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CRITICAL CARE

REVIEW

β-blockers in critically ill patients: from physiology to clinical evidence

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Abstract

This article is one of ten reviews selected from the Annual Update in Intensive Care and Emergency Medicine 2015 and co-published as a series in Critical Care. Other articles in the series can be found online at http://ccforum.com/series/annualupdate2015. Further information about the Annual Update in Intensive Care and Emergency Medicine is available from http://www.springer.com/series/8901.

Introduction

β-blockers are commonly used in the treatment of cardiovascular diseases and to reduce the risk of re-infarction and the related mortality after myocardial infarction [1]. In fact, they almost universally reduce myocardial oxygen consumption and hence the degree of cardiac ischemia. Two randomized controlled trials (RCT) demonstrated that the perioperative use of β-blockers could reduce the incidence of cardiac complications responsible for significant morbidity and mortality after cardiac surgery [2,3]. However, these results were not confirmed in three subsequent RCTs and in a large cohort study [4-7]. Similarly, the Perioperative Ischemic Evaluation Study (POISE) found that individuals receiving metoprolol succinate 30 days before surgery had a reduced risk of postoperative myocardial infarction compared to the control group but an increased risk of stroke and death associated with an increased incidence of hypotension, bradycardia and bleeding [8]. Over the years, these surprising results led to different changes in practice guidelines; specifically, the recent 2014 American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend that perioperative β-blockers should be started only in patients considered to be at intermediate or high risk for myocardial ischemia [9].

The physiopathological concept that β-blockers can decrease tissue oxygen consumption has led several authors to investigate the role of β-blockers in critical illness, which is characterized by increased resting energy expenditure due to sympathetic activation and a hypermetabolic state. Critically ill patients admitted to an intensive care unit (ICU) are affected by different degrees of systemic inflammatory response syndrome and cardiovascular comorbidities. In this context, Christensen et al. performed the first study to investigate the association between preadmission β-blocker use and 30-day mortality among ICU patients and found reduced mortality in β-blocker users [10]. Over the last 10 years, there has been a growing interest in this topic (Table 1). The aim of this clinical review is to review the literature regarding the use of β-blockers in critically ill patients affected by sepsis, acute respiratory failure and traumatic brain injury (TBI).

Beta-blockers: basic concepts

β-blockers act on β-adrenergic receptors interfering with the ability of catecholamines or sympathomimetics to induce β-adrenergic responses. The clinical effects of β-adrenergic agonism or antagonism depend on the subtypes of receptor and on their locations. β_1-adrenergic receptors are located in the heart, on cardiomyocytes, sino atrial node and atrioventricular node, in the kidney, on adipocytes and on the platelets, causing an increase in heart rate, contractility, speed of atrioventricular conduction, renin secretion, lipolysis and aggregation of platelets, respectively. They can also be found presynaptically where their activation causes an increase in norepinephrine release.

β_2-adrenergic receptors are located on smooth muscle fibers of bronchioles, arteries, arterioles and of visceral organs, and on liver cells. Their activation results in bronchodilation, vasodilatation, glycogenolysis in the liver and tremor in skeletal muscle [11].

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Table 1 Clinical studies investigating the role of β-blocker exposure in critically ill patients

