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Unloading the Left Ventricle in Venoarterial ECMO: In Whom, When, and How?

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ABSTRACT: Venoarterial extracorporeal membrane oxygenation provides cardiorespiratory support to patients in cardiogenic shock. This comes at the cost of increased left ventricle (LV) afterload that can be partly ascribed to retrograde aortic flow, causing LV distension, and leads to complications including cardiac thrombi, arrhythmias, and pulmonary edema. LV unloading can be achieved by using an additional circulatory support device to mitigate the adverse effects of mechanical overload that may increase the likelihood of myocardial recovery. Observational data suggest that these strategies may improve outcomes, but in whom, when, and how LV unloading should be employed is unclear; all techniques require balancing presumed benefits against known risks of device-related complications. This review summarizes the current evidence related to LV unloading with venoarterial extracorporeal membrane oxygenation.

Key Words: extracorporeal membrane oxygenation ■ heart-assist devices ■ heart failure ■ hemodynamics ■ myocardial infarction ■ shock ■ shock, cardiogenic

Cardiogenic shock is a syndrome of inadequate perfusion of vital organs attributable to primary cardiac dysfunction.[1] Despite many advances in acute cardiac care in the past 2 decades, the mortality rate after cardiogenic shock remains unacceptably high, at ≈50%. Early revascularization when cardiogenic shock complicates acute myocardial infarction (AMI) is the only intervention to have shown unequivocal benefit.[2] Circulatory support with intra-aortic balloon pump (IABP), percutaneous left ventricular assist devices (pLVADs), or inotropic therapy has not shown a clear survival benefit.[3]

Venoarterial extracorporeal membrane oxygenation (VA-ECMO) is a mechanical circulatory support (MCS) strategy that provides extracorporeal blood flow of 4 to 6 L/min and sufficient gas exchange to support systemic perfusion in severe cardiorespiratory failure. Support is provided as a bridge to recovery, transplantation, durable MCS, decision, or palliation. A significant downside is that VA-ECMO support results in a nonphysiological continuous infusion of blood into the arterial vasculature. In the peripheral configuration (Figure 1), blood flows retrograde in the aorta, increasing afterload on an already failing left ventricle (LV). If the LV is unable to overcome this increase, rising pressure and volume within the LV result in a vicious circle of LV distension, reduced coronary perfusion pressure, reduced stroke volume, and, eventually, blood stasis within the left heart and aortic root, leading to thrombus formation.[4] Transmission of increased filling pressures to the pulmonary venous circulation may result in hydrostatic pulmonary edema and even hemorrhage[5] (Figure 2). Adjunctive strategies to decompress the LV include LV unloading (during which interventions are focused on reducing LV work) or LV venting (during which interventions reduce LV filling pressures but do not necessarily reduce LV work). These strategies are increasingly used to prevent or treat complications of VA-ECMO, but they lack definitive evidence and can cause adverse outcomes in their own right. The utility of VA-ECMO itself remains unproven in cardiogenic shock; to date, a single randomized trial has been reported. The ECMO-CS (Extracorporeal Membrane Oxygenation in the Therapy of Cardiogenic Shock) study (URL: https://www.clinicaltrials.gov; Unique identifier: NCT02301819)

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Nonstandard Abbreviations and Acronyms

AMI	acute myocardial infarction
IABP	intra-aortic balloon pump
LV	left ventricle
LVEDP	left ventricular end-diastolic pressure
MCS	mechanical circulatory support
MVO_2	myocardial oxygen consumption
PCWP	pulmonary capillary wedge pressure
pLVAD	percutaneous left ventricular assist device
VA-ECMO	venoarterial extracorporeal membrane oxygenation

randomized 122 patients with rapidly deteriorating or severe cardiogenic shock to receive either immediate VA-ECMO or conservative therapy, and found no significant difference in the occurrence of a composite primary end point of death, resuscitated cardiac arrest, or need for another MCS device at 30 days (63.8% versus 71.2%; P=0.21).[6] However, it is important to note that an unloading strategy was used in only 16% of participants; whether protocolized use of unloading may have improved outcomes remains to be proven.

PHYSIOLOGICAL BASIS OF LV UNLOADING

Afterload of the LV is an indirect measure of the mechanical forces imposed on the myocardium during systole. Cardiac mechanical load is often considered synonymous with LV wall stress, a continuous measure throughout the cardiac cycle that is proportional to intracavitary pressure of the LV and radius and inversely proportional to ventricular wall thickness.[7] Continuous LV intracavitary pressure and volume readings can be used to generate LV pressure–volume (PV) loops, which provide estimates of afterload by metrics such as arterial elastance. Arterial elastance is the ratio of ventricular systolic pressure (at end systole) to stroke

