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Editorial

Levosimendan And Septic Cardiomyopathy: A Key That May Have Found Its Lock?

SEPTIC CARDIOMYOPATHY (SCM) is an increasingly recognized complication of septic shock, which may present acutely with profound ventricular failure. This entity complicates the pharmacologic management of septic shock, as catecholamines may have limited efficacy in this setting. Hence, the authors eagerly read the study by Sun et al. investigating the efficacy of the noncatecholamine inotrope levosimendan in this population.[1] Sun et al. performed a prospective, single-blinded, randomized controlled study of 30 patients with severe SCM (left ventricular ejection fraction [LVEF] ≤35%), in which they compared hemodynamics and clinical outcomes among patients supported with fixed-dose levosimendan or dobutamine.[1]

Septic cardiomyopathy is a startlingly common complication of sepsis and septic shock, affecting as many as 13%-to-65% of patients with sepsis.[2,3] Investigations related to the diagnosis, pathophysiology, and support (both pharmacologic and mechanical) of SCM have improved the authors' understanding of this entity, but many questions remain. Septic cardiomyopathy is generally characterized by a global reduction in either left, right, or biventricular function, with recovery typically in 7-to-10 days.[2,3] Several mechanisms to describe the pathophysiology of SCM have been proposed, including circulating myocardial depressant factors, bacterial toxins, cytokines, and gaseous mediators, such as nitric oxide, due to their ability to induce negative inotropic effects and impair both mitochondrial function and intracellular calcium homeostasis. More recently, the heterogeneous group of pathogen-associated molecular patterns and damage-associated molecular patterns have been implicated as mediators of cell and tissue stress and injury.[2] Recognition of SCM is important, as the available literature suggests worse outcomes in septic shock complicated by SCM.[2,3] Identifying acute ventricular failure in septic shock requires a high index of suspicion and increased monitoring, as myocardial dysfunction can develop rapidly and precipitate multiorgan failure without appropriate intervention. Several relevant points regarding echocardiographic parameters to detect SCM should be noted. A preserved LVEF and the absence of LV dilation may be misleading: LVEF is highly influenced by preload, afterload, and contractility, and may be difficult to interpret in the septic patient. The absence of adaptive LV dilation in the setting of sepsis-related myocardial depression has been associated with increased mortality.[2] Left ventricular longitudinal strain, LV diastolic function, and right ventricular function may be better suited for the echocardiographic evaluation of patients with SCM.[2] Management of septic shock complicated by SCM includes optimizing sepsis therapies such as antibiotics, fluid resuscitation, source control, vasopressors, and inotropic support. When a low-output state due to myocardial dysfunction is recognized, the choice of inotropic therapy is often at the discretion of the clinician. Conventional inotropes, such as dobutamine and epinephrine, have shown limited efficacy in these patients. Mechanistically, this may be explained by reduced beta-adrenergic responsiveness in septic shock.[4] Catecholamines also increase the risk of arrhythmias and increase myocardial oxygen demand. This is particularly relevant as, even with preserved coronary blood flow, septic patients are at an increased risk of atrial and ventricular arrhythmias.[5]

In contrast, the inotrope levosimendan is a unique noncatecholamine inodilator that improves myocardial contractility by increasing the sensitivity of troponin C to calcium.[6] This mechanism is not energetically costly to the myocardium and is not associated with an excessive risk of arrhythmias.[6,7] Additional effects include cardioprotection and vasodilation via an opening of potassium channels in mitochondria and smooth muscle cells of blood vessels, respectively.[7,8] Initiating an agent with vasodilatory properties in the setting of septic shock may be counterintuitive, but for many reasons, this effect may be beneficial, given the pathophysiology of SCM. In SCM, an energetic mismatch between arterial vasoconstriction and ventricular dysfunction occurs. This may be corrected with the inodilator effects of levosimendan, which reduce LV afterload and augment myocardial function by increasing cardiac output (CO) and stroke volume without increasing myocardial oxygen demand. Hypotension related to vasodilation is a possible effect of the drug, but may be limited by adequate

