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Viewpoint

The pros and cons of beta-blockers in sepsis: Where do we stand in 2024?

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Septic shock is associated with severe vasoplegia, increased permeability, maldistribution of regional blood flows, and microvascular alterations. Hemodynamic management includes fluid and vasopressor agents and, in selected cases, inotropic agents. However, several patients remain tachycardic after initial resuscitation. Tachycardia is frequently observed in sepsis and is associated with a poor outcome.[1] Given the negative impact of tachycardia, the use of short-acting beta-blockers was proposed.[2] Of note, tachycardia was suggested to be protective in patients with increased lactate levels whereas opposite effects were observed in patients with normal lactate levels.[3] The impact of tachycardia should hence not be evaluated without looking at tissue perfusion. In addition, patients in septic shock with elevated left ventricular (LV) ejection fraction (EF) at echocardiography present an increased risk of death. In a retrospective single-center study including 1014 patients, an elevation in LVEF was found to be independently correlated with mortality (odds ratio=3.90 [2.09–7.40]).[4] In another cohort of patients with sepsis and septic shock, the relationship between LVEF and mortality showed a *U*-shaped pattern, with severely impaired (<25%) and elevated (≥70%) EF, both being independently associated with an increased risk of death.[5] In tachycardic hyperkinetic hearts, beta-blockers are expected to be particularly useful. Several randomized controlled trials (RCTs) evaluated the impact of short-term beta-blockers to control tachycardia in septic patients, sometimes with diverging results. In this review, we analyze the results of three main RCTs to discuss whether there is a place for the use of beta-blockers in septic patients with tachycardia.[2,6,7]

The Initial Promises

The trial by Morelli et al.[2] was an eye-opener. This single-center RCT randomized 77 patients with septic shock to receive esmolol, titrated to reach a target heart rate (HR) between 80/min and 94/min for 96 h, or placebo. The primary outcome, HR reduction, was successfully reached. Interestingly, stroke volume (SV) or arterial pressure was preserved. The authors reported a significant reduction in 28-day and 90-day mortality. Some concerns were made. First, even though cardiac output (CO) was reported to be preserved, oxygen delivery decreased by 20%. Second, the mortality rates in the control group were exceptionally high, reaching 80.5% at 28 days and more than 90% at 90 days.

In a subsequent observational study, the authors reported that the improvement of SV with beta-blockers was not solely ascribed to the prolongation of diastolic time, allowing not only the better filling of the left ventricle, but also related to a decrease in afterload. The improvement in arterial elastance may be related to better synchronization between reflected pressure waves and aortic valve closure,[6] improving the ventriculo-arterial coupling. Improvement in ventriculo-arterial coupling was further confirmed by an increase in the dicrotic notch pressure during esmolol infusion.[7]

Systematic reviews and meta-analyses suggested that esmolol was safe and effective.[8,9] A meta-analysis conducted in 2020, aggregating 5 RCTs totalizing 363 patients, reported that esmolol controlled ventricular rates with no notable adverse effects on tissue perfusion and even reduced 28-day mortality.[8] Another meta-analysis published in 2021 including 7 studies with 613 patients, suggested that the use of esmolol or landiolol can significantly reduce 28-day mortality.[9] Of note, several of the aggregated trials included patients with sepsis without shock.

The Disillusion

Although these results appeared promising, they were challenged by other trials.

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Table 1
Comparison of the two main interventional studies on beta-blockers in septic shock.

Items	Morelli et al.[2]	Whitehouse et al.[10]
Design	Monocentric, open label	Multicentric, open label
Randomization process	Sealed envelopes	Central
Primary outcome	HR reduction	Modified SOFA score during first 14 days
Inclusion criteria	Adult patients with septic shock receiving norepi to achieve MAP ≥65 mmHg despite adequate fluid resuscitation and presenting HR ≥95 beats/min	Adult patients with septic shock receiving norepi ≥0.1 mcg/(kg·min) for >24 h but <72 h, lactate >2 mmol/L and presenting HR >95 beats/min
Exclusion criteria	Pronounced cardiac dysfunction Beta-blockers before ICU admission	Tachycardia due to pain/discomfort, non-septic vasodilatory shock
Intervention	Esmolol continuous infusion (25–2000 mg/h)	Landiolol continuous infusion (1.0 mg/(kg·min) adapted to HR)
Target HR	80–94 bpm	80–94 bpm
Timing of intervention	From randomization (24 h after starting norepi infusion) to the end of ICU stay	From randomization (24 h after starting norepi infusion) to 12 h after cessation of vasopressors
Control group	Usual care, beta-blockers prohibited during ICU stay	Usual care, beta-blockers prohibited during ICU stay
Hemodynamic measurements	Arterial pressure + HR + CO + PAP + PAOP + CVP	Arterial pressure + HR
Echocardiography	Before esmolol but not during infusion	No
Advanced hemodynamic monitoring	Pulmonary artery catheter	None
$SvO_2/ScvO_2$	Yes, per protocol	Yes, per protocol
Lactate	Yes, per protocol	Yes, per protocol
SOFA score	No	Yes, per protocol
Mortality 28/30 days	Esmolol/control (p)	Landiolol/control (p)
Mortality 90 days	Esmolol/control (p)	Landiolol/control (p)

CO: Cardiac output; CVP: Central venous pressure; HR: Heart rate; ICU: Intensive care unit; MAP: Mean arterial pressure; PAOP: Pulmonary artery obstruction pressure; PAP: Pulmonary artery pressure; SOFA: Sequential Organ Failure Assessment; $ScvO_2$: Central venous oxygen saturation; SvO_2 :Venous oxygen saturation.

