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Review

Beta-blockers in septic shock: What is new?

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ABSTRACT

The use of beta(β)-blockers during septic shock aimed at countering peripheral adrenergic stress may be justified by the early reduction in deleterious effects resulting from sympathetic overactivation, and could improve the prognosis of patients in septic shock. Animal studies have demonstrated either a maintenance or increase in cardiac output (CO) despite the decrease in heart rate (HR) associated with improved myocardial performance. The mechanism by which β-blockers alter hemodynamics in septic shock is debated; however, preclinical and clinical data show that β-blockers are safe when started at a low dose. Recent publications (2019–2021) on adrenergic β1 receptor antagonists used in septic shock indicate that esmolol and landiolol should not be used in the early phase. While there is no optimal timing for their administration, a minimum of 12 h after the initiation of vasopressor therapy in stabilized euvolemic patients is a reasonable option. Patients should have a normal cardiac function, although a slight depression is compatible with landiolol use under hemodynamic monitoring. Slow titration in patients who remain tachycardic is preferable to rapid titration. When used to decrease HR, landiolol is also effective in reducing the incidence of new arrhythmias. Results of a well-performed and well-powered randomized controlled trial (RCT) demonstrating a positive effect on survival – or at least on hard surrogates such as the incidence/duration of organ failure – are pending.

Introduction

Activation of the sympathetic nervous system through the release of norepinephrine and epinephrine is a key step in the initial phase of sepsis. The effects include an increase in inotropism, tachycardia, and vasoconstriction, which counteract toxins and/or the initial inflammatory response to infection. However, a persistently high level of activation can be deleterious and lead to sympathetic dysautonomia syndrome.[1] This occurs at an early stage (within the first 24 h) of septic shock and its intensity – reflecting adrenergic sympathetic overactivation – is associated with greater clinical severity and mortality.[2,3] This is counterintuitive for clinicians as it suggests an adverse effect of excess catecholamine, although this is a cornerstone of septic shock therapy. Indeed, adrenal insufficiency contributes to hemodynamic disturbance in septic shock.[4] Owing to its vascular α1-agonist effect, norepinephrine is used to treat vasoplegia and capillary leakage but can cause tachycardia and dysautonomia and alter cardiac hemodynamics while vascular tone may be improved. Epinephrine + dobutamine *vs*. epinephrine alone (control) did not improve survival in a randomized controlled trial (RCT), suggesting that there is no potential benefit from β-adrenergic stimulation in septic shock.[5] A treatment approach that decreases peripheral adrenergic stress may be justified by the early reduction in deleterious effects resulting from sympathetic overactivation and may improve the prognosis of patients in septic shock.

The principle of adrenergic re-equilibrium or decatecholaminization as evaluated with a cardioselective β1-blocker is based on robust scientific evidence.[6,7] Adrenergic receptor (ARs) are categorized as α- and β-ARs. The healthy human heart expresses a mixed population of β-AR subtypes with

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Table 1
Preclinical studies on the utility of β-blockers for sepsis treatment published from 2019 to 2021.

Authors	Animal	Sepsis model	Drug	Main conclusion
Kimmoun et al. [10]	Wistar rat	CLP	Esmolol	BB improved cardiac contractility, upregulated vascular α1 AR expression, and exerted an anti-inflammatory effect (as measured by NF-κB level)
Bedet et al. [14]	Mouse	CLP	Atenolol ivabradine	Unlike ivabradine, BB reduced SAP and CO; none of the examined drugs had an effect on 60-h survival
Bangash et al. [20]	Wistar rat	Endotoxemia LPS	Dopexamine* salbutamol	β-Agonists reduced leucocyte–endothelial adhesion in postcapillary veinules as assessed by intravital microscopy
Stolk et al. [21]	C57BL/6 J mouse	Endotoxemia LPS and CLP	Norepinephrine vasopressin	Norepinephrine enhanced immunoparalysis by attenuating production of proinflammatory mediators and stimulating IL-10 production
Van Loon et al. [22]	Sheep	Endotoxemia LPS	Esmolol	BB increased pressure dependency of renal blood flow to renal perfusion pressure by impairing renal autoregulation
Van Loon et al. [23]	Lamb	Endotoxemia LPS	Esmolol	Esmolol improved VACR by decreasing the RV end-systolic pressure in a single-beat PV loop assessment
Carrara et al. [41]	Pig	Intraperitoneal instillation of autologous feces	Esmolol ivabradine	Sepsis-induced cardiac dysautonomia was improved by esmolol and ivabradine, but only esmolol continued to provide benefit under norepinephrine treatment
Carrara et al. [42]	Pig	Intraperitoneal instillation of autologous feces	Esmolol ivabradine	Esmolol improved vascular function via increased peripheral vascular resistance
Guo et al. [43]	SD rat	CLP	Esmolol	Esmolol inhibited inflammation and apoptosis in the intestinal tissue via overexpression NF-κB p65

