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Beta-blockers in sepsis: time to reconsider current constraints?

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New insights into the mechanisms of action of beta-blockers, and the potential consequences for clinical practice, are continually evolving. Originally, this class of drugs was targeted towards treatment or prevention of hypertension, arrhythmias and myocardial ischaemia. Their therapeutic potential then expanded towards the reduction of mortality after myocardial infarction and heart failure.[1] Although these indications are now widely accepted, they were not immediately apparent. So why may the use of beta-blockers be beneficial in patients already suffering from impaired myocardial contractility? Clinical observations suggested that the beneficial effect of beta-blockers was greater in patients with the worst cardiac performance.[2] Concurrent findings that chronic use of an oral beta-agonist was associated with increased mortality led to re-evaluation of the paradigm,[3 4] fuelled new research that unravelled the concept of maladaptive sympathetic overstimulation in heart failure,[5] and changed clinical practice towards the use of beta-blockade.

In parallel to these evolving indications in cardiovascular disease, the role of beta-blockers in sepsis was also being explored. The classical concept of sepsis and septic shock described an overproduction of nitric oxide (NO), leading to an inability to adequately maintain vasomotor tone and hyporeactivity to both endogenous and pharmacological catecholamines.[6] In addition to NO, pathogen-associated molecular patterns, damage-associated molecular patterns (including histones) and cytokines all contribute to the development of sepsis-induced myocardial dysfunction.[7] In general, the first line of treatment for these life-threatening symptoms is a combination of alpha and beta-agonist, most commonly noradrenaline and dobutamine. Within this context there seems to be no indication for beta-blockers; indeed, they were traditionally contraindicated. However, this view was challenged by several observations. Retrospective data suggested an independent association between the number, duration and dose of alpha- and beta-agonists and mortality in sepsis.[8 9] Such data are however always hampered by the bias of indication: the sicker the patient, the more the drug will be administered. Statistical adjustments by multivariate analysis or propensity scoring models help to overcome this problem to some extent, but such design clearly cannot provide definitive answers. Despite these limitations the increased odds of dying within 90 days after a septic insult are reported to be as high as 2.3 in patients with dobutamine, in comparison with well-matched patients without dobutamine.[9] Epidemiological data also hinted towards the same direction. Analogous to statins, a significant reduction in 30 day mortality was observed in a large cohort of mixed Intensive Care Unit (ICU) patients (including those with sepsis) who were taking beta-blockers before ICU admission.[10] A recent randomized controlled trial found that use of the short-acting beta-blocker esmolol in a high-risk cohort of septic shock patients was not only associated with a significant reduction in mortality, but also with better cardiac performance.[11]

In this issue of the *British Journal of Anaesthesia*, Fuchs and colleagues[12] add another perspective to the already shifting paradigm. In a retrospective analysis, they investigated the potential influence of cessation of pre-existing use of beta-blockers in the course of a sepsis-related ICU admission.[12] Using multivariate analysis they observed an independent association between discontinuation of beta-blockers and 90 day mortality in a cohort of 296 patients with sepsis or septic shock. The odds of dying within 90 days was 0.57 (confidence interval 0.39–0.83) for those who remained on beta-blockers, in comparison with patients in whom the use of beta-blockers was stopped in the acute phase of their sepsis treatment, suggesting a substantial effect. These data are in line with the BASEL-II-ICU study where a protective effect of the continuation of pre-existing use of beta-blockers on short- and long-term mortality was observed.[13] In ICU patients admitted for acute respiratory failure in whom the pre-existing using of beta-blockers was continued at discharge, the 1 yr mortality was 16% *vs* 46% for patients discharged from hospital without a beta-blocker. This was independent of either a cardiac or non-cardiac origin of the respiratory failure.

There are several potential mechanisms underlying the observed 'protective' effects of beta-blockers in the course of sepsis, both cardiac and non-cardiac. The design of the study does not allow conclusions to be drawn beyond an association. It is conceivable that (dis)continuation of beta-blockers is a marker of severity of illness. Statistical 'correction' by multivariate analysis can mitigate this effect to some extent, but does not rule out unknown biases. An alternative explanation is that beta-blockers protect against ischaemic heart disease, not uncommonly present in sepsis patients as a pre-existing

