# The Starling Relationship and Veno-Arterial ECMO: Ventricular Distension Explained

Marc L. Dickstein

**The use of veno-arterial (VA) extracorporeal membrane oxygenation (ECMO) to support patients with acute heart failure has been associated with ventricular distension and pulmonary edema, the mechanism of which is not fully understood. This study examined the impact of VA ECMO on left ventricular (LV) Starling curves to elaborate a framework for anticipating and treating LV distension. A previously developed and validated model of the cardiovascular system was used to generate pressure–volume (PV) loops and Starling curves while holding mean arterial pressure (mABP) constant at a range of values either by adjusting systemic resistance or by adding VA ECMO support. It was found that under all conditions of similar mAPB, the Starling curve was unchanged; therefore, the degree of LV distension is obligated by the mAPB (irrespective of whether controlled pharmacologically with or without ECMO support and independent of heart rate), LV contractility, and target stroke volume. The Starling relationship provides a conceptual framework for understanding the risk and treatment of LV distension during VA ECMO support. *ASAIO Journal* 2017; XX:00–00.**

**Key Words: extracorporeal life support, extracorporeal membrane oxygenation, cardiogenic shock, acute lung injury, pulmonary edema, cardiovascular physiology**

Veno-arterial (VA) extracorporeal membrane oxygenation (ECMO) is being used with increasing frequency to support patients with acute heart failure (AHF) of various etiologies.[1,2] The use is advocated for patients suffering cardiac arrest undergoing chest compressions (ECPR),[3–5] primary graft dysfunction after heart transplant,[6] circulatory support during episodes of acute decompensated left ventricular (LV) failure,[7,8] acute right heart failure,[9] and postcardiotomy shock syndrome.[10] There have been a greater appreciation of the risk of patients developing worsened LV distension after initiation of VA ECMO, the occurrence of which may seem counter-intuitive given the diversion of venous return from the heart to the ECMO circuit. The consequences of failing to anticipate, recognize, and adequately treat ventricular distension are grave and include acute pulmonary edema,[11] LV thrombus formation from blood stasis,[12,13] and exacerbation of myocardial injury.[14] Therefore, the purpose of this study is to elaborate the physiology of cardiac function on VA ECMO in order to anticipate which patients are at risk for ventricular distension and to effectively treat ventricular distension should it occur.

The Starling relationship is one of the most widely known and clinically referenced descriptions of cardiac function. Starling's Law of the Heart, first described in 1918, states that "the energy of contraction, however measured, is a function of the length of the muscle fiber."[15] The graph of ventricular end-diastolic pressure (EDP) plotted against stroke volume (SV), with its classic shape of diminishing slope as filling pressures increase, clearly conveys the dependency of cardiac output on volume status. Furthermore, the shift of this curve in response to changes in contractility and afterload provide valuable insights into the influence of myocardial function and the vasculature on cardiac performance. Although it is generally appreciated that VA ECMO confers an afterload stress to the failing heart, it is not known how the presence of VA ECMO may alter the Starling relationship. Therefore, we designed this study to examine the Starling relationship in the normal and failing ventricle and explore the impact of VA ECMO support.

## Materials and Methods

### *The Model*

A previously developed and validated model of the cardiovascular system was used to generate pressure–volume (PV) loops and Starling curves under varied conditions (see Figure SDC1, Supplemental Digital Content, http://links.lww.com/ASAIO/A196), which diagrams the model used for simulating VA ECMO). The vasculature is represented as a series of resistors and capacitors, and the cardiac chambers are described by a time-varying elastance model. Normal values for all of the model parameters were taken from the literature where available and adjusted to provide baseline hemodynamics in the normal range. Details of this type of model have been recently reviewed.[16]

### *Simulation Protocol*

A typical Starling curve was derived by examining the relationship of SV and pulmonary capillary wedge pressure (PCWP) while adjusting stressed blood volume in steps from 300 to 1500 ml. Four additional Starling curves were generated while adjusting systemic vascular resistance (SVR) to hold mean arterial blood pressure (mABP) constant at 80, 70, 60, and 50 mm Hg despite the change in cardiac output at each new volume step. Next, LV contractility (LV end-systolic elastance) was

From the Department of Anesthesiology, Columbia University, New York, New York.

Submitted for consideration March 2017 ; accepted for publication in revised form August 2017.