* β-Agonist. Esmolol improved VACR by decreasing the RV end-systolic pressure.
AR: Adrenergic receptor; BB: β-blocker; CLP: Cecal ligation and puncture; CO: Cardiac output; IL-10: Interleukin 10; LPS: Lipopolysaccharide; NF-κB: Nuclear factor κB; PV: Pressure–volume; RV: Right ventricle; SAP: Systolic arterial pressure; SD: Sprague–Dawley; VACR: Ventriculo-arterial coupling ratio.

approximately 80% β1 and 20% β2;[8] meanwhile, the vasculature expresses α1-AR, which mediates vasoconstriction. β2-AR is expressed in both vascular and bronchial smooth muscle (mediating vasorelaxation and bronchorelaxation, respectively). β1-ARs activate the G protein–adenylyl cyclase–cyclic adenosine monophosphate (AMP)–protein kinase A signaling cascade and induce positive inotropic and chronotropic effects.[9] Cardioselective β-blockers (BB) are characterized by a high $\beta1/\beta2$ ratio (*i.e.*, with a higher affinity for β1 than β2 receptors) and can confer cardioprotection without systemic adverse effects.

In this review, we summarize experimental (Table 1) and clinical studies (Table 2) that have evaluated the efficacy of β1-blockers in the treatment of septic shock. Relevant articles including experimental and clinical studies, systematic reviews, meta-analyses, and ongoing trials published between 2019 and 2021 were identified through a search of the National Library of Medicine's controlled vocabulary database performed according to PRISMA guidelines using the MeSH terms "septic shock" and "adrenergic beta-1 receptor antagonists."

Experimental Studies

Experimental studies using small and large animal models of septic shock have investigated the effects of BBs on cardiovascular function and inflammation. The main models that have been used are polymicrobial sepsis induced by cecal ligation and puncture (CLP) and endotoxic shock induced by lipopolysaccharide (LPS) injection, which lead to sepsis of variable severity.

Rodent studies have demonstrated that BBs either maintain or increase cardiac output (CO) despite a decrease in heart rate (HR).[10,11] Myocardial external work is reduced, allowing for higher global myocardial work efficiency at a lower energetic cost.[12] Vascular function and responsiveness to vasopressor treatment are also improved.[10] These hemodynamic effects are associated with a reduction in lactatemia that could potentially reflect a lower tissue oxygen demand, and thus, higher oxidative metabolism.[13] β1-Blockers were also shown to improve survival in small animal models of septic shock.[14,15]

ARs are broadly expressed in the immune system except by type 2 T helper cells. The impact of adrenergic stimulation on immunomodulation is debated. Upon adrenergic stimulation, monocytes differentiate into mature macrophages that are functionally distinct in their cytokine response.[16] Catecholamine exposure enhances post-aggression immunoparalysis and can be partly reversed with BBs.[17] β-Adrenergic blockade inhibited splenocyte apoptosis in a murine model of septic shock under epinephrine stimulation,[18] as well as the release of proinflammatory cytokines such as interleukin (IL)−6 and tumor necrosis factor (TNF)-α into plasma and nuclear factor (NF)-κB translocation in the early phase of septic shock.[10,19] Intravital microscopy revealed that β2 agonist treatment reduced leucocyte–endothelial adhesion in postcapillary veinules, which could explain the anti-inflammatory effect of catecholamine.[20] In LPS-challenged healthy volunteers, norepinephrine enhanced plasma IL-10 concentrations and inhibited the release of the proinflammatory cytokine interferon (IFN)-γ; β-blocker restored the cytokine balance. Additionally, norepinephrine was shown to dysregulate the immune response in mouse and human and compromised host defense, possibly contributing to sepsis-induced immunoparalysis.[21]

Effects of esmolol on renal blood flow and right ventricle (RV) function

The effects of esmolol on HR control were investigated in a sheep model of endotoxic shock.[22] After successful septic shock resuscitation, esmolol was infused to reduce HR by 30% and was stopped 30 min after this target was reached. Arterial and venous pressures as well as renal blood flow were continuously recorded. Renal autoregulation was assessed by the renal blood

Table 2
Clinical studies on the utility of β-blockers for sepsis treatment published from 2019 to 2021.

