Chapter 3
Indications and Physiopathology in Venovenous ECMO on Severe Acute Respiratory Distress Syndrome

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3.1 Introduction

Mechanical ventilation remains the cornerstone of respiratory support for acute respiratory failure (ARF) patients. However, high pressure and volume associated with tidal ventilation are known to aggravate lung injury in this setting [1]. In the most severe forms of the disease, profound gas-exchange abnormalities threatening patients' lives can occur despite using the conventional salvage therapies [2, 3]. Venovenous extracorporeal membrane oxygenation (VV-ECMO) was developed more than 40 years ago [4, 5] to rescue these dying patients. ECMO also permit "ultraprotective" mechanical ventilation with further reduction of volume and pressure that might ultimately enhance lung protection and improve clinical outcomes of ECMO [6, 7]. More recently, the successful use of ECMO for the most severe ARDS cases associated with the recent influenza A (H_1N_1) pandemic who failed on conventional ventilation [8–10] and positive results of the randomized CESAR trial [11] have been associated with a steep increase in the number of VV-ECMO procedures performed in very recent years.

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3.2 How Does It Work?

3.2.1 Settings

In recent years, major technological advances occurred, and the latest ECMO devices with polymethylpentene hollow-fiber membrane lungs and Mendler-designed centrifugal pumps offer lower resistance to blood flow, have smaller priming volumes, higher effective gas exchange properties, and are coated with more biocompatible materials. The extracorporeal system consisted of polyvinyl chloride tubing, a membrane oxygenator, and a centrifugal pump. An oxygen-air blender is used to ventilate the membrane oxygenator (2–14 $l.min^{-1}$). Venovenous ECMO provides complete extracorporeal blood oxygenation and decarboxylation using high blood flows (4–6 L/min) and large (20–30 Fr) cannulas [12–15]. Blood is usually drained from the right atrium or the inferior vena cava through a multiperforated cannula inserted percutaneously into the right femoral vein and is returned to the superior vena cava through a cannula inserted percutaneously into the right internal jugular vein (Femorojugular setting) or in the right atrium through a cannula inserted into the femoral vein (Femoral–femoral setting). During the procedure, using transthoracic or transesophageal echocardiography is fostered to properly set the position of the drainage cannula.

3.2.2 Determinants of Oxygenation on VV-ECMO

The main determinants of oxygen delivery (DO_2) to peripheral tissues, which is critical to preserve organ function, are hemoglobin concentration, SaO_2, and cardiac index [16]. When DO_2 falls below a critical threshold, oxygen consumption becomes dependent on DO_2 and lactate concentration may increase, reflecting activation of anaerobic metabolism. To prevent tissue hypoxia, recommended oxygenation objective is to maintain SaO_2 ≥88% using high PEEP and high FiO_2 in mechanically ventilated ARDS patients [17, 18]. However, when refractory hypoxemia develops, recourse to VV-ECMO is a reasonable therapeutic option [8, 9, 11, 19, 20]. In this circumstance, blood oxygenation may become completely dependent on membrane oxygenator oxygen transfer capability. Factors determining oxygenator oxygen transfer in this setting are blood oxygen saturation in the ECMO drainage cannula, hemoglobin concentration, blood flow in the ECMO circuit, and intrinsic membrane oxygenator properties, which depend on the exchange membrane surface and diffusibility of O_2 through hollow microfibers. O_2 transfer through recent modern oxygenator is theoretically >400 ml O_2/min when blood flow through the ECMO circuit is >6 l/min, while oxygen saturation in the ECMO drainage cannula is 70% and hemoglobin concentration is 15 g/dl [21]. However, since both drainage and return cannulae are positioned within the venous system in VV-ECMO, blood recirculation into the oxygenator occurs, that is, a proportion of returned blood is drained again into the circuit instead of passing through the right heart, thus markedly

