Venoarterial extracorporeal membrane oxygenation in cardiogenic shock

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VA-ECMO in cardiogenic shock – indications, mode of operation, current evidence

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ABSTRACT

Purpose of review: Temporary circulatory support (TCS) with venoarterial extracorporeal membrane oxygenation (VA-ECMO) is increasingly used as a salvage therapy for patients with refractory cardiogenic shock. This article provides an overview of VA-ECMO principles, indications, management, complications and discusses the results of recent case series and trials.

Recent findings: VA-ECMO is utilized as a bridge to "decision" that includes weaning after cardiac function recovery, transplantation, long-term mechanical circulatory support and withdrawal in case of futility. VA-ECMO is considered the first-line TCS since it allows rapid improvement in oxygenation, is less expensive, and is also suitable for patients with biventricular failure. Combining Impella or intra-aortic balloon pump support with VA-ECMO might decrease left ventricular pressure and improve outcomes. Massive pulmonary embolism, sepsis-associated cardiomyopathy, refractory cardiac arrest are among emerging indications for TCS.

Summary: TCS have become the cornerstone of the management of patients with cardiogenic shock, although the evidence supporting their efficacy is limited. VA-ECMO is considered the first-line option, with a growing number of accepted and emerging indications. Randomized clinical trials are now needed to determine the place VA-ECMO in cardiogenic shock treatment strategies.

Keywords: temporary circulatory support; venoarterial extracorporeal membrane oxygenation; cardiogenic shock; intra-aortic balloon pump; percutaneous active mechanical circulatory support devices.

ABBREVIATIONS

AMI: acute myocardial infarction

CPR: cardiopulmonary resuscitation

ECPR: extracorporeal cardiopulmonary resuscitation with ECMO

ESC: european society of cardiology

IABP: intra-aortic balloon pump

LV: left ventricle

NIRS: near-infrared spectroscopy

PE: pulmonary embolism

PCA: percutaneous coronary angiography

SAPS II: simplified acute physiology score II

SAVE: survival after venoarterial extracorporeal membrane oxygenation

TAVI: transcatheter aortic valve insertion

TCS: temporary circulatory support

VA-ECMO: venoarterial extracorporeal membrane oxygenation

VT: ventricular tachycardia

A. INTRODUCTION

Temporary circulatory support (TCS) devices have become the cornerstone of the management of patients with severe or refractory cardiogenic shock, although their use only received a Class IIb recommendation from the European Society of Cardiology (ESC)(1). However, the intraaortic balloon pump (IABP) is now not recommended by ESC guidelines, since the large IABP-SHOCK II trial, which randomized 600 patients with cardiogenic shock complicating acute myocardial infarction (AMI), found no difference in mortality and any of the secondary study endpoints between IABP or conventional treatment(2). More recently, a large propensity matched case-controlled series showed that routine treatment with an Impella device was also not associated with lower 30-day all-cause mortality compared with matched patients from the IABP-SHOCK II trial(3).

Venoarterial extracorporeal membrane oxygenation (VA-ECMO), which provides both respiratory and cardiac support and adequate blood flow to vital organs in shock patients, might be associated with better outcomes in this setting, although high-grade scientific evidence is still lacking(4). This article provides an overview of VA-ECMO principles, indications, management, complications and discusses the results of recent case series and trials in this setting.

B. GENERALITIES ON VA-ECMO

Description and accepted indications

In the last decade, VA-ECMO has been increasingly used in the setting of cardiogenic shock, since it provides both respiratory and cardiac support, is easy to insert, even at the bedside, provides stable flow rates, and is associated with less organ failure after implantation compared to large biventricular assist-devices that require open-heart surgery. Accepted indication for VA-ECMO includes patients with medical (AMI, myocarditis, intoxication with cardiotoxic drugs, end-stage dilated cardiomyopathy), post-cardiotomy or post-transplantation cardiogenic shock refractory to conventional treatments(5–8). Most of these patients receive the device as salvage therapy after having already developed signs of refractory cardiogenic shock with multiple organ failure. In these

situations, VA-ECMO is used as a bridge to decision-making if the patient survives the first days. In patients with potentially reversible heart failure (e.g. myocarditis, myocardial stunning post-AMI), VA-ECMO may also be used as a bridge to cardiac function recovery(9–11).

