Veno-Arterial-ECMO in the Intensive Care Unit:From Technical Aspects to Clinical Practice

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Content

Summary

The use of Veno-Arterial ExtraCorporeal Membrane Oxygenation (VA-ECMO) as a salvage therapy in cardiogenic shock is becoming of current practice. While VA-ECMO is potentially a life-saving technique, results are sometimes mitigated, emphasizing the need for selecting the right indication in the right patient. This relies upon a clear definition of the individual therapeutic project, including the potential for recovery as well as the possible complications associated with VA-ECMO. To maximize the benefits of VA-ECMO, the basics of extracorporeal circulation should be perfectly understood since VA-ECMO can sometimes be detrimental. Hence, to be successful, VA-ECMO should be used by teams with sufficient experience and initiated after a thorough multidisciplinary discussion considering patient's medical history, pathology as well the anticipated evolution of the disease.

Introduction

Veno-Arterial Extra-Corporeal Membrane Oxygenation (VA-ECMO) or Extra-Corporeal Life Support (ECLS) are two terms that designate devices originally created to replace heart and lung functions. Both denominations are synonymous and we will keep the term "VA-ECMO" throughout this review for the sake of consistency. While VA-ECMO was initially dedicated to cardiac surgery (*i.e.* cardiopulmonary bypass), technical evolutions such as pump miniaturization, better circuit biocompatibility and easier cannulation have enabled this technique to enter the Intensive Care Unit (ICU). VA-ECMO was tested in various indications [1–7]. Nevertheless, because of inconsistent success rates [1–7], significant complications, and high-related costs, it is of paramount importance to accurately identify the patients in whom VA-ECMO may be reasonably initiated.

The goal of this article is to describe some key technical aspects of VA-ECMO, to present a literature overview on the use of VA-ECMO in critically ill patients and ultimately to help the intensivist to identify the appropriate indications for VA-ECMO.

Principles and technical aspects

The principle is directly derived from extra corporeal circulation techniques used during cardiac surgery. Venous deoxygenated blood is mechanically suctioned, from a large central vein through a venous cannula, by a centrifugal pump. It is then oxygenated, warmed and restituted into systemic circulation through an arterial cannula. Hence, VA-ECMO is used to assist the heart by insuring part or all the systemic blood flow (Figure 1).

Vascular access - Peripheral versus Central VA-ECMO

Among VA-ECMO circuits, a distinction has to be made between those inserted centrally or peripherally.

Peripheral ECMO

The typical configuration for *peripheral* VA-ECMO involves blood drainage from a femoral venous access and reinfusion through a femoral arterial cannula. With this configuration, the reinfusion cannula generates a retrograde flow up in the aorta that may encounter the anterograde flow generated by the left ventricle [8].

For peripheral VA-ECMO configurations, percutaneous ultrasound guided femoro-femoral access is usually a quick and efficient way of insertion [9], even though it can become more difficult in case of profound arterial hypotension or hemostasis disorders for instance. The alternative is a surgical insertion that allows for a direct visualization of the vessels as well as a simultaneous insertion of the reperfusion cannula (see below) but depends upon the availability of the surgical team.

Whatever the insertion technique chosen, peripheral VA-ECMOs carries specific complications. First, peripheral VA-ECMO may lead to an obstruction of the common femoral artery that can cause lower limb ischemia [10–13]. It is thus advised to place a

reperfusion catheter in the ipsilateral superficial femoral artery [11]. Another drawback of peripheral VA-ECMO is the competition between the retrograde flow generated by the VA-ECMO and the native anterograde flow [8]. This competition may induce or worsen 2 types of complications: 1) LV overload; and 2) Harlequin syndrome.

Left Ventricle (LV) overload

Even when the VA-ECMO support is fully covering the cardiac output, there is still blood entering the cardiopulmonary circulation since part of the coronary circulation ends up into the cardiac chambers, including the left atrium or ventricle, through the Thebesian veins [14]. This residual filling of a failing left ventricle (LV) may cause a pulmonary edema especially with peripheral VA-ECMO. In this case, whilst VA-ECMO unloads the right heart, the increase in the LV afterload generated by the assistance itself may overload the LV [15].

Thus, inotropes should be maintained or introduced in case of ventricular dilation or evidence of pulmonary edema. Mean arterial pressure should always be tightly controlled, and adapted to both organ perfusion and cardiac function. In some cases, vasodilators may also be used, in order to adjust the mean arterial pressure.

