RESEARCH PAPER

Impact of Chronic Beta-Blocker Use on Vasopressor Response to Norepinephrine in Critically Ill Patients

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ABSTRACT

Background: Norepinephrine is the first-line vasopressor for septic and vasodilatory shock, yet patient responses vary widely. Chronic beta-blocker therapy may modify adrenergic responsiveness and alter vasopressor requirements during critical illness.
Objective: To assess the effect of chronic pre-admission beta-blocker use on norepinephrine dose requirements and early hemodynamic recovery in critically ill patients.
Methods: This prospective observational study included 100 ICU patients with septic or vasodilatory shock requiring norepinephrine. Patients were grouped based on pre-admission beta-blocker use. Norepinephrine dose, time to mean arterial pressure stabilization, lactate clearance, vasopressor duration, ICU length of stay, and 28-day mortality were compared.
Results: Chronic beta-blocker users required higher norepinephrine doses, had delayed MAP stabilization, slower lactate clearance, and longer vasopressor dependence and ICU stay. Mortality was higher but not statistically significant.
Conclusion: Chronic beta-blocker therapy is associated with altered vasopressor responsiveness and delayed hemodynamic recovery in shock.
Keywords: *Beta-blockers; Norepinephrine; Septic shock; Vasodilatory shock; Vasopressor response; Intensive care unit*

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1. INTRODUCTION

Shock is a life-threatening clinical syndrome defined by acute circulatory failure and inadequate tissue perfusion, leading to cellular hypoxia, metabolic acidosis, and progressive organ dysfunction. It is among the most common and serious conditions encountered in intensive care units (ICUs) worldwide. Septic and vasodilatory shock account for the majority of cases and continue to be associated with high mortality rates despite improvements in early recognition, antimicrobial therapy, and supportive care (Vincent et al., 2018). Even with advances in critical care protocols, mortality from septic shock remains between 30% and 45%, emphasizing the importance of optimizing hemodynamic management strategies.

Vasopressor therapy is central to the management of shock, particularly when hypotension persists after adequate fluid resuscitation. Among available agents**, norepinephrine is currently recommended as the first-line vasopressor** for both septic and vasodilatory shock due to its potent α-adrenergic vasoconstrictive effects, modest β-adrenergic activity, and favorable safety profile (Evans et al., 2021). By increasing systemic vascular resistance, norepinephrine restores mean arterial pressure (MAP) and improves organ perfusion. However, the clinical response to norepinephrine is highly variable. While some patients stabilize rapidly with low doses, others develop refractory hypotension requiring escalating doses and prolonged infusion, which are associated with increased morbidity and mortality (Guarracino et al., 2023).

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This inter-individual variability in vasopressor response reflects a complex interplay between disease severity, comorbidities, endogenous catecholamine reserve, adrenergic receptor sensitivity, microcirculatory function, and prior pharmacologic exposures. Among these, **chronic beta-blocker therapy** represents a particularly important but understudied determinant of hemodynamic responsiveness in critically ill patients.

Beta-blockers are among the most widely prescribed cardiovascular medications worldwide. They are routinely used for hypertension, ischemic heart disease, heart failure, atrial fibrillation, and other arrhythmias. As the global population ages and the prevalence of cardiovascular disease rises, an increasing proportion of ICU patients are receiving long-term beta-blocker therapy prior to admission. While beta-blockers confer substantial survival benefits in chronic cardiovascular disease, their physiological effects in the context of acute shock are complex and may be paradoxical (Brüning et al., 2021).

Beta-blockers act by antagonizing β-adrenergic receptors, thereby reducing heart rate, myocardial contractility, and sympathetic tone. Chronic exposure induces adaptive changes at both the receptor and post-receptor level, including **β-receptor downregulation, altered G-protein coupling, reduced cyclic adenosine monophosphate signaling, and modification of autonomic reflex pathways** (Henneicke et al., 2014). These adaptations may persist even after discontinuation of therapy and can profoundly alter cardiovascular responses during acute stress states.

