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Venoarterial Extracorporeal Membrane Oxygenation in Cardiogenic Shock

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ABSTRACT

Venoarterial extracorporeal membrane oxygenation has emerged as a viable treatment for patients in cardiogenic shock with biventricular failure and pulmonary dysfunction. Advances in pump and oxygenator technology, cannulation strategies, patient selection and management, and durable mechanical circulatory support have contributed to expanded utilization of this technology. However, challenges remain that require investigation to improve outcomes.
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Extracorporeal membrane oxygenation (ECMO) has been increasingly used over the past decade for support of patients with cardiopulmonary collapse (1,2). Venoarterial extracorporeal membrane oxygenation (VA-ECMO) provides cardiopulmonary support for patients in profound cardiogenic shock (CS) as a bridge to myocardial recovery, durable mechanical circulatory support (MCS), or heart transplant (HT), whereas venovenous extracorporeal membrane oxygenation (VV-ECMO) is primarily used in patients with isolated pulmonary disease (3). In this review, we focus on VA-ECMO, emphasizing technological advances, patient selection, management and weaning guidelines, outcomes, complications, and economic challenges.

EVOLUTION IN ECMO TECHNOLOGY

The death of a patient from a massive pulmonary embolism at Massachusetts General Hospital in February 1931 inspired the initial use of extracorporeal circulation (4). Advances in pump and oxygenator technology, percutaneous cannulation techniques, critical care management, and durable MCS options synergized to foster the maturation of ECMO as a viable lifesaving modality. Currently over 87,000 patients have been enrolled in the Extracorporeal Life Support Organization registry, including 12,566 adults with VA-ECMO, with the number of VA-ECMO centers increasing markedly in the last decade.

In a VA-ECMO circuit, deoxygenated blood is pulled from the venous circulation by a pump via a large-bore cannula. Patients may be cannulated centrally (**Central Illustration, A**) or peripherally (**Central Illustration, B**). Blood passes through the pump into an oxygenator where gas exchange occurs. Oxygenated blood returns via another large-bore cannula to the arterial circulation.

Although an exhaustive summary of circuit technology is beyond the scope of this review, it is important to note 2 critical advances. First, the development of hollow tube fiber membranes in the oxygenator allowed low resistance and improved

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ABBREVIATIONS AND ACRONYMS

CS = cardiogenic shock

ECMO = extracorporeal membrane oxygenation

HT = heart transplant

LV = left ventricle

MCS = mechanical circulatory support

RV = right ventricle

V-AV = veno-arteriovenous

VA = venoarterial

VV = venovenous

blood compatibility characteristics (5). Second, redesigned centrifugal pumps limited heat generation and thrombogenicity, making extended duration of support feasible (6). These advances have recently been coupled to miniaturized circuits, facilitating transport of patients on ECMO.

Although central cannulation remains the primary approach in post-cardiotomy patients, novel percutaneous approaches have resulted in wider utilization of ECMO, including in-hospital based programs that place patients in cardiac arrest on ECMO support (extracorporeal cardiopulmonary resuscitation), service delivery programs with "in the field" ECMO cannulation, and periprocedural ECMO in cardiac catheterization laboratories. Distal perfusion catheters that direct a proportion of the returned oxygenated blood flow from the ECMO circuit to the distal limb of the cannulated leg significantly limit risks for critical limb ischemia in femoral arterial cannulation (**Central Illustration, C**) (7). More recently, upper extremity peripheral cannulation approaches allow increased mobility for some patients (**Central Illustration, D1 and D2**).

Hybrid ECMO configurations are increasingly used in patients with severe lung injury or in those inadequately supported with VA- or VV-ECMO. The veno-arteriovenous (V-AV) configuration is one of the more commonly used approaches. Venous blood returns to the oxygenator in the usual fashion and is reinfused via an arterial cannula to the femoral artery and a second venous cannula to the right heart at the level of the tricuspid valve, providing supra-oxygenated pulmonary blood flow. This configuration avoids harlequin (north/south) syndrome, in which deoxygenated cerebral blood flow occurs during retrograde perfusion with peripheral cannulation, discussed in the section Prevent Upper Body Hypoxia [Harlequin (North/South)] Syndrome. VV-ECMO can also be converted to V-AV ECMO when cardiac function deteriorates in a patient initially presenting with isolated pulmonary failure (8).

Advances in circuit technology required parallel advances in bedside management of ECMO patients, including development of multidisciplinary ECMO teams including cardiac surgeons, cardiologists, intensivists, ECMO specialist nurses, perfusionists, and pharmacists.

DEVICE SELECTION

Percutaneous devices used in CS are compared in Online Table 1. ECMO is the only form of support useful in cases of hypoxemia due to pulmonary failure and the only device that simultaneously supports the right ventricle (RV).

