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Venoarterial Extracorporeal Membrane Oxygenation in Refractory Cardiogenic Shock and Cardiac Arrest

Marie-Eve Brunner , Carlo Banfi and Raphaël Giraud

Additional information is available at the end of the chapter

Abstract

The aim of this chapter is to discuss the indication and the role of a venoarterial extracorporeal membrane oxygenation (VA-ECMO) in the refractory cardiogenic shock and cardiac arrest.

Cardiogenic shock occurs in 5–10% of patients following acute myocardial infarction, and mortality remains high at 50–80% when using only medical treatment, while cardiac arrest has a poor prognosis, and despite conventional cardiopulmonary resuscitation maneuvers, only a few patients can fully return to a normal lifestyle.

VA-ECMO is a rapidly deployable temporary system for supporting the circulatory and respiratory systems. It allows time for reversible cardiac failure to recover and can prevent end-organ damage from hypoperfusion. Emergency VA-ECMO has been described for the treatment of refractory cardiogenic shock following acute myocardial infarction, electrical storm, myocarditis, and pulmonary embolism as well as in refractory cardiac arrest. VA-ECMO is used as bridge to decision to sustain life until a full clinical evaluation can be completed, as bridge to recovery until intrinsic cardiac function recovers, as bridge to candidacy to make an ineligible patient eligible for transplantation/LVAD, and sometimes as direct bridge to transplantation.

However, morbidity on VA-ECMO is rather high and has an impact on the outcome. Bleeding, lower limb ischemia, infections, and irreversible central nervous system damage still remain as serious complications.

After a few days of mechanical assistance, patients implanted with VA-ECMO for cardiogenic shock or cardiac arrest can sometimes be successfully weaned from the device, when they have partially or fully recovered from the condition that indicated ECMO use. Weaning parameters are discussed.

Finally, prognosis and survival of patients on VA-ECMO are discussed as well as the ethical aspects.

1. Introduction

Venoarterial extracorporeal membrane oxygenation (VA-ECMO) is a temporary technique for supporting the cardiac and the pulmonary system in patients suffering from refractory cardiogenic shock [1]. It allows time for reversible forms of cardiac failure to recover and can prevent end-organ damage from under perfusion.

Cardiogenic shock (CS) is defined as critical end-organ hypoperfusion due to low cardiac output and myocardial contractile dysfunction without hypovolemia [2]. CS has a broad spectrum from mild hypoperfusion to refractory CS. Experts' recommendations for the management of adult patients with cardiogenic shock from the French-Language Society of Intensive Care (Société de Réanimation de Langue Française), with the participation of the French Society of Anesthesia and Intensive Care, the French Cardiology Society, the French Emergency Medicine Society, and the French Society of Thoracic and Cardiovascular Surgery recommend the use of peripheral VA-ECMO if temporary circulatory support is needed with a strong agreement [3]. Five percent of patients with acute myocardial infarction (AMI) develop a CS, with high mortality rates [4]. Despite optimal maximal therapy such as inotropes, Vasoconstrictors, intra-aortic balloon pump (IAPB), revascularization techniques, and mechanical circulatory support, CS remains the most frequent source of hospital death ranging between 60 and 70% compared to patients with AMI without advanced CS which is about 10% [5]. Cardiac arrest (CA) is the main cause of sudden death and occurs in almost 22% of patients with AMI [6]. CA has obviously a poor prognosis, and only a small percentage of the patients can return to a normal lifestyle. The principal causes for very poor outcome and prognosis in CA are an absence of return of spontaneous circulation (ROSC), long CPR, hypoxic encephalopathy, and out-of-hospital CA. In both refractory CS and CA following AMI, which are very critical circumstances, VA-ECMO has been proposed and utilized during the last decades to obtain rapid resuscitation, stabilization, and subsequent triage to bridge treatment. ECMO has remarkably progressed over the recent years; it became an invaluable tool in the care of adults with severe CS refractory to conventional management [7, 8].

The aim of this chapter is to describe VA-ECMO techniques, the more recent indications, and results in the use of the VA-ECMO in patients with refractory CS and CA.

2. ECMO techniques in CS and CA

VA-ECMO drains blood from the vascular system, which circulates outside the body by a mechanical pump, and is then re-infused into the circulation. In the circuit, hemoglobin

