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Review

Venoarterial Extracorporeal Membrane Oxygenation in Adults With Septic Shock: Hope or Hype?

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ABSTRACT

Septic shock is associated with significant morbidity and mortality, but a subset of patients with sepsis will experience transient myocardial depression, termed sepsis-associated cardiomyopathy, which markedly increases observed mortality. Although venoarterial extracorporeal membrane oxygenation (VA-ECMO) can provide temporary mechanical circulatory support in medically refractory sepsis, survival in patients with VA-ECMO for sepsis has been historically poor. Concerns regarding numerous potential harms associated with VA-ECMO, including further seeding of infection, exacerbation of inflammation and vasoplegia, bleeding, thrombosis, and distal limb ischemia have further tempered enthusiasm in the setting of sepsis. However, there may be a subset of patients with profound sepsis refractory to medical therapy that could potentially derive some benefit from VA-ECMO. This review provides an overview of the pathophysiology, diagnosis, and treatment of sepsis-associated cardiomyopathy and then focuses on the utility of VA-ECMO in this patient population. A summary of the scant published outcomes of VA-ECMO in sepsis-associated cardiomyopathy is provided, followed by a discussion of important management considerations to optimize outcomes in these extremely sick patients, and finally the pros and cons of VA-ECMO in the setting of sepsis are presented. Using available published data and current state-of-the-art practice, we conclude that VA-ECMO may be a reasonable consideration in highly selected patients with low ejection fraction sepsis-associated cardiomyopathy and refractory hypoperfusion in appropriately equipped health care systems, but more supportive data are required before VA-ECMO can be generally recommended in patients with septic shock.

RÉSUMÉ

Le choc septique est associé à une morbidité et à une mortalité importantes. Un sous-ensemble de patients atteints de septicémie présentera une dépression myocardique transitoire appelée « cardiomyopathie septique » qui augmente considérablement la mortalité observée. L'oxygénation extracorporelle par membrane (ECMO) par voie veino-artérielle (ECMO-VA) offre une assistance circulatoire mécanique temporaire en cas de septicémie réfractaire aux traitements pharmacologiques, mais le taux de survie n'a pas toujours été bon chez les patients ayant bénéficié d'une telle intervention. Les inquiétudes suscitées par les nombreux risques associés à l'ECMO-VA, notamment la propagation de l'infection, l'exacerbation de l'inflammation et la vasoplégie, les saignements, la thrombose et l'ischémie dans les membres distaux, sont venues tempérer davantage l'enthousiasme dans le contexte de la septicémie. Pourtant, un sous-ensemble de patients présentant une septicémie profonde réfractaire aux traitements pharmacologiques pourrait tirer un bienfait de l'ECMO-VA. Ce compte rendu donne un aperçu de la physiopathologie, du diagnostic et du traitement de la cardiomyopathie septique; il s'intéresse ensuite à l'utilité de l'ECMO-VA dans cette population de patients. Les quelques articles parus sur l'utilisation de l'ECMO-VA en présence d'une cardiomyopathie septique y sont résumés, et les éléments importants de la prise en charge pour optimiser le pronostic chez ces patients gravement malades y sont débattus. Enfin, les avantages et les inconvénients de l'ECMO-VA en cas de septicémie sont présentés. Les données publiées et les meilleures pratiques actuelles nous amènent à conclure qu'il est raisonnable d'envisager l'ECMO-VA chez un petit nombre de patients triés sur le volet présentant une cardiomyopathie septique avec diminution de la fraction d'éjection et une hypoperfusion réfractaire, dans un établissement de soins de santé qui dispose de l'équipement nécessaire, mais d'autres données s'imposent avant que l'ECMO-VA puisse faire l'objet d'une recommandation générale chez les patients présentant un choc septique.

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Standard of care for the treatment of sepsis, according to the 2021 Surviving Sepsis Campaign Guidelines, includes early initiation of antibiotics, fluid resuscitation, and addition of

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vasopressors such as norepinephrine to maintain adequate perfusion pressure.[1] Up to 65% of patients experience transient myocardial dysfunction in the setting of sepsis, referred to as sepsis-associated cardiomyopathy or septic cardiomyopathy, and in some cases this reversible myocardial depression can be profound.[2,3] Whereas mild myocardial dysfunction may be well tolerated in sepsis, severe myocardial dysfunction is associated with up to 80% mortality.[2,4,5]

Venoarterial extracorporeal membrane oxygenation (VA-ECMO) is a form of temporary mechanical circulatory support used for cardiopulmonary failure, most often for refractory cardiogenic shock. VA-ECMO comprises a circuit in which a drainage cannula will direct blood from a large central vein (eg, femoral vein or internal jugular vein) or the right atrium into an oxygenator membrane with a centrifugal or roller pump, filter, and various sensors. The oxygenated blood is then directed back into the body through a cannula in a major artery (eg, femoral artery, axillary artery, or aorta). Patients who require VA-ECMO are generally extremely sick, and overall survival in these cohorts of patients has been poor. Pooled international data from the Extracorporeal Life Support Organization (ELSO) suggests an overall survival to discharge of approximately 44% for patients requiring VA-ECMO for cardiac reasons. An individual patient data meta-analysis of 4 randomized control trials showed no difference in survival for patients undergoing VA-ECMO for myocardial infarction-related cardiogenic shock,[6] largely driven by the results of the **E**xtra**c**orporeal **L**ife **S**upport in Infarct-Related Cardiogenic **Shock** (ECLS-SHOCK) trial.[7] In addition to no consistent evidence for efficacy in randomized control trials, VA-ECMO is also associated with significant complications including bleeding and peripheral vascular ischemia.[6] Despite these findings, the use of VA-ECMO continues to increase around the world.[8]

The use of VA-ECMO in the setting of sepsis is controversial. In the pediatric setting, VA-ECMO has been used with some success in septic shock, leading to a weak recommendation for its use as salvage therapy in the Surviving Sepsis Campaign for Children.[9-11] However, the utility of VA-ECMO in septic shock complicated by severe myocardial dysfunction has been met with less enthusiasm in adults because of variable results.[2,12-17] The Surviving Sepsis Campaign Guidelines has not made recommendations for the utility of VA-ECMO in the setting of sepsis with severe myocardial dysfunction in adults because of lack of evidence demonstrating consistent improvement in outcomes.[1]

