

Extracorporeal Membrane Oxigenation Support Following Cardiac and Respiratory Disease: Review

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ABSTRACT

Extracorporeal membrane oxygenation (**ECMO**) offers an alternative to patients who need cardiac and lung support for a period of days to weeks. ECMO provides a survival benefit in patients with high rates of morbidity and mortality, offering reasonable long-term outcomes for the ECMO survivors. The use of ECMO in adults with severe respiratory and cardiac failure is now increasing because of several reasons. Firstly, there have been advances in technology (safer ECMO devices, easier to implement, which include more efficient ECMO circuit components). Secondly, there is a higher institutional experience, which implies the specialization of anesthesiologists, cardiac surgeons, cardiologists, perfusionists and nurses that are actively involved in the perioperative care of patients on ECMO. In this chapter we show the use of ECMO for treating severe cardiac and respiratory failure in adults, referring to the following concepts: who are suitable candidates for ECMO (veno-venous and veno-arterial), central or peripheral cannulation for ECMO (techniques and special considerations), perioperative anesthetic management (hemodynamic and respiratory support, echocardiography and weaning from ECMO) and the main complications in patients on ECMO (hematologic, neurologic and infectious complications, limb ischemia and cardiac or vascular perforations).

Keywords: Extracorporeal membrane oxygenation (**ECMO**); Respiratory failure; Heart failure; Perioperative anesthetic management

INTRODUCTION

Extracorporeal membrane oxygenation (**ECMO**) is a well-established mechanical support for the heart and/or lungs when all conventional therapies have failed and the patients are at risk of death. ECMO has been available for decades. Guidelines have been developed by the Extracorporeal Life Support Organization (**ELSO**) [1]. This organization maintains an international registry data of ECMO cases provided by registered centers from all over the world. ECMO can be used as a bridge to treatment, transplantation or long-term cardiac support therapies. If only lungs are damaged, a venovenous (**VV**) ECMO is required; however, if heart alone or heart and lungs are compromised, the patient is suitable for a venoarterial (**VA**) ECMO [2].

The use of ECMO in our institution has considerably increased in the last few decades. The development of a multi-disciplinary programme based on high-specialized professionals with broad-experience on ECMO procedures has enable this progress. At the same time, technological advances on ECMO (oxygenators, blood pumps, cannulas and cannulation mechanisms), careful selection of patients and the use of echocardiography has improved the survival by decreasing the incidence of complications developed in patients supported by ECMO.

The purpose of this chapter is to show the relevance of the ECMO support on the adult patient (indications and contraindications for ECMO, technical considerations, perioperative anesthetic management and potential complications). We also show our experience using the echocardiography in this patients. It provides information for every single step in the management of the therapy including confirming indication, cannulas insertion, progress monitoring, complications detection, recovery evaluation and support weaning.

WHO IS CANDIDATE FOR ECMO

The indications and contraindications for each type of ECMO in the adult patient are mainly based on the ELSO Guidelines [3], as it is detailed below:

Indications for VV ECMO [4]

- *Hypoxic respiratory failure* due to any cause. ECMO should be considered when the risk of mortality is greater than 50% ($\text{PaO}_2/\text{FiO}_2 < 150$ with $\text{FiO}_2 > 0.9$ or Murray Score of 2-3) and is indicated when risk of mortality rises up to 80% ($\text{PaO}_2/\text{FiO}_2 < 80$ with $\text{FiO}_2 > 0.9$ or Murray Score of 3-4).
- *Hypercapnia and acidosis* despite adequate mechanical ventilation (plateau airway pressures of >30 cm H_2O).
- *Severe air leak syndromes*.
- *As a bridge to lung transplantation*.
- *Respiratory collapse* despite of optimal conventional care.

As declared in a Cochrane review [5], the largest randomized clinical trial made in adults with severe Acute Respiratory Distress Syndrome (**ARDS**) is the CESAR trial [6]. This trial showed better outcomes in ARDS patients treated with ECMO compared to the group that received conventional care. However, this study has some methodological issues that complicates the interpretation of the results and the possibility to provide general recommendations. On the other hand, there is an on-going trial, named the EOLIA trial (Extracorporeal Membrane Oxygenation to Rescue Lung Injury in Severe Acute Respiratory Distress Syndrome) which intends to solve these issues and to clarify whether ECMO is beneficial or not for this subset of patients. This trial is due to 2018.

Indications for VA ECMO [7]

- *Carcinogenic shock* despite optimal medical treatment and with a reversible cause. In these cases, ECMO may be used in combination with the intra-aortic balloon pump (**IABP**) [8].
- *Cardiac arrest*: the last American Heart Association (**AHA**) guidelines recommends considering ECMO in patients who returned to spontaneous circulation under excellent cardiopulmonary resuscitation conditions [9].
- *Bridge to cardiac transplantation* or *ventricular assist device* (**VAD**).
- *Prevention of Ventilation Induced Lung Injury (VILI)*: Despite not being a formal indication, there is some clinical experience in using a pump less VA ECMO to remove CO₂ in ARDS patients that receive ultra-protective lung ventilation (Vt=3ml/kg) [10]. SUPERNOVA trial (A Strategy of Ultra Protective lung ventilation with Extracorporeal CO₂ Removal for New Onset moderate to severe ARDS) is an on-going trial that aims to evaluate whether a strategy of ultra-protective lung ventilation will improve clinical outcomes compared to standard-of-care lung-protective ventilation.

Contraindications for ECMO

- Patients with severe neurologic injuries, intracranial hemorrhage, untreatable malignancy, severe immuno suppression, irreversible multi-organ failure or pre-existing chronic illness with poor long-term prognosis [11].
- Existence of *aortic dissection* or *severe aortic regurgitation*.
- In ARDS patients, a relative contraindication may be *prolonged mechanical ventilation with high airway pressures*. ECMO in severe ARDS should be initiated early in the course of the disease.
- Patients with *prolonged cardiac arrest, unrecoverable heart disease, who received sub-optimal cardiopulmonary resuscitation (CPR) or who are not candidates to cardiac transplantation or VAD insertion*.
- *Elderly patients*: The use of ECMO in elderly patients is controversial but may become acceptable as the technology improves and the ECMO-related complications decrease [12].
- *Obesity* [13] or *contraindication for anticoagulation* are also relative contraindications.

TYPES OF ECMO: VENO-VENOUS AND VENO-ARTERIAL

Components of the ECMO Circuit

It is important to know the general components of ECMO before explaining the different types of support. Except for the differences in the cannulas, identical circuits are used in ECMO [3,14,15] (Figures 1 and 2):

Pump: Ventricular assistance with continuous flow, normally centrifugal. Blood flow is preload and after load dependent, and therefore a rise in the mean arterial pressure or hypovolemia may cause disturbances in the pump speed and drainage.