	Author	Study design	N°	β-blocker	Groups	Main Outcomes	Limitations
ICU	Christensen, 2011 [10]	Observational	8087	Metoprolol (63.4%), others (36.5%)	β-blockers: 1556	β-blocker group: lower 30-day mortality	No data on in-hospital β-blocker use
				Preadmission oral use	No β-blockers: 6531		No data on severity scores
							Study design
Septic Shock	Gore, 2006 [20]	Interventional clinical study	6	Intravenous esmolol	Septic, mechanically ventilated patients: 6	↓ 20% HR	No control group
				3 hours of infusion			Small population
				6–22 mg/min to achieve 20% ↓ HR		↓ Cardiac index	
						O_2 consumption not altered	
	Schmittinger, 2008 [22]	Retrospective	40	Enteral metoprolol	Septic shock and cardiac depression in patients with chronic β-blocker therapy: 40	↓ HR (target 65–95 bpm); ↑ SVI	No control group
				Within 48 hours after the onset of shock or ICU admission		↓ NE, AVP and milrinone dosages	Study design
						↓ lactate, creatinine	
	Macchia, 2012 [23]	Retrospective	9465	Preadmission oral use	β-blockers: 1061	β-blocker group: lower 28-day mortality	Study design
					No β-blockers: 8404		No data on severity scores
							Lack of information on β-blockers
	Morelli, 2013 [13]	RCT	154	Intravenous esmolol	β-blocker: 77	β-blocker group:	Single center
				ICU treated to maintain HR 80–94 bpm	Usual care: 77	↓ HR (80–94 bpm)	Arbitrary selection of HR threshold
						↑ SVI	
						↓ NE	
				25–2000 mg/h		↓ fluids	
						↓ 28-day mortality	
Acute Respiratory Failure	Noveanu, 2010 [29]	Retrospective	314	Preadmission oral use	In-hospital non-survivors: 51	More β-blocker use in survivors	Study design
				Metoprolol (36%), carvedilol (18%), bisoprolol (16%), nebivolo (22%), atenolol (4%), sotalol (3%), celiproplol (2%)	In-hospital survivors: 263	↑ mortality if discontinuation of β-blockers	Post-hoc analyses
	Kargin, 2014 [35]	Retrospective	188	Intravenous bolus metoprolol + enteral maintenance; enteral bisoprolol or carvedilol	β-blockers: 74	Similar mortality	Study design
					Other HRLD: 114		No data on spirometry
				ICU treatment			
Trauma	Arbabi, 2007 [47]	Retrospective	4117	In hospital treatment	β-blocker: 303	Similar mortality rate	Study design
					No β-blocker: 3814		No data on HR
							No data on severity scores

Table 1 Clinical studies investigating the role of β-blocker exposure in critically ill patients *(Continued)*

							Lack of information on β-blockers
	Cotton, 2007 [46]	Retrospective	420	β-blocker therapy for 2 or more consecutive days in hospital Metoprolol, propranolol, labetalol, atenolol, esmolol, sotalol	β-blocker: 174 No β-blocker: 246	β-blocker: reduction in mortality despite more severe injury, older patients, lower predicted survival	Study design Lack of information on β-blockers Different β-blockers No data on neurological outcomes
TBI	Riordan, 2007 [48]	Retrospective	446	Esmolol (e.v.), propranolol (e.v. or enteral), labetalol (e.v.), metoprolol (e.v. or enteral)	β-blocker: 138 No β-blocker: 308	Reduced mortality in β-block group despite older and more severely injured patients	Study design Different β-blockers
	Inaba, 2008 [42]	Retrospective	1156	In-hospital treatment	β-blocker: 203 No β-blocker: 953	Reduced mortality in β-block group despite older and more severely injured patients	Study design Lack of information on β-blockers
	Schroeppel, 2010 [49]	Retrospective	2601	In-hospital treatment Atenolo, carvedilol, esmolol, labetalol, metoprolol, nadolol, propranolol, sotalol	β-blocker: 506 No β-blocker: 2095	Similar mortality between groups despite older and more severely injured β-blocker patients	Study design Different β-blockers

