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Hemodynamic response to β-blockers in severe sepsis and septic shock: A review of current literature

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ABSTRACT

The administration of β-blockers in patients with sepsis is a trending topic in intensive care medicine since the landmark study by Morelli and colleagues, showing a striking decrease in 28-day mortality compared to standard care. While the available evidence suggests that the use of β-blockers in septic shock is safe, the effects on hemodynamics are controversial. In this paper, we review the effect of β-blockade in septic shock on hemodynamics from animal models to critically ill patients.

1. Introduction

Sepsis is one of the leading causes of death among hospitalized patients and is a frequent cause of admission to intensive care units [1]. Morbidity and mortality caused by sepsis remain high, despite an improved understanding of the pathophysiology [2,3]. Therefore, the search for a more effective therapeutic strategy remains highly relevant [4].

Heart rate control using β-blockers could potentially be such a novel therapeutic strategy. A reduced heart rate might improve the cardiac mismatch of oxygen demand and supply in septic patients, by decreasing myocardial oxygen consumption [5]. Sepsis can cause an adrenergic storm with the release of catecholamines that is associated with cardiac dysfunction. It has been postulated that β-blockers attenuate these "toxic" effects. Despite this theoretical benefit of controlling the adverse effects of sepsis by β-antagonists, it is unclear if this mechanism truly benefits the cardiovascular system [4].

The physiological rationale behind the clinical application of β-blockers in septic shock is not limited to the modulation of the cardiovascular effects, but also to coagulopathy, attenuation of the hypermetabolic state and immune-modulating effects. In this review we will focus on the interaction between β-blockers and the cardiovascular system, in particular the cardiovascular physiological consequences of β-blocker therapy and the concerns that have been expressed regarding the risk of reducing cardiac output and subsequently blood pressure [6-8].

2. Methods

PubMed was searched by one of the researchers (LvL) for all references through August 2018 for both animal and human studies relating to septic shock and the use of β-blockers. We included candidate articles which were identified using the following criteria: "septic shock" or "severe sepsis" with "beta-blocker" or "beta-blockade", in combination with the presentation of ≥1 of the following cardiovascular parameters: cardiac output, systemic vascular resistance, stroke volume, blood pressure, oxygen consumption, microcirculatory flow. Additional manual search was conducted, exploring the list of references of the relevant articles.

3. Results

3.1. Preclinical data (Table 1)

We identified 16 experimental studies evaluating hemodynamic response to β-blockers (i.e. atenolol, esmolol, landiolol, metoprolol, propranolol) in animal models (i.e. dogs, pigs, rats, mice, sheep) of septic shock induced by endotoxin infusion or cecal ligation and puncture [5,9-23]. The duration of the experimental protocols mainly depended on the size of the animal model. Smaller animal such as rats and mice were studied for 14 h to 24 h, while the large animal models were studied for 4 h on average. The heart rate reduction was targeted using a threshold (range 80–100 beats per minute) or a percentage decrease from baseline (range 10–30%). Hemodynamics measurements focused

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Table 1
Summary of preclinical data evaluating the effect of β-blockade on the cardiovascular system in models of experimental septic shock. Showing that the influence on hemodynamic parameters depends on dose, timing, gender, concomitant therapy, species, the severity of shock, and cardiac function.