PATIENT SELECTION AND CLINICAL OUTCOMES

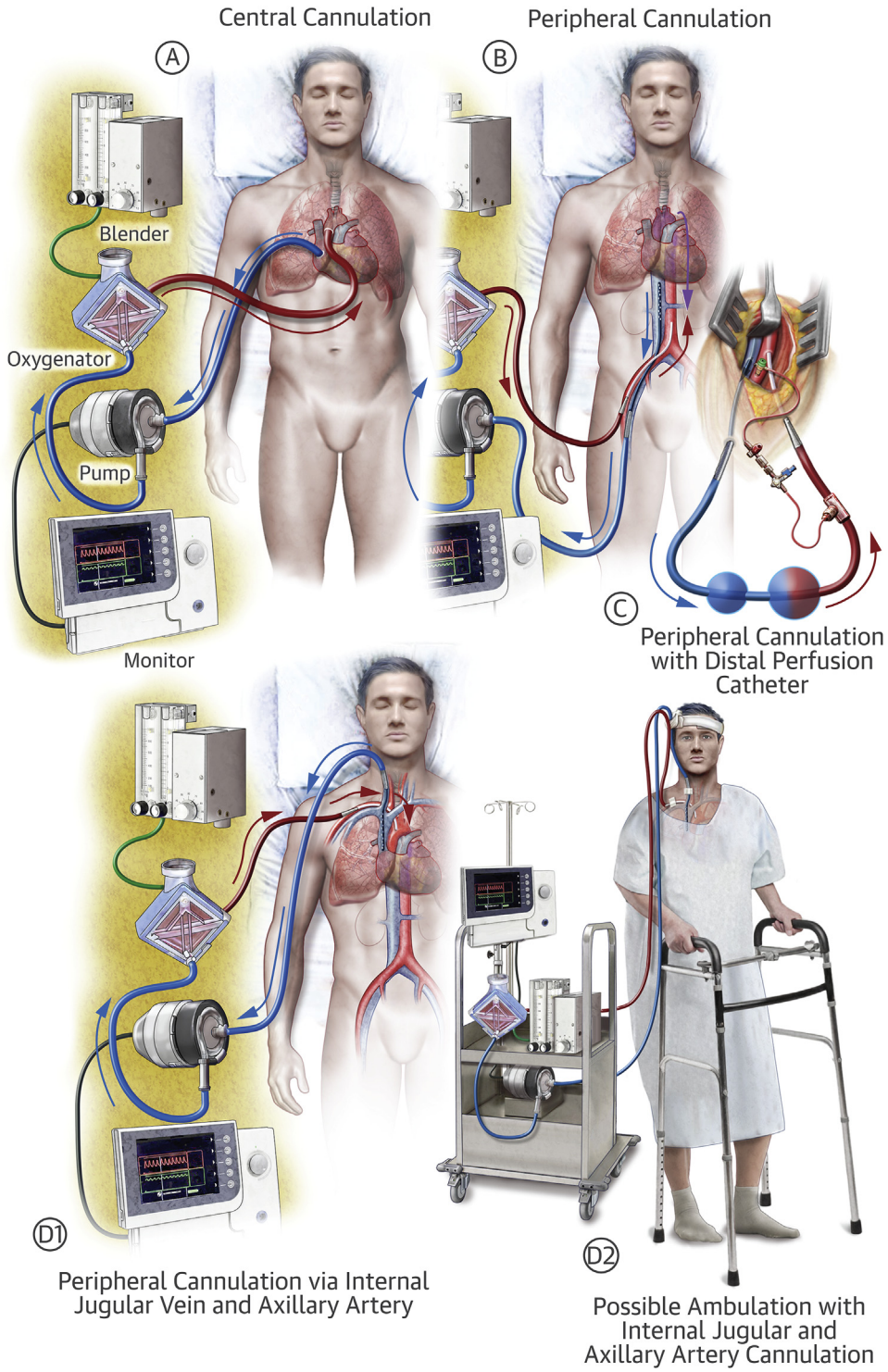
Despite advances in technology, survival among patients on VA-ECMO support remains modest, with in-hospital mortality of 50% to 60% and 6-month survival as low as 30% (1,9,10). Just as ECMO technology has evolved, so too has our understanding of the importance of appropriate patient selection to optimize outcomes, efficiently allocate resources, and avoid medical futility. Indications and contraindications for ECMO application are outlined in **Table 1**.

Several studies have highlight the importance of the underlying diagnosis in determining survival, as summarized in **Table 2**. Patients with potentially reversible causes of myocardial injury, such as fulminant myocarditis or primary graft failure, have better survival than patients with CS after surgery or acute myocardial infarction (11–14). Patients for whom ECMO is deployed during or immediately after cardiac arrest have an especially poor prognosis (1,15–17). Whether extracorporeal cardiopulmonary resuscitation is superior to conventional cardiopulmonary resuscitation for out-of-hospital arrest remains unclear (16,17).

In addition to underlying diagnoses, pre-ECMO risk factors independently associated with poor outcomes include older age, female sex, and higher body mass index, as well as markers of illness severity including renal, hepatic, or central nervous system dysfunction, longer duration of mechanical ventilation before deployment, elevated serum lactate levels, and reduced prothrombin activity (1,12,14,18). Risk scores have been developed that incorporate these variables to aid in decision-making regarding utility (vs. futility) of ECMO deployment (14,18,19). Most recently, the survival after veno-arterial-ECMO (SAVE) score was developed using data from 3846 adult patients enrolled in the international Extracorporeal Life Support Organization registry to stratify patients into 5 risk categories that correlated with post-ECMO survival (**Table 3**) (14).

Given the importance of end-organ function in determining outcomes, timing of ECMO initiation is key. Just as premature utilization may expose a patient to undue risks and complications, delayed initiation may be medically futile. The ideal window for deployment is after other, less invasive treatments have been considered or exhausted but before the onset of significant end-organ dysfunction. Recognizing this, some centers developed mobile

CENTRAL ILLUSTRATION **Basic Cannulation for VA-ECMO Support**



Keebler, M.E. et al. J Am Coll Cardiol HF. 2018;■(■):■–■.

(A) Central cannulation. **(B)** Peripheral cannulation. **(C)** Peripheral cannulation with distal perfusion catheter. **(D1)** Upper extremity cannulation with internal jugular venous cannula and axillary artery arterial cannula. **(D2)** Patients with this configuration may be able to ambulate if clinically appropriate. ECMO = extracorporeal membrane oxygenation; VA = venoarterial.

TABLE 1 Common Indications, Contraindications, and Considerations for VA-ECMO Deployment

Indications	Contraindications
Refractory CS in the setting of	Absolute
Acute coronary syndrome	Disseminated malignancy
Acute heart failure	Unwitnessed cardiac arrest
Post-cardiotomy, unable to wean from bypass	Severe irreversible brain injury
Myocarditis	Severe aortic incompetence
Primary graft failure after heart transplantation	Low likelihood of myocardial recovery, unless a candidate for durable MCS or heart transplantation
Refractory ventricular arrhythmias	Severe, irreversible multiorgan failure
Severe infection or drug intoxication complicated by cardiac depression	Severe peripheral arterial disease (for peripheral cannulation)
Severe hypothermia (<28°C) with cardiac instability	Relative
	Advanced age
	Bleeding diathesis

Considerations
Have less invasive therapies been exhausted?
In the event of no myocardial recovery, does the patient have an "exit strategy"?
For centers without ECMO capabilities, is timely collaboration with a high-volume ECMO center feasible?
Is the anticipated duration of needed support compatible with available technology?
Has the optimal time window for ECMO deployment expired (i.e., will ECMO be medically futile?)
Have all the key players been involved in the decision-making process (e.g., cardiologists, surgeons, heart failure specialists, intensivists, palliative care specialists)?
Are the patient's wishes for advanced therapies known?