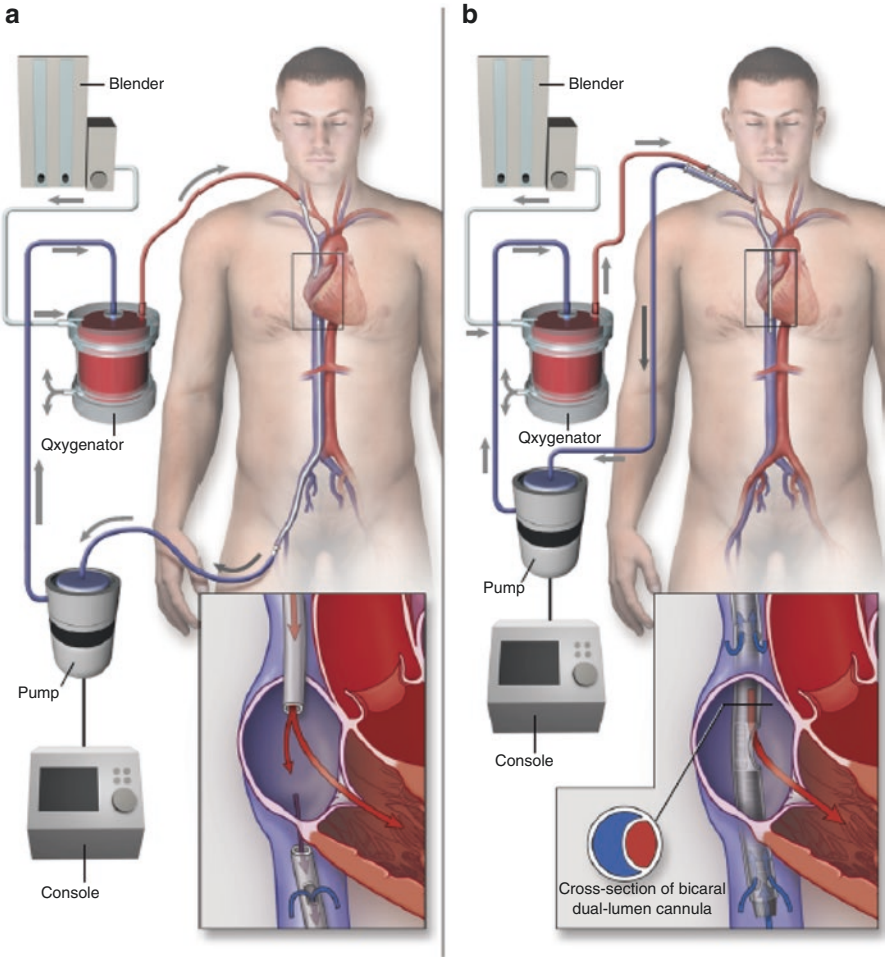

Fig. 3.1 Single-site and two-site approaches to venovenous ECMO cannulation (With permission [13] (du NEJM)). (**a**) A two-site approach to venovenous ECMO cannulation. (**b**) A single-site approach to venovenous ECMO cannulation.

reducing O_2 transfer efficiency [22]. To minimize blood recirculation into the circuit, it can be configured in several ways [19, 20]. In the bifemoral setting, drainage cannula is positioned in the inferior vena cava (IVC), and a femoral return cannula is advanced to the right atrium (see Fig. 3.1a). However, 50% of the patients who received bifemoral VV-ECMO for H_1N_1-induced ARDS in the ANZICS ICUs also needed a second (jugular) drainage cannula, because of insufficient blood drainage [8]. Alternatively, a single bicaval dual-lumen cannula (Avalon Elite®) can be inserted via the right jugular vein and positioned to allow drainage from the IVC and SVC and oxygenated blood return via a second lumen in the right atrium [23] (see Fig. 3.1b). This setting minimizes blood recirculation, but insertion of the

jugular catheter requires an experienced and skilled operator and recourse to fluoroscopy or TEE guidance for its adequate positioning. Lastly, femorojugular setting for VV-ECMO allows minimizing blood recirculation if the tip of the return cannula is positioned away from that of the inflow cannula. To achieve this goal, mean distance between both cannulae should be measured on the chest X-ray. A minimal distance of 12 cm is generally advocated. Additionally, it has been shown in a previous study that, compared to the jugulofemoral configuration, the femorojugular bypass provided higher maximal ECMO flow, higher pulmonary arterial mixed venous oxygen saturation, and required comparatively less flow to maintain an equivalent mixed venous oxygen saturation [24].

To improve oxygen blood transfer in the oxygenator and to increase oxygen transport to peripheral organs, a recent study has demonstrated that besides ECMO cannulae configuration, ECMO flow through the ECMO circuit is the major determinant of blood oxygenation. ECMO flow >60% of systemic blood flow permitted adequate peripheral oxygenation [25]. Thus, depending on the patient size, cardiac output, oxygen consumption, and lung shunt, circuit blood flow between 4–7 l/min will typically be required to achieve arterial oxygen saturations >88–90%, while maintaining safe lung ventilation. Therefore, large size (24–30 Fr) and multihole drainage cannula should be preferred to obtain high flows with reasonable negative pressure in the drainage cannula. Indeed, if small cannulae are used with high flows, the suction created by the centrifugal pump can cause excessive depression and cavitation in the inflow line resulting in massive intravascular hemolysis [19, 20]. Physiological in vivo study demonstrates that, for patients who received VV-ECMO for refractory hypoxemia and whose native lung gas exchange function was almost completely abolished, the determining factors of arterial oxygenation are VV-ECMO blood flow and FiO_{2ECMO}. Specifically, using the femorojugular ECMO setting, achieving VV-ECMO flow >60% of systemic blood flow was constantly associated with arterial blood saturation >90%.

