BETA-BLOCKERS IN SEPSIS: FACT OR MYTH?

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In the early phase of septic shock, overwhelming inflammation leads to vasodilation and capillary leakage, which decreases cardiac output due to both absolute and relative hypovolemia (1). In sepsis, the host responds to infection by activating hemodynamic, metabolic and immunological processes to attempt to restore homeostasis. The adrenergic system serves as an initial adaptive response to maintain homeostasis. Endogenous epinephrine and norepinephrine levels in serum are markedly elevated in septic patients. However, excessive catecholamine surge can cause adverse effects such as persistent tachycardia, which worsens the prognosis in patients with sepsis, and a plethora of nonhemodynamic effects (2). Besides of the increased sympathetic activity with endogenous catecholamine excess, the increasing of heart rate may be caused by the other multiple factors such as systemic and myocardial inflammation, pain, fever, hypovolemia, administration of catecholamines, autonomic dysfunction with decreased parasympathetic control of the heart, direct effects of toxins such as lipopolysaccharide and cytokines such as thromboxane A2 and prostaglandins on the myocardium, and a physiologic response to absolute or relative hypovolemia (2,3).

Patients who remained tachycardic 24 hours after fluid resuscitation and the initiation of norepinephrine infusion had a threefold higher risk of death compared to those without tachycardia (4,5). The studies indicated that patients who have been prescribed chronic beta blockers might experience better survival outcomes if they later develop sepsis and are admitted to the ICU (6). Despite several theoretical benefits of beta blockers in the early stages of sepsis, clinicians may still find the use of this therapy to be unconventional or unexpected. Sepsis-induced myocardial injury is thought to be driven by two main mechanisms: an overproduction of catecholamines and an overabundance of cytokines (1,2). Beta blockers, which affect both processes, have been suggested as potential therapies to lower mortality rates. So, the conventional view that beta blockers are inappropriate for sepsis or septic shock patients, because of cardiac suppressive effects, is now being questioned, and the use of beta -blockers in sepsis has gained increasing attention, particularly for patients with tachycardia. Decatecholaminisation is the reduction of endogenous and exogenous adrenergic stimulation (7).

Morelli et al. analyzed 45 patients with septic shock with an HR 95beats/min after at least 24 hours of resuscitation, requiring norepinephrine (NE) to maintain a MAP 65mm Hg and who were treated with a continuous esmolol infusion to achieve and maintain a target HR between 80 and 94 beats/min during their entire ICU stay (8). Out of the 45 patients included in the original study, 22 patients (48.9%) experienced a decrease in art dP/dtmax 4 hours after

reducing HR with esmolol. Compared to baseline values, the HR reduction caused a significant decrease of the CO only in the group of patients with low art dP/dtmax after esmolol administration (CO reduction from 5.0 [1.3] to 4.4 [1.0] L/min). However, in patients with high values of art dP/dtmax after esmolol administration, it was found a significantly increased SV (from 48 [12] to 67 [14] ml) with consequently maintained CO (even non-significantly increased) despite the reduction in HR (8). The increase in stroke volume (SV) following heart rate (HR) reduction helped to maintain cardiac output. The heart rate reduction to 80–94bpm over a 4-hours period could have initially led to a decrease in cardiac output (8). However, the lower heart rate was balanced by increased ventricular filling time and volume, along with a reduction in left ventricular afterload, ultimately resulting in an increase in stroke volume, compensating for the decrease in heart rate. Notably, the left ventricular ejection fraction remained unchanged throughout the process. This change in hemodynamic can be viewed as a way to reduce myocardial workload and oxygen consumption, which in turn lowers the risk of myocardial ischemia. The reduction in arterial elastance (Ea) and the resulting improvement in ventricular-arterial coupling, combined with the reduction in myocardial workload and oxygen consumption, likely play a role in preserving myocardial efficiency, particularly in the context of established septic shock (8).

The J-land 3S study (9), multicenter, open-label, randomized controlled trial (54 hospitals) included 151 patients with sepsis and persistent tachyarrhythmia (atrial fibrillation - AF, atrial flutter - Afl, Sinus tachycardia - ST), who were randomized to 2 groups: 76 patients who received Landiolol and standard therapy (Landiolol group) - mandatory for the first 96 h and 75 patients who received standard therapy (Control group). This study demonstrated that a higher proportion of patients in the Landiolol group achieved target heart rates compared to the control group, with a notable reduction in new arrhythmias. Specifically, 41 patients (55%) in the Landiolol group reached a heart rate of 60–94 beats/min 24 hours after enrollment, whereas only 25 patients (33%) in the control group did. This difference was statistically significant ($p=0.0031$). Additionally, the incidence of new arrhythmias within 7 days was significantly lower in the Landiolol group (9%) compared to the control group (25%) ($p=0.015$). However, there was no significant difference in 28-days mortality rates between the two groups (9).

Another clinical multicenter, randomized, open-label, phase 2b study (10) published in JAMA in 2023 (The Study into the Reversal of Septic Shock with Landiolol STRESS-L) did not support the use of Landiolol in sepsis. The result found that administering Landiolol to sepsis patients did not decrease the SOFA score (Landiolol group 8.8 ± 3.9 vs. control group 8.1 ± 3.2 ($p=0.24$) but increased the 28-days mortality (37.1% in the Landiolol group vs. 25.4% in the control group, $p>0.05$) and 90-days mortality (43.5% rates in the Landiolol group vs. 14.9% in the control group, $p > 0.05$)). More importantly, the incidence of serious adverse events in the Landiolol group (25.4%) was significantly higher than that of the control group (6.4%), with a statistical difference between the groups ($p=0.006$). However, there were several limitations to this study that was stopped prematurely, including: 1) the outcomes of Landiolol administration when given before or after the 24-hours norepinephrine treatment window, at different doses of norepinephrine, or in various patient sub-phenotypes;

2) the absence of data on cardiac function, either through cardiac output monitoring or echocardiography; and 3) the reduced ability to identify specific patient groups that may have either benefited from or been harmed by the intervention (10).