In shock, where endogenous and exogenous catecholamines play a central role in maintaining perfusion, such receptor-level changes may significantly influence the effectiveness of vasopressors. Although norepinephrine primarily exerts its vasopressor effects via α-1 adrenergic receptors, adequate cardiovascular compensation also requires intact β-adrenergic–mediated cardiac reserve and baroreflex sensitivity. Chronic beta-blockade may therefore necessitate higher vasopressor doses to achieve comparable hemodynamic endpoints and may delay recovery of tissue perfusion (Heliste et al., 2022).

In recent years, interest has grown in the **acute administration of short-acting intravenous beta-blockers** such as esmolol and landiolol during septic shock. Several randomized controlled trials have demonstrated that controlled heart-rate reduction in stabilized septic patients may improve myocardial efficiency and reduce the harmful effects of excessive sympathetic activation, without compromising hemodynamic stability (Morelli et al., 2018). A recent meta-analysis by Al Sulaiman et al. (2024) concluded that beta-blocker use in septic shock did not increase vasopressor requirements and was associated with reduced 28-day mortality in selected populations.

However, these trials largely excluded patients who were already receiving chronic beta-blocker therapy and focused on **acute, titratable beta-blockade initiated during critical illness**. As a result, their findings cannot be directly extrapolated to patients who present with long-standing adrenergic modulation. This distinction is critical, as chronic beta-blockade is associated with more profound receptor adaptations and altered cardiovascular reflexes than short-term intravenous therapy (Guarracino et al., 2023).

Observational studies examining pre-admission beta-blocker use in sepsis and shock have yielded inconsistent results. Some investigations have suggested neutral or protective associations with mortality, possibly due to attenuation of catecholamine-induced myocardial injury and arrhythmias. In contrast, other studies have reported altered hemodynamic profiles, including higher vasopressor requirements, delayed stabilization, and prolonged ICU stays (Tan et al., 2019; Brüning et al., 2021). These discrepancies likely reflect heterogeneity in patient populations, beta-blocker selectivity, dosing, duration of exposure, and differences in resuscitation strategies.

Beyond macrocirculatory effects, chronic beta-blockade may influence **microcirculatory function and metabolic recovery.** Lactate clearance is widely used as a surrogate marker of tissue perfusion and resuscitation adequacy. Delayed lactate normalization is associated with increased mortality and organ dysfunction in shock (Vincent et al., 2018). Tan et al. (2019) demonstrated slower lactate clearance in septic patients with premorbid beta-blocker exposure, suggesting persistent microcirculatory dysfunction despite restoration of MAP.

Similarly, the **duration of vasopressor therapy** and **ICU length of stay** are clinically meaningful outcomes that reflect the pace of hemodynamic recovery and overall disease burden. Prolonged vasopressor dependence is associated with higher rates of ischemic complications, arrhythmias, secondary infections, and increased healthcare costs. Heliste et al. (2022) reported longer vasopressor duration and ICU stays among critically ill patients with pre-existing beta-blocker therapy, supporting the hypothesis that chronic adrenergic modulation influences early clinical trajectories.

Despite the growing body of literature, **current guidelines offer limited guidance** on how to incorporate chronic beta-blocker therapy into vasopressor decision-making. The Surviving Sepsis Campaign emphasizes early norepinephrine initiation and MAP-guided resuscitation but does not address how pre-existing adrenergic blockade may alter vasopressor responsiveness (Evans et al., 2021). The SIAARTI expert consensus acknowledges that pre-admission beta-blocker use may modify adrenergic responses and should be considered in hemodynamic management, yet robust clinical data remain scarce (Guarracino et al., 2023).

Given the widespread use of beta-blockers and the central role of vasopressors in shock management, elucidating the interaction between chronic beta-blocker therapy and norepinephrine responsiveness is of considerable clinical relevance. Understanding whether pre-existing adrenergic

modulation influences vasopressor requirements, metabolic recovery, and clinical outcomes may help refine resuscitation strategies and promote more individualized hemodynamic management.