The other important parameter that might be manipulated to enhance tissue oxygen delivery and maximize extracorporeal circuit efficiency is blood hemoglobin concentration [16] (Table 3.1). In patients under ECMO support, guidelines from the Extracorporeal Life Support Organization (ELSO) and investigators of the CESAR trial recommend maintaining normal hematocrit (40–45%) and hemoglobin concentrations at 14 g/dl, respectively [11, 26]. However, critically ill patients and specifically those already suffering from diffuse alveolar damage may be at even greater risk of transfusion-related acute lung injury [27–29]. Accordingly, a restrictive transfusion strategy with red-cell transfusion threshold set at 7–8 g/dl in most patients under ECMO is doable. Schmidt et al. demonstrated that despite mean hemoglobin concentration and DO_2 at 8.0 $g.dl^{-1}$ and 679 ml/min, respectively, every patient had adequate SaO_2, and no sign of VO_2/DO_2 mismatch was observed [25]. Lastly, transfusion of blood products increases volemia, which might also complicate the course of ARDS, since a study reported slower lung function improvement and longer mechanical ventilation duration when a liberal strategy of fluid management was used in patients with acute lung injury [30].

Table 3.1 Main determinants of oxygenation and decarboxylation on ECMO

Determinants of oxygenation on VV-ECMO
1. Intrinsic membrane oxygenator properties (size, type of microfibers, etc.)
2. Blood flow in the ECMO circuit
3. Blood oxygen saturation in the ECMO drainage cannula (i.e., recirculation)
4. Hemoglobin concentration
5. FmO_2 on the membrane
Determinants of decarboxylation on VV-ECMO
1. Size of the membrane
2. $PaCO_2$ level
3. Sweep gas flow

3.2.3 Determinants of Decarboxylation on VV-ECMO

The determining factor of blood decarboxylation is the rate of sweep gas flow ventilating the membrane lung, while $PaCO_2$ is unaffected when ECMO blood flow and FiO_{2ECMO} are reduced to <2.5 l/min and 40%, respectively.

CO_2 transfer through the membrane lung also depends on ECMO flow, with maximum transfer being >300 ml/min when ECMO flow is >6 l/min with the Quadrox® oxygenator. However, since CO_2 diffuses 20 times faster than O_2, large amount of CO_2 can be exchanged through the membrane lung even when low flow is applied through the circuit [25]. For instance, recent data showed that $PaCO_2$ remained unchanged when ECMO blood flow was reduced to <2.5 l/min. Indeed, this property is the basis for developing low-flow extracorporeal CO_2 removal devices, for which CO_2 removal is >70 ml/min at blood flows of only 450 ml/min [31, 32]. Alternatively, sweep gas flow across the oxygenator is the main determinant of CO_2 removal by ECMO [25].

3.3 Main Indications of VV-ECMO for Severe ARDS

Indications are usually based on: (1) severe hypoxemia (e.g., PaO_2 to FiO_2 ratio <80 mmHg, despite optimization of mechanical ventilation (tidal volume set at 6 ml/kg and trial of PEEP≥10 cm H_2O)) for at least 6 h in patients with potentially reversible respiratory failure and possible recourse to adjunctive therapies (NO, prone position, etc.) and/or or (2) uncompensated hypercapnia with acidemia (pH <7.15) despite the best accepted standard of care for management with a ventilator and/or

(3) excessively high end-inspiratory plateau pressure (>32 cm of water). However, considering the CESAR trial, the ongoing EOLIA trial, and the recommendations of the Extra Life Support Organization (ELSO), the thresholds of PaO_2 to FiO_2 ratio, pH, or plateau pressure may vary considerably across studies and guidelines.

Relative contraindications are usually mechanical ventilation for more than 7 days, limited vascular access, and any condition or organ dysfunction that would limit the likelihood of overall benefit from ECMO, such as malignancies with fatal prognosis within 5 years, moribund patients, or those with irreversible neurological pathologies and decisions to limit therapeutic interventions. Contraindication to the use of anticoagulation therapy is mentioned in several reviews or guidelines. However, several publications have stressed that, while using new-coated heparin circuit, anticoagulation on ECMO VV may be safely withheld for days or weeks.