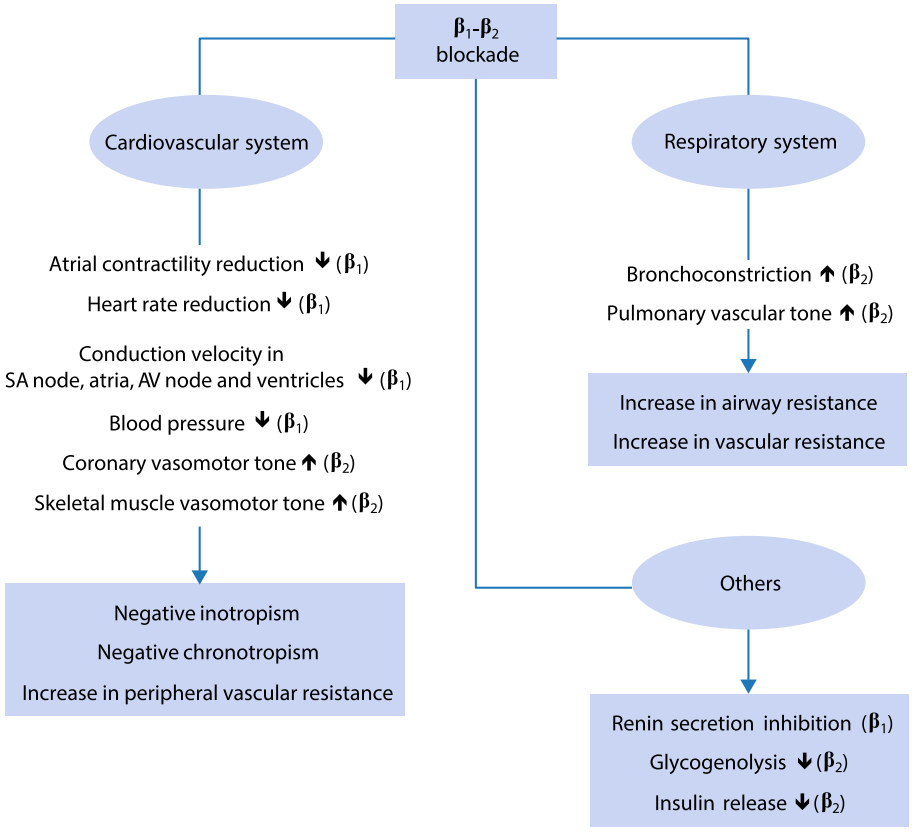
Selection of clinical studies from the last 10 years. Studies are grouped according to specific categories of critical illness: General admission to ICU, septic shock, acute respiratory failure, trauma and traumatic brain injury.

ICU: intensive care unit; HR: heart rate; BP: blood pressure; TBI: traumatic brain injury; HRLD: heart rate-limiting drug; SVI: stroke volume index; NE: norepinephrine; AVP: arginine-vasopressin; RCT: randomized control trial; bpm: beat per minute; e.v.: endovenous.

β-adrenoceptor antagonists with a specific affinity for β_1-receptors are defined as cardioselective (atenolol, bisoprolol, esmolol, metoprolol), those acting on β_1- and β_2-receptors are defined as non-selective (propranolol, pindolol, timolol and nadolol). This receptor selectivity is dose-dependent and is lost when large doses of antagonist are administered.

The clinical effects and comparative characteristics of β-adrenergic receptor antagonists are summarized in Figure 1. The principal properties exploited in clinical practice are negative inotropism and chronotropism to reduce heart rate, blood pressure and myocardial work. Of course, the decrease in heart rate also ensures an improvement in diastolic perfusion time and consequently in myocardial perfusion [12].

β-blocker molecules differ from each other because of their elimination half-time. The long action of some β-adrenergic blockers represents an obvious limit for their



	Receptors	Clearance	Half-time	Route
Propranolol	$\beta_1 - \beta_2$	Hepatic	2-3 hours	Oral/Intravenous
Pindolol	$\beta_1 - \beta_2$	Hepatic-Renal	3-4 hours	Oral/Intravenous
Timolol	$\beta_1 - \beta_2$	Hepatic	3-4 hours	Oral/Intravenous
Nadolol	$\beta_1 - \beta_2$	Renal	20-24 hours	Oral
Atenolol	β_1	Renal	6-7 hours	Oral/Intravenous
Bisoprolol	β_1	Renal	9-12 hours	Oral
Metoprolol	β_1	Hepatic	3-4 hours	Oral/Intravenous
Landilol	β_1	Plasma Hydrolysis	3-4 minutes	Intravenous
Esmolol	β_1	Plasma Hydrolysis	10 minutes	Intravenous

Figure 1 Clinical effects and comparative characteristics of β-adrenergic receptor antagonists. SA: sinoatrial; AV: atrioventricular.

application in critically ill patients. By contrast, the pharmacological characteristics of esmolol, an ultrashort acting β-selective drug, allow titration of the dosage to specific hemodynamic endpoints, thus minimizing the incidence of adverse events, which has recently led to investigation of its application in septic shock [13].

