Commentary

Beta-blockers in patients with septic shock: plenty of promise, but no hard evidence yet

Won-Young Kim, Sang-Bum Hong

Department of Pulmonary and Critical Care Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
Correspondence to: Sang-Bum Hong, MD, PhD. Department of Pulmonary and Critical Care Medicine, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-Gil, Songpa-gu, Seoul 05505, Korea. Email: sbhong@amc.seoul.kr.

Submitted Jul 13, 2016. Accepted for publication Jul 18, 2016.
doi: 10.21037/jtd.2016.08.52
View this article at: http://dx.doi.org/10.21037/jtd.2016.08.52

Septic myocardial depression, or septic cardiomyopathy, can be defined as a global (that is, affecting systolic and diastolic pressure), but reversible, dysfunction of both the left and right sides of the heart in septic shock (1). The pathogenesis of septic myocardial depression involves a complex interaction between genetic, molecular (including calcium channels, nitric oxide, endothelin-1, cytokines, and toll-like receptors), metabolic (including mitochondrial dysfunction and oxidative stress), autonomic, and hemodynamic variables (2-7). However, most studies of this condition have been performed in animals, and their results are not readily applicable to humans. In addition, no specific treatment of septic myocardial depression exists, other than hemodynamic stabilization with fluid therapy, vasopressors, and inotropic agents (8), despite the proposal of a number of potential mechanisms. Systolic dysfunction in sepsis can be explained in terms of impaired ventricular-arterial (V-A) coupling, which represents the interaction between the left ventricle (LV) and the arterial system, and which can be defined as the ratio of the arterial elastance (Ea) to the ventricular end-systolic elastance (Ees) (9). In septic shock, V-A decoupling persists, and is further exacerbated by heightened afterload caused by administration of vasopressors (which increase Ea) and by tachycardia-induced myocardial dysfunction (which decreases Ees) (10).

In a study that has now been described in *Intensive Care Medicine*, Morelli and colleagues investigated the effects of reduction of heart rate (HR) by administration of the beta-blocker esmolol on Ea in patients with septic shock (11). Patients with septic shock (n=45), with an HR ≥95 bpm and requiring norepinephrine to maintain mean arterial pressure (MAP) ≥65 mmHg, received esmolol-infusion therapy to maintain HR between 80 and 94 bpm. Data from right-heart catheterization, echocardiography, arterial-waveform analysis, and norepinephrine requirements were obtained at baseline and at 4 h after esmolol administration. Ea was calculated as MAP/stroke volume (SV). The main finding was that esmolol infusion to achieve HR <95 bpm was associated with a decrease from baseline in Ea (from 2.19±0.77 to 1.72±0.52 mmHg/L) and arterial dP/dtmax (from 1.08±0.32 to 0.89±0.29 mmHg/ms), and with an increase in SV (from 48±14 to 59±18 mL). These changes were all statistically significant (P<0.001). Cardiac output and ejection fraction were unchanged, whereas norepinephrine requirements were reduced by esmolol treatment (from 0.7±0.7 to 0.58±0.5 μg/kg/min; P=0.01).

These results demonstrate that treatment with beta-blockers modulates sepsis-induced cardiovascular alterations. In the early phase of septic shock, patients typically show the features of a state of high cardiac output, such as tachycardia and subsequent myocardial dysfunction (12). Beta-blockers decrease myocardial oxygen consumption and prolong diastole and coronary perfusion by decreasing HR, reducing the risk of myocardial ischemia. In addition, several clinical studies demonstrate positive effects on hemodynamics of the administration of the beta-blockers esmolol or metoprolol (13,14). In the presence of an adequate preload, a reduction in HR improves ventricular filling during diastole (increasing Ees), thereby increasing SV. In patients with similar cardiac outputs, a hemodynamic profile characterized by a relatively slow HR and concomitantly high SV can be interpreted as an improvement in cardiac efficiency, or V-A coupling. Sepsis induces substantial pro-inflammatory and anti-inflammatory cascades, and the administration of beta-blockers down-regulates the pro-inflammatory response (including the release of TNF-α, IL-1β, and IL-6) and up-regulates the anti-

inflammatory pathway (including IL-10) (15). Along with reduction of vascular oxidative stress and modulation of nitric oxide pathways, beta-blockers may improve endothelium-dependent relaxation by exerting anti-inflammatory effects (16). This phenomenon could reduce Ea, enabling the LV to generate a higher SV with less contractility and lower energetic cost than in the absence of beta-blockers, thereby reducing vasopressor requirements. The results presented by Morelli and colleagues (11) are consistent with previous findings: HR reduction with esmolol effectively improved Ea, contributing to cardiovascular efficiency in septic shock.