In a recent multicentric RCT, Whitehouse et al.[10] reported that landiolol, another short-acting beta-blocker, failed to improve organ function (the primary outcome) despite effectively reaching target HR. The main characteristics of the trials are reported in Table 1. Although both groups were similar at inclusion, lactate tended to be more elevated in the landiolol group and received higher doses of norepinephrine during landiolol infusion to achieve the same arterial pressure. Unfortunately, mortality was significantly higher in the landiolol-treated than in control patients, both at day 28 (37.1% *vs.* 25.4%) and at day 90 (43.5% *vs.* 28.6%). No hemodynamic monitoring data were collected at baseline or during landiolol infusion.

A third large-scale multicentric RCT trial on landiolol in patients with septic shock (LANDI-SEP) was on the other hand neutral (completed February 2022 not yet published but results are available on the EU registry [EudraCT Number: 2017-002138-22 – Clinical trial results – EU Clinical Trials Register], with the protocol published in trials[11]). This trial, including 195 patients, demonstrated that landiolol was able to achieve HR within the target and able to maintain it (primary outcome achieved, P <0.001). However, vasopressor doses increased during the landiolol administration. There was no difference in 28-day mortality (control 40.2% *vs.* landiolol 43.9%, P=0.59).

How to Reconcile the Results of These Studies?

The most important conclusion is that these three trials show that beta-blockers can effectively control HR. Safety concerns were raised due to the increase in vasopressor doses, and, potentially, a risk of increased mortality if beta-blockers were given without prior cardiac evaluation. Myocardial depression frequently occurs, affecting the systolic and diastolic functions of the LV as well as the right ventricle (RV) at a variable intensity.[12]

Echocardiography may be helpful for identifying patients in whom beta-blockers are considered. Morelli et al.[2] excluded patients with severely impaired left heart function, which perhaps contributed to the better results in that study. Echocardiography identified several sub-phenotypes: adequately resuscitated, predominant RV dysfunction, LV dysfunction, still hypervolemic and hyperkinetic.[12] In a recent meta-analysis, hyperkinetic LV function was observed in 18% of the patients with sepsis.[13] In addition, dynamic outflow tract or mid-ventricular obstruction has also been reported in up to 20% of the patients.[14] Beta-blockers are probably indicated in tachycardic patients with hyperkinetic hearts and obstruction but are contraindicated in patients with LV and RV dysfunction.

In addition, evaluation of the hemodynamic response to beta-blockers should include monitoring CO, cardiac function, and tissue perfusion. This is particularly relevant as short-acting beta-blockers are used and these can thus rapidly be stopped if adverse hemodynamic effects occur.[15] Using pulse contour CO measurements, Morelli et al.[7] showed that approximately 50% of the patients improved their CO together with neutral effects or minimal improvement in indices of LV and RV functions. On the other hand, the remaining half of the patients deteriorated CO and indices of contractility.

Whenever possible, monitoring of the cardiovascular effects of the beta-blocker infusion should include the evaluation of cardiac function by echocardiography. No modification was found in the LVEF or in the global longitudinal strain (GLS) of the LV as was reported in a small-sized randomized trial in China.[16] This study did not evaluate the changes in individual patients. In another study, Du et al.[17] looked at the individual response and found no difference in baseline hemodynamics, but reported that a better-preserved systolic function at baseline, identified by a mitral annular plane systolic excursion (MAPSE) above 1.32 cm, separated patients who increased CO from those who decreased CO during esmolol infusion.

Before Thinking at Beta-Blockers, Some Simple Actions May be Considered

Beyond preload optimization, a few simple measures should be undertaken before discussing the use of beta-blockers. Fever

should be controlled as temperature control may help decrease HR and help achieve hemodynamic stability.[18]

Catecholamine sparing regimen may be considered in patients with septic shock and tachycardia. Hydrocortisone should be introduced. Also, vasopressin may be considered as it allows to decrease HR and limits the risk of arrythmias.[19] In patients with septic shock receiving norepinephrine and presenting LV tract obstruction, the introduction of vasopressin allowed for decreased norepinephrine and improved obstruction.[20]

Conclusions

The systematic administration of beta-blockers in tachycardic patients with septic shock remains debatable. Echocardiography should be performed to identify patients who may potentially benefit from beta-blockers. When beta-blockers are administered, we recommend cautiously titrating the dose and closely evaluating their effects with advanced hemodynamic monitoring and by echocardiography.

CRediT Authorship Contribution Statement

Daniel De Backer: Writing – review & editing, Writing – original draft, Validation, Supervision, Conceptualization. **Dechang Chen:** Writing – review & editing, Writing – original draft, Validation, Supervision, Conceptualization.

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Ethics Statement

Not applicable.

Conflict of Interest

Daniel De Backer: Edwards Lifesciences, Philips, Baxter, Viatris, Pharmazz.

Dechang Chen: No conflicts.

Data availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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