CHAPTER 196

Extracorporeal Membrane Oxygenation for Pulmonary Support

Alberto Zanella, Eleonora Carlesso, and Antonio Pesenti

OBJECTIVES

This chapter will:

1. Describe the main aspects of venovenous extracorporeal membrane oxygenation (ECMO) circuit and functionality.
2. Describe the indication to start and to stop ECMO for pulmonary support.
3. Detail the currently available literature.
4. Acknowledge limitations and complications of venovenous ECMO.

Extracorporeal membrane oxygenation (ECMO) is a temporary artificial support used for respiratory and/or cardiac failure refractory to conventional treatments. During ECMO venous blood is drawn from the patient through a vascular cannula and is driven by a mechanical pump into an artificial lung, which oxygenates the blood and removes the carbon dioxide. The arterialized blood then is circulated back to the patient venous system during pure respiratory support or to the arterial system for cardiac and/or respiratory support. This chapter focuses on ECMO for pulmonary support in adult patients.

BACKGROUND

Origin and Technical Evolution of Membrane Oxygenators

Frey and Gruber performed the first experience with extracorporeal oxygenation of isolated organs at the end of 19th century.[1] Fifty years later, John Gibbon started his laboratory investigations that led, in the mid-1950s, to the first use of a cardiopulmonary bypass in the operating room.[2] Unfortunately the bubble oxygenators used at that time directly exposed blood to the oxygen flow, thus leading to an elevated risk of hemolysis and hemorrhage resulting from the high demand for systemic anticoagulation. Clowes tried to tackle this problem, introducing a cellophane membrane with the attempt to separate gas from blood phase.[3] Over the years, with the purpose of optimizing oxygenators, different materials (silicone, polypropylene, polyethylene, polymethylpentene) and types of surfaces (microporous or continuous) were developed and tested. In the 1970s, Kolobow developed his membrane lung consisting of a silicone membrane long envelope containing a spacer net, wound around a central plastic spool.[3] Oxygen flowed inside the envelope through the space created by the spacer net, while blood flowed in the outside. Kolobow's membrane lung earned great success and was used extensively, even for prolonged extracorporeal supports, for the following 30 to 40 years.

The latest generation of artificial lungs is represented by hollow-fiber devices with different designs (shell/tube and cross-flow). These membranes are included in circuits built of new materials such as polymethylpentene and heparin-coated surfaces, with great improvement of biocompatibility of the whole extracorporeal system.

Clinical Pioneering of Extracorporeal Respiratory Support

The first successful use of long-term ECMO was reported by Hill in 1972 in an adult patient with posttraumatic respiratory failure.[4] Four years later, Robert Bartlett applied the first successful treatment in newborns.[5] Several encouraging case series[6–8] and two prospective randomized controlled studies with positive results[9,10] made ECMO the standard treatment for neonatal respiratory failure.

Following the enthusiasm for this new technique, the National Institutes of Health (NIH, Bethesda, MD) sponsored a randomized trial comparing venous-arterial ECMO to conventional mechanical respiratory support in adult patients suffering from severe acute respiratory distress syndrome (ARDS).[11] The trial was stopped for futility after the enrollment of 90 patients, because the mortality in both groups was around 90%. At that time the main concern for mechanically ventilated patients was identified with the high inspired oxygen fraction and not with the harm of ventilation. Therefore in this trial, the only difference concerning mechanical ventilation between treatment and control patients was a lower FiO_2 in the ECMO group, whereas all the other parameters, today known as determinants of lung injury, were similar between the two arms. In addition, ECMO was applied with a venoarterial configuration, leading to severe increases in the ventilation-perfusion ratios of the native lungs. Moreover, the risks and complications were high, particularly bleeding, with a reported transfusion approximating 5 L of blood per day. The discouraging results of the NIH study led to the abandonment of the ECMO technique worldwide.

Gattinoni and Kolobow nevertheless proposed to exploit the ECMO support to "rest" the injured lungs by reducing respiratory rate, tidal volume, and airway pressure (low frequency positive pressure ventilation, LFPPV), thus fostering lung healing. The concept, when pushed to the extremes, involved the application of continuous positive airway pressure, maintained by a continuous oxygen supply to compensate for the natural lung oxygen consumption while carbon dioxide removal would be granted by the artificial lung (ECCO2R), with no need for any ventilation (apneic oxygenation).

