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Unloading the left ventricle in veno-arterial ECMO: in whom, when and how?

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Abstract

Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) provides cardio-respiratory support to patients in cardiogenic shock. This comes at the cost of increased left ventricular (LV) afterload that can partly be 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 of presumed benefits against the known risk of device-related complications. This review will summarize the current evidence regarding LV unloading with VA-ECMO.

Keywords

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Introduction

Cardiogenic shock is a syndrome of inadequate perfusion of vital organs due to primary cardiac dysfunction [1]. Despite many advances in acute cardiac care over the last two decades, the mortality following cardiogenic shock remains unacceptably high at around 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 (pLVAD) or inotropic therapy has not shown a clear survival benefit [3].

Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is a mechanical circulatory support (MCS) strategy that provides extracorporeal blood flow of 4–6 liters per minute and sufficient gas exchange to support systemic perfusion in severe cardio-respiratory 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 an unphysiological, continuous infusion of blood into the arterial vasculature. In the peripheral configuration (Figure 1) blood flows retrogradely 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 (where interventions are focused on reducing LV work) or LV venting (where 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 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 study (NCT02301819) 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% vs 71.2%, p=0.21)[6]. It is important to note however, that an unloading strategy was only used in 16% of participants and whether protocolized use of unloading may have improved outcomes remains to be proven.

Physiological basis of LV unloading

Left ventricular afterload is an indirect measure of the mechanical forces imposed on the myocardium during systole. Cardiac mechanical load is often considered synonymous with left ventricular wall stress, a continuous measure throughout the cardiac cycle that is proportional to left ventricular intracavitary pressure 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, that provide estimates of afterload by metrics such as arterial elastance (Ea). Ea is the ratio of ventricular systolic pressure (at end systole) to stroke volume and reflects arterial load (Figure 3a). Arterial load is closely

related to cardiac afterload and, if increased, impairs ventricular performance by reducing stroke volume and hence cardiac output, if contractility and end-diastolic volume (EDV) remain constant (Figure 3c). In (patho-)physiological conditions a significant increase in afterload is accompanied by backward failure, venous congestion and higher preload. A higher preload may increase LV EDV, that should in turn 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 this is exhausted the LV becomes sensitive to increased afterload particularly in the context of limited contractile reserve [8,9]. When preload reserve is exhausted the PV loop shifts upwards and to the right, increasing the pressure volume area (PVA) and myocardial oxygen consumption (MVO_2). Increased contractility represents a second compensatory mechanism by which the LV can maintain stroke volume but at the cost of increased PVA and therefore MVO_2 (Figure 3d), thereby potentially adversely impacting on myocardial recovery. In cardiogenic shock the LV usually lacks the preload and contractile reserve to overcome the increased afterload associated with VA-ECMO, thus increasing myocardial oxygen demand on a failing ventricle.

LV unloading refers to strategies that reduce PVA and hence reduce MVO_2 (3b) [10]. Unloading has two key goals: firstly, to prevent or treat clinically manifest complications and secondly to promote LV recovery, even in those without apparent complications. LV venting in contrast refers to a reduction in left ventricular end diastolic pressure (LVEDP) with the goal of reducing pulmonary congestion, not all patients will therefore require venting in the absence of elevated LVEDP but may still benefit from unloading [11]. Emerging evidence suggests unloading may offer cardioprotection beyond mechanical effects, with reduced inflammatory cytokine expression, as 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 to facilitate LV recovery in the absence of overt complications is more difficult, due to the fine balance between risk and benefit of placing additional MCS devices. Unloading device use can be associated with significant bleeding and vascular complications, hemolysis and coagulation disorders in a population of patients who are 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 anticoagulation, monitoring vascular access sites and difficulty in repositioning the patient. These risks need to be balanced against the potential benefits of unloading as approximately 30–70% of patients treated with VA-ECMO develop increased afterload, which is 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, and if so, the timing of insertion and choice of device will be determined by the treatment goals for an individual patient as well as the experience of the multidisciplinary team, guided by the contemporary evidence base. Hemodynamic, echocardiographic and clinical features may help identify those at risk for developing complications or identify these complications.

Hemodynamic predictors

Reduced arterial pulsatility is a readily available measure of increased afterload in VA-ECMO patients; a pulse pressure <15mmHg correlates strongly with reduced native cardiac output of <1 Liter/min [20] whilst a pulse pressure of <20mmHg 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 measured directly) is a useful metric. Patients with raised PCWP prior to the initiation of VA-ECMO are particularly vulnerable to the impact of increased afterload as their preload reserve is exhausted. A PCWP of >15mmHg measured at the time of VA-ECMO initiation was found to predict response to unloading with IABP [23], whilst others have suggested a threshold of >18mmHg [24]. A target LVEDP of 12–18mmHg suggests adequate LV decompression when unloading has been initiated [25]. Right and left ventricular interdependence is an important consideration particularly in patients with preserved right ventricular function, who maybe be at increased risk of complications due to a higher volume of transpulmonary blood flow resulting in increased LV filling pressures [26].

