Chapter

ECMO Weaning Strategies to Optimize Outcomes

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Abstract

Survival to discharge in patients presenting with cardiogenic shock who are managed using extracorporeal membrane oxygenation (ECMO) remains low at ~50%. This speaks to the acuity and severity of individuals being placed on ECMO, as well as the time dependent risk for complications associated with this therapy. Although some patients are able to be weaned from ECMO to either recovery, left ventricular assist device or heart transplantation, other individuals do not survive after device removal, suggesting that current protocols may not be identifying individuals with enough intrinsic cardiac recovery to maintain adequate end-organ perfusion. The decision to wean an individual from ECMO is complex and entails several factors that are dynamic and evolving daily while on full circulatory support. Objective clinical, hemodynamic and biological markers are needed to be controlled prior to trialing device weans but many times the decision relies on clinical experience and intuition. The purpose of this chapter will be to: (1) outline the survival and risks associated with ECMO which encourages early weaning trials and (2) identify patient factors related to either successful weaning or early referral for durable mechanical support or transplant.

Keywords: venoarterial ECMO, weaning, cardiac recovery, echocardiography, hemodynamics

1. Introduction

Cardiogenic shock to date remains associated with a significant mortality (50–80%) even after revascularization [1]. For these patients and in those with other forms of refractory cardiogenic shock or cardiac arrest, circulatory support with the use of venoarterial extracorporeal membrane oxygenation (VA-ECMO) has been utilized to stabilize and improve their survival. Its rapidly expanding use across many centers has favorably altered outcomes in severely critically ill patients and in many instances it serves as a bridge to decision or recovery [2]. However, weaning of VA-ECMO represents a significant challenge depending on the initial indication for its use. Moreover, there is a paucity of data on factors that predict weaning success from VA-ECMO and no clear guidelines to determine which patients will survive after device removal.

With the rapid evolving technology of short term mechanical circulatory support and the increasing number of ECMO use across many centers, there needs to be a clear understanding of the indications, hemodynamic impact, limitations and risks associated with its application to determine who will be a good candidate for device wean and removal.

In this chapter we will review the basic principles of VA-ECMO function, predictors of survival, conditions conducive towards successful weaning and lastly, weaning strategies.

2. Venoarterial extracorporeal membrane oxygenation function

VA-ECMO support is a well-established technology that allows for full cardiopulmonary support with the goal to recover organ injury. Patients who may require this therapy include: refractory cardiogenic shock (CS), cardiac arrest (CA), refractory ventricular arrhythmia, acute or decompensated biventricular failure (AHF), pulmonary hypertension associated with right ventricular failure, fulminant myocarditis, and postcardiotomy cardiogenic shock (PCCS) [3].

The primary goal of VA-ECMO is restoration of tissue perfusion and avoidance of permanent end organ dysfunction. It has a unique hemodynamic effect due to its dual circulatory support circuit. The venous drainage cannula reduces flow through the lung vasculature, decreasing stress on the right heart while the arterial outflow cannula increases flow to the systemic arterial vasculature and the afterload to the left ventricle proportionate to the pump speed/flow. With incremental changes in speed and flow, the increased afterload reduces aortic valve opening and, in cases of severe left ventricular dysfunction, severe right ventricular dysfunction or asystole, the aortic valve may not open at all. The implications of the latter include increased LV end diastolic pressure and the development of pulmonary edema.

3. Venoarterial extracorporeal membrane oxygenation outcomes

VA-ECMO has been shown to increase survival to hospital discharge in patients with advanced heart disease with some cases having favorable long-term survival [4]. However, outcomes differ depending on the underlying etiology of cardiopulmonary collapse at the time of VA-ECMO cannulation. In a large national inpatient database from Japan with 5263 patients receiving ECMO, the in-hospital mortality was 37.9%, with 64.4% weaned off the device. Cardiac arrest at the time of hospital presentation was recognized as the primary factor for poor survival compared to cardiogenic shock alone. Moreover, higher age and smaller BMI were associated with in hospital mortality. The majority of patients presenting with cardiogenic shock had underlying ischemic heart disease, followed by heart failure, valvular heart disease and myocarditis. Notably, the preponderance of patients discharged from the hospital after weaning from ECMO were those with heart failure (31.1%) and myocarditis (41.9%) compared to those with ischemic heart disease (20.3%). In-hospital mortality after weaning however remained elevated with about half of the patients who were weaned dying in the hospital. This high mortality suggests non-modifiable risk factors with persistence of critical illness even after weaning VA-ECMO, as well as differences in survival depending on the underlying etiology of shock, with those having ischemic heart disease at the time of presentation experiencing a 79.1% in-hospital mortality [5].