This strategy first was applied in spontaneously breathing healthy sheep[12] and, as a rescue treatment, in premature

lambs.[13] In 1980 it was applied successfully on three patients with refractory acute respiratory failure in whom conventional treatment had failed. Those patients were treated with an extremely low respiratory rate (3 bpm), thus avoiding possible pulmonary and extrapulmonary complications related to mechanical ventilation, while CO_2 was removed through a venovenous extracorporeal bypass with low blood flow.[14] The results of a clinical study designed to evaluate the effects of LFPPV-ECCO2R in 43 patients with severe acute respiratory failure were published in 1986. Lung function improved in 73% of the cases, and survival rate was 49%[15]; no major technical accidents were reported in more than 8000 hours of perfusion. Zwischenberger et al. refined the LFPPV-ECCO2R technique, developing a simplified arteriovenous extracorporeal CO_2 removal technology, AVCO2-R, featuring a low-resistance membrane gas exchanger.[16]

In 1994[17] Morris published the results of a second randomized clinical trial. Pressure-controlled inverse ratio ventilation followed by LFPPV-ECCO2R (21 patients) was compared with conventional positive pressure ventilation (19 patients) in ARDS patients. The trial did not show an improved survival in the patients treated with the extracorporeal support (42% in the control group vs. 33% in the ECMO group). However, the survival rate was improved significantly compared with the previous trial. However, a lot of criticism has been raised, mainly regarding the inhomogeneous ventilatory settings applied in the ECMO group, the high peak pressure used, and the elevated number of complications related to systemic blood anticoagulation. After this trial, only few centers around Europe continued to provide venovenous extracorporeal support in selected series of patients, usually as a last resource.[18] In the United States, Bartlett et al.[19,20] continued to provide extracorporeal support as an alternative to mechanical ventilation with very encouraging results. Since 1989 The Extracorporeal Life Support Organization (ELSO) maintains the largest registry of data on patients receiving ECMO and provides yearly data about the worldwide use of this technique (http://www.elso.med.umich.edu).

Cesar Trial and H1N1 Flu Pandemics

A renewed interest on ECMO rose after the publication of the conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR) trial, a prospective randomized trial conducted in the United Kingdom. The trial clearly showed outcome advantages when patients with severe respiratory failure were centralized in an experienced center and eventually treated with ECMO if required, compared with conventional ventilatory support performed in peripheral centers.[21] The study included 180 patients from 68 centers; 90 patients were enrolled in the ECMO group (68 effectively treated with ECMO) and 90 in the conventional treatment group. In the control group the intensivists could use any type of management they felt appropriate, but the NIH ARDS strategy was recommended. The authors found that the primary end point, survival at 6 months free of disabilities, was 63% in the ECMO group versus 47% in the control group, and they concluded that referral of severely hypoxemic ARDS patients to a specialized center able to provide ECMO may increase survival.

The study is characterized by two major limitations. First, not all patients allocated to the ECMO group received ECMO, because they either died before or during transportation (5 patients) or improved with conventional treatment after transportation to the ECMO center (17 patients). Second, the nonstandardized protocol for mechanical ventilation in the control group resulted in few patients receiving a protective ventilatory strategy. However, despite these limitations, the results of this study have certainly contributed to strengthen the motivation of "ECMO believers" and to increase the interest in ECMO around the world.

However, the widespread use of extracorporeal support was due to its use as a rescue therapy in Australia and New Zealand during the 2009 H1N1 flu pandemics.[22] Between June and August 2009, 68 patients with severe H1N1 influenza-associated ARDS were treated with ECMO with a survival rate of 78%. Before ECMO institution, these patients, characterized by a median age of 34 years, had severe respiratory failure despite advanced mechanical ventilatory support. After the Australian experience, several countries worldwide instituted a national ECMO network and numerous case series, reporting 70% to 80% survival rates, were published.[23–27]

In the United Kingdom, a cohort study compared ECMO-referred patients with matched patients who were not referred for ECMO.[28] ECMO-referred patients were defined as patients with H1N1-related ARDS who were referred, accepted, and transferred to one of the four adult ECMO centers in the United Kingdom during the H1N1 pandemic in winter 2009 to 2010. The study clearly demonstrated an impressive advantage of this strategy compared with conventional mechanical ventilation. In Italy, as in other countries, a national network was established, reporting a survival rate of about 70%.[29]

However, a similar case-matching study conducted in France did not show the same results.[30] Although the French study was conducted with a different matching approach, causing some limitations, its results should be taken as well into account.

The H1N1 flu pandemic coupled with several technical improvements, promoted, far beyond any previous randomized trial, the use of ECMO in patients with severe ARDS.

The Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA) randomized control trial is currently ongoing in France (NCT01470703). This trial is testing the usefulness of ECMO as an adjunct to mechanical ventilation in patients with ARDS.

INDICATIONS

The primary indication for venovenous ECMO (VV-ECMO) is hypoxemic respiratory failure refractory to conventional rescue therapies. According to ELSO guidelines, extracorporeal support should be considered when the expected mortality is 50% or greater ($PaO_2/FiO_2 < 150$ mm Hg on $FiO_2 > 90\%$ and/or Murray score 2–3), whereas it is indicated when the expected mortality is 80% or greater ($PaO_2/FiO_2 < 100$ mm Hg on $FiO_2 > 90\%$ and/or Murray score 3–4 despite optimal care for 6 hours or more).[31]

There are no absolute contraindications to ECMO. Risks and benefits should be evaluated in each patient. However, there are conditions that are associated with a poor outcome despite ECMO institution, and thus could be considered as relative contraindications:

1. Mechanical ventilation at high settings ($FiO_2 > 99\%$, Plateau pressure > 30 cm H_2O) for 7 days or more
2. Major pharmacologic immunosuppression (absolute neutrophil count < 400/mm^3)
3. Central nervous system (CNS) hemorrhage that is recent or expanding