Disclosure: The author has received speaking honoraria from Abiomed, Inc.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML and PDF versions of this article on the journal's Web site (www.asaiojournal.com)

Correspondence: Marc L. Dickstein, Division of Cardiothoracic Anesthesia, Columbia University Medical Center, 630 West 168th Street, 5th Floor, New York, NY 10032. Email: mld2@cumc.columbia.edu.



**DOI: 10.1097/MAT.0000000000000660**

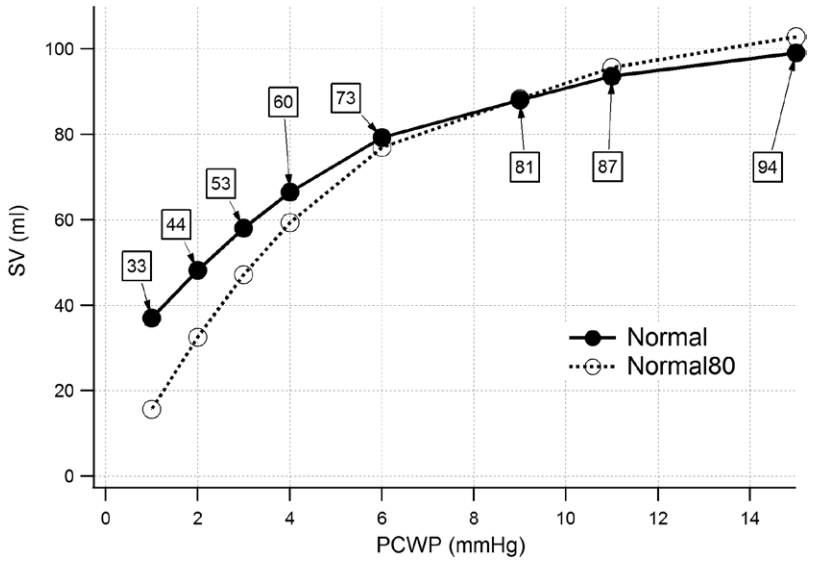


**Figure 1.** The Starling curve for the normal heart is shown in the solid line. As preload is changed, both stroke volume (SV) and mean arterial blood pressure (mABP, listed at each point in the box frame) are changed. The Starling curve generated while mABP is maintained at 80 mm Hg is shown in the dashed line. PCWP, pulmonary capillary wedge pressure.

reduced to 1/3 the normal value (AHF), and the same series of Starling relationships was generated; this was repeated after doubling heart rate (HR) to 120. Next, VA ECMO (flow rate 3.5 L/min) was added to the AHF model, and the same series of Starling relationships were generated at fixed values of mABP. Last, the relationship between pre-ECMO ejection fraction (EF) versus post-ECMO PCWP was explored by a sequential reduction of LV contractility; pre-ECMO blood pressure was set at either 80 or 50 mm Hg by titration of SVR, and post-ECMO SV was fixed at 30 ml by volume titration while post-ECMO mABP was fixed at either 80 or 50 mm Hg by titration of SVR.

## Results

The normal Starling curve, along with a Starling curve generated while holding mABP constant at 80 mm Hg by adjusting SVR, is shown in **Figure 1**. The effect of maintaining mABP on the Starling curve was to increase the slope at any point; the increase in afterload at lower filling pressures amplified the reduction in SV; the decrease in afterload at higher filling pressures amplified the increase in SV. The associated PV loops are shown in **Figure 2**. When mABP was allowed to vary with SV, the slope of the arterial elastance line (Ea) was unchanged; when mABP was fixed, the slope of the Ea line changed reflecting the change in afterload.

The Starling curve generated after contractility LV was reduced (AHF) is shown in **Figure 3**. Compared with the normal LV, this curve is shifted downward and has a flatter slope at higher filling pressures. Also shown in **Figure 3** are the Starling curves generated at a series of fixed mABP by SVR adjustment. With each successive increase in mABP, the curves shift progressively downward; the impact of fixing mABP is more pronounced than what was observed in the normal LV.