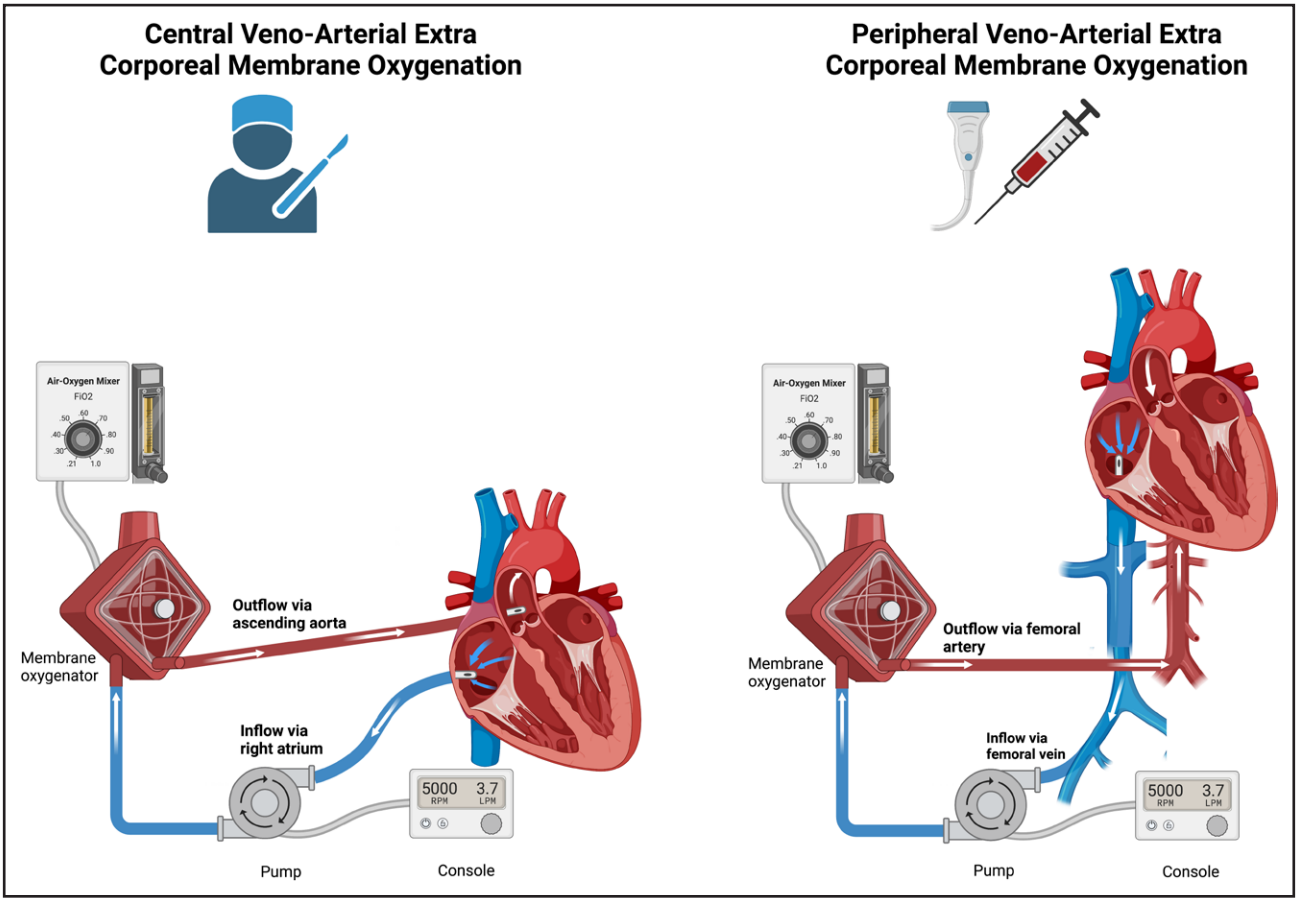

Figure 1. Comparison of central vs peripheral cannulation of VA-ECMO.
VA-ECMO maybe cannulated centrally via surgery or peripherally percutaneously. In central VA-ECMO, the arterial outflow cannula is placed in the ascending aorta, resulting in antegrade flow in the aorta in contrast to peripheral VA-ECMO, in which the outflow cannula is usually sited in the iliac artery, resulting in retrograde flow. Different configurations of the venous inflow cannula can be used in both central and peripheral circuits (eg, femoral vein inflow cannula use in a central VA-ECMO circuit). VA-ECMO indicates venoarterial extracorporeal membrane oxygenation.

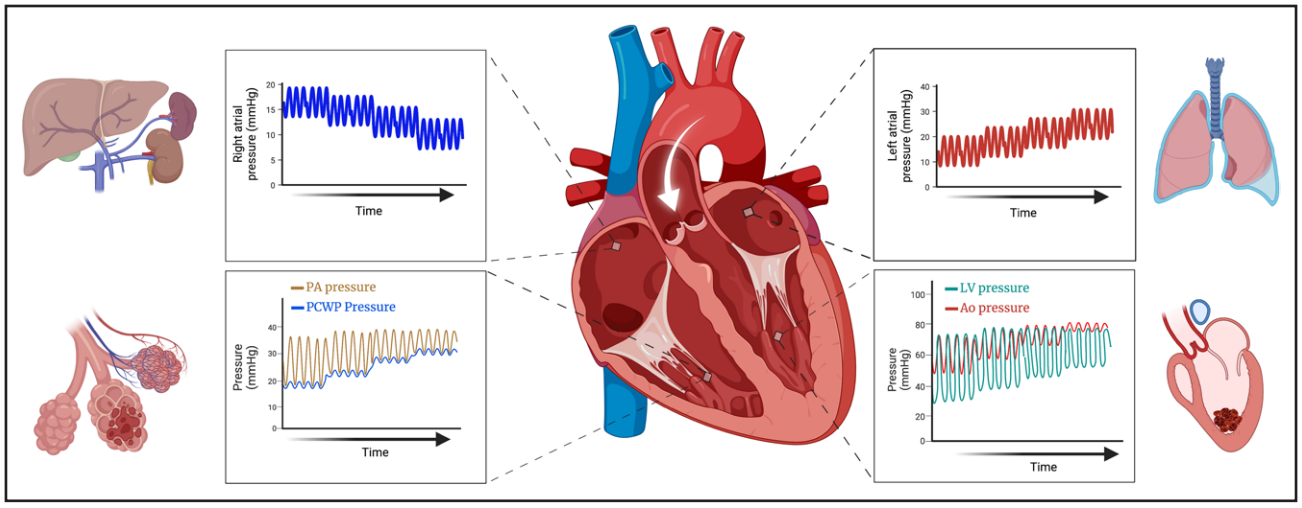

Figure 2. Hemodynamic effects of VA-ECMO.
VA-ECMO reduces right atrial pressure, decongesting the liver and kidneys. Mean aortic pressure rises, increasing afterload; if the LV is unable to overcome the increased afterload, stroke volume falls, resulting in loss of aortic pulsatility and stagnation of blood, potentiating thrombus formation. Rising LV end-diastolic pressure transmitted to the left atrium leads to pulmonary congestion. Backward failure eventually increases PCWP and PA diastolic pressure with loss of PA pulsatility and worsening lung injury. A_0 indicates aortic; LV, left ventricle; PA, pulmonary artery; PWCP, pulmonary capillary wedge pressure; and VA-ECMO, venoarterial extracorporeal membrane oxygenation.

volume and reflects arterial load (Figure 3A). Arterial load is closely related to cardiac afterload, and, if increased, it impairs ventricular performance by reducing stroke volume and, hence, cardiac output, if contractility and end-diastolic volume (EDV) remain constant (Figure 3C). In pathophysiological conditions, a significant increase in afterload is accompanied by backward failure, venous congestion, and higher preload. A higher preload may increase LVEDV, which, in turn, should increase stroke volume via the Frank-Starling mechanism (Figure 3D). The ability to increase stroke volume by increasing LVEDV is known as the preload reserve; if exhausted, the LV becomes sensitive to increased afterload, particularly in the context of limited contractile reserve.[8,9] When the preload reserve is exhausted, the PV loop shifts upward and to the right, increasing the PV area (PVA) and myocardial oxygen consumption (MVO_2). Increased contractility represents a second compensatory mechanism by which the LV can maintain stroke volume, but it comes at the cost of increased PVA, and, therefore, MVO_2 (Figure 3D), which may have a potentially adverse impact on myocardial recovery. During cardiogenic shock, the LV usually lacks the preload and contractile reserve to overcome the increased afterload associated with VA-ECMO, thereby increasing myocardial oxygen demand on a failing ventricle.

LV unloading refers to strategies that reduce PVA, hence reducing MVO_2 (Figure 3B).[10] Unloading has 2 key goals: (1) preventing or treating clinically manifested complications; and (2) promoting LV recovery, even in those without apparent complications. In contrast, LV venting refers to a reduction in LV end-diastolic pressure (LVEDP) with the goal of reducing pulmonary congestion; therefore, not all patients will require venting in the absence of elevated LVEDP but may still benefit from unloading.[11] Emerging evidence suggests that unloading may offer cardioprotection beyond mechanical effects with reduced inflammatory cytokine expression, such as that found in fulminant myocarditis.[12] In a swine model of AMI, LV unloading reduced infarct size,[13] with genomic studies identifying a cardioprotective shift in gene expression, leading to preserved mitochondrial integrity.[14]

WHOM TO UNLOAD?