becomes fully saturated with O_2, and CO_2 is removed. Oxygenation is determined by flow rate, and CO_2 elimination can be controlled by adjusting the rate of countercurrent gas flow through the oxygenator.
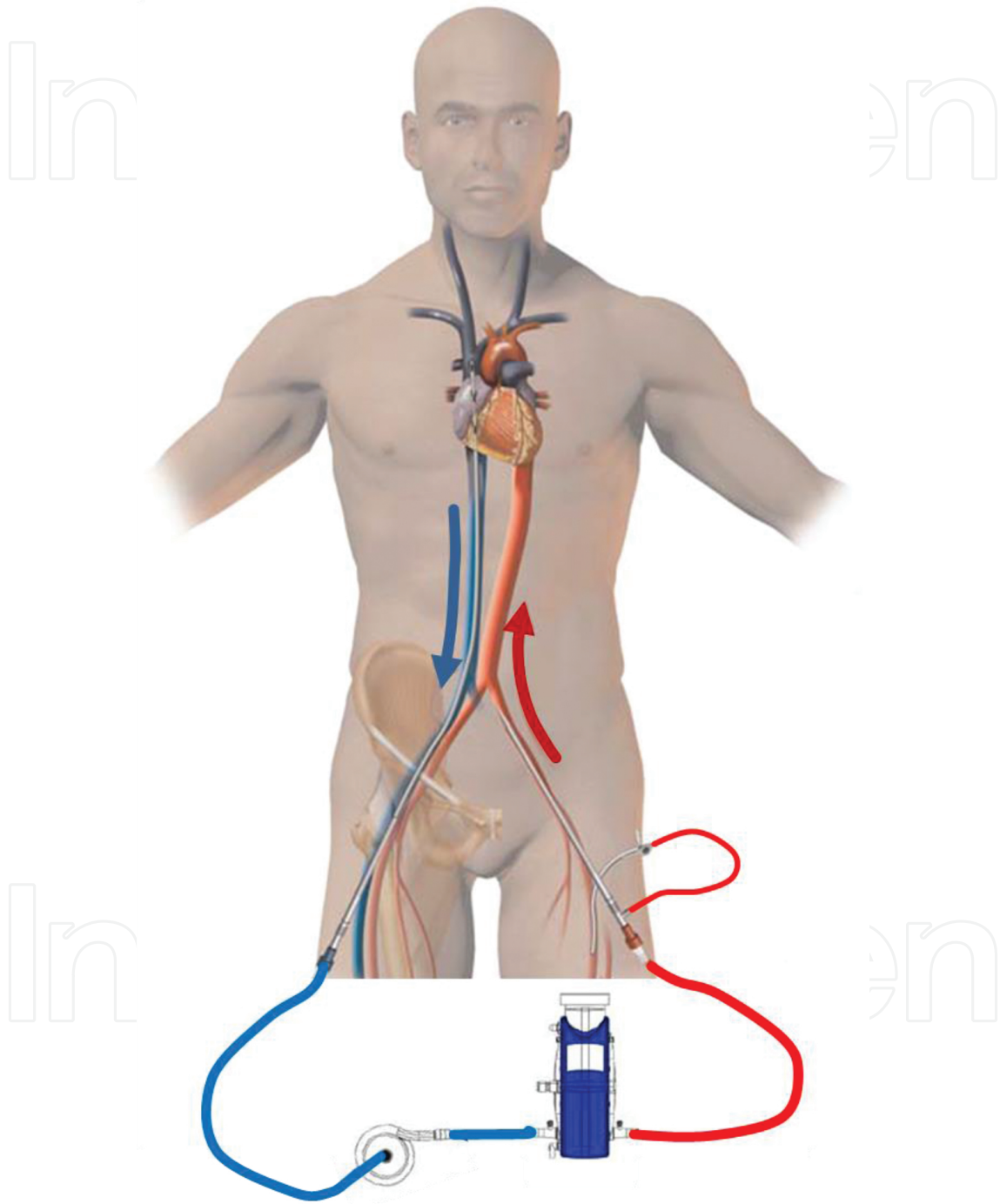

Figure 1. Percutaneous femoro-femoral VA-ECMO cannulation.

In CS and CA, where the cardiac circulation needs to be supported, a venoarterial configuration is required. This system includes a membrane oxygenator and a centrifugal pump to supply

up to 5 L/min of support. VA-ECMO can be performed either peripherally or centrally. In peripheral VA-ECMO, a venous cannula is inserted via the femoral vein to the right atrium for drainage and an arterial cannula is inserted via the femoral artery into the ascending aorta for perfusion [9] (**Figure 1**).

Peripheral VA-ECMO cannulation can be performed both surgically by semi-Seldinger cut down and percutaneously. Intensive care physicians, interventional cardiologists, and obviously cardiac surgeons can perform the percutaneous technique whereas only cardio-thoracic surgeons can perform central VA-ECMO [10].

3. Indications

There are a number of emergency indications. CS can occur in previously healthy patients or patients with chronic cardiac failure and with acute decompensation.

Refractory CS can take place after a myocardial infarction [11], any cardiomyopathy [12], a fulminant myocarditis [13, 14], intoxication with cardiotoxic drugs, electrical storm [15, 16], valvular insufficiency, massive pulmonary embolism [17], or CA with certain conditions.

Post cardiotomy CS (PCCS) can also occur after a cardiac surgery (heart transplantation for example) when it is not possible to wean from bypass [18].

Four types of situations can be described and are resumed in **Table 1**: bridge to decision, bridge to recovery, bridge to candidacy , and bridge to transplantation.

Bridge to decision (BTD)	Use of VA-ECMO in patients with drug-refractory acute circulatory collapse and at immediate risk of death to sustain life until a full clinical evaluation can be completed and additional therapeutic options can be evaluated.
Bridge to recovery (BTR)	Use of VA-ECMO to keep patient alive until intrinsic cardiac function recovers sufficiently to remove VA-ECMO.
Bridge to candidacy (BTC)	Use of VA-ECMO to improve end-organ function in order to make an ineligible patient eligible for transplantation/LVAD.
Bridge to transplantation (BTT)	Use of VA-ECMO to keep a patient at high risk of death before transplantation alive until a donor organ becomes available.

Table 1. VA-ECMO: Types of situations.

