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Weaning Strategy from Veno-Arterial Extracorporeal Membrane Oxygenation (ECMO)

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Abstract

Background: Significant advances in extracorporeal technology have led to the more widespread use of veno-arterial extracorporeal membrane oxygenation (VA ECMO) for cardiac failure. However, procedures for weaning from VA ECMO are not standardized. High death rate after successful weaning shows that many questions remain unresolved in this field.

Objectives: In this review, we discuss data from the literature and propose a strategy to optimize the weaning process.

Data synthesis and conclusions: It is especially important that the VA ECMO is not removed while the patient is still recovering from the condition that necessitated the use of VA ECMO implantation. Damaged organs need to recover before attempting weaning and the patient should be considered hemodynamically stable. The etiology of cardio-circulatory dysfunction must be compatible with myocardial recovery. Finally, weaning trials using echocardiographic and hemodynamic assessments are indispensable to assess the behavior of the ventricles and to determine whether the VA ECMO can be removed.

Keywords: ECMO, weaning, echocardiography, load conditions

Abbreviations

LV EF	Left Ventricular Ejection Fraction
LV	Left Ventricle

RV	Right Ventricle
VA ECMO	Veno-Arterial Extracorporeal Membrane Oxygenation

1. Introduction

Veno-arterial extracorporeal membrane oxygenation (VA ECMO) is used to support patients with refractory cardiogenic shock [1, 2]. It has been successfully used as a bridge to myocardial recovery, cardiac transplantation, or implantation of a ventricular assist device in patients with overt cardiac failure of various causes, e.g., acute myocardial infarction, end stage dilated cardiomyopathy, viral or toxic myocarditis, complications of cardiac surgery, or cardiac arrest.

After a few days of mechanical assistance, the device can sometimes be successfully removed if the patient has partially or fully recovered from the condition that necessitated the use of ECMO. However, to date, only a few studies have reported strategies for weaning from VA ECMO [3, 4].

Moreover, weaning does not signify survival because 20–65% of patients weaned from VA ECMO support do not survive to hospital discharge.

This review will discuss the various factors influencing survival after weaning in addition to weaning strategies proposed in the literature. Based on this information, we will propose a strategy to optimize the weaning process.

2. Principles of VA ECMO

Patients with significantly impaired cardiac function (with or without impaired gas exchange) require venoarterial configuration for circulatory support. A venous cannula inserted into the right atrium drains blood from the patient into the pumping mechanism of the ECMO circuit. The blood is oxygenated through a membrane oxygenator and perfused in the aorta by a centrifugal pump via a second cannula [1, 2].

The typical configuration for VA ECMO involves femoral venous drainage and femoral arterial reinfusion. With this configuration, the reinfusion jet flows retrograde up the aorta and may meet resistance from antegrade flow generated by the left ventricle.

An ECMO circuit can be set up centrally through the right atrium and the ascending aorta, or peripherally through the femoral vein and the femoral or axillary artery. ECMO can support both heart and lung function and assists the two ventricles.

3. Indications for ECMO

The main indication for VA ECMO is medical cardiogenic shock, including that associated with acute myocardial infarction, fulminant myocarditis, acute exacerbation of severe chronic

heart failure, drug intoxication, hypothermia, and acute circulatory failure due to intractable arrhythmia.

VA ECMO is also used in some particular situations for patients with postcardiotomy cardiac failure, after cardiac transplantation, or cardiac arrest requiring cardiopulmonary resuscitation [1, 2].

Furthermore, VA ECMO is starting to be used for patients with pulmonary embolism, sepsis associated cardiomyopathy, and pulmonary hypertension [1, 5].

4. Outcome of patients receiving VA ECMO

VA ECMO is used as a bridge to myocardial recovery and cardiac transplantation. It may also be used as “a bridge to a bridge”, i.e., before implantation of a ventricular assist device [6]. No randomized controlled trials have compared VA ECMO to other mechanical support systems in patients with cardiogenic shock. However, several nonrandomized studies suggest that the early use of ECMO offers a survival advantage in such circumstances [1, 2, 5, 7–13]. The percentage of patients with refractory cardiogenic shock who are successfully weaned from ECMO varies from 31% to 76%, depending on the underlying cause of cardiogenic shock [7–14]. Patients successfully weaned from VA ECMO are defined as those having ECMO removed and not requiring further mechanical support because of recurring cardiogenic shock over the following 30 days [3].