In patients presenting with PCCS, VA-ECMO is a viable salvage strategy associated with increased survival to hospital discharge. In a meta-analysis of 21 studies with 1866 patients, survival to hospital discharge was achieved in 20.8–65.4% of patients placed on VA-ECMO [6]. Even more, PCCS patients undergoing VA-ECMO have an acceptable 5-year survival of 55.8% compared to other types of cardiogenic shock [7].

These findings drastically differ to those presenting with acute myocardial infarction associated CS (AMI-CS) where their survival to hospital discharge remains low (33–59%) [8]. This could potentially be mitigated by early intervention at the time of AMI-CS presentation and VA-ECMO support, specifically in those undergoing simultaneous revascularization. In a study of 334 patients with ST elevation AMI, the group that underwent early VA-ECMO support at the time of percutaneous intervention had a lower 30-day mortality compared to those without the support (30.1 vs. 41.7%) with a strong benefit in those with profound shock—defined as systolic blood pressure <75 mmHg despite intravenous inotropic agent administration and intra-aortic balloon pump (IABP) support associated with altered mental status and respiratory failure—compared to those without (72 vs. 39.1% for 30-day death) [9]. Among notable predictors for 30 days mortality were the presence of advanced heart failure (defined as NYHA ≥ III), post intervention TIMI flow grade ≤2 and profound cardiogenic shock.

Lastly in those with AHF, outcomes on VA-ECMO are less promising depending on the original insult. For those with acute presentations, outcomes on VA-ECMO are more favorable compared to those with a chronic cardiomyopathy [10–12]. Specifically, those with fulminant myocarditis and CS or CA survival to discharge ranged from 60 to 88% [10], compared to only 56% in those with chronic cardiomyopathy [11, 12]. In those with long standing heart failure though the decision to bridge to another salvage strategy is of paramount importance as their cardiac reserve is limited (characterized by low cardiac index and cardiac power) with 77–79% requiring more advanced MCS support including durable VAD to allow for both short-term and long-term survival [11, 12]. Nevertheless, the high mortality rates in patients who receive VA-ECMO heighten the importance of limiting patient selection to those who can be weaned from device support.

When patients present with CS, inserting a VA-ECMO as a bridge to decision device allows for assessment of neurological and end-organ recovery, making short-term prognostication possible. In many instances, commencing support prior to hemodynamic deterioration and multiorgan failure or cardiac arrest can allow for transition to viable long-term therapies including VAD or heart transplantation. Studies have shown that in patients presenting with refractory cardiogenic shock requiring mechanical circulatory support, 56% survive with 26% of patients transitioning to an implantable VAD, 11% undergoing heart transplantation and 18% showing cardiac recovery [12, 13].

4. Venoarterial extracorporeal membrane oxygenation complications

Although ECMO can improve survival to hospital discharge, several studies show significant morbidity with rates increasing with prolonged duration on support. A meta-analysis of 20 studies including 1866 patients demonstrated bleeding as one of the most common complications (40.8%), followed by requirement of dialysis (46%), significant infection (30.4%), limb ischemia (16.9%), and stroke (5.9%). Vascular complications, bleeding and blood transfusions were associated with significant in-hospital mortality [6]. Many of the complications relate to the vascular access site, with femoral cannulation requiring surgical intervention in 20% of the cases [14]. A negative downstream effect of cannulation is distal ischemia which can lead to arterial thrombosis and gangrene. This complication can be mitigated by preemptively placing a small antegrade perfusion cannula to bypass the area of obstruction from the ECMO arterial cannula [15]. Moreover, vascular complications can lead to unsuccessful weaning trials as serious bleeding events increase the need for blood product transfusions and the incidence of thrombotic

events. Specifically, thrombotic events were noted to occur in 17% of patients, mostly as lower extremity arterial thromboses, and can impact the duration on support, increase morbidity and affect overall outcomes [16, 17].