Despite positive results, the studies of the potential of beta-blockers for treatment in septic shock have notable limitations. First, the heart is only one part of the cardiovascular system, and the whole system is constantly responding to various hemodynamic changes. Distinguishing between direct cardiac effects of sepsis and the cardiac response to changes in preload, afterload, and neurohumoral activity that occur during sepsis is challenging (17), especially when cardiovascular drugs are involved. For instance, Cariou and colleagues (18) assessed hyporesponsiveness of LV Ees in 10 patients with septic shock. However, all patients in this study were already receiving dobutamine at baseline, making it difficult to separate the effects of sepsis-related autonomic dysregulation from those of previous exposure to exogenous inotropic agents. Second, most previous studies were not designed with appropriate controls, and neither was the study conducted by Morelli *et al.* (11). Positive findings in these studies could be the consequence of successful standard therapy for septic shock (8), such as fluid resuscitation, appropriate antibiotic therapy, and early infection control, rather than the effect of esmolol-induced HR reduction. Morelli and colleagues have also performed an open-label, single-center, randomized phase 2 study (13) involving 154 patients in septic shock, who had similar characteristics to those in their latest study (11). Treatment with esmolol successfully achieved the primary outcome (reduction of HR to 80–94 bpm) in all patients, and was associated with significantly lower 28-day mortality compared with standard treatment alone (49.4% versus 80.5%; P<0.001) (13). The esmolol group also had increased SV and stroke work index, reduced requirements of fluid and norepinephrine to maintain a MAP of 65–75 mmHg, and no adverse effects on cardiac index and organ function (13). However, the results should be treated with caution, because the trial was not designed to detect changes in mortality, which was very high in the control group. A substantial proportion of patients in both groups received infusion with the inodilator levosimendan (49.4% in the esmolol group versus 40.3% in the control group; P=0.39 for the difference between these groups) (13). Third, without further evaluation, currently available results cannot be applied to patients with low cardiac output or LV ejection fraction, because most studies have only involved patients in a hyperdynamic state, with preserved LV function after hemodynamic optimization.

Pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) and nitric oxide could act as myocardial depressant factors (2,3), and might also contribute to septic myocardial depression. Another contributory factor could be ineffective cardiac metabolism caused by high levels of free fatty acids (19). Glucose-insulin-potassium (GIK) may be beneficial in this situation, because treatment with insulin leads to reductions in circulating levels of myocardial depressant factors, elevation of anti-inflammatory signal transduction, and suppression of levels of free fatty acids (20). However, results from clinical trials that support this conclusion are currently lacking. We have evaluated 45 patients with refractory septic shock, who were treated with GIK (unpublished data). In 12 patients with myocardial depression determined by echocardiography, MAP increased and HR decreased from baseline during the first 72 h of GIK therapy. The total insulin dose correlated with the improvement in MAP (r=–0.61; P=0.061) and the cardiovascular Sequential Organ Failure Assessment score (r=–0.64; P=0.045) at 72 h. However, these findings were not replicated in patients without myocardial depression, suggesting that the short-term improvement in hemodynamics on GIK administration in septic shock depends upon the presence of myocardial depression. However, it should be noted that our study did not have a control group, and 16% of patients received dobutamine prior to GIK infusion.

Together with findings from previous reports, the results presented by Morelli and colleagues (11) suggest that HR reduction with esmolol could effectively improve cardiovascular efficiency by normalizing V-A decoupling in patients with septic shock who remain tachycardic despite standard resuscitation. Limitations in the currently available evidence suggest that additional studies are necessary to confirm this proposal. These studies should be designed to examine not only the hyperdynamic state of septic shock, but also earlier phases of septic shock that are associated with lower cardiac output or LV function.

