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Commentary

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Beta blockers in critical illness: promising but appropriate subphenotyping is needed

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Beta blockers (BB) are widely used for the treatment of cardiovascular diseases to reduce heart rate and hence the myocardial oxygen consumption [1]. Of note, studies found BB may confer clinical benefits in critically ill patients, though confirmatory evidence is still lacking.

BB in severe burns

In a recently published secondary analysis, Hundeshagen et al. analyzed data from the RE-ENERGIZE trial [2], showing that patients who were male, younger, and presented with larger total body surface area (TBSA) burns were more likely to receive BB. BB was commonly started early after burn injury [5 (2–11) days], and the majority of patients were prescribed BB until hospital discharge [3]. Clinically, BB was associated with reduced in-hospital and 6-month mortality. However, the exact type and precise dosing of BB were unknown as such information was not collected in the original trial.

Severe burns trigger a plethora of pathophysiological stress responses characterized by sympathetic overstimulation, hypermetabolism, and hyperinflammation [4, 5]. Sympathetic overstimulation causes persistent release of stress hormones such as catecholamines, dopamine, glucagon, and glucocorticoids [6]. Catecholamines are primary mediators of the hypermetabolic response characterized by increased resting energy expenditure (REE), elevated body temperature, total body protein loss, and muscle atrophy [7]. Hypermetabolism leads to severe catabolism, which is associated with protein breakdown in skeletal muscles and other organs. Severe burns also have a distinct impact on the immune system. A burn injury involving more than 80% TBSA caused marked systemic elevations of cytokines [8].

The pathophysiological consideration that BB can decrease tissue oxygen consumption has led to attempts to investigate the role of BB in this population. In severely burned pediatric patients, short-term and long-term use of propranolol, a nonselective BB was proved beneficial in hyperdynamic, hypermetabolic, and hypercatabolic responses. For short-term, four-week treatment of propranolol (average dose, 6.3 mg/kg/d) aimed at reducing the resting heart rate by 20% has been shown to decrease REE and increase net muscle-protein balance in the acute phase of injury [9]. However, it is important to note that hypotension is the main side effect of propranolol due to decreased cardiac output and should be closely monitored. In long-term usage of BB, propranolol (mean dose, 4 mg/kg/d) targeted at lowering heart rate by 15%, given for one year, was found to reduce central mass and fat accumulation, prevent bone loss, and improve lean body mass accretion [10]. Few episodes of bradycardia and no significant decreases in blood pressure were observed with the 4 mg/kg/d dose. In a large randomized controlled trial involving 406 severely burned children, William et al. closely monitored heart rate, mean arterial pressure, and cardiac function. They found that initial administration of propranolol at 1 mg/kg per day reduced heart rate by 15%, which was then increased to 4 mg/kg per day within the first 10 days to sustain treatment benefits without deleterious effects on blood pressure [11]. Taken together, it can be concluded that propranolol administered at doses ranging from 1 to 4 mg/kg/d is probably beneficial and safe for severely burned children. On the other hand, the efficacy and safety of propranolol in burn adults were not as well studied as in children. Starting propranolol on the

third postburn day with the goal of achieving a reduction in maximum heart rate by up to 20% has been shown to be beneficial in reducing morbidity, mortality, and hospital stay in a small trial involving 70 patients [12]. In a phase II randomized controlled trial where propranolol was initiated at a dosage of 10 mg QiD aiming to decrease the heart rate below 100 bpm, the results showed that propranolol significantly improved stress responses [13]. The recent secondary analysis provided additional evidences suggesting that BB may directly improve short-term clinical outcomes in severely burned adults [3]. However, it is important to note that this is a secondary analysis, and the strength of the evidence is potentially weak. Therefore, it is currently challenging to propose a treatment strategy concerning BB for severely burned adults.

BB in severe acute pancreatitis

Severe acute pancreatitis (SAP) is an acute inflammatory disease sharing similar pathophysiology with burn patients. It is characterized by overwhelming inflammation associated with sympathetic overstimulation in the early phase [14]. Our previous study, which enrolled 41 acute phase SAP patients, found that heart rate variability, an indirect estimator of autonomic balance, was strongly associated with the occurrence of multiple organ dysfunction syndrome [15]. In the following *in vivo* study, we found that the administration of esmolol, a selective β-1 adrenergic blocker in SAP rats, resulted in a reduction in pancreatic and lung injury, accompanied by a decrease in the systemic inflammatory response [16]. Based on the above encouraging results, the Chinese Acute Pancreatitis Clinical Trials Group (CAPCTG) conducted the BENICE (efficacy and safety of active heart rate with β-**B**locker esmolol on the **e**volutio**N** of organ fa**I**lure in a**C**ute pancr**E**atitis patients with early organ failure) trial to explore further effects of esmolol on organ failure in SAP patients (ChiCTR2400080160).

