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Editorial

Left ventricular unloading during VA-ECMO: A Gordian knot of physiology

Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is a powerful hemodynamic support strategy for patients with cardiogenic shock and out-of-hospital cardiac arrest (OHCA).[1,2] Given that significant proportions of patients presenting with cardiogenic shock and refractory OHCA exhibit critical underlying coronary disease,[3–6] VA-ECMO provides the stability necessary for revascularization and, therefore, treatment of the underlying aetiology of the arrest. The ongoing cardiopulmonary support then mitigates risk of rearrest and supports recovery of end-organ function while minimizing the harmful effects of vasopressors and ventilator support.[7,8]

Expert centres have shown that VA-ECMO can produce considerable cardiac recovery[9] and survival benefit[6,10–16] when used as part of extracorporeal cardiopulmonary resuscitation (ECPR) strategies for patients who suffer OHCA from acute coronary syndrome. Although ECPR is becoming more widely used to treat OHCA, OHCA continues to have a lethal prognosis for most patients. Accordingly, clinicians have focused on how to optimally deploy VA-ECMO and ECPR strategies to further improve patient outcomes. One proposed solution has been the widespread use of left ventricular (LV) venting or unloading strategies to limit the hypothetically detrimental effects of VA-ECMO.

In this issue, Nishimura *et al* evaluated the association between unloading with an intra-aortic balloon pump (IABP) and 30-day survival in patients who suffered from acute coronary syndrome and were treated with ECPR.[17] In their investigation, they evaluated patients from the SAVE-J II registry and compared 30-day survival between 702 patients who received unloading with an IABP after VA-ECMO placement to 175 patients who did not receive an IABP with VA-ECMO. They did not find any significant differences in survival to discharge, 30-day survival or favourable neurological status at 30 days between the two groups in adjusted analyses. The authors should be commended for focusing on this key question and on a specific sub-group in a well-phenotyped registry.

This investigation had several key limitations. Importantly, as stated by the authors, there was no protocolized approach to IABP utilization with potential differences between hospitals and physicians. The difference in IABP placement frequency implies selection bias toward early IABP usage in patients with favourable arrest characteristics, particularly given key differences in rates of witnessed arrest, bystander CPR, and arrest in an ambulance. The prevalence of coronary disease and revascularization also suggests selection. Vascular complications and length of stay were not compared between the two groups.

Other investigations have suggested that LV unloading may improve survival in patients with acute coronary syndrome treated with ECPR. Gaisendrees *et al* performed a matched cohort study to compare survival between 18 patients who also received a percutaneous ventricular assist device (pVAD) and 90 patients who did not.[18] The authors found a survival benefit in patients treated with ECPR and concomitant pVAD in unadjusted analyses. Adjusted analyses were understandably not performed in this small study, leaving the study susceptible to residual confounding. Thevathasan *et al* later performed a propensity-matched analysis among patients to compare survival between patients who also received a pVAD and those that did not as part of an ECPR strategy.[19] While concomitant treatment with a pVAD was associated with improved survival, the overall survival rate of the ECPR cohort was ~10%. This is well below published rates in expert centres (~30–40%).[6,11,14] The differences in survival outcomes suggest that we, as a field, are missing key details in clinical trial design.

How, then, does the field reconcile these conflicting data?

We suggest that the best way to break the Gordian knot of unloading is to refine our understanding of VA-ECMO physiology.

Left ventricular unloading has been theoretically proposed to have two main physiologic benefits in patients on VA-ECMO: (1) reduction in left ventricular afterload and (2) a reduction of LV preload and, consequently, pulmonary vascular pressures – particularly pulmonary capillary wedge pressure. However, these theoretical benefits are not supported by strong physiologic data.

There is a conspicuous dearth of invasive hemodynamic data from humans to confirm that there is a significant rise in LV afterload with VA-ECMO and that it is actually deleterious to LV function. In fact, we have previously demonstrated with invasive left heart catheterization that this rise in afterload is modest.[20] Further, robust LV recovery has been demonstrated in patients with refractory OHCA who are treated with ECPR without routine unloading.[6,11,14]

Current dogma suggests that the rise in LV afterload leads to a concomitant rise in LV end-diastolic pressure (LV preload).[21] This is hypothesized to lead to LV ballooning and further LV injury in the setting of cardiogenic shock and/or OHCA. This dogma also conflicts with emerging real-world hemodynamic data. We have shown that high VA-ECMO flow considerably reduces LV end-diastolic pressure compared to low VA-ECMO flow.[22] Further, we believe that the dramatic decrease in LV preload that VA-ECMO produces is far more energetically important to the ailing LV. We demonstrated this by showing that total LV energetic consumption (as measured by LV

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pressure–volume area) was significantly lower on high VA-ECMO flow *despite* the modest increase in afterload. Thus, the theoretical dogmas related to LV afterload and LV preload appear to be contrary to real-world, invasive hemodynamic human data.

The traditional assumptions regarding LV afterload, LV end-diastolic pressures, and pulmonary pressures may not apply with VA-ECMO. Pulmonary capillary wedge pressure is assumed to reflect LV end-diastolic pressure and LV loading during VA-ECMO support.[23] We believe that this is an inaccurate assumption. We have previously demonstrated that pulmonary capillary wedge and LV end-diastolic pressures were discrepant in patients on VA-ECMO who underwent simultaneous left and right heart catheterization.[20] Many patients suffering from OHCA have dysrhythmias, profound reductions in atrial function/compliance, and significant intrapleural elevation due to lung and chest wall injury. These may cause the discrepancies between the pulmonary capillary wedge pressure and LV end-diastolic pressure.

Left ventricular unloading is also thought to prevent LV thrombus. This has been appropriately used as a justification for LV unloading. However, one case series reported an incidence of just 4% of LV thrombus among 281 patients treated with VA-ECMO using an activated clotting time goal of 160–180 s.[24] Therefore, this relatively infrequent occurrence seems to be insufficient justification for the routine use of unloading.

We propose several solutions to addressing the discrepancies between clinical data. Firstly, we propose hemodynamic studies that evaluate cardiac physiology immediately after VA-ECMO initiation. Given that this is thought to be the most sensitive time for the ailing LV, this may offer key insights into how VA-ECMO initiation affects native cardiac physiology. Secondly, we propose in vivo hemodynamic studies to be repeated with unloading strategies in place. These should measure ventricular and pulmonary pressures separately. Finally, we propose that the physiology of specific, high-risk patient groups be studied carefully. Patients with univentricular LV dysfunction and recovered RV function may represent one group that may benefit from unloading, as the recovered RV may lead to loading of the pulmonary circuit despite venous unloading by VA-ECMO. We suggest that these benchmarks are achieved before clinical studies randomize patients and expose patients to unnecessary harm from unloading.[25]

In summary, the discrepant clinical outcomes for routine LV unloading are in the context of limited physiologic evidence in patients receiving VA-ECMO. The study by Nishimura *et al* confirms this. Therefore, rather than conducting large, resource-intensive patient-based clinical trials, the disentanglement of the Gordian knot of unloading requires a much more direct solution – a refined understanding of the physiology of VA-ECMO and unloading in vivo. Only when the physiology of VA-ECMO is directly understood can clinicians better understand the value proposition of LV unloading.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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