Echocardiographic predictors

Transthoracic echocardiography provides detailed non-invasive information on LV geometry and performance to inform the decision on unloading. Serial assessments are recommended, though 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 left ventricular outflow tract velocity time integral (LVOT VTI) 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.

Left ventricular ejection fraction (LVEF) before instituting VA-ECMO is predictive of afterload sensitivity, with lower LVEF associated with raised PCWP and reduced stroke volume on initiation of VA-ECMO [9] and increased risk of death [27]. Given 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 VTI can be used to estimate stroke volume and cardiac output; a LVOT VTI <10 cm reflects an insufficient intrinsic cardiac output and therefore predicts unsuccessful weaning from VA-ECMO and sensitivity to increased afterload [29].

Echocardiography can also be used to detect complications including blood stasis, LV thrombus and/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 patients supported with VA-ECMO found 22% had spontaneous echo contrast on echocardiography, this was associated with a lower LVEF and pulsatility index with a higher incidence of intracardiac thrombus (46% vs 13%) and stroke (36% vs 7.9%) [30]; the development of spontaneous echo contrast therefore identifies a high risk group who should be considered for immediate unloading.

Clinical predictors

Whilst hemodynamics and cardiovascular function will be the primary determinants of complications of increased afterload, the etiology of shock will have important influences on these parameters and merits consideration in deciding which patients should receive LV venting or unloading.

In shock complicating 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 including 7581 patients suggest that AMI is the pathology with the greatest mortality benefit with unloading with an absolute risk reduction of 6.65% giving a number needed to treat of 15 to prevent one death [32].

Patients with chronic heart failure often have an elevated PCWP at baseline, making them particularly vulnerable to increased afterload as their preload reserve will be exhausted [33]. The 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?

A number of mechanical circulatory strategies can be used to achieve LV unloading or venting if conservative measures prove insufficient. Each method is associated with its own contra-indications, risks, cost and potential advantages. The section below outlines the characteristics, hemodynamic effects and clinical evidence for each technique.

Non-invasive and pharmacological approaches

Efforts should be made to reduce preload and afterload by 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 whilst minimizing afterload. Lower flow rates (<2.2 L/min/m^2) can provide adequate systemic perfusion while reducing LV distension [37], though caution must be exercised as very low rates (particularly <1.5 liter/minute) may increase the risk of thrombotic complications within the ECMO circuit, with potentially

severe consequences [38]. In 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 and/or hemofiltration may be tried in 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 in all patients [40].

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

Venting

<u>Catheters:</u> 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. 7Fr Pigtail catheters inserted into the LV under transesophageal echocardiography guidance have been used to achieve transaortic unloading with a reduction in LV dimensions and volume [43]. The use of 5Fr and 6Fr LV catheters has been reported, showing reduction in LV dimensions and increases in mean arterial pressure and pulse pressure. However, the size of percutaneous catheters limits the maximum flow that can be achieved, with a higher risk of hemolysis and therefore this approach is not routinely recommended [44,47].

Unloading

<u>Percutaneous atrial septostomy:</u> Percutaneous atrial septostomy is created with the use of a percutaneous blade or balloon, typically under fluoroscopic or transesophageal echocardiographic guidance. Whilst widely utilized in pediatric populations, limited data are available in adults. Reductions in left atrial pressure, 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]. This could, however, increase the risk of a non-ejecting LV and potential LV or aortic root thrombus due to the lack of forward flow through the aortic valve [50]. Furthermore, 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 (LAVA-ECMO) has been described, where a multistage venous drainage cannula is placed in the left atrium via transseptal puncture. This allows simultaneous bi-atrial drainage thereby unloading the right and left ventricles, with a reduction in PCWP demonstrated [51]. This approach may be particularly helpful in patients with LV thrombus or unilateral peripheral vascular disease that precludes a second large-bore femoral arterial access. It may be the preferred choice in patients with severe aortic

stenosis or a mechanical aortic valve replacement, where transaortic device placement is contraindicated.

An alternative method to achieve left atrial drainage is with the use of TandemHeart (LivaNova Plc., London, UK), this centrifugal pump-based system uses a 21Fr 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 bi-atrial drainage with subsequent bi-ventricular 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-stage or multi-stage cannulas can be used for this purpose. The ProTek Duo (CardiacAssist Inc., Pittsburgh, PA) dual lumen cannula can also be used as a method 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 29 or 31Fr cannula sizes and is inserted via the jugular vein, enabling flows of up-to 4.5L and is commonly used as a right atrium to pulmonary artery bypass circuit to support the right ventricle.

