Left Ventricular Distension in Veno-arterial Extracorporeal Membrane Oxygenation: From Mechanics to Therapies

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Veno-arterial (V-A) extracorporeal membrane oxygenation (ECMO) is increasingly commonly used to treat acute cardiac or pulmonary failure because of a wide range of etiologies. However, despite progressively improving outcomes, the mortality associated with V-A ECMO, particularly when used to treat cardiac failure (its most common indication), continues to be high. Consistent with this, V-A ECMO is associated with numerous morbid complications. Left ventricular (LV) distension is a major complication of V-A ECMO, and is challenging both to treat and diagnose. The author review the pathophysiology underlying LV distension, and construct a systematic diagnostic and therapeutic approach. *ASAIO Journal* 2019; 65:1–10.

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Although veno-arterial (V-A) extracorporeal membrane oxygenation (ECMO) is often successfully used as a life-saving therapy for cardiac and/or respiratory failure, the mortality and morbid complications associated with it, particularly when used to treat cardiac failure (its most common indication), continue to be high.[1] Left ventricular (LV) distension is a serious and challenging complication of V-A ECMO. Takayama and colleagues[2] from Columbia-Presbyterian Medical Center, in a recent publication in the *ASAIO Journal*, identified an incidence of LV distension mandating immediate decompression of 7%, and a "subclinical" (not warranting immediate decompression) incidence of 22%, in patients undergoing V-A ECMO.

Simply summarized, LV distension in the setting of V-A ECMO occurs because of inadequate or absent trans-aortic valvular (AV) ejection of LV blood volume. In the absence of a ventricular dysrhythmia, for distension to occur, two conditions must be satisfied. First, there must be source(s) of LV end-diastolic volume (EDV) or preload despite cardiopulmonary bypass (CPB) provided by V-A ECMO. Second, the volume-loaded LV must have an impaired or absent ability to open the AV. Inability to open the AV is because of a combination of depressed LV contractility and/or elevated LV afterload. This is the physiologic basis of LV systolic dysfunction even in the native circulation, that is, "afterload mismatch."[3] This second criterion is generally satisfied *per definitionem*, because V-A ECMO is most commonly instituted in the setting of LV failure. The pathophysiology of LV distension on V-A ECMO thus is the first topic to be reviewed, to formulate a conceptual framework with which to approach previous studies and future patients.

It is important to discuss the general effects of V-A ECMO on LV loading conditions and function, particularly because of divergent findings in the literature. Moreover, decades of studies of the effects of conventional intraoperative CPB on LV loading conditions and function have yielded results that differ substantially from studies performed on V-A ECMO. Everyday experience and formal studies both have shown that CPB very effectively volume-unloads the LV,[4–6] and regardless of effects on LV afterload (see below), thereby reduces myocardial oxygen (O_2) consumption. This is because nearly the entirety of LV filling is because of right ventricular (RV) output under normal circulatory circumstances. Venting of the LV does provide additional reductions in intracavitary LV pressure/volume and myocardial O_2 consumption,[7–10] which are certainly beneficial. However, an experimental study of canine hearts[11] demonstrated that volume unloading alone reduced myocardial O_2 consumption by 50%, with cardioplegic arrest reducing the unloaded level of O_2 consumption by 50% (*i.e.*, 75% reduction relative to baseline), consistent with the earliest pioneering studies of LV mechanoenergetics (see Figure 3 of Sagawa and colleagues[12]). Moreover, in humans undergoing CPB, the bulk of LV volume reduction is because of RV volume reduction[13] as opposed to direct left-sided venting. In contrast, as will be reviewed subsequently, experimental studies of V-A ECMO physiology have yielded highly variable results. A literature review is the second topic of this study. Third and finally, how to approach patients with potential or active LV distension in the setting of V-A ECMO support is discussed.

Pathophysiology of LV Distension on V-A ECMO: A Conceptual Checklist

Preload: Working Retrograde Through the Circulation

A common question that cardiac surgeons and trainees have to ask and answer intraoperatively is, "What are sources of blood in the LV while on CPB?" As V-A ECMO is a form of CPB, albeit without a reservoir, the answers to this question are generally applicable to LV distension during V-A ECMO support. A systematic approach, working retrograde through the circulation, is outlined below (**Figure 1**).

First, retrograde blood flow into the LV may occur in the setting of pre-existing aortic valve regurgitation (AR). AR is a well-recognized cause of LV distension on both V-A ECMO and CPB.[14] Depending on extracorporeal circuit dynamics in

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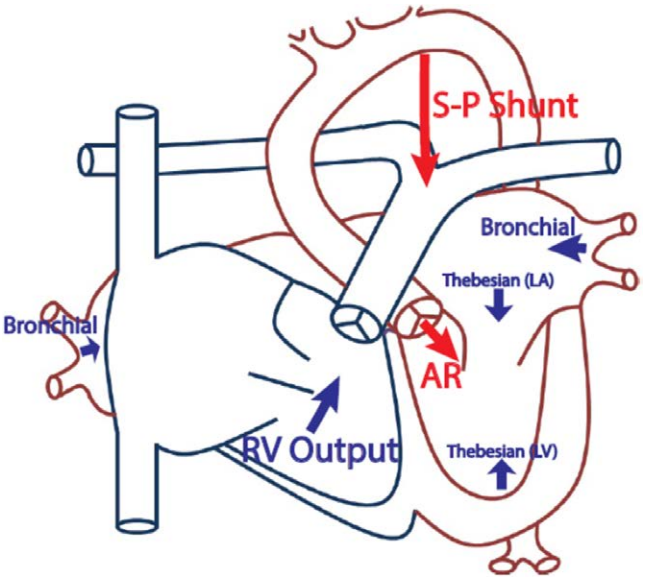

Figure 1. Sources of LV preload while on V-A ECMO support. A Mullins-type diagram of the heart is displayed. Arrows indicate blood flow paths. AR directly fills the LV retrograde. LV and LA Thebesian return fill the LV antegrade with deoxygenated blood, as does bronchial circulatory return, because these sources are postcapillary from tissue beds. S-P artery shunts fill the right-sided circulation with oxygenated blood that augments transpulmonary blood flow and pulmonary venous return. Finally and most importantly, incomplete systemic venous drainage increases RV output, transpulmonary blood flow and pulmonary venous return, with the oxygen content of this blood being contingent on pulmonary function. AR, aortic valve regurgitation; LA, left atrial; LV, left ventricular; RV, right ventricular; S-P, systemic-to-pulmonary; V-A ECMO, veno-arterial extracorporeal membrane oxygenation.

comparison to native circulatory dynamics, the excessively preloaded LV in AR may actually become more distended on initiation of CPB or V-A ECMO. Specifically, if ECMO support increases either the systemic arterial pressure and consequently the regurgitant volumetric flow rate (this being the norm after ECMO initiation), or worse, if the regurgitant fraction is actually worsened because of load-induced augmentation in the size of the regurgitant orifice, LV EDV will be greater post-ECMO initiation than pre-ECMO.[15] AR is more common than many other causes of LV preload during V-A ECMO support, but in an absolute sense is far less common than other etiologies (bronchial circulation and incomplete systemic venous drainage, as discussed below). Second, a fraction of LV myocardial blood flow may flow through Thebesian veins directly into the LV cavity. This is relatively minor, however.