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fluid resuscitation prior to levosimendan use, avoidance of a loading dose, and concomitant vasopressor support.[9] Additional benefits of vasodilation and increased CO from levosimendan include improved splanchnic perfusion, which may mitigate the inflammatory response that occurs in shock due to mucosal hypoperfusion.[9] When compared to dobutamine, levosimendan may improve microcirculatory function and, possibly, mitochondrial energy use in septic shock.[9] Even with added vasopressors, this approach aims to result in a higher CO and improved end-organ perfusion. Although levosimendan is widely considered a safe and efficacious inotrope alternative in medical and cardiac surgical patients, existing data are mixed regarding its impact on improving outcomes compared to other inotropic agents.[4,6,10-13] In nonseptic populations, 1 large meta-analysis of 45 randomized controlled trials (RCT) and 5,480 patients demonstrated a possible survival benefit of levosimendan over placebo and dobutamine in decompensated heart failure or cardiac surgery.[13] A large subsequent RCT in cardiac surgery patients, however, did not show a survival benefit when levosimendan was used compared to the standard of care.[11]

Considering the unique pathophysiology of SCM, levosimendan appears to be a well-suited agent, but evidence of improved outcomes is also limited and, again, mixed. Two recent meta-analyses that included small RCTs comparing levosimendan to standard therapy (often dobutamine) in septic shock, not specifying SCM, found that patients who received levosimendan had higher cardiac indices and lower lactate levels.[4,14] Whereas Zangrillo et al. in 2015 also found a mortality benefit with the use of levosimendan compared to standard of care, Liu et al. in 2021 did not find a mortality benefit of levosimendan in their respective analyses.[4,14]

The study by Sun et al. is, therefore, timely given the ongoing debate about the ideal role for levosimendan and, particularly, its role for the treatment of SCM. Sun et al. enrolled 30 patients who met sepsis 3.0 criteria in a prospective, single-blinded RCT to receive levosimendan or dobutamine for the treatment of SCM. These patients were within <48 hours of sepsis onset and had severe SCM as defined by an LVEF ≤35%. The patients received fluid resuscitation and vasoactive drug support and were then randomized. The patients received either a fixed dose of levosimendan, 0.2 μg/kg/min, or dobutamine, 5 μg/kg/min, for 24 hours. The primary outcome was 28-day mortality. Both groups showed similar baseline hemodynamic values at enrollment. Hemodynamics were assessed by minimally invasive hemodynamic monitoring and echocardiography. After 24 hours of ongoing inotropic therapy, compared to the dobutamine group, patients in the levosimendan group had higher cardiac indices, LVEF, central venous oxygen saturation levels, and slightly more positive fluid balances while requiring less norepinephrine. Three days after enrollment, patients who received levosimendan also showed lower cardiac troponin I levels, suggestive of less myocardial injury. Despite a trend, there were no significant differences in 28-day mortality (levosimendan 40% *v* dobutamine 53%). No differences in intensive care unit length of stay and intensive care unit treatment cost were noted between the groups.