IABP: 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, whilst inflation in diastole improves coronary blood flow [54]. The IABP provides less unloading compared to a pLVAD with an animal model finding a PVA reduction of 12% driven by a reduction in potential energy as opposed to stroke work (3f) [55]. The use of an IABP has also been shown to improve cerebral blood flow in patients with cardiogenic shock on VA-ECMO with a pulse pressure of >10mmHg prior to initiation of the IABP whilst reducing it in those with a pulse pressure of <10mmHg [56]. These findings suggest IABP may be most effective in those who retain a degree of native LV ejection, an observation consistent with the known physiological effects of counterpulsation in patients with cardiogenic shock where IABP was used as the sole MCS device.

No randomized data exist to support the use of IABP for unloading, whilst observational data are conflicting. In AMI shock the use of IABP unloading is associated with improved short-term mortality (OR 0.82, 95% CI 0.75–0.89, p=<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 post cardiotomy shock found mortality was similar with the combination of VA-ECMO + IABP compared to VA-ECMO alone [58]. A larger meta-analysis of 4,653 patients found similar short-term mortality in patients who did or did not receive an IABP, except for in the subgroup of AMI shock where mortality was lower with IABP [59]. The heterogenous populations and observational confounding included in these meta-analysis 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; though this should be confirmed through more robust, randomized studies.

pLVAD: The combination of a percutaneous left ventricular assist device (pLVAD) and VA-ECMO is being increasingly 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, PVA (Figure 3f) and therefore MVO_2 [60]. The Impella CP (Abiomed, Danvers, CA) is most commonly used for LV unloading, a configuration referred to as ECMELLA or ECPELLA. The pLVAD is usually inserted percutaneously via the contralateral femoral artery to the ECMO outflow cannula, though surgical implantation via the axillary artery and percutaneous transcaval insertion can be considered [61]. Contra-indications 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 (14 French), as well as anticoagulation delivered directly through the device purge solution, however recent evidence suggests a bicarbonate-based purge solution maybe a safe alternative in 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 the use of pLVAD for LV unloading. A registry of 510 propensity matched patients found ECPELLA was associated with 21% lower mortality at 30 days compared with VA-ECMO alone, despite increased rates of severe bleeding (38.4 % vs 17.9%) and hemolysis (33.6% vs 22.4%) [15]. These findings highlight the potential tradeoff that needs to be considered when utilizing pLVAD with respect to reducing mortality (with a number needed to treat of 15 in this observational study) balanced against the risk of increased bleeding and limb ischemia (number needed to harm 5 and 11, respectively). The use of distal perfusion cannula incorporated into the ECMO outflow circuit maybe considered in patients displaying signs of limb ischemia distal to the pLVAD access site, but further increases the complexity of the MCS system and risk of complications.

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 to 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 weaning preferentially from VA-ECMO. Particular attention must be given to patients with hypoxemic respiratory failure where high pLVAD flow rates may draw deoxygenated blood from the left ventricle 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 can classically be seen with LV recovery and ongoing pulmonary edema. Careful counterbalancing is also required to ensure sufficient LV preload to prevent suction at the pLVAD inflow, that may cause hemolysis. Those with biventricular shock may have lower LV preload due to poor RV function and therefore unloading with pLVAD may be less effective and associated with more frequent complications, though recent experimental data from a porcine model of cardiogenic shock found pLVAD use

resulted in septal shift towards the LV, resulting in an increase in RV stroke work and cardiac output without increasing LV stroke work [67].

Initial pLVAD flow rates are generally lower than those that can be achieved by the devices and limited data exists to guide adjusting flow 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 non-invasive method of assessing the effects of LV unloading [64].

A larger bore version of the Impella device (Impella 5.5) can provide up to six liters per minute of antegrade flow, providing enough forward flow to support systemic perfusion in isolation in most cases. When used as an initial unloading device, the Impella 5.5 may therefore allow earlier weaning of VA-ECMO or lower VA-ECMO flow rates to support the right ventricle and oxygenation until improvement allows decannulation of VA-ECMO. The device is inserted surgically via the axillary artery and can remain in situ for significantly longer than the Impella CP device, with durations of up to 83 days reported, though current licensing permits 30 days in Europe and 14 days in the USA[68]. This development has potential advantages in allowing patient ambulation and reduced hemolysis and thrombosis [69], 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 or in whom the chances of LV recovery are considered low, or if it is anticipated MCS is likely to be required for a prolonged duration. The benefits of these devices must be balanced against the risk, complexity and expense of a large-bore surgically implanted device. It is important therefore in such cases 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 post-cardiotomy shock or with graft failure following heart transplantation where a 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 left ventricular outflow tract and aortic root may still occur due to impaired LV contractility. This may be potentiated by prolonged ischemic time during cardio-pulmonary bypass with a canine model of hypothermic cardioplegia finding impaired subendocardial perfusion and ventricular performance in those with distended ventricles (LVEDP >20mmHg) [31]. These considerations have led some centres to routinely unload all patients treated with peripheral or central VA-ECMO for post-cardiotomy shock[71], with a meta-analysis of 2324 patients finding a non-significant (RR 0.93 0.85–1.01, p = 0.09) reduction in mortality but a significantly higher chance of weaning from ECMO[32].