Membrane lung (oxygenator): With a biocompatible surface coating of non-micro porous fibers, the membrane allows gas exchange with a limited activation of the coagulation cascade and the inflammatory mediators.

Inflow and outflow cannulas: Blood drains out of the patient through the inflow cannula into the ECMO and then is pumped through the oxygenator back into the patient through the outflow cannula. For most adults, the inflow cannula should be from 21 to 28 French (F), and the outflow cannula from 15F to 21F.

ECMO console: for the management and monitoring of hemodynamic parameters.

Heat exchanger: which controls the temperature (37- 40°C).

Gas blender: for the delivery of air and oxygen. FiO_2 determines blood oxygen tension and gas flow determines the blood carbon dioxide tension.



Figure 1: ECMO membrane (oxygenator), inflow and outflow cannula.



Figure 2: ECMO and its components.

Types of ECMO

There are two general types of ECMO: Venoarterial (**VA**) which provides support for the heart and lungs, and venovenous (**VV**) which provides support for the lungs only [14,16] (Figure 3).

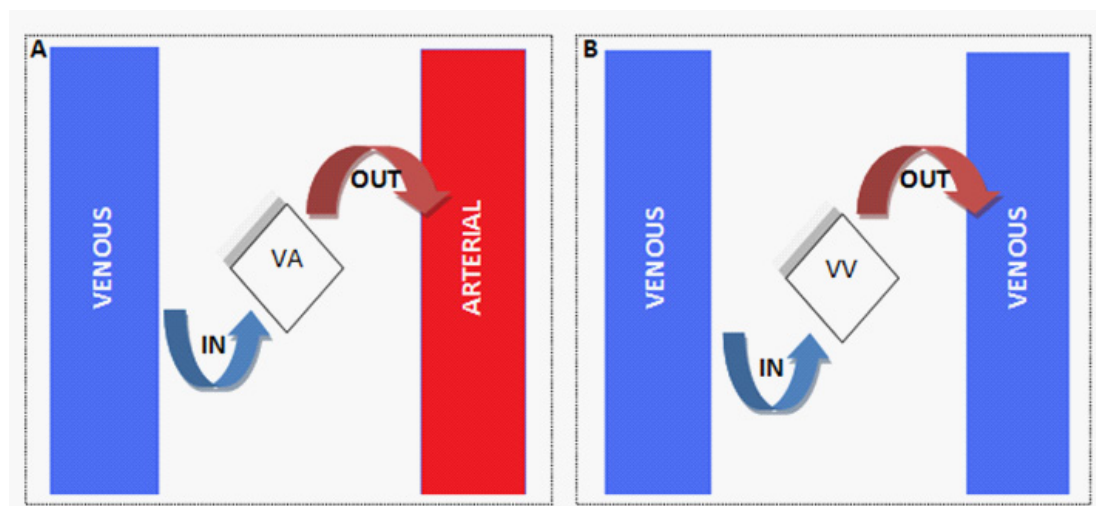


Figure 3: Schematic view of blood flow in 2 types of ECMO. (A) VA ECMO. (B) VV ECMO. In blue it is represented the venous blood, whereas in red it is shown the arterial blood. In: Inflow cannula. Out: Outflow cannula.

Veno-arterial ECMO

VA ECMO is used in patients with refractory cardiogenic shock or cardio-respiratory failure. Similar to standard cardiopulmonary bypass, VA ECMO has an inflow cannula with the systemic venous blood received from the patient's venous system, and the outflow cannula that provides oxygenated blood into the arterial system of the patient.

Systemic arterial blood flow is the addition of the ECMO circuit flow and the ejection from the left ventricle (LV). In the absence of LV ejection, the patient's systemic arterial oxygen saturation (SaO_2) depends totally on the ECMO outflow cannula. If there is LV ejection SaO_2 depends from both ECMO circuit and blood ejected. This fact could be relevant in patients with impaired lung function and femoral cannulation of the ECMO outflow cannula, following an upper body hypoxemia with coronary and cerebral hypoxia (as proximal branches of the aorta are receiving deoxygenated blood). With ventricular ejection this complication can be avoided if the cannula is placed centrally (proximal aorta) or into axillary artery position, increasing blood flow to limit left ventricular ejection, or with conversion to a VV ECMO by addition of an extra-venous reinfusion cannula [17]. Because of this and other reasons, depending on the patient's situation, the peripheral or central cannulation for the ECMO will be decided. In all cases it is important to confirm decompression of the left ventricle with echocardiography.

There is a third type of ECMO: the arteriovenous (AV) ECMO, specifically for the CO₂ removal [3]. Also known as "*artificial lung*", it can be used in patients with acute lung injury and stable cardiovascular status. Unlike VA and VV ECMOs, the AV circuit does not include a pump to maintain blood flow. Therefore, adequate blood pressure and cardiovascular stability are required to maintain blood flow in this configuration.

Veno-Venous ECMO

In VV ECMO both inflow and outflow cannulae are placed in a systemic vein. It is used in the management of patients with refractory pulmonary failure and stable cardiovascular status, avoiding the risk of potential systemic embolism [3,14]. There is no direct support of cardiac function, and the resulting effect of VV ECMO support is an increase of the oxygen content of the blood returning to the lung.

The oxygenated blood from the outflow cannula mixes with the systemic venous blood in the pulmonary artery and through the lungs. Ideally, only deoxygenated systemic venous blood enters in the inflow cannula, nevertheless in some situations the position of the cannula can trigger the phenomenon of recirculation, reducing the delivery of oxygenated blood [17].

The SaO_2 is determined by the ECMO flow, the pulmonary residual function, the patient's systemic venous return, the oxygen saturation of systemic venous blood (SvO_2) and the degree of recirculation. A SaO_2 above 85% can be succeed with VV ECMO with minimal or even absent pulmonary function [3].

VV ECMO provides a partial or total support of the function of the lungs and minimizes the main contributing risks to the development of ventilator-induced lung injury: high ventilation volumes and pressures and high FiO₂ levels [17].

Comparative review: VA ECMO and VV ECMO

In addition to the vascular access site of ECMO insertion, the main factor involved on the cardiovascular function of ECMO is the type of support. This factor has much less effect on the patient’s hemodynamics in VV compared to VA ECMO. The first one is established functionally in series with the patient’s heart, whereas the VA ECMO is in parallel [17,18]. In Table 1 it is summarized the particular characteristics of the two types of ECMO support [3,18]:

Table 1: Comparative review of VA ECMO versus VV ECMO (**IABP**: Intra-aortic balloon pump; **SvO₂**: Systemic venous blood).