Acknowledgements

None.

Footnote

Provenance: This is an invited Commentary commissioned by the Section Editor Zhongheng Zhang (Department of Critical Care Medicine, Jinhua Municipal Central Hospital, Jinhua Hospital of Zhejiang University, Jinhua, China).
Conflicts of Interest: The authors have no conflicts of interest to declare.

Comment on: Morelli A, Singer M, Ranieri VM, *et al.* Heart rate reduction with esmolol is associated with improved arterial elastance in patients with septic shock: a prospective observational study. Intensive Care Med 2016. [Epub ahead of print].

References

1. Vieillard Baron A, Schmitt JM, Beauchet A, et al. Early preload adaptation in septic shock? A transesophageal echocardiographic study. Anesthesiology 2001;94:400-6.
2. Kirkebøen KA, Strand OA. The role of nitric oxide in sepsis--an overview. Acta Anaesthesiol Scand 1999;43:275-88.
3. Vincent JL, Bakker J, Marécaux G, et al. Administration of anti-TNF antibody improves left ventricular function in septic shock patients. Results of a pilot study. Chest 1992;101:810-5.
4. Levy RJ, Vijayasarathy C, Raj NR, et al. Competitive and noncompetitive inhibition of myocardial cytochrome C oxidase in sepsis. Shock 2004;21:110-4.
5. Galley HF. Oxidative stress and mitochondrial dysfunction in sepsis. Br J Anaesth 2011;107:57-64.
6. Sharshar T, Annane D, de la Grandmaison GL, et al. The neuropathology of septic shock. Brain Pathol 2004;14:21-33.
7. Nichol AD, Egi M, Pettila V, et al. Relative hyperlactatemia and hospital mortality in critically ill patients: a retrospective multi-centre study. Crit Care 2010;14:R25.
8. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013;41:580-637.
9. Chantler PD, Lakatta EG, Najjar SS. Arterial-ventricular coupling: mechanistic insights into cardiovascular performance at rest and during exercise. J Appl Physiol (1985) 2008;105:1342-51.
10. Guarracino F, Ferro B, Morelli A, et al. Ventriculoarterial decoupling in human septic shock. Crit Care 2014;18:R80.
11. Morelli A, Singer M, Ranieri VM, et al. Heart rate reduction with esmolol is associated with improved arterial elastance in patients with septic shock: a prospective observational study. Intensive Care Med 2016. [Epub ahead of print].
12. Furian T, Aguiar C, Prado K, et al. Ventricular dysfunction and dilation in severe sepsis and septic shock: relation to endothelial function and mortality. J Crit Care 2012;27:319.e9-15.
13. Morelli A, Ertmer C, Westphal M, et al. Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: a randomized clinical trial. JAMA 2013;310:1683-91.
14. Schmittinger CA, Dünser MW, Haller M, et al. Combined milrinone and enteral metoprolol therapy in patients with septic myocardial depression. Crit Care 2008;12:R99.
15. de Montmollin E, Aboab J, Mansart A, et al. Bench-to-bedside review: Beta-adrenergic modulation in sepsis. Crit Care 2009;13:230.
16. Kimmoun A, Louis H, Al Kattani N, et al. β1-Adrenergic Inhibition Improves Cardiac and Vascular Function in Experimental Septic Shock. Crit Care Med 2015;43:e332-40.
17. Hochstadt A, Meroz Y, Landesberg G. Myocardial dysfunction in severe sepsis and septic shock: more questions than answers? J Cardiothorac Vasc Anesth 2011;25:526-35.
18. Cariou A, Pinsky MR, Monchi M, et al. Is myocardial adrenergic responsiveness depressed in human septic shock? Intensive Care Med 2008;34:917-22.
19. Mjos OD. Effect of free fatty acids on myocardial function and oxygen consumption in intact dogs. J Clin Invest 1971;50:1386-9.
20. Das UN. Insulin: an endogenous cardioprotector. Curr Opin Crit Care 2003;9:375-83.

Cite this article as: Kim WY, Hong SB. Beta-blockers in patients with septic shock: plenty of promise, but no hard evidence yet. J Thorac Dis 2016;8(9):E1041-E1043. doi: 10.21037/jtd.2016.08.52