CS = cardiogenic shock; ECMO = extracorporeal membrane oxygenation; MCS = mechanical circulatory support; VA-ECMO = venoarterial extracorporeal membrane oxygenation.

ECMO services, in which ECMO teams travel to initiate ECMO remotely and return to the center for ongoing management (20).

Ultimately, patient selection for ECMO utilization must take into consideration the underlying diagnosis, patient-specific risk factors, anticipated duration of support, and, perhaps most importantly, whether a viable exit strategy such as recovery, durable MCS, or HT exists. Given the high mortality and complication rates, early consultation with palliative care specialists should be considered.

PATIENT MANAGEMENT

Suggested goals of ECMO support are listed in Table 4. The primary goal is restoration of tissue and end-organ perfusion to allow stabilization or recovery of function. Nuances of ECMO management, including left ventricular (LV) venting, focus on achieving myocardial recovery and preventing pulmonary damage. When recovery is unlikely, ECMO provides time to assess neurological function, social barriers, and other disease processes that may prohibit durable LV assist device and/or transplant.

SET AND MONITOR VA-ECMO FLOW. Parameters typically monitored during ECMO support are outlined in Online Table 2. Although insufficient evidence exists to recommend specific goals, the initial goal flow for VA-ECMO should be 50 to 70 ml/kg/min with a mean arterial pressure >60 mm Hg. ECMO flow is adjusted to maintain or restore normal renal, hepatic, and pulmonary function, acid-base balance, and neurological status.

Patients supported with VA-ECMO should be monitored with an arterial line, ideally placed in the right arm. In this location, blood gas sampling is more indicative of the oxygen content of cerebral blood flow, particularly with peripheral cannulation. Moreover, arterial line monitoring allows monitoring of pulse pressure (pulsatility) as a reflection of cardiac contractility during support and weaning. Absent or low arterial pulsatility indicates that the LV is not ejecting or is ejecting small volumes, leading to blood stasis and an increased risk of thrombus formation. Higher pulsatility indicates possible myocardial recovery.

MANAGE GAS EXCHANGE. Maintaining appropriate oxygenation is a critical component of ECMO management. Oxygen delivery can be adjusted via the ECMO circuit (Figure 1A) or by mechanical ventilation, using strategies to reduce barotrauma and promote lung rest (21). Although the deleterious effects of prolonged hypoxia are well known, supranormal levels of oxygen (hyperoxia) are uniformly associated with worse outcomes, with 1 multicenter study of adults post-cardiac arrest demonstrating a 24% increase in mortality for every 100 mm Hg increase in Pa_{O_2} (22,23). Hyperoxia on VA-ECMO occurs because of the high efficiency of modern oxygenators and can be avoided by reducing the Fi_{O_2} of gas passing through the oxygenation filter (sweep gas) (Figure 1A) to maintain Pa_{O_2} values between 60 and 100 mm Hg.

Respiratory acidosis should be avoided. Because of decreased transpulmonary blood flow during VA-ECMO, the ability of the lungs to clear CO_2 is impaired, independent of existing air space disease. CO_2 clearance can be controlled by increasing the sweep gas flow relative to blood flow through the membrane filter to remove excess CO_2 or by decreasing it if alkalosis occurs. In mechanically ventilated patients, ventilator settings may be modified, but high tidal volumes and/or peak and plateau pressures that exceed 25 cm H_2O should be avoided whenever possible to avoid barotrauma (21,24).

REDUCE LV PRELOAD ("VENT THE LV"). LV decompression is a fundamental component of VA-ECMO management to prevent lung injury related to elevated pulmonary venous pressures, avoid stasis within the LV, and promote myocardial recovery.

TABLE 2 Outcomes for VA-ECMO by Cardiac Indication

Reference	Population	Design	Duration (days)	Key Results
Post-cardiotomy				
Rastan et al. 2010 (Online Ref. 1)	N = 517, refractory shock, mixed procedures	Prospective cohort, multicenter	3.3 ± 2.9	Weaned: 63% In-hospital mortality: 75% Survival: 6 months 18%, 1 yr 17%, 5 yrs 14%
Biancari et al. 2017 (Online Ref. 2)	N = 148, shock or respiratory failure after isolated CABG	Retrospective cohort, multicenter	6.4 ± 5.6	Weaned: 49% In-hospital mortality: 64% Survival: 1 yr 31%, 2 yrs 28%, 3 yrs 26%
Post-transplantation				
D'Alessandro et al. 2010 (Online Ref. 3)	N = 54, recipients with early graft failure for any cause	Retrospective cohort, single-center	7 ± 3	Weaned: 67% In-hospital mortality: 50% Survival: 1 yr 73%
Marasco et al. 2010 (Online Ref. 4)	N = 39, recipients with primary graft failure	Retrospective cohort, single-center	6.8 ± 2.6	Weaned: 87% In-hospital mortality: 26% Survival: 1 yr 73%
CS				
Xie et al. 2015 (Online Ref. 5)	N = 1,199 (22 studies), CS or CA	Meta-analysis	NR	In-hospital mortality: 60% (95% CI: 53%–66%) Survival: 3 months 56%, 1 yr 54% Survival at 1 month CS 53% vs. CA 36%
Dangers et al. 2017 (Online Ref. 6)	N = 105, ADHF	Prospective cohort, single-center	NR	Survival: 1 yr 42% (many received a transplant)
Myocarditis				
Cheng et al. 2014 (Online Ref. 7)	N = 170, acute myocarditis	Meta-analysis	NR	In-hospital mortality: 33% (95% CI: 26%–41%)
Cardiac arrest				
Maekawa et al. 2013 (Online Ref. 8)	N = 53, out-of-hospital CA with CPR >20 min	Prospective cohort, propensity matched	NR	Survival to discharge: ECMO 38% vs. CPR 13% (p = 0.09) Survival: 3-month. ECMO 38% vs. CPR 8% (p = 0.04)
Choi et al. 2016 (Online Ref. 9)	N = 320, out-of-hospital CA in South Korea	Retrospective cohort, propensity matched	NR	Survival to discharge: ECMO 18% vs. CPR 16% (ECMO adjusted OR: 0.61; 95% CI: 0.39–0.94)
Mixed				
Chang et al. 2016 (Online Ref. 10)	N = 4,227, supported in Taiwan	Retrospective cohort, administrative	2 ± 1	In-hospital mortality: 65% Survival: 1 month 40%, 1 yr 23%
Batra et al. 2016 (Online Ref. 11)	N = 1,286, supported in New York state	Retrospective cohort, administrative	NR	In-hospital mortality: 54% Survival: 1 month 48%, 1 yr 38%
Aso et al. 2016 (Online Ref. 12)	N = 5,263, supported in Japan	Retrospective cohort, administrative	NR	Weaned: 64% In-hospital mortality: 73% (shock 74%, PE 64%)