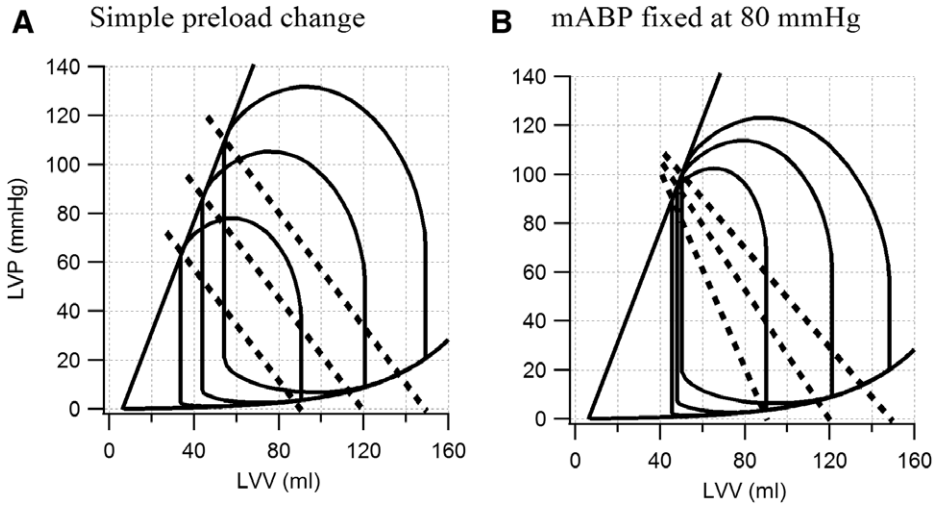


**Figure 2. A**: PV loops generated by a changes in preload. **B**: PV loops generated while holding mABP constant at 80 mm Hg by adjusting SVR. The dashed lines show arterial elastance (Ea); the slop of Ea remains constant in (**A**) and increases as preload is reduced in ( **B**) reflecting changes in afterload. mABP, mean arterial blood pressure; PV, pressure–volume; SVR, systemic vascular resistance.

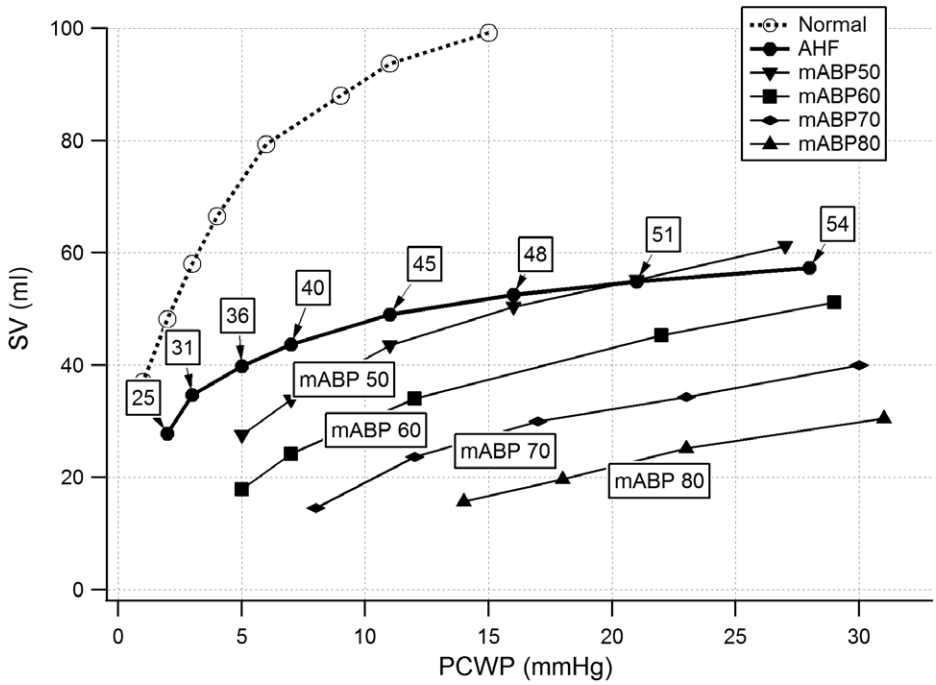


**Figure 3.** The Starling curves for the normal (dashed line) and AHF state (thick solid line) are shown as the two top-left lines; the AHF is associated with a downward shift and a flattening of the slope. The Starling curves generated in the AHF state while mABP is maintained at a series values (from 50 to 80 mm Hg) are also shown: with each successive increase in mABP, the Starling curves are shifted progressively downward. AHF, acute heart failure; mABP, mean arterial blood pressure; PCWP, pulmonary capillary wedge pressure; SV, stroke volume.