With the improvement of biomaterials and technologies, VA-ECMO can now stay in place several days or even weeks, as a bridge to "decision" that includes recovery, transplantation, long-term mechanical circulatory support or withdrawal in case of futility(12). Compared to percutaneous active mechanical circulatory support devices, VA-ECMO is less expensive, allows rapid improvement in oxygenation and is the only short-term device suitable for patients with severe biventricular failure.

ECMO programs

The use of ECMO has considerably increased in the last two decades. In the National Inpatient Sample in the United States, admission of ECMO patients rose 361% from 2008 to 2014 with patients' comorbidity score increasing and mortality decreasing from 62.4% to 42.7%(13). As with other complex techniques in medicine, a volume-outcome relationship has been suggested in ECLS, with patients receiving ECMO at hospitals with more than 30 adult annual ECMO cases had significantly lower odds of mortality(14). Consistent with this observation, a position paper of an international group of ECMO specialists proposed an organization of ECMO programs for cardiac failure in adults defining the concept of "ECMO teams" and advocating for the establishment of ECMO programs worldwide. Multidisciplinary team of experts are required to guide the institutional use of VA-ECMO and the care of patients receiving it. Rigorous patient selection and careful attention to potential complications are key factors in optimizing patients' outcome. Clearly defined pathways for the referral of VA-ECMO patients to care centers capable of providing long-term assisting devices or heart transplantation are mandatory to provides the highest level of care for those patients unable to be weaned from the device(15). Lastly, a mobile ECMO rescue team should allow the retrieval on ECMO of patients hospitalized at remote hospitals without ECMO capability, a strategy

which was associated with similar patient's prognosis as compared to patients who received ECMO at the ECMO center(16).

Long-term quality-of-life

There are few data on the long-term quality-of-life of patients supported by VA-ECMO. In 81 patients given VA-ECMO supports, 34 (42%) survived to hospital discharge. Mean Short-Form 36 scores (evaluating sequelae and health-related quality-of-life) in the 28 long-term survivors were significantly lower than matched healthy controls for physical role, general health and social functioning but higher than those reported for patients on chronic hemodialysis, with advanced heart failure or after recovery from acute respiratory distress syndrome(17).

C. EMERGING INDICATION FOR VA-ECMO

Massive pulmonary embolism

Some patients with massive pulmonary embolism (PE) will develop right ventricular failure, hypoxemia, and severe hemodynamic instability. In this setting, VA-ECMO might lower their right ventricular overload, improve hemodynamic status, and restore tissue oxygenation(18). However, whether VA-ECMO should be used as a stand-alone therapy or associated with surgical or catheter-based embolectomy is still debated. In a large series of 180 high-risk PE, 52 patients received VA-ECMO: as a standalone therapy (n=18), after failed fibrinolysis (n=20) or before/after embolectomy (n=7/n=10). Mortality was higher in patients under VA-ECMO (62% vs. 43%, p=0.008) with the patients in the VA-ECMO + embolectomy group (30-day mortality 29%) having the most favorable outcome(19).

Sepsis-associated cardiomyopathy

Profound myocardial depression may develop because of severe septic shock. There are emerging data suggesting that VA-ECMO may rescue patients who develop refractory cardiac failure

in this setting(9,20). A recent study reported poor outcome in 71 patients implanted with VA-ECMO for refractory septic shock with a 15.5% weaning rate and a 7.0% hospital discharge survival(21). Larger studies are still needed to determine whether the benefit of ECMO outweighs the risks, especially in cases where septic shock is complicated by marked disturbances in coagulation.

Circulatory support for high-risk invasive procedures

In patients with acute heart failure, some invasive procedure may be at high-risk while they are mandatory for the patient's condition to improve. Several reports suggest that VA-ECMO may be used as circulatory support during these procedures.