Additional therapies may be necessary to unload the LV. The use of an Intra-Aortic Balloon Pump (IABP) was reported to be associated with a reduction in the LV afterload [15,16]. It may help to restore pulsatile condition, and lower the Pulmonary Artery Occlusion Pressure in VA-ECMO patients [17,18]. Nevertheless, although an IABP may improve macrocirculatory parameters without significant complications [19], its benefits remain uncertain [20,21].

In case of refractory pulmonary edema, a LV vent may be added to the extracorporeal circuit. Percutaneous Trans-Aortic, or surgical vent are possible in this context. Recent data suggest that either the percutaneous trans-Aortic devices or the surgical vents may be beneficial to unload the LV in case of pulmonary edema [22–25] and improve survival in this context [26].

Since there is no argument for a clear benefit of one technique over the other [25,27,28], the choice of a percutaneous or a surgical vent should be based upon the VA-ECMO settings (centrally or peripherally inserted - see below -) and the availability of the surgical team.

Harlequin Syndrome

In case of a concomitant respiratory failure, and especially in the cardiac recovery period, the blood flow competition may also cause a Harlequin syndrome [8,29,30]. Indeed, if the residual heart function is able to generate a native perfusion, the interface (or watershed) between the anterograde (native and poorly oxygenated blood) and retrograde (assisted and well oxygenated blood) flows may be located at the level of the supra-aortic trunks. Its clinical expression (cyanosis in the upper part of the body, with subsequent risk of cerebral or myocardial ischemia, constrasting with pink well-perfused lower part of the body, generating this aspect of "Harlequin") results from a selective upper body hypoxia.

It is recommended [31] to monitor oxygen saturation at left hand, while getting blood sample for arterial blood gas analysis on the right hand, in order to detect promptly a discrepancy between right and left arms. Managing a Harlequin syndrome may include: VA-ECMO withdrawal if cardiac recovery is sufficient, increase of the VA-ECMO flow to reduce the relative participation of the native hypoxemic flow to brain perfusion, "centralization", or addition of a partial reinjection cannula into the internal jugular vein (so called veno-arterial-venous ECMO, VAV-ECMO) [32]. If the circulatory support is no longer needed, but respiratory support is still requested, a switch toward a veno-venous ECMO can be considered.

Central ECMO

Central VA-ECMOs are always inserted surgically. The venous cannula is placed in the right atrium and the arterial cannula in the ascending aorta. The oxygenated blood is injected

anterogradely in the aorta through the arterial cannula. Thus, with central ECMO there is no competition between with the native heart thereby reducing the risk of LV overload and virtually no risk of Harlequin syndrome.

At the population level, no cannulation site has proven its superiority over the other in terms of outcome or hemodynamic stability [33]. The choice of the best technique essentially depends on the situation (emergent or less emergent VA-ECMO), on the indication and on the risk of complications at the individual level. Central VA-ECMO is typically considered in case of post-cardiopulmonary bypass related heart failure. It needs a surgical team to be inserted and is associated with a higher risk of complications such as mediastinitis or bleeding, as compared with peripheral VA-ECMO [12,33]. Peripheral VA-ECMO, whether inserted surgically or percutaneously, can be implanted faster, but is associated with higher risk of LV overload or Harlequin syndrome. Thus, any emergent indication for cardiorespiratory assistance should typically lead to prefer peripheral insertion while central VA-ECMO can be considered as an alternative to peripheral VA-ECMO in case of refractory pulmonary edema, Harlequin syndrome or limb ischemia occurring downstream the femoral arterial cannula despite reperfusion.

Gas exchanges determinants during VA-ECMO

VA-ECMO creates a Venous to Arterial shunt, bypassing the native cardiopulmonary circulation. In order to allow for adequate gas exchanges, the VA-ECMO circuit has to provide optimal oxygen delivery and CO_2 removal. In the artificial lung (*i.e* the oxygenator), as well as in the native lungs, blood oxygenation and decarboxylation result from double convective exchanges occurring alongside a semipermeable membrane. Therefore, during VA-ECMO, PaO_2 and $PaCO_2$ both depend upon extra-corporeal circulation settings and patient's characteristics.