ECMO	VA	VV
Patient	<ul style="list-style-type: none"> - Cardiovascular failure with or without respiratory failure. - Lack of response to inotropes and/or IABP. 	<ul style="list-style-type: none"> - Hypoxemic patients with competent cardiovascular function - Oxygenation problems, refractory to conventional therapies - Often with high cardiac output due to infection/sepsis
Cardiac effects	<ul style="list-style-type: none"> Preload: decreased After load: increased Pulse pressure: lower Left ventricular blood: desaturated 	<ul style="list-style-type: none"> - May reduce right ventricular after load. Rest is unaffected - Hyperoxia with reduced vascular pulmonary resistance and improved cardiac output
Circuit	Parallel	Series
Flow targets	3 L/m ² /min for SvO ₂ > 70%.	60-80 ml/kg/min
Circulatory support	Partial/complete	No direct support
Situations	<ul style="list-style-type: none"> - Cardiogenic shock (acute coronary syndrome, refractory cardiac arrhythmic storm, sepsis, drug overdose/toxicity, myocarditis, pulmonary embolism, isolated cardiac trauma, acute anaphylaxis) - Post-cardiotomy - Post-heart transplantation - Chronic cardiomyopathy - Perioperative support for high-risk interventions - Bridge to transplant 	<ul style="list-style-type: none"> - Acute respiratory distress syndrome (severe bacterial or viral pneumonia, aspiration syndromes, pulmonary alveolar proteinosis) - Extracorporeal assistance to provide lung rest (airway obstruction, pulmonary contusion, smoke inhalation) - Perioperative period of lung transplantation (primary graft failure, bridge to transplant, intraoperatively) - Lung hyperinflation: status asthmaticus - Pulmonary hemorrhage or massive hemoptysis

CANNULATION STRATEGIES IN ADULT ECMO: TECHNIQUES AND SPECIAL CONSIDERATIONS

The most common configuration in adults is the “peripheral ECMO” with a femoro-femoral cannulation. Another option for peripheral approach is the axillary artery, while the carotid artery

is avoided in adults because of potential neurological complications. In “central ECMO” circuit, the outflow cannula is placed in the ascending aorta and works as a temporary VAD. However unlike VAD, central ECMO has the advantage of incorporating an oxygenator that enables adequate oxygenation and correction of hypercapnia [19].

Mainly there are two types of techniques: percutaneous and surgical cannulation. At the time of electing the ECMO cannula, as a general rule, the size must be no more than two-thirds of the vessel diameter [20].

Percutaneous Cannulation

Percutaneous cannulation is the first choice and less invasive technique. Vascular ultrasound is a very useful tool in this field, helping to locate and measure the diameter of the vessels [3].

VA ECMO implantation is usually an emergent procedure. It includes a Seldinger technique, in which firstly one guide wire is progressed from the femoral vein into the inferior vena cava approaching the right atrium, and secondly another guide wire is advanced from the femoral artery close to the aortic valve. Then, the cannulae are introduced over the wires: the venous cannula is progressed until the cannula tip is located in the mid-right atrium; and the arterial cannula is advanced for its complete length into the iliac artery. Lines are de-aired with physiological saline and connected to the ECMO circuit. In a non-emergent procedure, a distal perfusion catheter is positioned in the superficial femoral artery before the insertion of the arterial cannula. Another alternative is a retrograde limb perfusion cannula via posterior tibial artery [21].

Percutaneous approach is the election technique in VV ECMO. The jugular vein and the femoral vein are usually used and less frequently subclavian vein [19].

1. Femoro-jugular approach: One operator approaches of the femoral vein whereas the other operator takes over the internal jugular vein. Care must be taken with cannulation of the jugular vein proximal to the right atrium and the associated risk of pneumothorax. The inflow cannula should be placed in the femoral position to minimize recirculation with the tip at least 2 cm below the diaphragm, and the outflow cannula with the tip at the junction between superior vena cava and right atrium [22].

2. Femoro-femoral approach: Firstly, the inflow cannula is inserted. The tip of the inflow cannula will be positioned at the level of the vertebrae L1-L2 (to receive the blood from the renal veins) and the tip of the outflow cannula should be placed close to the junction between the inferior vena cava and the right atrium, at the level of T10-T11. This technique has a higher risk of recirculation.

3. Double lumen cannula: a single vessel is approached with a double lumen cannula. It has to be introduced through the internal jugular vein; the tip will be placed in the inferior vena cava. Blood is drained from the superior and inferior vena cava while the reinfusion takes place

through a separated lumen near the tricuspid valve. This cannulation is more comfortable for the patient and allows respiratory physiotherapy with fewer sedatives [22-24].

Surgical Cannulations

Surgical cannulation allows direct visualization of the vessels, the placement of a direct purse-string suture, an adequate position of the cannula as well as effective hemostasis. There are three possibilities: direct cut-down cannulation, poly tetra fluoroethylene anastomosis (PTFE) or Dacron graft, and the semi-Seldinger technique [3,25].

A) Peripheral Cannulation

Femoral vessels

Direct/cut-down cannulation technique: the artery is clamped proximally and distally and longitudinal arteriotomy is made. The insertion of arterial cannula with its tip in the external iliac artery is performed and the purse-string suture is closed. Common femoral vein is clamped proximally and distally. A venotomy is made within the purse string, the venous cannula is inserted, and the proximal and distal clamps are removed. The cannula is advanced up to the right atrium. Instead of clamping the vessels and performing an arteriotomy or venotomy, a Selinger technique with direct vision can be realized in an open approach. This has the advantage of avoiding stenosis of the vessels produced when sutures are closed. Longitudinal purse-string sutures in vessels are performed and Seldinger technique is carried out under direct vision, firstly in femoral artery.

Semi-Seldinger technique: the catheter is inserted into the artery under direct vision. This catheter is used to place the large guidewire in the same way as Seldinger technique. It facilitates insertion of the insertion of the cannulas with a low angle ($\leq 30^\circ$), and avoids external bleeding around the cannulae [25,26].

Chimney graft technique: after arteriotomy, a 10 mm PTFE or Dacron graft is sewn in an end-to-side anastomosis. The cannula is then inserted and the wound is closed. This technique lowers the risk of distal leg ischemia and simplifies decannulation.

There is a more practical alternative in the peripheral ECMO with surgical cannulation:

.Inflow cannulation with percutaneous approach in the right femoral vein (left femoral vein cannulation is more difficult due to the presence of lumbar branches).