Third, and by far most commonly, antegrade transmitral blood flow into the LV may preload it. Within this third etiology, systematically working from distal inflow sources retrograde to proximal inflow sources is useful, such that no potential cause is missed. Aortopulmonary shunts, either iatrogenic or congenital (e.g., patent ductus arteriosus, aortopulmonary window) augment pulmonary venous return. Intracardiac shunts generally should not have this effect while on CPB or V-A ECMO, see below). These are relatively uncommon, however. Thebesian venous drainage from the left atrial (LA) flows across the mitral valve into the LV. This too is minor, however. Next, bronchial circulatory drainage combines with pulmonary blood flow to comprise the totality of pulmonary venous return, and is present in all patients. Intralobar pulmonary sequestration similarly augments pulmonary venous return, but is rare. Finally, inadequate systemic venous drainage by the systemic venous cannula, that is, incomplete bypass such that RV output is augmented, is the most common source of LV preload while on V-A ECMO, *via* increased pulmonary venous return, and must be so because the other causes outlined are not routinely present (*e.g.*, AR), or if routinely present, are minor in magnitude (*e.g.*, Thebesian venous return). In contrast, incomplete systemic venous drainage, particularly in the absence of a venous reservoir as is present in CPB, is the norm during V-A ECMO. Of note, intracardiac shunts generally should not cause LV preloading (unless, *e.g.*, a bicaval cannulation strategy is used with both caval tapes snared), because systemic venous cannula suction and resultant right-sided chamber pressure reduction should maintain or render such shunts left-to-right.

Left-Sided Preload in V-A ECMO Versus CPB: The Reservoir Is the Principal Difference

How is conventional CPB different from V-A ECMO with respect to LV preload? Most patients placed on CPB have excellent LV unloading and absent AV opening, which can be maintained for reasonably long periods of time during the courses of cardiac operations. Left ventricular unloading on CPB is "indirect," that is, the LV is unloaded by virtue of the RV and pulmonary circulation being unloaded through systemic venous drainage. Moreover, CPB has been shown to reduce myocardial O_2 consumption, and left-sided cardiac venting has been shown in experimental models to be unnecessary to prevent LV distension.

To the extent that V-A ECMO provides left-sided cardiac unloading, as a form of CPB it does so indirectly as well. However, an essential difference between CPB and V-A ECMO is the presence of a reservoir in the former. The reservoir permits controlled exsanguination, *that is*, the removal of blood volume from the native circulation, and its compartmentalized storage within the circuit. Without a reservoir, V-A ECMO support does not inherently alter the volume of the native circulation. As such, V-A ECMO cannot unload either side of the circulation as effectively as CPB, although right-sided drainage is at least direct. However, other methods may be used to effectively reduce circulating volume while on V-A ECMO support. Diuretics, and hemofiltration with or without dialysis, may reduce blood volume substantially. Moreover, using large inflow cannulae (with optimal systemic venous drainage) and strategies for volume removal may permit V-A ECMO to facilitate left-sided cardiac unloading. This has implications for a second, albeit nonuniversal, distinction between V-A ECMO and CPB. Veno-arterial ECMO is typically employed using peripheral vascular cannulation, in contrast to CPB. Peripherally inserted cannulae are longer and smaller diameter, that is, cannula impedance is substantially higher. Thus, the aforementioned strategy of using larger diameter inflow cannulae to facilitate right-sided and indirect left-sided unloading may be limited in the context of peripheral cannulation used for V-A ECMO. Finally, as will be discussed, two anatomically distant sources of systemic arterial outflow are created with peripheral systemic arterial cannulation. This has potentially important effects on the distribution of blood flow and O_2 delivery within the systemic circulation.

Contractility and Afterload

The definitions and determinations of both contractility and afterload, and how V-A ECMO support alters them, will be discussed in detail below. Contractility is traditionally understood to convey the intrinsic ability of the LV contract, that is, that it ought to be independent of loading conditions (preload and afterload). Some biologically relevant exceptions to the independence of variables exist, but they may be viewed as indirect. Insofar as myocardial oxygen delivery influences LV contractility, changes in afterload, preload, or antecedent contractility may indirectly influence future contractility. Left ventricular distension itself is a more difficult exception, as will be discussed, because the mechanisms by which distension reduces contractility could be direct, or indirect *via* effects on myocardial blood flow. Yet, the presence of such nonlinear relationships should not be construed as an inability to derive indices (*i.e.*, independent variables) that quantify contractility and loading conditions. Similarly, loading conditions ought to be defined independent of the contractile state of the ventricle. Afterload is taken to convey the summation of all forces that act to impede LV ejection.

The quantification of LV contractility long has been one of the goals of cardiovascular physiologists and bioengineers. Numerous indices of LV contractility have been proposed and developed. All isolated ejection phase indices of LV function, most notably the LV ejection fraction, depend on both contractility and afterload. Moreover, other indices of LV function, such as LV-developed systolic pressure and wall stress, the first time derivative of LV systolic pressure (LV $\partial P/\partial t$), and stroke work (SW), while afterload independent, are proportional to LV volume.

However, indexing these indices to LV preload, particularly *via* derivative relationships, has yielded load-independent indices of LV function. Two have achieved particular prominence. First, the end-systolic pressure–volume relationship (ESPVR), developed by Sagawa *et al.*[16] in the context of pressure–volume (P–V) loop analyses, is a relatively load-independent index of LV systolic function. As this relationship is generally linear—although this fails at low-end and high-end LV afterloads and volumes[17]—the first derivative (end-systolic elastance, E_{es}) of the ESPVR is the principal index of LV contractility and is proportional to it. The volume intercept represents the LV volume at which no pressure is generated, and thus is inversely related to LV contractility. E_{es} is comparatively straightforward to assess, and by virtue of making assessments only at end-systole, is relatively easy to ascertain.