Nr	First author	Year	Species	β –blocker	HR target	Timing	Pressor usage	Stroke volume	Mean arterial pressure	Systemic vascular resistance	Tissue function	O2 uptake	Effect of β-blockade on hemodynamics
[9]	Suzuki	2005	Rat	Esmolol	Dose response	24 h after sepsis	n/a	↑	↓	n/a	=	↑	Improved oxygen utilization of myocardium and preserved myocardial function
[16]	Ackland	2010	Rat	Metoprolol	20% reduction	6 h after sepsis	n/a	=	=	n/a	=	n/a	Cardioprotective effects
[17]	Aboab	2011	Pig	Esmolol	20% reduction	1 h after sepsis	n/a	↑	=	=	=	=	Preload positive effect.
[18]	Calzavacca	2014	Sheep	Atenolol	Fixed dose	8 h after sepsis	n/a	↑	↓	↑	=	=	Increased vascular reactivity
[19]	Kimmoun	2015	Rat	Esmolol	No info	4 h after sepsis	=	↑	=	↑	n/a	n/a	Enhanced intrinsic cardiac contractility and improved vascular responsiveness
[20]	Jacquet-Lagreze	2015	Pig	Esmolol	<90 bpm	After hemodynamic stabilization	↑	=	=	=	=	=	Well tolerated
[21]	Hernandez	2016	Sheep	Esmolol	20–30% reduction	After hemodynamic stabilization	=	n/a	=	n/a	=	n/a	Well tolerated and increased exogenous lactate clearance
[13]	Wang	2016	Mice	Esmolol	Fixed dose	Direct after septic insult	n/a	↑	↑	n/a	n/a	n/a	Improved cardiac function
[15]	Wei	2016	Rat	Esmolol	Dose response	4 h after sepsis	n/a	↑	↑	↑	n/a	n/a	Inflammatory modulation
[22]	Du	2017	Dog	Esmolol	10–15% reduction	After hemodynamic stabilization	n/a	↑	=	=	↓	n/a	Restores vascular waterfall
[5]	Hosokawa	2017	Sheep	Esmolol	80–100 bpm	2 h after sepsis	n/a	↑	↓	=	=	↓	Despite earlier onset of hypotension, save to use.
[23]	Kurita	2017	Pig	Landiolol	Dose response	30 min after sepsis	n/a	↑	↓	n/a	↓	↓	Depending on dose and stage of shock
[10]	Aboab	2018	Pig	Esmolol	10% reduction	1 h after sepsis	n/a	n/a	n/a	n/a	n/a	n/a	Promotion of parasympathetic activity
[11]	Boselli	2018	Pig	Esmolol	<90 bpm	After hemodynamic stabilization	n/a	=	=	↑	n/a	n/a	Well tolerated, with no change in parasympathetic activity
[12]	Mathieu	2018	Rat	Landiolol	No target	1 h after sepsis	n/a	↓	↓	n/a	n/a	n/a	Depending on gender by gene expression
[14]	Van Loon	2018	Sheep	Esmolol	30% reduction	After hemodynamic stabilization	n/a	↓	↓	n/a	=	n/a	Reduced right ventricular function

on both physiological output (e.g. cardiac output, blood pressure) and dynamic interactions of hemodynamic variables (e.g. left ventricular systolic function, vascular reactivity). Animal studies on the use of β-blockade do not give consistent and predictable results, reporting both hemodynamic improvement and deterioration [24]. These differences in results cannot be attributive to the size of the animal nor to the used β-blocker, but seem related the time of administration (Table 1).

3.2. Clinical data (Table 2)

3.2.1. Nonrandomized human studies

Studying the direct effect of β-blockers on hemodynamics during septic shock using nonrandomized studies and case series is challenging, since progression of the actual shock and concomitant use of inotropes and vasopressor agents cannot be eliminated (Table 2). One retrospective study also showed improved hemodynamics from enteral metoprolol in 40 septic shock patients with cardiac depression. However, the effect of concomitant administrated milrinone should not be ignored [25]. Interestingly, all studies showed a remarkable record of clinical safety in patients with septic shock [26-31] without cardiovascular deterioration [28].

3.2.2. Randomized control trials

Clinical data on the use of β-blockers in septic shock is limited [32,33] (Table 2). Up until now, two randomized control trials (RCTs) have been published of which the most relevant one is a single-center, open-label, phase 2 study by Morelli and colleagues [27]. In this study, 154 septic patients were randomized to receive esmolol infusion after 24 h of hemodynamic stabilization. Prerequisite was that patients were on noradrenaline infusion and heart rate was >95 beats per minute. β-blockade successfully achieved the primary outcome (reduced hear rate) in all patients and was associated with an increased stroke volume and systemic vascular resistance while leaving mean arterial pressure and oxygen consumption unaffected. This study by Morelli et al. has increased the interest for β-blocker administration in patients with septic shock, although it is not without debate [34-37]. As there is no structured hemodynamic assessment, the suggested positive effect of β-blockade on the cardiovascular system remains highly speculative. Despite the criticism concerning this trial, the findings are tantalizing and suggest that β-blockers could play a key role in the treatment of patients with septic shock.