There is a lack of high-quality data to guide which patients supported with VA-ECMO may benefit from LV venting or unloading. The development of overt complications of increased afterload (such as pulmonary edema or failure of aortic valve opening) is a widely accepted indication for unloading (Table 1). The decision to unload primarily for facilitation of LV recovery in the absence of overt complications is more difficult because of the fine balance between the risks and benefits of placing additional MCS devices. Use of unloading devices can be associated with significant bleeding and vascular complications, hemolysis, and coagulation disorders in a population of patients already prone to profound coagulopathy and systemic inflammatory response syndrome.[15,16] The use of additional MCS for unloading also adds practical complexity, not only in managing device settings, but also for anticoagulation, monitoring vascular access sites, and difficulty repositioning the patient. These risks need to be balanced against the potential benefits of unloading: ≈30% to 70% of patients treated with VA-ECMO develop increased afterload, which is

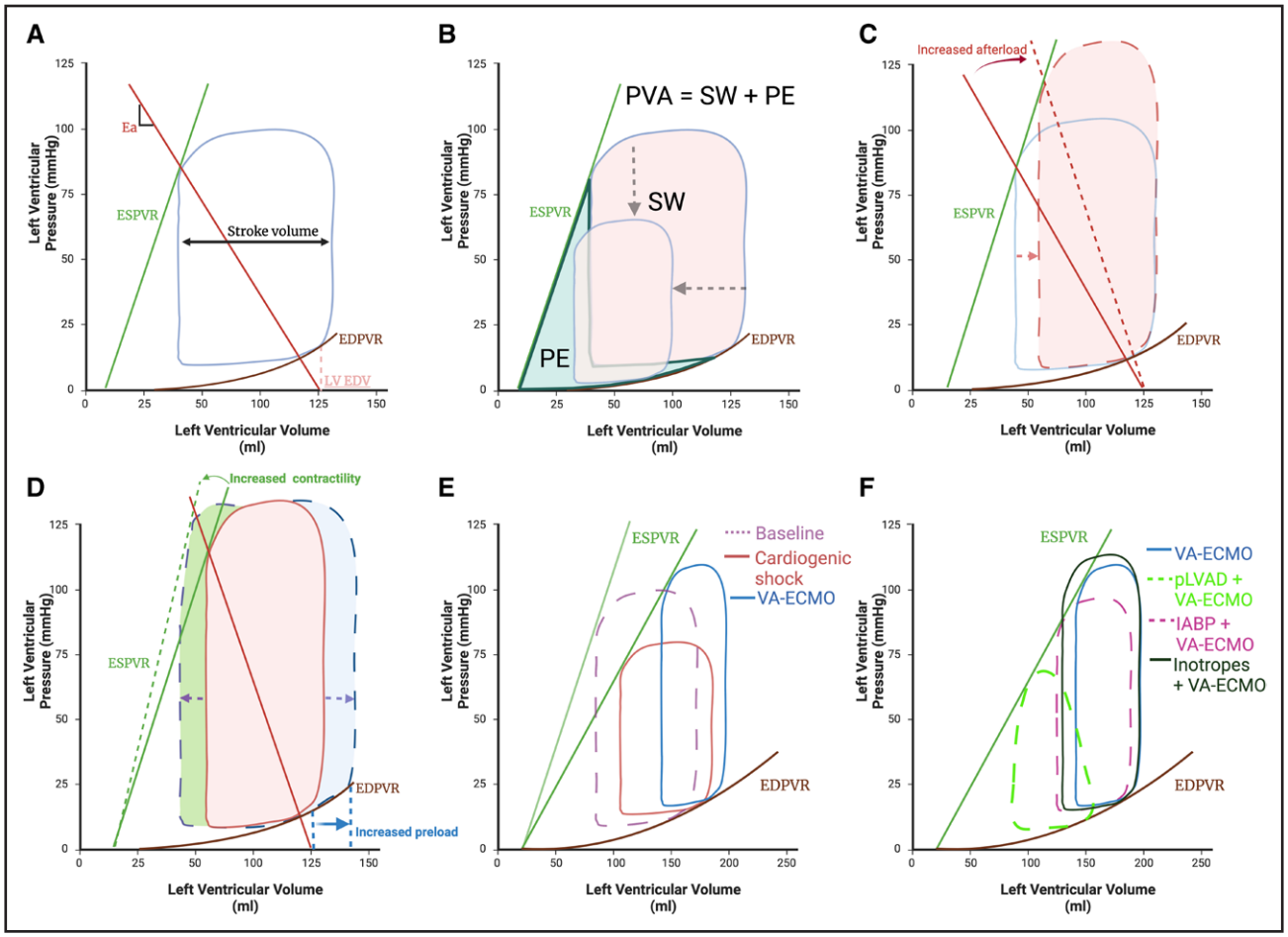

Figure 3. PV loop basics.

A, Normal PV loop. Boundaries are created by the ESPVR and the nonlinear EDPVR. Effective Ea reflects afterload and is the slope of the line between the EDV and the ESPVR. **B**, SW is the work required to eject blood; PE is energy generated during contraction but not converted to SW. PVA correlates linearly with myocardial oxygen consumption (MVO_2) and is the sum of the SW and PE. Ventricular unloading is defined by a reduction in the PVA. **C**, Increased afterload while maintaining the same level of contractility and preload reduces SV. **D**, SV can be increased by increasing preload (however, in a dilated ventricle, because of the nonlinear EDPVR, this will cause a significant rise in EDP) or by increasing contractility (but this also increases MVO_2). **E**, Cardiogenic shock results in loss of contractility and increases EDP and EDV. VA-ECMO raises systolic pressure, EDP, and afterload, thereby increasing PVA and further reducing SV. **F**, IABP reduces afterload, increasing SV without significantly reducing EDP, EDV, or PVA. In contrast, pLVAD actively unloads the ventricle, reducing afterload, EDV, and EDP, thereby significantly reducing PVA. Inotropes increase contractility, improving SV; however, this increases PVA. Ea indicates arterial elastance; EDP, end-diastolic pressure; EDV, end-diastolic volume; EDPVR, end-diastolic pressure volume relationship; ESPVR, end-systolic pressure volume relationship; IABP, intra-aortic balloon pump; LVEDV, left ventricular end-diastolic volume; PE, potential energy; pLVAD, percutaneous left ventricular assist device; PV, pressure–volume; PVA, pressure–volume area; SV, stroke volume; SW, stroke work; and VA-ECMO, venoarterial extra corporeal membrane oxygenation.

associated with increased mortality.[17] LV unloading in these patients has been associated with a higher rate of recovery or bridge to advanced therapies,[18] more successful weaning from VA-ECMO,[19] and lower in-hospital mortality.[16]

The decision to use a mechanical unloading strategy, as well as the timing of insertion and choice of device, will be determined by the treatment goals for an individual patient in addition to the experience of a multidisciplinary team guided by the contemporary evidence base. Hemodynamic, echocardiographic, and clinical features may help identify those at risk for developing complications or identify the complications.