co-morbidity. However, previous studies suggest the protective effect of beta-blockers was not restricted to patients with pre-existing cardiovascular disease.[10 13] As a result of high levels of endogenous and exogenous catecholamines, there is a high likelihood of sympathetic overstimulation in sepsis, with a typical persistence of tachycardia despite adequate fluid resuscitation. This can lead to diastolic dysfunction, the predominant phenotype in sepsis-related myocardial dysfunction, and classically an indication for beta-blockers. Morelli and collegues showed a substantial improvement in stroke volume with esmolol.[11] This may not only be explained by heart rate reduction allowing better diastolic filling, but also by attenuation of catecholamine-induced cardiomyocyte toxic effects, characterized by inflammation, oxidative stress and abnormal intracellular calcium trafficking, leading to stunning, apoptosis and even necrosis.[14 15] Adverse effects of catecholamine toxicity can also affect organs other than the heart. Examples include pulmonary oedema, gut ischaemia, hypercoagulability, immunomodulation and stimulation of bacterial growth, impaired glucose tolerance, muscle wasting and hyperlactataemia.[16] Finally, the results by Fuchs and colleagues potentially indicate prevention of the beta-blocker withdrawal syndrome, provoked by a mild and transient hypersensitivity of cardiac beta-adrenergic receptors.[17] Symptoms include tachycardia, sweating, tremors, headaches and angina pectoris. Acute interruption in the use of beta-blockers under conditions other than sepsis, such as pre-existing heart failure, are associated with an attributable risk of death.[18]

How should these observations be translated into clinical practice? Further research is needed to confirm any benefit of continuation of beta blockers in a prospective multicentre study, and to clarify potential differences between the various subtypes of beta-blockers. In the meantime, evidence suggests that it may be worthwhile to maintain use of beta-blockers in patients who are on long-term beta-blocker therapy prior to the septic period. This challenges current dogma where continuation of beta-blockers is generally viewed as an unnecessary risk or even contraindicated, especially when there is marked cardiovascular instability. Changing behaviour may be more difficult than anticipated; despite well-accepted indications for beta-blockers, additional strategies are often needed to assure compliance.[19]

Authors' contributions

Wrote the first draft of the article: E.C.B.

Revised it critically for important intellectual content: M.S.

Approved of the final version to be published; agree to be accountable for all aspects of the work thereby ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: both authors.

Declaration of interest

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CRITICAL CARE

Continuing chronic beta-blockade in the acute phase of severe sepsis and septic shock is associated with decreased mortality rates up to 90 days

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Abstract

Background. There is growing evidence that beta-blockade may reduce mortality in selected patients with sepsis. However, it is unclear if a pre-existing, chronic oral beta-blocker therapy should be continued or discontinued during the acute phase of severe sepsis and septic shock.

Methods. The present secondary analysis of a prospective observational single centre trial compared patient and treatment characteristics, length of stay and mortality rates between adult patients with severe sepsis or septic shock, in whom chronic beta-blocker therapy was continued or discontinued, respectively. The acute phase was defined as the period ranging from two days before to three days after disease onset. Multivariable Cox regression analysis was performed to compare survival outcomes in patients with pre-existing chronic beta-blockade.

Results. A total of 296 patients with severe sepsis or septic shock and pre-existing, chronic oral beta-blocker therapy were included. Chronic beta-blocker medication was discontinued during the acute phase of sepsis in 129 patients and continued in 167 patients. Continuation of beta-blocker therapy was significantly associated with decreased hospital ($P=0.03$), 28-day ($P=0.04$) and 90-day mortality rates (40.7% *vs* 52.7%; $P=0.046$) in contrast to beta-blocker cessation. The differences in survival functions were validated by a Log-rank test ($P=0.01$). Multivariable analysis identified the continuation of chronic beta-blocker therapy as an independent predictor of improved survival rates (HR = 0.67, 95%-CI (0.48, 0.95), $P=0.03$).

Conclusions. Continuing pre-existing chronic beta-blockade might be associated with decreased mortality rates up to 90 days in septic patients.

Key words: adrenergic beta-antagonists; critical care outcomes; mortality; sepsis

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Editor's key points

- Evidence is emerging that beta-blockade may be beneficial in some patients with sepsis.
- In this study there was an association between continuation of beta-blocker and decreased in-hospital, 28-day and 90-day mortality in patients with sepsis.
- However, the data are from a retrospective secondary analysis of a single centre study, with possible confounding factors.
- These results add to the evidence that beta-blockade may influence outcome in sepsis but should be interpreted with caution.

The high prevalence of cardiovascular diseases leads to an increasing proportion of hospital patients taking chronic oral beta-blocker therapy.[1] Physicians have to decide on a daily basis whether or not to continue chronic beta-blocker medication and these decisions can markedly influence outcome. For example, continuing chronic beta-blocker therapy has been associated with reduced mortality in patients with acute respiratory failure.[2]

In septic patients, limiting beta-adrenergic stimulation may also be beneficial.[3] In a randomized controlled trial, a newly initiated esmolol infusion in fluid resuscitated septic shock patients with tachycardia increased stroke volume, reduced norepinephrine and fluid requirements and lowered 28-day mortality rate.[4] Furthermore, a pre-existing chronic beta-blocker therapy was associated with improved 28-day survival despite a higher risk profile in this cohort.[5] However, whether oral beta-blockers were continued or not during sepsis in that study is unknown. Notably, current guidelines give no recommendation how to manage chronic beta-blocker medication during sepsis.[6]

The primary aim of the present study was to compare 90-day mortality rates for discontinued or continued chronic beta-blocker therapy in patients with severe sepsis and septic shock. Secondary outcomes included length of stay, ICU (intensive care unit), hospital and 28-day mortality.