BB in septic shock

In contrast to patients with severe burns or SAP, the clinical value of BB in patients with septic shock is controversial. In 2013, Morelli et al. published a single-center, open-label, randomized trial [17], showing that early and continuous infusion of esmolol in septic shock patients with persistent tachycardia despite initial resuscitation resulted in a reduction in 28-day mortality. Meanwhile, no obvious safety issues rated to esmolol were found. Nevertheless, the more recent STRESS-L [18] trial was prematurely terminated after the recruitment of 126 patients (the planned sample size was 340) as they found landiolol infusion was unlikely to confer clinical benefits and could potentially cause harm. The primary outcome, the mean SOFA scores in the landiolol group was 8.8 (3.9) compared with 8.1 (3.2) in the standard care group ($P = 0.24$). The mortality to day 28 in the landiolol group was 37.1% and 25.4% in the study group and the standard care group, respectively ($P = 0.16$).

The discrepancy between the two trials highlights the importance of appropriate subphenotyping in sepsis patients. The pathophysiology of septic shock comprises both warm (hyperdynamic) and cold (hypodynamic) types [19]. The early phase of septic shock is typically hyperdynamic, characterized by high cardiac output and low peripheral vascular resistance. Excessive sympathetic activation led to tachycardia to maintain high cardiac output at the expense of increased cardiac workload and myocardial oxygen consumption [20], potentially contributing to sepsis-induced myocardial dysfunction (SIMD). BB would be theoretically beneficial in this phase after intravascular volume is restored. On the other hand, the later phase, or cold shock, comprises concomitant hypotension followed by hypodynamic, low cardiac output, and poor peripheral perfusion [19]. In such scenario, BB would be potentially harmful by further decreasing cardiac output and aggravating tissue hypoperfusion.

In addition, SIMD, as defined as a sepsis-associated acute syndrome of nonischemic cardiac dysfunction, is a common finding in critically ill patients [21]. Studies on patients with septic shock lasting more than 48 hours have found that 24% to 44% of patients had systolic left ventricular dysfunction, and 44% had echocardiographic evidence of diastolic dysfunction [19], which may partly explain the contrary results in the two abovementioned trials. The key protective mechanism of BB is to reduce myocardial oxygen demand by decreasing heart rate. Therefore, SIMD patients with systolic dysfunction may not benefit from BB since the reduction of heart rate may further worsen cardiac output, thereby leading to underperfusion in peripheral organs [22]. In Morelli et al.'s study, they included patients with a mixed-venous saturation higher than 65% and prescribed positive inotropes, like levosimendan, to ensure that adequate cardiac output was maintained. On the contrary, the STRESS-L trial reported no data on sophisticated hemodynamic data; thus, the increased heart rate may be a compensatory response to decreased stroke volume in some study patients who were likely to be harmed from landiolol treatment. Besides, a notable discrepancy was observed in the mortality rates of the control group between the STRESS-L study and Morelli et al.'s study. The Surviving Sepsis Campaign database demonstrated that the mortality from septic shock patients requiring vasopressors and presenting with hyperlactatemia was 42.3% [23]. The mortality rate in the control group from Morelli was as high as 80%, whereas it was only 28.6% in the STRESS-L study, both of which deviated from the typical population. Taken together, it is hard to conclude whether BB is beneficial in septic shock for the time being.

In conclusion, BB therapy is of clinical potential in critically ill patients from both pathophysiological and clinical perspectives. BB is likely to be beneficial for severe burns and SAP, particularly in the early phase, though randomized trials are needed. For septic shock patients, it is important to subphenotype this heterogeneous population and test BB in the hyperdynamic patients under close hemodynamic monitoring Figure 1.