However, 20–65% of patients weaned from ECMO do not reach survival to discharge [3, 7–11]. The most frequent reasons for death are cardiac and multisystem organ failure. These observations demonstrate the difficulties in predicting the future of patients after the removal of ECMO [8, 9].

5. Factors predicting death in weaned patients

Successful weaning from ECMO does not signify patient survival. Several studies have assessed the predictors of death after ECMO weaning in particular situations or settings, mainly in postcardiotomy shock and out-of-hospital cardiac arrest [10, 11, 15]. Markers associated with death after weaning include: door-to-VA ECMO implantation time (i.e., the elapsed time between cardiogenic shock and ECMO), cardiopulmonary resuscitation time, poor renal and liver function, high lactate levels, diabetes, obesity, and SOFA score [10, 11, 15]. These death-associated factors reflected the severity and the progression of multiorgan failure at the time of ECMO implantation. They should be considered prior to weaning from ECMO.

6. Factors predicting successful weaning from VA ECMO

Few studies have aimed to identify criteria to predict which patients can be successfully weaned from ECMO.

Fiser et al. studied 51 postcardiotomy patients receiving ECMO to identify factors that could predict when to discontinue ECMO [7]. They found that patients aged over 65 years or with ejection fractions of less than 30% after 48 hours of ECMO were less likely to survive after weaning.

Aissaoui et al. assessed the ability of clinical and echocardiographic variables to predict successful weaning in 51 patients receiving VA ECMO due to medical cardiogenic shock or postcardiotomy shock [3]. Among these 51 patients, 38 hemodynamically stable patients underwent at least one ECMO flow reduction trial, in which the flow rate was reduced to 1.5 L/min under clinical and Doppler echocardiography monitoring. Twenty patients were ultimately weaned from ECMO. High values of arterial systolic and pulse pressure, aortic velocity-time integral, LVEF, and lateral mitral annulus peak systolic velocity were associated with successful weaning. All patients weaned from ECMO had an LVEF ≥ 20 –25%, an aortic velocity-time integral of ≥ 12 cm and a lateral mitral annulus peak systolic velocity of ≥ 6 cm/s under minimal ECMO support. In this study, successful weaning-associated factors are simple and easy-to-acquire echocardiographic variables evaluating LV systolic function (LVEF and lateral mitral annulus peak systolic velocity) and LV flow (aortic velocity-time integral) (**Figure 1**).