Indeed, the Cardiac Output (CO) and the Pump Flow Rates (PFR), and more specifically their ratio (PFR/CO), are both of crucial importance. If the PFR/CO ratio is close to 0 (*i.e.* the artificial shunt is null), the fraction of oxygenated blood coming from VA-ECMO is negligible and so is the benefit in terms of PaO_2. However such a situation should not be encountered since the minimal Pump Flow Rates should never be lower than 1500 ml/min (risk of circuitry thrombosis, or back flow into the circuitry). If the PFR/CO is close to 1, the CO entirely flows through the membrane, and may thus be oxygenated. Nevertheless, at high PFR, the oxygenator performance by itself and more precisely the quality of the membrane may limit oxygen transfer. Indeed, the membrane may be deteriorated by clots, thereby reducing its performance and its lifetime.

Another determinant is the Inspired Oxygen Fraction (FiO_2). The latter drives the oxygen partial pressure on the VA-ECMO side of the oxygenator, and thus also determines the gradient for oxygen exchange across the membrane. Sweep gas flow which is a major determinant for CO_2 removal, has almost no impact on O_2 exchanges unless it is turned down close to zero. Indeed, the magnitude of oxygen gradient through the membrane as well as its high permeability for oxygen, explain that oxygen transfer rate is very high.

Blood decarboxylation depends on PFR/CO ratio [34] and sweep gas flow. At membrane entry, CO_2 partial pressure is zero and CO_2 removing gradient equals CO_2 venous partial pressure. As CO_2 exchange occurs alongside the membrane, the gradient decreases, thereby reducing CO_2 transfer, unless the sweep gas is sufficient to “wash” out the CO2 accumulated on the VA-ECMO side of the membrane.

Circulatory support during VA-ECMO

VA-ECMO is used to restore adequate systemic perfusion. Pump flow depends on the size of the vascular accesses, venous circuit resistance, and the pump itself.

For a given Pump Flow Rate, the size of the *venous cannula* is a major determinant of the inflow. Indeed, pump preload depends on the resistance (or the size) of the venous cannula and on the blood volume in the inferior vena cava and the right atrium. The position of the venous cannula is optimal when the tip is located in the right atrium. When positioned in the inferior or the superior vena cava, the risk of venous collapse is more important.

Pump rotation speed is an important determinant of the flow rate and of the pressure gradient. Modern VA-ECMO machines use preferentially centrifugal pumps, which allow for high rotation speed and flow rate with a lower risk of hemolysis. Increasing pump rotation speed increases the flow rate (and decreases the right atrial pressure [35]), unless the suction generated precipitates a transient venous or atrial collapse (Kicking lines) (Figure 2). In such a situation, one must decrease pump rotation speed and/or administer intravascular fluids in order to restore venous/atrial transmural pressure. In addition, to avoid complications such as hemolysis, the maximum theoretical pressure generated by the pump should not exceed -300 mmHg on the venous side, and +400 mmHg on the arterial side [31].

The impact of the size of the *arterial cannula* is less important as the pump easily overcomes the resulting afterload. Nevertheless, a too small arterial cannula may cause hemolysis, alter the performance of the pump and limits the flow. Similarly, mean arterial pressure should be tightly controlled in order to limit the increase in afterload and avoid deleterious consequences (see “Specific Management section”).

Specific Management during VA-ECMO

While non-specific ICU care should be provided during VA-ECMO management, careful attention should be paid on VA-ECMO and ventilator settings as well as anticoagulation therapy.

ECMO management

Modifying pump flow rates can induce substantial alteration in hematosis or worsen a preexisting cardio-respiratory insufficiency. Therefore, daily ICU care should be provided with great caution. For instance, a simple patient mobilization can cause accidental decannulation, with catastrophic consequences. VA-ECMO could also prevent from appropriately positioning the patient. During patients' positioning it is of paramount importance to carefully verify the cannula, in order to prevent any extracorporeal circulation mobilization or soft tissue alteration. Semi-recombinant position may be difficult with a peripheral VA-ECMO, while central VA-ECMO is not compatible with prone positioning. Prone positioning has been described during peripheral Veno-Venous-ECMO in case of refractory Acute Respiratory Distress Syndrome (ARDS), as described by Otterspoor [36], Kimmoun [37] and Kipping [38]; however, in peripheral VA-ECMO, the risks of kinking of the reperfusion line or accidental withdrawal of the arterial cannula justify that in case of refractory ARDS while on VA-ECMO, a safer alternative to prone positioning can be the addition of a reinjection cannula into the right internal jugular vein (Veno-Arterial-Venous - ECMO).