3.4 Recent Data of ECMO VV in ARDS

The most recent trial (CESAR trial) which was conducted in the UK from 2001 to 2006 evaluated a strategy of transfer to a single center (Glenfield, Leicester) which had ECMO capability, while the patients randomized to the control group were treated conventionally at designated treatment centers [6]. The primary endpoint combining mortality or severe disability 6 months after randomization was lower for the 90 patients randomized to the ECMO group (37% vs. 53%, $p = 0.03$). However, results of that trial should be analyzed carefully. First, 22 patients randomized to the ECMO arm did not receive ECMO (died before or during transport, improved with conventional management at the referral center, or had a contraindication to heparin). Second, no standardized protocol for lung-protective mechanical ventilation existed in the control group, and the time spent with "protective" mechanical ventilation was significantly higher in the ECMO arm. Third, more patients received corticosteroids in the ECMO group. In the most recent series, patients benefited from the latest ECMO technology, which include a centrifugal pump, a polymethylpentene membrane oxygenator, and tubing with biocompatible surface treatment. Mortality rates ranged from 36 to 56% in the studies performed in the last 15 years and reporting outcomes of >30 ECMO patients (Table 3.1). Interestingly, ECMO was provided through a mobile ECMO rescue team in some of these studies. For example, in a series of 124 patients treated at a Danish center between 1997 and 2011 [33], survival was 71%, and 85% of these patients received ECMO via a mobile unit before being transferred to the referral hospital. Similarly, in the Regensburg cohort, 59/176 received ECMO at another hospital by a mobile unit [34]. In a multicenter French cohort of 140 patients treated between 2008 and 2012, 68% patients were retrieved via a mobile ECMO team, and their prognosis was comparable to those who received VV-ECMO support in their initial center hospital [35]. ECMO support might also cause severe and potentially life-threatening complications, such as bleeding, infections, intravascular hemolysis, thrombocytopenia, or consumption coagulopathy [35–39].

Mortality rates of ECMO for pandemic influenza A (H_1N_1)-associated ARDS ranged from 14 to 64% in the 16 studies from 11 countries reporting on the experience

of ECMO for influenza A (H_1N_1)-associated ARDS [8–10, 35, 40–50]. The Australia and New Zealand collaborative group (ANZICS) was the first to report its experience [8]. Despite extreme disease severity at the time of ECMO initiation (median PaO_2/FiO_2 ratio 56 mmHg, median positive end-expiratory pressure [PEEP] at 18 cm H_2O, and median lung injury score of 3.8), only 25% of the 68 ECMO patients died. A British collaborative cohort series [9] depicted the outcome of 80 patients transferred into ECMO referral centers in United Kingdom of whom 69 received ECMO. Mortality in this cohort was 27.5%. A propensity-matched analysis comparing survival of patients referred for consideration of ECMO to other ARDS patients showed better outcomes for referred patients. Alternatively, mortality of propensity-matched patients treated conventionally was comparable to that of ECMO patients in French ICUs of the REVA network. However, only 50% of ECMO patients were successfully matched with control ARDS patients, while unmatched ECMO patients were younger, suffered more severe respiratory failure, and had considerably lower mortality [10]. Interestingly, a higher plateau pressure under ECMO was independently associated with mortality, indicating for the first time that an ultraprotective ventilation strategy with reduction of plateau pressure to around 25 cm H_2O following ECMO installation might improve outcomes. Lastly, mortality was 29% on a cohort of 49 proven influenza A (H_1N_1) patients from the 14 ECMO centers of the ECMO-NET Italian collaborative group [51]. In this series, patients ventilated for <7 days before ECMO initiation had a significantly higher survival.

3.5 Mortality Risk Factors and Predictive Survival Models

Factors associated with poor outcomes after ECMO for acute respiratory failure include older age [34–36, 52–55], a greater number of days of mechanical ventilation before the ECMO establishment [35, 36, 52, 53, 55], a higher number of organ failure [34–36, 52–55], low pre-ECMO respiratory system compliance [55], as well as immunosuppression [35, 55, 56]. Predictive survival models have been recently developed which might help clinicians select appropriate candidates for ECMO [35, 54–57]. For instance, the RESP-score [55] constructed on data extracted from a large multicenter international population (n = 2355) computes 12 simple pre-ECMO parameters to provide a relevant and validated tool predicting survival after ECMO for acute respiratory failure. Cumulative predicted hospital survival were 92, 76, 57, 33, and 18% for five RESP-score risk class I (≥6), II (3 to 5), III (−1 to 2), IV (−5 to −2), and V (≤−6), respectively.

3.6 Conclusions

Recent technological advances have improved the safety and the simplicity of ECMO use in ARDS. In addition, mobile ECMO team has made this therapy more accessible for all patients. Actual literature has reported that early implementation of VV-ECMO in refractory and severe ARDS can strongly reduce pressures and

volumes applied on the alveoli in order to minimize ventilation-induced lung injury. However, strong evidence of its benefit and optimal timing for cannulation are still lacking. Therefore, results of next multicenter randomized trials (i.e EOLIA trial) are needed before wide spreading this promising technology.

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