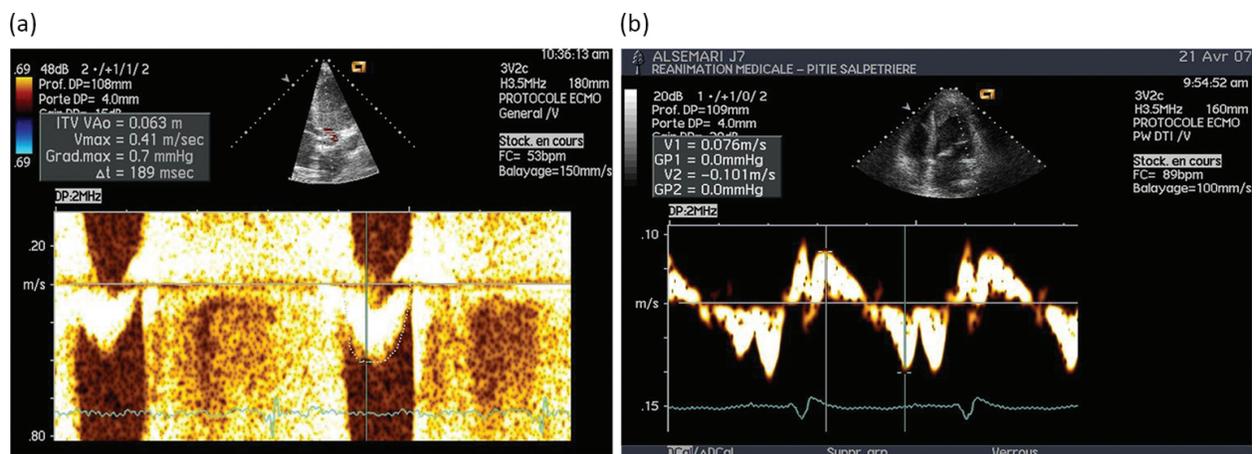


Figure 1. Echocardiographic variables measured by the Doppler method. A. Aortic velocity-time integration obtained by pulsed Doppler measured at the LV outflow tract. B. Lateral systolic peak obtained by spectral Doppler tissue imaging at the lateral mitral annulus.

Luyt et al. examined whether biomarkers could predict cardiac recovery in patients receiving VA ECMO [16]. They studied 41 consecutive patients with potentially reversible cardiogenic shock, and examined circulating concentrations of the N-terminal fragment of the B-type natriuretic peptide, troponin Ic, the midregional fragment of the proatrial natriuretic peptide, proadrenomedullin, and copeptin on days 1, 3, and 7 post-ECMO. There was no difference in

the absolute values of these biomarkers or in their kinetics during the first week between patients who were weaned from ECMO and those who were not.

Thus, the current data suggest that echocardiography is an important tool to determine both the recovery of LV function and the readiness of patients for weaning from ECMO support, whereas early measurements of cardiac biomarkers are not useful for identifying those who will recover [17,18].

7. Appropriate conditions to attempt weaning from ECMO

According to the Extracorporeal Life Support Organization (ELSO) guidelines, hepatic function should have recovered prior to any attempt to wean patients from ECMO, irrespective of the findings of cardiac assessment [19].

In addition, it is unusual to attempt weaning in the first 72 hours after VA ECMO implantation because damaged organs need time to recover. However, the duration of ECMO may be shorter in cases of drug intoxication, and VA ECMO weaning can be attempted earlier [20–22]. In most previous studies, the mean duration of support was at least of 3.3 ± 2.9 days and was even 8.0 ± 6.0 days in one study [3, 9–11, 23]. This time period is also necessary to allow the recovery of a potentially “stunned” myocardium [7]. In these studies, the mean duration of support was longer for patients successfully weaned from ECMO than those who were not [3, 11].

It is not necessary to wait for the recovery of renal function. Restoration of acute renal injury after cardiogenic shock can take up to four weeks after the improvement of cardiac output, by which time significant decreases in elevated filling pressures may have occurred [23, 24]. Other considerations include pre-ECMO status (age, comorbidities, cardiopulmonary resuscitation) and the etiology of cardio-circulatory dysfunction, which must be compatible with myocardial recovery (acute myocarditis, acute myocardial infarction, post-cardiotomy, drug intoxication, septic cardiomyopathy) [1, 2, 6].

VA ECMO should not be removed if the patient has not recovered from the condition which necessitated VA ECMO implantation (high volume overload and high doses of inotropic agents). Volume overload must be managed by diuretic or hemofiltration. Doses of inotropic agents should be decreased to a minimum. Furthermore, pulmonary edema must be resolved and pulmonary oxygenation of the blood must not be compromised [19]. The $\text{PaO}_2/\text{FiO}_2$ ratio should be more than 200 and the oxygen fraction delivered by the extracorporeal circuit should be 21% and that delivered by the ventilator circuits should be less than 60% [25]. These measurements should be made with an ECMO flow rate of less than 1 L/minute and a sweep gas flow rate of 1 L/minute. In case of persistent severe respiratory failure despite cardiac recovery, VA ECMO should be switched to VV ECMO [5].

Factors indicating cardiac recovery and thus patients who can be potentially weaned from ECMO include an increase in blood pressure, and return of pulsatility or an increase in the pulsatility of the arterial pressure waveform [19].

The patient should be considered hemodynamically stable, i.e., they should have a baseline mean arterial pressure (MAP) of >60 mmHg in the absence or at low doses of vasoactive agents, and a pulsatile arterial waveform maintained for at least 24 hours [3].

8. Utility of weaning trials

Weaning trials are essential to assess the behavior of the left ventricle during increases in preload, and to determine whether the ECMO can be removed.

