,62</sup> Moreover, no methods to predict outcomes have been validated. Whether patients originally placed on ECLS as a bridge to recovery should be considered for lung transplantation if they show no long-term improvement is also unclear. Improved understanding is required of the long-term physical, mental, and quality-of-

### Search strategy and selection criteria

We searched the Cochrane Library, PubMed, and Embase for papers published from inception to May, 2013, with the terms: "extracorporeal circulation", "extracorporeal support", "extracorporeal membrane oxygenation", "extracorporeal life support", "extracorporeal gas exchange", "extracorporeal CO<sub>2</sub> removal", "extracorporeal carbon dioxide removal", "interventional lung assist" for extracorporeal life support; and "acute respiratory failure", "acute lung injury", "acute respiratory distress syndrome", "adult respiratory distress syndrome" for respiratory failure. We limited the search to papers describing treatment of adults and human beings, and those published in English. Articles that dealt only with extracorporeal life support as a bridge to lung transplantation, chronic respiratory failure, and refractory cardiogenic shock were excluded. We also searched the reference lists of identified articles and selected those we deemed most relevant.

life outcomes in patients with acute respiratory distress syndrome undergoing ECLS, who are critically ill and have severe hypoxaemia and borderline oxygen delivery.

The use of ECLS as a bridge to a decision is controversial. In patients who develop severe acute respiratory distress syndrome and quickly progress to life-threatening hypoxaemia or hypercapnia, timely assessment of the reversibility of lung injury or whether patients might become candidates for lung transplantation (with continued ECLS bridging) is difficult. Thus, ECLS support might avert immediate, life-threatening states to provide time for further investigations and assessments.

The CESAR trial<sup>10</sup> in the UK revealed that, despite initially high costs related to ECMO, overall it was a cost-effective intervention. More detailed investigations of cost-effectiveness of the use of ECLS in patients with severe acute respiratory distress syndrome are needed in multiple jurisdictions because this therapeutic strategy is scarce, invasive, and expensive.

### Conclusions

Technological advances have improved the size, safety, and simplicity of ECLS, and might lead to an important advance in the management and outcome of patients with acute respiratory distress syndrome. ECLS is already being used as a rescue treatment in adults with severe acute respiratory failure. Rigorous evidence on the optimum timing, disease characteristics, and indications for ECLS in patients with severe acute respiratory distress syndrome, and its ability to improve short-term and long-term outcomes, must be assessed further before widespread adoption. ECLS should be considered for patients with life-threatening hypoxaemia or hypercapnia refractory to conventional mechanical ventilation. In the prevention of ventilator-induced lung injury, although promising and physiologically sound, ECLS remains experimental and results require confirmation.

#### Contributors

LDS and EF conceived the Review. LDS did the literature search and drafted the paper. All authors contributed to critical review and revision of the paper and saw and approved the final version.

#### Conflicts of interest

We declare that we have no conflicts of interest.

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