Yet, from a perspective of pump thermodynamics, the ESPVR and E_{es} are conceptually flawed. By conducting assessments only at end-systole, they are definitionally "path-independent" assessments, and thus, do not capture events during the temporal course of pump action. In fact, the initial study of Sagawa and colleagues[12] did evaluate "time-varying elastance," or $E(t)$; however, this adds complexity by necessarily including time as a variable, and snapshot assessments at either maximal or end-systolic elastance were developed. In contrast, SW, first proposed as a contractility index by Sarnoff and colleagues,[18] which incorporates LV P and V and is thus afterload-insensitive, captures LV systolic function throughout systole. A simple example illustrates this. Two LV P–V loops could have identical LV P and V at AV opening and closure, but have dramatically different P and V during the course of LV ejection (AV stenosis is a plausible example). The E_{es} of both LVs may be the same, but SW would be substantially different (**Figure 2A**). These concepts apply both to the native circulation, and for the LV in the setting of V-A ECMO mechanical circulatory support (MCS).

However, SW itself is proportional to preload; this in fact is the Frank–Starling relationship, which in turn is simply a three-dimensional readout of the length–tension relationship for cardiac muscle. Glower *et al.*,[19] in one of the most important studies in modern cardiovascular physiology, developed the relationship between SW and EDV, as the thermodynamic expression of the Frank–Starling concept. As the relationship between SW and EDV is roughly linear at physiologic EDVs (**Figure 2B**), the first derivative, "preload-recruitable stroke work" (PRSW), is itself EDV-independent. Left ventricular distension, however, is defined by EDVs that are sufficiently high such that SW and stroke volume (SV) are reduced; in this range of EDVs, the idea of PRSW as a generalized "slope" of the SW–EDV relationship fails because there is no constant slope (in the linear range, $\partial(\text{SW})/\partial(\text{EDV}) = \text{PRSW slope}$, whereas it does not in the nonlinear range). As shown in **Figure 2B**, in the high EDV ranges of more typical of LV distension, contractility might better be defined simply by the ratio of SW to EDV (since the first derivative goes to zero and then negative in the range of the descending limb), or also by modeling the relationship and determining both the first derivative and the second derivative $\partial^2(\text{SW})/\partial(\text{EDV})^2$; the latter is zero in the "linear" range and negative in the range of the "plateau" and "descending" limbs.

Conceptually, what PRSW means is for a given EDV (independent variable), the SW (dependent variable) to which it translates. A greater SW for a given EDV means a greater amount of work performed by the LV, and thus, greater intrinsic LV contractility. Similarly, a lesser SW for a given EDV indicates lower LV contractility. Preload-recruitable stroke work is perhaps properly viewed as the gold standard for LV systolic function assessment. While one could examine elastance as a function of time during systole—both during isovolumetric contraction and ejection—this requires determining functional relationships not only between pressure and volume but between both of these and time. In contrast, PRSW is a more comprehensive index of LV systolic function relative to elastance snapshots at particular times, although it is inadequate to capture LV distension.

Veno-arterial ECMO support, similar to CPB, is not typically hypothesized to directly affect LV contractility. However, V-A ECMO support may enhance LV contractility, most plausibly by enhanced myocardial perfusion (discussed in Literature Review). In addition, while LV contractility is inversely related to the development of LV distension, extreme LV chamber enlargement can impair myocardial contractility, this also being in large part because of secondarily impaired myocardial blood flow. This manifests in the descending limb of the Frank–Starling relationship (**Figure 2B**), in which $\partial(\text{SW})/\partial(\text{EDV})$ is negative. As discussed above, the concept of a linear SW–EDV relationship with a constant slope indicating PRSW fails in this range of EDVs. Further, it highlights why LV distension is challenging to treat, as a vicious cycle of distension and contractile dysfunction ensues.

Myocardial O_2 delivery is the product of volumetric coronary blood flow and coronary arterial O_2 content. Thus, intracoronary delivery of inadequately oxygenated blood, that is, coronary hypoxemia, may cause myocardial hypoxia and