Methods

Design

The present secondary analysis of a single-centre prospective observational trial[7] on critically ill patients with severe sepsis or septic shock was performed at an interdisciplinary, surgical ICU of the tertiary University Hospital of Greifswald, Germany. The original study was conducted as part of the local quality improvement program for the improvement in diagnosis and treatment in patients with severe sepsis or septic shock. Data were entered into a study database (Sepsis Information System for Quality Assurance, SIQ; G.punkt Medical Services, Magdeburg, Germany). The local ethics committee approved the study (Identifier: BB 133/10) and waived a written informed consent because of the observational nature of this quality improvement initiative and the anonymous data collection. The study was performed from January 1st, 2010 to December 31st, 2013.

Study population

During the study period, all patients of the ICU were screened daily by study nurses for the first episode of a systemic inflammatory response syndrome (SIRS) and at least one organ dysfunction within the last 24 h. SIRS, organ failure, severe sepsis and septic shock were defined according to ACCP/SCCM consensus criteria.[8] SIRS was diagnosed if at least two of the following criteria were fulfilled: body temperature >38 °C or <36 °C, heart rate >90 min^{-1}, respiratory failure with a respiratory rate >20 min^{-1} or a partial carbon dioxide pressure of <4.3 kPa and a white blood cell count of >12,000 cells μL^{-1} or <4000 cells μL^{-1} or the presence of more than 10% immature neutrophils. Organ dysfunctions were defined as systolic bp below 90 mm Hg in the absence of other causes and despite adequate fluid resuscitation, lactate acidosis (>1 mmol L^{-1}), oliguria (urine output <0.5 mL kg^{-1} h^{-1} for at least two h despite adequate fluid resuscitation) or an acute alteration in mental status. In a second step, the records were screened for signs of severe sepsis (to specify organ failure) or septic shock (hypotension or need of catecholamines despite adequate fluid replacement) and for the focus of infection (microbiological probes, X-rays etc.). Experienced intensivists in the study team (4 consultants) reviewed every case and decided based on all available documents whether SIRS and organ failure were probably caused by an infection or not. The study team did not change during the study period. All patients aged≥18 yr, who met the criteria for the first episode of severe sepsis or septic shock, were included in the study. A second episode of sepsis was not registered to exclude phenomena such as the compensatory anti-inflammatory response syndrome.[9]

Definitions

The onset of sepsis was defined as the first time point when patients fulfilled the ACCP/SCCM criteria for severe sepsis or septic shock.[8] The onset of severe sepsis or septic shock was identified retrospectively by study nurses and validated by intensivists based on laboratory and haemodynamic variables and notes in the patient management system.

The place where sepsis was deemed to have occurred was determined according to dates of onset of sepsis, admission to hospital and ICU. Community-acquired sepsis was defined as an infection that occurred <48 h after hospital admission. ICU-acquired sepsis was defined as an infection >48 h after ICU admission. Otherwise, sepsis was categorised as hospital-acquired sepsis. Pre-existing chronic health problems were defined as at least one of the following: chronic kidney failure, metastatic cancer, haematological malignancies, AIDS, other causes of immunosuppression, severe hepatic failure, NYHA class IV and pre-existing chronic severe hypoxia.

The electronic patient management system or the patient's documents were reviewed, or the general practitioner was contacted to find which patients were receiving chronic beta-blocker medication. Pre-existing oral beta-blocker therapy was defined as a treatment started at least seven days before sepsis onset. The individual indications for beta-blockers could not be evaluated in detail but maybe inferred from the comorbidities (Table 1). Discontinuation was defined as an interruption of a pre-existing beta-blocker therapy for more than 24 h within the acute phase of severe sepsis and septic shock. The acute phase of severe sepsis and septic shock was narrowly defined as the period ranging from two days before to three days after sepsis onset, to evaluate the impact of beta-blockade during the period of highest haemodynamic instability and highest sympathetic tone.