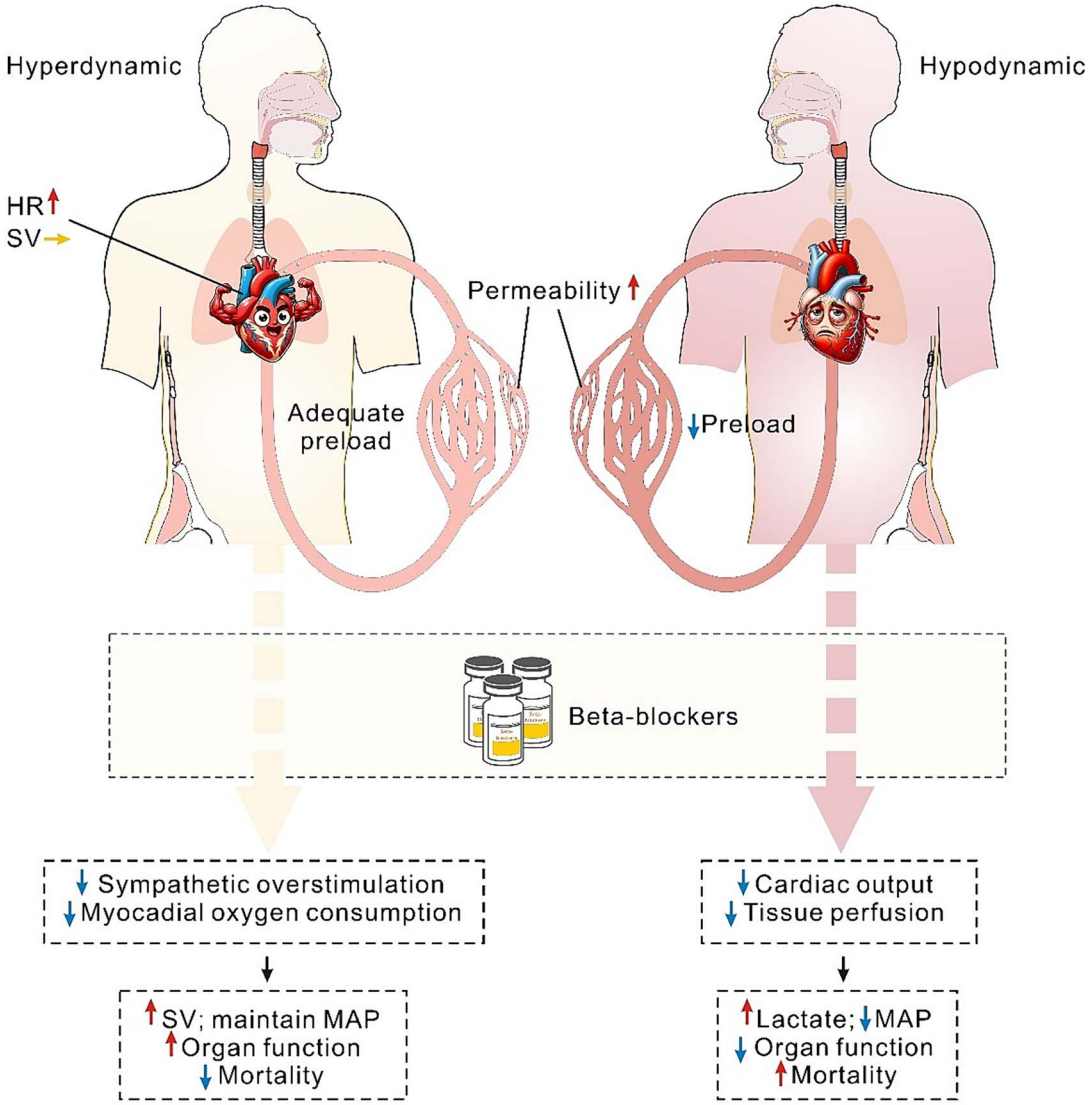

Figure 1. Beta blockers (BB) may play different roles in different subphenotypes of septic shock. In hyperdynamic septic shock, excessive sympathetic activation results in tachycardia to sustain high cardiac output. Despite adequate fluid resuscitation, some patients continue to experience persistent tachycardia. In these cases, BB could reduce heart rate and myocardial oxygen consumption, consequently increasing stroke volume, maintaining MAP, and thereby enhancing organ function. Conversely, in hypodynamic septic shock, which many patients suffer from sepsis-induced myocardial dysfunction and rely on tachycardia to maintain sufficient cardiac output. BB may have potentially detrimental effects by further reducing cardiac output and exacerbating tissue hypoperfusion in such scenarios. *HR* heart rate, *SV* stroke volume, *MAP* mean arterial pressure

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Authors' contributions

Luyao Zhang researched data and wrote the draft for the article. Lu Ke concepted and revised the article.

Conflict of interest:

None declared.

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