Historically, VA-ECMO has not been recommended for sepsis because of concerns of exacerbating the dysregulated host response to infection. VA-ECMO and sepsis share some common pathophysiological features including vasoplegia and immune system suppression (immunoparesis). Once blood contacts the nonendothelialzed ECMO circuit, the complement system, coagulation cascade, and cellular immune response are activated. Activation of these systems compounds the vasoplegia, capillary leak, immunoparesis, thrombotic, and bleeding sequelae that can be seen in advanced sepsis.[18] Furthermore, the potentially increased risk of persistent bacteremia or spread of infection caused by colonization of the ECMO circuit may result in an amplified inflammatory insult. Despite these concerns, some have suggested a benefit of VA-ECMO in refractory sepsis in very specific populations, including patients with sepsis and significant cardiac dysfunction.[3]

Effective use of VA-ECMO in refractory sepsis requires careful consideration of multiple intersecting concerns, including phenotype of hypoperfusion, state of septic inflammation and microcirculatory dysfunction, source control, baseline comorbidities and burden of acute organ dysfunction, and anatomic considerations. Nonetheless, VA-ECMO may represent an additional treatment modality for septic patients with refractory shock, particularly those with significant sepsis-associated cardiomyopathy. The current review aims to summarize the available data on the utility of VA-ECMO in refractory sepsis and make recommendations to provide a framework based on contemporary clinical practice in the context of limited efficacy data.

Pathophysiology of Sepsis-Associated Cardiomyopathy

Sepsis-associated cardiomyopathy results from the sequelae of a dysregulated host response to infection, presenting as isolated left ventricular (LV) dysfunction, isolated right ventricular dysfunction, or—more often—biventricular dysfunction. It may manifest as systolic dysfunction, diastolic dysfunction, or both.[5,19] Initially, patients with normal baseline cardiac function may continue to have apparently normal left ventricular ejection fraction (LVEF), but this is in the context of decreased preload and afterload caused by increased vasodilatation and vascular permeability.[5,21] After appropriate fluid loading, the LV dilates, and the LVEF may decrease.[5,21] In fact, decreased LVEF and LV dilatation may suggest adequate preload and appropriate myocardial adaptation to the loading conditions of sepsis as a result of increased LV end diastolic volume and preserved stroke volume.[5,21,22] Sepsis-associated cardiomyopathy is often transient; survivors often recover with normal myocardial function after 1 to 2 weeks.[5,20]

The precise pathogenic mechanisms underlying sepsis-associated cardiomyopathy remain incompletely elucidated, but several factors have been implicated: oxidative and nitrosative stress, abnormalities in calcium handling and myofilament sensitivity, mitochondrial dysfunction, coronary microvascular dysfunction, downregulation of sarcomeric and mitrochondrial genes, circulating myocardial depressant substances, and adrenergic pathway downregulation.[3,21,23,24] Pattern recognition receptors (PRRs) that bind to pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) promote a proinflammatory signaling cascade, leading to subsequent cell/tissue injury and death.[25] Key cytokines known to be myocardial depressant factors, such as tumour necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), and nitric oxide, depress cardiac contractility by impairing mitochondrial function, disrupting calcium homeostasis, and depressing the reticuloendothelial system.[3] Mitochondrial dysfunction, thought to be central to sepsis-associated cardiomyopathy, involves disrupted oxidative phosphorylation, increased reactive oxygen species (ROS), and altered energy metabolism. Damaged mitochondria lead to reduced adenosine triphosphate (ATP) synthesis, calcium release, and activation of proapoptotic proteins, contributing to myocardial dysfunction.[26] Elevation of biomarkers such as troponins and brain

natriuretic peptides occurs following these processes, which may prove useful as prognostic indicators.[3,27-29] Ultimately, an improved understanding of the pathophysiology of myocardial dysfunction in sepsis will fundamentally improve our ability to diagnose, prognosticate, and manage this high-mortality entity in sepsis.

Diagnosis

The decision to initiate VA-ECMO in patients with sepsis refractory to medical management obligates assessment of cardiac function. Patients with ongoing end-organ malperfusion despite antibiotics, administration of fluids, and vasopressor infusion should trigger an evaluation of cardiac function (Fig. 1). Evaluation of cardiac function includes echocardiography and invasive hemodynamics, including pulmonary artery catheterization. Diagnostic echocardiography remains among the most accessible formal imaging tools for diagnosis of myocardial dysfunction. Although some groups are working on categorizing different cardiovascular phenotypes of sepsis based on echocardiography,[30] there are, at present, no widely accepted classifications or criteria for diagnosis of sepsis-associated cardiomyopathy. Because of the fluctuating nature of loading conditions seen in sepsis (eg, fluid resuscitation and vasoplegic shock), echocardiographic measurements influenced by preload and afterload may be unreliable.[3] LVEF may help provide a "gestalt" of myocardial function but should not be taken on its own to make the diagnosis, as LVEF fluctuates with preload and afterload.[31] Nonetheless, most studies reporting VA-ECMO in sepsis-associated cardiomyopathy use LVEF as a marker.[2,17,32,33] In contrast, LV longitudinal strain via speckle tracking, which is less dependent on preload and afterload, may provide better indication of myocardial dysfunction in sepsis.[34] LV global longitudinal strain may also be more prognostic of poor survival compared with LVEF.[35] Right ventricular (RV) function is also essential to assess on echocardiography.[5] Tricuspid annulus plane systolic excursion (TAPSE) and fractional area change (FAC) are important for determination of isolated or concomitant RV dysfunction, as RV dysfunction is associated with high mortality in sepsis.[36] Echocardiography should be repeated at multiple time points because of the dynamic loading conditions seen in sepsis.[19]

Use of pulmonary artery catheterization provides continuous hemodynamic monitoring and may help with the delineation of various components of shock. Obtaining mixed venous oxygen saturation, cardiac index, systemic vascular resistance (SVR), and central venous pressure may facilitate the accurate diagnosis of mixed shock states. These data points may also assist in guiding management including optimizing volume status and preload, titration of inotropes, and vasoactive medications. Low cardiac index (< 2.2 L/min/m^2) after adequate fluid resuscitation and normal filling pressures with congruent findings on echocardiography should trigger assessment for potential VA-ECMO.

