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EDITORIAL COMMENT

Vent to Prevent?*

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Cardiogenic shock is defined as a severe decrease in cardiac output, triggering a cascade of hypoperfusion and organ failure, and ultimately leading to death.[1] Venoarterial extracorporeal membrane oxygenation therapy (VA-ECMO) is increasingly used to treat cardiogenic shock because it provides sufficient tissue perfusion and thereby tackles the culprit of cardiogenic shock. However, there is a caveat, because VA-ECMO, which is most commonly deployed via femoral vessels in cardiogenic shock, provides retrograde perfusion of the aorta and, therefore, an increase in left ventricular afterload.[2] It is feared that this increase in left ventricular afterload hampers myocardial recovery and negatively impacts on a patient's outcomes. To mitigate the negative hemodynamic impact of VA-ECMO in these patients and to promote myocardial recovery, it has been suggested to add a second device for active left ventricular unloading. This suggestion is based on the encouraging findings from retrospective analyses that indicate lower mortality risk with this approach, and is currently being tested in a prospective randomized controlled trial (UNLOAD-ECMO, NCT05577195).[3]

In this issue of *JACC: Basic to Translational Science*, Everett et al[4] looked closer by exploring the actual effects of active left ventricular unloading with vs without VA-ECMO on the myocardium. In a preclinical (porcine) model of acute myocardial infarction (via percutaneous occlusion of the left anterior descending artery), Everett et al[4] investigated differences in infarct size, pressure volume area, cardioprotective signaling, as well as mitochondrial function between 4 groups: 1) animals treated without any mechanical circulatory support; 2) those treated with VA-ECMO only; 3) those treated with active left ventricular unloading and then subsequently with VA-ECMO; and 4) those treated with VA-ECMO and then subsequently with active left ventricular unloading (for groups 2 to 4, devices were activated 30 to 45 minutes before reperfusion). Within this setting, the authors could show that VA-ECMO alone indeed increases infarct size despite reducing the pressure volume area (most likely because the increase in left ventricular afterload offsets the reduction in left ventricular preload). Importantly, concomitant use of active left ventricular unloading seems to mitigate the increase in infarct size observed with VA-ECMO, but only to the level of reperfusion alone (eg, without any mechanical circulatory support). Also, active left ventricular unloading on top of VA-ECMO, but not VA-ECMO alone, triggered cardioprotective signaling and reduced the level of apoptosis, although neither set-up reversed mitochondrial dysfunction. Investigating the relevance of sequence of device activation furthermore showed that active left ventricular unloading before, but not after, VA-ECMO activation reduced the pressure volume area.

Obviously, these findings are subject to certain biases. Aside from the general bias that applies when findings from animal studies are transferred to actual patients, the most relevant bias seems to be that the experiments were conducted in healthy animals. In clinical practice, patients presenting with severe cardiogenic shock are very likely to have either a high comorbidity burden and/or to be affected by several disease modifiers, such as concomitant respiratory failure or prior cardiac arrest. These factors might dilute the potential beneficial effect of active left

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ventricular unloading, or any other intervention, but introducing competing risks (eg, higher risk of anoxic brain injury in patients after cardiac arrest). Additionally, all devices were implanted under perfect conditions and after ample preparation in this experiment, whereas in clinical practice, devices are usually implanted in critically ill patients and under suboptimal circumstances, introducing the risk of device-related complications (eg, access-site bleedings).

Nevertheless, these findings are relevant to the field and are of utmost interest because they provide pathophysiological rationale for the use of active left ventricular unloading during VA-ECMO, but also indicate a need for more research. These findings confirm: 1) the initial hypothesis that the artificial increase of left ventricular afterload with VA-ECMO has negative effects on left ventricular function and recovery; 2) that concomitant use of active left ventricular unloading can mitigate these effects; and 3) that active left ventricular unloading should best be used before, not after, initiation of VA-ECMO. This is in line with previous clinical (retrospective) studies advocating for early left ventricular unloading in patients with cardiogenic shock and treated with VA-ECMO.[5] However, these results also show that the ceiling here is the level of injury from reperfusion alone, and that other factors outside of load parameters are key drivers of myocardial injury in this setting - venting the left ventricle seems to prevent the VA-ECMO-associated damage, but does not seem to mitigate the overall damage associated with reperfusion injury. By unraveling this, the authors urge us to not solely lean on counteracting the negative hemodynamic consequences of VA-ECMO, but to look beyond the "hemodynamic pictures," acknowledging that cardiogenic shock is a multifaceted disease.[1]

Ultimately, this study is a good example for translational research going from bedside to bench—after observing a potential benefit in clinical practice, Everett et al[4] made a great effort to provide the "how" in their experimental research. This is important because we can only fully optimize the application of a given intervention in clinical practice if we really understand its effects on all relevant levels.

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REFERENCES

1. Naidu SS, Baran DA, Jentzer JC, et al. SCAI SHOCK stage classification expert consensus update: a review and incorporation of validation studies: this statement was endorsed by the American College of Cardiology (ACC), American College of Emergency Physicians (ACEP), American Heart Association (AHA), European Society of Cardiology (ESC) Association for Acute Cardiovascular Care (ACVC), International Society for Heart and Lung Transplantation (ISHLT), Society of Critical Care Medicine (SCCM), and Society of Thoracic Surgeons (STS) in December 2021. *J Am Coll Cardiol*. 2022;79:933–946.

2. Schrage B, Burkhoff D, Rubsamen N, et al. Unloading of the left ventricle during venoarterial extracorporeal membrane oxygenation therapy in cardiogenic shock. *J Am Coll Cardiol HF*. 2018;6:1035–1043.

3. Schrage B, Becher PM, Bernhardt A, et al. Left ventricular unloading is associated with lower mortality in patients with cardiogenic shock treated with venoarterial extracorporeal membrane oxygenation: results from an international, multicenter cohort study. *Circulation*. 2020;142:2095–2106.

4. Everett KD, Swain L, Reyelt L, et al. Transvalvular unloading mitigates ventricular injury due to venoarterial extracorporeal membrane oxygenation in acute myocardial infarction. *J Am Coll Cardiol Basic Trans Science*. 2023;8:769–780.

5. Schrage B, Sundermeyer J, Blankenberg S, et al. Timing of active left ventricular unloading in patients on venoarterial extracorporeal membrane oxygenation therapy. *J Am Coll Cardiol HF*. 2023;11:321–330.

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