LV distention in VA-ECMO. When contemplating weaning trials to assess for LV recovery, consideration should be taken on the loading effect that VA-ECMO has on the left ventricle. Proper unloading of the LV can avoid complications from LV distention including pulmonary edema, worsening oxygenation, increased left ventricular wall stress, reduced myocardial blood flow and ventricular arrhythmias. In fact, acute pulmonary edema in the setting of peripheral VA-ECMO has been associated with mortality, with many patients dying within hours after implant or requiring conversion to central VA-ECMO [18]. In a study of 121 patients on ECMO with LV distention, 16% required decompression with an Impella device and cardiac recovery was inversely related to the degree of LV distention. Furthermore, those presenting with LV distention requiring decompression had lower survival in the first 30 days following VA-ECMO compared to those not requiring decompression. More so, the study noted that those presenting with acute decompensated heart failure had a delayed LV decompression strategy which was associated lower survival [19]. This may suggest that more aggressive unloading is required upfront when clinical signs of LV distention are present. In one study, adding an Impella device improved 30-day survival in those presenting with AMI compared to other groups. Additionally, in those with cardiogenic shock due to acute decompensated systolic heart failure, unloading can help to stabilize and bridge them to the next strategy. In a series of 52 patients with ADHF, 71% required an LV venting device with the vast majority transitioned to a durable device support [12].

5. Factors associated with successful weaning from VA-ECMO

Determining successful weaning from VA-ECMO relies on multiple variables which can be partitioned into pre-implant and during support factors.

5.1 Pre-ECMO factors

Patient selection. Many risk scores have identified several variables that rely on clinical and biochemical markers. The SAVE score is a tool that discriminates between survivors and non-survivors of refractory cardiogenic shock on VA-ECMO. While younger patients, acute myocarditis, post-heart transplant, refractory arrhythmias and high diastolic blood pressure are protective factors, those with chronic renal disease, prolonged intubation, pre-ECMO organ failure, lower pulse pressure and lower bicarbonate are associated with poor survival. (http://www.save-score.com/) [20]. Similarly to SAVE, the ENCOURAGE survival score utilizes predictors for those presenting with CS due to AMI, however unlike SAVE it places more weight placed on gender, body mass index, Glasgow coma score and level of serum lactate. Survival was also directly proportional to the patient's risk score (probabilities of survival were 80%, 58, 25, 20, and 7% for classes 0–12, 13–18, 19–22, 23–27, and ≥28, respectively [21].

5.2 During ECMO factors

Once VA-ECMO support is initiated, there is a very narrow window to assess end organ function recovery and decide on need for advanced therapies. In a cohort of 124 consecutive patients receiving VA-ECMO for CS, about two thirds of the deaths occurred during the first 4 days due to multiorgan failure, however those

who were supported for more than 6 days had a reduced in-hospital mortality, with 50%, achieving successful device wean. In addition, prolonged support provided an opportunity for improved patient selection with 60% reaching cardiac recovery, 26% undergoing heart transplantation and 14% ventricular assist device (VAD) implant. After a median follow up of 2.4 years, survival at 1 year was 78% for those who achieved cardiac recovery, 51% for those who underwent heart transplant and 75% with VAD implant [18].

LV unloading. Ventricular decompression with an IABP during implant can allow for weaning and survival, bridge to LVAD or transplantation, while its non-use has been associated with increased risk for death during support or after VA-ECMO is withdrawn [22]. A recent meta-analysis of 17 observational studies comprising 3997 patients with 42% receiving an LV unloading device (IABP 92%, percutaneous VAD 5.5%, trans-septal left atrial cannulation 3%) showed a reduction in mortality when utilizing LV unloading devices compared to those without LV unloading (54 vs. 65%, RR 0.79, CI 95% 0.72–0.87). Secondary outcomes for limb ischemia, bleeding, need for renal replacement therapy, multiorgan failure, stroke or transient ischemic attack were not different among all cohorts [23].