Finally, out-of-ICU exams are also more difficult in patients under ECMO. Double pliers must always be readily available to interrupt quickly the extracorporeal circulation. A manual wheel should always be present to replace the pump in case of outage or dysfunction. The

membrane should be checked daily, particularly for clots formation (dark red deposit on the membrane). If requested, blood gases can be performed before and after the membrane to evaluate its performance. When blood gases are performed after the membrane, oxygen partial pressure should be greater than 200 mmHg. Arterial and Venous cannulas should also be carefully screened. There should be a substantial color difference between dark venous blood and red arterial blood. Non-cyclic oscillations of the circuit associated with decrease in the blood flow, should prompt the team to check the inflow pressure and take the appropriate decisions (decrease Pump Flow Rate, administer fluids, etc). Daily examination of cannulation sitesis also mandated, tracking for bleeding or infection. In case of peripheral ECMO, clinical and Doppler examination of the peripheral pulse should be part of the nurse surveillance, in order to promptly identify any lower limb ischemia.

Ventilator Settings

Ventilator settings should be adapted, in order to avoid ventilator-induced lung injury. Positive pressure ventilation may decrease left and increase right ventricular afterload. This can be either beneficial or detrimental depending on the global cardiac function. For instance, positive pressure ventilation may improve a pulmonary edema on the one hand, while worsening a right heart failure on the other hand. It is proposed to use a protective ventilation strategy with a Tidal Volume of 6 to 8 ml/kg of ideal body weight, with a maximum PEEP of 10 cmH2O and/or a plateau pressure of 20-25 cmH2O, and to adjust the latter settings to the cardiorespiratory function [39]. The recent ELSO guidelines recommend the use of the smallest possible volume and pressure, in order to allow lung rest and recovery [31].

Anticoagulation

Anticoagulation therapy should also be used, except in presence of a specific bleeding risk. Potentially life threatening bleeding events are the most frequent complication during VA-ECMO [40]. The extracorporeal circuit by itself induces an activation of the inflammatory

and the coagulation pathways. This, in turn, favor bleeding or clotting complications such as stroke or pulmonary embolism [41,42].

In a study reporting 405 patients under VA-ECMO, the bleeding rate was 31% [42]. In a recent study, Aubron et al. [40] reviewed the complications of veno-venous and veno-arterial ECMO, and evaluated their impact on mortality. Bleeding was the most frequent adverse event (27 %), regardless of the type of ECMO. Moreover, the total number of transfused packed red blood cells was an independent predictor of death during VA-ECMO.

On the other hand, avoiding anticoagulation could lead to thrombotic events including stroke. Indeed, clots in the extracorporeal circuit could lead to scatter emboli into the intracranial circulation. On addition, insertion of the arterial cannula into the aorta may damage an atherosclerotic intima, potentially resulting in emboli and multifocal cerebral infarctions. In Hemmila et al. study [42], 5.5% of the patients on VA-ECMO had ischemic neurological adverse events. When a CT scan was performed systematically, Lindegran et al. [41] reported a 45% rate of intracranial hemorrhage or infarction. Consistently, Mateen et al. [43] evaluated 42 patients under VA-ECMO, and observed neurological events in 50% of them. However, in the latter study, VA-ECMO indication was refractory cardiac arrest in 16% of the patients, a condition highly prone to neurologic complication.

Consequently, anticoagulation is necessary but has to be managed carefully during VA-ECMO. Generalized use of heparine-coated circuit allows for low dose intravenous heparinization with a TCA ratio target around 1.5 [31]. This is especially possible if the pump rotation speed is high enough as the risk for clotting formation is maximal when the pump flow rate is below 1500 ml/min.

Infections and other Complications

Aubron et al. [40] reported a high incidence of bloodstream infection (13% for va- and vv-VA-ECMO). Hemmila et al. [42] reported a global infection rate of 38%. Consistently, a recent meta-analysis including 1,866 patients from 20 studies [44] confirmed the high infection rate under VA-ECMO (30 [20 - 44] %).

Figure 3, using results of [44], summarizes the rates and the types of complication occurring during VA-ECMO for acute cardio-respiratory failure.

Indications

The main indication for VA-ECMO is cardiogenic shock resulting from acute myocardial infarction, fulminant myocarditis, acute decompensation of severe chronic heart failure, drug intoxication, hypothermia or intractable arrhythmia. VA-ECMO is also used in some specific situations such as post-cardiotomy cardiac failure or cardiac arrest requiring cardiopulmonary resuscitation. Furthermore, VA-ECMO is proposed for patients with pulmonary embolism, sepsis-associated cardiomyopathy and pulmonary hypertension.