The Starling curves generated while on VA ECMO are shown in **Figure 4**. The changes in the Starling curves at a mABP of 80 were the same whether mAPB was held constant by adjusting SVR or by addition of systemic flow via VA ECMO; the curve was also unchanged when HR was doubled to 120 bpm. This finding is also shown in the PV loops in **Figure 5** where, at

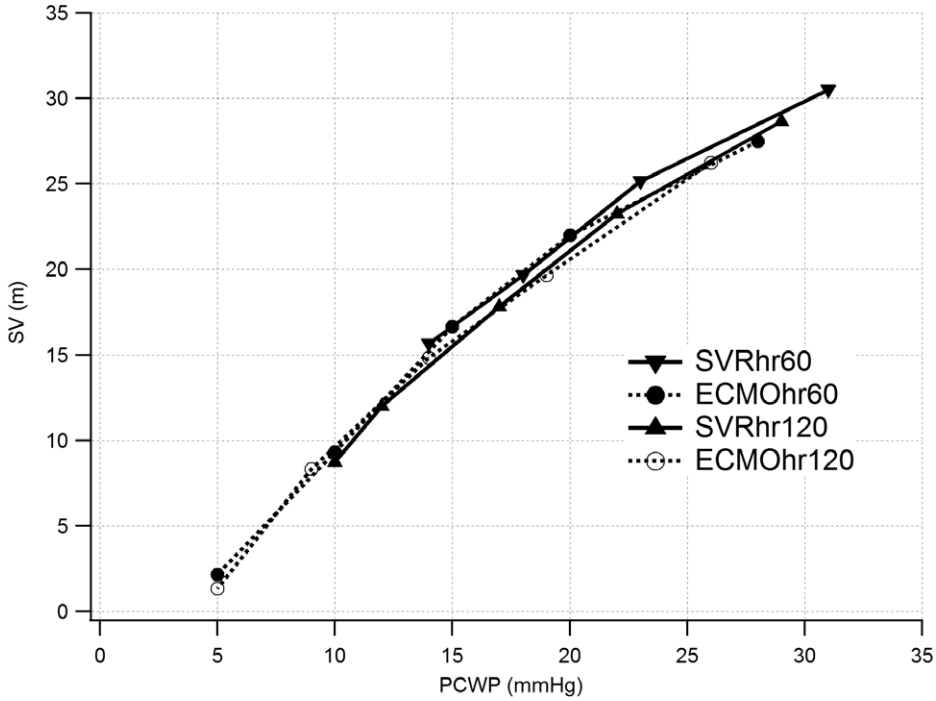


**Figure 4.** A series of Starling curves all generated during AHF at a fixed mABP of 80. Two of the curves were generated at a heart rate (HR) of 60, and the other two at a HR of 120. At each HR, one curve was generated by adjustment of SVR alone (SVRhr60,SVRhr120); the other curve was generated during VA ECMO flow and adjustment of SVR (VADhr60,VADhr120). The curves are virtually identical under all conditions. AHF, acute heart failure; mABP, mean arterial blood pressure; SV, stroke volume; SVR, systemic vascular resistance; VA ECMO, veno-arterial extracorporeal membrane oxygenation.