Before VA-ECMO implantation, we should have several considerations. First of all, the likelihood of organ recovery has to be weighted. Initiation of VA-ECMO is appropriate only if the organ failure is thought to be reversible. When recovery is not expected, others options as transplantation or long term assist device as bridge to transplant versus destination therapy may be considered. The place of VA-ECMO in CS is shown in **Figure 2**.
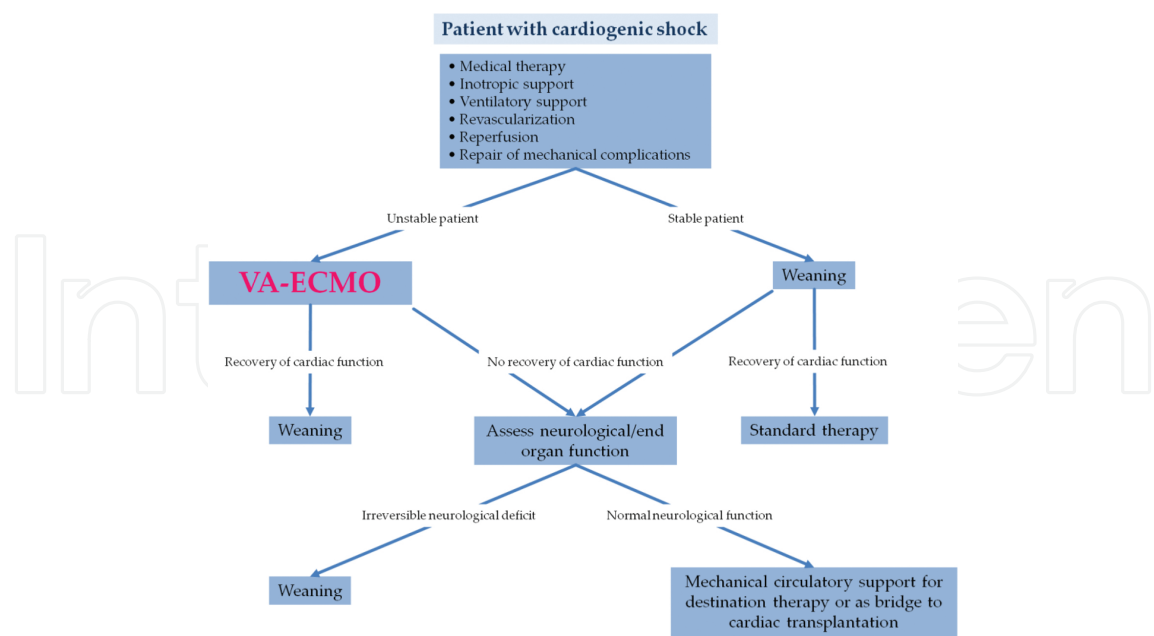
Figure 2. Place of VA-ECMO in CS.

Cardiogenic shock / Severe cardiac failure due to almost any cause	Myocardialinfarction
	Cardiacarrhythmicstorm refractory to other measures
	Fulminant myocarditis
	Massive pulmonary embolisms
	Drug overdose/toxicity with profound cardiac depression
	Septic cardiomyopathy
Post-cardiotomy	Inability to wean from cardiopulmonary bypass after cardiac surgery
Post heart transplant	Primary graft failure after heart or heart-lung transplantation
Refractory cardiac arrest (No ROSC despite 30 min of optimal CPR)	Indications: • Age < 65 years • First rhythm: "shockable" rhythm • No flow ≤ 5 min • Witnessed cardiac arrest • $EtCO_2$ per CPR > 10 mmHg • Time to ECMO < 60–90 min

Table 2. Main VA-ECMO indications for cardiogenic shock and cardiac arrest.

Advanced age, severe brain injury, long time cardiac arrest, disseminated malignancy are considered as contraindications to the institution of VA-ECMO. Finally, aortic insufficiency or aortic dissection are both major contraindications.

Indications for VA-ECMO are resumed in **Table 2**.

Clinical and biological signs as well as therapeutic measures leading to VA-ECMO implantations in cardiogenic shock are resumed in **Table 3**.

Clinical and biological signs	Therapeutic measures
SBP < 90 mmHg OR MAP < 60 mmHg	Fluid for optimal preload
	Vasoactive drugs (first choice: norepinephrine)
CI <2.2 l/min/m^2	Inotropes (first choice: dobutamine)
S(c)vO$_2$ < 50%	IABP
LVEF < 20%	
VTI < 10 cm	
SaO$_2$ < 92%	Mechanical ventilation + sedation
Urine output < 30 ml/h	
Malignant arrhythmia	IV Loading of amiodarone and/or lidocaïne
	External electric shock
If despite these measures lactate levels significantly still increase within 2 hours	
→ Consider VA-ECMO implantation	

SBP: Systolic blood pressure, MAP: Mean arterial blood pressure, Cl: Cardiac index, S(c)vO2: Mixed/central venous saturation, LVEF: Left ventricular ejection fraction, VTI: Velocity time integral, SaO2: Arterial oxygen saturation, IABP: Intra aortic balloon pump.

Table 3. Clinical and biological signs of cardiogenic shock as well as therapeutic measures leading to VA-ECMO implantations.