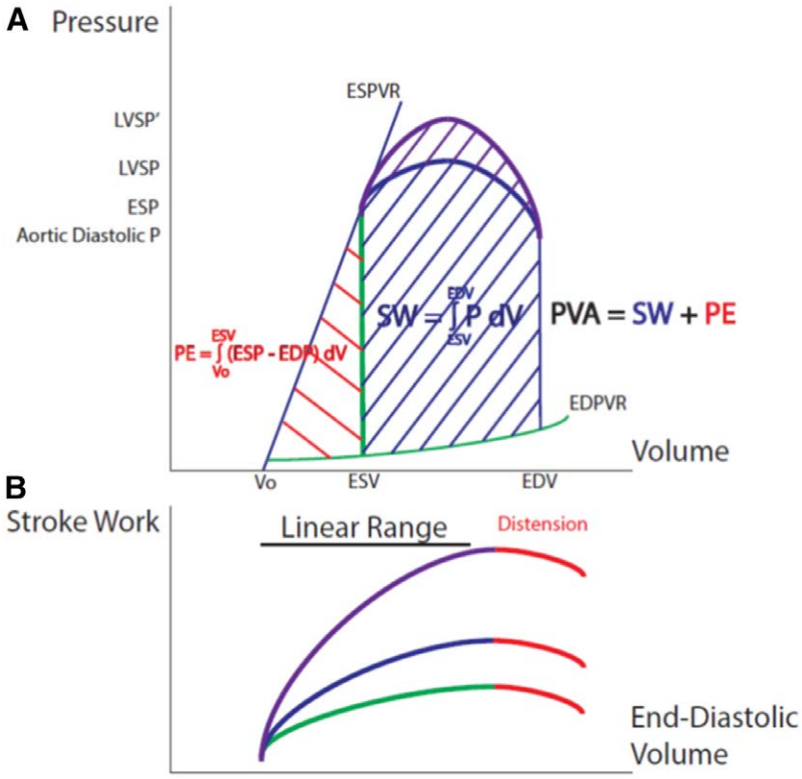

Figure 2. Systolic ventricular mechanics and LV distension. **A**: Pressure–volume diagram for the LV. Systole (blue or purple) and diastole (green) are depicted. Diastolic filling commences along the EDPVR, until the mitral valve closes. Isovolumetric contraction ensues. AV opening occurs at the lowest aortic pressure, that is, the diastolic pressure, and LV ejection commences. The maximum LVSP is reached, and ejection continues until the AV closes when aortic and LV pressure equalize; at this point, the LV pressure is the ESP, and LV volume is the ESV. The ESPVR depicts ESP as a function of ESV, with the first derivative (E_{es}, the slope as it is roughly linear) as an index of contractility. However, as shown, the LV may have identical AV opening and closing pressures, but the maximum LVSP may be substantially different (LVSP' *vs.* LVSP). SW, the work that the LV performs during a cardiac cycle, thus may differ despite identical ESPVRs. The LV, as a pump, imparts mechanical energy to blood to generate flow. SW indicates the mechanical energy transferred from the LV; a component of this is dissipated because real systems are nonideal, and the majority is imparted to blood to generate flow (this is the work-kinetic energy theorem). PE is the LV energy expended without contributing to LV wall motion, as such, it is a reflection of mechanical inefficiency. The PVA is an expression of total LV mechanical energy expenditure, and is the sum of SW and PE. Myocardial oxygen consumption (V_{O_2}) is proportional to the PVA, with the nature of this relationship expressing the efficiency of conversion of biochemical to mechanical energy. For a given EDV and afterload, contractility is proportional to SW; positive inotropes increase SW and myocardial V_{O_2}, while negative inotropes do the opposite. For a given contractility and afterload, EDV is proportional to SW; volume expansion increases SW and myocardial V_{O_2}, whereas volume reduction does the opposite. For a given contractility and EDV however, afterload is unrelated to SW; rather, afterload is proportional to PE, and impedance increases elevate PE and myocardial V_{O_2}, whereas afterload reduction accomplishes the opposite. Mechanical efficiency is proportional to contractility and preload generally, and inversely proportional to afterload. **B**: Relationship between SW and EDV. Over a physiologic range of EDVs, the relationship between SW and EDV is approximately linear. Shown are relationships in the setting of normal (blue), increased (purple), and decreased (green) LV contractility (purple). The first derivative (slope) of this relationship, PRSW, is an expression of contractility. **A** describes why PRSW is conceptually superior to the ESPVR as a contractility index. In LV distension, even PRSW—as a linear concept—is insufficient to explain the physiology of LV distension; however, if SW/EDV were used as a contractility index, it would continue to be valid in the nonlinear range, unlike PRSW defined in linear terms. At excessively high EDV, SW and SV are reduced; this is the descending limb of the Frank–Starling relationship. AV, aortic valvular; EDPVR, end-diastolic pressure–volume relation; EDV, end-diastolic volume; ESP, end-systolic pressure; ESPVR, end-systolic pressure–volume relationship; ESV, end-systolic volume; LV, left ventricular; LVSP, LV systolic pressure; PE, potential energy; PRSW, preload-recruitable stroke work; PVA, pressure–volume area; SV, stroke volume; SW, stroke work.

secondary cardiomyocyte contractile dysfunction. In patients with coexistent hypoxemic respiratory failure supported on V-A ECMO, it is conceivable that "differential" hypoxemia (the difference being between the LV-ejected blood and V-A ECMO systemic arterial outflow blood) may cause LV systolic dysfunction, and potentially LV distension. In this context, it is important to note that differential hypoxemia and LV distension are complications of V-A ECMO with important similarities and differences. Left ventricular distension requires LV volume loading, and low contractility relative to afterload such that inadequate or absent AV opening occurs. In contrast, differential hypoxemia also requires LV volume loading—and specifically with hypoxemic blood—while LV contractility is sufficiently high relative to afterload such that robust AV opening occurs. Consequently, for the two states to coexist, a set of conditions in a narrow window have to be satisfied: an LV filled with hypoxemic blood, but with sufficient initial contractility relative to afterload, is able to cause enough AV opening and resultant intracoronary hypoxemia, such that eventual LV dysfunction and distension ensue. Moreover, for differential hypoxemia to cause persistent LV dysfunction and distension in this scenario, a narrow range of AV opening must

stably exist such that the degree of valve opening and LV ejection does not permit the LV to unload itself, but does cause intracoronary hypoxemia. This is because if severe LV contractile dysfunction occurred, AV closure would result, and coronary blood flow would be V-A ECMO-dependent (this being well-oxygenated blood). This would in turn ameliorate myocardial hypoxia. In summary, for differential hypoxemia to contribute to LV systolic dysfunction and afterload mismatch resulting in distension, present robust AV opening and delivery of hypoxemic blood to the coronary arterial circulation must eventually beget future LV dysfunction and impaired AV opening. While plausible, a narrow range of LV contractility and loading conditions, as well as V-A ECMO circuit dynamics, are requisite for coronary arterial hypoxemia and LV distension to coexist.

As challenging as contractility is to assess, afterload is perhaps even more challenging and poorly understood. Moreover, how to define and quantify afterload in the context of dual native and extracorporeal circulations is particularly difficult. Afterload is the summation of all impedances to LV ejection. In the native circulation, this is best quantified by the impedance of the systemic circulation, which is time varying as are pressure and flow rate, unlike resistance; when expressed in Fourier series, the 0th harmonic of impedance is the systemic vascular resistance (SVR). However, even this does not capture, for example, direct "anti-ventricular" forces, such as the effects of intrapleural or pericardial pressure on LV dynamics.

It is vitally important to understand that systemic arterial pressure or LV systolic pressure and wall stress should not be construed as indices of afterload in the native circulation. Although commonly used, this approach is deeply flawed. This is because as a pump, the LV itself is the physical source of wall stress and pressure during systole. It is logically unsound to suggest that the LV generates the load against which it contracts; in contrast, resistance and impedance better capture afterload, as they are variables that are independent of, rather than dependent on, LV function. A counterexample illustrates this. In LV failure, the SVR is high, whereas systemic arterial blood pressure is not, that is, the two variables do not covary with each other. No one would suggest that cardiogenic shock is a low-afterload state; on the contrary, it is a high afterload state, and to the extent that SVR reduction is feasible, it is part of the treatment of LV systolic dysfunction.

However, in the setting of V-A ECMO support, systemic arterial pressure does capture LV afterload better than in the native circulation.[20] How is this discrepancy explained? The classical studies of LV function, including those in which LV P–V analysis were developed, used preparations in which the proximal aortic pressure could be extrinsically controlled, as opposed to being determined by the action of the LV. As a result, the systemic arterial pressure was an independent variable, rather than a dependent variable. This is similar to V-A ECMO, in which the extracorporeal pump extrinsically pressurizes the aorta. Systemic arterial pressure more reasonably approximates the afterload to which the LV is subjected. Systemic arterial pressure is in turn dependent on the source of parallel blood flow, that is, the pressure generated by the extrinsic pump, although native LV ejection does contribute to systemic arterial pressure if AV opening occurs. Thus, V-A ECMO support augments LV afterload, *via* circuit pump-driven proximal aortic pressurization.

A potentially important open question is whether the location of systemic arterial outflow impacts on LV afterload, holding other parameters constant. In principle, if the notion of a global LV afterload is valid, it is a "lumped" parameter, that is, the global locus of afterload as downstream from the LV is sufficient to model it. Spatial variations, or specific locations of afterload within the systemic circulation, are deemed unimportant. However, this may be incorrect. The typically femoral arterial source of V-A ECMO outflow clearly has implications for the distribution of native LV *versus* circuit-driven outflow, as discussed; however, whether central *versus* peripheral arterial outflow impacts on the LV is unknown.