.Outflow/arterial cannulation with surgical approach and a Dacron graft in the left femoral artery. The Dacron graft is exteriorized upon the skin trough a small incision 2 cm distal to the main incision, similar to semi-Seldinger technique. The outflow cannula is introduced through the Dacron graft.

With this strategy the patient only has undergo one single surgical procedure. Weaning from the ECMO is simple, the inflow/venous cannula can be withdrawn with manual compression and the outflow/arterial cannula with a complete suture of the Dacron graft.

Axillary vessels

It involves the right axillar artery and right axillary vein. Some of its advantages: it facilitates antegrade flow, it allows direct closure of chest after postcardiotomy shock, it has an easy decannulation, and a lower rate of complications [27]. It has to be considered in postcardiotomy patients, important peripheral vascular disease, limb complications related to femoral artery cannulation, and patients under peripheral ECMO support with inadequate upper body oxygenation. For this approach, a horizontal incision is made below the medial third of the clavicle. Another option is the deltoideo-pectoral approach with an 8 cm incision below and parallel to the lateral two thirds of the clavicle [25]. Axillary vein lies superficial to the artery, so it is preferable to cannulate the artery first. Usually a chimney graft is used in this type of cannulation. The mayor disadvantage of this approach is that it cannot be used during an emergency procedure.

Cervical vessels

It affects the right jugular vein and carotid artery, and it is the best peripheral cannulation approach in neonates and children weighing less than 15 kg.

The antegrade flow is a theoretical advantage with aortic and auxiliary cannulations. This may be beneficial over femoral cannulation when IABP is used during ECMO, ensuring continuous coronary perfusion.

B) Central Cannulation (VA ECMO)

With the central cannulation, larger cannulae are required (20-22-Fr arterial cannula, 50-52 Fr venous cannula), ensuring greater flow. The flow is antegrade and avoids the upper body hypoxemia, as previously commented. The inflow cannula is placed in the right atrium and the outflow cannula in ascending aorta (Figure 4). Problems concerning weaning from cardiopulmonary bypass, postoperative cardiac surgery, peripheral vascular disease, impossibility of peripheral cannulation or insufficient left ventricular unloading with peripheral ECMO, are some of the situations where central ECMO is indicated.

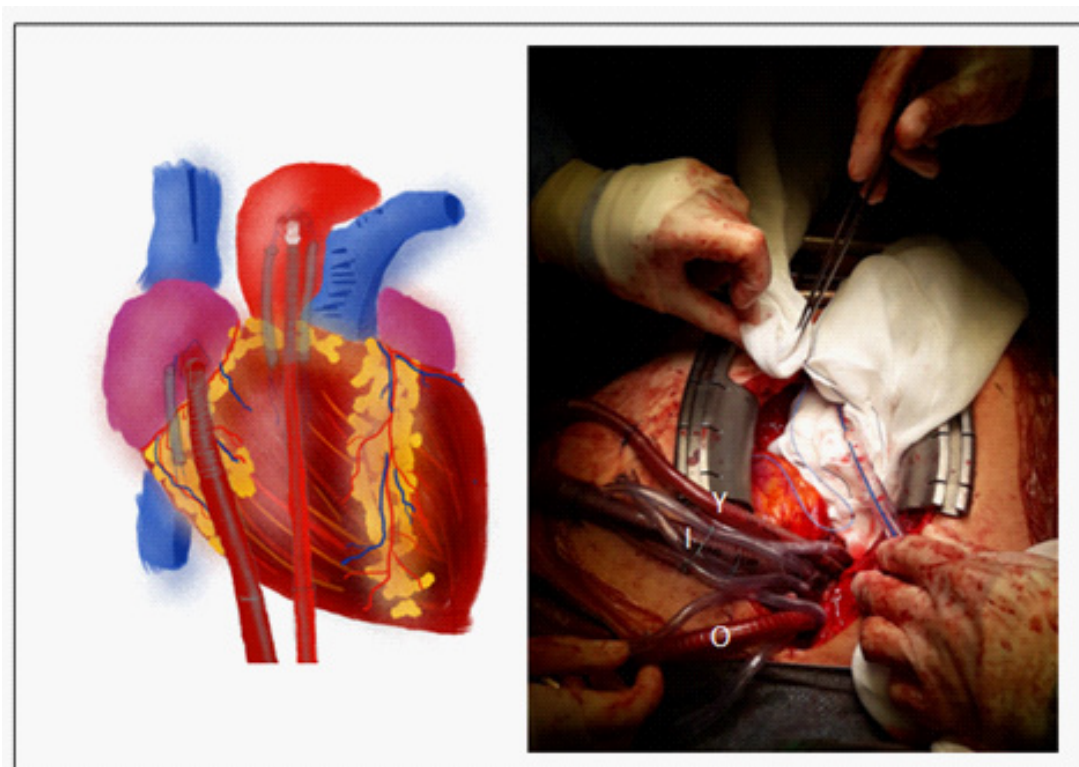


Figure 4: Left; Central cannulation with the inflow cannula in the right atrium and the outflow cannula in the ascending aorta. Cannulae can be tunneled and exteriorized in the upper abdomen. Right; Central cannulation: an additional cannula is placed in the left atrium to improve drainage. I: inflow cannula (right atrium); Y: inflow cannula (left atrium); O: outflow cannula (aorta).

In case of difficult weaning from cardiopulmonary bypass the original cannulae are kept and the circuit is changed. Venting on the left side should be considered if the left ventricle distension is noted at the surgical field or/and in the transesophageal echocardiography (TEE); surgical vents can be placed via the LV apex or into the left atrium [21,22,25]. The best option is to place a cannula in the left atrium and then progress it into the LV.

In our experience the peripheral ECMO with femoro-femoral percutaneous cannulation (on both sides) is the fastest and more reproducible configuration in the non-surgical patient with a “bridge to decision” intention. On the other hand, to obtain better hemodynamics parameters with greater durability of the circuit, we recommend the surgical cannulation in the femoral or axillary position as the preferable sites. In the patient who has undergone cardiac surgery, central ECMO is the first option, taking advantage of the cannulas and closing the sternum to avoid complications.

ANESTHETIC MANAGEMENT DURING ECMO

Whilst on ECMO, the aim is to ensure adequate cardiac and pulmonary support and to guarantee a suitable rest of both organs. Once the patient is clinically improving, a gradual weaning from ECMO support should be performed without delay in order to minimise the risk of complications.

Institution of ECMO

After ECMO cannulation the circuit is unclamped and the patient is commenced on the initial standard ECMO settings, which are described in Table 2. The initial sweep gas flow should be started at the same speed as the ECMO blood flow, and adjusted later based on pH and pCO₂ levels. ECMO blood flow may also be adjusted based on the pO₂ levels [28].