Hemodynamic Predictors

Reduced arterial pulsatility is a readily available measure of increased afterload in VA-ECMO patients; a pulse pressure <15 mm Hg correlates strongly with reduced native cardiac output <1 L/min,[20] whereas a pulse pressure <20 mm Hg has been associated with reduced survival.[21] Binary cut-off values for reduced pulsatility are designed to aid decision-making in clinical practice, but there is likely a continuous spectrum of risk as pulsatility decreases.[22]

LVEDP (more often estimated by pulmonary capillary wedge [PCWP] rather than by direct measurement) is a useful metric. Patients with raised PCWP before initiation of VA-ECMO are particularly vulnerable to the impact of

Table 1. Indications for Left Ventricular Unloading

Parameter	Indication
Hemodynamic	Pulmonary capillary wedge pressure >18 mm Hg
	Lack of arterial line pulsatility (pulse pressure <15 mm Hg)
Echocardiographic	Increasing left ventricular dimensions
	Stasis of blood within the left ventricular cavity
	Left ventricular thrombus
	Absence of aortic valve opening
	Left ventricular outflow tract velocity time integral <10 cm
Clinical	Development of pulmonary edema
	Refractory ventricular arrhythmia

increased afterload, as their preload reserve is exhausted. A PCWP >15 mm Hg measured at the time of VA-ECMO initiation was found to predict a response to unloading with IABP,[23] whereas others have suggested a threshold >18 mm Hg.[24] A target LVEDP of 12 to 18 mm Hg suggests adequate LV decompression when unloading has been initiated.[25] Right ventricle and LV interdependence is an important consideration, particularly for patients with preserved right ventricular function who may be at increased risk of complications because a higher volume of transpulmonary blood flow results in increased LV filling pressures.[26]

Echocardiographic Predictors

Transthoracic echocardiography provides detailed noninvasive information on LV geometry and performance to inform the decision on unloading. Serial assessments are recommended, although achieving accurate and reproducible measurements can be challenging in this patient population. Where limited echocardiographic assessment is available, focused assessments of aortic valve opening and the LV outflow tract (LVOT) velocity time integral may provide the most objective markers. Transesophageal echocardiography can be considered in patients with particularly limited transthoracic imaging windows, acknowledging that there is often limited provision for serial reassessment using this technique.

The LV ejection fraction observed before instituting VA-ECMO is predictive of afterload sensitivity: a lower LV ejection fraction is associated with increased PCWP and reduced stroke volume on initiation of VA-ECMO,[9] as well as increased risk of death.[27] Because of the importance of LV geometry in determining afterload and contractility, the finding of increasing LV dimensions despite a fixed ECMO flow rate may prompt consideration of unloading.[28] The LVOT velocity time integral can be used to estimate stroke volume and cardiac output; an LVOT velocity time integral <10 cm reflects an insufficient intrinsic cardiac output, thereby predicting unsuccessful weaning from VA-ECMO and sensitivity to increased afterload.[29]

Echocardiography can also be used to detect complications such as blood stasis, LV thrombus, or absence of aortic valve opening. Worsening secondary or diastolic mitral regurgitation may reflect rising LV pressures, and is an early marker of impending pulmonary edema. A study of 98 VA-ECMO–supported patients found that 22% had spontaneous echocardiographic contrast associated with lower LV ejection fraction and pulsatility index on echocardiography, as well as higher incidence of intracardiac thrombus (46% versus 13%, respectively) and stroke (36% versus 7.9%, respectively).[30] Therefore, the development of spontaneous echo contrast identifies a high-risk group for whom consideration for immediate unloading should occur.

Clinical Predictors

While hemodynamics and cardiovascular function are the primary determinants of complications from increased afterload, the etiology of shock has important influences on these parameters, and therefore, merits consideration in deciding which patients receive LV venting or unloading.

For shock that complicates AMI, increased LV pressure results in reduced subendocardial perfusion. In addition to the deleterious effects on infarct size and genomic changes, this impairment of subendocardial perfusion can exacerbate ischemia and further impair ventricular performance.[31] Data from a meta-analysis of 62 studies (7581 total patients) suggest that the greatest mortality benefit seen in unloading is when shock is secondary to AMI, which has an absolute risk reduction of 6.65% and a number-needed-to-treat of 15 to prevent 1 death.[32]

Patients with chronic heart failure often have elevated PCWP at baseline, making them particularly vulnerable to increased afterload because their preload reserve will be exhausted.[33] Use of an IABP in shock caused by acute on chronic heart failure significantly reduces systemic vascular resistance and augments cardiac output by 23% compared with 10% in AMI shock.[34] This group would potentially benefit from prophylactic unloading, given their vulnerability to increased afterload, with demonstrable improvements in cardiac output by reducing afterload and reduction in the incidence of hydrostatic pulmonary edema.[35]

HOW TO UNLOAD?

Several mechanical circulatory strategies can be used to achieve LV unloading or venting if conservative measures prove to be insufficient. Each method is associated with its own contraindications, risks, costs, and potential advantages. The How To Unload section outlines the characteristics, hemodynamic effects, and clinical evidence for each technique.

Noninvasive and Pharmacological Approaches

Efforts should be made to reduce preload and afterload using conservative measures before considering invasive LV unloading strategies.[36] Extracorporeal blood flow increases mean arterial pressure and, hence, afterload; therefore, the optimal VA-ECMO flow rates should be adequate to provide systemic perfusion while minimizing afterload. Lower flow rates (<2.2 L/(min·m^2) can provide adequate systemic perfusion while reducing LV distension,[37] although caution must be exercised, as very low rates (particularly, <1.5 L/min) may increase the risk of thrombotic complications within the ECMO circuit, with potentially severe consequences.[38] For patients requiring higher extracorporeal blood flow to maintain perfusion, intravenous vasodilators may reduce mean arterial pressure and restore ventricular ejection.[39] A trial of fluid optimization with diuresis or hemofiltration may be tried for patients with raised LV filling pressures who have not developed overt complications of increased afterload; a lower total fluid balance has been associated with better outcomes and may avoid the need for mechanical LV unloading, yet may not be achievable for all patients.[40]

Inotropes may be used to increase LV contractility and, therefore, stroke volume. This approach is often employed as either an initial strategy to counteract mild degrees of increased LV afterload or as a bridge to definitive unloading for those who have developed or are at increased risk for developing complications.[36] However, inotropes increase myocardial oxygen demand (Figure 3F); inotrope use has been associated with increased mortality in observational studies.[41] A propensity-matched cohort of 231 VA-ECMO patients found significantly worse 30-day survival (25% versus 48%) for those treated with epinephrine in the first 24 hours compared with either no inotropes or inodilators.[42]

Venting

Catheters

Percutaneous catheters can be placed into the LV cavity, left atrium, or pulmonary artery[43–46] and connected to the inflow cannula of the VA-ECMO circuit. Pigtail catheters (7F) inserted into the LV with transesophageal echocardiography guidance have been used to achieve transaortic unloading with a reduction in LV dimensions and volume.[43] The use of 5F and 6F LV catheters has been reported, showing reduction in LV dimensions and increased mean arterial and pulse pressures. However, the size of percutaneous catheters limits the maximum flow that can be achieved because of a higher risk of hemolysis; therefore, this approach is not routinely recommended.[44,47]

Unloading

Percutaneous atrial septostomy

Percutaneous atrial septostomy is created with the use of a percutaneous blade or balloon, typically under fluoroscopic or transesophageal echocardiographic guidance. Although widely used in pediatric populations, limited data are available for adults. Reductions in left atrial pressure, as well as resolution of LV distention and pulmonary edema, have been reported.[48] A porcine model of cardiogenic shock supported with VA-ECMO demonstrated that atrial septostomy reduced PVA driven by a reduction in stroke volume.[49] However, this could increase the risk of a nonejecting LV and potential LV or aortic root thrombus because of the lack of forward flow through the aortic valve.[50] Further, the residual atrial septal defect may increase the risk of stroke after removal of the venous cannula, particularly after prolonged periods of VA-ECMO support.