A. Refractory CS post myocardial infarction

Refractory CS post myocardial infarction is the main cause of death in hospitalized patients with acute myocardial infarction. It occurs in 5–10% of patients [19]. The use of early PCI in those patients was associated with improved survival [11]. No randomized controlled trials compare VA-ECMO with other mechanical supports, but non-randomized studies show a survival benefit with the early use of VA-ECMO. One study tested the hypothesis that early ECMO offered additional benefits in improving 30-day survival in patients with acute myocardial infarction complicated by profound CS undergoing primary percutaneous coronary intervention. The VA-ECMO group had a significantly lower 30-day mortality (39.1% versus 72%, p=0.008). This study was limited by the fact that the two cohorts were enrolled in two different periods (Non-VA-ECMO Group: 1993–2002, versus VA-ECMO group: 2002–2009) and also because coronary stents were unavailable until 1998 [20]. To date, only case reports or case series showed a benefit in implanting VA-ECMO in refractory cardiogenic

shock. It appears essential to implant VA-ECMO before multiorgan failure but no defined criteria are yet available to decide exactly when the device should be implanted. Randomized controlled trials are needed to determine if there is a true benefit in the use of VA-ECMO in CS post myocardial infarction to determine if early VA-ECMO in conjunction with optimal medical treatment would improve clinical outcomes at 30 days as compared with optimal medical treatment alone.

B. Electrical storm induced CS

In electrical storm induced CS, appropriate and timely VA-ECMO support helps to maintain and preserve vital organ perfusion. The period of stability offered by VA-ECMO support can allow optimization of anti-arrhythmic medication particularly the use of anti-arrhythmic agents most of whom have profound negative inotropic and hypotensive effects, and prevents left ventricular dilation [15]. It also prevents the low flow syndrome and multi-organ failure. VA-ECMO implantation should be considered early when conventional maneuvers fail to control the cardiac rhythm [21]. Early-onset VA-ECMO support may be lifesaving and should be considered in the management of hemodynamically unstable arrhythmias when conventional therapy fails to convert refractory ventricular tachycardia [16, 22]. While recommendations for VA-ECMO to handle refractory ventricular tachycardia remain to be set, success in using VA-ECMO in this case rely upon the correct selection of patients in the emergency department, and the prompt implantation before multiple organ failure occurs. Prompt institution of VA-ECMO support achieves the best outcome [21].

C. Fulminant myocarditis

Fulminant myocarditis is a non-ischemic, clinical manifestation of cardiac inflammation with rapid onset and severe hemodynamic compromise. Infective etiologic process is usually the most frequent finding. Inotropic therapy and intra-aortic balloon pump might not be sufficient to treat the pump failure. VA-ECMO support may be required to provide time to enhance heart recovery in this normally self-limiting disease. A recent 5-Year Multi-Institutional Experience showed a VA-ECMO weaning rate of 81% and discharge rate of 72% in the overall patient population [13]. Mirabel et al. shows that patients with fulminant myocarditis, who would have died without emergent initiation of circulatory support, had favorable short- and long-term outcomes with 68% hospital survivors and 46% partial or complete native heart function recovery [14]. In both studies, VA-ECMO implantations were performed when maximal medical therapy failed to improve hemodynamic status. In the study of Lorusso et al., pre-ECMO patient characteristics showed a systolic blood pressure at 61.8 ± 30.4 mmHg, pH at 7.2 ± 0.1 and lactate levels at 12.0 ± 4.6 mmol/L, corresponding to severe cardiogenic shock states [13].

D. Massive pulmonary embolism

A pulmonary embolism (PE) is a common illness that can cause death [23]. Massive acute PE (MAPE) results in CA in 41% of cases and is associated with a high mortality rate [24, 25]. Clinical practice guidelines recommend fibrinolytic therapy for patients with MAPE and CA,

although few data are available to guide decisions about the agent, dose, rate, and frequency of administration [26, 27]. Fibrinolysis offers a rapid onset of action and ease of administration, and it is readily available in most hospital settings. The use of fibrinolysis during CPR in patients with presumed pulmonary embolism may improve survival [28, 29]. Fibrinolytic therapy is the first-line treatment in patients with high-risk pulmonary embolism presenting with CS in absence of contraindications. However, in several cases, there are absolute contra-indications for this therapy. Catheter-based intervention is recommended for patients with circulatory collapse due to MAPE and is equivalent to surgical embolectomy [30]. Emergent VA-ECMO provides an opportunity for improving the prognosis of an otherwise near-fatal condition and should be considered in the algorithm for managing MAPE in an unstable patient [31]. The survival rate in patients with MAPE who receive VA-ECMO and anticoagu-lation or surgical embolectomy was 62% [31]. Thus, ECMO can provide lifesaving hemody-namic and respiratory support in critically ill patients with MAPE in patients hemodynamically unstable to support any other interventions or have not responded to medical therapies. Success in ECMO for MAPE is determined by the return of sufficient RV function [32]. ECMO may be considered in early management of patients with MAPE unre-sponsive or contraindicated to pharmacological treatment [33].

E. Pulmonary arterial hypertension

In addition, VA-ECMO is also a supportive option for patients with decompensated pulmo-nary arterial hypertension. In fact, pulmonary arterial hypertension is associated with high morbidity and mortality, particularly in patients with progressive RV failure. In this case, VA-ECMO can be used as a bridge to lung transplant or bridge to recovery when medical therapy is not sufficient to prevent cardiopulmonary failure in the acute setting [34].

F. Post-cardiotomy CS

Post-cardiotomy CS (PCCS) is very rare, but is a lethal complication in post cardiac surgery. PCCS occurs in 2–6% of patients undergoing surgical revascularization or valvular surgery [35, 36]. Approximately 0.5–1.5% of patients is refractory to maximal inotropic and intra-aortic balloon pump (IABP) support [37]. Post-cardiotomy CS occurs in perioperative cardiac surgery in patients with normal preoperative myocardial function as well as those with pre-existing impaired function [38]. Refractory PCCS leads rapidly to multi-organ dysfunction and is nearly always fatal without the use of advanced mechanical circulatory support [35]. VA-ECMO is used to salvage patients who develop refractory PCCS [39]. However, even if outcomes in patients requiring such support for PCCS continue to be poor [40], VA-ECMO may be used as temporary post-operative cardiovascular support.