Table 2: Initial settings and goals for ECMO. * >150.000 mm³ if active bleeding (FiO₂: Fraction of inspired oxygen; SvO₂: Oxygen saturation in mixed venous blood; paCO₂: Partial pressure of arterial carbon dioxide; MAP: Mean arterial blood pressure; ACT: Activated clotting time; APTT: Activated partial thromboplastin time; AT-III: Antithrombin III; Hb: Hemoglobin).

Parameters	Initial settings
ECMO circuit flow	50-80 mL/kg/min
ECMO sweep gas flow	50-80 mL/kg/min
Inlet pressure (centrifugal pump)	>100 mm Hg
ECMO FIO ₂	100%
Oxygen saturation (outflow cannula)	100%
Oxygen saturation (inflow cannula)	>65%
Arterial oxygen saturation VA	- VA: >95%
	- VV: 85-92%
SvO ₂	>65%
paCO ₂	35-45 mmHg
pH	7.35-7.45
MAP	65-95 mmHg
Hematocrit	30-40%
Platelet count	>100.000 mm ³ *
ACT	- VA: 180-220 s
	- VV: 160-180 s
APTT	1.5-2 times normal
INR	<1.5
Fibrinogen levels	>2g/dL
AT-III levels	80-120%
Free plasma Hb	< 10mg/dL

Once the ECMO is implemented, regular laboratory testing should be performed to ensure cardiopulmonary function of ECMO and also to diagnose potential complications early (Table 3).

Table 3: Investigations for initial assesment and follow-up during ECMO. * Includes fibrinogen and D-dimer. ** Includes renal function, electrolytes and liver function tests (ACT: Activated clotting time).

Investigations	Periodicity
ACT	1-2 hourly
Arterial blood gas	3-4 hourly
Pre-, post-oxygenator blood gas	Daily
Chest X ray	Daily
Full blood count	6 hourly
Coagulation tests *	6 hourly
Blood chemistry **	12 hourly
Tromboelastography	12 hourly
Plasma free hemoglobin	12 hourly
Blood cultures (from ECMO circuit)	Daily

Hemodynamic Support

Supporting cardiovascular function is crucial in patients on VA ECMO and not necessary in patients on VV ECMO, who commonly have a single organ failure. ECMO function can be combined with inotropic and vasoactive agents, also with intra-aortic balloon pump for selected patients, such as those with acute cardiac failure after coronary bypass graft surgery [29]. Absence of pulsatility may reflect deterioration of the left ventricular function [28].

Echocardiography imaging should be regularly performed to check left and right function, ECMO cannula position and flows. It can also be useful to discard potential complications such as hypovolemia, pericardial or pleural effusions. [14].

Respiratory Support

Once the ECMO support has been established, ventilator should be started on resting lung function settings to prevent ventilator-induced lung injury. This strategy includes a peak airway pressure ≤ 35 cm H₂O, mean airway pressure ≤ 25 cm H₂O, PEEP 10-15 cm H₂O, tidal volume ≤ 100 mL, respiratory rate of 10-15 bpm, and FiO₂ ≤ 0.7 [14,28].

Typically, within the first few days of ECMO the patient develops a systemic inflammatory with a marked vasodilatation, requiring inotrope and vasoactive agents as well as great amounts of fluid challenges which compromise lung function This picture is correlated to worsening acute lung injury and development of “white out” lungs on the chest x ray. Adequate and deep sedation may be required at this point, which in many instances is combined with neuromuscular blockade to avoid high intrathoracic pressures [28].

Once the acute phase is over, fluid restriction and fluid removal is desirable to improve pulmonary function. Diuretics are sometimes replaced by continuous veno-venous hemofiltration,

even in the absence of acute renal failure [14]. The lack of improvement despite an aggressive restrictive fluid management often associates pulmonary hypertension and/or right ventricle failure. In these cases it may be useful to insert a pulmonary artery catheter for cardiovascular monitoring [28].

Heparinization

After a bolus (50-100 units/kg) of heparin for cannulation, and infusion is started at a rate of 10 units/kg/h. Coagulation is carefully monitored typically by the activated clotting time most of the times, which can be quickly obtained at the bedside. Other coagulation tests used on ECMO are heparin blood concentration, thromboelastography (TEG) and activated partial thromboplastin time [14].

Anticoagulation target should be individualized according to ECMO flow rates (lower flows require greater anticoagulation), hematological status and end organ injury (basically renal and liver dysfunction). The initial goals for the non-bleeding patient with a normal platelet count are described in Table 2 [14,28].

In patients requiring ECMO after cardiopulmonary bypass, heparin infusion is usually started 12-24 hours after surgery, once the patient is normothermic, without signs of active bleeding or severe coagulopathy (chest drainage is <100 ml/h, INR < 1.6 and platelets >70.000).

If contraindicated, heparin could be replaced by other anticoagulants, such as danaparoid sodium, lepirudin, bivalirudin or argatroban which can be as effective as heparin but at the same time they are associated with significantly more bleeding complications [30-33].

Fluid Management

Fluid administration goal is to avoid hypovolemia and ensure appropriate organ blood flow. Colloid administration is preferred to crystalloids as it can increase preload reducing the risk of third spacing. Monitoring serum lactate levels can be useful to evaluate the adequacy of tissue perfusion. Administration of red blood cells (RBC) is highly recommended in ECMO patients with low elevated serum lactate levels in the presence adequate ECMO flow rates [14].

Hematological Management

Close monitoring of the hematological status is necessary as exposition of blood to ECMO circuit surface triggers a massive inflammatory response leading to disbalance of procoagulant and anticoagulant components [34]. On one hand it induces the formation of blood clots whereas on the other hand it can also generate consumption of clotting factors, hemolysis, mechanical thrombocytopenia and fibrinolysis. Other causes of coagulopathy in patients on ECMO include heparinization as well as subsequent heparin- induced thrombocytopenia.

Transfusion of blood products (RBC, FFP, platelets) is strongly recommended in ECMO patients with active bleeding or severe coagulopathy in order to maintain parameters as described in

Table 2. Active fibrinolysis is the anteroom of disseminated intravascular coagulation, and therefore it is very important to detect and treat it in the shortest time possible [28]. It associates elevated serum D- dimer levels, a decrease in the maximum amplitude and an increase clot lysis appearance on the TEG. In these cases, early administration of tranexamic acid and fibrinogen or even recombinant factor VII a should be considered [35].