A recent meta-analysis pooled 23 studies (n=1,199) in which VA-ECMO was initiated to treat cardiogenic shock or refractory cardiac arrest. Long-term mortality was reported in 16 studies and overall one-year survival rate was 54.9% [45].

Cardiac Arrest

Over the past decade, there has been a growing interest for VA-ECMO in out-of-hospital refractory cardiac arrest. However, the benefit of VA-ECMO is apparently higher in patients with intra-hospital cardiac arrest [1,46–50]. This is confirmed in a recent observational propensity-matched study [51] including 320 VA-ECMO for cardiac arrest. Nevertheless, when reducing time to implantation, by implementing pre-hospital ExtraCorporeal Cardio-

Pulmonary Resuscitation (eCPR), Lamhaut et al. found no difference in mortality between in- and out- of hospital cardiac arrest patients, resuscitated with VA-ECMO [52]. Cardiac arrest caused by hypothermia or poisoning have better outcomes than cardiac arrest due to other reasons [2,53–56]. The French council for cardio-pulmonary resuscitation as well as the French society of Anesthesiology and Intensive Care Medicine have limited the indications for VA-ECMO initiation in refractory cardiac arrest to "reasonable" low flow durations (< 100 min), and to cardiac arrests resulting from poisoning or with deep hypothermia (< 32°C) [57]. North American guidelines still do not recommend VA-ECMO in this indication [58].

VA-ECMO has also been used for Post Cardiac Arrest syndrome (PCAS), i.e., patients suffering from a profound cardiogenic shock after return of spontaneous circulation. However, with or without VA-ECMO, mortality reaches 72 to 80% in this indication [59,60].

Acute Cardiac failure

Acute Coronary Syndrome (ACS)

Even if European and American guidelines recommend VA-ECMO use in case of ACS leading to heart failure refractory to medical treatment, with IIa and IIb proof levels respectively [61,62], to our knowledge, no randomized study has ever reported any benefit of VA-ECMO as compared to medical treatment alone. These guidelines are only supported by results from observational series [3,63–65]. Indeed, a historical case-control study published in 2010 reported a benefit of VA-ECMO on 30-day survival (OR = 0.22 ; 95%CI [0.06-0.80]) in 71 patients with profound cardiogenic shock and acute coronary syndrome [65]. Mortality in the VA-ECMO group was 31.9 %. In a study on 98 patients, Sakamoto et al. [3] reported a much higher mortality rate (67 %). However, the latter study included patients on VA-ECMO for both cardiogenic shock and refractory cardiac arrest. In addition, VA-ECMO-

related complications were frequent in this population, and this was associated with a worst prognosis (OR = 4.72 ; 95%CI [1.39–16.1]; p = 0.013). In an attempt to better identify the patients who benefit from VA-ECMO, Muller et al. identified 7 prognostic factors (age > 60, female sex, body mass index >25 kg/m^2, Glasgow coma score < 6, creatinine > 150 μmol/L, lactate > 2, mmol/L, and prothrombin activity < 50%) in 138 patients under VA-ECMO for Acute Myocardial Infarction [66]. These factors entered into the ENCOURAGE score allowed to predict hospital mortality with an AUC of 0.84, 95%CI [0.77-0.91]

Fulminant Myocarditis

Fulminant myocarditis or intoxications with cardio-depressant agents are two of the best examples of a bridge to recovery situations. In this pathology, myocardial depression is usually transient and VA-ECMO is used to wait for heart function recovery. VA-ECMO has thus been used with good results and several studies reported survival rates as high as 60-70% [4,67]. VA-ECMO was shown to improve the outcome in this context [4,68].

Septic Cardiomyopathy

Myocardial depression is a well-recognized consequence of severe septic shock. Septic cardiomyopathy was reported in up to 60% of septic shocks [69]. Because this myocardial depression is potentially fully reversible, VA-ECMO was proposed with survival rate from observational series ranging from 21 to 85% [5,70,71]. However, the level of evidence is still too low to recommend VA-ECMO in this situation.

Post cardiotomy cardiogenic shock

Postcardiotomy cardiogenic shock occurs in approximately 1% of the patients after cardiac surgery. In such cases, VA-ECMO may be used as a bridge-to-recovery. However, survival rates in this indication are inconsistent, ranging from 24 to 39% [6,72].

