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EDITORIAL COMMENT

ECMO

We Need to Vent About the Need to Vent!*

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The use of venoarterial extracorporeal membrane oxygenation (VA ECMO) to support patients with cardiogenic shock and cardiac arrest has been expanding at a rapid pace over the past decade. With increased experience, clinicians have gained both a deep appreciation for the therapeutic benefits of ECMO and a healthy respect for associated adverse events. Despite 50 years of ECMO research, this unique form of circulatory support continues to ignite debate among clinicians concerning many aspects of how to optimize its use for best clinical outcomes across the wide spectrum of patients for which it is used.

One such debate relates to the need for and the optimal timing and type of a left ventricular (LV) venting strategy to counteract the potential overloading effects on the left ventricle that can occur during VA ECMO support. Several LV unloading strategies are available and recent advances have made them easier to deploy and use.[1,2] However, the interactions between a patient's cardiovascular system, the ECMO machine, and an additional unloading device are complex, multifactorial, and dynamic. In the absence of clear data, an understanding of fundamental hemodynamic principles can help guide daily clinical decision making. In the end, however, robust clinical evidence is needed to address unresolved questions to achieve optimal patient care.

In this issue of the *Journal of the American College of Cardiology*, Grandin et al[3] set out to address several of these critical questions related to mechanical venting strategies in an extensive analysis performed on data from the Extracorporeal Life Support Organization (ELSO) Registry that includes >12,000 patients who received VA ECMO over a time span of almost 10 years. The analysis was restricted to adult patients with peripheral femoro-femoral cannulation and excluded patients with multiple VA ECMO runs, patients with pulmonary embolism, and patients with heart transplant, congenital heart disease, and

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valvular heart or aortic disease or where there could be anatomic considerations precluding a mechanical unloading strategy with an intra-aortic balloon pump (IABP) or temporary percutaneous ventricular assist device (pVAD). The main conclusions of the analysis are succinctly summarized by the authors: use of either an IABP or an Impella device (generically referred to as a pVAD) is associated with statistically better survival despite increased complications and that pVAD use is associated with more complications despite comparable survival with IABP. So, for the practicing clinician, based on the authors' conclusions, do the results of this study mean, as implied, that all ECMO patients should be treated with an IABP? No; and it is highly unlikely that clinical specialists, despite this conclusion, will interpret the findings that way. There are a number of reasons as to why this conclusion is unwarranted.

MAGNITUDE OF THE EFFECT

It is first important to consider the magnitude of the effect identified. In-hospital mortality was 59.3% of 9,335 patients without mechanical unloading

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compared to 56.6% of 3,399 patients with unloading ($P = 0.006$), an absolute difference of 2.7%. The results were similar following 1:1 propensity matching of 3,079 patients: 58.6% mortality without unloading compared to 55.8% morality with unloading, with an absolute difference of 2.8% ($P = 0.026$). This means that the number needed to treat with unloading to save 1 life is ~30. Stated another way, 29 of every 30 patients treated with a mechanical unloading device would be exposed to the risks of the device without receiving a positive impact on their survival.

TIMING AND DURATION OF UNLOADING INTERVENTION

Of the registry patients receiving mechanical unloading, 86.4% had the device in place before initiation of ECMO support. This implies that, in the mechanically unloaded cohort, ECMO presumably represented an escalation or intensification of therapy from an existing therapy that was considered ineffective; not necessarily an indication of upfront or pre-emptive use of an unloading strategy. Furthermore, the database lacks information concerning the time in shock before first therapy, the duration of first therapy before ECMO, and timing of ECMO initiation relative to the onset of shock, each of which can be considered a critical determinant of outcome. Importantly, the study also lacks information regarding how long the unloading devices were left in place following ECMO support. Thus, patients in whom devices were removed very shortly after initiation of ECMO would have been grouped along with those in whom devices remained in place for days. These uncertainties further complicate the primary findings because these factors cannot be accounted for even with multiregression analyses or propensity matching. Thus, even as implied by the authors, the conclusion that outcomes were not influenced by the timing of unloading is at best tenuous.

IABP VS pVAD

In addition to the major limitations noted above, the comparison of outcomes with IABP versus pVAD as the form of mechanical unloading is further complicated by additional key factors. pVADs are underrepresented compared to IABPs (580 vs 2,782 of 12,734 total patients) and the rapid technological evolution in recent years towards more powerful devices (eg, from Impella 2.5, to Impella CP, to Impella 5.5) has not been taken into account. There is no assessment of the number of patients who received both an IABP and pVAD. Finally, different centers or individual practitioners have different criteria for the use of IABP and pVAD. None of these important factors can be accounted for making the validity of conclusions related to IABP versus pVADs uncertain.

STUDY LIMITATIONS

As with any retrospective study, the inherent methodological limitations are appropriately acknowledged by the authors. Such limitations are of particular importance in retrospective analyses of therapies for cardiogenic shock. Although it is assumed that multiregression analyses, propensity matching, and imputation solve problems related to complete unavailability of key parameters and missing data, we must question whether this is indeed the case, especially when many of the parameters in question noted above have such a fundamental impact on outcomes.

RATIONAL USE AND STUDY OF MECHANICAL UNLOADING DURING ECMO

The analysis performed by Grandin et al[3] purports to approach the issue of unloading, in essence, as whether or not it should be used in all patients. Demonstrating a reduction of mortality from ~59% to ~56% in a retrospective analysis, especially considering all the inherent limitations of a retrospective analysis as listed above, is not likely to provide convincing sufficient evidence to influence clinical practice. Nor should it! Indeed, most clinicians take a more measured approach, basing the decision on multiple factors aiming to tailor ECMO settings and the choice and timing of an unloading strategy to match the circulatory needs of individual patients especially those with evidence of LV overload. There is little debate that clinical factors such as echocardiographic evidence of minimal aortic valve opening; “smoke” in the left atrium, left ventricle, or aorta (indicating stasis of blood); reduced arterial pulse pressure; or edema on a chest x-ray (especially when occurring in clusters) require intervention to enhance blood flow through the heart.[4] When available, pressures measured by a pulmonary artery catheter provide specific, objective evidence of LV overload which should also trigger an LV unloading intervention. Careful monitoring and timely intervention minimizes putting the heart and lungs under undue hemodynamic stress and, in principle, enhances the likelihood of heart recovery and overall survival. Ultimately, these outcomes are what an appropriately designed prospective clinical trial of mechanical unloading should strive to investigate. Enriching a study’s population with patients who show evidence

of stasis and/or LV overload who would be more likely to benefit from an unloading strategy could potentially show a greater benefit (while minimizing the number exposed to risk without benefit) than when applied indiscriminately to all ECMO patients. This is not easily achievable in a retrospective study. Such a prospective study could also incorporate protocolized routine conservative measures to address overload such as lowering arterial blood pressure, reducing intravascular volume, and reducing extracorporeal flow to acceptable levels before progressing to a mechanical unloading strategy.[1,2]

The authors state in their introduction that "uncertainty remains about a net benefit of [mechanical unloading] during VA ECMO." In the end, we more or less wind up in the same place—"uncertainty remains." It is an obvious conclusion that prospective, randomized studies are required. This study should serve as the clarion call to initiate a prospective randomized trial to address the uncertainty that currently exists. Until robust evidence is generated from such a trial, what is a clinician to do in the meantime? We would encourage use of an unloading strategy based on active, frequent monitoring of clinical, imaging, and hemodynamic evidence of LV overload not responsive to conservative maneuvers. Such monitoring should continue after initiation of unloading to ensure its effectiveness and guide further refinement as needed.

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