Sepsis and septic shock

Physiologic rationale

Despite recent advances in the management of septic shock [14], mortality and morbidity remain unacceptably high and sepsis treatment is an active area of research. Recent data suggest that β-blockers can provide beneficial effects in the setting of sepsis. As is well-known, sepsis is the systemic inflammatory response to infection, characterized by a multitude of pathophysiological changes in terms of cardiovascular alterations, metabolic derangements and immunomodulation. The mechanism underlying these modifications is the production of mediators, such as epinephrine, which is the adrenergic response of our organism to an external aggression. This intense adrenergic stimulation results in cardiac (increased contractility, heart rate and myocardial energy demand) and extra cardiac (catabolic state, hyperglycemia, hypercoagulability, release modulation of systemic inflammatory cytokines) effects [15,16].

Although these physiological responses allow the human body to react against injury, the sympathetic activation can become deleterious when excessive and its clinical effects persist. In fact, when sepsis progresses or tachycardia persists after fluid resuscitation and pain/agitation control, cardiac energy demand can overcome supply with the risk of cardiac dysfunction and multiorgan failure [17].

The heart is the main victim of the adrenergic stimulation because adrenergic stress is mainly mediated by β-receptors and 80% of myocardial adrenergic receptors are β_1 subtype [13]. In early sepsis, the adrenergic response increases cardiac contractility and heart rate to meet metabolic demands, but then cardiac depression with impaired left ventricular ejection fraction (LVEF), apical ballooning, myocardial stunning, apoptosis and necrosis occurs in up to 60% of patients with septic shock and contributes to increased mortality [18]. It has been hypothesized that the sepsis-induced cardiac depression is due to catecholamine-induced cardiomyocyte toxic effects following excessive sympathetic activation. However, it could be, at least partially, an adaptive and protective mechanism from an overwhelming stress response, whereby the heart tries to attenuate the adrenergic response by downregulation of β-adrenergic receptors and depression of post-receptor signaling.

In this context, increasing cardiac output above supernormal values by dobutamine administration showed no benefit [19], while the use of β-blockers to modulate this pathway has been suggested to have a protective role [17]. The physiologic rationale behind the clinical application of β-blockers in septic shock is not limited to the modulation of the cardiac effects of excessive sympathetic stimulation but also to the modulation of the extracardiac effects. In fact, the overwhelming adrenergic response during sepsis induces an overall catabolic state, an impairment of glucose metabolism and a derangement of the physiologic inflammatory state.

Literature findings

Preclinical studies on the use of β-blockers in different models of sepsis have provided conflicting results. Nevertheless, Berk et al. in 1970, testing the administration of propranolol infusion in 5 septic patients with refractory shock, and Gore and Wolfe in 2006 testing a 3-hour esmolol infusion in 6 normotensive septic patients, reported no detrimental cardiac effects [20,21]. Subsequently, Schmittinger et al., in a retrospective study enrolling 40 septic shock patients who were given enteral metoprolol to achieve a target heart rate of less than 95 beats/min, reported increased stroke volume and blood pressure with stable cardiac index and lactate, although no data on outcome were presented [22].