The extent of pressurization is proportionally related to circuit pump speed, as pump speed determines the pressure difference across the pump. The volumetric flow rates through the circuit pump, as well as the native LV, also depend on the downstream impedance of the systemic arterial circulation. Consequently, because of the two pumps in parallel and a shared downstream systemic impedance, LV afterload and extracorporeal pump afterload are both complex to define. Simulation studies are particularly useful under such circumstances.

Literature Review

Pressure–Volume Loop Simulations

Antaki and colleagues,[21] and Burkhoff *et al.*,[22] have conducted comprehensive simulation studies of the effects of MCS strategies on LV mechanics and energetics, using lumped parameter models. The former has focused on studying the effects of LV assist device (LVAD) support on LV, interventricular septal, and RV dynamics in the setting of unimodal (nonlinear with a local maximum) ESPVRs, whereas the latter has studied the effects of different MCS cannulation strategies. Using P–V loop analyses, Burkhoff *et al*.[22] show that V-A ECMO support augments LV afterload and preload, both of which are deleterious to the failing LV, particularly in the setting of ischemia and infarction. This is because increasing afterload increases the SW-unrelated potential energy component of myocardial O_2 consumption, and while preload augments SW, yet increases the SW-related component of myocardial O_2 consumption (**Figure 2A**). In contrast, direct left-sided cardiac unloading has relatively beneficial effects, albeit with important differences between LA and LV unloading. Left atrial unloading reduces preload, but increases afterload *via* the same mechanism as V-A ECMO (see below), that is, pressurization of the aorta caused by the artificial pump. Left ventricular unloading is the most beneficial, reducing both preload and afterload—the latter by ongoing pressure gradient generation during LV contraction (*i.e.*, systolic unloading that effectively eliminates isovolumetric contraction—which is why pulsatility in the systemic arterial pressure waveform can occur in the absence of AV opening) and the relaxation phase of diastole (*i.e.*, diastolic unloading that effectively eliminates isovolumetric relaxation, with diastolic unloading terminating at the point that the summed LV diastolic pressure and LVAD-generated pressure difference are less than the aortic outflow pressure).

It should be noted, although not studied by the author, that although overall LV afterload is reduced by MCS with LV drainage, there are complex individual effects because of dual outflow paths; overall LV afterload is reduced by the presence

of a second and new low-afterload circuit with a pump downstream in series, but the afterload with respect to trans-AV ejection is actually increased. All of these simulation findings are qualitatively predictable by physiologic theory antecedent to the studies themselves, but the studies provide a quantitative framework for comparing different MCS strategies. **Figure 3** displays these theoretical predictions, and depicts findings similar to those of Burkhoff *et al*.[22]

Experimental Studies

With respect to experimental studies, variable results have been observed. It is essential to note at the outset, that comparisons between V-A ECMO for LV failure and direct left-sided cardiac support generally assume comparable inflow cannula, pump, and outflow cannula characteristics, so that isolated "fair" comparisons of the strategies may be undertaken. However, holding such variables constant is highly inconsistent with clinical practice; some of the relative advantages and disadvantages of a given technique, for example, may relate to differences in available cannula sizes or pump characteristics.

Some experimental studies conducted in large animal models across different eras are highlighted. Bavaria *et al*.[23] conducted an early important experimental study of the effects of V-A ECMO on LV loading conditions and function. In an ovine model of global myocardial ischemia induced by aortic cross-clamping while on V-A ECMO support, the authors compared the effects of ECMO support on post-crossclamp release LV loading conditions and contractility in comparison to the nonischemic state. Of note, the ECMO circuit did include a reservoir, although it is unclear to what if any extent volume was exsanguinated into it. In addition, transaortic LV venting was undertaken, but only during the period of cross-clamping, while the LV was fibrillating. Effects on the RV were in principle mitigated by topical cooling restricted to the RV. The author found that for normal LVs, V-A ECMO reduced the systolic stress integral [$\int \sigma(t)\, dt$ from t = end-diastole to end-systole, where σ represents circumferential wall stress at the LV equator]. Specifically, LVEDV was significantly reduced and LVESV was unchanged (*i.e.*, SV was reduced), with modest decreases in LV systolic pressures. However, for postischemic LVs, the systolic stress integral increased as a function of ECMO circuit volumetric flow rate, LVEDV and LVESV were both significantly reduced (with SV relatively unchanged), and LV systolic pressures were significantly increased. It is crucial to emphasize that pressure and stress are not truly indices of afterload, as the LV generates and is the physical source for them. Indeed, Bavaria *et al*.[23] actually demonstrated that both LV contractility and afterload increased in response to V-A ECMO support. The former increased most likely because of enhanced myocardial blood flow, a consequence of the "Gregg effect,"[24] which identified a proportional relationship between myocardial blood flow and oxygen consumption, that is, dependence of oxygen consumption on oxygen delivery. In contrast, the latter increased because of the ECMO circuit flowing in parallel acting to pressurize the aorta. For this reason, SV and other ejection phase indices of LV function, which are depending on both LV contractility (proportional) and afterload (inversely proportional), were relatively unchanged in this study.

After this seminal study, Shen *et al*.[25] developed a swine model of V-A ECMO support in the absence of LV injury or dysfunction. They found that V-A ECMO support was