Published Studies and Outcomes

Limited published data on the use of VA-ECMO in the setting of sepsis and significant cardiac dysfunction is available; all are retrospective with relatively small numbers of patients because of the inherent challenges of studying this acutely sick patient population.[12,32] Reported outcomes range widely, likely because of heterogeneity in patient population and presentation, variable disease processes, available health care resources and expertise, timing of intervention, selection, and reporting bias, among other reasons.

Survival

Table 1 summarizes the published literature reporting outcomes in VA-ECMO for sepsis-associated cardiomyopathy. Early survival (hospital or 30-day survival) for septic patients undergoing VA-ECMO ranges extremely widely (7% to 90%). Ro et al.[12] examined VA-ECMO in all-comers with medically refractory sepsis and found an abysmal early survival rate of 7% in these patients. Similarly, Huang et al.[37] found a survival rate of 15% in patients with normal LV function and refractory sepsis undergoing salvage VA-ECMO. These results not only highlight the poor outcomes of patients with refractory sepsis but also emphasize the importance of careful patient selection.

In contrast, 2 studies that included only patients with sepsis and significant LV dysfunction found reasonable early survival with VA-ECMO.[17,32] Brechot et al.[32] found in their study of patients with refractory sepsis and LVEF 10% to 30% (mean 16%) that survival was 71% at up to 13 months. All survivors had fully recovered LV function. Falk et al.[17] found in their cohort that the subgroup of patients with LV failure (LVEF 20% to 30%; mean 25%) and sepsis had an incredible hospital survival of 90% when managed with VA-ECMO. Long-term survival in these patients was 75%. Vogel et al.[33] found that in patients that required transition from VV-ECMO to VAV-ECMO for sepsis-associated cardiomyopathy, survival was 75% to hospital discharge and at 6-month median follow-up. LVEF improved from 16% to 41% before decannulation of arterial limb support, and all surviving patients recovered to normal LV function.

However, published outcomes even in these low-EF septic patients are conflicting. Park et al.[14] found an early survival of 22% in patients undergoing VA-ECMO for refractory sepsis, even though patients had a median LVEF of 25%. As would be expected, these authors found that patients were less likely to survive if they received cardiopulmonary resuscitation before initiation of VA-ECMO. Myers et al.[38] found that in their patient population with median LVEF of 37%, survival to hospital discharge was 45%. Overall, available data might support the notion that myocardial dysfunction in sepsis-associated cardiomyopathy is transient, and temporary support with VA-ECMO may offer a bridge to highly selected patients during this time of multifactorial shock, but further study is necessary.

Quality of life

Using the Short Form-36 (SF-36) survey, Brechot et al.[2] found in their retrospective comparison study that patients who survived sepsis with VA-ECMO went on to have a satisfactory quality of life. In a smaller study, Brechot et al.[32] also found improved quality of life in survivors of VA-ECMO after sepsis. Both studies followed patients for approximately 1 year.

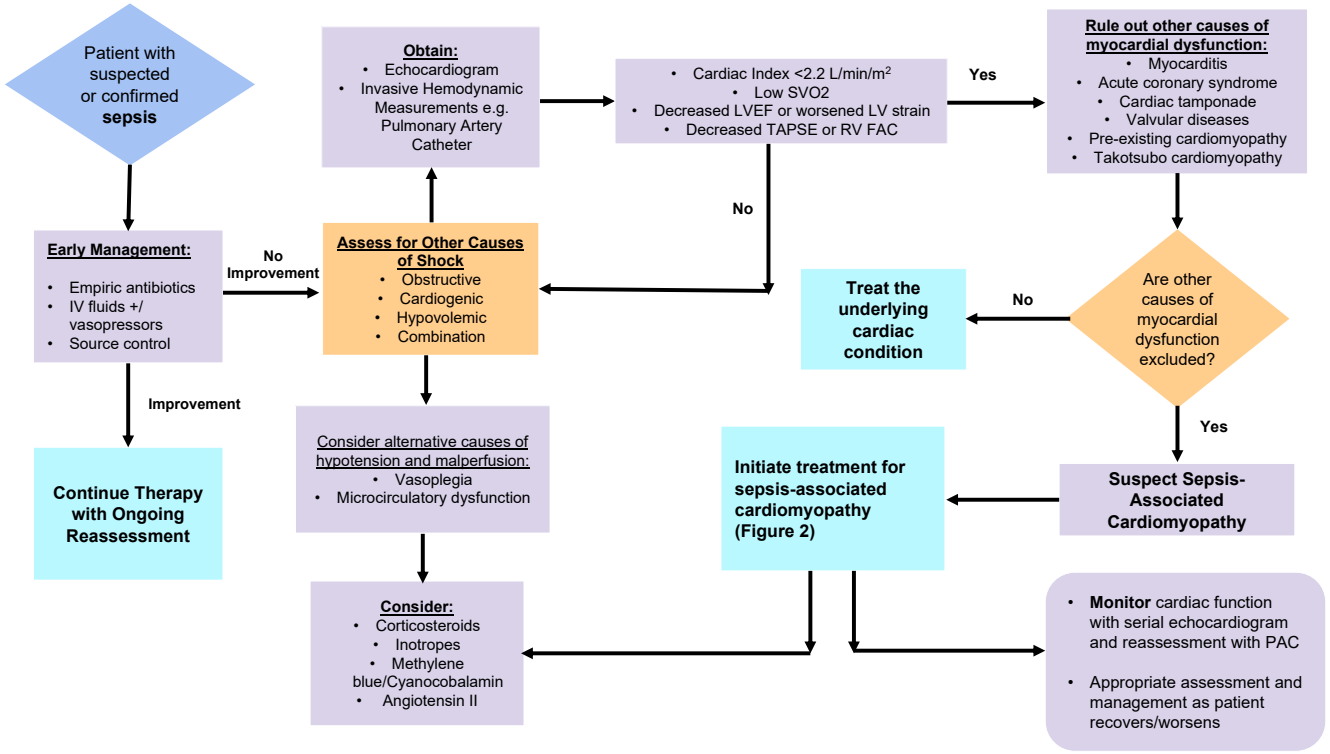

Figure 1. Diagnosis of sepsis-associated cardiomyopathy.