Hasegawa et al. (11) performed a systematic review and meta-analysis, combining data from six randomized controlled trials with a total of 572 patients. Their analysis revealed that administering ultrashort-acting beta-blockers resulted in a reduction in heart rate (HR), an increase in stroke volume (SV), and no significant changes in cardiac index, mean arterial pressure, or norepinephrine dose. Moreover, the treatment was linked to a notable decrease in 28-days mortality (risk ratio 0.68 [0.54–0.85]; P< .001).

Meta-analysis of 8 out of 10 RCTs with 797 participants reported 28-days mortality outcomes (12). The results indicated that administering ultrashort-acting β- blockers (esmolol/Landiolol) to patients with sepsis who had persistent tachycardia despite initial resuscitation was significantly associated with a lower 28-days mortality rate (RR: 0.73; 95% CI: 0.57–0.93; and p<0.01). But subgroup analysis revealed that the use of esmolol in sepsis patients was significantly linked to reduced 28-days mortality (RR: 0.68; 95% CI: 0.55–0.84; and p<0.001), while there was no significant difference between the Landiolol and control groups (RR: 0.98; 95% CI: 0.41–2.34; and p=0.96). It may be that the limited sample size prevented the identification of survival benefits with Landiolol (12).

Recent findings (13) indicate that in the early stages (< 24 hours) of septic shock, using esmolol to reduce heart rate increased the risk of hypotension and decreased the cardiac index. While lactate levels and microcirculatory markers remained stable, there was a reduction in most of the pro-inflammatory markers (13), suggesting that beta-blockade might have an immunomodulatory effect. Importantly, there was not registered increasing in extravascular lung water, implying that myocardial contractility, while reduced, remained adequate. This is consistent with preserved stroke volume and perfusion parameters. The results highlight that achieving optimal preload, ventricular filling, and myocardial contractility may require careful, gradual titration, potentially leading to a longer time needed to safely reach hemodynamic stability at a lower heart rate (13).

Given these findings, it is recommended to refrain from administering beta-blockers during the early stages of septic shock to minimize the risk of hindering the chronotropic response, which is crucial at this point for compensating the reduced stroke volume. The choice of short acting I.V. beta1-selective adrenergic antagonist (esmolol, Landiolol) with limited effect on blood pressure and inotropy may have advantage in aim to achieve optimal bradycardic effects.

The primary challenge is to accurately differentiate between tachycardia (9) caused by compensatory mechanisms (due to low stroke volume) and tachycardia driven by non-compensatory factors, such as sympathetic overstimulation (14). This distinction is essential in determining whether controlling tachycardia will be beneficial or potentially harmful to the patient (14). While conventional hemodynamic markers and echocardiography

can provide guidance on when tachycardia should not be addressed, they may not detect subtle declines in myocardial contractility that are common in septic shock, as these are often compensated by an elevated heart rate. Such myocardial dysfunction may only become noticeable after reducing the heart rate. As a result, rapid titration of beta-blockers should be avoided, and any reduction in heart rate should be carefully monitored. In practice, as heart rate increases, the rate of beta-blocker titration should be slowed accordingly. During treatment it is of utmost importance to titrate beta-blocker to the heart rate that helps to optimize hemodynamic profile in the individual patient (15). A clinically relevant drop in blood pressure or an increase in noradrenaline requirement, respectively, during short action beta-blocker titration should prompt dose reduction or discontinuation of the drug (15).

Some authors concluded that heart rate control by beta blockers may be beneficial in specific subgroups of septic patients. Until now, the only promising maker to discriminate tachycardic patients with sepsis qualified for beta-blocker use is the systolic-dicrotic notch pressure difference (16).

The difference between systolic and dicrotic pressure (SDP difference - is the result of the coupling between myocardial contractility and a given afterload) might be helpful in discriminating the origin of tachycardia. A low SDP difference in patients with septic shock with tachycardia might indicate a high risk of decompensation in case of pharmacological reduction in heart rate (16).

Echocardiographic evaluations should be performed both before and during treatment to identify any potential contraindications and monitor hemodynamic performance. Subgroups that may benefit from heart rate control in septic shock include patients with atrial fibrillation and those with preserved ejection fraction (17). This hypothesis is currently being explored in a multicenter trial (HyperBetashock, NCT04748796).

It was shown that the using of beta-blockers may be useful particularly in patients with LV hyperkinesia and well‑resuscitated phenotype, but not useful or detrimental in left ventricular (LV) systolic dysfunction, still hypovolemic patients, and in right ventricular failure (18).

Left intraventricular flow obstruction (IVO) is typically associated with asymmetric hypertrophic cardiomyopathy. Dynamic IVO can also occur following aortic stenosis or mitral valve repair, particularly if the positioning of the mitral prosthesis interferes with the left ventricular outflow tract (LVOT). Obstruction may also be observed in patients at risk for hypovolemia, tachycardia, or those exposed to catecholamines, as well as in individuals with a narrowed LVOT, a small LV lumen and LV hyperkinesia. In these cases, beta-blocker therapy may be considered, provided the patient has received adequate fluid resuscitation (19).

In conclusion, beta-blocker therapy could be advantageous for septic patients, but it requires careful consideration. Proper patient selection is crucial, with short-acting beta-blockers

being the preferred option. Echocardiography plays an important role in identifying patients who might not tolerate beta-blocker treatment.

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