Recently, left atrial VA-ECMO has been described, in which a multistage venous drainage cannula is placed in the left atrium via transseptal puncture. This allows simultaneous biatrial drainage, thereby unloading the right and left ventricles and demonstrating reduced PCWP.[51] This approach may be particularly helpful for patients with LV thrombus or unilateral peripheral vascular disease, in which second large-bore femoral arterial access is precluded. It may be the preferred choice for patients in whom transaortic device placement is contraindicated, such as those with severe aortic stenosis or mechanical aortic valve replacement.

An alternative method to achieve left atrial drainage is with the use of TandemHeart (LivaNova, UK), which is a centrifugal pump–based system that uses a 21F transseptal cannula sited in the left atrium, forming the inflow limb with the outflow limb sited in the femoral artery. An oxygenator can be added to the system, or, alternatively, the left atrial cannula can be connected into the inflow limb of a VA-ECMO circuit via a Y connector, achieving biatrial drainage with subsequent biventricular unloading.[52]

Pulmonary artery drainage

Placement of an ECMO inflow cannula into the pulmonary artery can indirectly reduce LV pressure and volume by decreasing preload. Single- or multi-stage cannulas can be used for this purpose. The ProTek Duo (CardiacAssist Inc, USA) is dual-lumen cannula that can also be used to drain both the right atrium and pulmonary artery when both lumens are spliced together as an inflow circuit for VA-ECMO. ProTek Duo is available in 29F or 31F cannula sizes and is inserted via the jugular vein, enabling flows of up to 4.5 L. It is commonly used as a right atrium–to–pulmonary artery bypass circuit for support of the right ventricle.

Intra-aortic balloon pump

The IABP is the most frequently used adjunct MCS device for LV unloading.[53] It is placed in a standard position

in the descending aorta, with deflation in systole decreasing afterload during LV ejection and promoting forward flow through the aortic valve, while inflation in diastole improves coronary blood flow.[54] The IABP provides less unloading compared with pLVAD; an animal model found a 12% PVA reduction driven by a reduction in potential energy, as opposed to stroke work (Figure 3F).[55] The use of an IABP has also been shown to improve cerebral blood flow in patients with cardiogenic shock on VA-ECMO and pulse pressure >10 mm Hg before initiation of the IABP, in contrast in those with a pulse pressure <10 mm Hg cerebral blood flow is reduced.[56] These findings suggest that IABP may be most effective for those retaining a degree of native LV ejection, an observation consistent with the known physiological effects of counterpulsation on patients with cardiogenic shock for whom IABP was used as the sole MCS device.

No randomized data exist to support the use of IABP for unloading; observational data are conflicting. During AMI shock, the use of IABP unloading is associated with improved short-term mortality (odds ratio [OR], 0.82 [95% CI, 0.75–0.89]; $P \leq 0.001$) at the cost of increased major bleeding (OR, 1.09 [95% CI, 1.0–1.18]; $P=0.03$) compared with VA-ECMO alone.[57] A meta-analysis of 2251 patients with postcardiotomy shock found that mortality was similar to the combination of VA-ECMO and IABP compared with VA-ECMO alone.[58] A larger meta-analysis of 4653 patients found similar short-term mortality in patients either receiving or not receiving an IABP, except in the subgroup of AMI shock, in which mortality was lower with IABP.[59] The heterogenous populations and observational confounding included in these meta-analyses may explain the differing results. The findings may also suggest a differential effect of IABP based on the etiology of shock, with ischemic patients gaining additional benefit from augmentation of coronary perfusion; this should be confirmed through more robust, randomized studies.

Percutaneous left ventricular assist device

Increasingly, the combination of the pLVAD and VA-ECMO is being used. pLVADs are transvalvular microxial flow pumps that continuously displace blood from the LV cavity to the aortic root, resulting in a significant decrease in stroke work and PVA (Figure 3F), and, therefore, MVO_2.[60] The Impella CP (Abiomed) is most commonly used for LV unloading, a configuration referred to as ECMELLA or ECPELLA (combining venoarterial extracorporeal membrane oxygenation and Impella). The pLVAD is usually inserted percutaneously via the contralateral femoral artery to the ECMO outflow cannula, although surgical implantation via the axillary artery and percutaneous transcaval insertion can be considered.[61] Contraindications to the use of pLVADs include mechanical aortic valve replacement, severe aortic regurgitation, LV thrombus, and peripheral vascular disease. The Impella CP device requires large-bore arterial access (14F) and anticoagulation delivered directly through the device purge solution; however, recent evidence suggests a bicarbonate-based purge solution may be a safe alternative for patients with bleeding concerns.[62,63]

ECPELLA has been shown to reduce PCWP, improve pulmonary flow by reducing right ventricular afterload, and reduce LV dimensions[64,65]; however, as with IABP, no randomized data exist to support pLVAD use for LV unloading. A registry of 510 propensity-matched patients found that ECPELLA was associated with 21% lower mortality at 30 days compared with VA-ECMO alone, despite increased rates of severe bleeding (38.4% versus 17.9%, respectively) and hemolysis (33.6% versus 22.4%, respectively).[15] These findings highlight the potential tradeoff that must be considered when using pLVAD; reduced mortality (number-needed-to-treat of 15 in this observational study) must be weighed against the risk of increased bleeding and limb ischemia (number-needed-to-harm, 5 and 11, respectively). Use of a distal perfusion cannula incorporated into the ECMO outflow circuit may be considered for patients displaying signs of limb ischemia distal to the pLVAD access site. However, its use further increases the complexity of the MCS circuit.