Echocardiography. Several echocardiographic indicators exist when considering a weaning trial. Improvement in underlying LV function with an ejection fraction ≥35%, LV outflow tract velocity-time integral >10 cm, tissue Doppler peak systolic velocity of the mitral annulus ≥6 m/s, absence of LV dilatation, and no cardiac tamponade while on minimal support have been shown as good predictors of successful weaning [24, 25]. Similarly, significant improvement in right ventricular function during weaning identifies greater opportunity for survival. In a study of 46 patients on VA-ECMO, RV ejection fraction (RVEF) was assessed by 3D echocardiography. RV free wall strain, RV fractional area change, and central venous pressure were found to be independently associated with RVEF. A cutoff RVEF of >24.6% was found to be a predictor for weaning success after first cannulation with lower values associated with increased all-cause mortality at 30 days (HR 15.86; 95% CI, 3.56–70.73; $p < 0.001$) [26].

Hemodynamics parameters. Multiple hemodynamic variables have been found to be predictive of successful weaning. Presence of a pulse pressure greater than 50 mmHg, elevated systolic pressure greater than 100 mmHg has been associated with good prognosis and survival [25]. Maintaining a perfusion mean arterial pressure (MAP) >60 mmHg with minimal inotropic support is critical [27]. Right heart catheterization data shows that a pulmonary capillary wedge pressure <24, PVR < 1.1 WU, mean pulmonary arterial pressure <25, transpulmonary gradient <10 are recommended parameters to achieve prior to a weaning trial and that inotropic agents as well as pulmonary vasodilators can be of assistance during weaning efforts [26].

Biomarkers. Serological markers of poor perfusion have been associated with worse prognosis. Lactate has been recognized as a biomarker for macrovascular tissue perfusion and early clearance at 24 hours after VA-ECMO initiation has been correlated with weaning and survival [28]. Loforte et al., analyzed 228 patients supported on VA-ECMO primarily post-cardiotomy CS. The authors found that blood lactate level (>3 mmol/L) and a CK-MB index of 10% 72 hours after ECMO initiation, was predictive of a 50% probability of 30-day mortality [29]. An elevated creatinine on the day of withdrawal or weaning trial has been associated with poor outcome with a four-fold risk of death when the level is above 1.4 mg/dL [18].

Tissue perfusion. Derangements in the microvasculature have been noted in both severe sepsis as well as cardiogenic shock, with measures of microcirculation emerging as new markers for tissue perfusion [30]. In those supported by VA-ECMO, there is observational data suggesting that preserved microcirculation

at time of VA-ECMO cannulation may be more specific than hemodynamic measures for identifying successful VA-ECMO weaning and survival. This discordance between the micro and macro-circulation has been described previously as a loss of hemodynamic coherence in part due to heterogeneous flow the organs receive during support, alterations in capillary density and presence of tissue edema [31]. Specifically, one study which assessed microcirculation serially, found that even in the presence of preserved lactate, tissue perfusion as estimated by parameters of microcirculation did not improve on VA-ECMO and those with compromised microcirculation—measured as perfused capillary density and proportion of perfused vessels—could not be weaned from VA-ECMO [32]. A separate study looking specifically at 28-day survival in cardiogenic shock patients placed on VA-ECMO, found that while MAP, pressor requirement and lactate did not differ, microcirculation was better preserved in survivors compared to non-survivors within 12 hours of VA-ECMO support [33]. However, further research is needed to determine if microcirculatory assessment can help guide timing of VA-ECMO weaning.

5.3 Post VA-ECMO wean

Survival post VA-ECMO is predicated on correcting the underlying cause for shock or cardiac arrest, ultimately allowing device removal. However, weaning does not always signify that individuals will survive. Individual factors have to be considered to predict long term survival such as age, comorbidities, complications arising during circulatory support, underlying ventricular function and end organ function. On the latter, renal failure (signified by elevated creatinine level) or hepatic failure (marked by elevated total bilirubin and elevated INR) at the time of wean can impact short-term and long-term survival with multiorgan failure being the predominant mode of death after weaning [22]. If myocardial recovery is unlikely but other factors have been controlled and improved (including renal and hepatic function, lactate and resolution of pulmonary edema), durable VAD or heart transplantation should be taken into consideration, as longer duration on VA-ECMO can reduce the likelihood of survival to discharge or success towards a bridging option. In a small observational study, survival to discharge was higher for those transitioned within 14 days from VA-ECMO support to a VAD compared to those transitioned longer than 14 days (92 vs. 25%, $p < 0.05$) [34].