Load conditions can be modified by varying the flow of the VA ECMO centrifugal pump. When ECMO flow is decreased, preload is increased, and afterload is decreased [18].

Aissaoui et al. varied ECMO flow and examined hemodynamic variables of the failed left ventricle in 22 patients receiving VA ECMO. With this approach, they found significant variations between patients who were successfully weaned and those who were not. Indeed, increased preload and decreased afterload were associated with increased systolic function in patients who survived weaning. These changes in systolic variables that occurred during modifications to ECMO flow identified a load-dependent contractile reserve, following the Frank-Starling law. The presence of this contractile reserve was associated with successful weaning [18].

A weaning trial is also very important to evaluate right ventricular (RV) function because the ECMO circuit creates negative pressure and drains venous blood from the right atrium. In these conditions, it is difficult to determine RV function in maximal ECMO flow [3, 4, 17, 18]. A reduction in ECMO flow results in an increase in preload and enables RV function to be assessed.

Cavarocchi et al. assessed the behavior of both ventricles during decreased ECMO support, volume loading and inotropic support in 21 patients [4]. They showed that a weaning trial involving left and right ventricle assessment by transesophageal echocardiography could accurately predict both successful weaning from ECMO and successful left VAD implantation without the occurrence of right ventricular heart failure. The assessment of RV function is very useful specifically in two cases: for patients receiving ECMO for postcardiotomy shock after heart transplantation and for those receiving ECMO prior to VAD implant surgery. Ideal candidates for LVAD placement are those who have isolated LV failure with reasonably recovered RV function. Failure to identify significant coexisting RV dysfunction may significantly increase the risk of postoperative morbidity and mortality in patients undergoing LVAD placement after ECMO, and requires prolonged use of inotropic agents, biventricular support, or extracorporeal support [26].

9. Strategies for carrying out ECMO weaning trials

Two echocardiographic strategies for carrying out an ECMO weaning trial have been reported in the literature: the first strategy involves trans-thoracic echocardiography (TTE) [3], and the second involves hemodynamic transesophageal echocardiography (hTEE) [4].

In the TTE study conducted by Aissaoui et al., an ECMO weaning trial was undertaken daily if: (1) the patient was considered hemodynamically stable, i.e., they had a baseline mean blood pressure of >60 mmHg in the absence or at low doses of vasoactive agents and a pulsatile arterial waveform maintained for at least 24 h; and (2) pulmonary oxygenation of the blood was not compromised [3]. The ECMO flow was decreased to 66% of the initial flow rate for 10–15 min. It was then decreased to 33% for 10–15 min and then to a minimum of 1–1.5 L/min for another 10–15 min.

If mean blood pressure dropped significantly and was constantly <60 mmHg during the trial, ECMO flow was returned to 100% of the initial flow and the trial was stopped. Doppler echocardiography was repeated at each ECMO flow rate. The removal of ECMO was considered if the patient had no end-stage cardiac disease, was partially or fully recovered from the initial cardiac dysfunction, tolerated the full weaning trial, and had a LVEF of >20–25% and aortic VTI of >10 cm under minimal ECMO support.

In the TEE study conducted by Cavarocchi et al., the weaning trial consisted of four stages and involved hemodynamic transesophageal echocardiography [4]. In the first stage, baseline LV and RV volume and function were assessed on full-flow ECMO support. During the second stage, ECMO flow was gradually decreased in increments of 0.5 L/min to half of the original flow rate (stage 2). Throughout the weaning protocol, LV and RV function and hemodynamic responses (heart rate and blood pressure) were monitored continuously to assess ventricular volume and function. If LV or RV distension or significant hypotension occurred, the weaning trial was stopped and the ECMO support was returned to full flow. Stage 3 consisted of monitoring hemodynamic responses during both volume challenge with 5% albumin (10 mL/kg) and a reduction of ECMO flow to a minimum rate of 1.2–1.5 L/min. Volume loading was used to achieve an appropriate preload. During the last stage (stage 4), left and right ventricular function was assessed during the infusion of inodilators (dobutamine and/or milrinone). These drugs were used to assess right ventricle function in patients with LV dysfunction under consideration for LVAD placement. The definitive removal of the ECMO was considered if both LV and RV functions recovered. If LV dysfunction persisted without RV failure, LVAD implantation was considered. An external right VAD placement was considered in cases of isolated, persistent RV dysfunction. If biventricular dysfunction remained, total artificial heart replacement was considered if the patient was a candidate for heart transplantation.