Comparison Studies

Ling et al.[13] performed a meta-analysis including 468 patients who underwent VA-ECMO for refractory septic shock, reporting an overall survival rate of 36%, with significantly higher survival observed in patients with LVEF $< 20\%$ compared with those with LVEF $> 35\%$ (62% vs 32.1%, $P = 0.05$).[13] Kim et al.[39] published a comparison study of VA-ECMO for patients with cardiogenic shock, septic shock, and mixed shock, finding that patients in the pure septic shock group had the highest 30-day and 1-year mortality.

The largest multicentre retrospective cohort study comparing patients with sepsis-associated cardiomyopathy treated with VA-ECMO to propensity-score matched controls treated without VA-ECMO demonstrated that VA-ECMO was associated with improved lactate clearance, reduced catecholamines, and a consequent improved survival in patients with sepsis-associated cardiomyopathy.[2]

These data reinforce the notion that VA-ECMO can be considered as a bridge to recovery for patients with refractory septic shock characterized by severe cardiac dysfunction and end-organ hypoperfusion. Given the poor survival of septic patients on VA-ECMO without significant LV dysfunction, VA-ECMO is not recommended for patients with isolated vasodilatory septic shock without significant myocardial dysfunction.[13]

Specific Considerations and Management for VA-ECMO in Sepsis

Before VA-ECMO is considered, standard medical therapy should be optimized and exhausted. Patients should be appropriately fluid resuscitated, be on appropriate antibiotics, be on adequate doses of vasopressors/inotropes and corticosteroids (+/− mineralocorticoids), and have infectious source control. Depending on other clinical factors, consideration should also be given to adjunct therapies such as methylene blue, hydroxocobalamin, and angiotensin II.

It is important to consider and rule out or treat other causes of myocardial dysfunction in the setting of sepsis. Fulminant viral myocarditis may present similarly to sepsis-associated cardiomyopathy but requires diagnosis with appropriate viral testing and endomyocardial biopsy; both are transient cardiomyopathies with resolution in the 7-day to 10-day range.[5] Takotsubo cardiomyopathy is also a transient entity that may complicate sepsis. Other etiologies of cardiac dysfunction that may complicate sepsis include type I and type II myocardial infarction, pericardial effusion and tamponade, significant valvular disease, and pre-existing cardiomyopathy.

Once sepsis-associated cardiomyopathy is diagnosed and deemed refractory to standard therapy, barring any contraindications, VA-ECMO can be considered in a timely matter for highly selected patients. Although initial inotropic support may improve cardiac function, if cardiac output is inadequate for end-organ perfusion in medically refractory cases of sepsis, delaying mechanical support will significantly diminish any potential benefit. For the routine management of VA-ECMO, guidelines by ELSO should be followed in addition to institution-specific practices.

In our experience, consideration is given to VA-ECMO in the setting of septic shock once the following criteria are met: ongoing hypotension and malperfusion despite maximal medical management, evidence of myocardial dysfunction on echocardiography, and evidence of poor and worsening cardiac index and decreased mixed venous oxygen saturation

Table 1. Outcomes in VA-ECMO and sepsis-associated cardiomyopathy

Study, year, and country	N	Source of infection (%)	Criteria for initiation of ECMO	Pre-ECMO cardiac function	ECMO duration (days)	Hospital survival (%)	ECMO-related complications (%)
Brechot et al.[32] 2013 France	14	Lungs: 79 Abdominal: 14 Pharyngitis: 7	LVEF: < 25% Low cardiac index (< 2.2 L/min/m^2) Very high-dose catecholamines (epinephrine > 1 μg/kg/min or dobutamine > 20 μg/kg/min with norepinephrine > 1 μg/kg/min).	LVEF: Median 16% CI: Median 1.3 (0.7-2.2)	Nonsurvivors: 3 Survivors: 5.5	71	Hemorrhage: 29 Wound infection: 21 Bacteremia: 21 Limb ischemia: 7 Ischemic stroke: 7 Hemolysis: 7
Huang et al.[37] 2013 Taiwan	52	Lungs: 48 Abdominal: 21 Urinary tract: 10 Other: 21	Circulatory collapse despite fluid resuscitation and inotropic therapy for septic shock	LVEF: Nonsurvivors: Mean 55.5% Survivors: mean 56.5%	All patients: 1.8 Nonsurvivors: 1.1 Survivors: 6.8	15	Oxygenator failure: 17. Cannula repositioning: 8 Circuit thrombosis: 2 Hemorrhage: 8
Cheng et al. (A)[16] 2013 Taiwan	108 (n = 86; 80% of patients on VA-ECMO configuration)	Lungs: 40 Myocarditis: 25 Bloodstream: 19 Abdominal: 7 Endocarditis: 4	"Circulatory failure was defined by the requirement for sustained cardiopulmonary resuscitation, inability to maintain mean arterial pressure greater than 60 mm Hg, or progressive lactic acidosis and end-organ dysfunction despite 2 or more continuous infusions of high-dose inotropes. Dopamine or dobutamine infusions > 20 μg/kg/min and norepinephrine and epinephrine infusions greater than 0.5 μg/kg/min were typically considered high doses."	N/A	6.6	29	Circuit thrombosis: 34 Major bleeding: 16 Neurologic deficit: 2

Continued

Table 1. Continued.