Mortality rates were determined in ICU, hospital, and 28 days and 90 days after sepsis onset. Study nurses determined

Table 1 Patient's characteristics of patients with continued and discontinued beta-blocker therapy during acute phase of severe sepsis or septic shock. Missing values omitted for the calculation of: # – absolute frequency, % – relative frequency, med, median, IQR, interquartile range, m, mean, SD, standard deviation, CI, 95% confidence interval, §of survivors only, (first 24 h) refers to the first 24 h after sepsis onset

		Discontinued			Continued			P value
Baseline variables	Levels	N=129			N=167			
		med		*(IQR)*	*med*		*(IQR)*	
Age, yr		72.7		(60.6–77.3)	74.9		(65.9–79.4)	0.02
APACHE II score at sepsis onset		21.0		(16.2–26.0)	20.0		(15.0–24.5)	0.25
SAPS II score at sepsis onset		45.5		(39.0–58.0)	43.0		(35.0–52.0)	<0.01
Lactate (first 24 h), mmol L^{-1}		3.5		(2.0–6.5)	2.3		(1.5–3.8)	<0.01
		#	%		#	%		
Sex	male	75	58.1		107	64.1		0.34
Chronic disease	yes	58	45.0		80	47.9		0.64
Arterial hypertension	yes	106	82.2		136	81.4		1.00
Coronary heart disease	yes	33	25.6		61	36.5		0.06
Atrial fibrillation	yes	32	24.8		53	31.7		0.20
Pre-existing administration of angiotensin converting enzyme inhibitor and/or angiotensin receptor blocker	yes	86	66.7		95	56.9		0.09
Pre-existing administration of calcium antagonists	yes	34	26.4		40	24.0		0.69
Pre-existing administration of statins	yes	38	29.5		69	41.3		0.04
Pre-existing administration of other drugs (minoxidil, moxonidine, nitrates, molsidomine)	yes	12	9.3		16	9.6		1.00
Sepsis severity	severe sepsis	26	20.2		47	28.1		
	septic shock	103	79.8		120	71.9		0.14
Origin of infection	community acquired	61	47.3		80	47.9		
	hospital (Non-ICU) acquired	48	37.2		61	36.5		
	ICU acquired	20	15.5		26	15.6		0.99
Site of infection	pneumonia	28	22.2		52	32.1		
	abdominal	67	53.2		63	38.9		
	bone and soft part	13	10.3		19	11.7		
	others	18	14.3		28	17.3		0.10
Reason for ICU admission	non-surgical	24	18.6		53	31.7		
	Emergency surgery	99	76.7		100	59.9		
	elective surgery	6	4.7		14	8.4		0.01
Known nosocomial pathogen on admission	yes	6	4.7		16	9.6		0.12
Nosocomial acquired pathogen	yes	24	18.6		27	16.3		0.64
Tachycardia	yes	108	85.7		130	79.3		0.17
Antibiotic therapy before sepsis	yes	55	43.7		78	47.3		0.56
		med		*(IQR)*	*med*		*(IQR)*	
Heart rate (first 24 h), min^{-1}		118		(97.0–135.5)	111		(97.0–132.8)	0.20
Body temperature, °C		37.0		(35.2–38.2)	38.1		(35.7–38.7)	<0.01
White blood cells before sepsis onset, 10^9 L^{-1}		14.2		(8.9–21.1)	13.7		(9.1–18.8)	0.40
C-reactive protein (first 24 h), mg L^{-1}		186		(125.5–269.5)	225		(142.5–301.5)	0.10