Values are mean ± SD or median (interquartile range). References for Table 2 can be found in the Online Appendix.

ADHF = acute decompensated heart failure; CA = cardiac arrest; CABG = coronary artery bypass graft; CI = confidence interval; CPR = cardiopulmonary resuscitation; CS = cardiogenic shock; ECMO = extracorporeal membrane oxygenation; NR = not reported; OR = odds ratio; PE = pulmonary embolism; VA-ECMO = venoarterial extracorporeal membrane oxygenation.

When pulmonary edema persists after ECMO initiation despite diuresis and inotropes, additional LV decompression is necessary, although the optimal strategy to achieve unloading remains unclear (25). LV end-diastolic pressure can be reduced by intra-aortic balloon pump or with a temporary LV MCS device such as the Impella (Abiomed, Danvers, Massachusetts). In 1 study, ECMO plus intra-aortic balloon pump was associated with lower mortality than ECMO alone (hazard ratio: 0.74; 95% confidence interval: 0.63 to 86) (26). Atrial septostomy allows shunting of blood from the left atrium to the right atrium and the venous cannula (27). The LV may be directly vented through the apex or transseptally (25). Ideally, LV filling pressure is reduced to normal, restoring pulmonary artery and pulmonary artery wedge pressure to normal, allowing lung healing and reducing RV afterload.

A hybrid circuit configuration, along with variations of LV and other vents, allows selective decompression of either ventricle when myocardial recovery is the goal. For example, a V-AV circuit with the venous infusion cannula at the level of the pulmonary artery rather than the tricuspid valve can selectively offload the RV if the goal is RV recovery after bridge to an LV assist device. If the goal is biventricular recovery, an LV vent spliced into the venous return line unloads both ventricles. Placing additional lines within the circuit should be done with caution,

TABLE 3 SAVE Score Parameters, Risk Classifications, and Predicted Survival

Parameter	Score
Diagnosis	
Myocarditis	3
Refractory VT/VF	2
Graft failure post heart or lung transplant	3
Congenital heart disease	−3
Other diagnosis	0
Age (yrs)	
18-38	7
39-52	4
53-62	3
≥63	0
Weight (kg)	
≤65	1
65-89	2
≥90	0
Acute pre-ECMO organ failure (include all that apply)	
Liver failure	−3
CNS dysfunction	−3
Renal failure	−3
Chronic kidney disease (eGFR <60 ml/min/1.73 m^2 for ≥3 months)	−6
Duration of intubation pre-ECMO (h)	
≤10	0
11-29	−2
≥30	−4
Peak inspiratory pressure ≤20 cm H_2O	3
Pre-ECMO cardiac arrest	−2
Diastolic blood pressure before ECMO ≥40 mm Hg	3
Pulse pressure before ECMO ≥20 mm Hg	−2
HCO_3 before ECMO ≤15 mmol/l	−3
Constant value to add to all calculations	−6
Total	−35 to 17

Hospital Survival Classification by SAVE Score	Risk Class	Survival
>5	I	75
1 to 5	II	58
−4 to 0	III	42
−9 to −5	IV	30
≤−10	V	18

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CNS = central nervous system; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; VF = ventricular fibrillation; VT = ventricular tachycardia; SAVE = survival after veno-arterial-ECMO.

TABLE 4 Patient Management Goals on VA-ECMO

Unload the LV (when necessary) to promote myocardial recovery
Unload the LV (when necessary) to allow lung healing and prevent further lung damage
Restore optimal intravascular volume
Restore normal oxygenation and acid-base balance, when necessary
Unload the RV
Prevent upper body hypoxia [harlequin (north/south) syndrome]
Maintain distal limb perfusion (peripheral ECMO)
Balance prevention of thrombosis with bleeding
Maintain some LV ejection to reduce risk of intracardiac thrombus
Monitor and promote recovery of renal and hepatic function
Implement adequate nutrition and physical therapy
Determine wishes of patient and/or family for durable MCS and/or transplantation as well as wishes for duration of ECMO support could serious complications occur
Bridge patient to myocardial recovery, durable LVAD support, and/or transplantation when desired and medically appropriate or to desired end of life

ECMO = extracorporeal membrane oxygenation; LV = left ventricle; LVAD = left ventricular assist device; MCS = mechanical circulatory support; RV = right ventricle; VA-ECMO = venoarterial extracorporeal membrane oxygenation.