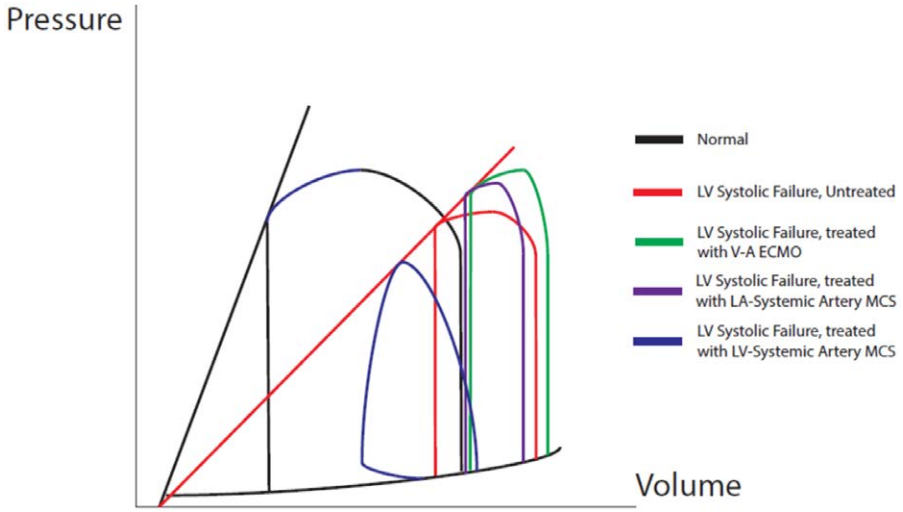

Figure 3. Effects of different MCS strategies on LV loading conditions, as displayed on pressure–volume diagrams. The black loop indicates normal contractility, EDV, and afterload. LV failure (red) manifests with depressed contractility (reduced E_{es}), increased EDV, and similar afterload. MCS strategies are assumed not to influence LV contractility, although this may not necessarily be the case. V-A ECMO support (green) increases EDV, ESP, and thus ESV. LA inflow (purple) decreases EDV, but increases ESP and ESV as V-A ECMO does. For both strategies, isovolumetric contraction and relaxation are preserved. LV inflow (blue) decreases EDV, ESP, and ESV. Moreover, as long as the sum of LV pressure and the pressure difference generated by the MCS pump are high enough to drive flow across systemic afterload, LV volume unloading occurs. Consequently, normal isovolumetric contraction and relaxation are not present. Effects of MCS strategies on LV contractility (*vis-à-vis* changed in myocardial O_2 delivery) are not exhibited in this figure, because the extent to which such effects occur is difficult to predict. For example, V-A ECMO and LA-systemic artery MCS both result in enhanced aortic pressure—which would be predicted to increase coronary blood flow, but LV chamber enlargement and increased LV wall tension may increase coronary vascular resistance and the outlet pressure for the coronary circulation—which would be predicted to decrease coronary blood flow. EDV, end-diastolic volume; ESP, end-systolic pressure; ESV, end-systolic volume; LV, left ventricle; MCS, mechanical circulatory support; V-A ECMO, veno-arterial extracorporeal membrane oxygenation.

associated with marked reductions in ejection phase indices of LV contractility, but PRSW (*i.e.*, true intrinsic LV contractility, definitionally independent of afterload) was unaffected. Consequently, they demonstrated increased LV afterload in response to V-A ECMO support. However, LV end-diastolic dimensions were unaffected by V-A ECMO support, that is, preload was not increased—albeit not in a model with antecedent LV dysfunction.

Most recently, Esposito *et al*.[26] recently published a comparative study of V-A ECMO and TandemHeart (LA-systemic artery MCS) with respect to effects on LV loading conditions and function, in the *ASAIO Journal*. Cannula diameters for both modalities of support were held constant, permitting rigorous assessment of the effects of the different circuitries on LV loading conditions and function. Unsurprisingly, the author found that TandemHeart support provided superior unloading relative to V-A ECMO support, within equivalent volumetric flow rates between the two groups. However, while holding cannula sizes and pump characteristics constant is required to fairly compare the effects of different drainage strategies, it is clinically unreasonable at best. Although 21 Fr cannulae may be used for systemic venous drainage/inflow purposes, larger diameter cannulae are most commonly used. I typically use 25 Fr cannulae, which have, for the same cannula length, a much lower resistance to flow; under Poiseuille flow regimes, the resistance of a 21 Fr cannula is just over twice the resistance of a 25 Fr cannula. Other surgeons and MCS practitioners use even larger bore cannulae. Similarly, larger systemic arterial cannulae may be used for V-A ECMO, and pumps with greater flow capacities at physiologic heads may be used. Even if LA-systemic artery MCS did not use the TandemHeart pump and systemic arterial cannula, it is constrained by the high resistance LA cannula. Nonetheless, this experimental study supports the simulation predictions of Burkhoff *et al*.[22], and is consistent with fundamental physiologic theory.

Why Does LV Distension Not Occur in All Patients with LV Failure Who Have Persistent Aortic Valve Closure or Do Not Undergo LV Venting?

Let us conduct a gedankenexperiment. Most of us have observed in patients placed on V-A ECMO, particularly in the setting of cardiac arrest, that lack of AV opening/pulsatility may be present post-ECMO initiation in the absence of left-sided cardiac venting, even with recovery of a satisfactory rhythm. Left ventricular distension typically does not occur even in these patients. This, however, is an apparent paradox.

In the scenario of V-A ECMO support without AV opening, let us even stipulate that maximal and outstanding systemic venous drainage is present, and that there is no AR. Left ventricular distension and pulmonary edema ought to ensue within minutes to a few hours. Why? Because bronchial (and Thebesian) return always preload the LV, which is not ejecting in this scenario. The normal volumetric flow rate through the bronchial circulation is in the range of 0.5% of normal cardiac output. This is approximately 25 ml/min for a cardiac output (in the nonpulsatile patient, *i.e.*, without native cardiac output, this is the ECMO circuit volumetric flow rate) of 5 L/min. This would mean that within 40 minutes, an entire 1 L of blood would be translocated into the left-sided circulation, that is, downstream of the pulmonary capillaries. With an adult blood volume of ~5 L and a circuit volume of ~1 L, this would be 1/6 of the total circulating blood volume. Within 2 hours, 3 L would similarly be translocated, or 1/2 of the total circulating blood volume. Thus, even with normal LV compliance and pulmonary circulatory capacitance ($\partial V/\partial P$ for the LV and the pulmonary circulation respectively) and vascular permeability, LV distension and pulmonary edema ought to occur rapidly. This "back of the envelope" calculation is consistent with a recent model ECMO circuit study by Kim *et al*.[27] in the *ASAIO Journal*. But this is not consistent with clinical experience. Moreover, for those of us who place pulmonary artery (PA) catheters in patients on V-A ECMO, the absence of AV opening often does not translate to elevated PA and PA occlusion pressures.

I leave this as an open question, but solutions to this apparent paradox must exist. How can the LV not distend in the setting of AV closure, even in the absence of AR and the presence of maximal right-sided drainage? Some mechanism must exist whereby bronchial and Thebesian return does not fill and progressively distend the LV.

Diagnosis

The manifestations of LV distension are usually obvious, and the diagnosis straightforward. These are reviewed below.

