Rev Esp Cardiol. 2025;78(6):504–506

Editorial comment

VA-ECMO and ventricular unloading. A game-changer or just a glimmer of hope?

ECMO-VA y descarga ventricular. ¿Una estrategia que puede marcar la diferencia o solo un rayo de esperanza?

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Article history:
Available online 20 December 2024

The use of venoarterial extracorporeal membrane oxygenation (VA-ECMO) for circulatory support in patients with cardiogenic shock (CS) has increased significantly in the past decade. There is, however, a lack of robust scientific evidence on the survival benefits of this strategy.[1,2] It is important to note that VA-ECMO is not a ventricular assist device and that the circulatory support it provides can increase peripheral vascular resistance, impeding adequate left ventricular (LV) unloading. Inadequate LV loading increases filling pressures in the left-sided heart chambers, potentially leading to coronary ischemia, pulmonary congestion, and intracavitary thrombosis. Several strategies for unloading the left-sided chambers have been employed to mitigate these effects. The strategies, which can be combined, include pharmacological approaches with inotropes and diuretics and mechanical methods involving additional mechanical circulatory support (MCS) devices.[3] Interactions between the cardiovascular system, VA-ECMO, and an additional unloading device, however, are complex, multifactorial, and dynamic. Numerous observational studies have reported a potential survival benefit associated with the use of MCS unloading devices in patients receiving VA-ECMO.[4] One study of nearly 13 000 patients from the Extracorporeal Life Support Organization registry found that approximately 25% of patients on VA-ECMO were managed with mechanical LV unloading.[5] While the patients experienced more complications, they had higher in-hospital survival (59.3% vs 56.6% for those on VA-ECMO only, $P = .006$). It is worth highlighting, however, that the absolute reduction in mortality was less than 3% and that this benefit did not improve after propensity score matching. In other words, for every 30 patients receiving an MCS device to facilitate unloading, 1 would survive, but 29 would be exposed to complications without receiving a survival benefit.

Several hypotheses have been proposed to explain the neutral results observed in the ECLS-SHOCK trial. One of the main criticisms is that just 5.8% of patients in the VA-ECMO group received active LV unloading.[6] These criticisms gained further relevance when the DanGer (Danish-German Cardiogenic Shock) trial evaluating the use of a percutaneous ventricular assist device (pVAD) (Impella CP; Abiomed, USA) in patients with CS and acute myocardial infarction (AMI) showed lower mortality in the pVAD group than in controls (45.8% vs 58.5%, $P = .04$).[7] The findings suggest that patients managed with devices that directly unload the LV are more likely to experience cardiac recovery.

Three ongoing clinical trials are investigating the effects of unloading on outcomes in patients receiving VA-ECMO. The UNLOAD ECMO (NCT05577195) and REVERSE (Impella CP With VA-ECMO for Cardiogenic Shock, NCT03431467) trials are evaluating the ability of the Impella CP device to reduce mortality and improve myocardial recovery, while the ANCHOR (Assessment of ECMO in Acute Myocardial Infarction Cardiogenic Shock, NCT04184635) trial is addressing the limitations of VA-ECMO by comparing VA-ECMO combined with intra-aortic balloon pump (IABP) and optimal medical treatment in patients with AMI and CS.

Many authors argue that the benefits of unloading depend on both choice and timing of method. Several observational studies have shown that early unloading can improve prognosis. Schrage et al.[8] showed that implantation of a pVAD within 2 hours of VA-ECMO initiation was associated with a 36% relative risk reduction in 30-day mortality compared with late unloading.[8] Several mechanisms may explain these findings. On one hand, animal model studies have shown that early unloading can activate cardioprotective signaling pathways and reduce apoptosis levels in AMI.[9] On the other hand, unloading may enhance coronary flow and mitigate reperfusion injury, ultimately reducing infarct size.[10] Although these findings would appear to suggest a clear need for early unloading, it should be noted that 2 randomized trials found no impact for unloading with transseptal cannulation on 30-day mortality.[11,12]

CAN VENTRICULAR UNLOADING IMPROVE HEART TRANSPLANTATION OUTCOMES?

The use of VA-ECMO as bridging therapy for patients awaiting heart transplantation (HTx) has also seen significant growth worldwide, although its use in Spain has remained stable.[13] One

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https://doi.org/10.1016/j.rec.2024.09.005

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https://doi.org/10.1016/j.rec.2024.11.011

key factor that may partly explain this leveling off is the less favorable outcomes reported for VA-ECMO compared with other MCS devices in Spain.[14]

In a recent article published in *Revista Española de Cardiología*, Enríquez-Vázquez et al.[15] presented a retrospective analysis of 16 Spanish heart transplant centers that evaluated 245 patients undergoing HTx with VA-ECMO support between 2010 and 2020. The authors compared patients bridged with VA-ECMO and mechanical LV unloading (54.3%) vs VA-ECMO alone. Femoral cannulation was predominant in both groups (81.2%), and the most widely used unloading strategy was IABP (84.2%), followed by apical ventricular cannulation (9%). Surprisingly, a pVAD was used in just 2 patients. The primary outcome was 1-year post-HTx mortality, while secondary outcomes included incidence of primary graft dysfunction (PGD) and other complications such as bleeding and infections. One-year post-HTx survival was 74.4% in the VA-ECMO unloading group and 59.8% in the VA-ECMO-only group ($P = .025$). Multivariate analysis showed that unloading was associated with a reduction in 1-year mortality (adjusted hazard ratio = 0.50; 95%CI, 0.32-0.78; $P = .003$), with no significant differences observed between IABP and other devices.