Authors	Study design	Trial process	Number of patients in each treatment arm	Primary outcome	Secondary outcome
Liu et al. [44]	Prospective RCT	Esmolol *vs.* placebo	50 *vs.* 50	28-day mortality, 62% *vs.* 68% ($P = 0.529$)	NS for lactate level, hospital length of stay, norepinephrine use
Pham et al. [45]	Retrospective cohort study	Premorbid BB exposure *vs.* not in sepsis on serum lactate level	189	Mean serum lactate level was 0.87 (0.05–1.65); lower under BB	NA
Chan et al. [46]	Prospective observational study (BeLLa study)	Serum lactate level in premorbid BB exposure *vs.* not septic	70	Serum lactate level, 1.78 mmol/L *vs.* 1.70 mmol/L (NS)	NA
Bosch et al. [47]	Retrospective cohort study	BB *vs.* CaB *vs.* amiodarone *vs.* digoxine on HR in septic patients	666 (10.1% BB, 33.8% CaB, 50.6% amiodarone, 5.6% digoxine)	BB improved HR control < 110 beats/min after 1 h *vs.* amiodarone, digoxin, and CaB	NA
Morelli et al. [37]	*Post-hoc* analysis	SDP > 35 mmHg to predict dP/dt drop during esmolol infusion	23 stable dP/dt *vs.* 22 dP/dt drop	Significantly lower SDP in stable dP/dt *vs.* decreased dP/dt group, 40 *vs.* 53 ($P = 0.01$)	Lower SDP was associated with CO and SV reductions; higher SDP was associated with stable SV and CO
Kakihana et al. [39]	RCT	Landiolol *vs.* control	76 *vs.* 74	HR (60–95 beats/min) at 24 h, 55% *vs.* 33% ($P = 0.0031$)	Safety analysis showed similar AE rates between groups
Kuo et al. [33]	Retrospective observational study	β1-selective BB *vs.* nonselective BB *vs.* control	137 *vs.* 72 *vs.* 1053	ICU mortality of 9.5 *vs.* 15.3% *vs.* 20.6% ($P = 0.005$)*	NA
Tan et al. [32]	Retrospective observational study (BEAST study)	Premorbid BB exposure *vs.* not in sepsis	1536 *vs.* 2550	ICU mortality, OR = 0.80; 95% CI: 0.66–0.97 ($P = 0.025$)	BB improved neurologic and respiratory SOFA score
Li et al. [35]	Meta-analysis of five RCTs	Esmolol *vs.* control	161 *vs.* 161	28-day mortality, RR = 0.49; 95% CI: 0.48–0.74	NA
Hasegawa et al. [34]	Meta-analysis of six RCTs	Esmolol/landiolol *vs.* control	286 *vs.* 286	28-day mortality, RR = 0.68; 95% CI: 0.54–0.85 ($P < 0.001$, in favor of BB)	NA

* Significant for β1-selective BB *vs.* control.
AE: Adverse event; BB: β-blocker; CaB: Calcium blocker; CI: Confidence interval; CO: Cardiac output; dP/dt: Maximal rate of rise of left ventricle pressure; HR: Heart rate; ICU: Intensive care unit; NA: Not available; NS: Nonsignificant; RCT: Randomized controlled trial; RR: Risk ratio; SDP: Systolic-diastolic notch pressure; SOFA: Sequential Organ Failure Assessment; SV: Stroke volume.

flow response to renal perfusion pressure. It was observed that β-blockade with esmolol significantly increased the pressure dependency of this response. Halting esmolol infusion confirmed that the impaired renal autoregulation was reversible, underscoring the importance of exercising clinical diligence and caution when treating septic shock with esmolol.