Study, year, and country	N	Source of infection (%)	Criteria for initiation of ECMO	Pre-ECMO cardiac function	ECMO duration (days)	Hospital survival (%)	ECMO-related complications (%)
Park et al.[14] 2015 South Korea	32	Lungs: 34 Abdominal: 22 Urinary tract 13 Other: 31	Refractory shock, defined as evidence of organ hypoperfusion despite adequate intravascular volume and the inability to maintain mean arterial pressure > 65 mm Hg despite infusion of very high-dose catecholamines (norepinephrine > 1 μg/kg/min, dopamine > 20 μg/kg/min, or epinephrine > 1 μg/kg/min with dobutamine > 20 μg/kg/min)	LVEF: Median 25.0% Nonsurvivors: Median 25.0% Survivors: Median 23.0%	3.5	22	Limb ischemia: 16 GI bleeding 3 Brain hemorrhage 3
Cheng et al.[15] (B) 2016 Taiwan	151 (n = 100; 67% of patients on VA-ECMO configuration	Lungs: 50 Myocarditis: 20 Bloodstream: 15 Abdominal: 8	"Refractory septic shock defined by the requirement for sustained cardiopulmonary resuscitation, inability to maintain mean arterial pressure greater than 60 mm Hg, or progressive lactic acidosis and end-organ dysfunction despite fluid resuscitation and 2 or more continuous infusions of high-dose inotropes (> 2 hours) in the context of severe sepsis. Dopamine or dobutamine infusions greater than 20 mg/kg/min	N/A	7.9	30 (total, including VA-ECMO and VV-ECMO)	Circuit thrombosis 42 Major bleeding: 17 Neurologic deficit: 15 Peripheral limb ischemia: 40

			and norepinephrine and epinephrine infusions > 0.5 mg kg/min typically were considered high doses."				
Von Bahr et al.[46] 2017 Sweden	255	Pneumonia bacterial: 53 Pneumonia viral: 12 Pneumonia aspiration: 7 Other: 28	Respiratory failure or sepsis. No specific criteria provided.	N/A	8	64	N/A
Ro et al.[12] 2018 South Korea	71	Lungs: 69 Abdominal: 11 Urinary tract: 4 Other: 15	"Persistent circulatory collapse despite these [fluids, antibiotics, vasopressors] aggressive medical treatments."	N/A	Nonsurvivors: 1.1 Survivors: 7.5	7	Limb ischemia: 1.4
Vogel et al.[33] 2018 United Kingdom	12	Lungs: 83 Other: 17	Patients transitioned from VV-ECMO to VAV-ECMO for "septic cardiomyopathy". No specific criteria provided	LVEF median 16.25%	4	75	Limb ischemia: 8.3 Major cannula-related bleeding: 8.3 Stroke: 16.6
Banjas et al.[47] 2018 Germany	19	Lungs: 53 Abdominal: 42 Soft tissue: 5	Persistent hypotension despite adequate volume replacement and the need for noradrenaline infusion at a dose > 0.5 µg/kg/min to maintain a mean arterial blood pressure ≥ 65 mm Hg	N/A	14 (9-25)	42	N/A
Falk et al.[17] 2019 Sweden	37	Lungs: 57 Gastrointestinal: 5 Pyelonephritis: 11 Fasciitis: 11 Urine: 3 Blood: 11 Myocarditis: 3	Persistent lactate > 5 mmol/L SvO2 < 55% Cardiac index < 2 L/min/m^2 (> 1hr) Rapidly deteriorating ventricular function Refractory arrhythmia vasoactive inotropic score (VIS) > 50 (> 1 hour), greater than 45 (> 8 hours), or greater than 40 if myocarditis	LVEF LV failure group: 25% Non-LV failure group: 52.5%	N/A	90 in patients with LV failure (LVEF 20%-30%) who underwent VA-ECMO	VA-ECMO subgroup: Limb ischemia: 3 Cannulation site bleeding: 5

Continued

Table 1. Continued.

Study, year, and country	N	Source of infection (%)	Criteria for initiation of ECMO	Pre-ECMO cardiac function	ECMO duration (days)	Hospital survival (%)	ECMO-related complications (%)
Brechot et al. 2020 Multicentre	212	Lungs (78% in VA-ECMO patients vs 38% in non−VA-ECMO patients)	Cardiac index < 3.0 or LVEF < 35% with inotrope requirement or lactate ≥ 4.0	LVEF ECMO group: 17.1% Non-ECMO group: 27.5% CI ECMO group: 1.54 Non-ECMO group: 2.21	5.8	Unadjusted: 60 (VA-ECMO) vs 25 (non −VA-ECMO)	VA-ECMO patients: Transfusion: 88 Insertion site hemorrhage: 21 Insertion site infection: 21 ECMO-related bacteremia: 12 Critical limb ischemia: 5 Major amputation related to ECMO: 2
Myers et al.[38] 2020 USA	11	Lungs: 55 Genitourinary: 9 Unknown: 36	No specific criteria provided. Institutional practices for initiation of VA-ECMO were based on the Extracorporeal Life Support Organization guidelines.	LVEF 37%	7.1	45	Cardiac arrythmia: 45 Bleeding: 27 ECMO membrane thrombosis: 27
Kim et al.[39] 2023 South Korea	100	Lungs: 49 GI: 27	No specific criteria provided.	LVEF cardiogenic shock group: 48%	15	Cardiogenic shock group: 31	Bleeding 10 Ischemic stroke 1 Limb ischemia 2

CI, cardiac index (L/min/m^2); ECMO, extracorporeal membrane oxygenation; GI, gastrointestinal; LV, left ventricular; LVEF, left ventricular ejection fraction; SvO2, mixed venous oxygen saturation; VA-ECMO, venoarterial extracorporeal membrane oxygenation; VAV-ECMO, venoarterial venous extracorporeal membrane oxygenation; VV-ECMO venovenous extracorporeal membrane oxygenation.