4. Nonrecoverable comorbidity such as major CNS damage or terminal malignancy
5. Old age: no specific age contraindication but consider increasing risk with increasing age

PHYSIOLOGY

Artificial Lung

During ECMO, arterial blood gases are determined by the interplay between the residual function of the natural lung (NL) and the performances of the membrane lung (ML). Extracorporeal gas transfer is affected by the intrinsic characteristics of each ML and is related to the membrane surface area and the hollow-fiber thickness and material. The clinician cannot alter these determinants at the bedside, but he or she can modify the blood flow (BF) and the sweep gas flow (GF) to affect the amount of oxygen delivered to the extracorporeal blood and the amount of CO_2 removed from the extracorporeal blood by the membrane lung (VO_2ML, and VCO_2ML respectively). VO_2ML is a direct function of the BF, whereas VCO_2ML is primarily a function of the sweep gas flow. The oxygen and carbon dioxide partial pressure gradients between the sweep gas flow and the blood are the primary determinants of the gas transfer.

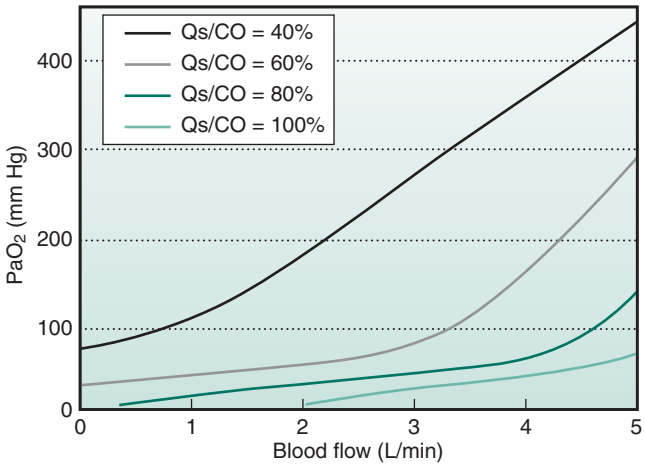

FIGURE 196.1 Relationship between ECMO blood flow (L/min) and oxygenation in patients with increasing Qs/CO (%). Simulations were performed by a theoretical model (http://www.ecmomodel.unimi.it) introducing the following parameters: cardiac output (7 L/min), VO_2TOT (250 mL/min), FiO_2 Natural Lung (100%), FiO_2 Membrane Lung (100%), R/BF (15%), Hb (10 g/dL), temperature (37°C), pH (7.4), $PaCO_2$ (40 mm Hg), Qs/BF (10%), COhb (1%), MetHb (0.6%).

Oxygenation

A simplified model can explain the basic physiology of oxygenation during VV-ECMO.[32,33] The model considers the natural lung and the artificial lung in series. In static conditions the total body oxygen consumption (VO_2) is equal to the sum of oxygen supplied to the blood by the natural lung and by the membrane lung. The venous blood drained into the inlet cannula is pumped toward the membrane lung where it is loaded with oxygen. A fraction of the oxygenated blood moved back into the venous system through the outlet cannula reenters into the inlet cannula (recirculation fraction, R) reducing the overall amount of oxygen delivered by the membrane lung. The higher the recirculation fraction is, the lower the oxygen delivered by the membrane lung.

Three factors determine the oxygen delivery of the membrane lung:

1. The intrinsic properties of the membrane lung (membrane surface area, thickness and material of the membrane)
2. The partial pressure gradient of oxygen between blood and sweep gases. FiO_2 determines the oxygen partial pressure in the sweep gases. The ventilation/perfusion matching, the hemoglobin concentration, and the transit time affect the oxygen transfer through the membrane lung. When the oxygen partial pressure increases in the blood crossing the membrane lung, hemoglobin becomes more saturated. Eventually, when fully saturated, only a little additional oxygen, the physically dissolved, can be further loaded; therefore also an additional increase in gas flow FiO_2 will determine a minimal increase in the membrane lung oxygen delivery. Conversely, recirculation and increased inlet blood PO_2, may vastly reduce VO_2ML.
3. Increasing the extracorporeal blood flow (up to a "rated flow") determines almost linear augmentation of VO_2ML. After the rated flow value VO_2ML may only slightly increase.

The oxygenated blood leaving the membrane lung mixes with the deoxygenated venous blood returning to the right heart. The resulting effect of VV-ECMO application is the increase of the oxygen content of mixed venous blood. Therefore VV-ECMO improves arterial oxygenation specifically in the presence of a high intrapulmonary shunt (Fig. 196.1).

Any increase in blood flow, without changes in cardiac output (CO) and recirculation, always determines an improvement in arterial oxygenation and tissue oxygen delivery. Similarly any decrease in R always improves oxygenation.