Therefore, the present study was undertaken to evaluate the impact of **chronic pre-admission beta-blocker use** on norepinephrine dose requirements, time to MAP stabilization, lactate clearance, duration of vasopressor therapy, ICU length of stay, and short-term mortality in critically ill patients with septic or vasodilatory shock. By directly comparing patients with and without chronic beta-blocker exposure, this study aims to clarify how long-term adrenergic modulation influences acute hemodynamic and metabolic responses during critical illness.

A clearer understanding of these relationships may support more personalized vasopressor strategies, improve monitoring of resuscitation adequacy, and ultimately enhance outcomes for critically ill patients with complex pharmacologic backgrounds.

2. MATERIALS AND METHODS

2. Materials and Methods

2.1 Study Design and Setting

This was a prospective, observational cohort study conducted over a period of 12 months (January 2025 to December 2025) in the Medical Intensive Care Unit (MICU) of a tertiary care teaching hospital. The study was designed to evaluate the influence of chronic beta-blocker therapy on vasopressor responsiveness in critically ill patients requiring norepinephrine for the management of septic or vasodilatory shock. The ICU is a 20-bed, closed unit with 24-hour intensivist coverage and standardized protocols for hemodynamic management and sepsis care.

2.2 Study Population and Sample Size

A total of 100 adult patients admitted to the MICU who required norepinephrine infusion for hypotensive shock were enrolled. Patients were divided into two equal groups based on documented pre-admission beta-blocker use:

- **Group A:** Chronic beta-blocker users (n = 50)
- **Group B:** Non-users (n = 50)

The sample size was determined based on feasibility and average ICU admission rates during the study period, as no prior regional data were available to perform a precise power calculation.

2.3 Sampling Technique

A non-probability consecutive sampling method was used. All eligible patients admitted during the study period were screened, and those fulfilling the inclusion criteria were recruited until the required sample size was reached.

2.4 Eligibility Criteria

2.4.1 Inclusion Criteria

- Age 18 years and above
- Diagnosis of septic or vasodilatory shock, defined by persistent hypotension requiring vasopressors to maintain MAP ≥ 65 mmHg after adequate fluid resuscitation
- Requirement of norepinephrine infusion as the primary vasopressor
- Availability of complete pre-admission medication history
- For Group A: documented beta-blocker therapy for at least three months prior to ICU admission

2.4.2 Exclusion Criteria

- Cardiogenic shock
- Acute coronary syndrome or recent myocardial infarction
- Severe valvular heart disease
- Advanced heart failure (left ventricular ejection fraction < 30%)
- Requirement of inotropes other than norepinephrine
- Pregnancy
- End-stage renal disease on dialysis
- Advanced chronic liver disease
- Do-not-resuscitate or comfort-care-only orders

2.5 Data Collection

After enrollment, demographic data, comorbidities, smoking status, type of shock, and details of beta-blocker therapy (drug, dose, duration) were recorded. Baseline physiological parameters including heart rate, blood pressure, and lactate were documented at the time of norepinephrine initiation.

2.6 Hemodynamic Monitoring and Vasopressor Protocol

All patients underwent invasive arterial blood pressure monitoring. Norepinephrine was initiated at 0.05 μg/kg/min and titrated every 5–10 minutes to achieve MAP ≥ 65 mmHg according to institutional protocol. Fluid resuscitation was guided by dynamic indices.

2.7 Biochemical Assessment

Serum lactate was measured at baseline, 6 hours, and 24 hours. All samples were analyzed in the central laboratory.

2.8 Outcome Measures

Primary outcome: maximum norepinephrine dose.

Secondary outcomes: time to MAP stabilization, lactate clearance, vasopressor duration, ICU length of stay, and 28-day mortality.

2.9 Statistical Analysis

SPSS v22 was used. Student's t-test or Mann–Whitney U test compared groups. Multivariate regression identified independent predictors. $p < 0.05$ was significant.

2.10 Ethical Considerations

The Institutional Ethics Committee approved the study. Written informed consent was obtained.