Continued

Table 1 Continued

Baseline variables	Levels	Discontinued N=129			Continued N=167			P value
Procalcitonin (first 24 h), ng mL^{-1}		6.8		(2.0–22.0)	4.0		(1.3–17.0)	0.12
Treatment variables		#	%		#	%		
Blood culture sampling before antibiotic therapy	yes, pathogen known	11	8.5		29	17.4		
	yes sterile	26	20.2		42	25.1		
	no	92	71.3		96	57.5		0.03
Blood culture sampling after initiation of antibiotic therapy	yes, pathogen known	17	13.2		35	21.0		
	yes sterile	76	58.9		90	53.9		
	no	36	27.9		42	25.1		0.22
Microbiological samples of the septic focus	yes, pathogen known	73	57.0		105	63.3		
	yes sterile	30	23.4		30	18.1		
	no	25	19.5		31	18.7		0.47
Antimycotic therapy	yes	44	34.1		55	32.9		0.90
Use of red cell concentrates (first 24 h)	yes	30	23.3		46	27.5		0.42
Use of dobutamine	yes	33	25.6		40	24.1		0.79
Use of low-dose steroids	yes	45	34.9		41	24.6		0.05
Use of epinephrine	yes	6	4.7		5	3.0		0.54
Use of norepinephrine	yes	119	92.2		152	91.0		0.83
		med		*(IQR)*	*med*		*(IQR)*	
Crystalloids first 6 h, L		2.0		(0.88–3.00)	1.5		(0.78–2.80)	0.19
Crystalloids first 24 h, L		5.0		(3.00–8.90)	4.2		(2.71-6-52)	0.049
Outcome variables								
Case fatality rate		#	%		#	%		
ICU		49	38.0		46	27.5		0.06
Hospital		62	48.1		59	35.3		0.03
28 days		53	41.1		48	28.7		0.04
90 days		68	52.7		68	40.7		0.046
Length of stay		*m*	*SD*	*(CI)*	*m*	*SD*	*(CI)*	
Before sepsis onset, days		7.5	11.9	(5.4–9.5)	6.9	12.6	(5.0–8.8)	0.70
ICU after sepsis onset, days[§]		14.8	14.9	(11.5–18.1)	20.2	19.1	(16.8–23.7)	0.04
Entire hospital stay, days[§]		48.4	33.9	(40.1–56.7)	43.4	26.9	(38.2–48.5)	0.28
		med		*(IQR)*	*med*		*(IQR)*	
Before sepsis onset, days		2.2		(0.3–11.9)	3.0		(0.5–8.4)	0.42
ICU after sepsis onset, days[§]		8.4		(3.7–25.4)	12.8		(6.4–31.1)	0.02
Entire hospital stay, days[§]		40.0		(23.5–59.7)	34.6		(22.5–59.1)	0.54
Cause of death		#	%		#	%		
sepsis		37	66.1		33	66.0		
circulatory		6	10.7		3	6.0		
other		13	23.2		14	28.0		0.63

the right censored survival time or date of death by calling the patients themselves, their general practitioner or by scanning the hospital data management system. Patients received sepsis management in accordance with the respective Surviving Sepsis Campaign Guidelines.[6 10]

Study groups

Based on the presence of an oral pre-existing chronic beta-blocker therapy and its management during the acute phase of severe sepsis and septic shock two groups of patients were defined:

- **Discontinued**: pre-existing chronic beta-blocker therapy, but administration was discontinued or paused for more than 24 h during the acute phase of severe sepsis and septic shock
- **Continued**: pre-existing chronic beta-blocker therapy that was continued during the acute phase of severe sepsis and septic shock

Study endpoints

The primary goal was to investigate the effects of a continued *vs* a discontinued pre-existing oral beta-blocker therapy during the acute phase of severe sepsis and septic shock on 90-day mortality. Secondary endpoints included mortality rates 28 days after sepsis onset, during hospital and ICU stay and lengths of stay (LOS).

Statistical analysis

Statistical analyses were performed using MATLAB R2016a (Natick, Massachusetts) and GNU R version 3.3.1 (Language and Environment for Statistical Computing, R Core Team, Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics are provided by counts and percentages for categorical data. Because of skewness numerical data are expressed as median and interquartile range. Table 1 additionally includes means, standard deviations and 95% Clopper-Pearson confidence limits for the mean (95%-CI) for lengths of stay to facilitate comparisons with previous clinical trials. Two-tailed *P* values were represented to compare the pre-existing presence of an oral beta-blockade during the acute phase of severe sepsis and septic shock ('discontinued' *vs* 'continued'). Therefore, Fisher's exact tests for categorical features with two levels, χ^2 tests for categorical features with more than two levels and Student's *t*-test or Wilcoxon–Mann–Whitney *U*-test for numerical data were performed. Missing values were omitted for the descriptive part. The number of missing values is listed in the supplementary material (Supplementary Table S1). The survival functions were computed using the Kaplan-Meier estimator and a Log-rank test was performed.

The multivariable Cox model consists of variables representing disease severity at sepsis onset (APACHE II score, sepsis severity, site of infection, chronic diseases, heart rate, body temperature, lactate level, white blood cells, C-reactive protein, procalcitonin) and baseline characteristics (age, sex, known nosocomial pathogen, hospital-acquired infection, antibiotic therapy before sepsis onset, coronary heart disease, pre-existing administration of statins and angiotensin converting enzyme inhibitor and/or angiotensin receptor blocker) to reduce the indication bias. Numerical data (age, body temperature, lactate level, white blood cells, C-reactive protein and procalcitonin) were transformed into categorical variables in order to take the nonlinear influence of this features into account. This was executed based on reference ranges and restricted cubic splines. The categorization and the restricted cubic spline estimation are illustrated in the Supplementary material (Supplementary Fig. S1). The proportional hazards assumption for the Cox regression model was verified visually by graphs of the scaled Schoenfeld residuals and χ^2 tests were performed. To handle the problem of overfitting a cross-validated LASSO for Cox regression models[11] was performed in R using "cv.glmnet" of the "glmnet"-package.[12]

Results

During the four-yr study period 6473 ICU patients were screened. After exclusion of patients younger than 18 yr, patients without infection and chronic beta-blocker therapy and those not fulfilling the criteria for severe sepsis or septic shock, 296 patients were included: 73 with severe sepsis (25%) and 223 with septic shock (75%). Beta-blockers were continued during the acute phase of severe sepsis and septic shock in 167 patients and discontinued in 129 patients (Fig. 1). Chronic beta-blocker treatment included cardioselective agents ($ß_1$) (atenolol, bisoprolol, metoprolol, nebivolol, talinolol) and nonselective agents (β_{1+2}) (carvedilol, propranolol, sotalol).