History and Physical Examination

The history provides a clinical context into which a possible diagnosis of LV distension may fit. Left ventricular failure as the indication for V-A ECMO, known entities leading to LV filling (*e.g.*, AR, aortopulmonary shunts), and systemic arterial hypertension, all increase the likelihood of LV distension. Assessment of vital signs and intensive care unit-monitored cardiopulmonary variables follows next. Insofar as systemic arterial pressure relates to afterload while on V-A ECMO support, the presence of hypertension should increase the suspicion for LV distension. However, depending on intrinsic LV contractility, the absolute value of the systemic blood pressure could be increased, normal, or reduced when LV distension occurs. More importantly, absent or minimal pulsatility of the systemic arterial pressure waveform, which reflects absent or reduced aortic valve opening, is a necessary—albeit not sufficient—condition for LV distension to develop. In patients with PA catheters, elevated and progressively increasing PA occlusion and diastolic pressures will be present if LV distension occurs. Because many or most patients without aortic valve opening do not develop LV distension, PA catheters are particularly useful; moreover, increasing PA occlusion and diastolic pressures may be present temporally before the development of pulmonary edema. Central venous pressures may be difficult to accurately and precisely determine, because of the presence of the venous cannula generating suction.

Next, with respect to pulmonary parameters, patients are most often mechanically ventilated. Pulmonary edema causes reduced lung compliance, which is evident by reduced tidal volumes in pressure-controlled ventilation, or increased airway pressures (assuming that airways resistance is not affected) in volume-controlled ventilation. Impaired gas exchange generally is not evident, because in the absence of aortic valve opening, ECMO circuit arterial outflow accounts for the entirety of

systemic perfusion. However, blood gas data obtained from PA catheters in wedged position may demonstrate impaired intrapulmonary gas exchange, that is, hypoxemia and possibly hypercapnia.

Physical examination findings are consistent with those of LV dysfunction. However, V-A ECMO support may cause some differences. For example, because the aortic valve is typically persistently closed, a normal second heart sound in the aortic position should not be present. Inspiratory crackles may be present because of pulmonary edema.

Imaging

Chest radiography is often the basis for confirming LV distension on V-A ECMO. Although the history, intensive care unit data, and physical examination are able to diagnose LV distension, evidence of new onset or exacerbated pulmonary edema on chest radiography is most commonly the criterion used to confirm it. Cardiac imaging most commonly involves echocardiography. Aortic valve closure or minimal opening is observed. However, AR may be observed if it is contributory to LV distension. Absent or severely reduced LV systolic motion will be observed, unless mitral regurgitation is present as a pathway for LV ejection. The LV may or may not be dilated, depending on the acuity of LV failure. Finally, the LA should be dilated.

Cardiac Catheterization

In my opinion, PA catheters are indispensable in patients on V-A ECMO. This is because LV distension does not necessarily translate to LV dilatation, but is defined by excessively elevated LV diastolic pressure. The simplest correlate of this is an increased PA occlusion pressure. In addition, if the PA occlusion pressure is disproportionately elevated relative to the mean or systolic PA pressure, this implicates a left-sided etiology of LV distension, as opposed to a systemic-to-PA shunt or incomplete systemic venous drainage.

Treatment

Having established LV distension on V-A ECMO, several therapeutic strategies exist. These are reviewed below.

Pharmacological

Left ventricular distension occurs in the context of afterload mismatch: low contractility and high afterload, and is defined by excess LVEDP. As such, pharmacologic treatment is no different from the treatment of LV systolic dysfunction. This includes positive inotropes, agents with vasodilatory effects in the systemic arterial circulation, and diuretics. Importantly, the first of these therapies will increase myocardial O_2 demands, whereas the latter two will reduce it. Finally, ensuring an optimal cardiac rhythm increases the likelihood of LV ejection.

Catheter Based

At least four minimally invasive, catheter-based approaches exist to achieve LV decompression. These are presented working retrograde through the circulation. The first is intraaortic balloon pump (IABP) counterpulsation. The IABP is not direct left-sided cardiac venting. Rather, it should be viewed as "facilitated" LV venting. The afterload reduction that the IABP provides promotes LV ejection, that is, the LV vents itself just as it would with pharmacotherapy. Anecdotally, I have never observed LV distension on V-A ECMO when an IABP has also been in place simultaneously in a patient with a satisfactory cardiac rhythm. That is, an IABP in place before V-A ECMO cannulation ought not be removed, as it provides prophylaxis against LV distension.

Next, catheter-based LV drainage can be undertaken. The most popular example of this is the Impella micro-axial catheter-based LVAD. As discussed, LV drainage has advantages over LA drainage. However, the Impella device itself is constrained by the fact that the pump mechanism itself is catheter mounted and therefore miniaturized. This results both in a limited flow capacity in comparison to LVADs with larger pump mechanisms and in a substantial incidence of hemolysis. However, for the purposes of LV venting, the volumetric flow rate requirements should not be high,[28] and even the smaller Impella devices ought to be sufficient.

The largest of the Impella family of miniaturized short-term LVADs is the Impella 5.0. In our practice, this not only serves as a highly effective LV venting device—even though higher volumetric flow rates are typically not required—but perhaps more importantly, serves as a bridging strategy from V-A ECMO that not only provides LV MCS but provides LV unloading.[29] In addition, when inserted *via* proximal arteries, notably the axillary artery, patient ambulation is facilitated. Although the Impella 5.0 LVAD only provides LV MCS, should RV MCS be required, catheter-based miniaturized RVADs can be used as part of a comprehensive minimally invasive strategy for biventricular MCS. Both the Impella RP and the TandemHeart (in principle, any paracorporeal pump mechanism may be used) pump coupled with the Protek Duo dual lumen cannula with right atrial inflow and pulmonary arterial outflow may be used. The latter approach has the advantages of: 1) being able to splice a gas exchanger into the circuit, should coexistent severe respiratory failure be present, and 2) permitting ambulation.

The LA can be percutaneously accessed trans-septally, for example, using the TandemHeart system, with a cannula spliced into the venous return to the ECMO circuit thereby venting the left side of the heart. Relative to the Impella, this approach has higher flow capacities and lower degrees of hemolysis. However, as discussed previously, LA unloading is less beneficial to the LV than direct LV unloading. In addition, trans-septal LA access is more technically arduous and operator dependent.

Finally, the right-sided circulation can be accessed. Percutaneous placement of PA vent catheters may be performed *via* systemic venous access. Pulmonary artery venting can provide indirect left-sided drainage, but this is retrograde across the pulmonary circulation, and thus inferior to direct left-sided drainage unless the etiology of LV distension clearly is inadequate systemic venous drainage. Additionally, if impaired systemic venous drainage either is not a contributor or only a minor contributor to LV distension, PA venting may not reduce pulmonary capillary pressures and pulmonary edema sufficiently, due to these vessels being collapsible as Starling resistors. However, if impaired systemic venous inflow is the principal cause of LV distension—which is likely true in the majority of cases—then PA cannulae or additional venous

cannulae spliced into the systemic venous line of the ECMO circuit will substantially reduce pulmonary venous return and thus, LV distension.