Incorporating a surgical venting cannula (16–20 Fr) sited at the LV apex, pulmonary vein or pulmonary artery in to the venous drainage limb of the VA-ECMO circuit via a Y connector can provide effective bi-ventricular unloading[53]. Minimally invasive surgical techniques have been described utilizing a subxiphoid and anterolateral thoracotomy approach [72]. Limited data exists regarding outcomes of these methods in adult patients, one study retrospectively compared 23 patients with a surgical vent to 22 patients with a pLVAD

finding similar 30-day mortality [73]. Both methods significantly reduced pulmonary artery diastolic pressure and had a similar rate of complications.

Choice of strategy: The mechanism of action of 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, in cases where there is a dilated non ejecting ventricle with significantly raised filling pressures active unloading with either a pLVAD or surgical vent is likely to be required [74].

The HERACLES trial (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/volumes. Whether a tailored approach utilizing hemodynamic and clinical criteria to individualize the unloading strategy may improve outcomes remains to be seen. Whilst randomized data are urgently required to make firm recommendations on choice of unloading method, at the present time decisions should be made in a pragmatic manner, based on local expertise and the strategies available to the particular multidisciplinary shock team (Figure 4).

When to unload

Unloading devices may be inserted before, at the same time 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, weighed against the potential risks of increased complications and cost [75]. Alternatively, unloading maybe 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 where implantation was delayed [76]. A larger registry of 337 ECPELLA patients found that early pLVAD implantation improved short term mortality whereas delayed unloading, i.e., >2 hours after VA-ECMO implantation, did not [15]. Finally, a propensity matched cohort of 74 patients found a significantly lower mortality in those in whom an pLVAD was inserted prior to VA-ECMO compared to VA-ECMO first [77].

A retrospective analysis comparing prophylactic LAVA-ECMO to reactive unloading with either percutaneous or surgical methods found a lower 30-day mortality and transition to durable VAD or cardiac transplantation in the prophylactic unloading group [78]. A meta-regression 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 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 RCT (NCT04775472) is aiming to recruit 116 participants comparing early unloading (within 12 hours of VA-ECMO) versus bailout unloading, with atrial septostomy as the mode of unloading in both groups. The primary outcome is all cause mortality at 30 days, whilst secondary outcome measures including need for bailout atrial septostomy, need for long term heart replacement therapies and resolution of pulmonary edema are likely to be informative. The REVERSE study (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 endpoint is of particular interest given 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 (NCT03637205) will not specifically address the question of unloading, but may also 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 VTI <10 cm^2 or increasing LV dimensions on echocardiography. The impact of this reactive unloading approach, utilizing subgroup analyses comparing these patients to the standard care group and to the non-unloaded group, will be of considerable interest.

Unloading targets

Once unloading has been initiated continued close monitoring of the patient is essential to ensure any clinical complications such as pulmonary edema which triggered unloading resolve. ECMO flows and unloading device parameters should be continually optimized targeting a MAP adequate to provide systemic perfusion, PCWP <15mmHg 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 with an improvement in arterial pulsatility, as the hemodynamics improve efforts should be made to wean vasoactive medications. If there is evidence of cardiac recovery (pulse pressure >10mmHg, MAP >60mmHg on low doses of vasoactive medication, LVEF >30%) then weaning of VA-ECMO maybe considered [22]. Where an additional MCS device such as pLVAD or IABP has been utilized, if possible, VA-ECMO should be weaned first thereby reducing afterload and MVO$_2$ potentially improving the chances of myocardial recovery. This is particularly pertinent in cases where 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 where myocardial recovery is considered unlikely VA-ECMO maybe continued as a bridge to transplantation. Finally, some patients will fail to show meaningful improvements despite unloading or develop multi organ failure, early involvement of the palliative care team is encouraged in such cases.

Conclusion

VA-ECMO is a powerful MCS strategy able to support systemic perfusion and provide oxygenation, but the additional hemodynamic load on the failing ventricle may cause complications and impair myocardial recovery. Patients with a limited contractile reserve or who have 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, and potential benefits must be weighed against the risks of an additional MCS device. Finally, the choice of unloading method depends on local expertise with a paucity of data to guide the choice of one method over another. Detailed physiology studies may help personalize this decision. We present a suggested unloading algorithm (Figure 5) whilst awaiting randomized trials to determine when, in whom and how best to unload the LV in VA-ECMO supported patients.