A critical aspect of managing patients treated with ECPELLA is balancing flow rates of both the VA-ECMO circuit and the pLVAD device to achieve adequate systemic perfusion and LV unloading. This balance must be managed in a dynamic manner, with a tendency toward higher VA-ECMO flow to achieve adequate systemic perfusion during the initial stabilization, followed by a gradual transition to increased pLVAD support to aid cardiac recovery, and ultimately wean preferentially from VA-ECMO. Particular attention must be given to patients with hypoxemic respiratory failure for whom high pLVAD flow rates may draw deoxygenated blood from the LV into the systemic, coronary, and cerebral circulation, exaggerating a phenomenon well described as the “Harlequin” or “North-South syndrome”[66]; in this situation, it is preferable to set the pLVAD flow at a lower level until an improvement in respiratory function allows titration of pLVAD and weaning of ECMO flow. The same phenomenon is classically seen with LV recovery and ongoing pulmonary edema. Careful counterbalancing is also required to ensure sufficient LV preload through preventing suction at the pLVAD inflow which can cause hemolysis. Those with biventricular shock may have lower LV preload because of poor right ventricle function; therefore, unloading with pLVAD may be less effective and associated with more frequent complications, although recent experimental data from a porcine model of cardiogenic shock found that pLVAD use resulted in a septal shift toward the LV, resulting in increased right ventricle stroke work and cardiac output without increased LV stroke work.[67]

Initial pLVAD flow rates are generally lower than those that can be achieved by these devices, and limited data exist for guiding flow adjustment to hemodynamic targets. End-tidal carbon dioxide has been found to directly correlate with increased pulmonary flow and reduced LV dimensions with increasing pLVAD flow and may offer a convenient noninvasive method of LV-unloading effect assessment.[64]

A larger-bore version of the Impella device (Impella 5.5) can provide up to 6 L/min of antegrade flow, providing enough forward flow to support systemic perfusion in isolation for most cases. When used as an initial unloading device, the Impella 5.5 may allow earlier weaning of VA-ECMO or lower VA-ECMO flow rates to support the right ventricle and oxygenation until improvement allows for decannulation. The device is inserted surgically via the axillary artery and can remain in situ for significantly longer than the Impella CP device (eg, durations of up to 83 days have been reported), although current licensing permits 30 days in Europe and 14 days in the United States.[68] This development has potential advantages in allowing patient ambulation and reduced hemolysis and thrombosis,[69] thereby acting as a potential bridge to transplant or durable LVAD implantation after ECMO decannulation.[70] This approach may be advantageous in patients with decompensated chronic heart failure, those in whom the chances of LV recovery are considered low, or those in whom MCS placement is anticipated to be for a prolonged duration. The benefits of these devices must be balanced against the risks, complexities, and expenses related to a large-bore, surgically implanted device. In such cases, it is important that the multidisciplinary shock team make a careful assessment of potential futility before committing to mechanical unloading.

Surgical approaches

Central VA-ECMO is typically instituted in postcardiotomy shock or with graft failure after heart transplantation when sternotomy has already been performed. Although cannulation of the ascending aorta avoids the retrograde flow associated with peripheral VA-ECMO, ventricular distension and reduced forward flow through the LVOT and aortic root may still occur because of impaired LV contractility. This may be potentiated by prolonged ischemic time during cardiopulmonary bypass, with a canine model of hypothermic cardioplegia finding impaired subendocardial perfusion and ventricular performance in those with distended ventricles (LVEDP >20 mm Hg).[31] These considerations have led some centers to routinely unload all patients treated with peripheral or central VA-ECMO for postcardiotomy shock[71]; a meta-analysis of 2324 patients found a nonsignificant reduction in mortality (relative risk [RR], 0.93 [95% CI, 0.85–1.01]; *P*=0.09), but a significantly higher chance of weaning from ECMO.[32]

Incorporating a surgical venting cannula (16–20F) sited at the LV apex, pulmonary vein, or pulmonary artery into the venous drainage limb of the VA-ECMO circuit via a Y connector can provide effective biventricular unloading.[53] Minimally invasive surgical techniques using a subxiphoid and anterolateral thoracotomy approach have been described.[72] There are limited data regarding outcomes of these methods for adult patients: one study retrospectively compared 23 patients with surgical venting with 22 patients with pLVAD and found similar 30-day mortality.[73] Both methods significantly reduced pulmonary artery diastolic pressure and had similar complication rates.

Choice of strategy

The mechanism of action for each unloading strategy is likely to be distinct,[36] and there are no reliable head-to-head comparisons of clinical effectiveness. Registry data suggest that the IABP may be suitable for less severe degrees of increased afterload; however, for cases in which there is a dilated nonejecting ventricle with significantly raised filling pressures, active unloading with either pLVAD or surgical venting is likely required.[74]

The HERACLES trial (Hemodynamic Effects of Reducing Left Ventricular Afterload With Impella or Intraaortic Balloon Counterpulsation During Venoarterial Extracorporeal Membrane Oxygenation in Cardiogenic Shock; URL: https://www.isrctn.com; Unique identifier: ISRCTN82431978) will be the first randomized comparison of unloading strategies, randomizing 36 patients supported with VA-ECMO to unloading with either IABP or pLVAD and comparing the physiological impact of each device on coronary flow and ventricular pressures and volumes. Whether a tailored approach using hemodynamic and clinical criteria to individualize the unloading strategy may improve outcomes remains to be seen. Although randomized data are urgently required to make firm recommendations on unloading method choice, currently, decisions should be made in a pragmatic manner, based on local expertise and strategies available to a particular multidisciplinary shock team (Figure 4).

WHEN TO UNLOAD

Unloading devices may be inserted before, at the same time as, or shortly after initiation of VA-ECMO. This prophylactic approach may help protect the vulnerable ventricle and promote myocardial recovery by avoiding exposure to increased afterload, which should be weighed against the potential risks of increased complications and cost.[75] Alternatively, unloading may be reactive when undertaken only in response to adverse hemodynamic, clinical, or echocardiographic manifestations of increased afterload, reducing the risk of complications from the unloading device itself, but potentially jeopardizing myocardial recovery.

In a series of 106 consecutive ECPELLA patients, survival was similar in those who had concomitant pLVAD

implantation at the time of VA-ECMO cannulation and those for whom implantation was delayed.[76] A larger registry of 337 ECPELLA patients found that early pLVAD implantation improved short-term mortality, whereas delayed unloading (ie, >2 hours after VA-ECMO implantation) did not.[15] Finally, a propensity-matched cohort of 74 patients found significantly lower mortality in those for whom pLVAD was inserted before VA-ECMO compared with those receiving VA-ECMO first.[77]

A retrospective analysis comparing prophylactic left atrial VA-ECMO with reactive unloading with either percutaneous or surgical methods found a lower 30-day mortality and transition to durable ventricular-assist device or cardiac transplantation in the prophylactic unloading group.[78] A metaregression of observational studies found that prophylactic unloading had a significant inverse relationship with mortality.[79] However, these data are confounded with differing indications for prophylactic unloading and definitions for reactive unloading. Although current data suggest that prophylactic unloading up to 2 hours after the initiation of VA-ECMO appears beneficial, randomized trials are needed to establish treatment efficacy (Table 2).

The EARLY-UNLOAD trial (Early Left Atrial Septostomy Versus Conventional Approach After Venoarterial Extracorporeal Membrane Oxygenation; URL: https://www.clinicaltrials.gov; Unique identifier: NCT04775472) aims to recruit 116 participants for comparing early unloading (ie, within 12 hours of VA-ECMO) with bailout unloading, with atrial septostomy as the mode of unloading in both groups. The primary outcome is all-cause mortality at 30 days, whereas secondary outcome measures (eg, the need for bailout atrial septostomy, long-term heart replacement therapies, and resolution of pulmonary edema) are likely to be informative. The REVERSE study (Impella CP with VA-ECMO for Cardiogenic Shock; URL: https://www.clinicaltrials.gov; Unique identifier: NCT03431467) will recruit 96 patients comparing early (within 10 hours) unloading with Impella to VA-ECMO alone with a primary outcome of recovery from cardiogenic shock at 30 days; the chosen primary end point is of particular interest because the aim of unloading is not just to treat or avoid complications of increased afterload, but also to facilitate myocardial recovery.