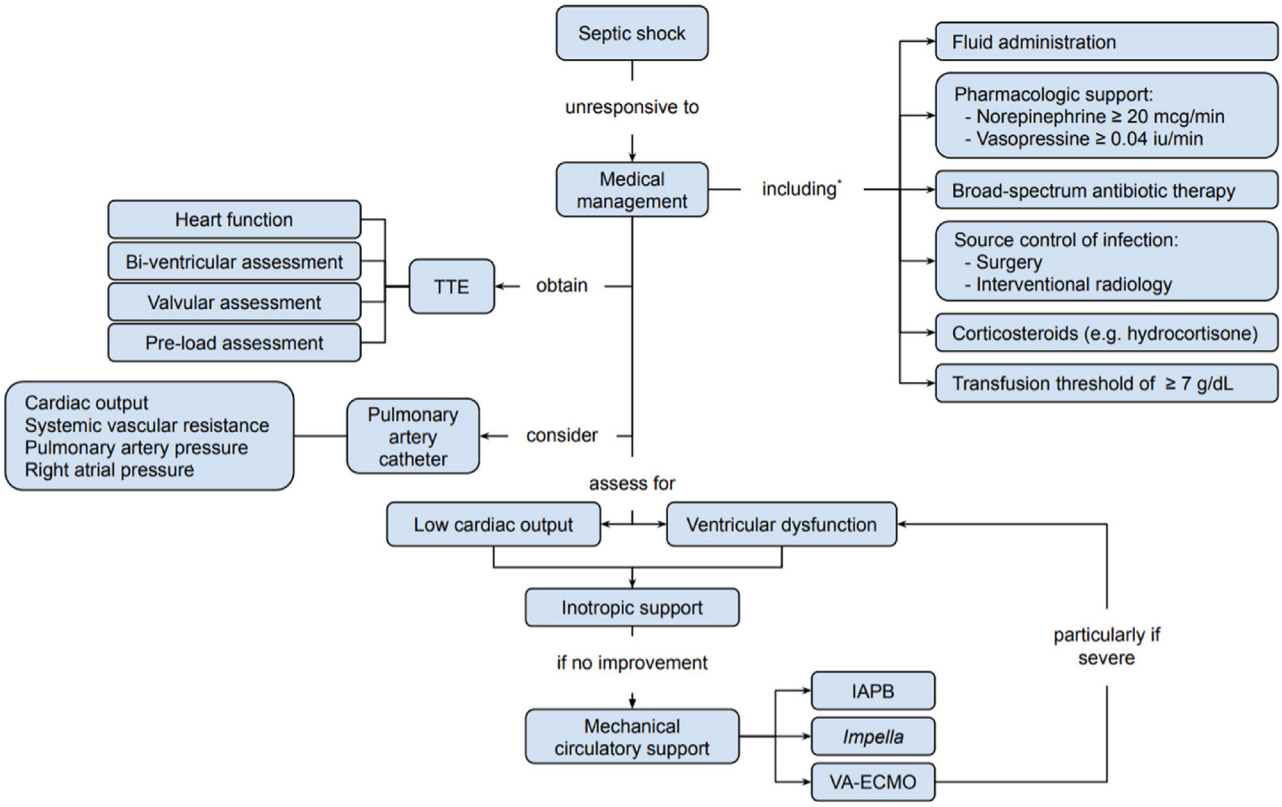

Fig 1. Proposed septic cardiomyopathy treatment algorithm. Adapted from Plack et al. J Cardiothorac Vasc Anesth 2022.[2] SCM, septic cardiomyopathy.

Interestingly, the duration of mechanical ventilation was shorter in the levosimendan group.

Although the presented results seemed to support the use of levosimendan in SCM, the study had methodologic limitations. Given the small sample size, there are some concerns whether the study was sufficiently powered to detect clinically important effects and to minimize the chances of false-positive findings. As the authors readily admit, the use of fixed doses of dobutamine and levosimendan does not represent the clinical bedside approach to inotropic therapy and, thus, may affect the generalizability of the findings. That being said, the authors provided extensive hemodynamic variable tracking that illustrated how levosimendan improves hemodynamics in SCM.

Despite the potential benefit of levosimendan in SCM as demonstrated by Sun et al., not all patients can be supported with medical management alone. Septic cardiomyopathy may present and progress rapidly, ultimately leading to multiorgan dysfunction if appropriate interventions are not carried out. Selected patients who are not responding to medical management should be considered for mechanical circulatory support (MCS), including venoarterial extracorporeal membrane oxygenation (VA ECMO).[2,3] Early initiation of VA ECMO in the setting of refractory shock due to SCM may provide a mortality benefit, with survival rates as high as 50%-to-70%.[15,16] Short durations of ECMO support (mean of 5-6 days) have been reported in this population as myocardial recovery occurred quickly.[16] A suggested approach to medical management and consideration of MCS in SCM is included below in Figure 1.

The multifaceted approach to SCM care is evolving, and medical therapies are limited. Although MCS can be an option for a selected subcohort of SCM patients in tertiary-care centers, there is an unmet need for pharmacologic rescue treatments for this vulnerable population. The study by Sun et al., which suggested that levosimendan may find a clinical home in the treatment of SCM, is therefore very welcome.

Conflict of Interest

None.

Misty Radosevich, MD*,[1]
Etienne J. Couture, MD†
Christoph Nabzdyk, MD*

*Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, MN
†Department of Anesthesiology and Department of Medicine, Division of Intensive Care Medicine, Institut universitaire de cardiologie et de pneumologie de Québec - Université Laval, Quebec, Canada

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