Acknowledgements

Abbreviations

AMI	acute myocardial infarction
IABP	intra-aortic balloon pump
LAVA-ECMO	left atrial veno-arterial extra corporeal membrane oxygenation
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	Veno-arterial Extra Corporeal Membrane Oxygenation

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Central Veno-Arterial Extra Corporeal Membrane Oxygenation

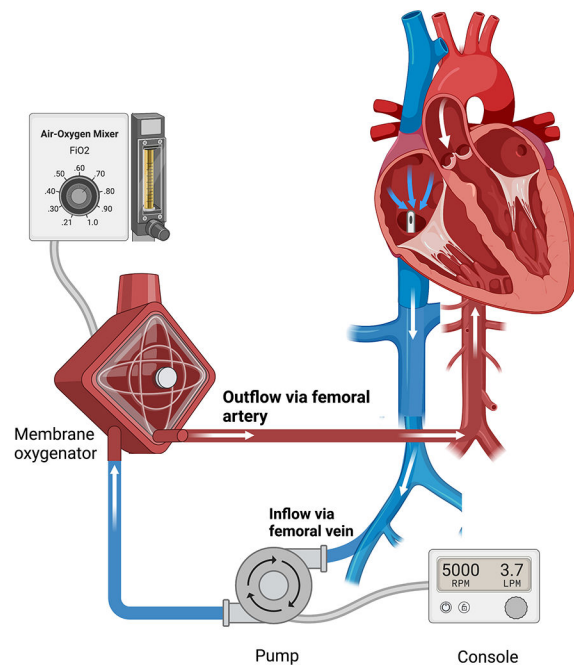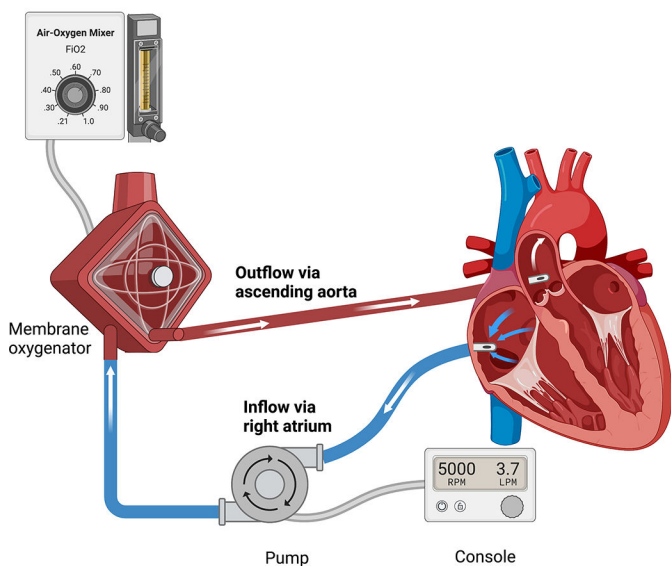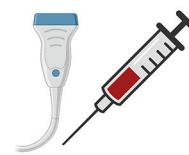## Peripheral Veno-Arterial Extra Corporeal Membrane Oxygenation

Figure 1: A 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 where 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 for example femoral vein inflow cannula use in a central VA-ECMO circuit.
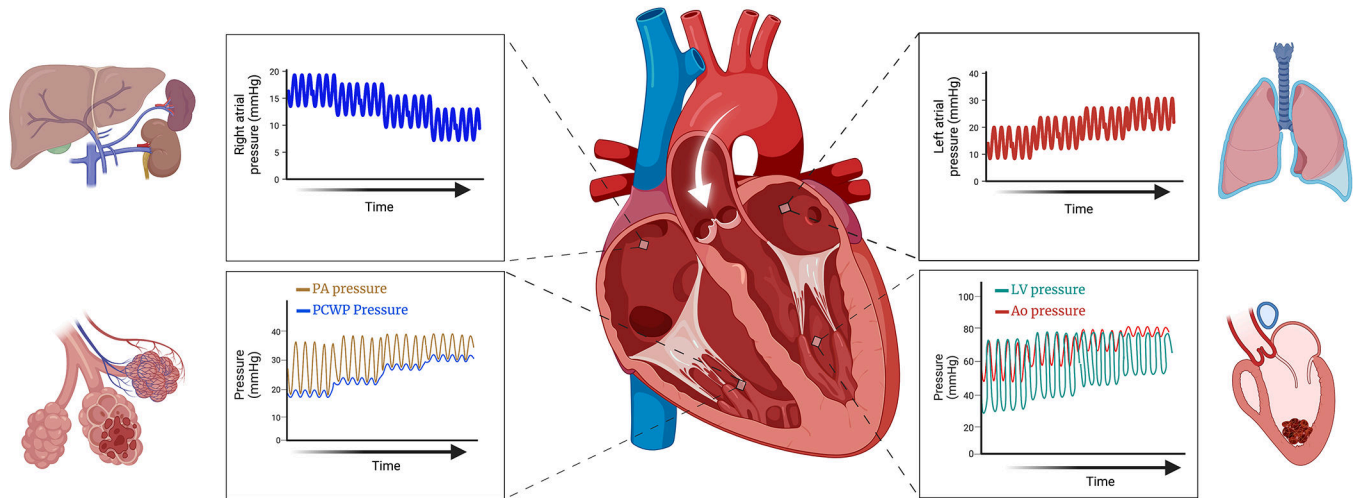
Figure 2: Hemodynamic effects of VA-ECMO