The ECLS-SHOCK trial (Extracorporeal Life Support in Cardiogenic Shock; URL: https://www.clinicaltrials.gov;

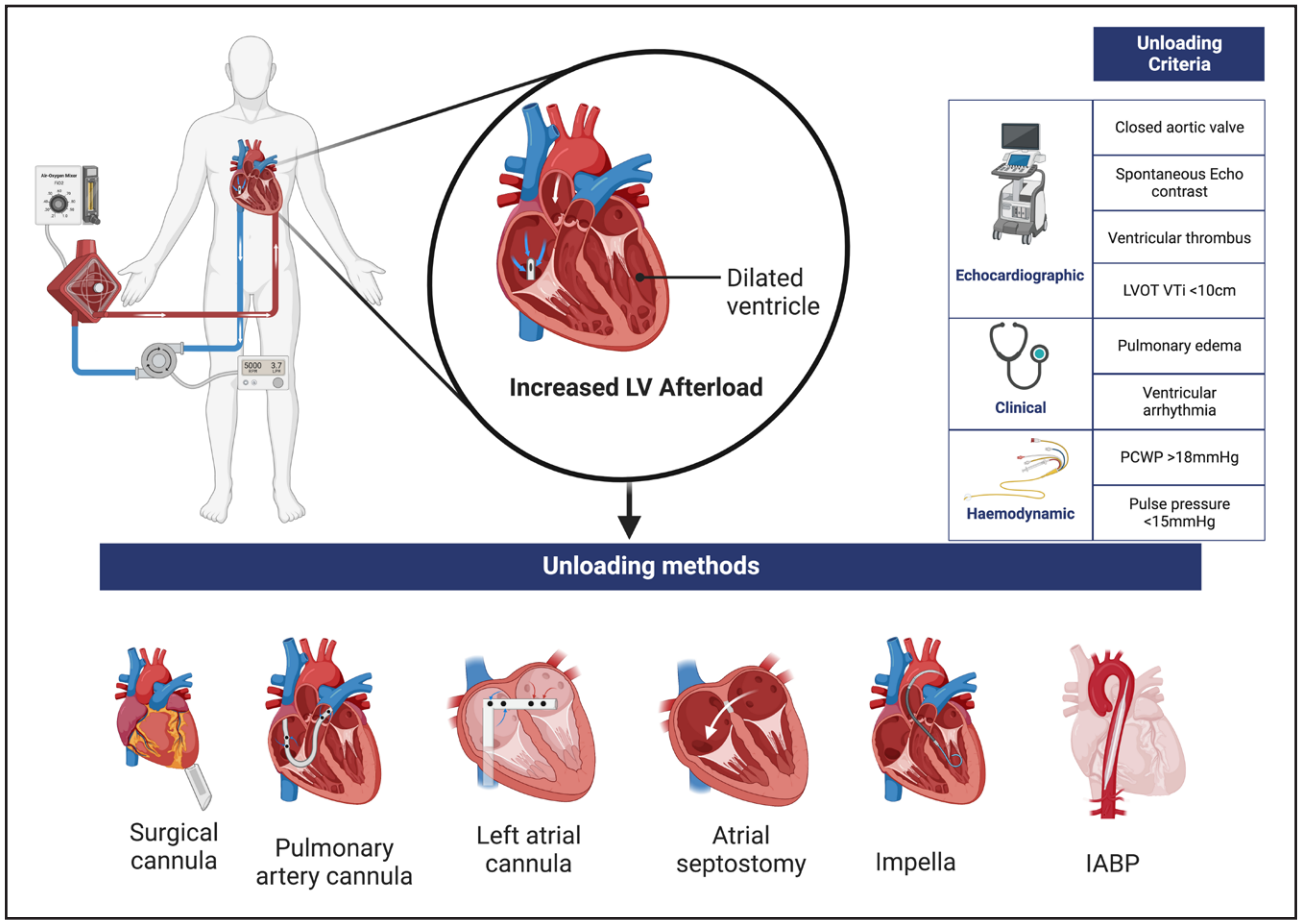

Figure 4. LV unloading criteria and methods.
IABP indicates intra-aortic balloon pump; LV; left ventricle; LVOT VTi, left ventricular outflow tract velocity time integral; and PCWP, pulmonary capillary wedge pressure.

Table 2. Current Randomized Clinical Trials of VA-ECMO

Trial name	Inclusion criteria	No. of participants	Intervention	Control	Institution	Primary outcome	Key secondary outcomes	Estimated study completion
EARLY-UNLOAD (NCT04775472)	Cardiogenic shock	116	VA-ECMO + atrial septostomy within 12 hours	VA-ECMO alone	Chonnam National University Hospital, Korea	All-cause mortality at 30 days	Rate of atrial septostomy in control group Incidence of cardiac death	October 2023
REVERSE (NCT03431467)	Cardiogenic shock	96	VA-ECMO + Impella CP	VA-ECMO alone	Multicenter, United States	Recovery from cardiogenic shock at 30 days (survival; free from MCS, transplant, or inotropic support)	Survival to hospital discharge	January 2025
ECLS-SHOCK (NCT03637205)	Cardiogenic shock secondary to acute myocardial infarction	420	VA-ECMO +/- LV unloading	Standard care (escalation to other MCS [eg, IABP or pLVAD] allowed)	Multicenter, Germany	All-cause mortality at 30 days	Time to death at 6- and 12-month follow-up; duration of catecholamine therapy	November 2023
ANCHOR (NCT04184635)	Cardiogenic shock secondary to acute myocardial infarction	400	VA-ECMO + IABP	Standard care (no MCS device allowed)	Multicenter, France	Treatment failure at 30 days (death in ECMO group or rescue ECMO in the control group)	Mortality at 30 days; MACE at 30 days	November 2024
HERACLES (ISRCTN82431978)	Cardiogenic shock being treated with VA-ECMO	36	VA-ECMO + Impella CP	VA-ECMO + IABP	Multicenter, United Kingdom	Change in device coronary flow reserve	Change in LVEDP; time to VA-ECMO decannulation	February 2025

ANCHOR indicates Assessment of ECMO in Acute Myocardial Infarction Cardiogenic Shock; EARLY-UNLOAD, Early Left Atrial Septostomy Versus Conventional Approach After Venoarterial Extracorporeal Membrane Oxygenation; ECLS-SHOCK, Extracorporeal Life Support in Cardiogenic Shock; ECMO, extracorporeal membrane oxygenation; HERACLES, Hemodynamic Effects of Reducing Left Ventricular Afterload With Impella or Intraaortic Balloon Counterpulsation During Venoarterial Extracorporeal Membrane Oxygenation in Cardiogenic Shock; IABP, intra-aortic balloon pump; LV, left ventricle; MCS, mechanical circulatory support; pLVAD, percutaneous left ventricular assist device; REVERSE, Impella CP with VA-ECMO for Cardiogenic Shock; and VA-ECMO, venoarterial extra corporeal membrane oxygenation.

