

## Commentary

# Myocardial protection in sepsis

Simon Shakar and Brian D Lowes

Division of Cardiology, University of Colorado Denver, Aurora, CO 80045, USA

Corresponding author: Simon Shakar, [Simon.Shakar@UCHSC.edu](mailto:Simon.Shakar@UCHSC.edu)

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See related research by Schmittinger *et al.*, <http://ccforum.com/content/12/4/R99>

### Abstract

Sepsis with myocardial dysfunction is seen commonly. Beta-blockers have been used successfully to treat chronic heart failure based on the premise that chronically elevated adrenergic drive is detrimental to the myocardium. However, recent reports on the acute use of beta-blockers in situations with potential hemodynamic compromise have shown the risks associated with this approach. In critical situations, the main effect of adrenergic activation is to support cardiovascular function. Caution should be exercised in designing studies to assess beta-blockers in septic patients.

Can  $\beta$ -blockers improve outcomes in septic patients with myocardial depression? In the previous issue of *Critical Care*, Schmittinger and colleagues [1] discuss the results of treating myocardial depression in septic shock patients with the combination of milrinone and metoprolol. They report on a retrospective cohort of 40 patients. All were intubated and 70% were dialyzed. Support included volume infusion, treatment with milrinone (a phosphodiesterase inhibitor) and rapid addition of norepinephrine then vasopressin (31 of 40 patients) based on hemodynamic measurements. Metoprolol, a  $\beta$ 1-selective adrenergic antagonist, was given enterally at low doses (25 to 47.5 mg/day). Over 96 hours of follow-up, inotropic and vasopressor doses decreased, heart rate decreased, and cardiac output remained stable. Lactate, pH, creatinine, and C-reactive protein improved.

The study limitations are noted by the authors. Specifically, on metoprolol, norepinephrine and milrinone dosages had to be increased in 22.5% and 15% of patients, respectively. Vasopressin was added in five patients. The safety of this strategy cannot be assessed without a control group. Dialysis makes interpreting creatinine changes difficult and the use of a linear mixed effects model for analysis can lead to less accurate type 1 error rates in small sample sizes. Despite these limitations, this remains an interesting study. This is one of the first trials to suggest the feasibility of acutely treating myocardial depression from sepsis with adrenergic antagonists. Despite advances in the care of septic patients, mortality remains very high, especially when myocardial

depression occurs. New care strategies and therapies are needed.

Myocardial injury and depression are common during sepsis and are likely multi-factorial in etiology. The adrenergic nervous system is activated in sepsis and pharmacological doses of  $\beta$ -agonists are commonly utilized during goal directed therapy to support oxygen delivery and maintain perfusion pressure [2,3]. There is a large body of evidence suggesting that excessive adrenergic levels can cause myocardial damage [4]. Transgenic animals with overexpression of genes involving adrenergic signaling develop myocardial apoptosis, fibrosis, contractile dysfunction and eventually left ventricular dilatation. In cell culture, catecholamines have been shown to cause myocardial cell death and induce maladaptive changes in gene expression. Severe head injury causes massive adrenergic discharge resulting in myocardial necrosis and cardiac dysfunction. In chronic heart failure, activation of the adrenergic nervous system is associated with increased mortality, and inotropic therapy worsens outcomes [5]. In contrast,  $\beta$ -blockers have been shown to improve mortality in chronic heart failure [6]. In general  $\beta$ -blockers are well tolerated even in severe heart failure when started at a low dose.

Recent large prospective trials would mandate caution when using  $\beta$ -blockers in acute settings of hemodynamic compromise. The COMMIT trial in acute myocardial infarction showed that metoprolol's benefit in reducing reinfarction and arrhythmia (10 per 1,000) was offset by an increase in cardiogenic shock (11 per 1,000) [7]. This was most prominent in the first day of therapy in elderly patients with tachycardia and low blood pressure, a population reminiscent of the one discussed in the current series. The POISE trial showed that metoprolol, started 2 to 4 hours before surgery in high risk cardiac patients, led to increased rates of death and stroke [8]. The rates of myocardial infarction were reduced. Hypotension was very instrumental in causing the adverse events. Interestingly, sepsis and infection were also clearly more common on metoprolol.

Myocardial depression with  $\beta$ -blockers could explain the need to escalate therapy with vasoactive drugs in the current series. Gore and colleagues [9] showed that esmolol acutely reduced cardiac output by 20% in septic patients. There was also a reduction in blood pressure and oxygen delivery. Kukin and colleagues [10] studied low dose  $\beta$ -blockers in chronic heart failure patients. They found that even 6.25 mg of metoprolol, given orally, acutely decreased cardiac output, stroke volume and stroke work index. After 3 months and uptitration to 50 mg bid, the administration of the drug continued to cause a decrease in cardiac output and stroke work index. The use of inotropes to bridge patients to  $\beta$ -blockade has only been reported in small heart failure studies [11].

Based on the above safety concerns, this strategy should be considered experimental until further randomized controlled studies are conducted. The reported incidence of hypotension and decreased cardiac output is high enough that it might cancel the potential metabolic and anti-adrenergic benefits of metoprolol. The likelihood that the changes observed in hemodynamic parameters are not due to metoprolol is high. This was noted by the authors and discussed above. If further studies are planned, smaller doses of metoprolol should be considered in dose ranging trials. The results seen with metoprolol should not be generalized to other  $\beta$ -blockers. Carvedilol and nebivolol have vasodilatory properties that could precipitate vascular collapse in this patient population. Non-selective  $\beta$ -blockers such as esmolol and propranolol may withdraw excessive adrenergic support and precipitate worsening myocardial function.

### Competing interests

The authors declare that they have no competing interests.

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