First of all, we would like to congratulate the authors on their efforts to test a hypothesis of major clinical importance that remains unanswered. However, we consider that the 15% reduction observed in 1-year mortality is strikingly higher than previously reported rates. A recent study of the United Network for Organ Sharing (UNOS) registry analyzed 624 patients undergoing HTx with VA-ECMO support between 2018 and 2023; 240 of the patients (38.5%) were managed with LV unloading (106 with Impella and 134 with IABP). Survival rates were comparable between the groups (88.0% for VA-ECMO alone vs 90.4% for VA-ECMO unloading, $P = .92$), and no significant differences were observed after multivariate analysis and adjustment for device type.[16] The discrepancies between the findings of the Spanish and UNOS registries are notable. Possible explanations related to the UNOS cohort include greater clinician experience, better patient management, and more recent data. Temporal trends are also evident in the study by Enríquez-Vázquez et al.,[15] who, on comparing data for 2010-2014 and 2017-2020, detected an improvement of approximately 20% in the VA-ECMO unloading group and 10% in the nonunloading group. These findings suggest the existence of a national learning curve for the treatment of these patients that may not have been fully captured by the adjustment methods employed.

As with any retrospective study, it is important to consider methodological aspects when interpreting results. Although regression analyses can mitigate some issues related to differences in key variables between groups, the study had 2 distinct populations: an LV unloading group with a profile consistent with AMI-related CS (smaller LVs, fewer devices and prior arrhythmias, more mechanical ventilation, and cardiac arrest) and a VA-ECMO-only group with a CS profile more closely linked to progressive heart failure. It is unlikely that multivariate analysis could account for all possible differences in this context. Propensity score analysis or inverse probability weighting for LV unloading might have provided better adjustment for the differences between the 2 groups. Likewise, decisions to use LV unloading are often dictated by institutional protocols or local practices not accounted for in the analysis. Center heterogeneity should have been addressed using a mixed-effects model, as higher-volume centers may well have used LV unloading more frequently. Greater use of LV loading may partly explain the differences observed.

The authors suggest that the 1-year mortality difference observed in the LV unloading group could be due to improved hemodynamics and clinical status. If this were the case, however, one would also expect to see a significant difference in early survival ($P = .134$ for 30-day survival) or a higher PDG rate (this difference was also nonsignificant). It is difficult to believe that the benefits conferred by LV unloading in patients on VA-ECMO—estimated as being much smaller in other registries—would have been so great as to improve survival beyond 30 days without affecting PGD, the main risk factor for early posttransplant mortality. Cause of death could have helped clarify whether improved hemodynamics could have plausibly contributed to the reduction in mortality observed, but this information was not reported.

Timing of follow-up initiation is another critical consideration. The authors started follow-up at the time of HTx. We believe that to properly assess the effects of LV unloading, they should have adjusted for PDG, as they did for ischemia time. PDG is a catastrophic complication typically detected within 24 hours of HTx. The authors also did not adjust for other factors linked to PGD and previously found to be associated with lower postoperative mortality by the same group. Examples include early and peripheral VA-ECMO cannulation.[17]

Starting follow-up at the time of HTx rather than VA-ECMO cannulation leaves the fundamental question the authors sought to address unanswered: whether VA-ECMO combined with LV unloading improves survival. We believe that this question remains to be resolved, especially considering that we do not know what proportion of patients in each group died before being placed on the HTx wait list or while on the list. Larger studies have suggested that while LV unloading can improve survival, it can also lead to more complications. It is reasonable, therefore, to imagine that complications preventing inclusion on the HTx wait list were more common in the LV unloading group. Conversely, the combination of VA-ECMO with a pVAD might have facilitated VA-ECMO decannulation, potentially leading to better recovery rates, but just 2 patients in the registry received this treatment. Regardless, the analysis presented by the authors excluded patients who did not receive an HTx or who underwent transplantation while on pVAD support. The decision to exclude these patients may have led to significant selection bias that would have made it impossible to answer the question being posed.

In conclusion, the results of this analysis of the Spanish national registry should be interpreted with caution. We consider that the study compared not only different interventions but also different populations, and it also tested a biological hypothesis with low plausibility due to the minimal hemodynamic effects of IABP. Finally, its findings were probably affected by selection bias in the sample. Nevertheless, as mentioned earlier, the authors should be commended for seeking to address such a challenging question of immense interest. We hope that this study will stimulate further interest and pave the way for future research evaluating LV unloading as a strategy to improve survival in patients with CS being considered for HTx.

FUNDING

No funding sources were used for the preparation of this manuscript.

CONFLICTS OF INTEREST

A. Uribarri has received fees for participating in expert panels sponsored by Johnson & Johnson. I. Ferreira-González has received fees for participating in expert panels sponsored by Biotronik. E. Ródenas-Alesina declares no conflicts of interest.

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