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EDITORIAL

Cardiogenic Shock: Searching for a Better Lifeboat

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Over the past decade, there has been increasing interest in cardiogenic shock (CS), with several approaches being tried to reduce the ≈50% mortality observed at 30 days following diagnosis.[1] The landscape is dominated by a scant evidence base, and those trials that exist have been uniformly disappointing. The largest trial in this space was a randomized trial of intra-aortic balloon pump (IABP) versus standard of care following percutaneous coronary intervention complicated by CS and showed no survival benefit of IABP placement in CS complicating acute myocardial infarction.[2] The microaxial continuous flow pump (Impella CP) was compared with the IABP in a small but critically ill population of patients with acute myocardial infarction and CS, and no difference in mortality was seen comparing the more potent pump with one that is associated with variable but lesser support.[3] Concurrent with these trials has been the exponential increase in the use of venoarterial extracorporeal life support (VA-ECLS), which provides a more robust hemodynamic support than either IABP or percutaneous microaxial flow pumps. The cost of equipment to support a patient with VA-ECLS is relatively modest, and many components are already used in centers with cardiac surgery programs. VA-ECLS is the most versatile platform, suitable to provide selective or complete biventricular support, depending on the cannulation strategy selected, and in some ways represents a lifeboat for patients on a proverbial sinking ship.

See Articles by Sperotto et al. and Hendrickson et al.

Increasing ECLS use has led to the recognition of the abnormal physiology imposed by retrograde aortic perfusion; in contrast to centrally cannulated cardiopulmonary bypass, which leads to decompression of the heart and lung circulation, peripheral VA-ECLS causes flow-dependent increases in left ventricular afterload, and clinical sequelae in critically ill patients.[4] Reports of catastrophic left ventricular clot formation, pulmonary vascular congestion, and poor rates of recovery of left ventricular function have led to hybrid strategies, including VA-ECLS and the addition of a "venting" strategy to reduce left ventricular pressure overload and enhance myocardial recovery.[5–7] This is analogous to a leaky lifeboat, which is sustained by throwing water overboard as quickly as it accumulates. Such strategies vary from use of the IABP to reduce afterload intermittently, to implantation of an Impella device, as well as use of balloon atrial septostomy to "decompress" the left heart (which is pressurized by VA-ECLS).[5,8,9]

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The use of the Impella series of catheters to "unload" the left ventricle is based on sound logic and machine simulations of hemodynamics, and it is reinforced by case series and experience.[5,8–11] However, given the relative dearth of trial data in CS, there have not been any prospective trials to support the use of VA-ECLS in patients with CS (with or without "unloading/venting"). Therefore, we are left to look at registry data for clues to the ultimate truth.

In this issue of the *Journal of the American Heart Association* (*JAHA*), Hendrickson and colleagues[12] provide a valuable analysis to shed light on the debate over venting in VA-ECLS. Using the Nationwide Inpatient Sample from 2016 to 2018, the authors identified 12 035 patients undergoing VA-ECLS (3% of a total of 460 040 patients admitted with CS during this time period). They further segmented the population into those with a second simultaneous mechanical circulatory support device (4595/12 035, 38%) and analyzed outcomes for these patients with a "vent." Most were cases with the second device placed following institution of VA-ECLS, although the granularity of detail in the Nationwide Inpatient Sample is limited. The authors examined 30-day survival comparing patients with and without the second device. The key results were that the use of the Impella for patients undergoing VA-ECLS dramatically increased over the time period studied (from 10% of patients to 18%; $P<0.001$), whereas the increase in IABP use in this hybrid approach was fairly minimal (from 25% to 26%; $P<0.001$). The final 6 months of 2018 saw the rate of dual mechanical circulatory support device use for VA-ECLS at 41% of patients, with 26% receiving IABP and 16% using Impella.

One would hope that with the large numbers of patients, real-world data, and the significant expenses incurred that there would be an evident benefit in this approach, which seems clinically logical but untested. Unfortunately, this was not the case. Despite careful multivariate adjustment, there were no differences in mortality or length of hospital stay with IABP/VA-ECLS, Impella/VA-ECLS, or VA-ECLS alone. Two device patients (either IABP or Impella) were less likely to be discharged to skilled nursing facilities. Several sensitivity analyses were conducted to assess various subpopulations. Limiting the data to those patients who underwent the second mechanical circulatory support device within 48 hours of VA-ECLS initiation resulted in a neutral effect on mortality with Impella but decreased odds of mortality in patients treated with IABP therapy. When examining only patients with acute myocardial infarction and CS, the mortality of patients undergoing VA-ECLS alone increased over the study period (from 61% to 63%) but was lower with a 2-device approach (from 62% to 59%; $P<0.001$ for all).

The overall message of this Nationwide Inpatient Sample analysis is that use of the second device for VA-ECLS is increasing, mortality is stagnant and extremely high, especially in the setting of acute myocardial infarction and CS, and neither device class seems particularly superior.

Although the preceding analysis focused specifically on adults, Sperotto and colleagues examined a different population and came to more definitive conclusions.[6] They used the Extracorporeal Life Support Organization database examining children with congenital and acquired heart disease undergoing open heart surgery with failure to wean from cardiopulmonary bypass. The authors identified risk factors for in-hospital mortality, and before adjustment, use of a surgical left atrial drainage method was associated with improved outcomes. There are no percutaneous methods of left cardiac decompression in children because IABP and transvalvular axial flow pumps are not suitable given their small body habitus, but the use of left atrial vent could be considered analogous to the active venting provided by Impella in adult patients. In the current study, the authors restrict the population to those children with biventricular failure physiology (not clearly defined in the article). The authors note that the group with left atrial decompression differed on a variety of demographics from those in whom decompression was not performed. To account for this, the authors constructed a propensity score reflecting the likelihood of left atrial decompression, and then used inverse probability of treatment weighting method to adjust the analyses to account for the differences in baseline characteristics.