More complicated are the effects of CO changes on oxygen delivery and arterial oxygenation. Assuming stable BF and R, severe ARDS patients with elevated CO necessitate higher BF to achieve normal arterial PO_2 levels. This does not necessarily mean that a lower cardiac output is desirable as an adequate CO is essential to ensure adequate oxygen delivery. However, a rise in CO is usually a sign of augmented tissue oxygen requirements (e.g., fever, agitation, sepsis) and also may change the intrapulmonary shunt and the recirculating flow. Considering that many tissues have different oxygen requirements and vasculature, it is particularly difficult to predict the effect of a change in CO on oxygenation of each district. Still, on this topic, scientific evidence is poor, and more research trials are needed to better understand the complex pathophysiology of the effects of CO modulation on oxygen delivery.

Finally, the oxygen delivery by the natural lung depends on the severity of the lung disease (mainly the intrapulmonary shunt fraction) and the ventilator setup. The worse the residual gas exchange capability of the natural lung, the higher blood flow and, consequently, cannula size are necessary. Indeed, if the intrapulmonary shunt is over 0.7, vital blood oxygenation can be obtained only by applying blood flow over 4 L/min (see Fig. 196.1). The use of adequately sized drainage cannulas is paramount in this situation. VV-ECMO replaces, partially or completely, the function of the natural lung and allows reducing all the risk factors contributing to the onset of ventilator-induced lung injury: high ventilation volumes and pressures and high FiO_2 level. However, an extremely "protective" ventilator strategy, based on low levels of FiO_2, PEEP, and minute ventilation,

temporarily may worsen the gas exchange function of the natural lung, and therefore an increase in extracorporeal support is often required.

Carbon Dioxide Removal

Removal of CO_2 during VV-ECMO is always more efficient than oxygen delivery. The total concentration of CO_2 transported in blood (mainly bicarbonate) amounts to nearly 55 mL/100 cc of blood; this means that 500 mL of venous blood contains an amount of CO_2 correspondent to the entire minute CO_2 production of an adult male. Hence, during ECMO support, the entire patient CO_2 production may be removed with low blood flow, in the range of 1.5 L/min. This can happen only if high sweep gas flows (e.g., 8–15 L/min, according to the oxygenator characteristics) are used. Rising sweep gas flow of a membrane lung reduces partial pressure of CO_2 inside the hollow fibers of the membrane lung, augments the partial pressure gradient in between blood and gas phase, and consequently augments CO_2 removal. Therefore for a given blood flow, the sweep gas flow rate is a major determinant of the amount of CO_2 transfer.[34] The dissociation between CO_2 removal and blood flow has important clinical consequences. First, during VV-ECMO the clinician selectively may change carbon dioxide removal of the artificial lung by altering sweep gas flow, maintaining oxygen delivery unaltered. Through this intervention, the ventilatory needs of the patient can be mastered and finely titrated to the desired level. As an example, in the most severe clinical conditions, extremely low tidal volume ventilation (and even apnea) can be achieved through elevated sweep gas flows.[35] Conversely, during weaning, a residual ventilatory drive can be maintained and spontaneous breathing guaranteed using a more moderate gas flow.[36]

Low blood flow VV-ECMO, aiming at primarily remove CO_2, is indicated when there is the necessity to reduce mechanical ventilation and avoid VILI in ARDS patients.[21] Moreover, during acute reacutization of chronic obstructive pulmonary disease (COPD)[37] and status asthmaticus,[38] it can mitigate dynamic hyperinflation and hypercapnia. Finally, it can be used as bridge to lung transplant.[39]

CIRCUIT

Basically, a standard ECMO circuit consists of vascular access (cannulas), mechanical blood pump, gas exchange device (membrane lung), and a heat exchanger, all connected together with circuit tubing.[40]

Tubing are made of polyvinylchloride, polyurethane, or silicon rubber. ECMO circuits may include several blood flow and pressure monitors, continuous oxyhemoglobin saturation monitors, and circuit access sites. All the circuitry can be coated with heparin and a biocompatible lining to reduce the risk of thrombosis and bleeding and systemic inflammatory response.

The geometry and the internal resistance of each component will induce a pressure drop that will influence the hemodynamics and management the system and the evolution of the patient.[41]

Pumps

Centrifugal pumps have almost completely substituted roller pumps for long-term applications. Blood enters the pump by the vortexing action of spinning impeller blades or rotating cones that are coupled magnetically with an electric motor and, when rapidly rotating, generate a pressure differential that causes the blood to move. Blood flow depends not only on the rotational rate of the pump but also on the preload (directly, a decrease in preload corresponds to a decrease in flow and vice versa) and afterload (inversely, a decrease in afterload corresponds to an increase in flow and vice versa).

The potential problems of a centrifugal pump head include stagnation and heating of blood in the pump head, leading to thrombus at low flows if the outlet line is occluded, or cavitation and hemolysis when the inlet line is occluded. New pump head designs have reduced the magnitude of many of these problems.

Membrane Lung

The gas exchange device included in the ECMO circuit is used to add O_2 and remove CO_2 from blood. It may contain several different biomaterials, including silicone rubber as in the classic membrane lungs used for years, polypropylene hollow fiber devices for short-term use, newer compressed surface polymethylpentene (PMP), as well as polyvinylchloride, polyurethane, and stainless steel. The surface area and blood path mixing determine the maximum oxygenation capacity of any gas exchange device. The rated flow of an oxygenator is defined as the flow of desaturated blood that nearly can be fully saturated per unit time.