A systematic review reported 203 (3.9%) patients from 9 studies requiring cardiopulmonary bypass or VA-ECMO peri-procedurally during transcatheter aortic valve insertion (TAVI) with a 29.8% short-term and 52.4% 1-year mortality(22).

A study comparing patients with refractory cardiogenic shock complicating ST-segment elevation AMI implanted with VA-ECMO before (n=12) or after (n=34) percutaneous coronary angiography (PCA) reported an improved 6-month survival (58.3% vs. 14.7%, p=0.006) in patients with early VA-ECMO implantation. However, the proportion of patients achieving door-to-balloon time <90 min was lower (9.1% vs. 32%)(23). In 106 consecutive patients implanted with VA-ECMO around PCA for refractory cardiogenic shock, the implantation of VA-ECMO before or during PCA granted the most favorable 30-day survival compared to implantation after PCA(24).

A study investigated the role of VA-ECMO as a circulatory support for ventricular tachycardia (VT) ablation in 64 patients. Forty (62%) patients presented with electrical storm and 14 (22%) had refractory cardiogenic shock. At least one VT was terminated in 81% of procedures with baseline inducible VT, and VT noninducibility was achieved in 69%. Acute heart failure occurred in 5 patients: 3 underwent emergency heart transplantation, 1 had left-ventricle assisting device implantation, and 1 patient eventually died. All other patients were discharged alive(25). Future randomized studies are warranted to determine the benefit of prophylactic VA-ECMO before high-risk invasive procedures.

Cardiac arrest

VA-ECMO support to restore circulation during cardiac arrest is known as extracorporeal cardiopulmonary resuscitation (ECPR). Although there are no randomized controlled trials reporting the efficacy of ECPR, its use has been steadily increasing(26), despite being the subject of controversies(27). Recent results from a US database suggest an increase in the use of VA-ECMO for ECPR from 2008 to 2014 (0.1% to 0.7%, p_{trend} <0.001) with 3650 (0.4%) patients hospitalized after out-of-hospital cardiac arrest implanted with VA-ECMO on the overall period. Survival to discharge was significantly higher in patients who were selected to receive TCS (56.9% vs. 43.1%, OR 1.16 95%CI (1.11-1.21), p<0.001)(28). In a propensity-matched retrospective study comparing the outcomes and the long-term neurologic prognosis of cardiac arrest treated with ECPR (n=80) or conventional cardiopulmonary resuscitation (n=80), survival to hospital discharge was not different between groups (ECPR 23% vs. 18%, p=0.4) while the cox-regression analysis stratified by matched pairs showed higher favorable neurological (Cerebral Performance Category 1-2) outcome rate in the ECPR group (log-rank test p=0.003)(29). VA-ECMO might also be initiated in the case of post-cardiac arrest cardiogenic shock. In a series reporting the outcomes of 94 patients implanted with VA-ECMO in this setting, hospital and 12-month survival rates were 28 and 27 %, respectively and all 1-year survivors were cerebral performance category 1(30).

D. MANAGEMENT OF VA-ECMO PATIENTS

Left ventricle unloading

Since VA-ECMO provides retrograde blood flow in the aorta, it increases left ventricle (LV) afterload, may decrease or abolish heart ejection and may induce pulmonary edema by increasing LV end-diastolic pressure(31,32). In a recent meta-analysis including 17 studies and 3997 patients, mortality was lower (54% vs. 65%, RR 0.79 95%CI [0.72-0.87]; p<0.00001) in patients with concomitant LV unloading which most frequently combined ECMO and IABP(33). In a retrospective

study including 259 VA-ECMO patients, the 104 patients who received IABP had a lower frequency of hydrostatic pulmonary edema and more days off mechanical ventilation under VA-ECMO(31). LV unloading using Impella (2.5 or CP) in addition to VA-ECMO was successfully used in 106 patients with a 30-day survival of 35.8%, higher than predicted by SAVE (20%) or SAPS II score (6.9%) with a marked decreased of pulmonary capillary wedge pressure after addition of the device to VA-ECMO(34,35). Future randomized studies are warranted to determine if these combination strategies are superior to stand-alone devices.