3. RESULTS AND DISCUSSION

Table 1: Baseline Characteristics of the Study Population

Variable	Beta-blocker Users (n=50)	Non-users (n=50)	p value
Age (years)	62.4 ± 9.1	60.8 ± 10.2	0.42
Male sex, n (%)	31 (62)	29 (58)	0.68
Septic shock, n (%)	37 (74)	35 (70)	0.66
Hypertension, n (%)	41 (82)	18 (36)	<0.001
CAD, n (%)	28 (56)	10 (20)	<0.001
Baseline MAP (mmHg)	56.2 ± 6.3	57.1 ± 6.1	0.48
Baseline lactate (mmol/L)	4.6 ± 1.2	4.4 ± 1.1	0.48

Table 1 summarizes the baseline demographic and clinical characteristics of the 100 critically ill patients included in the study. The two groups were comparable with respect to age, sex distribution, baseline mean arterial pressure, baseline lactate levels, and type of shock. As expected, cardiovascular comorbidities such as hypertension and coronary artery disease were significantly more prevalent among patients with chronic beta-blocker use. This reflects the underlying indications for long-term beta-blocker therapy. Overall, the similarity in baseline hemodynamic parameters between the two groups suggests that subsequent differences in vasopressor requirements and clinical outcomes are unlikely to be attributable to initial disease severity.

Table 2. Norepinephrine Vasopressor Requirements

Parameter	Beta-blocker Users	Non-users	p value
Starting dose (μg/kg/min)	0.18 ± 0.06	0.12 ± 0.05	<0.001
Maximum dose (μg/kg/min)	0.32 ± 0.09	0.21 ± 0.08	<0.001
Time to MAP ≥65 mmHg (h)	5.6 ± 2.1	3.8 ± 1.9	<0.001
Duration of NE infusion (h)	62 ± 24	41 ± 19	<0.001

Table 2 demonstrates the differences in norepinephrine requirements between the two study groups. Patients with chronic beta-blocker exposure required significantly higher starting and maximum doses of norepinephrine compared with non-users. In addition, the time required to achieve target MAP ≥65 mmHg was significantly prolonged in the beta-blocker group. The duration of norepinephrine infusion was also longer in these patients. These findings indicate that chronic beta-blocker use is associated with reduced vasopressor responsiveness and delayed hemodynamic stabilization.

Table 3. Lactate Clearance

Time point	Beta-blocker Users	Non-users	p value
Baseline	4.6 ± 1.2	4.4 ± 1.1	0.48
6 hours	3.1 ± 0.9	2.4 ± 0.8	<0.01
24 hours	2.0 ± 0.6	1.5 ± 0.5	<0.01

Table 3 compares lactate levels at baseline, 6 hours, and 24 hours following norepinephrine initiation. While baseline lactate values were similar in both groups, patients with chronic beta-blocker use demonstrated significantly higher lactate levels at 6 and 24 hours. This indicates slower lactate clearance and suggests persistent tissue hypoperfusion or metabolic dysfunction in this group despite achieving macrocirculatory targets.

Table 4. ICU Outcomes

Outcome	Beta-blocker Users	Non-users	p value
Vasopressor days	3.1 ± 1.2	2.0 ± 0.9	<0.001
ICU stay (days)	9.2 ± 3.1	6.8 ± 2.4	<0.001
28-day mortality, n (%)	19 (38)	12 (24)	0.12

Table 4 presents key clinical outcomes in the two study groups. Patients with chronic beta-blocker exposure had significantly longer durations of vasopressor therapy and extended ICU length of stay compared with non-users. Although the 28-day mortality rate was higher among beta-blocker users, the difference was not statistically significant. These findings suggest that while chronic beta-blocker use may not directly influence short-term survival, it is associated with prolonged hemodynamic support and greater resource utilization.