G. Primary graft failure

Primary graft failure (PGF) after heart transplantation is a detrimental complication, and carries high morbidity and mortality. In a study involving 114 consecutive patients receiving orthotopic heart transplantation, 18 (15.7%) developed PGF requiring VA-ECMO support. Thirteen patients (72.2%) were able to be weaned from the support, and eight of them (44%)

were discharged [41]. Thus, as in PGF recovery is usually more frequent than in other cases of PCCS, due to the more probable reversibility of the damage, ECMO support could be used as bridge to graft recovery [42, 43].

H. Septic cardiomyopathy

Septic cardiomyopathy occurs with severe myocardial depression in septic shock. In a retrospective observational study, 14 patients with septic shock refractory to conventional treatment all had a severe myocardial dysfunction at VA-ECMO implantation. Mean LV ejection fraction (LVEF) was 16% and cardiac index was 1.3 L/min/m^2 in these patients. At ECMO implantation, mean pH was 7.16 and blood lactate was 9 mmol/L. Twelve patients were weaned off VA-ECMO. Ten patients survived after a follow-up of 13 months and recover a normal LVEF [44]. VA-ECMO may provide benefit to patients with a cardiac failure in the setting of a septic shock, but larger studies are needed.

I. Refractory cardiac arrest

Increasing number of papers has reported encouraging results on the use of VA-ECMO for refractory CA. Extracorporeal circulation ensures an adequate blood flow, time to perform diagnostic and therapeutic interventions even before a return of spontaneous circulation is achieved [43]. For patients with whom conventional advanced life support maneuvers are insufficient and/ or to make specific interventions possible (e.g., coronary angiography and percutaneous coronary intervention (PCI) or pulmonary embolectomy for MAPE), extracorporeal CPR (eCPR) has to be considered as a lifesaving therapy [45]. This practice is evolving and is used for both in-hospital (IHCA) and out-of-hospital (OHCA) CA despite few observational statistics. Observational studies suggest that eCPR for CA is correlated with enhanced survival [46] in case of reversible cause of CA, few comorbidity, witnessed CA, immediate high-quality CPR, and eCPR early implanted (e.g., within 1 h of CA) as well as when VA-ECMO is implanted by emergency physicians and intensivists [47–50]. eCPR involves significant resource and training. It has been correlated with enhanced survival after IHCA in selected patients [47, 51] when compared with manual or mechanical CPR. After OHCA, survival after eCPR is less favorable [52]. However, when deployed during and/or soon after resuscitation attempts, despite variations in practice and heterogeneity of outcomes, these interventions yield a good neurological survival in 12% of adults suffering a refractory OHCA [53]. In a retrospective observational study dividing CA patients in two groups (shockable rhythm and non-shockable rhythm), the authors found that non-shockable rhythms could be considered as a formal contraindication allowing a concentration of efforts on the shockable rhythms, where the chances of success are substantial. They conclude that VA-ECMO for refractory OHCA should be limited due to a very poor neurological outcome [54]. Indications for eCPR are detailed in **Table 2**. However, there is an urgent need for randomized studies of eCPR and large eCPR registries to identify the circumstances in which it works best, establish guidelines for its use and identify the benefits, costs and risks of eCPR.

4. Complications

Not surprisingly, VA-ECMO is associated with a lot of possible complications that can be lethal. This is why VA-ECMO must be done by well-trained teams in reference centers.

The most common complications listed with the use of VA-ECMO are: major or significant bleeding, re-thoracotomy for bleeding or tamponade, vascular complications as lower limb ischemia, lower limb ischemia requiring fasciotomy or compartment syndrome, lower extremity ischemia requiring amputation, neurologic complications like stroke, acute kidney injury requiring renal replacement therapy, and significant infection.

A. Bleeding

In a recent meta-analyze, 20 studies were analyzed including 1866 patients. Bleeding was the most frequent complications with an estimated rate of 41%. The most frequent source of hemorrhage is the femoral cannula insertion site [55]. In central ECMO, the rate of re-thora-cotomy for bleeding or tamponade was 42%. The average number of units of packed red blood cells transfused ranged from 12.7 to 29.0 units. Indeed, bleeding, thrombosis, and hemolysis remain the most common causes of morbidity and mortality for patients receiving ECMO therapy. These adverse effects have to be considered and should be monitored during ECMO therapy. Apart from surgical hemostasis problems, coagulation and inflammatory systems are immediately activated when blood comes in contact with the ECMO circuit, which necessitates systemic anticoagulation [56]. In a recent single center prospective randomized study on adult patients requiring ECMO therapy, hemostasis, anticoagulation, hemolysis, and inflammatory parameters were monitored. The results showed that median platelet count had dropped, prothrombin fragment 1.2, thrombin-antithrombin complex, and D-dimers increased, whereas fibrinogen values dropped [57]. However, antithrombotic therapy is necessary to maintain patency with the ECMO circuit and ultimately reduce the risk of clotting while decreasing the probability of hemorrhage. Currently, the most commonly used antithrombotic therapy is systemic anticoagulation with unfractionated heparin, which is associated with its well-known complications inclusive of bleeding (patient) and clotting (circuit). Systemic anticoagulation complications in ECMO support have not really reduced despite developments in technology and monitoring methods over the last few years.