Primary graft dysfunction (PGD) after transplantation

Primary graft failure is the first cause of early mortality after heart, lung, and heart-lung transplantation. Data from the International Society for Heart Lung Transplantation (ISHLT) Transplant Registry show 66%, 24.7% and 27 % mortality rates attributable to primary graft dysfunction, during the first 30 days following heart, lung and heart-lung transplantation, respectively [73–75]. The ISHLT states that mechanical support is the only viable therapeutic option in this context. Indeed, VA-ECMO can improve survival rates (as high as 82%) of patients with graft dysfunction following lung [76] or heart [7,77,78] transplantation.

Bridge to Destination Therapy

Destination therapies may be considered for end-stage heart failures. They include either heart transplantation or long term Left Ventricular Assist Devices (LVAD). As for lung transplantation, acute decompensation of an end-stage heart failure is associated with a worse prognosis. In this context, VA-ECMO has been proposed to allow recovery from multiple organ failure. In 1999, Pagani et al. [79] reported the feasibility of VA-ECMO as a bridge to destination therapy. The overall survival for patients bridged using VA-ECMO either to LVAD or to transplantation was of 43%. After successful VA-ECMO initiation, survival rates reached 71% at one year. Further studies have reported survival rates ranging from 50% to 73% [80] depending on whether the VA-ECMO was used as a bridge to LVAD (50%) or to transplantation (73%). “Bridge to bridge” VA-ECMO has also been reported: VA-ECMO used as a bridge to LVAD, the latter being used as a bridge to transplantation [81]. In this study, the use of VA-ECMO prior to LVAD did not affect mortality at 3 years (13% vs. 23%) or the duration of LVAD assistance (292 [153–448] vs. 311 [175–594] days). Analyses based on the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) registry including approximately 15,000 patients showed that even if VA-ECMO improves the survival rate of patients during decompensation of end-stage diseases, it is a strong

predictor of poor outcome. Better results are observed when a LVAD is implanted in patients with a stable condition [82–84].

Indications to Initiate a VA-ECMO

Because the risks associated with the technique are high, a thorough discussion about the best global therapeutic plan is mandatory, including: 1) the choice of the most appropriate cannulation site and type of assistance, 2) anticipation of the potential complications, and 3) of the weaning strategy. Thus, it is crucial to define whether the VA-ECMO is indicated as a bridge to recovery, to transplantation, or as a bridge to destination therapy [31,85].

A "Bridge to recovery" is an assistance initiated to wait for the recovery of a reversible life threatening condition. Typical examples are acute cardiorespiratory failure resulting from acute myocarditis, intoxication with cardiac depressant agents, or coronary syndrome with cardiogenic shock. Prior to inserting the VA-ECMO, the physicians hope that the condition is reversible and that the failing organ will recover after a brief period of support. In the absence of potential reversibility and if none of the alternative support (transplantation or long-term assist device) is deemed feasible, VA-ECMO should not be implanted.

VA-ECMO may be used as a "bridge to transplantation" when the failing organ no longer permits survival and needs to be supported. In this context, VA-ECMO may also allow for the recovery of organ dysfunction such as renal or liver failure or for an appropriate neurological evaluation after withdrawal of the sedation medications.

In the "bridge to destination therapy", VA-ECMO is used to support the heart while waiting for the possibility to implant a long-term mechanical assist device. This is indicated for end stage heart failure, when the patient is temporarily or definitely contraindicated to transplantation.

In the « Bridge to Bridge » strategy, VA-ECMO is implanted as a bridge to Left Ventricular Assist Device that is a more sustainable therapy allowing the patient to be discharged from the ICU, while waiting for a graft.

Weaning strategies

After VA-ECMO insertion, daily cardiorespiratory evaluation should be performed to consider VA-ECMO weaning. Indeed, since this assistance carries complications, it is wise to consider withdrawing the VA-ECMO as soon as possible. The evaluation should answers the following questions : i- Has the cardiac function recovered ? ; ii- Has the respiratory function recovered ? ; iii- Could a favorable evolution be predicted ? ; iv- Could further cardiopulmonary aggression be predicted (open heart surgery for example) ? ; v- Will a removal of the assistance be well tolerated ?

Weaning Eligibility

Weaning from VA-ECMO should usually not be attempted within the first 48 hours, since renal and/or hepatic function should recover first. In addition, the etiology of cardio-circulatory dysfunction must be compatible with myocardial recovery. Substantial myocardial recovery can be expected for acute myocarditis, acute myocardial infarction, post-cardiotomy cardiogenic shock or drug intoxication. On the contrary, in most cases, patients with end-stage cardiac disease cannot be taken off VA-ECMO unless for transplantation or insertion of a long-term assist device.