The only other RCT was published in the Chinese language and compared two small populations receiving standard treatment and esmolol infusion, with the goal to titrate heart rate below 100 bpm within 2 h [38]. From the English abstract and translated manuscript, the esmolol group showed no changes in blood pressure, stroke volume, and lactate compared to control. No information regarding mortality was provided. The incomplete appreciation of this study strongly limits its utility.

4. Discussion

Clinical data suggests that the use of β-blockers for heart rate control in septic shock is safe when started at a low dose. However, data are

Table 2
Summary of clinical trials evaluating the effect of β-blockade on the cardiovascular system in patients with severe sepsis and septic shock. Showing contradicting results for both mean arterial pressure and systemic vascular resistance.

Nr	First author	Year	Design	Pts (n)	β-blocker	HR target	Timing	Pressor usage	Stroke volume	Mean arterial pressire	Systemic vascular resistance	Tissue function	O2 uptake	Mortality	Safety
[65]	Berk	1972	Case series	26	Propranolol	No target	In late refractory septic shock	n/a	n/a	↑	↑	n/a	n/a	40% (no control)	Well tolerated
[25]	Schmittinger	2008	Retrospective	40	Metoprolol	<95 bpm	<48 h after septic shock	↓	↑	=	=	=	n/a	33% (no control)	Feasible
[30]	Balik	2012	Case series	10	Esmolol	20% reduction	2 h after sepsis	=	=	=	=	n/a	=	n/a	Safe to use
[66]	Morelli	2013	Pilot	25	Esmolol	80–94 bpm	After hemodynamic stabilization	↓	=	=	n/a	=	↓	n/a	Safe to use
[27]	Morelli	2013	RCT	144	Esmolol	80–94 bpm	After hemodynamic stabilization	↓	↑	=	↑	↑	↓	↓	No addition adverse events
[38]	Yang	2014	RCT	41	Esmolol	<100 bpm	6 h after sepsis	n/a	=	=	↑	=	n/a	n/a	Well tolerated
[53]	Wang	2015	Prospective	90	Esmolol	<95 bpm	Direct after septic shock	=	=	=	n/a	=	n/a	↓	Well tolerated
[29]	Wei du	2016	Prospective	63	Esmolol	15% reduction	<48 h after septic shock + hemodynamic stabilization	n/a	↑	=	n/a	=	n/a	6.3% (no control)	Safe to use
[28]	Morelli	2016	Pilot	45	Esmolol	80–94 bpm	After hemodynamic stabilization	↓	↑	↓	↓	n/a	n/a	n/a	Well tolerated

insufficient in unravelling the possible mechanisms driving the favorable effects in septic shock. In particular, the conflicting results on the influence of β-blockers on cardiac output, stroke volume and arterial pressure distracts the debate on the effectiveness of this therapy [32,33] (Table 2).

Preclinical studies show a wide variety in used models, targets and protocols. Furthermore, they show inconsistent and unpredictable results of the effects of β-blockade on hemodynamic output parameters. The duration of large animal models is relatively short, making their design inapplicable to study organ dysfunction and outcome. Similar to clinical data, preclinical data show both unaffected and improved cardiac output, stroke volume and both a decreased and unaffected arterial blood pressure. This inconsistency in data emphasizes that the effect of β-blockers on hemodynamics is multifactorial. Effects are determined by dose [15,23], timing [23], gender [12], concomitant therapy [21,30], species [39], the severity of shock [23] and cardiac function [19]. It is therefore more relevant to understand the functional physiological consequences of β-blockers in septic shock, rather than focusing on central hemodynamic output parameters. Experimental models of septic shock have addressed these different hemodynamic effects of β-blockers on vascular reactivity, cardiac function and/or their interaction (Table 1).