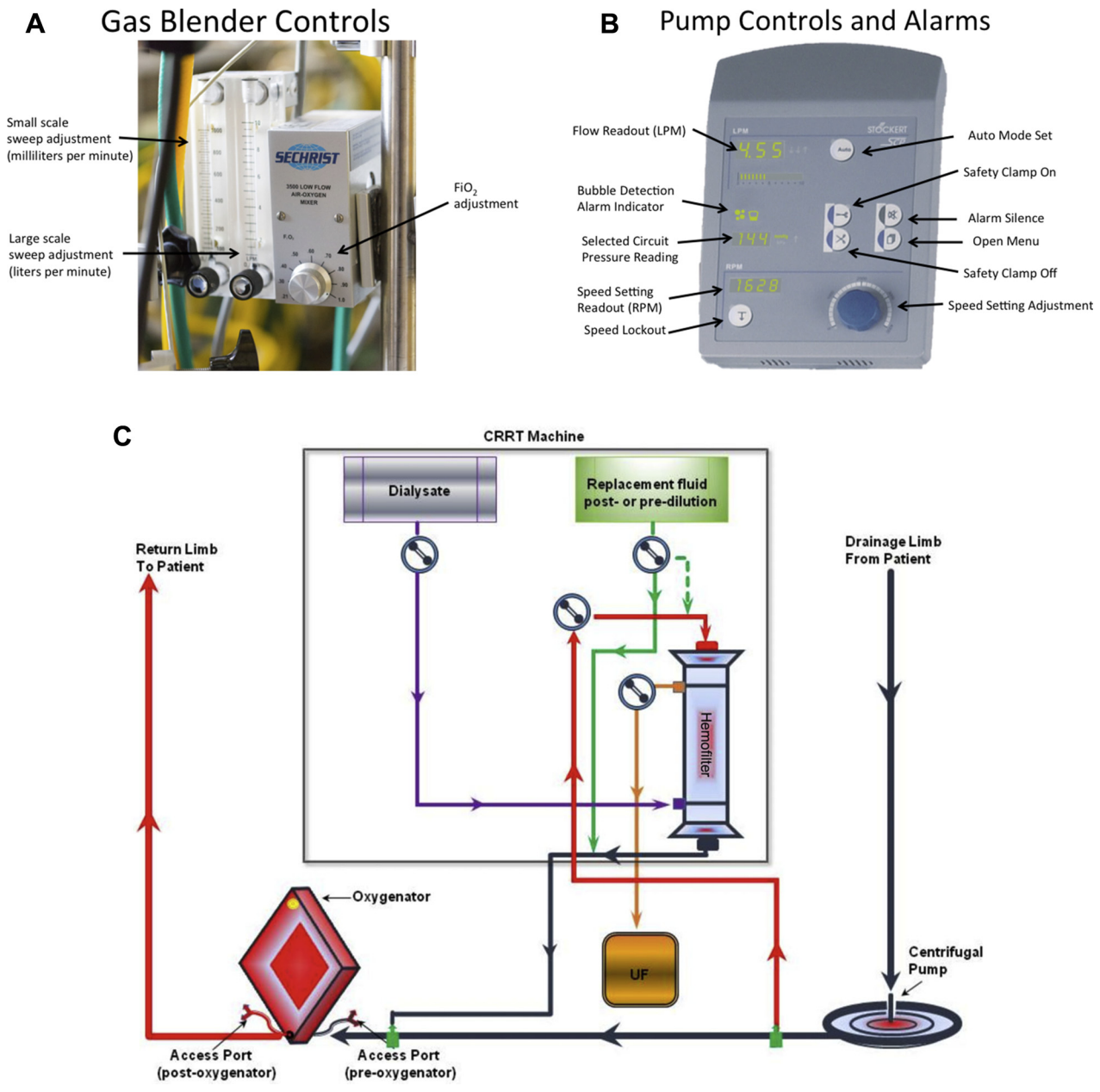
because each access point may be a source of infection, bleeding, or thrombosis (8).

MONITOR AND MANAGE VOLUME STATUS. Volume optimization is crucial to support LV decompression and allow improved end-organ function and should begin immediately after VA-ECMO support is initiated, as more positive fluid balances in this period have been associated with worse outcomes (28). Optimal fluid status may be achieved through diuresis or renal replacement therapy (29). In patients requiring renal replacement therapy, a dialysis filter may be added directly to the ECMO circuit, avoiding additional vascular access that may increase infectious, thrombotic, and bleeding complications (Figure 1C).

PREVENT UPPER BODY HYPOXIA [HARLEQUIN (NORTH/SOUTH) SYNDROME]. With VA-ECMO, blood ejected by the LV is a mixture of venous blood delivered by the RV and bronchial and pulmonary collateral blood flow. In the setting of abnormal pulmonary gas exchange, even when combined with fully oxygenated blood from the femoral arterial cannula, blood perfusing the brain, heart, and upper extremities may have a saturation below 90% causing upper body cyanosis, a condition termed harlequin (north/south) syndrome (30,31). Measures can be taken to improve oxygenation of pulmonary venous return (adjust ventilator settings or consider V-AV ECMO [8]) or to reduce mixing (decrease LV ejection). Central cannulation also mitigates this risk.

ANTICOAGULATION MANAGEMENT. Preventing thromboembolic complications is critically important in the management of patients on VA-ECMO support. Potential sources of emboli include intravascular stagnation (LV and aortic root if LV is not vented or ejecting) as well as the ECMO circuit itself. The oxygenator should be checked frequently for evidence of clot formation directly by visual inspection of the membrane and indirectly by assessing measures of hemolysis (lactate dehydrogenase, plasma free hemoglobin) and efficiency of gas exchange. Circuit line pressures should be monitored (Figure 1B) because significant changes