In another study by the same authors examining the effects of esmolol on RV function in an experimental model of LPS-induced septic shock, the > 30% reduction in HR induced by esmolol infusion following controlled resuscitation led to deterioration of RV function and macrocirculation, with microcirculation remaining depressed.[23] On the other hand, esmolol improved ventriculo-arterial coupling by decreasing RV end-systolic pressure. Discontinuing esmolol reversed the effects on both RV function and macrocirculation. In this animal model of acute severe endotoxic septic shock, early administration of esmolol decreased RV function, resulting in venous congestion and no improvement in microcirculation despite improved cardiac mechanical efficiency. However, caution is warranted because under physiologic conditions in humans, the RV does not undergo post-load isovolumetric relaxation. Single-beat assessment of ventriculo-arterial coupling has been challenging and is unlikely to be a reliable way to assess the RV pressure–volume (PV) loop.

In summary, the above-described studies aptly illustrate the difficulty in using β-blockers during septic shock, especially during the acute phase, with the beneficial effects counteracted by decreased arterial pressure and CO.

Clinical Studies

A single-center, prospective, randomized, open-label trial of esmolol *vs.* placebo was conducted to assess the efficacy of esmolol administration in reducing HR to 80–94 beats/min as well as esmolol tolerance in patients with septic shock and a HR ≥ 95 beats/min 24 h after admission.[24] Esmolol reduced HR to the target level but not CO, mainly because of an increase in stroke volume secondary to elongation of the diastolic period. Levosimendan – an inotrope calcium sensitizer that acts independently of ARs – was administered in a similar manner in both groups (esmolol: 49.4%, placebo: 40.3%, $P = 0.39$). The required dose of norepinephrine was lower in the esmolol group than in the placebo group while vascular resistance was higher; this was associated with a 31% decrease in mortality to 49.9% (as compared to 80% in the placebo group). These results have been extensively debated in the literature,[25–31] but four main points should be emphasized: (1) esmolol effectively reduces HR; (2) tolerance is excellent, although the provision of care is outside conventional practices as approximately 50% of patients received levosimendan; (3) the reduced requirement for norepinephrine in the esmolol group remains unexplained; and (4) the decrease in survival must be weighed against the mortality rate in the control group, which was unusually high and far from the result expected in 2013.

Retrospective cohort studies have reported results in line with those mentioned above. In the BEAST study, pretreatment

with BB for chronic comorbid conditions improved survival in sepsis patients.[32] Premorbid β1-selective BBs but not nonselective BBs reduced intensive care unit (ICU) mortality in sepsis patients.[33] A meta-analysis of seven RCTs revealed a survival benefit with BBs in sepsis or septic shock:[34] esmolol or landiolol use was significantly associated with lower 28-day mortality (risk ratio [RR]: 0.68; 95% confidence interval [CI]: 0.54–0.85; $P < 0.001$), although there was non-negligible heterogeneity across studies ($I^2 = 31\%$). The absolute risk reduction was 18.2% and the number of patients that needed to be treated to prevent one death was 5.5. A systematic review and meta-analysis showed that the use of β-blocker (esmolol) was safe and effective in improving 28-day mortality and controlling ventricular rate in patients with sepsis after fluid resuscitation, with no significant adverse effect on tissue perfusion;[35] this was confirmed by another meta-analysis.[36] However, as there is a lack of large-scale RCTs evaluating the effect of β-blockers on HR, further research is needed to validate the above findings.

The systolic–dicrotic notch pressure (SDP) difference has been proposed to identify tachycardic patients at risk of cardiovascular decompensation following pharmacologic HR reduction. An SDP difference threshold of 35 mmHg predicted early cardiac decompensation under BB therapy, revealing a covert loss of myocardial contractility that deteriorated after HR reduction with esmolol and was not detected by conventional echocardiographic parameters.[37] In terms of hemodynamic effects, there is sufficient preclinical and clinical data to suggest that β-blockade is safe when started at a low dose.