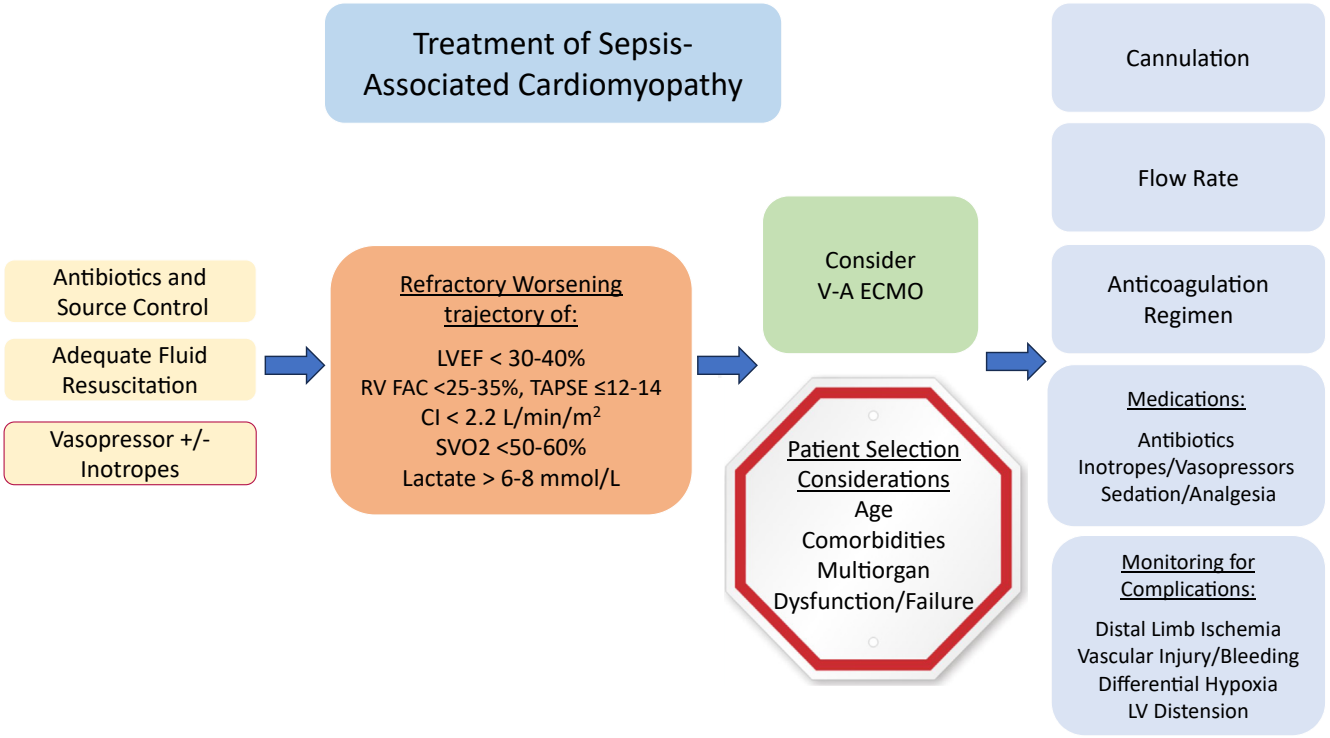

Figure 2. Management of sepsis-associated cardiomyopathy.

(SvO2) on pulmonary artery catheterization (Fig. 2). Once these criteria are met, we ensure that there are no contraindications to VA-ECMO, including irreversible conditions (eg, anoxic brain injury, advanced malignancy), advanced multiorgan failure, lack of reasonable expectation of recovery or multiple advanced comorbidities, severe aortic insufficiency, severe aortic pathology (dissection, severe aneurysmal disease, severe diffuse aortic atherosclerosis), poor vascular access, advanced age, severe coagulopathy with bleeding, or recent intracranial hemorrhage. Furthermore, a consideration of the risks of VA-ECMO must be considered, including the risk of vascular complications, limb ischemia, bleeding/coagulopathy, surgical/cannulation site infections, and bacteremia. These risks will all vary from patient to patient. Finally, a consideration of availability/allocation of resources should be taken into account, and transfer to a centre with more available resources and expertise may be required.

In general, we avoid VA-ECMO when patients remains bacteremic or without source control. However, in extremely highly selected younger patients experiencing cardiovascular collapse despite maximal medical therapy, VA-ECMO may have to be considered despite ongoing bacteremia or before gaining adequate source control. Expected outcomes in this particularly sick group of patients are foreseeably extremely poor; thorough discussion with the patient's family and immediate health care team is essential to set expectations after reviewing the patient's values and preferences to be sure such an invasive salvage manoeuvre would be consistent with the patient's wishes.

Decision making around timing of initiation of ECMO and weaning, cannulation, LV venting strategies, and anticoagulation are of paramount importance for optimal outcomes in VA-ECMO, and there are specific nuances to consider when contemplating VA-ECMO in septic patients. A thoughtful and careful approach is paramount for selecting appropriate patients, supporting patients at the appropriate time, and avoiding complications (Fig. 2).

Patient selection

Patients who do not respond within 1 to 2 hours of standard sepsis therapy should have prompt assessment of cardiac function with echocardiograms. Insertion of pulmonary artery catheters should be considered if there is evidence of LV, RV, or biventricular dysfunction or if echocardiography shows preserved cardiac function but there is still suspicion for cardiogenic component of shock with decreased cardiac output. Confirmation of sepsis-associated cardiomyopathy in this setting of persistent hypoperfusion despite exhausting standard therapy should initiate prompt evaluation for VA-ECMO. Discussion with a multidisciplinary team (intensivist, cardiologist, cardiovascular surgeon, infectious diseases specialist, perfusionist, nursing, social work) should occur, and a consensus decision should be made.

VA-ECMO should be avoided in septic patients with preserved LV function or evidence of hyperdynamic cardiac function (eg, high cardiac index or EF, decreased LV end-diastolic diameter). Hyperdynamic cardiac function is often an indication of ongoing profound vasoplegia, which will not be ameliorated by VA-ECMO. VA-ECMO should also be avoided in patients with refractory vasoplegia and profoundly low systemic vascular resistance. Be cautious about initiating VA-ECMO for septic patients requiring cardiopulmonary

Table 2. Pros and cons of VA-ECMO in sepsis

Pros	Cons
• Allows weaning of high-dose inotropes and vasopressors, decreasing their deleterious effects, while maintaining systemic perfusion • Improve metabolic derangements quicker (eg, lactate clearance, improvement of metabolic acidosis), which may prevent or ameliorate multiorgan failure • May improve survival in appropriately selected patients	Vascular and access site complications • Vascular injury and bleeding • Pseudoaneurysms • Infection Circuit-related complications • Membrane and circuit thrombus/thrombosis • Circuit disruption/failure, accidental decannulation • Blood component activation and inflammation, • Immunoparesis Anticoagulation-related complications • Hemorrhage • Thrombosis (both stasis related and blood disorder related such as heparin-induced thrombocytopenia and thrombosis) Cardiopulmonary physiology/pathophysiology • Differential hypoxemia (eg, "north-south syndrome" or "harlequin syndrome") • Increased LV afterload, need to manage LV distension with a venting strategy Variable observed survival in septic shock • Limited available data suggest no survival benefit in sepsis, but potential benefit in refractory septic shock with low-EF septic cardiomyopathy Resource intensive

EF, ejection fraction; LV, left ventricular; VA-ECMO, venoarterial extracorporeal membrane oxygenation.

resuscitation, as these patients have poor survival. Contraindications to VA-ECMO have been discussed previously.