VA-ECMO reduces right atrial pressure, decongesting the liver and kidneys. Mean aortic pressure rises increasing afterload, if the left ventricle (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. Backwards failure eventually increases pulmonary capillary wedge pressure (PCWP) and pulmonary artery diastolic pressure with loss of pulmonary artery pulsatility and worsening lung injury.
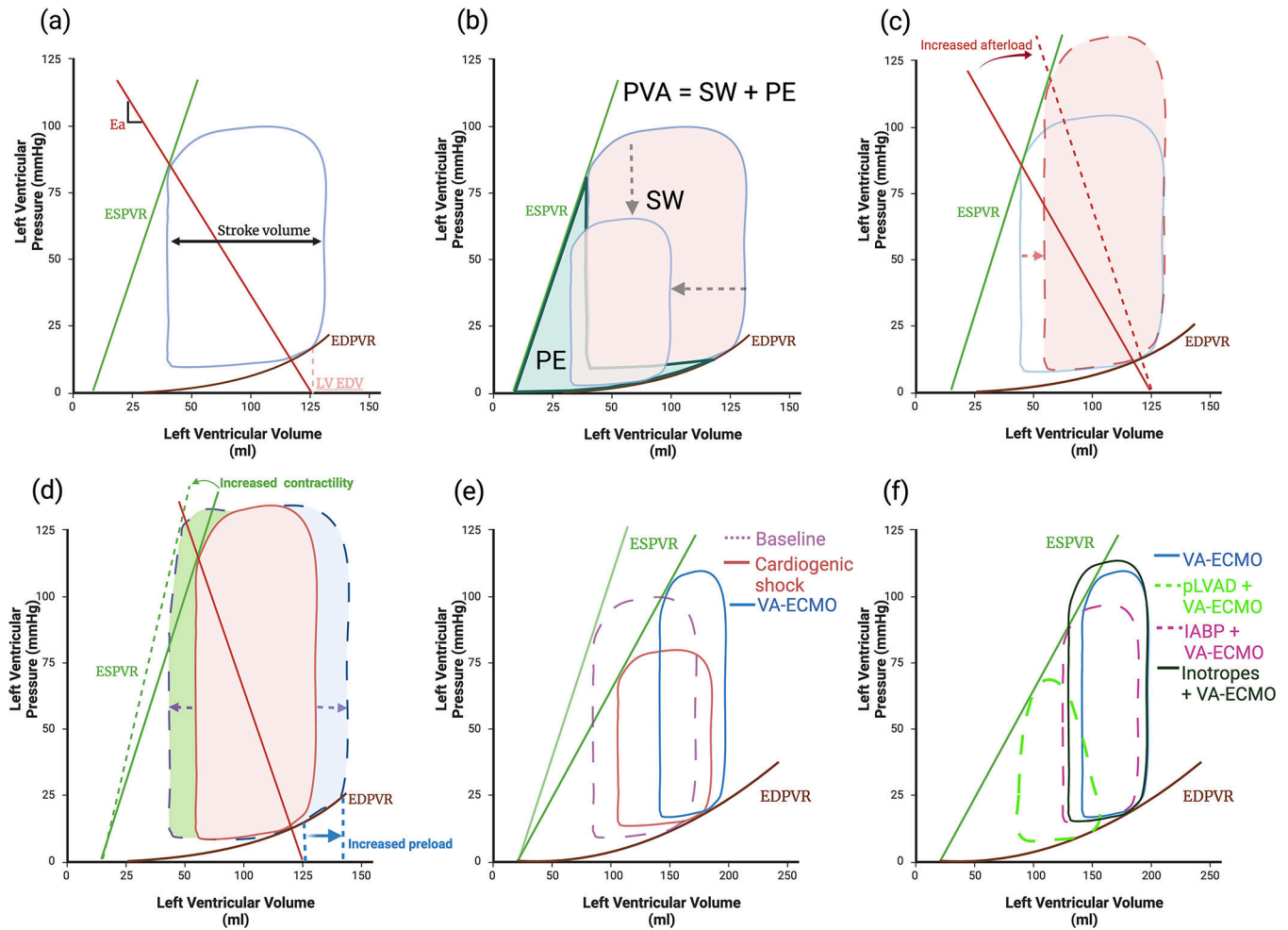
Figure 3: Pressure volume (PV) loop basics

