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The Challenges of Conducting Clinical Trials for Patients with Cardiogenic Shock

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The Challenges of Conducting Clinical Trials for Patients with Cardiogenic Shock

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Abstract

Cardiogenic shock due to ST-segment elevation myocardial infarction is associated with high morbidity and mortality. Patients in shock are acutely ill, and clinicians may lack equipoise, thus presenting a challenge to developing high-quality evidence to guide practice. This review will summarize these challenges and offer possible solutions.

Keywords: cardiogenic shock, STEMI, clinical trials

Background

Observational data is vital to research efforts; however, relying on observational data can often lead to incorrect conclusions about treatment strategies. For example, three large propensity-matched analyses compared different mechanical support devices but were potentially confounded by indication.[1-3] Thus, prospective clinical trials are needed to test hypotheses and verify theories. While there are challenges to doing clinical trials in the cardiogenic shock population, they are essential for determining the appropriate management of these patients. It is important to recognize that randomized clinical trials also have weaknesses, and their findings may not be applicable to every patient. Thus, nuance must be used when interpreting any results from observation or randomized trials.

Incidence, Prognosis, and Functional Outcomes

Despite the availability and adoption of primary percutaneous coronary intervention (PCI) for acute ST-segment elevation myocardial infarction (STEMI), data from the National Cardiovascular Data Registry indicate that the incidence of cardiogenic shock is increasing in the United States.[4]

In addition, the prognosis for patients with cardiogenic shock remains unchanged. In-hospital mortality and 30-day mortality have stayed around 30% to 50%.[4] The acuity and severity of the clinical presentation make studying cardiogenic shock a challenge. Enrollment into clinical trials is difficult in STEMI patients due to the urgency of the door-to-balloon time metric. Given that patients in shock are in extremis, enrollment into clinical trials seems prohibitive.

Though important, mortality is not the only outcome of interest. To date, functional outcomes are understudied. For those who survive hospitalization, there are no data detailing disability in patients presenting with AMI shock. Moreover, there are no studies showing how many of these patients transition to long-term care or the effects of their recovery on their caregivers.

Pathophysiology and Hemodynamics of AMI Shock

Occlusion of an epicardial coronary artery leads to myocardial ischemia, which prompts the spiraling cascade of events that leads to end-stage shock and often mortality. This chain of events guides the clinical priorities when treating these patients, which involves immediately trying to open the occluded artery and support end-organ perfusion. There are several points along the care continuum that lend themselves to research questions. One of which is: will supporting the patient before opening the artery improve outcomes or vice versa?

The hemodynamics of AMI shock, which are hypotension, increased left ventricular end-diastolic pressure, and reduced cardiac output,[5] lend themselves to another important research question: is a strategy of inotropes or mechanical circulatory support better for patient outcomes?

Big Data, Phenotypes, and Clinical Decision-Making

One of the benefits of the contentious use of electronic health record (EHR) systems is that a tremendous amount of information is automatically collected during the course of clinical care. It has long been the promise of EHR systems that patient information could be used to create support for clinical decision-making.

In a recent study, machine learning was applied to three EHR datasets of patients with cardiogenic shock—the Cardiogenic Shock Working Group MI cohort (CSWG-MI), the Cardiogenic Shock Working Group CHF cohort (CSWG-CHF), and the Danish Retroshock Registry (DRR)—to cluster potential phenotypes.[6] The results of this analysis identified three clusters of phenotypes: noncongested shock, cardiorenal shock, and cardiometabolic shock.

All phenotypes shared clinical features indicative of cardiogenic shock (eg, decreased blood pressure). However, each showed distinct differences, which warrant further study. As the name suggests, the noncongestive phenotype showed no evidence of congestion. The cardiorenal phenotype had mostly left ventricular dysfunction, while the cardiometabolic had mostly right ventricular dysfunction. Applying machine learning techniques to ascertain the phenotypes of our clinical populations could open many research possibilities.

Interestingly, each of the three phenotypes has a distinct relationship with mortality. Compared to patients with noncongested shock, patients with cardiometabolic shock had the highest mortality. Although this might be a marker of when these patients sought medical attention, this phenotypic finding supports the clinical convention of treating these patients emergently. EHR data and resultant phenotypic understanding hold the potential to validate the timing of interventions and guide clinical best practices.

Treatment Strategies for Acute MI

Without standardized guidelines, interventional cardiologists rely on empirical decision-making in light of what would be best for the patient. Decisions are based on results from the catheterization laboratory, with revascularization as the priority. Ruling out any mechanical complications (eg, free wall rupture, papillary muscle rupture, ventricular septal defect) also informs the treatment approach, as do options for hemodynamic support (eg, vasopressors, mechanical circulatory support). However, most of these decisions are not supported by randomized trial data. Given the promise of big data and the consistently poor outcomes in shock, developing randomized trials for patients with cardiogenic shock has become a priority.