Timing

Evidence to guide optimal timing for the initiation of VA-ECMO in sepsis is sparse. In a meta-analysis done by Ling et al.,[13] the time elapsed from diagnosis of septic shock to initiation of VA-ECMO was 23.4 hours, with a pooled -survival to discharge of 36.4%. Cheng et al.[15] found that "door-to-ECMO" times of < 96 hours were associated with improved mortality. These findings underline the importance of prompt diagnosis of sepsis and the initiation of VA-ECMO sooner than later in patients with a poor response to standard medical management.

Initiation

Most septic patients initiated on VA-ECMO should be done via peripheral cannulation approach. Peripheral VA-ECMO can be done at the bedside or in a procedural room and avoids bleeding and infection complications related to a central approach. When performing peripheral VA-ECMO, a distal limb reperfusion cannula should be used to avoid limb ischemia. A percutaneous or open surgical approach (ie, femoral cutdown) can be used depending on local expertise and anatomic factors. If a percutaneous approach is used, ultrasound guidance should be used to reduce vascular complications. Personnel performing the ECMO cannulation should be well experienced in the insertion of peripheral cannulas. Type of personnel (eg, cardiac surgeon, vascular surgeon, cardiologist, intensivist) will vary depending on institutional practice and local expertise.

Ongoing management and specific issues

ECMO circuit flow should be titrated to maintain goal-directed perfusion parameters, reflected in gradual improvement in markers of end-organ perfusion (eg, increased mixed venous oxygen saturation, down-trending lactate, improved urine output). One of the goals in sepsis-associated cardiomyopathy is to decrease vasopressor doses; not only will this reduce complications associated with high dose vasopressors, but—in addition—high SVR may be a barrier to adequate ECMO flows and LV ejection.

Appropriate anticoagulation and monitoring of anticoagulation is essential for the prevention of complications such as circuit thrombosis, arterial and LV thrombosis, hemorrhage, and ischemia. Unfractionated heparin is the most commonly used anticoagulant and can be monitored with activated partial thromboplastin time (aPTT). Typically, aPTT is maintained at approximately 50 to 70 seconds or 2 to 2.5 times above the normal level.[40] Activated clotting time (ACT) and factor Xa levels can also be monitored depending on institutional practice. ACT is generally kept in the 180-second to 220-second range, whereas anti-Xa levels are kept between 0.3 and 0.5 U/mL.[40] Again, institutional practices may vary. Alternative anticoagulants may be used, including bivalirudin, argatroban, and low molecular weight heparin. In selected cases with elevated bleeding risk, minimal anticoagulation can be used at the expense of increased risk for circuit (distal perfusion cannula and oxygenator)/vessel/cardiopulmonary thrombus or thrombosis. When anticoagulation is stopped, we generally recommend keeping the ECMO flow rates > 3L/min to prevent thrombosis and -hemostasis. Further recommendations regarding anticoagulation during ECMO can be found in the ELSO Anticoagulation Guidelines and International Society on Thrombosis and Haemostasis recommendations.[40,41]

VA-ECMO influences the pharmacokinetics and pharmacodynamics of medications by altering the volume of distribution and affecting drug clearance.[42,43] Combined with the altered physiology and metabolism seen during critical illness, the pharmacokinetics of medications during VA-

ECMO can be unpredictable.[42] Of particular importance in the setting of sepsis is antibiotic and antifungal pharmacokinetics. Although medications such as vasopressors, inotropes, sedatives, and analgesics can be titrated to specific endpoints, antibiotics do not have specific endpoints, and thus it can be challenging to administer the appropriate therapeutic levels. Different classes of antibiotics and antifungals may require different doses while on VA-ECMO.[43] The expertise of a clinical pharmacologist or pharmacist on the critical care team may be useful to assist in the dosing and administration of medications while patients are on VA-ECMO to ensure adequate therapeutic levels and to reduce toxicity; continuous infusions of antibiotics may have a role in these patients.

In femoral VA-ECMO, "North-South" or "Harlequin" syndrome describes a dual circulation phenomenon whereby the heart ejects poorly oxygenated blood in antegrade fashion while the VA-ECMO circuit returns fully oxygenated blood to the body in retrograde fashion. This leads to differential hypoxemia of the upper and lower body. The severity of this syndrome depends on VA-ECMO flow, lung function, and recovering cardiac function. Differential hypoxemia can be detected with O2 saturation monitoring of the right upper extremity. It can be improved with ventilator setting adjustments (eg, increasing fraction of inspired oxygen [FiO2], increasing positive end-expiratory pressure [PEEP]), or reconfiguration of the circuit to VAV-ECMO with the addition of an oxygenated venous return cannula via an internal jugular or subclavian vein; we do not use beta blockers in this setting of a recovering heart.

VA-ECMO increases afterload on the already failing heart, potentially leading to worsening LV distension and irreversible myocardial injury, pulmonary edema, intracardiac thrombus, and cardiopulmonary thrombosis. LV distension and function can be monitored with routine echocardiography, monitoring of filling pressures with pulmonary artery catheter, and monitoring pulse pressure in the arterial line. LV distension can be managed with inotropes, intra-aortic balloon pump (IABP), temporary mechanical circulatory support devices such as an Impella (Abiomed, Danvers, MA), percutaneous procedures such as an atrial septostomy, or a surgical LV vent. Careful consideration is required, as introducing more devices increases the risk of further vascular injury or limb ischemia and increases the potential of infection in the setting of sepsis.