Peripheral vascular complications

Vascular complications frequently occur in patients with VA-ECMO. A recent study of 432 patients with surgically inserted VA-ECMO reported 16.7% of major vascular complication with significant association to patient's prognosis. Obesity, association to IABP and hemostasis disorders were the main factors associated to major vascular complication(36). As malposition of the distal perfusion line can contribute to limb ischemia, a method using contrast-enhanced Doppler echography have been described to ensure correct position of the perfusion line(37). In a propensity-match study including 532 patients receiving VA-ECMO, percutaneous (n=266) compared to surgical (n=266) cannulation was associated to significantly less local infection (16.5% vs 27.8%, p=0.001), similar rated of limb ischemia (8.6% vs. 12.4%, p=0.3), sensory-motor complications (2.6% vs 2.3%, p=0.8) and improved 30-day survival (63.8% vs. 56.3%, p=0.03). However, more vascular complication following decanulation requiring surgical revision (14.7% vs. 3.4%, p<0.0001) occurred after percutaneous cannulation(38).

Neurological complications

The frequency of ECMO-related brain injury was 7.4% in 878 VA-ECMO patients, with 5.3% of ischemic strokes and 2.8% of intracranial bleeding. Intracranial bleeding but not ischemic strokes were associated with higher mortality(39). Early severe background abnormalities and the lack of

sleep transients on standard and continuous electroencephalography were associated with poor neurological outcome of VA-ECMO patients, suggesting the value of electroencephalography in predicting the neurological outcome in such patients(40). Cerebral near-infrared spectroscopy (NIRS) is a noninvasive monitoring technique that can provide continuous value of forehead regional oxygen tissue saturation, which represents the balance between cerebral oxygen delivery and cerebral oxygen consumption. A recent study reported the association between cerebral desaturation on NIRS with acute brain injury and mortality in VA-ECMO patients(41). NIRS could be an interesting and simple monitoring tool, introducing new therapeutic goals in VA-ECMO patients.

Hematologic complications

Hemorrhagic complications are frequent in VA-ECMO patient. In a center using a blood conservation protocol including: a transfusion trigger of hemoglobin <7.0g/dL and a low-dose anticoagulation targeting activated partial thromboplastin time of 40 to 60 seconds, 63.2% of patients required red blood cell transfusion while bleeding and severe bleeding occurred in 26.3% and 5.3% patients respectively(42). Several studies recently suggested the role of acquired von Willebrand syndrome in bleeding manifestation of VA-ECMO patients. An experimental study showed the impact of continuous-flow compared to pulsatile flow in the genesis of acquired von Willebrand syndrome, stressing the importance of pulsatility in mechanical circulatory devices(43). A retrospective study found no difference in terms of thrombotic complications, but a significant decrease in severe bleeding complications (11.5% vs. 32%, p=0.01), in 52 VA-ECMO patients treated without continuous heparin infusion compared to 50 patients treated with heparin aiming an activated clotting time between 180 to 220 seconds(44). A national French multicenter study reported a very low frequency of heparin-induced thrombocytopenia (0.36%, n=21/5797) in VA-ECMO with no impact on patient's survival(45).

Infections

Infections are one of the main complications in VA-ECMO patients. In a retrospective monocentric study including 220 patients under VA-ECMO, 64% developed a nosocomial infection including: ventilator associated pneumonia 55%, bloodstream infections 18%, mediastinitis 11% and cannula infections 10%. The only independent predictor of first nosocomial infection was a more critical condition at ICU admission defined by high day-0 SOFA score (HR 1.04 (1.00-1.08), p=0.05)(46). Besides being frequent, the treatment of infection under VA-ECMO is challenging, as little is known about the impact of ECMO membrane on antibiotic pharmacokinetics. Recent data suggested a marked increase of distribution volume in ECMO patients resulting in insufficient amikacin peak, especially in patients with low-BMI and positive 24-h fluid balance, that may require increase of amikacin administrated dose(47).