Moreover, bleeding and thrombosis comprise majority of all side effects that can occur on ECMO, and the inability to mediate and control this effectively can lead to catastrophic complications and increases mortality. Heparin monitoring is very challenging on ECMO. There are actually no universal protocols concerning anticoagulation management; however, some centers propose to target 45–60 s for aPTT and 0.2–0.3 IU/ml for heparinemia (anti-Xa activity) [58]. Hemoglobin threshold for red cell transfusion should be 7–8 g/dl and only severe thrombocytopenia complicated by bleeding should be corrected. There is no single test that correctly monitors all of the factors influencing the anticoagulation, including the heparinization. As a result, over time and experience, a variety of tests are used. More recently, the Extracorporeal Life Support Organization (ELSO) proposed guidelines for management of the anticoagulation with ECMO. The main parameters monitored during ECMO are the activated

coagulation time (ACT), the antifactor Xa assay (anti-Xa), and the activated partial thromboplastin time (aPTT). More recently, the thromboelastography (TEG) or the thromboelastometry (ROTEM) have been introduced to monitor ECMO patients. These tests add information about the phases of coagulation, platelet function, and fibrinolysis, which is very relevant in ECMO patients as they have coagulation abnormalities. While many centers have integrated those tests into their ECMO anticoagulation guidelines, more research is needed to understand the place of TEG and ROTEM monitoring in ECMO patients [59].

B. Vascular complications

Vascular issues are the second more frequent complication. The cumulative rate of lower extremity ischemia is around 17%. The cumulative rate of lower extremity fasciotomy or compartment syndrome is around 10%. The cumulative rate of lower extremity amputation occurs to 7 of 192 (5%) [60]. In another retrospective study, statistics of 100 patients with VA-ECMO inserted via percutaneous femoral approach for CS or refractory CA were examined. A 7-9 Fr percutaneous reperfusion catheter, distal to the arterial cannula, was positioned into the artery, if the leg showed sign of under-perfusion. Thirty patients with early ischemia benefited from a reperfusion cannula to improve perfusion of the limb and it succeeded in 26 of them. Seven patients suffered a compartment syndrome of the leg necessitating urgent fasciotomy. In two of those patients, the ischemia moved to irreversible ischemia necessitating amputation of the limb. The authors concluded that the majority of ischemic episodes were resolved with the insertion of a distal perfusion catheter. They did not observe any mortal vascular complication, nor was any of the observed complications related to increased mortality [61]. However, in another recent study, 84 peripheral VA-ECMO patients were separated into two groups depending on the presence of major vascular complications, defined as patients who required surgical intervention. The authors found that vascular complications negatively affect survival in patients receiving VA-ECMO support by means of femoral cannulation and that distal perfusion catheter can decrease the incidence of complications [62].

C. Hemolysis

Hemolysis during ECMO therapy remains of concern with a reported incidence between 5 and 18% [63–65]. Major contributors are technical-induced hemolysis that may consist of sub lethal damage to erythrocytes by shear stress, high ECMO blood flow particularly high flow velocity through small cannulas, cavitation particularly in case of hypovolemia, pressure changes within the oxygenator particularly in case of fibrin/thrombosis upon the membrane [66–72]. Free plasma hemoglobin (fHb) and lactate dehydrogenase can increase significantly during ECMO support [73, 74] because of red blood cell (RBC) destruction. fHb is cytotoxic causing cell necrosis [73, 75]. It also scavenges nitric oxide, leading to vasoconstriction, endothelial dysfunction, and platelet aggregation [76, 77]. Consequently, renal insufficiency or multiple organ failure can appear [78–80]. Then, prevention and rapid identification of hemolysis are crucial for ECMO patients.

D. Neurological complications

Neurological complications are rather common in patients on VA-ECMO [81]. These complications are generally related to thrombosis with cerebral infarction and intracranial hemorrhage [82]. Intracranial hemorrhage (ICH) in particular has been associated with higher rates of mortality [83]. A review on a large, multihospital database, the Nationwide Inpatient Sample of the Healthcare Cost and Utilization Project of the Agency for Healthcare Research and Quality reviewed patients between 2001–2011 receiving ECMO [84]. The authors showed that 10.9% suffered from neurological complications including seizure (4.1%), stroke (4.1%), and intracranial hemorrhage (3.6%). The outcome between seizure patients and patients without neurological complications did not differ. Patients with stroke or hemorrhage have a higher hospital length of stay, higher probability of discharge to a long-term facility, and patient who suffered of intracranial hemorrhage have a higher mortality rate. More research is still needed to prevent neurologic complications.

E. Infections

The ELSO registry found an overall prevalence of infection of 11.7%, ranging from 7.6% in neonates to 20.9% in adults, with little variation during the 11-year span of the registry data [85]. An increased rate of death was found in patients who acquired infection during VA-ECMO. Bloodstream infections were predominant in most studies that reported the site of infection, followed by surgical site infections, urinary tract infections, and respiratory tract infections [86]. A fungal infection developed in 12% of patients, with surgical site infections reported most commonly [87]. Currently, the ELSO Infectious Disease Task Force does not recommend routine antimicrobial prophylaxis during ECMO. This is confirmed by a recent review stating that there is no evidence to defend prophylactic antibiotics in most patients, even if infections during ECMO are serious complications. Infections should be prevented [86].