FIGURE 1 **ECMO Circuit Controls and In-Line Continuous Dialysis Configuration**

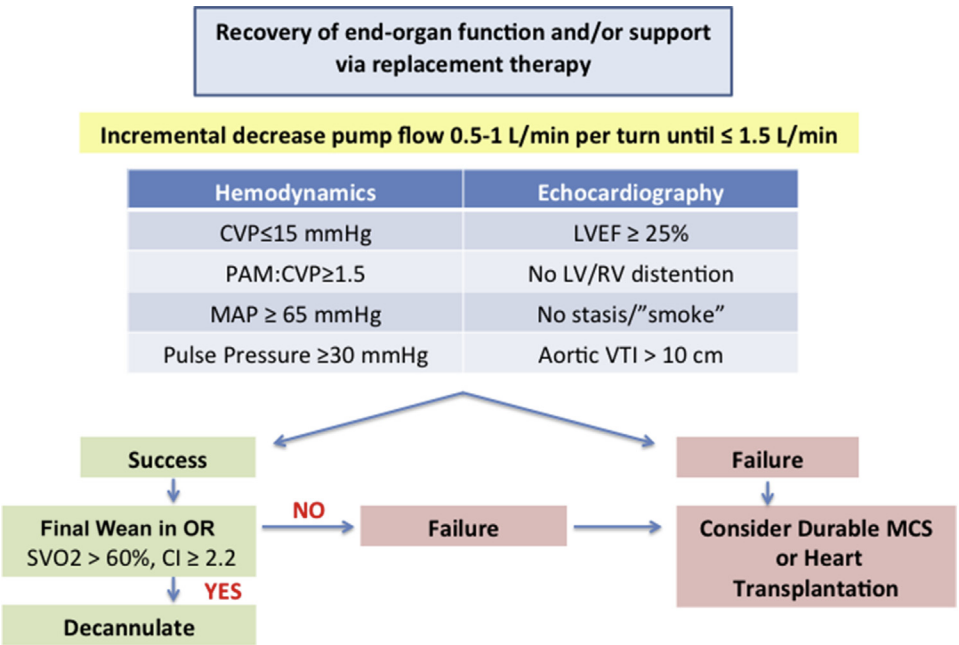


ECMO controls used to adjust flow and Fio_2 of sweep gas **(A)** and pump speed **(B)** to achieve appropriate pump flow for end-organ perfusion. Auto mode sets the goal flow, and speed automatically adjusts to maintain the set flow. Speed can also be set manually depending on the patient's condition. Monitors and alarms are incorporated into the control panel to alert providers of changes in line pressure or air in the circuit. **(C)** A dialysis filter can be incorporated into the circuit. CRRT = continuous renal replacement therapy; ECMO = extracorporeal membrane oxygenation. **(A)** Reprinted with permission from Sechrist. **(B)** Courtesy of LivaNova PLC/ Sorin Group. **(C)** Reprinted with permission from Seczyńska B, Królikowski W, Nowak I, Jankowski M, Szułdrzyński K, Szczeklik W. Continuous renal replacement therapy during extracorporeal membrane oxygenation in patients treated in medical intensive care unit: technical considerations. Ther Apher Dial 2014;18:523–34.

may indicate filter or tubing obstruction, potentially from thrombus.

Systemic anticoagulation is recommended unless there is active bleeding requiring blood transfusions (Online Table 3). Unfractionated heparin is the most widely used anticoagulant. However, direct thrombin inhibitors such as bivalirudin and argatroban have been reported to be safe and effective alternatives in

FIGURE 2 Suggested ECMO Weaning Algorithm



CI = cardiac index; CVP = central venous pressure; ECMO = extracorporeal membrane oxygenation; LV = left ventricle; MAP = mean arterial pressure; MCS = mechanical circulatory support; OR = operating room; PAM = pulmonary arterial mean pressure; RV = right ventricle; VTI = velocity-time integral.

patients with heparin-induced thrombocytopenia or heparin resistance (32,33).

Enhanced understanding of anticoagulation monitoring has been key in improving outcomes of patients on ECMO (34). ECMO programs commonly use activated clotting time, partial thromboplastin time, antithrombin III assay, and/or anti-Xa assay monitoring (35). Higher levels of anticoagulation are targeted for VA-ECMO compared to VV-ECMO because of the catastrophic nature of systemic thromboembolism or hemodynamic collapse from circuit failure.

Because patients on ECMO support are critically ill and typically have multiple indwelling lines and tubes coupled with anticoagulation and thrombocytopenia related to ECMO support, major bleeding requiring multiple blood product transfusions may occur. In this circumstance, anticoagulation should be stopped. A recent study demonstrated comparable outcomes in patients requiring interruption of anticoagulation versus those not requiring interruption while maintaining a minimum flow of 3 l/min (36). Although 3 l/min minimal flow is a useful benchmark, the ideal flow depends on multiple patient and ECMO variables.

Heparin-coated circuits have been used to minimize microthrombi formation and to reduce the dose of systemic heparin, but the benefits remain controversial (37).

ADJUST DRUG THERAPY FOR ALTERED PHARMACOKINETICS AND DYNAMICS. ECMO may alter the volume of distribution, particularly with lipophilic drugs, because of variable degrees of absorption by the circuit tubing and the oxygenator as well as increased volume of distribution from the tubing itself (38). Analgesics and sedatives along with antimicrobial agents are particularly affected (38). Consultation with a pharmacist is recommended.

IMPLEMENT ADEQUATE NUTRITION AND PHYSICAL THERAPY. When possible, ECMO patients should be mobilized to reduce deconditioning (39). Efforts to meet nutritional protein and caloric needs should be maintained (40).

WEANING ECMO SUPPORT

At the crux of the decision to wean support is the demonstration of adequate myocardial recovery to provide sufficient blood and oxygen delivery to