Unique identifier: NCT03637205) will not specifically address the question of unloading, but may provide informative data. The trial will enroll 430 patients with AMI cardiogenic shock and randomize them to VA-ECMO or standard care. The primary outcome will be all-cause mortality. Escalation to other MCS, including IABP and pLVAD, is permitted in cases of hemodynamic deterioration in the standard care group.[80] In the VA-ECMO group, unloading is only advised in response to lack of arterial pulsatility, lack of aortic valve opening, LVOT velocity time integral <10 cm, or increasing LV dimensions on echocardiography. The impact of this reactive unloading approach, using subgroup analyses comparing these patients with the standard care group and with the non-unloaded group, will be of considerable interest.

UNLOADING TARGETS

After unloading has been initiated, continued close monitoring of the patient is essential to ensure any clinical complications, such as pulmonary edema that triggered unloading, resolve. ECMO flows and unloading device parameters should be continually optimized to target mean arterial pressure that is adequate to provide systemic perfusion, PCWP <15 mm Hg, and consistent aortic valve opening on echocardiography. The echocardiogram will also provide key information on right ventricular function and recovery of native myocardial contractility that will be reflected by an improvement in arterial pulsatility; as hemodynamics improve, efforts should be made to wean vasoactive medications. If there is evidence of cardiac recovery (pulse pressure >10 mm Hg; mean arterial pressure >60 mm Hg on low doses of vasoactive medication; LV ejection fraction >30%), weaning of VA-ECMO may be considered.[22] When an additional MCS device (eg, pLVAD or IABP) has been used, VA-ECMO should be weaned first, if possible, thereby reducing afterload and MVO_2, which potentially improves the chances for myocardial recovery. This is particularly pertinent in cases in which improvement in right ventricular function and oxygenation allow de-escalation to isolated support of the LV. If myocardial recovery is expected, and weaning of VA-ECMO is not possible, consideration can be given to longer-term support, either with Impella 5.5 or a durable VAD. In cases in which myocardial recovery is

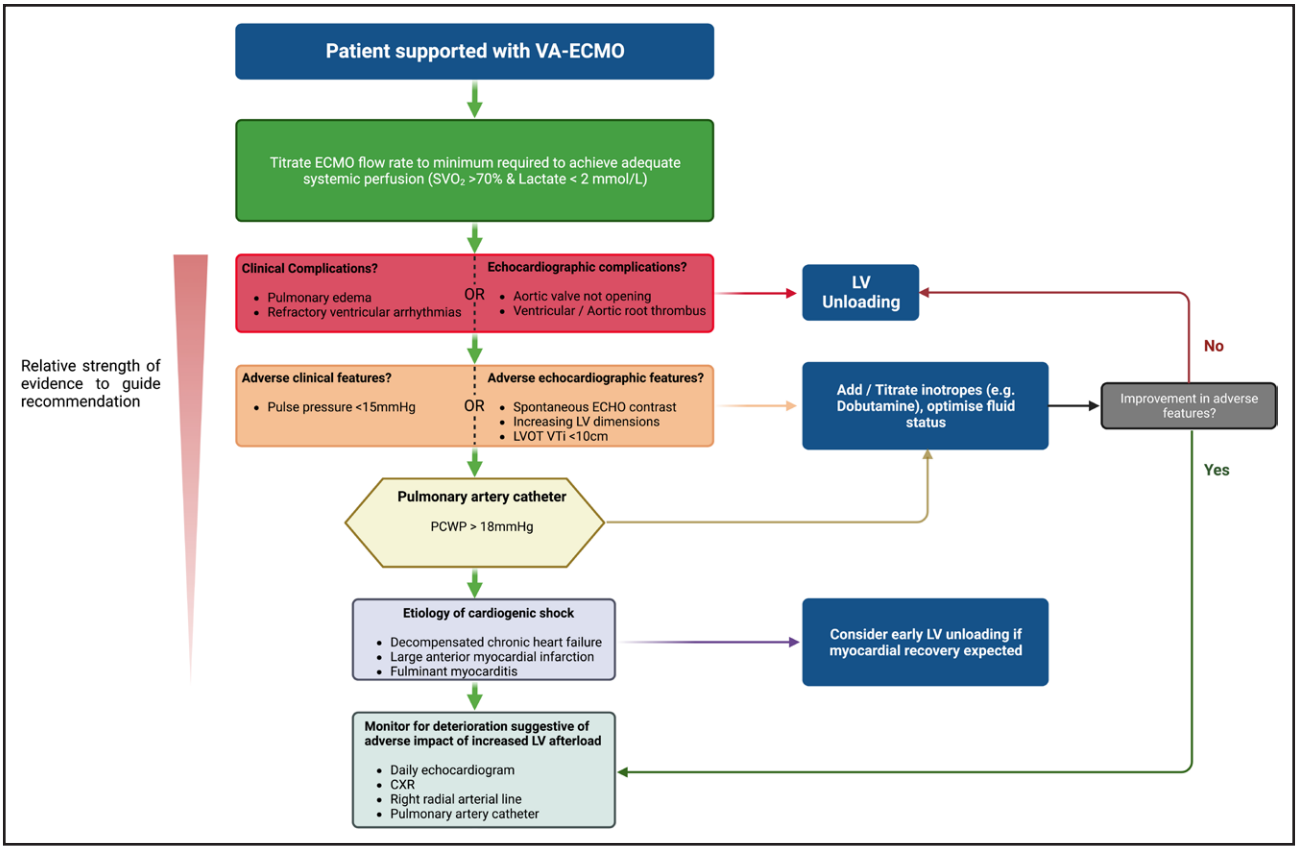

Figure 5. LV unloading algorithm.
CXR indicates chest radiograph; ECMO, extracorporeal membrane oxygenation; LV, left ventricle; LVOT VTi, left ventricular outflow tract velocity time integral; PCWP, pulmonary capillary wedge pressure; SVO_2, mixed venous oxygen saturation; and VA-ECMO, venoarterial extra corporeal membrane oxygenation.

considered unlikely, VA-ECMO may be continued as a bridge to transplantation. Finally, some patients will fail to show meaningful improvements despite unloading, or they may develop multiorgan failure; early involvement of the palliative care team is encouraged in such cases.

CONCLUSIONS

VA-ECMO is a powerful MCS strategy that is able to support systemic perfusion and provide oxygenation, but the additional hemodynamic load on a failing ventricle may cause complications and impair myocardial recovery. Patients with limited contractile reserve or exhausted preload reserve are particularly vulnerable to developing overt complications of increased afterload and may benefit from prophylactic LV unloading. Whether prophylactic unloading improves myocardial recovery and reduces mortality in patients without adverse consequences of LV afterload is unclear; potential benefits must be weighed against the risks of an additional MCS device. Finally, the choice of unloading method depends on local expertise; there is a paucity of data to guide the choice of one method in favor of another. Detailed physiology studies may help personalize this decision. We present a suggested unloading algorithm (Figure 5) for use while awaiting randomized trials that help determine when, for whom, and how best to unload the LV in VA-ECMO–supported patients.

ARTICLE INFORMATION

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