F. Refractory pulmonary edema

In case of peripheral VA-ECMO for refractory CS, patients with very low residual cardiac contractility and elevated afterload due to the ECMO can lead to an inadequate decompression of the left ventricle resulting in a refractory pulmonary edema, fatal pulmonary hemorrhage, and left ventricle (LV) clotting [88]. Various methods for left heart decompression are known, but there is no consensus about the appropriate method and timing of decompression. However, in this situation, the first therapeutic measures are the introduction of inotropic drugs associated with an intra-aortic balloon pump to help increase LV contractility allowing the opening of aortic valve, to decrease left ventricular afterload, and thus to unload the LV. Minimally invasive strategies such as percutaneous transseptal left atrial decompression [89] and subxiphoid surgical approaches to drain the left ventricle [90] have been described to reduce LV distension. The residual atrial defect may require correction once the patient has been weaned from mechanical support. Use of a percutaneously inserted VAD (Impella™; Abiomed, Aachen, Germany) to decompress the left ventricle has also been reported in this setting [91], alleviating the need for a high-risk septostomy or surgical venting. However, in

some circumstances depending of the patient's state and local resources, central cannulation with left ventricular decompression may be indicated [92].

G. Harlequin syndrome

Harlequin syndrome is a hypoxemia of the upper body due to a competition of the VA-ECMO flow with the systolic function of the native heart. In a femoro-femoral VA-ECMO, when the heart function recovers, there is a competition between VA-ECMO flow and native cardiac flow in the aorta. In case of significant impairment of pulmonary gas exchange leading to an upper body hypoxemia, despite optimization of the ventilator settings, ECMO configuration has to be adapted. VA ECMO flows can be increased in an attempt to better perfuse the aortic root with retrograde arterialized blood. In addition, the arterial outflow cannulation site can be switched from the femoral artery to the axillary or carotid artery. As they are in closer proximity to the aortic arch, these cannulation sites may be more effective in washing the root with oxygenated blood. However, cannulation of these smaller vessels will require a smaller cannula, which will decrease the maximum achievable flows. A VA-V-ECMO circuit can also be created where a portion of arterialized blood from the arterial outflow cannula is diverted via the right internal jugular artery to the right heart. This enriches the blood traveling through the pulmonary circulation and to the left ventricle to provide better oxygen delivery to the coronary and cerebral circulations. Finally, if cardiac function has recovered sufficiently, VA-ECMO can be converted to VV-ECMO to provide only gas exchange support until the lungs fully recover its function [93].

5. Weaning

After a few days of mechanical assistance, patients implanted with VA-ECMO for CS or CA can sometimes be successfully weaned from the device, when they have partially or fully recovered from the condition that indicated ECMO use. Hemodynamic parameters such as invasive arterial pressure and heart rate, intravenous inotropes and vasoactive drugs, blood lactate and blood gas analyses should be monitored. A daily echocardiography should be performed and those criterions are evaluated: LVEF; aortic time–velocity integral (VTI); transmitral early peak (E) and late diastolic velocities; spectral tissue Doppler lateral mitral annulus peak systolic (TDSa); and early diastolic (Ea) annular velocities. LV filling pressures are estimated with the E/Ea ratio. First of all, the patient has to be considered as hemodynamically stable: baseline MAP > 60 mmHg with no or low-dose vasoactive agents and a pulsatile arterial waveform present for at least 24 h, and no compromising of the pulmonary blood oxygenation. Only in these conditions, an ECMO weaning trial can be attempted. ECMO flow is gradually reduced to 66% for 10–15 min, then to 33% and/or to a minimum of 1–1.5 L/min for another 10–15 min. If the patient begins to present hemodynamical instability (MAP dropped under 60 mmHg), the trial is stopped, and ECMO flow has to return to the initial flow. In a study upon 51 patients, the authors assessed a weaning strategy following support for refractory CS to recognize clinical, hemodynamic, and Doppler echocardiography parameters predictive for efficacious ECMO removal. Patients who were considered as hemody-

namically stable underwent ECMO flow decrease trials to <1.5 L/min under clinical and Doppler echocardiography monitoring. Patients with partially or fully recovery from severe cardiac failure, weaning trial tolerance, LVEF >20–25% and VTI >10 cm under minimal ECMO support, had ECMO support removed. In this study, 38 patients endured the weaning trial and 20 were finally weaned of the ECMO support.

This study showed that echocardiographic parameters determine weaned and non-weaned patients more than all other factors examined. The authors concluded that patients who tolerate a full ECMO weaning trial and have aortic VTI ≥10 cm, LVEF >20–25%, and TDSa ≥6 cm/s at minimal ECMO flow can be weaned [94].

6. Predictors of survival and outcome

Survival after VA-ECMO for refractory CS depends on etiology and severity of the patient at the implantation of the VA-ECMO support.

Mirabel et al. described factors associated with unfavorable outcomes in myocarditis related CS as higher body mass index; severe comorbidity; ICU admission Simplified Acute Physiology Score II, Sepsis-Related Organ Failure Assessment, and Glasgow Coma Scale; VA-ECMO placed under cardiopulmonary resuscitation; elevated sodium, troponin Ic and blood lactate; and low hematocrit and arterial pH [14].

Health-related quality of life was also evaluated in those survivors and revealed persistent difficulties with work or other daily activities. Mental health and vitality were deemed satisfactory. Severe anxiety, depression, and PTSD symptoms were reported by 27–38% of the patients after a median follow-up of 18 months.