Patients' characteristics

Patients' clinical and therapeutic characteristics are presented in Table 1. Compared with patients with a continued beta-blocker therapy patients of the discontinued group were younger ($P=0.02$) but had increased SAPS II scores ($P<0.01$) and lactate concentrations at onset of sepsis ($P<0.01$). There were no significant differences between both groups with respect to origin ($P=0.99$), site of infection ($P=0.10$) or chronic disease ($P=0.64$). Pre-existing statins therapy was more frequent in patients with continued beta-blockade ($P=0.04$). Continuation of chronic beta-blocker therapy was not associated with an increased need for vasopressor or inotropic support, nor use of low-dose steroids ($P>0.05$ each), but was associated with reduced requirements of crystalloids during the first 24h ($P=0.049$).

Mortality rates and length of stay

Hospital, 28-day and 90-day mortality rates were significantly increased in patients with discontinued beta-blocker therapy as compared with beta-blocker continuation ($P<0.05$ each), but the difference in ICU mortality was not statistically significant ($P=0.06$). Though median ICU LOS after diagnosis was longer in patients with continued *vs* discontinued beta-blocker medication ($P=0.02$), there was no statistical difference in hospital LOS ($P=0.54$) (Table 1).

Survival analysis

Continued beta-blockade was associated with a decreased mortality rate (Log-rank test: $P=0.01$) (Fig. 2). Indeed, when other covariates were considered using multivariable Cox regression analysis there was an association between continuation of chronic beta-blocker therapy and hazard rate for survival (HR = 0.67, 95%-CI = (0.48, 0.95), $P=0.03$) (Table 2).

Discussion

The main results of the present secondary analysis of a prospective observational trial suggest that continuing a pre-existing