Clinical Studies

Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) Trial

Some randomized trials have been conducted. Perhaps the most noteworthy study—the SHOCK trial—randomly assigned patients with cardiogenic shock (N = 302) with either STEMI or non-STEMI to receive revascularization or medical therapy. The results showed no difference in treatment response at 30 days.[7]

Other mechanical support studies also showed no benefit at 30 days, suggesting that 30 days after PCI may be too soon to measure a meaningful benefit of a therapeutic strategy in shock patients.[8-9] Fortunately, patients in the SHOCK trial were followed for 10 years, which highlighted the difference between the treatment arms (P = .03). So, when considering the study design, the conventional 30-day endpoint might not be an ideal time point for a randomized trial.

Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock (CULPRIT-SHOCK) Trial

The CULPRIT-SHOCK trial set out to test a class 2B recommendation to perform multivessel PCI in patients with cardiogenic shock (N = 699). The researchers contended that upon opening the culprit artery, other compromising coronary diseases would be discovered in the patient. To prevent more ischemia, the subsequent opening of the other affected vessels was tested as potentially helpful to the patient. Unfortunately, this approach proved worse for patients that received multivessel PCI; they had worse relative risks of death, renal replacement therapy, and bleeding (relative risk 0.83 [95% CI 0.71 to 0.96], P = .01).[10]

This was a distinctly different outcome from what has been demonstrated in the COMPLETE trial for patients with STEMI who do not have cardiogenic shock, where multivessel

PCI reduced major adverse cardiovascular events compared with culprit artery PCI alone.[11] This dichotomy underscores the importance of understanding the interplay between clinical presentation and treatment strategy, especially in patients with cardiogenic shock.

Other Randomized Trials

The Dobutamine Compared with Milrinone (DOREMI) Trial compared milrinone with dobutamine in patients with cardiogenic shock (N = 192).[12] No significant differences were reported in the primary composite outcome of in-hospital death from any cause, resuscitated cardiac arrest, receipt of a cardiac transplant or mechanical circulatory support, nonfatal myocardial infarction, transient ischemic attack or stroke diagnosed by a neurologist, or initiation of renal replacement therapy. Similarly, another study (N = 1679) randomly assigned patients with various types of shock to receive one of these vasopressor agents. For the 280 patients with cardiogenic shock, norepinephrine was associated with a better outcome than dopamine.[13] These data challenged the conventional practice of using dopamine as the first-line vasopressor for patients with shock.

The same level of randomized evidence does not exist for mechanical circulatory support devices (MCS). Conducting trials of MCS is tremendously challenging, particularly in the United States. In Germany, the Intraaortic Balloon Pump (IABP) SHOCK II trial randomly assigned patients with cardiogenic shock to either IABP intervention or control.[14] This trial showed no difference in outcomes for patients with cardiogenic shock and STEMI between using IABP and not using IABP. As a result, the European guidelines have downgraded the use of balloon pumps. Practice patterns have changed, particularly in Germany, where the use of balloon pumps has plummeted since the publication of this study.[14] It is not clear if patterns of IABP use in other countries have followed suit.

A number of multicenter trials have been designed and opened to evaluate the Impella device (Abiomed).[15] Many of these trials were discontinued because of a lack of enrollment. The trials that were completed had very small sample sizes (N < 20) and were not informative to clinical practice. To address the evidence gap, a large randomized trial called RECOVER IV has been planned to compare the Impella device to the standard of care, including the IABP.

What Are the Challenges to Conducting Trials In Cardiogenic Shock?

The challenge to conduct cardiogenic shock trials—and enhance evidence-based practice—sits squarely on the shoulders of clinicians. Due to historical practice patterns, the severity of the patient's clinical situation, and the dearth of randomized data, clinicians may be unwilling to randomize patients because of the perceived lack of equipoise.

To develop robust, scientifically sound guidelines, there must be a willingness to randomize patients in shock. Shock is a heterogeneous disease with multiple etiologies; therefore, it is imperative to clearly and consistently define the clinical trial population. Further, shock has a relatively low prevalence. While the diagnosis of shock may be increasing, it still accounts for a small proportion of patients with AMI. Large networks are needed to ensure that enough patients are recruited in a reasonable timeframe. In addition, the devices and trials themselves are very expensive, and funding has been and will continue to be a challenge. Attaining patient consent for enrollment can be difficult as many cases are emergent and the patient and/or family is not in a position to provide full consent. Delayed and proxy consent are two possibilities that have been tried. Exemption from informed consent is a mode used in trauma trials that may offer another alternative. Emergency consent has been used in cardiac arrest trials, and other creative consent mechanisms may be needed. Finally, a good trial must have equipoise; thus, we must figure out a way to separate ourselves from our own lack of equipoise so that we can actually get truly randomized data to guide our field.

Conclusion

A statement from the American Heart Association explored the different types of cardiogenic shock presentations and the different strategies that can be used to manage and treat patients.[16] While the clinical community awaits more randomized data, these guidelines will serve to inform clinical practice.

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