Weaning

When a VA-ECMO patient is hemodynamically stable, is not suffering from end-stage cardiac disease and has partially or fully recovered from the initial cardiac dysfunction, a VA-ECMO weaning trial can be undertaken. The trial consists in reducing VA-ECMO flow <1.5L/min to assess hemodynamic tolerance and Doppler echocardiographic parameters. An aortic velocity time integral ≥ 12cm, a LV ejection fraction >20-25% and a spectral tissue Doppler lateral mitral annulus peak systolic ≥ 6cm/s at minimal VA-ECMO flow during the weaning trial have been associated with successful VA-ECMO weaning(48). In a retrospective monocentric study including 240 patients under VA-ECMO after cardiovascular surgery, the use of levosimendan, a calcium-sensitizing inotropic agent that improves myocardial function, was associated with successful VA-ECMO weaning(49). Further studies are required to determine the place of levosimendan in the weaning of VA-ECMO patients.

E. CONCLUSION

VA-ECMO has become the cornerstone of the management of patients with severe or refractory cardiogenic shock, although its use only received a Class IIb recommendation from the ESC(1).

Because it is less expensive than other devices, allows rapid improvement in oxygenation and is the only short-term device suitable for patients with severe biventricular failure, VA-ECMO has emerged as the first-line support system in this setting, with a growing number of accepted indications. Randomized clinical trials are now urgently needed to determine the benefit of VA-ECMO in strategies to treat cardiogenic shock patients(50).

KEY POINTS (3-5)

- TCS with VA-ECMO have become the cornerstone of the management of patients with severe or refractory cardiogenic shock.
- VA-ECMO has emerged as the first-line TCS in patients with severe or refractory cardiogenic shock, with a growing number of accepted indications (acute myocardial infarction, fulminant myocarditis, acute decompensation of chronic cardiomyopathy, cardiac arrest…).
- Impella and intra-aortic balloon pump may be associated to VA-ECMO to decrease LV pressures and improve outcomes.
- Sepsis-associated cardiomyopathy, massive pulmonary embolism and refractory cardiac arrest are among emerging indications for VA-ECMO.
- Randomized clinical trials are needed to determine the respective place of different mechanical circulatory devices in strategies to treat cardiogenic shock patients.

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REFERENCE DESCRIPTION

Mebazaa et al. [5]

*: this review article focused on the management of cardiogenic shock complicating myocardial infarction.

Guglin et al. [6]

**: Expert panel comprehensive review of VA-ECMO, which describes indications, management, complications and outcomes of adult patients who received VA-ECMO.

Abrams et al. [15]

**: Position paper of an international group of ECMO specialists for the organization of ECMO programs for cardiac failure in adults.

Meneveau et al. [19]

*****:*** this multicenter study on VA-ECMO in high-risk pulmonary embolism revealed a unfavorable outcome of VA-ECMO for failed fibrinolysis or as a standalone therapy but showed encouraging results if associated to surgical embolectomy.

Russo et al. [33]

**: this meta-analysis of 17 observational studies suggested that left ventricular unloading, mainly using intra-aortic balloon pump, in patients with VA-ECMO is associated with improved survival.

Scharge et al. [34]

*: this retrospective study reported the effect of left ventricular unloading with the Impella device in 106 consecutive VA-ECMO patients.

Yang et al. [36]

*: this retrospective study reported the frequency and factors associated with vascular complication in VA-ECMO patients.

Danial et al. [38]

**: this large retrospective study compared vascular complications and outcomes of VA-ECMO patients who received percutaneous or surgical arterial cannulation.

Le Guennec et al. [39]

**: this large retrospective study reported the frequency, associated factors and prognosis of neurological complications in 878 VA-ECMO patients.

Vincent et al. *[43]*

**: this bench-to-bedside study underlined the role of continuous flow of mechanical circulatory support in the genesis of acquired von Willebrand syndrome.

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