The most recent innovation are the nonporous hollow-fiber devices, characterized by polymethylpentene fibers that combined with nonthrombogenic coatings prevent plasma leakage and reduce the activation of the coagulation. The gas flows inside the hollow fibers while blood flows outside. They are characterized by high efficiency of gas exchange and low resistance to blood flow.[42] The design of these oxygenators allows to reduce the surface area of the membrane and heat exchanger, reducing the potential risk for thrombus formation and inflammatory activation and reducing the priming volume.

These new oxygenators also contain an integrated heat exchange device, making it possible to precisely control body temperature without the need for additional components.

Cannulas for Adult Patients

Vascular cannulas have undergone significant design changes to optimize the performance of the ECMO system and to meet the requirements of individual patients. Cannulas commonly are made of biocompatible polyurethane, coated with heparin or nonheparin polymers to reduce the inflammatory response and platelet activation.[43] Most cannulas have a wire-reinforced body to avoid kinking and can incorporate a malleable wire to customize the angle of insertion and facilitate the positioning. Cannula selection should be based on the flow rate to be provided and the size of the vessels to be accessed. As a general rule, the size of the cannula should not exceed two thirds of the vessel size. The cross-sectional area imparts resistance to blood flow and must be considered during cannula selection to achieve optimal venous drainage. Logically, the use of inflow and outflow cannulas with maximal diameter would reduce the pressure drop in the circuit. However, a balance has to be found between treating the pathology and minimizing trauma and discomfort to the patient caused by the presence of the cannulas in the vascular system.

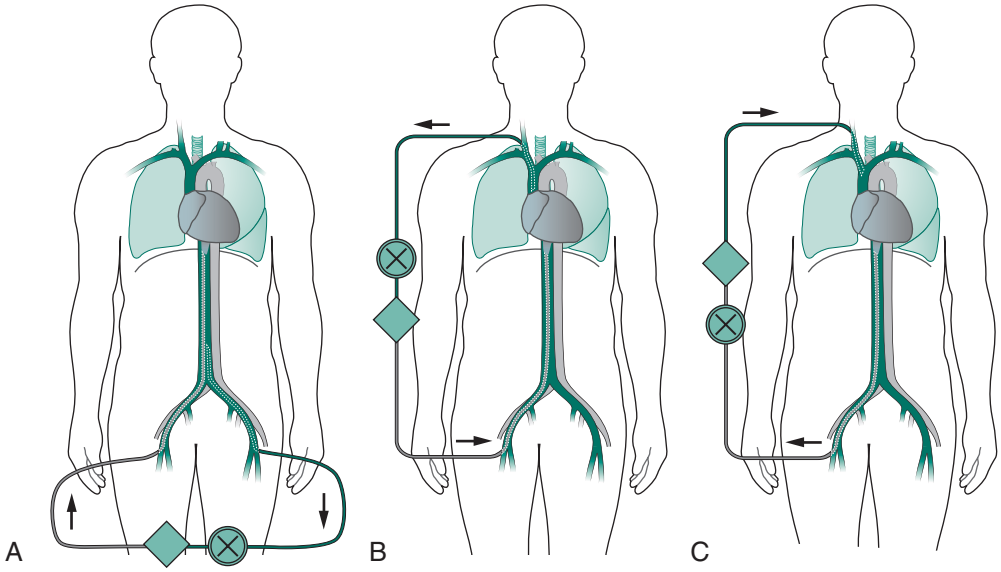

FIGURE 196.2 Schematics of possible VV-ECMO circuits. A, Femorofemoral cannulation; B, jugulofemoral cannulation; C, femorojugular cannulation. (Drawings by Simone Sosio, MD, Università degli Studi Milano Bicocca.)

Two main types of cannulas exist at the present time: single-lumen and double-lumen. In VV-bypass if single-lumen cannulas are used, multiple site venous access are required: the venous drainage usually is achieved by cannulation of the right atrium through the right internal jugular vein or, alternatively, through the right or left femoral vein (Fig. 196.2). Arterialized blood is returned through cannulation of the right or left femoral vein or to the jugular vein. The drainage cannulas are characterized by larger diameter than the reinfusion cannulas (±55 cm, 15–29 French, Fr) and a may have a long, multifenestrated flexible tip to facilitate the drainage and reduce the pressure drop. The reinfusion cannulas are smaller with a diameter comprised between 15-Fr and 23-Fr. They can contain a single end-hole or have a short fenestrated tip.

The femorojugular configuration is the most used as flow rates up to 6 to 7 L/min are obtained easily with inflow cannulas of 23-Fr to 25-Fr with minimal recirculation. The jugulofemoral approach is supposed to grant greater oxygen delivery and drainage at the cost of higher recirculation. Finally, the femorofemoral approach is the least effective as it is characterized by high recirculation or by limited drainage. Moreover, the mobilization of the patients' legs is limited. However, this approach is safe, with low possibility of cannula dislocation, and it is possible to support the patient effectively despite these limitations, sometimes adding a second drainage cannula to provide adequate blood flow.