(a) Normal PV loop, boundaries are created by the end systolic pressure volume relationship (ESPVR) and the non-linear end diastolic pressure volume relationship (EDPVR). Effective arterial elastance (Ea) reflects afterload and is the slope of the line between the end diastolic volume (LV EDV) and the ESPVR. (b) Stroke work (SW) is the work required to eject blood, Potential energy (PE) is energy generated during contraction but not converted to SW. Pressure volume area (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 whilst maintaining the same level of contractility and preload reduces stroke volume (SV) (d) SV can be increased by either increasing preload, however in a dilated ventricle this will cause a significant rise in end diastolic pressure due to the non-linear EDPVR or by increasing contractility but this also increases MVO_2. (e) Cardiogenic shock results in loss of contractility and increases end diastolic pressure (EDP) and volume (EDV). (b) VA-ECMO raises systolic pressure, EDP and afterload thereby increasing pressure volume area (PVA), whilst 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.
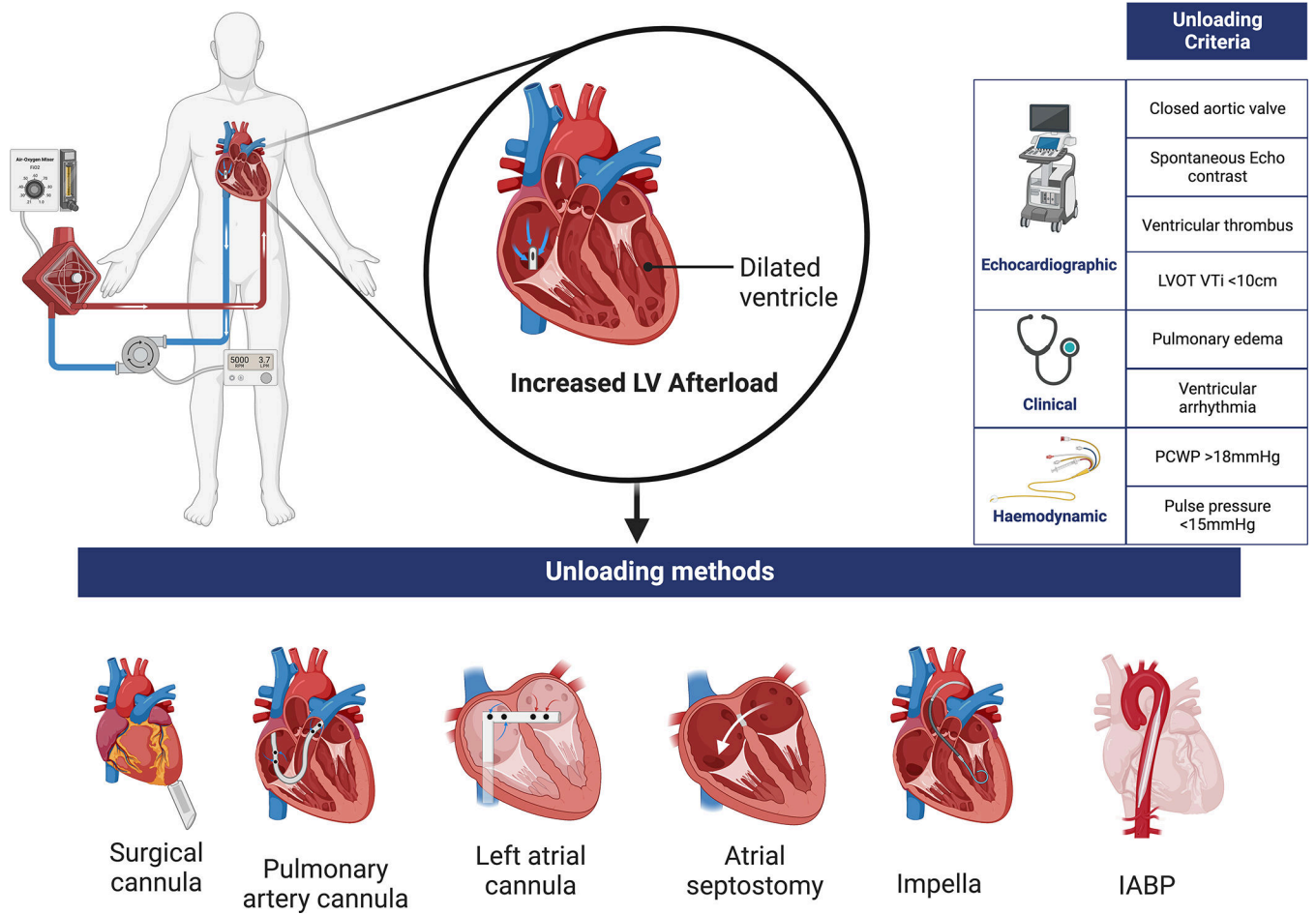
