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Editorial

What Is the Role of Medical Therapy in Cardiogenic Shock in the Era of Mechanical Circulatory Support?

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In patients hospitalized with cardiogenic shock (CS), contemporary short-term mortality rates are 30% to 50%.[1] To date, the only therapy that has definitively improved survival is revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass grafting in patients with myocardial infarction associated with CS.[2] Temporary mechanical circulatory support (MCS) devices can potentially increase cardiac output, reduce pulmonary congestion, and help to restore end-organ perfusion in patients with CS.[1,3,4] In principle, a pump that augments the failing heart ought to be clinically beneficial. These findings have likely fueled and exponential growth in the use of temporary MCS devices, including extracorporeal membrane oxygenation (ECMO) and Impella (Abiomed, Danvers, Massachusetts).[5-7] This shift in practice is juxtaposed against the potential complications and the scientific uncertainty of whether temporary MCS devices can meaningfully improve such clinical outcomes as mortality or quality of life.[8,9] To date, large high-quality randomized trials are lacking, and most international clinical practice guidelines assign temporary MCS a class IIb (C) recommendation.[10]

Temporary MCS is perhaps the most promising therapeutic technology that could potentially improve CS survival, and 2 pending randomized controlled trials, **Dan**ish-**Ger**man Cardiogenic Shock Trial (DANGER) and Testing the Value of Novel Strategy and Its Cost Efficacy in Order to Improve the Poor Outcomes in Cardiogenic Shock (EUROSHOCK), may help to inform the use of MCS in clinical practice.[11,12] They may not, however, clearly outline which patients are best suited for medical therapy alone vs MCS. This potential complexity is underscored by 2 recent publications that have helped frame the growing recognition of the hemodynamic and phenotypic diversity of CS. In addition, they may help inform future clinical and research frameworks to identify which patients might benefit from MCS. The American Heart Association (AHA) Scientific Statement of CS, based largely on secondary analyses of the **Sh**ould We Emergently Revascularize **O**ccluded **C**oronaries for Cardiogenic Shoc**k** (SHOCK) trial, emphasized that although all patients CS share reduced cardiac output, but pulmonary capillary wedge pressures, systemic vascular resistances, and right-ventricle (RV) function can vary.[1] In this framework, it is conceivable that patients with vasodilatory CS, caused by either a postinfarction inflammatory or mixed shock state, may—theoretically—be less likely to benefit from temporary MCS if a low systemic vascular resistance (SVR) is the dominant hemodynamic abnormality and/or there is concurrent multifactorial end-organ failure. Similarly, there is growing clinical recognition that in normotensive CS, patients with hypoperfusion—despite normal blood pressure potentially related to large compensatory SVR response—often respond well hemodynamically to inodilators, although definitive evidence on efficacy and safety is lacking. Layered on this diversity is the underlying etiology; although most vasoactive research has been performed in acute myocardial infarction with isolated left ventricular dysfunction, the vasoactive agent selection and hemodynamic goals in patients with CS due to dynamic outflow-tract obstruction, severe mitral stenosis, or isolated RV failure are very different and are based on physiologic principles in the absence of high-quality studies.

The second study is the Society of Cardiovascular Angiography and Interventions Expert Consensus CS classification.[13] The document, which was endorsed by the AHA, the American College of Cardiology, the Society of Critical Care Medicine, and the Society of Thoracic Surgeons and was designed to account for the dynamic nature of CS and the heterogeneity in acuity that is not fully captured with pre-existing Interagency Registry for Mechanically Assisted

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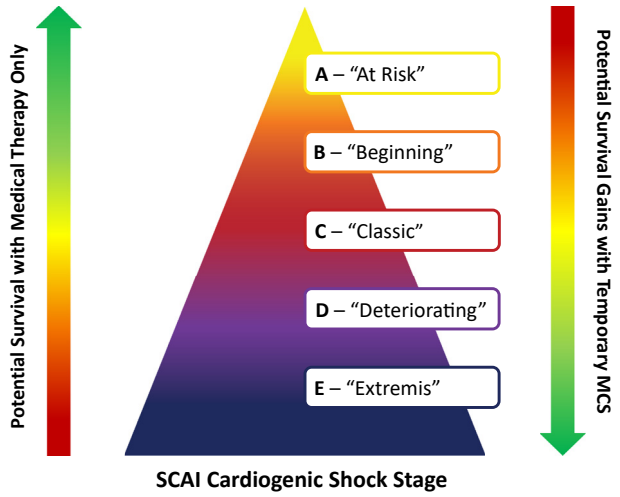

Figure 1. Potential role of medical therapy alone and temporary mechanical circulatory support stratified by stages of cardiogenic shock.