Dual-lumen cannulas provide VV support via a single jugular venous access site. Blood is removed from the patient via one lumen and then returned to the patient via a smaller lumen. The Avalon (Maquet) Bi-Caval dual-lumen cannula designed by Wang and Zwischenberger is the most popular at the moment.[44] The Avalon cannula has a diameter ranging from 13-Fr to 31-Fr, enabling its use to support neonates through the adults. It may be inserted through the internal jugular vein and simultaneously removes blood from the superior and inferior vena cava and return blood to the right atrium.

A bedside imaging technique (ultrasound or fluoroscopy) is therefore advisable during cannulation to control the guidewire position and its shape during dilatations of the vessel and to guide the correct cannula position.[45] Ultrasounds are easily accessible at the bedside; the patient's characteristics and expertise of the operator are the main determinants of adequate imaging.[46] Fluoroscopy would be the best imaging technique to visualize guidewire misplacements during cannulation[47] and therefore avoid ECMO cannula malposition. However, it is rarely available at the bedside and carries the risk of x-ray exposure. Furthermore, with the new technologic ICU beds, fluoroscopic vision of the entire procedure is sometimes very difficult.

MONITORING AND MANAGEMENT OF ARTIFICIAL LUNG

Management of ECMO is based on the setting of three parameters:

1. Blood flow. As we have seen, blood flow is the main determinant of patient oxygenation. It should be set to the lowest level that provides adequate oxygenation. The required blood flow will be a function of the target oxygenation level and the ventilator strategy applied to the natural lung.
2. Gas flow. It is the main determinant of CO_2 removal, and consequently it determines the minute ventilation we need to apply with the mechanical ventilator.
3. FiO_2 of sweep gas. It is generally set to 100% and progressively decreased as soon as the patient's clinical conditions improve.

The ECMO circuit should be monitored several times a day (at least once a day by a perfusionist). Careful monitoring of the ECMO system is aimed at answering the following questions:

1. Is the oxygenator performing well? If the FiO_2 of sweep gas is 100%, the expected PO_2 in the blood leaving the oxygenator should be very high (generally > 300–400 mm Hg). The postoxygenator PO_2 is usually higher than 500 mm Hg at lower BF and starts to decrease as BF approaches the rated flow for that type of oxygenator. Accounting for this effect, daily monitoring of the postoxygenator PO_2 allows detection of any decrease in oxygenator performance and

eventually prompts to a circuit substitution. In addition, as the oxygenator performance worsens, increasing gas flow rates are necessary to maintain the same arterial PCO_2.

2. Is drainage effective? Efficient blood drainage is crucial. Drainage effectiveness can be assessed by monitoring the pressure before the pump (suction pressure, Pin), by the BF/number of rounds per minute (RPM) ratio, and by clinical evidence of tubes oscillation and BF instability. Pin is an essential monitoring parameter. Appropriate drainage cannula size and blood flow should be selected to avoid excessively negative suction pressure. Pressure values less negative than −100 mm Hg are recommended. When drainage becomes less effective, Pin and BF will decrease and higher RPM must be set to keep the same BF level. Most commonly, a reduction of drainage is due to a change in patient volume status and/or to a decrease in venous blood flow proximal to the cannula tip. Volume expansion or temporary reduction of the extracorporeal BF are the easiest solutions. It is always important to check for any change in cannula position, tube kinking, or obstruction.
3. Is there any activation thrombosis in the circuit? Clot formation in the oxygenator may be detected by daily inspection of oxygenator surfaces, by monitoring the transmembrane pressure (difference between post- and preoxygenator pressure), and by monitoring of coagulation parameters (see below).

VENTILATORY MANAGEMENT OF THE NATIVE LUNG

The optimal setting of mechanical ventilation during ECMO is still a matter of debate and may vary from center to center. The main goal of VV-ECMO is to ensure adequate gas exchange while minimizing the risk of VILI. The first step after ECMO institution is to increase slowly the sweep gas flow with a concomitant reduction of the minute ventilation of the native lung by reducing tidal volume and respiratory rate.

All ECMO centers limit airway plateau pressure to 25 to 30 cm H_2O.[21,35,48,49] ELSO guidelines recommend limiting it lower than 25 cm H_2O.[31] In the CESAR trial, during ECMO, ventilator settings were reduced gradually to allow lung rest (i.e., peak inspiratory pressure 20 cm H_2O, end-expiratory pressure 10 cm H_2O, rate 10 breaths per minute, and FiO_2 30%).[21] The authors of the REVA research network concluded that under ECMO, an ultraprotective ventilation strategy minimizing plateau pressure may be required to improve outcome.[30] They found that a reduced plateau pressure (32 vs. 26 cm H_2O) the first day under ECMO was associated significantly with survival.

PEEP setting during ECMO is an open issue. The debate is to let the lung collapse or to keep it open to some extent, to avoid diffuse alveolar collapse with the resulting increase in pulmonary resistance, which could lead to acute failure of the right ventricle with the need to convert to venous-arterial ECMO.