Recently, Macchia et al. analyzed a database of Italian ICU patients hospitalized for sepsis and found a 28-day survival advantage in patients who were taking β-blockers at the time of admission and who subsequently developed sepsis [23]. The recent study conducted by Morelli et al. is the first RCT on this topic [13]. These authors reported that a continuous esmolol infusion titrated to maintain heart rate between 80 and 94 beats/min in septic shock patients with a heart rate of 95/min or higher and requiring norepinephrine to maintain mean arterial pressure (MAP) of 65 mmHg, initiated 24 hours after hemodynamic optimization, was associated with a significant reduction in norepinephrine and fluid requirements and with a decrease in 28-day mortality compared to standard care. Although Morelli et al. recognize that the right timeframe for intervention and the optimal heart rate threshold should be individualized according to a patient's hemodynamic status and preexisting comorbidities, their findings suggest that lowering heart rate improves cardiac efficiency without any detrimental effects in tissue perfusion [13]. However, some concern has been expressed regarding the interpretation of these results. In fact, the 80% mortality rate in the control group is unusually high compared to mortality rates reported in similar populations [24]; patients received large amounts of fluids during the first 96 hours although this strategy is recommended for the first 6 hours of resuscitation [14]; and the baseline

cardiovascular parameters were slightly worst in the control group [24].

Moreover, as Morelli et al. hypothesized, the non-cardiac effects of esmolol in modulating the adverse effects of catecholamines on the catabolic state, glucose metabolism, the coagulation system and cytokine production could have contributed to the observed improvement in mortality.

Indeed, it has been suggested that β-blockers can counteract the hypermetabolism of the hyperdynamic phase of sepsis to prevent the catabolic phase of the decompensated period of sepsis [11,15]. In particular, propranolol has been shown to decrease plasma glucose concentrations during stress, inhibiting the decrease in insulin-mediated glucose uptake and normalizing gluconeogenesis [25]. This mechanism does not seem to be influenced by selective β_1-antagonism [20], suggesting that non-selective β-blockade can be beneficial for glucose modulation in sepsis [11].

Moreover, it is well known that β-adrenergic receptors are involved in the cytokine production and the modulation of the cellular immune system [26,27]. However, results from sepsis models on the immunomodulatory role of β-blockade are conflicting and immunological effects in critically ill patients have not yet been investigated. In summary, from the literature in septic shock patients, the use of esmolol can reduce heart rate without adverse events; more research is necessary to investigate the effect of this approach on outcome and to reveal the clinical significance of extra-cardiac effects.

Acute respiratory failure

Physiologic rationale

Acute respiratory failure is one of the major complications that can occur in patients already admitted in the ICU [28]. Among patients admitted to the ICU for acute respiratory failure, patients with acute exacerbation of chronic obstructive pulmonary disease (COPD) are often treated with oral β-blockers [29].

COPD patients generally have cardiovascular comorbidities, for example a history of coronary artery disease, chronic heart failure, arterial hypertension, atrial fibrillation and diabetes mellitus. In these patients with a high risk of cardiac events, chronic respiratory therapy with β_2-agonists seems to increase the incidence of cardiovascular morbidity [30]. However, the use of β-blockers has been demonstrated safe and beneficial for outcome in patients with COPD and co-existing coronary artery disease because the potential benefits may outweigh the risks [31,32]. Despite this evidence in COPD patients, the use of β-blockers in patients with acute respiratory failure is controversial. It has been reported that both selective and non-selective β-blockers increase airway hyper-responsiveness [33].

On this basis, there is a growing interest in the clinical role of β-adrenergic antagonism in COPD patients with acute respiratory failure. Moreover, the acute respiratory distress syndrome (ARDS), independent of etiology, is a critical illness and is, therefore, accompanied by sympathetic overstimulation resulting in a hyperdynamic circulation that also affects the pulmonary vasculature. In this clinical context, the potential role of β-antagonists represents an interesting field of research.

Literature findings

The effect of β-blockers in critically ill patients with acute respiratory failure has been investigated recently, without any definitive results. In 2010, Noveanu et al. retrospectively explored the impact of oral β-blocker therapy at ICU admission or before hospital discharge on in-hospital and 1-year mortality in unselected ICU patients with acute respiratory failure [29]. Patients taking oral β-blockers at the time of admission had lower in-hospital and 1-year mortality rates than other patients. This study showed for the first time a positive effect on outcome of oral β-blocker therapy in ICU patients affected by acute respiratory failure and that discontinuation of established therapy during hospitalization was associated with higher mortality rates independent of the cardiac or non-cardiac etiology of the respiratory failure. Nevertheless, the retrospective nature of this study limits the relevance of the observed results [34].