10. Transthoracic echocardiography *versus* transesophageal echocardiography

The weaning assessment requires repeated measurements to be recorded over several days. Echocardiographic variables of LV systolic function (LVEF and lateral mitral annulus peak systolic velocity), LV flow (aortic velocity-time integral), and right ventricular diameters can be used to predict successful weaning. These parameters are factors that are simple and easy-to-acquire with transthoracic echocardiography. For these reasons, the transthoracic approach is a good option because it can be repeated many times [17, 18]. In case of poor echogenicity, the transesophageal echocardiography can be used [4].

11. Hemodynamic assessment during the weaning attempt

Hemodynamic assessment can be useful during the weaning trial. In particular, the presence of volume overload can be determined from measurements of pulmonary capillary wedge pressure and central venous pressure. Such measurements also enable the assessment of cardiac output (cardiac index). Hemodynamic measurements should be performed at full flow, after reducing the ECMO flow to 50% and after stopping the pump.

For patients to be considered for VA ECMO weaning, hemodynamic variables with the pump off should be as follows: cardiac index >2.4 liters/min/m², mean blood pressure >60 mmHg, pulmonary capillary wedge pressure <18 mm Hg, and central venous pressure <18 mmHg [13]. The absence of volume overload can also be verified from this hemodynamic assessment. Systolic RV and LV function have to be evaluated by echocardiography.

12. Anticoagulation during the weaning attempt

ECMO weaning and weaning trials are associated with a risk of thromboembolic complications due to blood stagnation during the reduction of ECMO flow. The ELSO recommends that anticoagulant drugs should be continued during the trial, and that the blood lines and access cannulas should be periodically unclamped to avoid stagnation [19]. The activated partial thromboplastin time should be between 1.5 and 2.5 times the normal value [19, 27].

13. Aids to optimize weaning

Some teams assessed the ability of some medications to facilitate weaning from VA ECMO [28, 29].

The Levosimendan was assessed in six VA ECMO patients with the hypothesis that its remaining effects could favor the weaning from ECMO. This inodilator drug was infused in

the patients 24 h before the planned weaning. In this small study, the use of Levosimendan was associated with an increased rate of successful weaning [28].

In an animal study, the author studied if thyroid hormone supplementation in refractory cardiogenic shock pigs improved abnormalities induced by ischemia-reperfusion, cardiac function, and rate of weaning from ECMO. They found that it improved cardiac function during VA ECMO [29, 30].

These strategies were reported for very small populations or animals and must be confirmed in larger series.

The use of an intra-aortic balloon pump may improve survival in ECMO patients [8, 11]. In a recent study conducted by Petroni et al., the use of an intra-aortic balloon pump in patients receiving VA ECMO restored pulsatility and decreased left ventricular afterload, and was associated with small left ventricular dimensions and low pulmonary artery pressure [31]. No study has assessed the value of intra-aortic balloon pumps during VA ECMO weaning.

14. Proposed weaning strategy

In light of all these data, we propose a strategy to optimize weaning from VA ECMO (Figure 2) [32].