Open Surgical

Open surgical approaches for venting the left side of the heart are the historical standard. Broadly, the principal advantage of surgical approaches is the ability to place anatomically secure, large-bore cannulae. In contrast, invasiveness is the major disadvantage of surgical techniques.

The Impella 5.0, the largest of the Impella devices, is generally placed surgically, either trans-aortically or *via* the axillary/subclavian arteries through side grafts. The LV may be directly vented transapically. This can be performed through an apical ventriculotomy secured by pursestring cannulation sutures or through a similar ventriculotomy but using a LVAD inflow sewing ring secured to the LV apex using an interrupted or continuous suturing technique. The LV also may be vented indirectly *via* access through the LA (dome) or through the right superior pulmonary vein, as is most commonly performed during cardiac surgical procedures. This is through pursestring cannulation sutures. Left atrial vent catheters may be maintained in the LA as well, draining the LA rather than the LV. Vent catheter return is spliced into the systemic venous line, as is the case with percutaneously placed catheters. Importantly, open surgical LA or LV venting may be constructed as part of a short-term LVAD strategy for MCS. In such a scheme, either LA or LV inflow is into a centrifugal/radial flow pump, which pumps into systemic arterial outflow. Such surgical short-term LVADs, in my experience, have good outcomes and excellent hemodynamic results, with high volumetric flow rates and excellent left-sided cardiac drainage inflow both being achieved.

Pulmonary artery vent catheters may be placed *via* open surgical technique, typically through the main PA. Finally, additional systemic venous cannulae may be added surgically, although this is typically in the context of a central cannulation strategy for V-A ECMO, that is, along with ascending thoracic aortic cannulation. This is because addition of systemic venous cannulae may be accomplished easily percutaneously. As is the case for conventional CPB cannulation, pursestring cannulation sutures are used.

Prophylactic Left-Sided Cardiac Venting: A "Data-Free Zone"

When clinically important LV distension with overt pulmonary edema has occurred, the need for venting the left side of the heart is obvious. What is far less clear is if, or when, prophylactic venting should be undertaken. Here, little, if any, data are present to function as guides. However, below are physiologically sound indications for prophylactic LV venting (inclusive of IABP placement); this is outlined in **Figure 4**.

If AV opening, as evidenced by pulsatility in the systemic arterial pressure tracing, is absent or minimal after initiation of V-A ECMO, the next question that needs to be addressed is the status of LV loading conditions and contractility. Most importantly, if LV end-diastolic pressure or volume is deemed high (*e.g., via* PA occlusion pressure or echocardiography), then if systemic venous drainage and right-sided cardiac decompression is adequate, LV venting *via* some modality is reasonable. If contractility is low, then whether a coordinated cardiac rhythm is present or absent should be determined; if absent, attempts must be made to establish an adequate cardiac rhythm—although LV distension may prevent this if it has developed but was unrecognized. If a satisfactory cardiac rhythm or sufficient LV contractility cannot be provided, or if inotropic support is deleterious (*e.g.*, in the setting of myocardial ischemia/

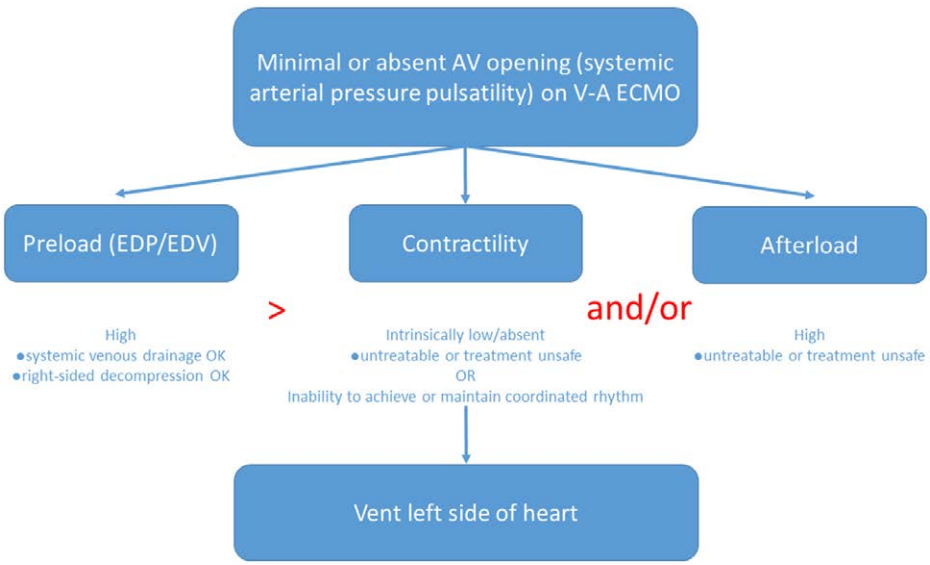

Figure 4. A proposed algorithm for prophylactic left-sided cardiac venting in the setting of V-A ECMO support. Minimal or absent AV opening suggests that LV distension may ensue, depending on the left-sided cardiac loading conditions, which then must be assessed. Increased LV end-diastolic pressure or volume (EDP and EDV, respectively), the former of which is proportionally related to impending LV distension and pulmonary edema, and the latter of which is LV preload, is proposed as the most important determinant of whether to undertake left-sided cardiac venting. Lesser indications (as indicated by the > sign) include low LV contractility or high LV afterload, if either condition cannot or should not be treated safely. AV, aortic valvular; EDP, end-diastolic pressure; EDV, end-diastolic volume; LV, left ventricle; V-A ECMO, veno-arterial extracorporeal membrane oxygenation.

infarction) to cardiomyocytes, then LV venting ought to be undertaken, perhaps even when LV end-diastolic pressure/volume are not increased, but definitely if those are increased. If afterload is assessed as being high, then this can be treated by one or more of the strategies above, including IABP placement if not present. If afterload reduction is either unwarranted or cannot be achieved if warranted, then prophylactic LV venting is reasonable. As is the case with low contractility, prophylactic LV venting is reasonable in the setting of high afterload even in the absence of increased LV preload, but definitely should be undertaken if LV end-diastolic pressure/volume is thought to be increased.

Conclusions

Left ventricular distension is a serious complication of V-A ECMO. The pathophysiology of LV distension is particularly challenging to understand, and determining causes in individual cases may be difficult. A wide range of treatment strategies are available, which may differ importantly in efficacy depending on the contributory mechanisms. If IABPs or direct left-sided cardiac venting systems are already in place at the time of V-A ECMO support initiation, they should be continued. Conversely, if LV distension has already occurred, treatment is required. However, whether left-sided cardiac venting should be performed prophylactically in all patients on V-A ECMO support *versus* selectively in patients thought to be at higher risk for developing LV distension, or only *post hoc* to treat distension, remains unclear.

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