Early esmolol use in hyperkinetic septic shock

Several studies have shown that HR control with selective β1-blockers is safe for the treatment of septic shock. In these trials, esmolol was administered 24 h after onset of septic shock in patients who remained tachycardic. While earlier use of β-blockers may be beneficial, this can be challenging because of the difficulty in distinguishing between compensatory and non-compensatory tachycardia. In a study of stabilized tachycardic hyperkinetic septic shock patients treated with norepinephrine for a minimum of 6 h, esmolol was infused over 6 h in order to decrease the HR by 20%. In three of the nine patients, the lowest dose of esmolol was halted early because of a marked increase in norepinephrine requirement reflecting persistent cardiac failure.[38] The use of esmolol was associated with a significant decrease in HR from 115 (110–125) to 100 (92–103) beats/min and in cardiac index from 4.2 (3.1–4.4) L/min/m^2 to 2.9 (2.5–3.7) L/min/m^2; indexed stroke volume remained unchanged while cardiac function index and global ejection fraction also decreased; and systolic, diastolic, and left ventricle and RV function parameters worsened by echocardiography. After esmolol cessation, all parameters returned to baseline values. Lactate and microcirculatory parameters were unaltered while the levels of most proinflammatory proteins decreased in all patients. Thus, in the very early phase of septic shock, HR reduction by fast esmolol titration was associated with an increased risk of hypotension and decreased cardiac index despite the maintenance of adequate tissue perfusion. The discrepancy between these findings and those of Morelli et al.[24] is likely attributable to the dose titration used by the latter investigators to achieve the predefined HR threshold, which lasted 12 h with a first data collection point conducted 24 h after the start of esmolol administration (and hence, 48 h after norepinephrine introduction as compared to 9 h in the study by Levy et al.[38])

Effects of landiolol treatment on sepsis-related tachyarrhythmia

Landiolol is an ultrashort-acting (half-life of 2.4–4.0 min) β-blocker[39] with a high selectivity for the β1 receptor and higher selectivity than esmolol, making it suitable for titration in critical care HR control. In a multicenter, open-label RCT conducted in Japan, adults with septic shock and stabilized catecholamine titration who were diagnosed with sustained supranodal tachycardia ($\geq$ 10 min) and a HR $\geq$ 100 beats/min within 24 h prior to randomization and within 72 h after entering an ICU were treated with conventional sepsis therapy without (control) or with landiolol.[39] More patients in the landiolol group had sepsis-related tachyarrhythmia with a HR of 60–94 beats/min at 24 h, along with a significantly lower incidence of new-onset arrhythmia. Landiolol also showed a trend of improving survival and prevented new-onset sepsis-related atrial fibrillation. However, there was no difference in HR between groups at 24 h, 48 h, and 96 h. These data suggest that landiolol improves clinical outcome via a mechanism other than chronotropic control. Serious adverse events (AEs) related to landiolol occurred in 5/77 (6%) patients; these included blood pressure decrease in three patients (4%) and cardiac arrest, severe bradycardia, and decreased ejection fraction in one patient each (1%). Therefore, landiolol should be used with appropriate blood pressure and HR monitoring because of the risk of hypotension in patients with sepsis and septic shock.

Synthesis

The main conclusion of the above-mentioned studies is that β1-blockers should not be administered in the early phase of septic shock as this may blunt a compensatory response, and should be administered by slow titration and only after initial resuscitation. As patients with severe cardiac dysfunction were excluded from the studies, cardiac function should be assessed prior to initiation of β1-blocker treatment. The use of esmolol/landiolol to reduce HR in tachycardic patients with normal cardiac function could be considered for HR control and to improve hemodynamics. Nonetheless, more evidence supporting the use of β-blockers for septic shock treatment is needed.

Ongoing Studies

The role of selective β-blockers is currently being investigated in a number of ongoing studies. One of these will address the effects of landiolol on survival in adult patients with septic shock (NCT04748796). In the LANDI-SEP study (EudraCT 2017–002,138–22), the primary endpoints are HR response (HR 80–94 beats/min), its maintenance, and the absence of increased vasopressor requirements in the first 24 h after initiating treatment.[40]

Conclusions

The use of selective short-acting β-blockers for sepsis is promising. There is now clear evidence that esmolol and especially landiolol should not be used in the early phase of septic shock. While there is no optimal timing for their administration, a minimum of 12 h after the introduction of vasopressor therapy in stabilized euvolemic patients appears reasonable. Patients should have a normal cardiac function although a slight depression is compatible with landiolol use under hemodynamic monitoring. Slow titration in patients who remain tachycardic is preferable to fast titration. When used to decrease HR, landiolol is also effective in reducing the incidence of new arrhythmias. Finally, the results of a well-performed and well-powered RCT demonstrating a positive effect on mortality – or at least on hard surrogates such as the incidence/duration of organ failure – are pending.

Conflicts of Interest

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