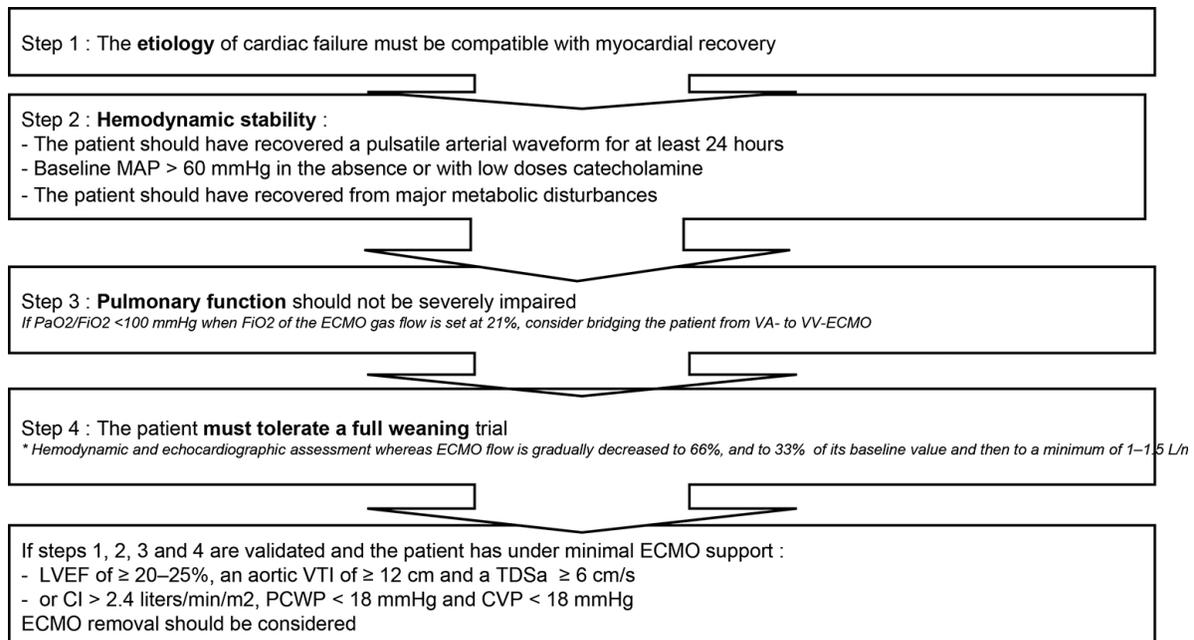


Figure 2. Recommendations for successful weaning from VA ECMO. MAP, mean arterial pressure; VTI, velocity-time integration; LVEF, left ventricular ejection fraction, TDS, tissue Doppler systolic velocity; RV, right ventricle, CI, cardiac index, PCWP, pulmonary capillary wedge pressure, CVP, central venous pressure.

First, some conditions should be gathered.

Hepatic function should first recover.

Patients with end-stage cardiac disease cannot be taken off ECMO. Indeed, the etiology of cardio-circulatory dysfunction must be compatible with myocardial recovery. Examples include acute myocarditis, acute myocardial infarction, post-cardiotomy, drug intoxication, and septic cardiomyopathy. The $\text{PaO}_2/\text{FiO}_2$ ratio should be more than 200.

Volume overload must be managed and doses of inotropic agents should be limited to a minimum.

The patient should be considered hemodynamically stable.

We advocate the use of transthoracic echocardiography over a transesophageal approach. Weaning trials are essential. The ECMO flow should be decreased progressively to a minimum of 1–1.5 L/min for at least 15 min.

The echographic evaluation has to take into account variables assessing LV systolic function (LVEF and lateral mitral annulus peak systolic velocity), LV flow (aortic velocity-time integral), and right ventricular diameters.

A hemodynamic assessment should be carried out to verify the absence of both volume overload and high capillary pressures.

Volume loading can be used to achieve appropriate preload and inotropic support to assess the RV during the weaning trial.

ECMO removal should be considered if the patient does not have end-stage cardiac disease, tolerates the full weaning trial, and has a LVEF of ≥ 20 –25%, an aortic velocity-time integral of ≥ 12 cm and a lateral mitral annulus peak systolic velocity of ≥ 6 cm/s under minimal ECMO support.

15. Conclusion

Weaning from VA ECMO remains a difficult decision because it unfortunately does not signify survival for the patient. We proposed a strategy to optimize the weaning process. It is especially important that the ECMO is not removed while the patient is still recovering from the condition that necessitated the use of VA ECMO implantation. Damaged organs need to recover before attempting weaning and the patient should be considered hemodynamically stable. The etiology of cardio-circulatory dysfunction must be compatible with myocardial recovery. Then, weaning trials and echocardiographic and hemodynamic assessments during these tests are indispensable to assess the behavior of the ventricles and to determine whether the ECMO can be removed.

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