Circulatory Support (INTERMACS) staging. The taxonomy of (A) *At risk*, (B) *Beginning*, (C) *Classic*, (D) *Deteriorating*, (E) *Extremis* was designed to provide a simple clinical communication tool that could be applied by multidisciplinary team members throughout the care continuum (Fig.1). This nomenclature, which has been validated by at least 1 group, could help refine MCS selection in the future.[14,15] Although CS outcomes are poor, more than 50% of patients in contemporary studies do survive with medical therapy alone.[16] Thus, it is plausible that a more targeted deployment of temporary MCS in more acute, profound, or refractory CS states that have been appropriately hemodynamically phenotyped could maximize the survival benefits and minimize health care costs. In the schema presented in the Figure, we surmise that the Society for Cardiovascular Angiography and Interventions (SCAI) stage D and E (and selected stage C) patients may be more likely to benefit from temporary MCS and less likely to survive with isolated medical therapy. Thus, stage B and C patients could conceptually receive a trial of medical therapy first, and deteriorating (stage D) would require temporary MCS support. Appropriately selected patients in stage E with ongoing resuscitation would be most suitable for extracorporeal cardiopulmonary resuscitation (eCPR).

It should be acknowledged, however, that the evidence supporting a stepwise escalation in MCS therapies is equally sparse as other more broadly proposed principles including door-to-unloading time in CS.[17] A phase 2 Study of Multistep Pharmacological and Invasive Management for Cardiogenic Shock (ALTSHOCK) of 24 patients in Italy with CS had a protocol driven escalation from inopressor therapy, to intra-aortic balloon pump, to ECMO, if necessary.[18] The authors reported an 88% 60-day survival and that 29% improved on medical treatment, 65% underwent ventricular assist device implantation, and 9% underwent transplant. Although these data clearly require replication in larger population, this proof of concept study re-enforces the potential for selective MCS deployment and that some patients can improve on medical therapy alone. Layered on this framework is the potential for early multidisciplinary management in the form of cardiogenic shock teams. Tehrani and colleagues recently reported that, in a single-centre cohort, the early activation of a shock team that included interventional cardiology, advanced heart failure, cardiac surgery, and critical care substantially improved 30-day survival from 47% to 77% over a 3-year period.[19] Although this study used protocol-driven hemodynamic criteria to guide early MCS therapy, it is impossible to disentangle the potential benefits of more proximal engagement of multispecialty stakeholders. The team-based approach may have plausibly improved therapeutic decisions owing to collective input, the vigilance with which individual patients were followed, and/or the ability escalate therapies when initial strategies were failing.

In this special Cardiac Support Therapies issue of the *Canadian Journal of Cardiology,* Kim highlights the unmet expectations for improvement of CS survival following the publication of the SHOCK trial, particularly with the growth of temporary MCS, and proposes the need for more proximal multidisciplinary care and the rapid triage of patients with CS to dedicated CS centres within Canada. [2,20] In addition, a number of authors highlight our collective understanding of MCS best practices in patients with CS and/or advanced heart failure in either the acute or subacute phases of care. Three reviews provide complementary perspectives on ECMO best practices indications and management, each with unique focuses. Bhatia et al. provides a comprehensive overview of the multimodal and multisystem monitoring requited to care for patients on ECMO; Guihaire et al. discuss the unique impact MCS devices have on hemostasis and hemolysis; and Singh et al. provide a practical and well—thought-out approach to ECMO weaning, all of which I believe are important contributions to the pre-existing body of ECMO review papers.[21-23]

In addition, Alviar et al. outline the physiologic cardiopulmonary interaction in patients with left and right ventricular failure requiring positive pressure ventilation and provide an approachable mechanical ventilation framework for the nonexpert in this tenuous population.[24] The review by O'Brien et al. provides a thought-provoking argument that the lactate-pyruvate ratio should be routinely monitored in this population to better delineate the interplay between tissue hypoxia and high-demand state.[25]

The second group of reviews focus on subacute care. Kiamanesh provides an approach to left-ventricular assist device care and complications, which blends accessible language and clinical accuracy that will undoubtedly be appreciated by its nonexpert clinician target audience.[26] Finally, Huitema and colleagues discuss therapies in transplant ineligible patients with a focus on how palliative care can reduce symptoms and hospitalizations in this challenging population.[27] The unifying themes among all the reviews is that many of the authors call for team-based care models and were careful to not misrepresent their clinical practice suggestions as standards of care based on high-quality evidence, and many simultaneously acknowledged the pressing needs need for more research in this field.

In the acute phase of CS, as we work to discover the best temporary MCS and medical treatment strategies, we believe there is a growing recognition that CS is an etiologically, phenotypically, and hemodynamically diverse condition. Although early temporary MCS therapy is the most promising

therapeutic technology that could improve the survival of patients with CS, the costs and potential complications together with the yet unproven survival advantage highlights the potential future research need for a more targeted MCS deployment strategy in patients who are the most likely the benefit or, conversely, the least likely to survive with medical therapy alone.

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