Transport to the Operating Room and Intra operative Management

Patients on ECMO are at high risk of developing severe bleeding and other complications, therefore surgical interventions should be delayed when possible.

Nevertheless, if patient requires intervention, appropriate vascular access and a fast access to blood products if necessary should be guaranteed. It is also very important to promote a good teamwork in order to minimise the potential risks during the patient's transfer to the operating room. Among these risks, accidental decannulation or kinking of the cannulae are the most feared ones. To prevent this, an appropriate sedation should be established and the perfusionist or ECMO specialist should make sure that an adequate ECMO support is maintained all over the transfer [14]. ECMO patient could be transported with or without the ventilator.

Intraoperative administration of inhalation anesthetic gases may not be reliable neither in VA nor VV ECMO patients, as blood flow totally or partially bypasses the lungs. This is the reason why intravenous anesthesia is the preferred induction agent in this group of patients[14].

Discontinuing ECMO Support

The risk of complications in patients with ECMO is directly correlated with the duration of therapy, making it necessary to wean from ECMO as soon as an improvement of cardiopulmonary function is noted. It usually takes a few days in patients on VA ECMO versus 1-2 weeks in patients with VV ECMO [28].

To ensure a successful decannulation (especially in borderline patients), a trial period of 30 minutes to 4 hours of clamping circuit and allowing recirculation is recommended. During this period, cannulae should be flushed periodically every 10 minutes to avoid thrombosis [36]. Strategies for discontinuing ECMO and predictors for successful weaning are summarized in Table 4.

Table 4: Timing and strategy for weaning from ECMO (Cardiac US; cardiac ultrasound; CXR: Chest X ray; FiO₂: fraction of inspired oxygen).

Types of ECMO	Optimal timing	Strategy	Predictors of success
V-A ECMO	Recovery of pulsatility (on the arterial waveform), improvement of ventricle function (on cardiac US), decrease of vasoactive/ inotropic doses	-Administration of heparin bolus (2000-5000 units) to prevent circuit clotting. -Gradual decrease of ECMO flows until 1-2 L/min and discontinue sweep gas flow	Maintenance of hemodynamic stability with inotropic support (below maximum doses)
V-V ECMO	Improvement of CXR images, static compliance and blood gas exchange	-Increase respiratory settings from resting to normal ranges	Satisfactory gas exchange and lung compliance on FiO ₂ <0.1

Arterial decannulation requires an open surgical procedure, whereas venous cannula can be removed outside the operating room, subsequently followed by manual compression for at least 20 minutes. Post-decannulation Doppler ultrasound of the lower limb should be performed to assess vascular flow and discard deep venous thrombosis.

COMPLICATIONS OF ECMO

ECMO is a highly specialized cardiopulmonary support device that is typically implemented in very sick patients. Therefore, recovery of these patients is commonly hampered by a wide number of complications [37,38]. Complications may arise from clinical inexperience, patient’s basal conditions or technical problems involving the ECMO circuit. The potential causes and recommended strategies to deal with these complications are included in Tables 5 and 6.

Table 5: Potential complications during ECMO support (Patient-related) (BP: Blood pressure, e.g.: for example; FiO₂: fraction of inspired oxygen; CRRT: Continuous renal replacement therapy).

Complication	Potential causes	Interventions
PATIENT- RELATED		
Bleeding	Excessive anticoagulation, ECMO/surgical- induced coagulopathy, invasive procedures, high BP	Administration of blood components, tranexamic acid, fibrinogen or a VII factor. Transient withdrawal of heparin infusion in severe cases. BP control. Surgical hemostasis.
Infection	Prolonged hospital stay, broad-spectrum antibiotics, prolonged vascular central access	Long-term use of antibiotics Vascular catheter replacement.
Hemolysis	Inadequate preload, obstructed cannula, high pump speed rates, appearance of blood clots in the ECMO circuit.	Adjust anticoagulation therapy. Fluid challenge administration. Decrease of pump speed rate. Release of cannula flow. Replacement of ECMO circuit.
Hypoxemia	Low ECMO circuit flow, low oxygenator FiO ₂ , recirculation, high oxygen consumption	Increase ECMO flow rate. Increase FiO ₂ in oxygenator. Increase of ventilation. Patient cooling. Muscle relaxants. Anemia correction.
Hypercarbia	Low sweep gas flow, low tidal volume	Increase sweep gas flow, increase ventilation.
AKI/liver dysfunction	Non-pulsatile ECMO perfusion, intravascular microembolization, sepsis, hypovolemia, nephrotoxic drug administration, hemodynamic instability.	Volume expansion, diuretics, CRRT
Neurological complications	Intracranial hemorrhage, acute cerebral stroke	Decompressive craniectomy, iv mannitol, cerebral protective measures, BP control.
Lower limb ischemia	Femoral artery cannulation	Femoral angioplasty.

Table 6: Potential complications during ECMO support (mechanical) (IABP: Intra-aortic balloon pump).

Complication	Potential causes	Interventions
ECMO MECHANICAL PROBLEMS		
Air embolism	Leaks within the ECMO system (connections, cannulation sites), sweep gas pressure exceeding tube blood pressures, large negative pressures achieved in the inflow cannula, cavitation	- Stop ECMO pump, clamp outflow cannula, place patient head down. - If embolus reaches the patient's arterial system: patient cooling, barbiturates, mannitol or steroids administration. - If embolus enters patient's venous system: remove clots by direct aspiration through the central venous central line
Blood clot formation	Insufficient anticoagulation therapy, low ECMO circuit flows	Increase anticoagulation doses, partial or total ECMO circuit or oxygenator replacement
Reduced blood flow (hemodynamic instability)	Intra-abdominal hypertension, decrease of ECMO preload (cardiac tamponade, cannula malposition, pneumothorax or hypovolemia), hypertension (if centrifugal pump)	Volume challenge, specific treatment for the underlying cause (e.g. decompressive laparotomy)
Pump failure	Electrical failure or pump head disengagement	- Clamp line and turn off or decrease pump speed - Increase ventilation and hemodynamic support - Re-insert pump head - Unclamp line and turn on pump
LV distension	Mitral and atrial regurgitation, severe left ventricle dysfunction	- Increase of pump blood flow, IABP, percutaneous atrial septostomy.

Patient-Related Complications

Bleeding is the most frequent complication related to ECMO support. Persistent coagulopathy in this group of patients promotes an increase in the risk of haemorrhage, particularly from cannulation and surgical sites. Less common but potentially more serious is the intracranial, intrathoracic or intra-abdominal spontaneous bleeding (including retroperitoneal). Bleeding episodes during or after ECMO support are associated with a poorer outcome and a higher rate of surgical interventions [14,28,39].