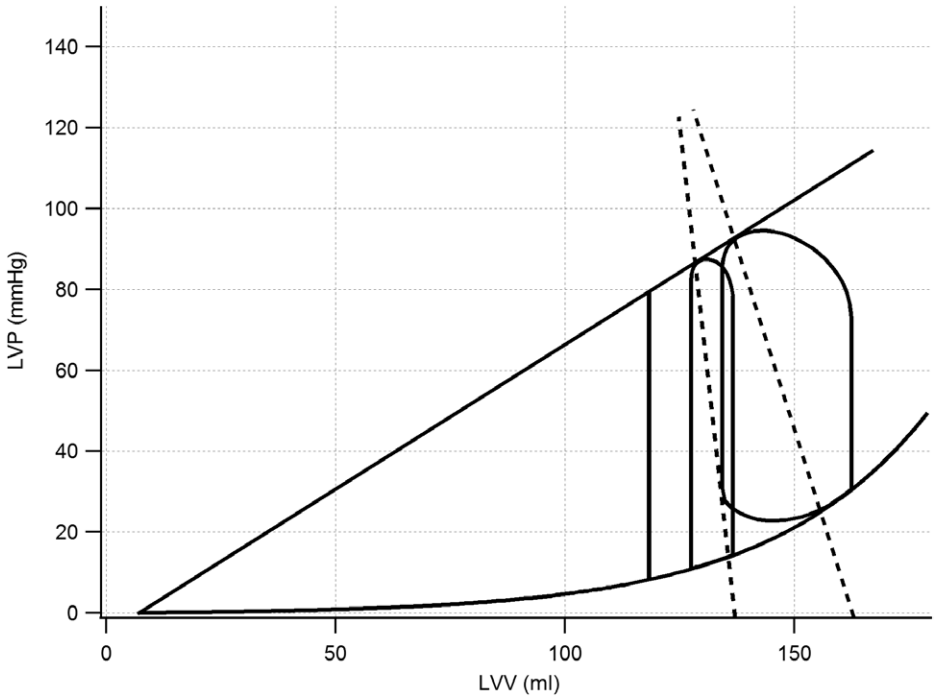


**Figure 5.** PV loops during AHF and VA ECMO flow with mABP held constant at 80 mm Hg. The flatted sloped of the ESPVR reflects the reduction in contractility. As end-diastolic volume nears the end-systolic volume that corresponds to an end-systolic pressure of 80, afterload (the slope of the Ea line) shown in black approaches infinity, and SV approaches zero (the width of the PV loop); this would correspond clinically to the point at which the aortic valve ceases to open. AHF, acute heart failure; mABP, mean arterial blood pressure; PV, pressure–volume; SV, stroke volume; VA ECMO, veno-arterial extracorporeal membrane oxygenation.

a given end-diastolic volume and contractile state, the end-SV is determined by the end-systolic pressure irrespective of whether this pressure is fixed by changes in SVR or by changes in systemic ECMO flow.

The relationship between pre-ECMO EF and post-ECMO PCWP is shown in **Figure 6**. The pre-ECMO mABP did not affect this relationship as long as the post-ECMO mABP did not change. However, if the post-ECMO mABP increased, the curve shifted rightward.

## Discussion

The establishment of VA ECMO does not directly affect LV contractile function. Therefore, when LV afterload is held constant at a specific systemic pressure, the Starling curve generated before initiation of ECMO flow would predict the filling pressure associated with any target SV at that systemic pressure. Importantly, this study demonstrates that the mechanism by which that specific systemic pressure is achieved, whether by addition of ECMO flow or alterations solely in SVR, does not alter the relationship between filling pressure and native LV SV. The appreciation of the maintained Starling relationship may be useful to predict ventricular distension during ECMO support.

In scenarios where VA ECMO is established in the absence of cardiogenic shock, it is possible to directly measure PCWP and LV SV at a systemic blood pressure that is at or near a target value post-ECMO support. In this case, the additional systemic flow conferred by ECMO may be offset by volume reduction to a target LV SV; the consequence would necessarily be a reduction in PCWP. In scenarios where VA ECMO is established for cardiogenic shock due to right ventricle failure, PCWP is typically low and the LV is relatively afterload insensitive. Therefore, the shift in the Starling curve with the increase in systemic pressure is slight, and a modest increase in PCWP would accompany the increase in LV afterload assuming no significant change in LV SV.

In scenarios where VA ECMO is established for cardiogenic shock due to acute LV failure, the shift in the Starling curve is substantial due to the LV afterload sensitivity and affected by the magnitude in the change in systemic pressure. Therefore, if PCWP is already high before initiation of VA ECMO, and in the absence of immediate and substantial improvement in LV contractility, there necessarily will be a dramatic rise in PCWP with LV distension as afterload is increased.

Given the concerns about LV and pulmonary venous distension leading to acute pulmonary edema and blood stasis in the left heart leading to thrombus formation, it is imperative to both unload the central circulation while maintaining a minimal LV SV. Unlike the standard cardiopulmonary bypass circuit that contains a venous reservoir, the amount of venous return to the left heart during VA ECMO support cannot be reliably controlled; any volume bypassing the venous cannula or coursing through the bronchial circulation is returned to the left heart; at steady state, this represents the LV output that adds to VA ECMO flow in the systemic circulation. While this additional flow may be altered by changes in circulating blood volume (*e.g.*, diuresis), this study underscores that the LV will require a specific preload to deliver a target SV (to prevent blood stasis) at a specific mABP. With a target SV of 30 ml, it is apparent that the risk of ventricular distention after initiation of VA ECMO is related to the preinitiation EF reflecting the impairment in