To be eligible for VA-ECMO weaning, patients under VA-ECMO should be deemed hemodynamically stable: mean arterial pressure (MAP) of > 60 mmHg under low doses of vasopressors and a presence of a pulsatile arterial waveform maintained for at least 24 hours.

Weaning Trial

The weaning trial relies on a thorough clinical and echocardiographic examination. The goal is to assess whether the patient would tolerate to be separated from the VA-ECMO on both respiratory and hemodynamic standpoints. To do so, the VA-ECMO blood flow should be decreased progressively to a minimum of 1 L/min for at least 15 min and the sweep gas flow

rate reduced to 1 L/minute, with a FiO2 on the VA-ECMO at 21%. If the MAP drops significantly and is constantly ≤ 60 mmHg during the trial, the VA-ECMO flow rate must be returned to 100% of the initial flow rate and the trial must be stopped. Echocardiography evaluation relies on the variables assessing LV systolic function (Left Ventricular Ejection Fraction - LVEF - and lateral mitral annulus peak systolic velocity), LV flow (aortic velocity-time integral) and right ventricular diameters and function index (Tricuspid Annular Plane Systolic Excursion - TAPSE). The latter right ventricular function indicators are nevertheless nonconsensual.

The oxygen fraction delivered by the extracorporeal circuit should be turned down to 21% and the one delivered by the ventilator should be less than 60%. The resulting PaO2/FiO2 ratio should not be lower than 200.

In summary, VA-ECMO removal can be considered if the patient does not have end-stage cardiac disease, tolerates well the weaning trial, and has a LVEF ≥ 20–25%, an aortic velocity-time integral ≥ 12 cm and a lateral mitral annulus peak systolic velocity ≥ 6 cm/s under minimal VA-ECMO support [86,87] .

Conclusion

VA-ECMO is an extracorporeal technique that may support cardiorespiratory functions. Because this technique has substantially improved over time, VA-ECMO use is no longer restricted to the operating room and has spread to intensive care units. However, VA-ECMO-related complications are potentially life threatening. Therefore, before starting a VA-ECMO program, it is mandatory to provide to the ICU staff a good understanding and practice of the technical aspects, including insertion of vascular accesses under cardiopulmonary resuscitation. In order to maximize the chances of success, it is of paramount importance to select carefully the patients who can benefit from VA-ECMO and to be able to have multi-disciplinary discussions (involving intensivists, cardiac surgeons and cardiologists) about i) VA-ECMO indications, ii) chances of recovery, iii) the overall plan of care and iv) the appropriate VA-ECMO technique. Hence, the decision to initiate a VA-ECMO and the choice of the best method is best taken by a team of experienced physicians potentially associating intensivists, cardiologists and cardiac surgeons.

Tables

Table 1: Summary of studies per VA-ECMO indication

Authors	Year	Type	Cohort Size	VA-ECMO Sample size	Mortality	Favouring treatment
Acute Coronary Syndrome						
Fujimoto K [64]	2001	Retrospective, Observational		9 pts	56%	Not Given
Chen JS [63]	2006	Prospective, Observational		36 pts	33%	Not Given
Sheu JJ [65]	2010	Retrospective, Observational	71 pts	46 pts	72%	No
Cardiac Arrest						
Chen YS [88]	2003	Retrospective, Observational		57 pts	68%	Not Given
Sung K [89]	2006	Retrospective, Observational		22 pts	54%	Not Given
Megarbane B [2]	2007	Prospective, Observational		17 pts	86%	Not Given
Ruttmann E [90]	2007	Retrospective, Observational	59 pts	25 pts	72%	Not Given
Chen YS [1]	2008	Propensity Matched	172 pts	46 pts	67%	No
Chen YS [91]	2008	Retrospective, Observational		135 pts	66%	Not Given
Lin JW [48]	2010	Propensity Matched	118 pts	27 pts	71%	No
Le Guen M[92]	2011	Prospective, Observational		59 pts	96%	Not Given
Liu Y [93]	2011	Retrospective, Observational		11 pts	64%	Not Given
Shin TG [94]	2011	Propensity Matched	406 pts	60 pts	68%	Yes
Avalli L [46]	2012	Retrospective, Observational		42 pts	74%	Not Given
Haneya A [95]	2012	Retrospective, Observational		85 pts	66%	Not Given
Sakamoto S [3]	2012	Retrospective, Observational		64 pts	72%	Not Given
Wu MY [96]	2012	Retrospective, Observational		40 pts	65%	Not Given
Leick J [97]	2013	Retrospective, Observational		28 pts	61%	Not Given
Maekawa K [98]	2013	Propensity Matched	162 pts	24 pts	69%	Yes
Schopka S [50]	2013	Retrospective, Observational		103 pts	72%	Not Given
Chou TH [47]	2014	Retrospective, Observational	66 pts	43 pts	65%	No
Johnson NJ [99]	2014	Prospective, Observational		26 pts	85%	Not Given