TABLE 5 Common Complications Associated With ECMO Support

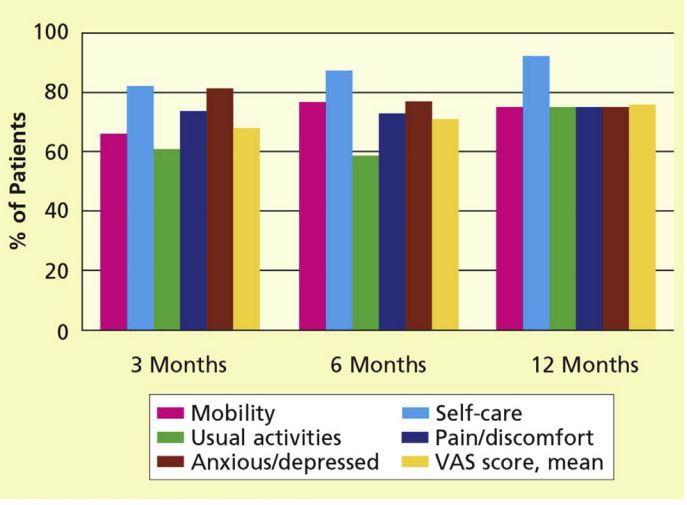
Complications	Incidence and Prevalence	Risk Factors	Risk of Mortality
Vascular (Online Refs. 1 and 2)	Reported prevalence of 20% to 30%. Limb ischemia more commonly reported, prevalence as high as 40%. Hyperemia is less common, but prevalence is estimated to be around 10% to 20%. Compartment syndrome	Femoral cannulation Percutaneous cannulation Absence of distal perfusion catheter Ipsilateral femoral arterial and venous cannulation Young age Axillary cannulation commonly associated with hyperemia	Approaches 60% in some series with limb ischemia Less clear with hyperemia
Neurological (Online Ref. 3)	Broad range of neurological complications have been associated, ranging from subclinical cognitive impairment, seizures, paraplegia, peripheral neuropathy, compartment syndrome, ischemic and hemorrhagic strokes, and death. Highly variable due to lack of standardized reporting criteria. Adult VA-ECMO patients have incidence rate of 13.3% for all neurological complications, and 5.9% to 7.8% for ischemic and/or hemorrhagic stroke. Imaging findings of neurological injury has been reported in nearly 50% of patients.	Solid or gaseous microemboli and thrombosis within cannula Differential hypoxia Hyperoxia Duration of ECMO support SIRS Anticoagulation Hemostatic imbalance between procoagulants and anticoagulants Renal failure	Nearly 90% with ICH
Infection (Online Ref. 4)	Bloodstream infections have reported prevalence of 3% to 18% and incidence of 2.98 to 20.55 episodes per 1,000 ECMO days in adults. Lower respiratory tract infections incidence is reported at 24.4 episodes per 1,000 ECMO days. Prevalence of urinary tract infections is reported between 1% to 2%, and incidence is reported to be 1 to 13.8 cases per 1,000 ECMO days.	Older age History of autoimmune disease Higher SOFA score Central VA-ECMO Duration of ECMO support	38% to 63%
Hemolysis (Online Refs. 5 and 6)	Improved incidence with newer pump designs Reported incidence between 5 to 18% (Online Ref. 6). Plasma free hemoglobin ≥100 mg/l was observed in nearly 67% of adults, and prevalence of severe hemolysis or thrombosis requiring circuit changes was noted to be 8.9% among adults (Online Ref. 5).	VV-ECMO Need and duration of continuous renal replacement therapy Hypercoagulable conditions History of inflammatory disease Hypovolemia or inadequate preload Technical complications (cannula malposition, kinking, excessive centrifugal pump speeds, among others)	Associated with higher risk of mortality (~32% for those with plasma free hemoglobin ≥100 mg/l) (Online Ref. 3)
Renal failure (Online Refs. 2,7–10)	Data limited by variable definitions of AKI across the studies; reported incidence between 33% to 55.6%. No significant difference in AKI incidence with type of cannulation. Prevalence of post-ECMO HD is reported between 28% and 52%.	Age >70 yrs Pre-operative serum creatinine >2 mg/dl Comorbidities (diabetes, obesity, cerebrovascular accident) Reoperation Thoracic aorta repair Incomplete sternum closure Bleeding and hemolysis Sepsis and DIC Mechanical ventilation	Overall hospital mortality 20% to 65% 1-yr post-HT survival of 52.3% for those with eGFR <45 ml/min/1.73 m^2 or on HD
Bleeding (Online Refs. 11–16)	Highly variable due to lack of standard definitions. Prevalence is 30% to 56%. 10 events per 100 ECMO days. Common sites are thorax, GI tract, and cannula site.	ECMO causes qualitative and quantitative platelet defects, destruction of large von Willebrand factor multimers, and fibrinolysis Number of anticoagulation levels above target range Increasing age Chronic hypertension Platelet count <50,000/μl mm HAT score (1 point each for hypertension, age >65 yrs, and VA-ECMO type) predicts bleeding; increasing score predicts increasing transfusion requirements, especially for platelets and fresh frozen plasma	Higher mortality associated more with number of red blood cell units transfused than bleeding itself

Continued on the next page

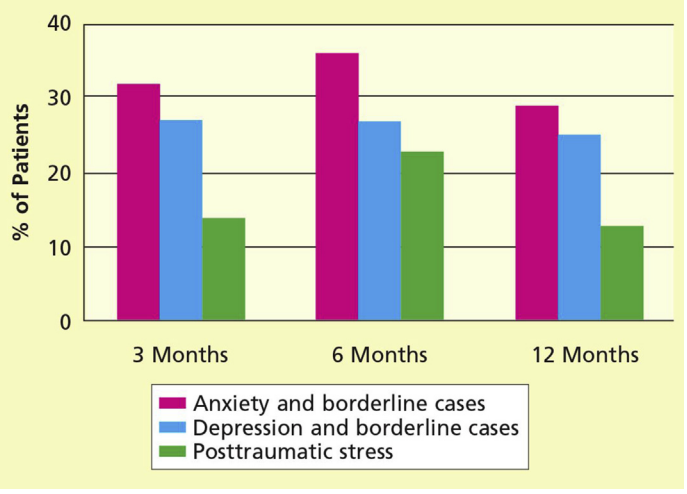
end organs to meet metabolic demands. Therefore, end-organ dysfunction, particularly pulmonary failure, should be either recovered or supported by other means (hemodialysis, mechanical ventilation) before decannulation. Therapeutic bronchoscopy to minimize dead space before weaning may be considered (41). Invasive hemodynamic monitoring and bedside echocardiography are complementary in evaluating hemodynamics and myocardial function as ECMO is being weaned (42). Although the