The authors examined the Extracorporeal Life Support Organization registry from 2000 to 2016 and identified 2950 pediatric cases with failure to wean from cardiopulmonary bypass, of whom 600 were excluded for a variety of reasons, including not having failure to wean, and an additional 814 with "univentricular physiology" as opposed to biventricular failure. Mortality was 50% in this cohort of critically ill children developing postcardiotomy CS. In-hospital adverse events were grouped as a composite outcome, including heart transplant while on ECLS, conversion to a ventricular assist device, and all-cause mortality. In the unadjusted analysis, left atrial decompression trended to predict the composite ($P=0.078$), but the adjusted analysis showed left atrial decompression to be a significant predictor of lower composite outcomes (odds ratio, 0.775 [95% CI, 0.644–0.932]; $P=0.007$). Predictors of higher incidence of adverse outcomes included higher ECLS flow rate, longer ECLS support duration, and the occurrence of ECLS-associated complications. A flow rate of ≤97 mL/kg per minute of ECLS flow was used as the reference, and 60% of patients required ECLS flows exceeding 100 mL/kg per minute in this study. Adverse events escalated with increasing ECLS flow rate in a significant manner.

What conclusions can we draw from these 2 different studies that examined markedly different populations?

1. Patients with CS requiring ECLS present high mortality despite technological advances in ECLS devices. Both adults and children have a 30-day survival of 50%, despite markedly different scenarios. Adults without cardiac surgery (in the analysis by Hendrickson et al[12]) and children with postcardiotomy shock (in the study by Sperotto et al[6]) had similar poor outcomes. Furthermore, in children, there appears to be a dose-dependent increase in adverse events with higher pump flow. This may be attributable to timing of initiation of therapy. A significant component of the mortality observed may be related to delayed implementation when irreversible end-organ damage has ensued. We would likely obtain better clinical results with lower rates of complication if we initiated mechanical circulatory support at earlier stages. For example, there is growing experience with axillary IABP or Impella 5.5 in patients with advanced heart failure who receive ECLS in a more compensated stage of shock and remain on support with low rate of complications for several weeks, even resulting in improvement of end-organ function.[13,14]
2. ECLS is not cardiopulmonary bypass. Despite the similarity of equipment, the critical distinction is that ECLS pressurizes the left heart, whereas cardiopulmonary bypass (most frequently established with central cannulation) provides consistent and complete drainage of the heart and pulmonary circulation, leading to reduced cardiac metabolism and a decompressed left ventricle.
3. ECLS plus Impella or IABP is not benign, nor is either proven to be superior to ECLS without such devices. Other techniques, such as left atrial veno arterial extracorporeal membrane oxygenation "(LAVA-ECMO)," which incorporate a cannula traversing the left and right atrium, seem intellectually appealing but are limited to case series and involve significantly more complex pathways to insertion.[7,15]

Beyond the issue of unloading, one must question why there has been so little progress in identifying therapies that improve mortality in CS. We believe that there are several considerations that will be important going forward.

1. Shock severity should be assessed in trials and registries at the onset of care.[16] Retrospectively classifying shock severity by the treatment chosen (eg, number of drugs and devices) is convenient to analyze data sets but does not capture the fundamental distinctions between various stages of shock (eg, by the Society for Cardiac Angiography and Intervention classification). For example, deterioration (Society for Cardiac Angiography and Intervention D) is not simply the use of a mechanical circulatory support device and an inotrope, but an assessment of a downward clinical trajectory.[17] By collecting data in this manner, differences in responses to treatment (if they exist) might be found and leveraged to build evidence for best practices when managing CS.
2. Granular detailed registries that capture longitudinal data about patients with CS and the responses to therapy are more likely to identify strategies that improve mortality than prospective randomized trials.[18] Although the highest level of evidence is a prospective randomized clinical trial, the difficulties with enrollment, inherent selection bias, and complete failure of prior prospective trials (with the exception of the should we emergently revascularize occluded coronaries for cardiogenic shock [SHOCK] trial[19]) suggest that a new strategy is warranted.
3. Research should focus on fundamental understanding of the transitions of stages of shock. When does the patient transition from "pump-responsive" phenotype (where sufficient cardiac output augmentation will reverse the physiologic derangements noted) to the "pump-unresponsive" phenotype (ie, cardiometabolic shock[20]) where augmentation of cardiac output does little to reverse the calamitous cycle of hemodynamic collapse? This is a similar situation to that of septic shock, which has few treatments and many failed interventions. Examining biomarkers in patients in a serial manner may give insights into the deranged pathways and allow targets for intervention to be identified.
4. Postcardiotomy shock should be carefully investigated as a unique entity and one that has the advantage of a clear timing of insult (cardiac surgery/cardiopulmonary bypass). Other forms of CS have heterogeneous types of inciting insult (acute coronary syndrome, heart failure, and others), timing that is unclear or sometimes unknown, and a monitoring environment that is often variable. On the other hand, postcardiotomy shock occurs with clear chronology, granular data on elements, such as vital signs, transfusions, and drug infusions, and frequent laboratory measurements. It is possible that mechanisms identified in the setting of postcardiotomy shock may not be universally applicable, but some pathways may be conserved across phenotypes.

The field of CS has been adrift for decades. In the years to come, we must find a better lifeboat for our patients with CS who are literally drowning. Doing so will be difficult and costly, and the path ahead is long and circuitous, but hopefully with new approaches, we will find the way to shore.

ARTICLE INFORMATION

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