4.1. Vascular reactivity

Despite the absence of β1-receptors on vessels, selective β-blocker infusion improved sepsis-induced hypo responsiveness to vasopressor treatment [15,18,19,22]. It is postulated that β-blockers increase pressor responsiveness, like clonidine [40], by restoring the sepsis associated down-regulation of α1-receptors [19]. Similar to preclinical data, Morelli et al. found an improvement in vascular tone related to a decrease in arterial elastance when septic patients were treated with esmolol [28]. This improvement of vascular reactivity may explain why the use of selective β-blockers in septic shock is associated with unchanged or even decreased vasopressor requirements, despite a reduced cardiac output [25,27]. Additionally, many septic patients are in need for vaso-active support but catecholaminergic drugs can, at the same time, deteriorate the cardiac function [41,42]. Therefore, reducing these exogenous catecholamine load could be a beneficial effect of β-blocker.

4.2. Cardiac

Although many studies have demonstrated that preventing cardiac injury is crucial to improving prognosis of septic patients [43], it is unclear if β-blockade is an effective treatment to attenuate this cardiac dysfunction. Preclinical data show attenuation of sepsis induced myocardial dysfunction, including improved myocardial contractility and relaxation of the left ventricle [13].

Both ex vivo [9] and in vivo [19] intraventricular measurements show an improvement in left ventricular intrinsic myocardial function. Strikingly, in humans the systolic function is reported to decrease after esmolol therapy assessed by transthoracic echocardiography [29]. Although it is not fully understood how the blockade of β-adrenoceptor pathway increases contractility of the septic heart, some investigators have attributed these effects to the suppression of cytokine production such as TNF-α [44].

Others suggest that β-receptor expression is increased after β-blocker therapy, resulting in an improved inotropic response to β-agonists [45]. Observational data shows that continuation of previous β-blocker therapy in septic shock is associated with an unchanged need of inotropic support and possibly an improved outcome [46]. However, too aggressive use of β-blockers could decrease the myocardial contractility by prevailing the chronotropic effects of β-receptor blockade. For this reason, clinical diligence and caution are necessary when treating septic shock with esmolol in the acute phase. A decreased heart rate could also improve diastolic perfusion time and consequently myocardial perfusion. Some studies argue in favour of this preload positive effect by showing an improved stroke volume, despite a decreased contractility [29]. The influence of β-blockers on the diastolic function of the right ventricle is still an unexplored area of interest [4,14,27]. While systolic dysfunction is not associated with mortality [47], diastolic dysfunction is a predictor of mortality in septic shock [48]. Nonetheless, the role of β-blockers on the diastolic function remains highly speculative as this concept is not supported by structured echocardiography or by in vivo load-independent markers.

4.3. Cardio-vascular interaction

Assuming that β-blockers leave the intrinsic myocardial function unaffected, they might still benefit the heart by reducing its afterload thereby allowing the heart to operate more economically. Attenuation of cardiac depression by improving its efficiency might support the physiological rationale of using β-blockers during septic shock [27]. Increased cardiac efficiency is defined by an improved ratio between ventricular to arterial elastance, i.e. the concept of ventricular-arterial coupling.

This physiological concept of improving cardiac efficiency using β-blockers seems to work in selected patients with septic shock [28]. In the presence of an adequate preload, heart rate reduction with esmolol could improve arterial elastance, thereby contributing to an improved cardiovascular efficiency while allowing adequate systemic perfusion in septic shock. The lack of direct measurements, resulting in numerous approximations and omissions, raises doubts about the relevance of these results [49]. Our own intraventricular data support the concept of improved ventricular-arterial coupling in experimental endotoxic shock after β-blockade [14]. However, lowering arterial elastance - in order to increase cardiac efficiency – is only beneficial when an adequate perfusion pressure is maintained.

4.4. Future perspectives

Taking both preclinical and clinical data into consideration, it makes sense to reduce myocardial oxygen consumption when its need outstrips the capacity. Still, excessive β-blockade with negative inotropic effects could put the cardiac output below the threshold that is needed to maintain organ and tissue perfusion. Answering the clinically important question of how to apply β-blockers safely while maximizing its beneficial effect depends on; timing, type of β-blocker, resuscitation targets and patient characteristics [50].