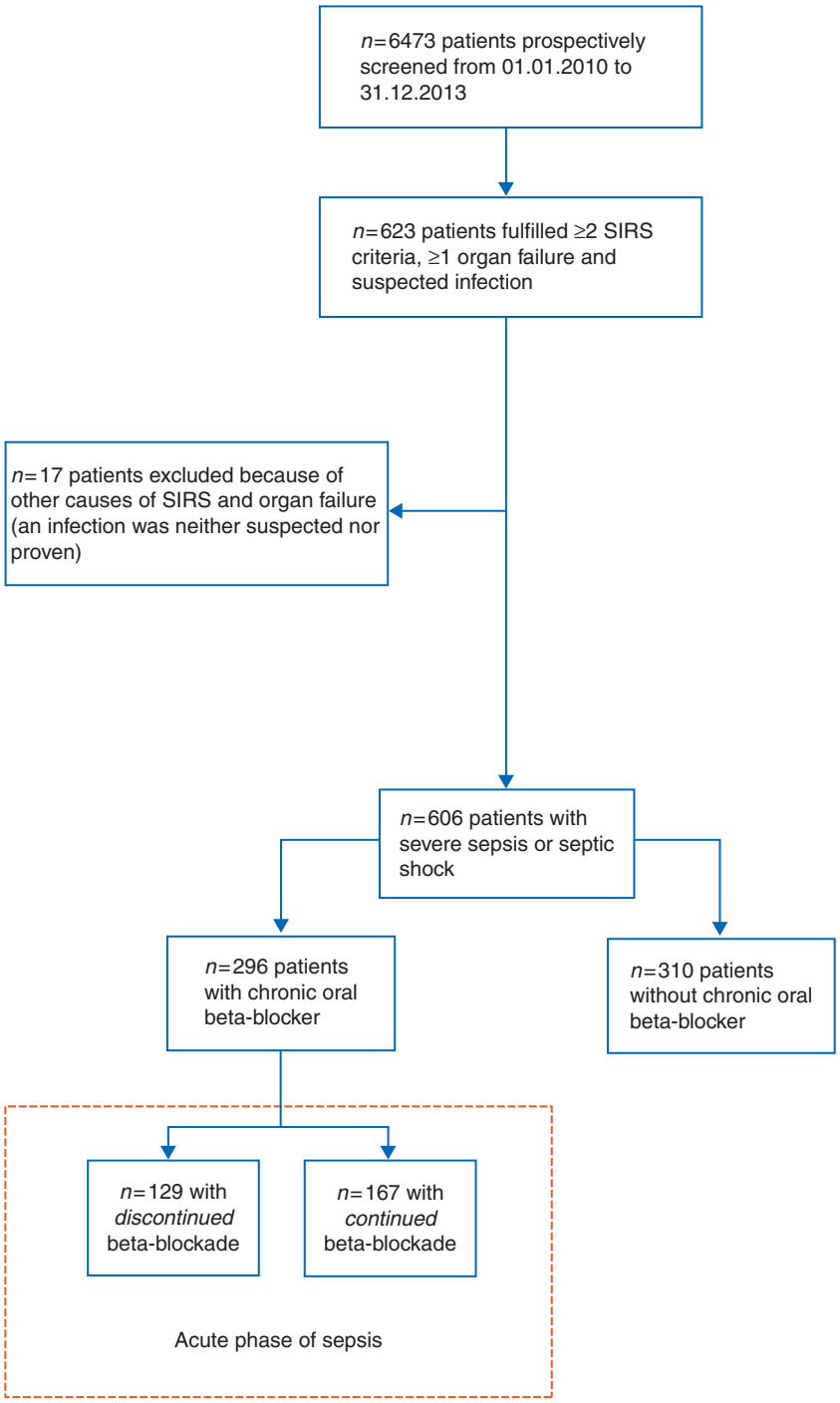

Fig 1 Study flow diagram. SIRS, Systemic Inflammatory Response Syndrome.

chronic oral beta-blocker therapy during the acute phase of severe sepsis or septic shock, is associated with decreased mortality rates up to 90 days, compared with patients with discontinued beta-blocker treatment. In addition, multivariable Cox proportional analysis identified the continuation of chronic beta-blocker therapy as an independent predictor of decreased 90-day mortality.

Beta-blockers have been shown to provide beneficial effects by limiting the adrenergic stress response in numerous subgroups of critically ill patients, such as burns[13 14], trauma[15 16] or

Fig 2 Kaplan-Meier estimates of the survival functions. Survival functions of the first 90 days after sepsis onset are given for patients with continued (red) and discontinued (blue) beta-blocker therapy with 95% confidence bounds. The survival information till 90 days is right censored (indicated by plus sign).

traumatic brain injury.[17] Despite this encouraging background, treating septic patients requiring vasopressor therapy to stabilize haemodynamics and potentially suffering from sepsis induced myocardial dysfunction with a negative chronotropic and inotropic drug seemed to be not advisable[18] and currently does not represent the standard of care.[19] However, after a successful pilot study[4] Morelli and colleagues[20] demonstrated in a randomized controlled trial that a titrated infusion of the short acting β_1-selective beta-blocker esmolol optimized stroke volume, reduced norepinephrine and fluid requirements and improved renal function in patients with septic shock. The present data might support the haemodynamic tolerance of beta-blocker therapy in fluid resuscitated patients with severe sepsis and septic shock, because there was not an increased need for vasopressor or inotropic support in the continued *vs* the discontinued group. Notably, the continuation of beta-blockade was associated with reduced fluid requirements; further supporting an improved haemodynamic stability as suggested by Morelli.[20 21] However, data on haemodynamic effects of beta-blockers in sepsis are inconsistent. In a small, uncontrolled, prospective study including 10 septic patients a continuous esmolol infusion decreased heart rate but did not improve stroke volume or reduce norepinephrine requirements.[22]

Chronic beta-blocker medication has been reported to be associated with an improved outcome in critically ill patients in general[23] and specifically in septic patients.[5 24] But these studies did not evaluate if beta-blockers were continued or discontinued during ICU or hospital stay.[5 23 24] Consequently, no conclusions about therapeutic consequences could be derived from these studies, because at the diagnosis of sepsis, pre-existing medication cannot be changed. Notably, in an ICU population with hypoxaemic respiratory failure the cessation of a chronic beta-blocker therapy within the first 24 h has been reported to be associated with higher mortality but patients with sepsis were excluded from this study.[2 25] The present data suggest an association between the continuation of chronic beta-blockade during the acute phase of severe sepsis and septic shock and reduced mortality rates up to 90 days compared with discontinuation. Potential explanations include the suppression of highly elevated sympathetic tone during the acute phase of sepsis and/or rebound phenomena after beta-blocker withdrawal. In addition to β_1-receptor mediated haemodynamic effects, further mechanisms of beta-blockers suggested by experimental studies include the β_2-receptor mediated modulation of inflammation,[26 27] coagulation[28] and metabolism.[29 30] Because of the retrospective nature of the present analysis and the fact that just four patients were treated with a nonselective beta-blocker, we cannot elaborate on the underlying mechanisms.

