Cardiogenic Shock in Acute Myocardial Infarction
The Era of Mechanical Support*

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Despite the marked reduction in mortality from acute myocardial infarction (AMI), which may be as low as 3% to 4% with today’s national guidelines for rapid, catheter-based revascularization to open the infarct-related artery, cardiogenic shock remains the leading cause of death from AMI, occurring in as many as 10% of all myocardial infarctions (1). Unfortunately, the outcome with current treatment approaches remains very poor, with mortality as high as 40% to 50% before hospital discharge (2,3).

The intra-aortic balloon pump (IABP), which was developed >4 decades ago, was the first device for mechanical support of the circulation in patients with cardiogenic shock, often when due to an AMI (4). The early and persistent enthusiasm for its use was on the basis of nonrandomized trials and registry data. However, this limited, but encouraging dataset led to endorsement of IABP use in national guidelines as a Class I indication, in part because of its appealing enhancement of coronary perfusion and the absence of other alternatives. However, when subjected to meta-analyses (5,6), as well as in the recently reported 600-patient randomized, controlled, prospective IABP-SHOCK II (Intraaortic Balloon Pump in Cardiogenic Shock II) trial (7), use of the IABP for AMI shock failed to demonstrate a significant difference in mortality over standard therapy at either 30 days or 1 year. The study (7) provided no guidelines for use of other forms of mechanical support, such as durable left ventricular assist devices (dLVAD), which were used in only 4% of patients. As a result of these trial data and meta-analyses, the use of IABP in AMI shock has been downgraded from Class I to Class IIA in the United States (8) and to Class IIB in Europe.

It was also clear that many patients with AMI shock have potentially significant amounts of stunned myocardium that could potentially recover within days post-revascularization, but they need more support than could be provided by the IABP. This gap has led to the development and rapid evolution of entirely new types of mechanical devices that are designed to provide greater temporary mechanical support (TMS) of the circulation (9,10). These devices can be implanted percutaneously (Impella [ABIOMED, Danvers, Massachusetts], Tandem Heart [CardiacAssist, Pittsburgh, Pennsylvania], extracorporeal membrane oxygenation), or via sternotomy (Abiomed and Centrimag [Thoratec, Pleasanton, California]) and provide from 2.5 to 5.0 liters of blood flow via connection to an external centrifugal pump capable of varying speed and flow as needed. They can provide significantly greater mechanical unloading of the ventricle via large catheters drawing blood directly from the left ventricle, or left or right atria, with associated significant improvement in cardiac and end-organ function, and other comorbidities. The devices capable of greatest decompression of the ventricle and highest flows often reduce pre-load to a degree that the ventricle does not have sufficient volume to generate a pulse, thereby significantly reducing left ventricle work and myocardial oxygen demand. Their initial intended use was for only 2 to 5 days, with vascular access in the percutaneous type initially via peripheral arterial and/or venous cannulation. However, more recently, their use has been extended to weeks of...
support and the cannulation often moved to axillary or neck vessels, which potentially allows patients to be out of bed and even to ambulate during support. The ability to temporarily reduce pump speed allows periodic assessment of recovery of native cardiac function and guide device removal.

To date, there have been few clinical trials conducted with TMS. Their largely nonrandomized design with small numbers of patients makes them underpowered to demonstrate a survival benefit, and there is only 1 meta-analysis (11), which has shown only modest improvement in survival with TMS use. There are several factors that help explain the reason why there is not more clinical trial data to demonstrate the superior mortality benefit of TMS over IABP in AMI due to cardiogenic shock (AMI-CS). This includes that fact that patients with the diagnosis of AMI shock are a heterogeneous group, with varying degrees of shock, previous infarction, and/or heart failure, and therefore variable potential for improvement, and are often very unstable, and therefore challenging to enroll in clinical trials.

However, the field of TMS has grown dramatically in the past several years, with percutaneous devices increasing by over 1,500%, compared with 103% for surgically implanted TMS devices from 2007 to 2012, including use extended beyond treatment for cardiogenic shock, such as for high-risk angioplasty (12). There are several new iterations of the original TMS devices that are now able to generate 5 to 6 liters of flow without commensurate increase in hemolysis, but it is too soon for that trial data to be reported. This greater degree of ventricular unloading is potentially more likely to be associated with improved outcomes. Despite the limited randomized trial data, the progress with percutaneous TMS has led to release of a consensus statement from the leading cardiovascular societies (including the American Heart Association, American College of Cardiology, Heart Failure Society of America, Society of Thoracic Surgeons, and Society of Cardiac Angiography and Interventions) on the use of percutaneous mechanical support devices in cardiovascular care, which endorses their use in patients with cardiogenic shock, including AMI (13). It will be very important going forward to conduct prospective trials to better define the optimal patient who might benefit from this therapy and develop the much needed criteria for when to initiate TMS and when to transition to dLVAD. These efforts will be aided by the creation of a registry for their use, which is currently being developed.

The most powerful type of mechanical support of the circulation and ventricular unloading is with dLVAD. This field has also grown significantly, with over 15,000 devices now included in the most recent INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) registry report (14). However, only approximately 3% of the total have been used for the indication of AMI-CS, in part because the early devices were quite large and required a major cardiac surgery, with the associated high risk of bleeding, often in the setting of dual antiplatelet therapy post-coronary revascularization, as well as the frequent occurrence of major comorbidities, including cardiac arrest and potential neurological damage, and unexplored psychosocial problems.