4.4.1. Timing of intervention

Just like any pharmacologic intervention, onset time has a major impact in determining its effect on the inflammatory response. Some experimental studies documented survival benefits particularly when β-blockers were administered before the septic insult [16]. Preclinical data show that starting β-blocker therapy right after hemodynamic stabilization [27] is probably not the best moment. However, progressive sepsis-induced cardiac systolic and diastolic dysfunction develops during the early stages of sepsis [43]. Early (low-dose) β-blockade might therefore be associated with a greater number of survivors with septic shock [51]. Even alternate sequences of "on and off" β-blocker administration have been proposed [52]. However, current evidence does not support this.

4.4.2. Type of β-blocker

Currently, esmolol is the only β-blocker that has been tested in a RCT. The pharmacological characteristics of esmolol, an ultrashort acting β1-adrenoceptor antagonist, allows titration of the dosage to specific hemodynamic endpoints. However, there is not enough evidence to propose the use of a specific agent in each specific critical condition. Clinical studies have investigated the concomitant use with inotropes in order to counteract the negative inotropic action of β-blockers, and suggested that the combination had positive effects on improving cardiac performance and mortality risk [25,53]. Here too, while combining β-blocker therapy with phosphodiesterase inhibitors seem feasible in patients with septic myocardial depression [25], there is not enough evidence to propose the use of a specific inotropic agent.

4.4.3. Resuscitation targets

For beneficial effects, β-blockers should be administered at limited doses, wherein a fixed dosage and even titration to heart rate is not appropriate [23]. Granting the septic heart more time to recover - by putting the cardiomyocytes in a hibernation-like state by β-blockade - requires resuscitation goals focusing on tissue perfusion rather than central hemodynamics. Previous findings even suggest that β-blockers may cause an increased tolerance to hypotension [5], emphasizing to leave blood pressure "cosmetics" behind and to move forward to permissive hypotension and a perfusion-based approach [54]. This approach would allow for reducing the possible adverse effects of fluid therapy and vasopressor agents in septic shock [42,55].

It would therefore be essential to monitor the response of the microvascular bed to β-blockers. Current data shows marginal effects on the sublingual and gut microcirculation, which remains depressed from septic shock [20]. A persistent depressed microcirculation is a well-known indicator of adverse outcome [4,56]. The impaired microcirculatory flow during septic shock triggers the generation of anaerobic lactate and potentially impairs hepatic lactate clearance [57,58]. Preclinical studies show that β-blockers are associated with lower arterial and portal lactate levels, and less impairment of exogenous lactate clearance with beneficial effects on gut lactate generation [21]. However, monitoring the response of lactate as a goal of early sepsis therapy should be done with extra care in patients receiving β-blockers since production of lactate might be masked by a reduced adrenaline production [59,60].

Still, titration to microcirculatory parameters, lactate and oxygen delivery in relation to oxygen demand seems advisable. We could allow for reduced cardiac output and arterial blood pressure, thereby protecting - not necessarily improving - the cardiovascular system.

4.4.4. Patient characteristics

Personalized treatment based on cardiac function, adequate preload, the presence of comorbidities and the degree of sympathetic activation may provide better results in terms of outcome [50]. Patients with good cardiac contractility before treatment and those who are still in their early stage of septic shock are more prone to benefited from β-blocker therapy [29].

In pediatrics, the role of β-antagonists is not clear. In a non-septic setting, Jeschke and colleagues successfully used propranolol in severely burned children and demonstrated attenuated hypermetabolism and without complications [61]. However young children are characterized by a physiological higher resting heart rate, higher resting contractility state, lower contractility reserve and higher afterload dependence. Combined with the myocardial depressant effects of sepsis makes the use of β-antagonists in these patients possibly less favorable [62-66]. The use of β-antagonists in young children in septic shock should first be studied carefully under controlled conditions.

5. Conclusion

Data are inconsistent in how β-blockers change hemodynamics in septic shock. Nevertheless, there is sufficient preclinical and clinical data to suggest that β-blockade is safe when started at low dose. They must be used carefully while focusing on optimizing hemodynamics with resuscitation goals focusing on tissue perfusion rather than central hemodynamics.

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Conflict of interest

The authors declare that there are no conflicts of interest.

Declarations of interest

None.

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