In the CESAR trial, PEEP was reduced abruptly to 10 to 15 cm H_2O[21]; by contrast, other experts suggest to keep PEEP unchanged or even to increase it.[31] The application of recruitment maneuvers can be an alternative to avoid lung collapse, but no data on their safety and efficacy in ECMO patients are available. Some centers use prone position during ECMO to improve the ventilation-perfusion matching, but it may be associated with potentially dramatic complications (compression or vascular cannulas removal).[50]

Ventilator FiO_2 is reduced to limit oxygen toxicity and the risk of resorption atelectasis but granting an arterial PO_2 of about 55 to 60 mm Hg. In the CESAR trial FiO_2 was reduced to 30%.

However, if the native lung still contributes to arterial oxygenation, a markedly reduced FiO_2 implies the use of high extracorporeal blood flows to compensate a significant worsening of oxygenation. It must be realized that the ventilatory strategy has a great influence on the level of blood flow and gas flow necessary to maintain adequate oxygenation; in addition, we have to remember that the worse the residual gas exchange capability of the natural lung, the higher blood flow and cannulas size are necessary.

When the native lung function and the patient's clinical conditions improve, some spontaneous breathing activity may be desirable. The patient may be switched from controlled to assisted ventilation, and ECMO support may allow to titrate patient effort. The use of neutrally adjusted ventilatory assist (NAVA) in these cases can be useful. NAVA minimize double triggering and allows the patients to take control of the breathing pattern.[51] Manipulation of CO_2 elimination acts as an external modulator of the drive to breathe.

During ECMO, there is a complex interplay between the patient's own respiratory drive, the level of sedation, and the ventilation of the artificial lung: by varying the level of sedation and the sweep gas flow, we can change the relative fraction of total CO_2 production that is removed by the native and the artificial lung. In other words, modulating the level of extracorporeal assist may facilitate the switch to an assisted modality of ventilation by controlling the patient's respiratory drive.

Monitoring the function of the natural lung is performed in many centers by pulmonary artery catheter (PAC), which allows the continuous measurement of SvO_2 and gives the possibility to measure the intrapulmonary shunt fraction. During ECMO, the shunt fraction is probably the parameter that better estimates natural lung function, and it is less affected by ECMO application. Finally, PAC provides the direct measurement of pulmonary arterial pressure, which may indicate the presence of pulmonary hypertension and the requirement of a specific treatment (inhaled nitric oxide, sildenafil) to prevent right ventricular failure.

ANTICOAGULATION AND HEMATOLOGIC MONITORING

During ECMO the continuous contact between circulating blood and foreign surfaces results in the shift from the normal hemostatic balance to a hypercoagulable state, with consequent risk of thrombosis. Consequently, an adequate antithrombotic therapy is necessary to prevent thrombosis while avoiding bleeding in the patient.[52]

Unfractionated heparin (UNFH) is the most widely used antithrombotic agent. UNFH inhibits thrombin after it is formed, but it does not prevent thrombin formation and it does not inhibit thrombin already bound to fibrin. Patients usually receive an initial UNFH bolus up to 100 units per kg body weight at the time of cannulation, and then UNFH is continuously infused during ECMO. The dose is usually of 7.5 to 20 units/kg/hr, lower in the adults and higher for pediatric and neonatal patients. Therapeutic anticoagulation, classically defined by ACT range of 180 to 220 seconds,

typically is achieved with UNFH infusion rates of 20 to 50 units/kg/hr.[53]

Antithrombin (AT) is an important endogenous anticoagulant protein. Because use of heparinized surfaces requires normal levels of antithrombin, an infusion of antithrombin III sometimes is suggested.

Currently, several in vitro tests exist to assess coagulation. Before ECMO initiation, baseline laboratory values should be obtained, if possible, and the correction of preexisting coagulopathy before initiation of extracorporeal support may facilitate the anticoagulation management.

Activated clotting time (ACT) remains the most commonly used test during ECMO to dictate UNFH dosage. It is low cost and available 24 hours per day in most centers. During ECMO, the ACT usually is maintained between 180 and 220 seconds.

Anti-factor Xa activity levels (anti-Xa) are employed to measure the anti-Xa activity of heparin in plasma. An optimal value, corresponding to an activated partial thromboplastin time (APTT) 1.5 to 2 times the baseline, is between 0.3 and 0.7 IU/mL.[54]

APTT has an acceptable degree of correlation with heparin concentration[54] and is therefore to be considered superior to the ACT for heparin treatment monitoring during ECMO. An APTT of 1.5 times the baseline APTT (50–80 s) is considered the target value during ECMO and usually corresponds to a heparin concentration of 0.2 to 0.3 IU/mL.[55]

Prothrombin time (PT) is a marker of the extrinsic and common coagulation pathways and should be performed to detect the level of coagulation factors and to guide their supplementation with fresh frozen plasma (FFP), prothrombin complex concentrates (PCC), or cryoprecipitates.

Platelet count, fibrinogen levels, and D-dimer assays should be performed daily because they determine the need for platelet concentrates, FFP, fibrinogen, and antifibrinolytics.