More recently, Kargin et al. performed a retrospective case-control study to compare the outcome of COPD patients admitted to the ICU for acute respiratory failure who received β-blockers (metoprolol, bisoprolol or carvedilol) *versus* non β-blocker drugs (diltiazem and/or digoxin and/or amiodarone) for heart rate control during the ICU stay [35]. Similar ICU, hospital and 30-day mortality rates and lengths of ICU stay were found between groups [35]. The rate of application of non-invasive ventilation was higher in patients treated with β-blockers, and the need for invasive mechanical ventilation was not significantly different between groups, suggesting that β-blockers did not lead to a worsening of respiratory conditions and that they can be used to limit heart rate in COPD patients with acute respiratory failure in the ICU. Unfortunately, spirometric data were not recorded [35]. However, previously, a meta-analysis had already demonstrated that selective β-adrenoceptor antagonists in COPD patients did not induce any significant changes in forced expiratory volume in 1 second (FEV_1) or in respiratory symptoms and did not significantly affect the FEV_1 treatment response to β_2-agonists [32]. Despite the limited evidence, β-blockers thus seem safe in patients with acute respiratory failure.

In experimental models, cardioselective β_1-blockers were found to be lung-protective. Hagiwara et al. tested the effect of landilol in a rat model of lipopolysaccharide (LPS)-induced sepsis. Wet-to-dry ratio, parenchymal congestion, edema, hemorrhage and inflammatory cells were significantly reduced in animals treated with the β_1-blocker [36]. More recently, an increase in the PaO_2/FiO_2 ratio was observed 3 hours after administration of esmolol in a pig model of endotoxin shock, suggesting that the β_1-blocker did not have any negative effects [37]. In these preclinical settings, the administration of β_1-blockers seems to reduce pulmonary vascular flow and, thereby, the endothelial damage in the injured lung.

The clinical effect of β_1-blocker therapy in ARDS patients in terms of mitigation of pulmonary blood flow without a decrease in systemic hemodynamics should be further investigated. Because of the lack of evidence, RCTs testing β-adrenoreceptor antagonists in acute respiratory failure are needed to confirm the potential benefits of β-blocker therapy [34,35].

Acute brain injury

Physiologic rationale

Acute brain injury, both traumatic and non-traumatic, is frequently associated with severe autonomic dysfunction. The underlying causes of death among patients with severe brain injury are the result not only of the primary head injury, but also of the development of non-neurologic organ dysfunction that appears to be due to sympathetic hyperactivity [38]. In fact, the interplay between the neuroendocrine system and the injured brain has been studied for decades.

The reduction in normal heart rate variability as well as the disruption in the autonomic control of heart rate was observed to correlate with the degree of the neurologic injury in patients with severe brain damage [39]. A catecholamine surge, as measured by plasma and urinary catecholamine levels, has been clearly demonstrated after TBI [38]. These abnormal levels correlated with the admission Glasgow Coma Scale (GCS) score, and with outcome, in particular with the GCS at 1 week, survival, length of stay and ventilator-dependent days. A similar hyperadrenergic state has been identified in patients with non-traumatic subarachnoid hemorrhage [40]. The clinical manifestations of these hyperadrenergic responses present with tachycardia, hypertension, mydriasis, diaphoresis, arrhythmias, ventricular wall abnormalities, myocardial ischemia and neurogenic pulmonary edema. Of note, the development of stress cardiomyopathy and of neurogenic pulmonary edema have been demonstrated to contribute to poor outcome independently of the severity of the initial brain injury [41].