ECMO patients are also prone to develop nosocomial infections, among which the most common is the bloodstream infection [40]. In this specific group of population, early detection of infection can be difficult as there is a generalized presence of leucocytosis and fever is very rarely produced. Leucocytosis is an expression of the systemic inflammation triggered by exposure to the ECMO circuit response and hyperpyrexia is interfered as central blood temperature depends directly of the ECMO heat exchanger [14]. Besides, patients are prone to suffer heat dissipation because of multiple blood transfusions as well as an active circulation of blood outside the patient into the ECMO circuit. There fore if infection is suspected, it is highly recommended to administer broad-spectrum empiric antibiotics without delay until microbiological results are obtained [28].

In this group of patients, hypoxemia is defined as an arterial $\text{SaO}_2 < 85\%$ despite adequate ECMO circuit flow. Among all the potential causes of hypoxemia, significant recirculation involves

reinfusion of oxygenated blood is withdrawn through the inflow cannula bypassing the systemic circulation. It involves patients on VV ECMO exclusively, and can be easily identified by a combination of low SaO₂ and high oxygen saturation of blood in the inflow cannula.

Cerebral stroke and intracranial haemorrhage are the most feared neurological complications in patients on ECMO [41]. Their detection is interfered by the deep sedation and neuromuscular paralysis requirements of these patients. Transcutaneous cerebral oximetry may be a useful tool in these conditions, warning about inadequate cerebral perfusion seems when a drop of >25% in the baseline values is noted [14]. Severe thrombocytopenia and female have been demonstrated as independent risk factors for intracranial haemorrhage development [28].

The ECMO support generates non-pulsatile blood perfusion which is associated with organ dysfunction. This condition may involve acute renal and/or liver failure, seizures, gastrointestinal bleeding or perforation [42]. Local ischemic complications such as leg acute ischemia usually occur at the insertion of the arterial cannula from the ECMO system.

An increase in plasma free haemoglobin levels $\geq 50\text{mg/dL}$ is related to intravascular haemolysis. This complication clinically presents with dark brown urine, renal function impairment as well as an increase in serum potassium and lactate dehydrogenase levels.

Mechanical Complications

Complications related to the ECMO system, such as massive gas embolism or catastrophic blood loss caused by tubing rupture or disconnection, are rare but can be life threatening.

Blood clots formation may also generate problems within the ECMO system, such as mechanical line obstruction or membrane oxygenator failure. When significant amount of air or blood clots reach the patient's arterial vascular system, ischemic acute events occur in brain, kidney, liver, guts and extremities.

Patients on ECMO who associate left ventricle dysfunction can develop left ventricle distension, as a result of a retrograde ejection of systolic blood flow through left cardiac cavities. Aortic and mitral regurgitation are risk factors for developing this complication, which can result in pulmonary edema and potentially lethal pulmonary haemorrhage [14].

ECHOCARDIOGRAPHY FOR ECMO

Echocardiography for ECMO Therapy

Echocardiography has a very important role in managing patients supported with VA or VV ECMO circuit. It provides information for every single step in the management of the therapy including confirming indication, cannulas insertion, progressive monitoring, detection of complications, recovery evaluation and support weaning. For this reason, transthoracic echocardiography (TTE) and TEE should be available at every hospital performing ECMO for critically ill patients [43,44].

ECMO Indication and Technique

Echocardiography prior to ECMO insertion for selecting can be useful for selecting patients, setting indication and contraindications, choosing VV or VA therapy or determining the correct position for cannulae depending on the patient’s anatomy and pathology [44] (Table 7 and Figure 5).

Table 7: Use of echocardiography for patient and ECMO therapy selection (LV: Left Ventricle; RA: Right Atrium).

Avoiding the need for ECMO (excluding reversible pathology)	Cardiac tamponade			
	Undiagnosed cardiac valve pathology			
	LV dysfunction			
Setting contraindications	Aortic dissection			
	Significant aortic valve regurgitation			
Guiding cannulation	Severe aortic atherosclerotic disease	Site	Central	
		Technique	Peripheral	
	Surgical			
	Percutaneous			
	Right-heart anatomy evaluation for placing venous cannula in RA	Prominent patent foramen ovale		
		Atrial septal defect or septal aneurysm		
Prominent Chiari network				
Pacemaker or implantable cardioverter-defibrillator presence				
			Tricuspid valve pathology (stenosis or prosthesis impairment)	
Choosing between VV or VA ECMO	Cardiac function assesment			

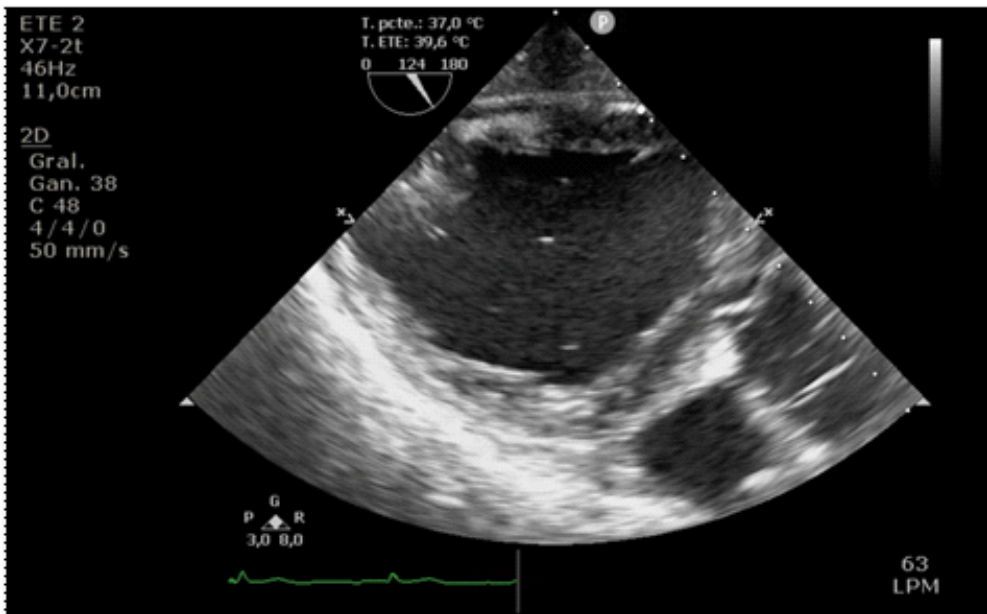


Figure 5: ECMO support indicated in a severe left ventricle dysfunction after extracorporeal circulation for mitral valve repair.