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However, in this issue of the Journal, Acharya et al. (15) provide an important advance in the understanding of the significant survival benefit possible when dLVAD are used to support patients with AMI shock. Using available data from 143 hospitals participating in the INTERMACS ventricular assist device registry between 2006 and 2012, the investigators compared the outcomes in 502 AMI shock patients supported primarily with large dLVAD to those from 9,727 patients with non-AMI indications. The data from this registry includes patients receiving LVAD for all intended end strategies, including bridge to transplant and bridge to decision, as well as destination therapy. The AMI patients in this study were perhaps the sickest ever studied, and far sicker than those with non-AMI indications, with 75% on IABP or extracorporeal membrane oxygenation support versus 37% in non-AMI patients, 67% considered in critical circulatory shock, and another 18% deteriorating on inotropic therapy. The AMI patients also had highly significant (p = 0.01) differences in other forms of major medical support at the time of dLVAD implantation, including use of mechanical ventilation (58% vs. 8%), dialysis, or ultrafiltration, as well as having sustained a cardiac arrest (33% vs. 3%). However, despite these significant differences and critical status of the AMI patients, their survival rates were an unprecedented 93% at 1 month, 77% at 1 year, and 70% at 2 years, which were not different from the non-AMI patients at any time period. There was a significant increase in adverse events and mortality hazard in the AMI group in the early period post-dLVAD implantation, but this difference did not persist when risk was adjusted. The investigators attribute some of this excellent survival, despite the AMI patients being much sicker at time of implantation, to the acute nature of the AMI, with no comparative comorbidities, which are often present in the chronic...
heart failure patients, including varying levels of malnutrition, functional limitations, and end-organ dysfunction.

However, the study by Acharya et al. (15) has several limitations, mainly because the data fields in the INTERMACS registry only record patients that have an LVAD implanted and therefore does not capture much of the data needed to confirm the comparative benefit over other potential strategies in these patients. This includes the prevalence of shock that was not treated with temporary mechanical support or dLVAD and the percentage of those patients not supported who either recovered or died, as well as the time from revascularization or diagnosis of shock to implantation. The average age of the AMI cohort of 57 years suggests some likely, but not inappropriate, bias in the selection of patients for mechanical circulatory support, likely excluding many older and sicker patients. However, no significant difference in outcome was found by age in 3 tertiles between 45 and >65 years of age.

This study, unfortunately, cannot provide criteria for optimal timing of when temporary mechanical circulatory support should be implemented, as well as when to transition to a dLVAD versus going directly to a large chronic LVAD. Similar to TMS, there are 2 new third-generation dLVAD in clinical trials that may offer easier, more rapid implantation, which could translate to even better outcomes in this population. Efforts are underway to create links to the ACC-NCDR (American College of Cardiology-National Cardiac Database Registry), INTERMACS, and UNOS (United Network for Organ Sharing) registries to provide critical information about the entire course of patients with AMI-CS.

Critics may suggest that the selection bias and lack of data on comparative potential outcomes limits the significance of this study, but it is an observational study, with several important lessons to be learned from this analysis. This includes that many patients are being referred very late in the course of the AMI shock for TMS or full mechanical circulatory support, as manifested by the high incidence of cardiac arrest, mechanical ventilation, and dialysis use at the time they were referred, and yet could achieve survival rates thought to be unattainable. This demonstrates a clear, expanded role for dLVAD as a powerful addition to the treatment options for these patients and defines a new benchmark for survival possible even in those with major complications of advanced and prolonged shock due to AMI. Given this new, higher bar for survival with AMI-CS, the field needs to define a new algorithm that provides the thresholds/guidelines for progression from intravenous inotropes and/or pressors to IABP or directly to TMS, as well as the criteria for use of durable VAD for those considered candidates who are not improving within several days of initial support. The key to this new algorithm is that consideration of these new options needs to begin in the catheterization laboratory with simple guidelines, such as need for vasopressor drugs or elevated plasma lactate as the guidelines to consider an early move to TMS.

A common benefit of temporary or durable mechanical support devices is significant unloading of the ventricle and secondary decrease in wall stress and oxygen consumption. These data raise the provocative hypothesis of possibly superior benefit of early mechanical ventricular unloading over immediate versus delayed (hours) percutaneous coronary intervention in AMI in salvaging functional myocardium. This hypothesis has recently been supported by a preclinical study by Kapur et al. (16) showing a significant advantage of unloading the ventricle with TMS and delaying reopening the infarct artery for several hours over early revascularization alone. This is an important and very testable new strategy that warrants prospective clinical trials in the near future. Reducing the high percentage of AMI patients that go on to develop heart failure may be an additional longer-term benefit that warrants extended follow-up when tested.

Collectively, this data would seem to provide the basis for a paradigm shift in the management of patients who develop shock in the setting of AMI and supports a new era of expanded use of mechanical support. Although proving sufficient in some patients, especially those with their first myocardial infarction and only mild congestion or transient shock, the IABP should no longer be seen as being in the class of the current generation of true mechanical circulatory support devices, as it cannot provide comparable support of the circulation or ventricular unloading. New paradigms are typically based on data from prospective randomized trials, as well as meta-analyses, registries, and databases developed from clinical trials. However, AMI shock patients are often very unstable and a challenge to conducting clinical trials. The mortality of shock from an AMI is so high that there can no longer be equipoise to randomize subjects to control or usual care. This new paradigm for use of mechanical support for cardiogenic shock is likely to be based more on registry data than usual, using expanded data fields that would provide the basis for defining the criteria for the algorithm to initiate mechanical support. There must also be some prospective clinical trials conducted to establish a clear evidence base for the use of these invasive and expensive, but life-saving devices. Given the very
encouraging data from the Acharya et al. study (15), these trials should receive high priority and funding, as the persistent high morbidity and mortality of AMI shock remains among the major limitations in cardiovascular medicine.

REFERENCES


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