Although the pathophysiology of stress cardiomyopathy (also called apical ballooning syndrome or Takotsubo syndrome) is still not completely understood, sympathetic overstimulation seems to have an important role in the development of the left ventricular dysfunction [34]. In this context, β-blockade exposure to modulate the effects of the catecholaminergic storm activated by acute brain injury after trauma or subarachnoid hemorrhage could be beneficial. Locally β-blockade may attenuate the vasoconstriction of parenchymal vessels and reduce the risk of secondary brain injury, improving perfusion and oxygenation [42]. Systemically, it can have a cardioprotective role in terms of rhythm disturbances, myocardial necrosis and left ventricular function.

Literature findings

Based on these physiological considerations, several authors have evaluated the potential benefit of β-blockers as a therapeutic option to attenuate the cerebral adverse effects and the systemic sequelae of the sympathetic activation after TBI. Unfortunately, although there are numerous preclinical studies on the use of β-blockers to mitigate inflammatory response and cardiac effects after acute brain insult, the results are conflicting. A relatively recent systematic review on the effects of β-blockers in controlled trials in TBI animal models suggested improved neurological outcome and lessened cerebral edema but with a poor methodological quality of the included studies [43].

Two small early RCTs found decreased intensity and duration of the hyperadrenergic state in patients with brain disease treated with propranolol but no data on mortality were provided [44,45]. More recently, two retrospective studies demonstrated that the use of β-blockers was associated with reduced mortality in TBI patients with GCS ≤ 13 [46,47]. In the most severe form of TBI, β-blocker exposure was associated with improved survival [48]. Similarly, Inaba et al. demonstrated that β-blocker exposure was an independent protective factor against death in 203 patients with isolated TBI compared to 903 patients who did not receive β-blockers. Moreover, a subgroup of elderly patients (>55 years old) with severe head injury who received β-blockers had a mortality of 28%, compared with 60% if they did not [42]. Similar findings were observed in a large retrospective study of 2601 blunt TBI patients [49].

Despite these results, the exact mechanism of the positive effects of β-blockers on the outcome of brain injured patients remains unclear. The current state of evidence suggests that the use of β-blockers in acute brain injury seems to have a valid rationale, although several unsolved problems regarding clinical application remain, such as whether to use selective or non-selective β-blockers, duration of treatment and dose.

Conclusion

Many questions about using β-blockers in critically ill patients are unanswered:

- *When should β-blocker treatment be started*? During septic shock, recent clinical data suggest starting a β-blocker 24 hours after hemodynamic optimization [13]. During acute respiratory failure some clinical and experimental studies seem to suggest starting a β-blocker before signs of fulminant sepsis occur, whereas after brain injury β-blocker treatment should be started as soon as possible.
- *Which β-blocker should be used?* Currently, esmolol is the only β-blocker that has been tested in a randomized controlled study. There is not enough evidence to propose the use of a specific agent in each specific critical condition.
- *How should the β-blocker be administered?* Probably, as studies on perioperative patients have demonstrated, a fixed dose is not a good choice; physiological titration to heart rate or oxygen delivery in relation to oxygen demand seems more advisable.
- *Finally, which patients may benefit from this therapy?* Individualized treatment based on presence of comorbidities and the degree of sympathetic activation may provide better results in terms of outcome.

In conclusion, further clinical research is needed to find a balance between β-blockade and β-stimulation in acutely ill patients.

Abbreviations

ACC/AHA: American College of Cardiology/American Heart Association; ARDS: Acute respiratory distress syndrome; AVP: Arginine-vasopressin; BP: Blood pressure; bpm: Beat per minute; COPD: Chronic obstructive pulmonary disease; e.v.: Endovenous; FEV_1: Forced expiratory volume in 1 second; GCS: Glasgow Coma Scale; HR: Heart rate; HRLD: Heart rate-limiting drug; ICU: Intensive care unit; LPS: Lipopolysaccharide; MAP: Mean arterial pressure; NE: Norepinephrine; POISE: Perioperative Ischemic Evaluation Study; RCT: Randomized control trial; SVI: Stroke volume index; TBI: Traumatic brain injury.

Competing interests

The authors declare that they have no competing interests.

Declarations

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