TABLE 5 Continued

Complications	Incidence and Prevalence	Risk Factors	Risk of Mortality
SIRS (Online Refs. 17,18)	Some degree of systemic inflammation occurs in most ECMO recipients and in about 30% after decannulation.	Infection Duration of ECMO Age (very young and very old)	Not enough data to determine (less significant in absence of sepsis)
Quality of life (Online Refs. 19-21)	In general, mental and physical activity are satisfactory but not normal. In 24 adult ECMO survivors using EQ-5D, physical activity was more impaired than mental function, and mental issues were 2 to 3 times more common than in normal subjects. In 28 long-term adult ECMO survivors (median follow-up of 11 months), 36-Item Short Form Health Survey scores were significantly lower than matched healthy controls for physical role, general health, and social functioning, but higher than those reported for patients on chronic HD, with advanced HF, or after recovery from acute respiratory distress syndrome.	Limited data Factors for improved quality of life include younger age and nonischemic disease	Not applicable



In 67 patients who survived ECMO for CS post-myocardial infarction, HRQOL was evaluated after median follow-up of 32 months. Mental health was satisfactory but persistent physical and emotional-related difficulties were reported: 34% with anxiety, 20% with depression, and 5% with PTSD symptoms.



References for Table 5 can be found in the Online Appendix. Figures in table reprinted with permission from Tramm R, Ilic D, Sheldrake J, et al. Recovery, risks, and adverse health outcomes in year 1 after extracorporeal membrane oxygenation. Am J Crit Care 2017;26:311-9.

AKI = acute kidney injury; DIC = disseminated intravascular coagulopathy; GI = gastrointestinal; HD = hemodialysis; HF = heart failure; HRQOL = health-related quality of life; HT = heart transplant; ICH = intracranial hemorrhage; PTSD = post-traumatic stress disorder; SIRS = systemic inflammatory response syndrome; SOFA = Sequential Organ Failure Assessment; VV-ECMO = venovenous extracorporeal membrane oxygenation; other abbreviations as in Tables 1 and 3.

degree of acceptable pharmacological hemodynamic support is debated, data suggest that lower levels of inotropes and vasopressors at the time of weaning are associated with improved outcomes (43), likely reflecting improved intrinsic myocardial function.

Both fast and slow weaning protocols have been described (43,44). Although data supporting a specific strategy are limited, an algorithmic approach is recommended (**Figure 2**). In patients deemed ready for weaning, a stepwise bedside decrease in ECMO flow increases preload to the heart, allowing the clinician to assess cardiac recovery using hemodynamic and echocardiographic data (42,43). Increasing pulse pressure on the arterial line waveform without concomitant LV or RV distention while ECMO circuit flows gradually decrease indicates improved cardiac contractility (42,45). Typically, a formal bedside wean is performed before the final wean, with pharmacological aid to optimize hemodynamic conditions. If the results are satisfactory, a final wean is scheduled in the operating room, which would allow controlled decannulation or expedited recannulation and reinstitution of support if necessary.

If cardiac recovery is unlikely or cannot be achieved despite medical optimization and recovery of end-organ function, direct HT or durable MCS should be considered (46,47). Direct HT from VA-ECMO support should be approached with caution, however, given poor post-transplant outcomes in this group. Renal insufficiency (estimated glomerular filtration rate <45 ml/min/1.73 m^2 or on hemodialysis) and mechanical ventilation predict worse prognosis (48). If no viable long-term support options exist, withdrawal of support is inevitable.

COMPLICATIONS WITH VA-ECMO SUPPORT

Use of VA-ECMO is associated with a broad range of complications, some of which significantly impact morbidity and mortality. In addition, patients undergoing ECMO often have pre-existing end-organ damage, making the attribution of adverse events difficult. Given the lack of randomized controlled trials, it is challenging to ascertain the exact prevalence and incidence of ECMO-related complications; however, single-center studies, multicenter registries, and meta-analyses provide valuable insight. **Table 5** summarizes some of the common complications encountered during ECMO support.

The studies summarized in **Table 5** are heterogeneous. Patient age, ECMO cannulation configuration (VA vs. VV, peripheral vs. central), and ECMO indication varied. Definitions of various complications were not standardized, further limiting the ability to characterize complications in a uniform, comprehensive way. Because most ECMO outcomes data come from small, single-center, observational reports or administrative data, inherent selection bias, regional differences, lack of granularity, and practice variation limit comparisons. Collection of prospective data using standardized protocols is needed.

ECMO ECONOMICS

Current trends in resource utilization to develop and maintain high-quality ECMO programs are of significant interest at multiple levels, including local institutions and government and third-party payers. The U.S. Nationwide Inpatient Sample documented a >700% increase in ECMO utilization between 2002 and 2012 (352 to 2715 total ECMO discharges) (2,49), with total national charges for ECMO rising from $109 million to greater than $700 million over this same general time period (50).

Cost estimates for in-hospital care of ECMO patients vary significantly, and more reliable methods to report costs will be critical as policymakers attempt to maximize value. Although comparison of costs in a private delivery model (such as the United States) and a public system (most systems outside the United States) are challenging, costs for ECMO in the United States generally exceed $100,000 per patient, whereas per-patient costs in half of international centers are less (51). Despite cost concerns, data suggest that percutaneous circulatory support utilization, including ECMO, results in decreased mortality and in-hospital costs for patients in CS, possibly due to an avoidance of end-organ dysfunction leading to shorter hospital stays (52).

CONCLUSIONS

Advances in technology and enhanced understanding of patient selection and management have enriched knowledge and utilization of ECMO in patients in CS, but survival and complication rates demonstrate room for continued improvement. Specifically, improved circuitry biomaterials that do not require anticoagulation may mitigate thrombotic and bleeding risks. Knowledge gaps persist regarding specific anticoagulation strategies and target parameters to optimize outcomes. How and when to

optimally unload the LV remains poorly defined, and weaning protocols have not been standardized. Although retrospective analyses are helpful to identify opportunities for further research, more rigorous investigation in the form of prospective, randomized controlled trials is required to inform treatment guidelines moving forward.

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APPENDIX For supplemental tables and references, please see the online version of this paper.