Despite the high number of refractory CS requiring VA-ECMO, predictive survival modeling has not been reported till 2015 with the SAVE Score: Predicting survival after VA-ECMO for refractory CS [95]. Using a large international cohort of 3846 patients treated with VA-ECMO for CS (Extracorporeal Life Support Organization: ELSO), prognostic factors were identified for hospital survival and created a well-calibrated and reasonably discriminatory in-hospital survival prediction score comprising 13 pre-VA-ECMO variables. Parameters are Acute CS diagnosis group (myocarditis, arrhythmias, post heart of lung transplantation, congenital heart disease or others diagnoses leading to refractory CS), age, weight, acute pre-VA-ECMO organ failure, chronic renal failure, and time of intubation before VA-ECMO implantation. All of them determine a 5-class survival risk with survival rate. A SAVE-score of zero is approximately equivalent to 50% survival with positive scores representing higher chances of survival [95].

While inappropriate VA-ECMO use raises resource utilization and hospital costs and is associated with unacceptably high mortality, early identification of mortality risk factors and detailed analyses of survivors' long-term outcomes are needed. A two-center retrospective study was designed to identify pre-ECMO factors associated with in-ICU death and then

derive a practical mortality risk score that might help physicians to select appropriate acute myocardial infarction (AMI) patients for VA-ECMO.

A study concerning 138 ECMO supporting AMI patients analyzed long-term survivors' health-related quality of life (HRQOL) and frequencies of anxiety, depression, and post-traumatic stress disorder (PTSD). The survivors were evaluated for HRQOL, psychological and PTSD status 6 months after discharge of ICU. This study showed that nearly 50% of all patients were still alive. The authors developed the ENCOURAGE score on the basis of multivariable logistic regression analyses including seven pre-ECMO parameters: age >60, female sex, body mass index >25 kg/m2, Glasgow coma score < 6, creatinine >150 μmol/L, lactate (<2, 2–8, or >8 mmol/L), and prothrombin activity < 50%. Six months after ECMO, probabilities of survival were 80, 58, 25, 20, and 7% for ENCOURAGE score classes 0–12, 13–18, 19–22, 23–27, and ≥ 28, respectively. The ENCOURAGE score ROC AUC (0.84) was significantly better than those of the SAVE, SAPS II, and SOFA scores. Survivors' HRQOL evaluated after median follow-up of 32 months revealed satisfactory mental health but persistent physical and emotional related difficulties, with 34% anxiety, 20% depression, and 5% PTSD symptoms reported. The authors concluded that the ENCOURAGE score might be a useful tool to predict mortality of severe CS in AMI patients who received VA-ECMO. However, it now needs prospective validation on other populations than AMI patients [96].

Prognosis is quite different regarding refractory CA patients. Early VA-ECMO implantation has been shown to give a better outcome in patient with CA. Low flow longer than 90 minutes offers a very bad prognosis [47].

In 2008, a French group proposed recommendations to limit the VA-ECMO implantation in case of refractory CA [97]. Our local ECMO alarms criteria for refractory cardiac arrest are shown in **Table 4**. Patients are evaluated according to these criteria by a multidisciplinary team including emergency physicians, intensivists, anesthesiologists, cardiologists, and cardiac surgeons. A consensual decision to implant a VA-ECMO or not is taken.

ECMO alarm criteria	
Indications	**Contraindications**
No-flow ≤ 3 min	No-flow > 5 min
OR immediate CPR by professional **OR** signs of life per CPR **OR** hypothermia	
Age ≤ 65 years	Obvious sign of death
First rhythm ≠ asystole	Comorbidities +++ → Futility
EtCO$_2$ ≥ 10 mmHg (≥ 1.3 kPa) under CPR	Time from cardiac arrest to ECMO > 100 min
Projected arrival at the hospital ≤ 60 min	

Table 4. E-CPR Geneva University Hospitals: refractory cardiac arrest algorithm (CPR ≥ 30 min).

Finally, some papers are now published about the ethical dimension of ECMO support [98]. In fact, ECMO technology now allows prolonged support with decreased complications, and

the need of early implantation, have led to a significant increase in the use of ECMO worldwide. This increasing use of a technology that is not a destination device in itself introduces many ethical dilemmas specific to this technology.

7. Conclusion

The use of VA-ECMO in patients with refractory cardiogenic shock and cardiac arrest is widely increasing and is now recognized as a standard technique because in these patients the mortality without the ECMO support would be dramatically higher. It seems essential to determine whether ECMO support should be initiated before organ dysfunction advances to preserve organ function. However, even if data in the literature show a progressive increase in the overall outcome, these devices are associated with serious complications such as bleeding, lower limb ischemia, infections, and CNS irreversible damage that remain problematic issues. Efforts to reduce or prevent them are necessary and strongly recommended to improve the outcome. Finally, as inappropriate VA-ECMO use raises resource utilization and hospital costs and is associated with unacceptably high mortality, early identification of mortality risk factors and detailed analyses of survivors' long-term outcomes are needed.

Author details

Marie-Eve Brunner[1*], Carlo Banfi[2] and Raphaël Giraud[3]

*Address all correspondence to: marie-eve.brunner@hcuge.ch

1 Geneva University Hospitals, Intensive Care, Department of Anesthesiology, Pharmacology and Intensive Care, Genève, Switzerland

2 University Hospitals, Division of Cardiovascular Surgery, Department of Surgery, Geneva, Switzerland

3 Geneva University Hospitals, Intensive Care, Department of Anesthesiology, Pharmacology and Intensive Care, Genève, Switzerland

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