Kim SJ [100]	2014	Propensity Matched	499 pts	52 pts	85%	No
Park SB [49]	2014	Retrospective, Observational		152 pts	68%	Not Given
Sakamoto T [101]	2014	Prospective, Observational	454 pts	260 pts	88%	Yes
Sawamoto K [53]	2014	Retrospective, Observational		26 pts	62%	Not Given
Wang CH [102]	2014	Prospective, Observational		230 pts	68%	Not Given
Han SJ [103]	2015	Retrospective, Observational		37 pts	81%	Not Given
Choi DS [51]	2016	Propensity Matched	36 227 pts	320 pts	82%	No
De Chambrun MP [59]	2016	Retrospective, Observational		94 pts	73%	Not Given
Bougouin W [60]	2017	Retrospective, Observational		52 pts	73%	No
Lamhaut L [52]	2017	Prospective, Observational	156 pts	156 pts	87%	Not Given
Fulminant Myocarditis						
Maejima Y [68]	2004	Retrospective, Observational		8 pts	25%	Not Given
Rajagopal SK [67]	2010	Retrospective, Observational		255 pts	39%	Not Given
Mirabel M [4]	2011	Retrospective, Observational		41 pts	34%	Not Given
Septic Myocarditis						
Bréchot N [5]	2013	Retrospective, Observational		14 pts	39%	Not Given
Huang CTH [104]	2013	Retrospective, Observational		52 pts	85%	Not Given
Park TK [71]	2015	Retrospective, Observational		32 pts	81%	Not Given
Post-Cardiotomy						
Doll N [6]	2004	Prospective, Observational		219 pts	76%	Not Given
Rastan AL [72]	2009	Prospective, Observational		517 pts	75%	Not Given
Ma P [15]	2014	Retrospective, Observational		54 pts	61%	Not Given
Primary Graft Dysfunction						
Mihaljevic T [77]	2010	Prospective, Observational		53 pts	57%	Not Given
Listijono DR [7]	2011	Retrospective, Observational	124 pts	17 pts	18%	No
Stehlik J [73]	2011	Retrospective, Observational	10 271 pts	180 pts	RR = 3,32	No
Hartwig MG [76]	2012	Prospective, Observational		28 pts	18%	Not Given
Lima EB [78]	2015	Prospective, Observational		11 pts	67%	Not Given
Bridge to Destination Therapy						
Pagani FD [79]	1999	Retrospective,		14 pts	50%	No

Chung [80]	2009	Observational Retrospective, Observational		31 pts	39%	Not Given
Marasco SF [81]	2015	Retrospective, Observational	58 pts	23 pts	13%	Not Given

1 pts : patients; RR : Relative Risk

Figures

Figure 1: Schematic representation of cannulation ways for implantation of peripheral and central VA-ECMO. A - Centrally inserted veno-arterial ECMO ; B - Peripherally inserted veno-arterial ECMO

Figure 2: Relationship Between Transmural Pressure (Ptm), Venous to Pump Pressure Gradient (Pp-v), and Venous Return Curve.
Black arrows represent the strength and the direction of the forces inside the vein. Blue arrows represent the net forces applied to the wall of the vein
The Venous Gradient (VG) is the difference between the Pressure in the venous system (Pv) and the pressure in the pump (Pp): VG = Pv - Pp. The Ptm is the difference between the Pressure inside (Pin) and outside (Pout) the vein: Ptm = Pin – Pout. The stronger the Pp-v, the higher the flow, until the critical point where the Pv exceeds the Ptm and leads the vein to collapse. 1) Decreasing the pump speed will decrease the VG and in turn will allow the blood to flow and/or 2) Giving fluid can increase the Pv and so the Ptm and can in turn allows the blood to flow

Figure 3: Main complications reported during circulatory support with veno-arterial ECMO. Barplot realized using data obtained from meta-analysis given in [44]. *Surgical Control of bleeding : Reintervention for bleeding at the insertion site. Haemorrhage : Bleeding complication others than insertion site (Gastro-Intestinal bleeding for example)*

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