Table 5. Multivariate Linear Regression for Maximum Norepinephrine Dose

Predictor	β coefficient	Standard Error	p value

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Age	0.002	0.001	0.09
Male sex	0.011	0.006	0.08
Baseline MAP	−0.004	0.001	0.01
Baseline lactate	0.031	0.009	<0.01
Septic shock	0.018	0.007	0.02
Chronic beta-blocker use	0.067	0.014	<0.001

Table 5 shows the results of multivariate linear regression analysis evaluating independent predictors of maximum norepinephrine dose. After adjusting for age, sex, baseline MAP, baseline lactate, type of shock, and comorbidities, chronic beta-blocker use remained a significant independent predictor of higher norepinephrine requirement. This confirms that the association between beta-blocker exposure and vasopressor dose is not explained solely by baseline severity or comorbid conditions.

This prospective observational study evaluated the influence of chronic beta-blocker therapy on the hemodynamic response to norepinephrine in critically ill patients with vasodilatory or septic shock. The findings demonstrate a consistent pattern of altered cardiovascular and metabolic recovery in patients with prior beta-blocker exposure. Specifically, these patients required significantly higher starting and maximal doses of norepinephrine, took longer to reach the target mean arterial pressure (MAP ≥65 mmHg), exhibited slower lactate clearance at early time points, and required prolonged vasopressor support and intensive care unit (ICU) stay when compared with patients who were not receiving beta-blockers. Although 28-day mortality was numerically higher among beta-blocker users, this difference was not statistically significant. These results collectively suggest that chronic adrenergic modulation influences the acute vasopressor response and early clinical trajectory in shock.

Vasopressor Requirements and Adrenergic Modulation

The most prominent result of this study was the significantly higher norepinephrine dose requirement among patients with chronic beta-blocker exposure. This observation supports the hypothesis that long-term beta-adrenergic blockade leads to receptor-level adaptations that blunt responsiveness to catecholamines. Chronic beta-blocker therapy has been shown to cause β-receptor downregulation, uncoupling of receptor–G-protein interactions, and reduced cyclic adenosine monophosphate signalling, all of which impair vascular and myocardial responsiveness during acute stress. These changes may persist even after discontinuation of therapy and thus influence acute hemodynamic responses in critically ill patients.

Although norepinephrine primarily exerts vasopressor effects through α-1 adrenergic receptors, the overall hemodynamic response depends on an intact β-adrenergic system to maintain cardiac output, heart-rate variability, and autonomic reflexes. In patients with chronic beta-blocker exposure, reduced cardiac reserve may necessitate greater peripheral vasoconstriction to achieve adequate perfusion pressure. Similar mechanistic explanations have been proposed in observational studies that identified altered catecholamine sensitivity in patients with chronic adrenergic blockade (Brüning et al., 2021; Heliste et al., 2022).

The present findings differ from randomized controlled trials investigating short-acting intravenous beta-blockers in septic shock, which reported stable or even reduced vasopressor requirements (Morelli et al., 2018). However, those trials involved acute, titratable agents administered under close monitoring and often after initial hemodynamic stabilization. In contrast, the current study reflects real-world patients with prolonged oral beta-blocker exposure, a population more likely to exhibit profound receptor adaptations. This distinction highlights the importance of differentiating between acute therapeutic beta-blockade and chronic adrenergic modulation when interpreting hemodynamic outcomes.

Time to Hemodynamic Stabilization

The prolonged time to achieve MAP ≥65 mmHg among beta-blocker users indicates delayed hemodynamic recovery. Persistent hypotension, even for short durations, is associated with increased risk of organ dysfunction and mortality. The delayed response observed may be attributed to impaired baroreflex sensitivity, diminished myocardial reserve, and altered vascular tone in chronically beta-blocked patients.

Fuchs et al. (2017) demonstrated that continuation of chronic beta-blockade during sepsis altered cardiovascular response curves, requiring higher catecholamine exposure to reach comparable hemodynamic targets. Similarly, Guinot et al. (2022) reported that adrenergic receptor modulation influenced time to stabilization and vasopressor responsiveness in critically ill patients. These findings support the prolonged stabilization times observed in the present study and emphasize the need for early recognition of altered vasopressor response patterns in this population.