Patients with sepsis and profound systemic inflammatory response who are then subjected to ECMO are at very high risk for refractory vasoplegia. Standard first-line therapy for the vasoplegic component of sepsis is with catecholamine activation via norepinephrine, vasopressin at a physiologic replacement dose, followed by phenylephrine and epinephrine. Corticosteroids are recommended for a catecholamine-sparing effect, accelerating resolution of shock state. Refractory vasoplegia should be addressed with methylene blue and hydroxycobalamin. Finally, Angiotensin II (Giapreza, La Jolla Pharmaceutical Company, Waltham, MA) may also be a useful adjunct in refractory vasoplegia, although not currently available in Canada.

In peripheral VA-ECMO, ipsilateral limb perfusion should be continuously monitored. In addition to frequent neurovascular examinations, objective measures should be taken. Monitoring may include manual Doppler signal interrogation in the distal lower extremities, but continuous tissue oxygen saturation measurement of the distal lower extremities using near-infrared spectroscopy is useful if available. As previously mentioned, limb ischemia can be avoided with the routine addition of a distal reperfusion cannula.

Further details regarding monitoring of patients on VA-ECMO can be found in a previously published comprehensive review in *The Canadian Journal of Cardiology* by Bhatia et al.[44]

Weaning

Sepsis-associated cardiomyopathy is a transient phenomenon that typically lasts 7 to 10 days.[5] Most studies have found that survivors are on ECMO for approximately 5 to 7 days with some authors demonstrating a median support time of 15 days (Table 1). Weaning of VA-ECMO should be done once cardiac function improves (as demonstrated by serial echocardiography and improved cardiac index and mixed venous O2 on pulmonary artery catheter) along with improvement of end-organ function and metabolic parameters (eg, increased urine output, normalization of lactate and liver enzymes, improved acidosis). This should also coincide with decreased vasopressor/inotrope requirements.

The goal for most patients is to wean off ECMO to inotropes alone, but some will require stepdown to a lesser mechanical support such as an IABP or Impella device. The patient should be able to tolerate VA-ECMO flows of 1 L/min for a period of time while on acceptable dose inotropes or IABP/Impella before complete weaning and removal. As discussed previously for the differential hypoxemia seen in "North South/Harlequin" syndrome, a transition from VA-ECMO to VV-ECMO may be required for patients experiencing cardiac recovery before lung recovery. Bhatia et al.[44] have provided a detailed guide on weaning from ECMO.

Pros and Cons of VA-ECMO in Septic Shock

Table 2 summarizes the pros and cons of VA-ECMO in septic shock.

Pros of VA-ECMO in sepsis

Survival improvement. Some studies, such as Von Bahr et al.,[32] Falk et al.[14] (Sweden), and Vogel et al.[29] (UK), demonstrate relatively high survival rates (64%, 70%, and 75%, respectively) for patients with sepsis, suggesting that VA-ECMO can potentially offer a survival benefit in highly selected cases.

Improvement in metabolic parameters: Brechot et al.[3] found improved clearance of lactate and reduced catecholamine doses in septic with severe myocardial dysfunction in patients undergoing VA-ECMO compared with patients not on VA-ECMO.

Cons of VA-ECMO in sepsis

The use of venoarterial VA-ECMO in patients with refractory distributive shock and normal or hyperdynamic cardiac function appears ineffective, but even in patients with septic cardiomyopathy, its use remains controversial. VA-

ECMO can enhance oxygen delivery and temporarily stabilize circulation; however, VA-ECMO will exacerbate vasoplegia and furthermore cannot restore microcirculation function or cellular oxygen uptake. Capillary leak complicates achieving adequate flow, crucial for oxygen delivery, and increasing ECMO flow may negatively affect LV performance by reducing preload, increasing afterload, and ultimately decreasing cardiac output in patients with otherwise adequate cardiac function. In addition, ECMO circuits can introduce or spread infection caused by the presence of endovascular catheters and the larger porous surface area of the membrane oxygenator.[45]

Vascular and circuit-related complications. VA-ECMO is associated with numerous complications including, bleeding, vascular injury, limb ischemia, and circuit-related phenomena such as circuit thrombosis. Brechot et al.[32] and Huang et al.[37] report high rates of hemorrhage, wound infections, and circuit thrombosis. Complication rates are summarized in Table 1.

Resource intensity. Beyond the resource requirement of VA-ECMO itself, patients who do end up surviving VA-ECMO for sepsis have prolonged intensive care unit (ICU) and hospital stays, which can be extremely resource intensive without a definitive benefit of long-term survival with acceptable quality of life. For example, Brechot et al.[2] reported that survivors were in the ICU for a mean of 41.3 days compared with 14.5 days for nonsurvivors. The overall hospital stay was 67.7 days for survivors compared with 15.0 days for nonsurvivors. Given the extremely high resource intensity associated with deployment of ECMO, in the context of limited health care resources and inadequate high-quality data to support outcome improvement, it may be a reasonable argument to limit VA-ECMO use in sepsis to prospective trials.

Conclusions

Although VA-ECMO can potentially offer support to improve survival in severe refractory septic shock, efficacy will vary based on patient characteristics, etiology, and management strategies. VA-ECMO is associated with a range of significant iatrogenic complications, including inflammation, bleeding, infection, and circuit issues, all of which adversely affect outcomes. Furthermore, when complicated by factors such as high inotropic support or cardiogenic shock, sepsis and septic shock portends a very poor functional outcome regardless of any potential VA-ECMO intervention.

Variability in reported survival rates underscores the importance of individualized patient management and multidisciplinary decision making. VA-ECMO can potentially be a reasonable tool in our armamentarium to manage refractory severe septic shock, particularly in the setting of sepsis-associated cardiomyopathy with low LVEF, but careful and thoughtful patient selection, appropriate timing, and optimal management are essential to optimize outcomes and mitigate associated risks. More supportive data are required before VA-ECMO can be generally recommended in selected adult patients with septic shock; until then, we believe there is hope within the hype.

Ethics Statement

This research report has adhered to the International Committee of Medical Journal Editors Recommendations and the Committee of Publication Ethics Guidelines.

Patient Consent

The authors confirm that patient consent is not applicable to this article. This is a review article that does not use identifiable and individual patient data, and thus patient consent was not required.

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