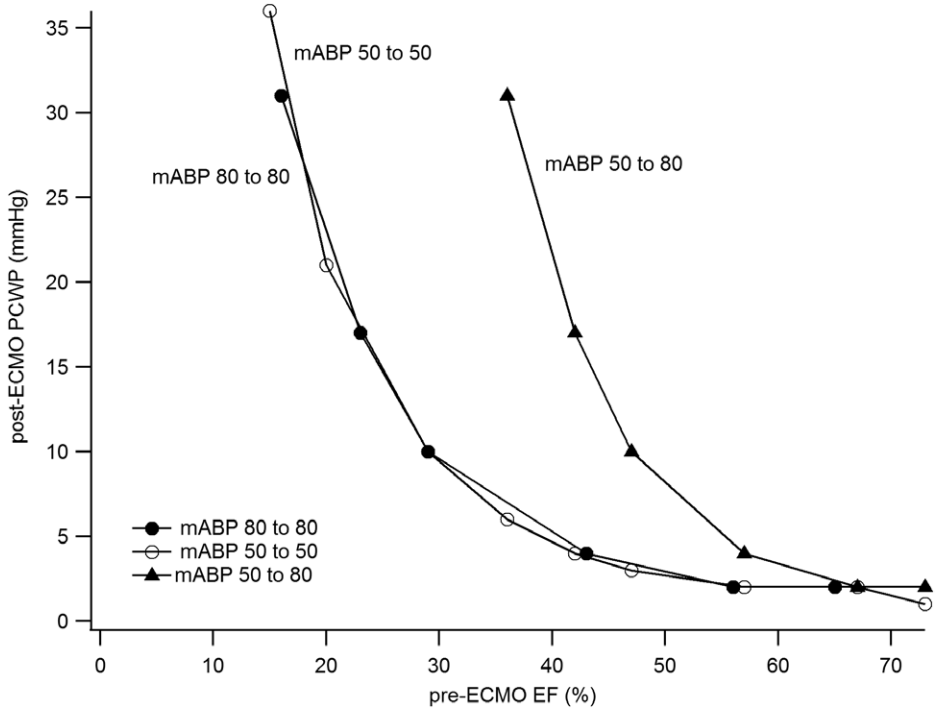


**Figure 6.** The relationship between pre-ECMO EF and post-ECMO PCWP at a post-ECMO SV held constant at 30 ml. As pre-ECMO EF is reduced, the post-ECMO PCWP increases. The tags on the graph indicate the pre- and post-ECMO mABP. The curves are virtually identical when the pre- and post-ECMO mABP are identical. However, when the mABP is raised from 50 to 80 mm Hg after initiation of ECMO, the curve is shifted to the right, reflecting the overestimation by EF of ventricular function. ECMO, veno-arterial extracorporeal membrane oxygenation; EF, ejection fraction; mABP, mean arterial blood pressure; PCWP, pulmonary capillary wedge pressure; SV, stroke volume.

LV contractility. When post-ECMO mABP is maintained the same as pre-ECMO mABP (*i.e.*, no change in afterload), an EF less than 30% was associated with high PCWP even after volume titration. However, given that EF is afterload dependent (with greater afterload sensitivity as contractile strength is reduced), even moderate reductions in pre-ECMO EF (less than 50%) were associated with high PCWP after initiation of ECMO when mABP increased as a result of VA ECMO support.

This study confirms that at any given target SV, the PCWP simply depends on LV contractility and mABP as the Starling relationship is unchanged by VA ECMO. Therefore, the initial hemodynamic evaluation of a patient being placed on VA ECMO should include an estimation of EF interpreted in the context of the anticipated change in mABP after initiation of VA ECMO. Placed in the setting of hypotension and cardiogenic shock, the increase in mABP after initiation of VA ECMO would be associated with a significant increase PCWP and decrease in LV SV.

Management of patients on VA ECMO should include careful attention to intravascular volume status, mABP, and PCWP. Volume status should be titrated to a minimally acceptable LV SV. The mABP should be carefully controlled by either titration of VA ECMO flow rates or by pharmacologic manipulation of SVR; PCWP is dependent on LV contractility and mABP but independent of the method by which mABP is controlled (at a given LV SV). Although typically interpreted as recovery of LV function, the appearance of pulsatility on the arterial waveform (signifying increased LV SV) may either reflect improvement in LV contractility or worsening volume overload; these two mechanisms may be distinguished by tracking PCWP or repeat echocardiographic assessment.

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