Figure 4: Left ventricular unloading criteria and methods
LVOT VTi: Left ventricular outflow tract velocity time integral, PCWP: Pulmonary capillary wedge pressure.
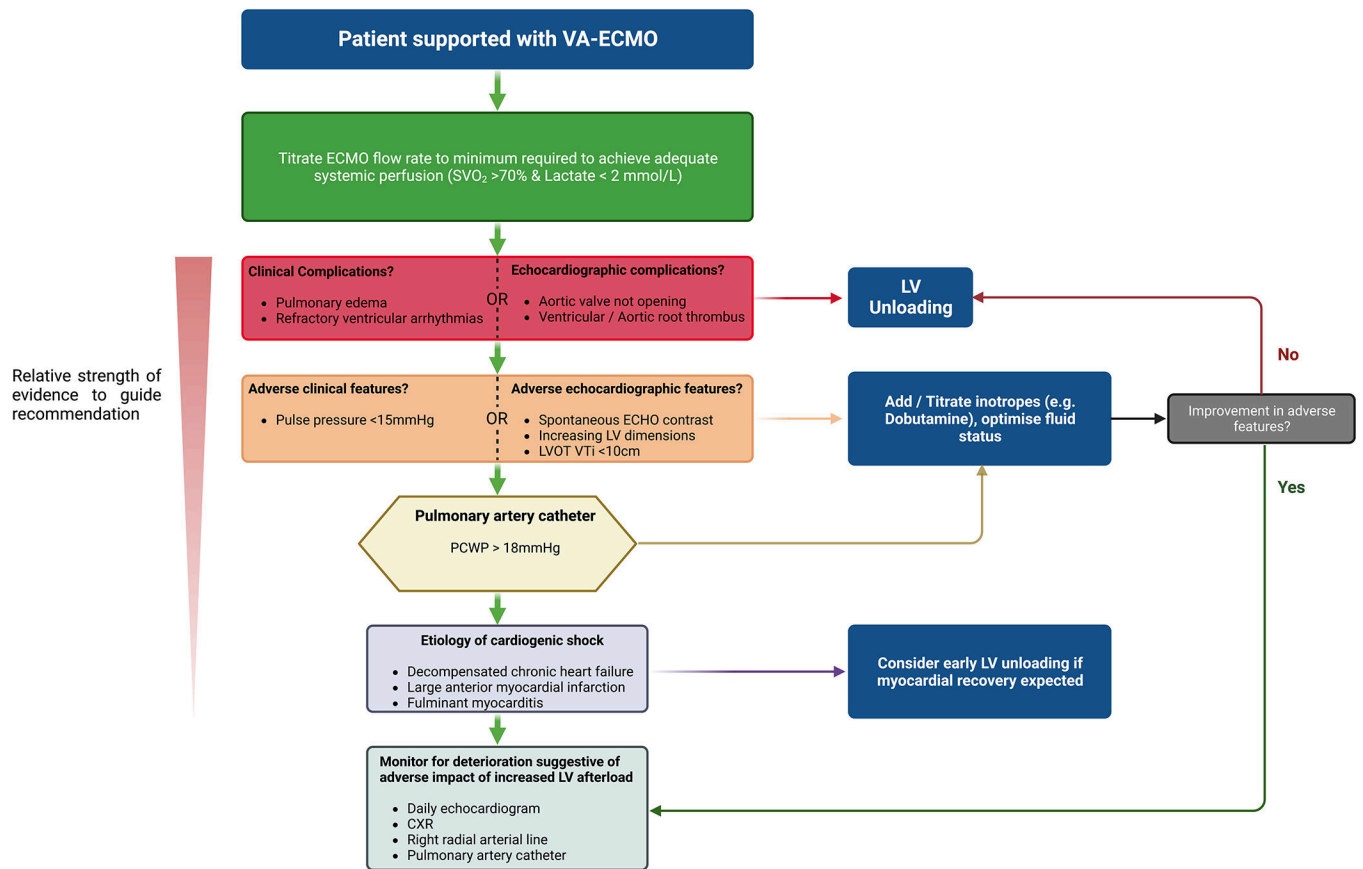
Figure 5: Left ventricular unloading Algorithm
CXR: Chest radiograph, LVOT VTi: Left ventricular outflow tract velocity time integral,
PCWP: Pulmonary capillary wedge pressure, SVO_2: Mixed venous oxygen saturation

Table 1.

Indications for left ventricular unloading

Hemodynamic
• Pulmonary capillary wedge pressure > 18mmHg • Lack of arterial line pulsatility (pulse pressure <15mmHg)
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

Table 2.

Current randomized clinical trials of VA-ECMO)

Trial Name	Inclusion Criteria	Participant number	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	Multi-center, USA	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 e.g., IABP or pLVAD allowed)	Multi-center, 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)	Multi-center, 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	Multi-center, UK	Change in device coronary flow reserve	Change in LVEDP Time to VA-ECMO decannulation	February 2025