Lactate Clearance and Microcirculatory Recovery

Lactate clearance is a widely accepted surrogate marker of tissue perfusion and metabolic recovery. In this study, beta-blocker users demonstrated significantly slower lactate clearance at both 6 and 24 hours. This suggests persistent microcirculatory dysfunction despite achievement of macrocirculatory targets. Several investigations have highlighted the dissociation between MAP normalization and microvascular perfusion in shock states.

Tan et al. (2019) reported delayed lactate normalization in septic patients with premorbid beta-blocker exposure, attributing this to impaired regional blood flow redistribution and mitochondrial dysfunction. Chronic

beta-blockade may limit the heart's ability to augment cardiac output in response to metabolic demand, resulting in persistent anaerobic metabolism. Additionally, adrenergic signaling influences microvascular tone and capillary recruitment; therefore, altered receptor activity may impair oxygen delivery at the tissue level. The present findings reinforce the importance of monitoring metabolic markers alongside hemodynamic parameters.

Vasopressor Duration and ICU Length of Stay

Patients with chronic beta-blocker exposure required vasopressor support for significantly longer durations and had extended ICU stays. These outcomes likely reflect a combination of delayed hemodynamic stabilization, persistent metabolic abnormalities, and increased illness complexity. Prolonged vasopressor therapy is associated with higher rates of ischemic complications, arrhythmias, and secondary infections, which may further prolong recovery.

Heliste et al. (2022) observed similar trends in critically ill patients with pre-existing beta-blocker use, reporting longer vasopressor dependency and ICU stays. Brüning et al. (2021) also noted that beta-adrenergic blockade was associated with prolonged hemodynamic support requirements. These data support the findings of the present study and emphasize the need for individualized hemodynamic management strategies that account for chronic pharmacologic exposure.

Mortality Trends and Statistical Considerations

Although mortality was higher among beta-blocker users, the difference was not statistically significant. This aligns with meta-analyses suggesting that pre-existing beta-blocker use does not consistently worsen survival (McChesney et al., 2020). The lack of significance may reflect limited sample size, heterogeneity in shock etiology, and confounding by cardiovascular comorbidities. Larger multicenter studies are required to clarify whether chronic beta-blocker exposure independently influences mortality in shock states.

Integration with Existing Evidence

The present findings highlight a critical distinction between chronic beta-blocker exposure and acutely administered beta-blockade in septic shock. While controlled, short-acting intravenous beta-blockers may confer hemodynamic or survival benefits in selected patients, chronic oral beta-blocker use appears to modify baseline adrenergic responsiveness in a manner that necessitates higher vasopressor doses and prolongs recovery.

These results underscore the importance of individualized hemodynamic strategies based on pre-admission medication history. Incorporating beta-blocker status into early shock management algorithms may improve vasopressor titration and monitoring strategies.

4. CONCLUSION

This study demonstrates that chronic pre-admission beta-blocker therapy significantly alters the hemodynamic response to norepinephrine in critically ill patients with septic or vasodilatory shock. Patients receiving long-term beta-blockers required higher starting and maximum doses of norepinephrine, experienced delayed attainment of target mean arterial pressure, and showed slower lactate clearance compared with patients not receiving beta-blockers. In addition, chronic beta-blocker use was associated with prolonged vasopressor dependence and extended intensive care unit stay, indicating delayed physiological recovery. Although short-term mortality was higher among beta-blocker users, the difference was not statistically significant, suggesting that the primary impact of chronic beta-blockade may be on early hemodynamic and metabolic responses rather than on survival. These findings highlight the importance of recognizing pre-admission medication history as a key determinant of vasopressor responsiveness in shock. Incorporating chronic beta-blocker exposure into early risk stratification and vasopressor titration strategies may improve hemodynamic management and help identify patients who require closer monitoring and more aggressive support. Further large-scale, multicentre studies are warranted to confirm these observations and to develop personalized resuscitation protocols for this growing patient population.

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