6. Weaning strategies

6.1 Pharmacological agents

The pharmacologic agents that have been used to assist with weaning trials have primarily been inotropic agents including dobutamine, epinephrine, dopamine, milrinone and levosimendan. Epinephrine, dopamine and dobutamine are catecholamines, with epinephrine and dopamine having alpha-1 activity and thus some crossover with norepinephrine as vasoconstrictors. Dobutamine acts predominantly on beta-1 and beta-2 receptors. Milrinone and levosimendan on the other hand are inotropes without direct adrenergic receptor targets. Milrinone is a type-3 phosphodiesterase inhibitor and augments myocardial contraction by increasing intracellular concentrations of cAMP and calcium. Levosimendan on the other hand is a calcium sensitizer and is postulated to augment myocardial contractility without increasing intracellular calcium and myocardial oxygen consumption. Current evidence supports the use of both milrinone and levosimendan to assist with VA-ECMO weaning [35, 36].

6.2 Weaning trials

Protocols for weaning VA-ECMO include:

1. A stepwise reduction in VA-ECMO flows either by percent of support or by 0.5–1.0 L/min.

2. A pre-specified time interval in which the VA-ECMO flow is reduced for which can range from 10–15 min to 24 h.

3. Baseline parameter thresholds and subsequent measurements assessing for hemodynamic tolerance and myocardial adaptation to changes in preload and afterload as flows decrease.

4. Using continuous or intermittent transthoracic or transesophageal echocardiogram.

5. Frequency of weaning trials may occur daily, but typically occur 24–72 hours after VA-ECMO institution to allow for reversal and recovery from the inciting injury [29, 37–40].

In addition to requiring full anticoagulation during weaning trials, flows cannot be turned down below 1–1.5 L/min because of concerns for thrombus formation within the VA-ECMO circuit. Thus, clinicians must monitor changes in hemodynamic and echocardiographic parameters as VA-ECMO flows are decreased and terminate weaning if evidence of hemodynamic compromise or intolerance to preload changes such as loss of pulsatility, ventricular dysfunction or increases in filling pressures are seen. Hemodynamic tolerance during the weaning trial is extrapolated to imply myocardial recovery has occurred and that decannulation will be tolerated by the patient. In order to allow clinical assessments off VA-ECMO support entirely, some centers are using arteriovenous cannula bridging strategies that form a circuit that bypasses the patient [41], or a separate technique pioneered in neonates that reduces pump flow until the circuit runs retrograde [42, 43].

7. Proposed weaning protocol

Assessing the readiness for VA-ECMO weaning involves withdrawal or reversal of the inciting injury, maintenance or recovery of extracardiac organ function, and lastly myocardial recovery. Prior to weaning attempts, hemodynamic stability and adequate tissue perfusion defined as a MAP ≥ 60–65 mmHg while on minimal pressor support, arterial pulsatility and lactate levels < 2 mmol/L should be achieved. VA-ECMO flow should be reduced by 0.5–1.0 L/min in 5–10-min intervals with continuous invasive hemodynamic and echocardiographic monitoring. In instances where adequate transthoracic windows cannot be achieved, transesophageal echocardiogram should be performed, and biventricular size and function monitored. Because some parameters of left ventricular function including aortic VTI and TDSa are not easily obtained by both transthoracic and transesophageal echocardiography, we recommend measuring changes in ventricular size and visual assessments of ventricular function and valvular regurgitation. In instances where CVP rises to greater than 1518 mmHg (depending on ventilator settings) and the RV dilates with worsening function and tricuspid regurgitation, the weaning trial should be aborted. Left sided function and loading conditions may vary depending on venting strategies, however, in cases where PCWP rises above 20 mmHg and

arterial line pulsatility is lost due to LV dysfunction, isolated LV mechanical support should be considered. Prior to final decannulation in the operating room, the VA-ECMO speed should be left at 1.5 L/minutes for an hour to assess stability of hemodynamic, echocardiographic and tissue perfusion parameters.

8. Conclusion

VA-ECMO can rapidly stabilize patients and provide organ perfusion to those with refractory cardiogenic shock or cardiac arrest. Albeit associated with multiple complications that increase with longer duration of support, in the right patient it can improve the survival. Weaning strategies should be implemented as soon as the underlying condition has been corrected and improvement in metabolic, hepatic, pulmonary and renal function has occurred. Use of hemodynamic, echocardiographic and serological markers of recovery should be taken into account prior and during each weaning trial to assess success of weaning or if need of VAD or heart transplantation should be considered.

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