ECMO Initiation

To commence ECMO therapy, echocardiography is needed to guide the placement of the guidewires and cannulas, warranting adequate flows and avoiding thrombus and embolus formation. It can also determinate the degree of ventricular unloading to determine if therapy can be established [44] (Table 8).

Table 8: Use of echocardiography for cannula placement and ECMO therapy initiation.

Optimal percutaneous guidewires placement	Before cannula placement		
Optimal cannulas placement (adequate flows)	VV ECMO	• Access cannula	Proximal inferior vena cava
		• Return cannula	Mid right atrium, clear from interatrial septum and tricuspid valve
		• Avalon Elite cannula	Dual-lumen placed correctly
	VA ECMO	• Central	<ul style="list-style-type: none"> • Right atrium • Aorta
		• Peripheral	<ul style="list-style-type: none"> • Access cannula in the mid right atrium • Return cannula in contralateral femoral artery and tip in the iliac artery or abdominal aorta
Degree of ventricular unloading	Correct functioning		

Notice that abnormal sites are more frequent for venous cannulas and cannula should be delivered in time over the guide wire to avoid thrombus formation and pulmonary embolus. When return cannula needs to be placed, passing a synthetic graft through femoral or axillary artery, echocardiography is useful using flow orientation and velocity. Echocardiography can avoid recirculation in VV ECMO as it can notice that distance between the two cannulae is excessively short [44].

Response to ECMO Therapy monitoring

Echocardiography helps clinicians to evaluate the patient situation after ECMO support has been started. Alterations in hemodynamics can be studied related to cannulas location and LV function. Variations in preload and afterload depend on VA or VV ECMO support [44] (Table 9).

Table 9: Use of echocardiography for ECMO therapy response monitoring (LV: Left Ventricle; AV: Aortic Valve).

	Condition	Echocardiography
Peripheral VA ECMO	<ul style="list-style-type: none"> • < Preload (< blood flow) • > Afterload (pressurized return) • Severe LV dysfunction • Mitral regurgitation 	LV distension / echo-contrast AV not opening
Peripheral VV ECMO	<ul style="list-style-type: none"> • No changes in LV preload • > Mixed venous oxygen saturation • Oxygen delivery improvement 	Improved LV function

Notice that loss of pulsatility when AV ECMO does not open can lead to stasis and thrombosis. Strategies to avoid this situation include left heart venting, percutaneous balloon atrial septostomy, increasing anticoagulation, the use of inodilators to reduce afterload or finally a conversion to a VAD.

Detection of ECMO Complications

While ECMO dysfunction, echocardiography allows detection mechanical complications such as tamponade, thrombosis or obstruction of the vessels and cannula displacement [45] (Table 10 and Figure 6).

Table 10: Use of echocardiography for ECMO complications detection.

Tamponade	<ul style="list-style-type: none"> • Cardiac filling and function • Difficult to establish pericardial effusion significance o Heart partially bypassed • Hemodynamics not necessarily affected o If cannula flow is correct o Important in weaning from ECMO
Thrombosis and Vessel obstruction	<ul style="list-style-type: none"> • Superior vena cava syndrome or thrombosis not predictable • Thrombus retained after cannula removal o TTE recommended
Cannula displacement	<ul style="list-style-type: none"> • Detect that the cannula is not placed in the correct/initial site, and rectify it's position

Notice that TEE is usually required if TTE has spatial resolution limitations [44].

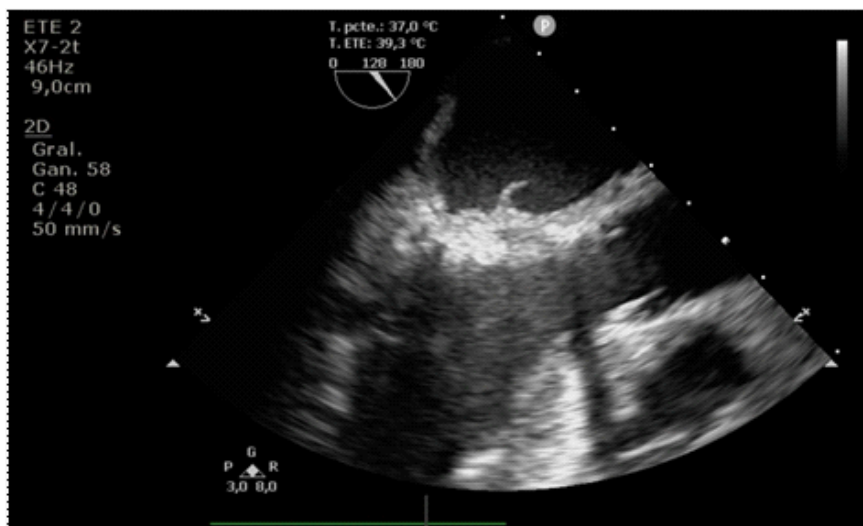


Figure 6: Risk of systemic embolism due to RA thrombosis with aortic valve opening in patient with VA ECMO therapy.

Weaning from ECMO when Patient has Recovered

Echocardiography has an important role to determine if patient is recovered and ready for the weaning from ECMO support, which is a complex process in terms of decision and timing [46]. Weaning can also be guided by a pulmonary artery catheter [47] (Table 11).

Table 11: Use of echocardiography for ECMO support weaning (LV: Left Ventricle).

Cardiac recovery	<ul style="list-style-type: none"> • LV ejection fraction 35-40% • LV outflow tract velocity-time integral > 10 cm • No LV dilatation • No cardiac tamponade
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Concerning hemodynamics, pulsatility on the arterial line tracing can suggest recovery, but recovery is also based in clinical and echocardiography findings. The use of a pulmonary artery catheter while a VA ECMO therapy can be unhelpful due to the fact a significant proportion of the circulating blood flow actually bypasses the pulmonary artery.

A common approach to wean is reducing the VA ECMO flows by 0.5 to 1.0 L/min increments and to assess the clinical, hemodynamic and echocardiographic parameters, never below 1 to 2 L/min, because of the risk for circuit thrombosis. For VV ECMO weaning is not necessary to decrease ECMO flow but it requires reduction of the gas flow through the ECMO circuit and conversion to conventional ventilation to assess oxygenation. For this reason echocardiography for patients weaning from VV ECMO is less useful compared to patients on VA ECMO.

CONCLUSION

The need for ECMO in adults has increased in the last few decades. Short courses of ECMO may allow critically ill patients to be salvaged, however the complications are not infrequent.

A programme based on multi-disciplinary experts with specialized professionals who are adequately trained and the use of echocardiography is increasingly important to improve the survival of patients supported with ECMO by decreasing the number of complications.

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