Thromboelastography (TEG) and thromboelastometry (TEM) are dynamic tests based on the viscoelastic properties of blood during the coagulation process.

Antifibrinolytic therapy should be initiated in presence of signs of ongoing hyperfibrinolysis at TEG/TEM or conventional tests. A certain degree of fibrinolysis is always present during ECMO; values of D-dimers around 300 μg/L are acceptable, but signs of progressive increase require a prompt intervention.[52]

Platelet count should be maintained above 80,000 cells/mmc in a patient with active bleeding or at high risk for bleeding, with platelet concentrate transfusions. Conversely, lower values (however >45,000 cells/mm^3) may be accepted in nonbleeding patients or patients at low risk for bleeding.

In presence of heparin-induced thrombotic thrombocytopenia (HITT), heparin infusion should be discontinued and an alternative anticoagulant such as argatroban may be used.[56,57]

EXTRACORPOREAL MEMBRANE OXYGENATION COMPLICATIONS

Technical complications is less frequent in modern ECMO system compared with older ones. In a recent report on 265 adult patients undergoing VV-ECMO, 83 patients had the need for exchange (pump head, oxygenator thrombosis, worse gas exchange); 45% of the cases were acute, 55% elective.[58]

Bleeding complications remain frequent in ECMO patients. ELSO registry (2012) reported 3.8% incidence of intracerebral bleeding in adults patients on VV-ECMO. Bleeding likely is due to the necessity to continuously infuse heparin and to a certain degree of platelet and endothelial dysfunction. Other possible (although rare) complications include infection at the site of cannula insertion, systemic thromboembolism resulting from thrombus formation within the arterial site of the membrane, entrance of air in the extracorporeal circuit, and hemolysis.[50] In the presence of generalized and persisting bleeding, heparin should be reduced or discontinued, and transfusion of fresh frozen plasma and platelets should be considered. Heparin-induced thrombocytopenia carries a high risk of thrombosis. Heparin infusion should be discontinued, and change to an alternative anticoagulant regime such as argatroban is advisable. To prevent bleeding it may be good practice to withhold or at least minimize risky procedures such as intramuscular or subcutaneous shots, thoracentesis, chest tube insertion, and substitution of nasogastric or urinary catheters.

WEANING FROM VENOVENOUS EXTRACORPOREAL MEMBRANE OXYGENATION

Weaning from ECMO can be commenced when natural lung gas exchange capabilities improve and lung rest is no longer necessary. This is determined by several aspects of the patient's respiratory function. Weaning typically is started when the patient's lung compliance improves (ARDS patients) and/or airway resistance decreases (severe asthma). According to the ELSO guidelines ECMO discontinuation can be considered when the natural lung provides 50% to 80% of the total gas exchange. Finally gas exchange (PO_2 and PCO_2) is considered adequate for weaning when values are acceptable at "moderate" ventilator settings, which can be FiO_2 lower than 0.5 to 0.6 and a low PEEP value. This requires clinical judgment and careful monitoring of the patient's progress.

A trial of temporary discontinuation of ECMO should be performed when the patient is judged ready for weaning. The trial can last from 1 to 12 hours, but even longer if needed. If the patient is in controlled mechanical ventilation, respiratory rate, plateau pressure, FiO_2, and PEEP should be adjusted to values acceptable off ECMO. Most commonly ECMO is discontinued when the patient is already in assisted spontaneous ventilation. In this case the level of sedation should be modulated carefully. When ventilator settings have been adjusted, the sweep gas can be turned off while blood flow can be continued. During the trial hemodynamic stability, adequacy of gas exchange, the respiratory pattern, and mechanics should be assessed carefully.

When the patient is considered ready, the extracorporeal support can be discontinued definitively and cannulas removed. To remove cannulas placed percutaneously, a purse-string suture, inserted around the cannulation site, is tightened immediately after decannulation and local pressure is applied for at least 30 minutes.

Key Points

1. The application of ECMO for respiratory support is a feasible technique in adults and in children,

provided that patients are centralized upon expert centers and correct indications for extracorporeal treatment start are present.

2. Venovenous ECMO is generally run via femorojugular approach in case of application of two single-lumen cannulas or via double-lumen cannulas placed in the right internal jugular vein. Centrifugal pumps typically are used in current setups. Heparin anticoagulation is used routinely.
3. One of the most important indications to VV-ECMO is hypoxic respiratory failure of hypercapnic respiratory failure: in these two conditions, very different ECMO setups are required.
4. During VV-ECMO, lung function actually is supported when it is possible to reduce barotrauma secondary to mechanical ventilation (protective ventilation): to make it possible, careful adjustments of ECMO and ventilator settings are required.
5. A trial of temporary discontinuation of ECMO should be performed when the patient is judged ready for weaning. The trial can last from 1 to 12 hours. If the patient is in controlled mechanical ventilation, respiratory rate, plateau pressure, FiO_2, and PEEP should be adjusted to values acceptable off ECMO.

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A complete reference list can be found online at ExpertConsult.com.

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