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Levosimendan for septic myocardial dysfunction: Not yet ready for prime time

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The estimated incidence of myocardial dysfunction in patients with severe sepsis is 40-50% (1). Clinically, it manifests as a systolic and diastolic left ventricle (LV) dysfunction with a reduction in LV ejection fraction ($< 45\%$) during the first few days of presentation after septic shock (2-5). The first published report about “circulating myocardial depressant” was based on the observation that serum obtained from patients with septic shock depresses the contractility of isolated rat myocardial cells (6, 7). Since then numerous investigators have explored possible mechanisms leading to septic myocardial dysfunction (8). Although the precise mechanism involved in myocardial dysfunction is unknown, several hypotheses have been proposed. These include down-regulation of adrenergic pathways, disturbed intracellular calcium (Ca^{2+}) trafficking and impaired electromechanical coupling at the myofibrillar level. In addition, cytokines including interleukin-6, tumor necrosis factor, and macrophage migration inhibitory factor have been shown to play an important role in myocardial depression.

Despite the knowledge gaps that currently exist in our understanding of myocardial dysfunction in sepsis, progress has been made in the treatment of sepsis-induced myocardial dysfunction. Pharmacological agents that attenuate or disrupt the inflammatory cascade and provide hemodynamic support are of great clinical interest and at the forefront of contemporary research. For example, levosimendan is a lipophilic pyridazolidine derivative that is approved in the European continent for use in decompensated heart failure patients (9). This Ca^{2+} sensitizing agent improves contractility and vasodilation by selective binding of cardiac troponin C, opening of ATP-dependent K_{ATP} channels and moderate inhibition of phosphodiesterase III (10, 11). Since levosimendan does not increase myocardial oxygen consumption, the side effects associated with the use of conventional inotropes are not observed with this medication.

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In addition to the Ca^{2+} sensitizing properties of levosimendan, the pleiotropic effects of levosimendan include anti-inflammatory and anti-apoptotic actions(12, 13). The use of levosimendan has been shown to improve endothelial function and suppress oxidative and nitrosative stress in heart failure patients (14). In this study, Dr. Wang and colleagues examine the benefits of levosimendan in a cecal ligation and puncture (CLP)-induced polymicrobial sepsismodel (15). The authors use a novel technique and implant a micro-osmotic pump in the peritoneal cavity after CLP that delivers levosimendan at 0.5 $\mu\text{g/kg/min}$ (2.5 times the maximum recommended dose for humans) or placebo. Levosimendan-treated mice demonstrated a significant improvement in LV function, higher mean arterial blood pressures, and reduced serum pro-inflammatory cytokine levels as compared to placebo-treated mice. These observations fit with other studies that have demonstrated a decrease in plasma interleukin 1, 6 and cleaved caspase-3 expression in the spleen of septic rats that were pre-treated with levosimendan(16).

Do the pleiotropic effects occur with the same magnitude in all doses of levosimendan? In a small prospective randomized controlled study, levosimendan (0.2 $\mu\text{g/kg/min}$) improved systemic hemodynamics and regional perfusion in patients with septic cardiac dysfunction even when dobutamine is no longer efficacious(3). By using a dose that is almost double the maximum recommended dose in humans, the authors cast some doubt about the relevance of these findings. High doses (at or above 0.4 $\mu\text{g/kg/min}$) can lead to hypotension, tachycardia and prolongation of the QTc interval. Further studies should investigate if we can achieve the same benefits with a clinically relevant levosimendan dose (0.2 $\mu\text{g/kg/min}$), thereby improving its risk-benefit ratio. The authors have not provided details about fluid resuscitation in these animals, but the presence of concurrent hypovolemia can exacerbate the vasodilatory properties of levosimendan leading to hypotension and tachycardia.

This study by Wang *et al.* supports the idea that levosimendan is a novel therapeutic agent for the treatment of myocardial dysfunction in sepsis and advances the field by exploring the potential mechanisms that underlie such benefit. Pre-treatment of lipopolysaccharide(LPS) stimulated macrophages with levosimendan was associated with a reduction in pro-inflammatory cytokines and chemokines. However, experiments that were aimed to identify a downstream pathway by which levosimendan regulates the cytokine secretion failed to demonstrate a role for mitogen-activated protein kinase and protein kinase B (Akt). Macrophage cells that were pretreated with levosimendan demonstrated decreased LPS-mediated high mobility group box (HMGB)-1 secretion into the medium as compared to untreated cells. Wang *et al.* first demonstrated the cytokine-like properties of HMGB1 and established HMGB1 as a prototype for endogenous danger signals or the so called “Alarmins”(17). Alarmins are cellular proteins rapidly released from cells in response to infection or tissue damage that serve to activate the immune system. Despite having significant insight into the function of HMGB1 as a late-acting mediator of sepsis, the mechanism of HMGB1 release in immune cells is somewhat unknown (18). HMGB1 protein undergoes several post-translational modifications e.g. phosphorylation, an important mechanism that redirects HMGB1 for nuclear export and subsequent secretion (19). The authors reveal that a possible mechanism includes the suppression of LPS-activated Ras-homologous (Rho) kinase signaling pathway by levosimendan. Rho kinase is

a small guanosine triphosphatase that acts as a molecular switch regulating numerous important cellular functions, such as cytoskeleton organization, cell migration, and reactive oxygen species formation (20). A shortfall of the study is that the authors fail to demonstrate HMGB1 phosphorylation by Rho kinase. Mechanistic studies to understand the role of Rho-kinase in HMGB1 phosphorylation and its participation in the nucleo-cytoplasmic shuttle are necessary. However, despite the lack of data on HMGB1 phosphorylation, it is intriguing that a Ca^{2+} sensitizing agent has a pleiotropic effect that confers a survival benefit in a murine septic model.

We applaud the authors' initiative in using a comprehensive approach including *in vitro* and *in vivo* studies to understand the benefits of using levosimendan in sepsis. The existing body of literature supports the use of levosimendan in septic shock as a safe and potentially useful adjunct to conventional therapy. In addition to the need for a prospective, randomized trial, efforts should also be made to evaluate the use of levosimendan as a rescue therapy. To this end, we look forward to the successful completion of the "*Levosimendan for the Prevention of Acute oRgan Dysfunction in Sepsis*" (LeoPARDS) trial, a multicenter, randomized, double-blind, parallel group, placebo-controlled trial that evaluates whether a 24-hour infusion of levosimendan will improve organ dysfunction in adults with septic shock. The study plans to recruit a total of 516 patients, and 401 patients have been enrolled so far. So, stay tuned.

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