There are some limitations of this study. The retrospective analysis of an existing database results in potentials for confounding and indication bias. For example, we do not have sufficient information about the indication for cessation or continuation of chronic beta-blockade. As there are currently no recommendations how to handle chronic beta-blocker therapy

Table 2 Cox proportional hazards regression

	Full model				Reduced model (LASSO)			
	Hazard Ratio	95%-CI of HR	t value	P value	Hazard Ratio	95%-CI of HR	t value	P value
Sex [male]	0.94	(0.64,1.37)	−0.34	0.73	0.84	(0.59,1.19)	−0.99	0.32
ICU admission after emergency surgery	1.12	(0.64,1.95)	0.40	0.69				
ICU admission after elective surgery	0.68	(0.27,1.70)	−0.82	0.42				
Known nosocomial pathogen [yes]	1.57	(0.85,2.88)	1.45	0.15	1.60	(0.91,2.80)	1.62	0.11
Nosocomial acquired pathogen [yes]	0.82	(0.50,1.35)	−0.78	0.44				
Origin of infection [ICU acquired]	1.40	(0.78,2.52)	1.14	0.26				
Origin of infection [Hospital (Non-ICU) acquired]	0.87	(0.57,1.35)	−0.61	0.55				
Sepsis severity [severe sepsis]	0.93	(0.58,1.51)	−0.28	0.78				
Site of infection [pneumonia]	1.52	(0.83,2.80)	1.35	0.18				
Site of infection [abdominal]	0.92	(0.50,1.70)	−0.27	0.79				
Site of infection [bone and soft part]	1.16	(0.52,2.65)	0.38	0.70				
Age [<50 yr]	0.51	(0.15,1.71)	−1.09	0.28				
Age [>80 yr]	1.48	(0.91,2.41)	1.59	0.11				
Chronic diseases [yes]	1.41	(0.95,2.11)	1.70	0.09	1.37	(0.95,1.99)	1.67	0.10
Coronary heart disease [yes]	1.07	(0.71,1.62)	0.33	0.74				
Pre-existing administration of statins [yes]	0.85	(0.57,1.26)	−0.81	0.42				
Pre-existing administration of angiotensin converting enzyme inhibitor and/or angiotensin receptor blocker [yes]	1.11	(0.76,1.62)	0.56	0.58				
Body temperature [<36.0 °C]	1.42	(0.92,2.17)	1.60	0.11	1.26	(0.88,1.80)	1.26	0.21
White blood cell count [<4 *10^9 L^{-1}]	1.50	(0.71,3.14)	1.06	0.29				
White blood cell count [>10 *10^9 L^{-1}]	1.39	(0.76,2.55)	1.06	0.29				
APACHE II score first 24 h	1.05	(1.02,1.09)	3.21	<0.01	1.06	(1.04,1.09)	4.74	<0.01
Heart rate	1.00	(1.00,1.01)	0.66	0.51				
Antibiotic therapy before sepsis onset [yes]	1.24	(0.83,1.84)	1.05	0.29				
Lactate first 24 h [>3 mmol L^{-1}]	1.66	(1.09,2.52)	2.36	0.02	1.57	(1.09,2.25)	2.44	0.02
C-reactive protein first 24 h [>200 mg mL^{-1}]	1.05	(0.71,1.56)	0.24	0.81				
Procalcitonin first 24 h [<2 ng mL^{-1}]	0.77	(0.44,1.34)	−0.93	0.35				
Procalcitonin first 24 h [>10 ng mL^{-1}]	0.73	(0.44,1.22)	−1.19	0.24				
Beta-blocker [continued]	0.59	(0.40,0.87)	−2.65	0.01	0.67	(0.48,0.95)	−2.24	0.03

by national and international sepsis guidelines, the decision how to manage chronic beta-blocker treatment was made by the intensivists in charge individually for each patient. To statistically reduce the risk of confounding and particularly to reduce the indication bias a multivariable Cox regression analysis was performed. Nevertheless, the observational and retrospective study design only allows us to generate hypotheses that need to be confirmed in future prospective trials.

The increased SAPS II scores and lactate levels at sepsis onset in the discontinued *vs* continued group potentially suggest a higher disease severity in patients of the discontinued group. This assumption is challenged by similar APACHE scores and younger patients in the discontinued group, both representing established predictors of worse outcome.[31] The lower lactate levels potentially are a consequence of the continued beta-blocker therapy as suggested by a retrospective study reporting decreased lactate levels in patients with beta-blocker therapy as compared with those without.[24] Of note, the proportion of septic shock patients in this study is especially high. This might be explained by local circumstances. The study site is a tertiary university hospital and a regional referral centre for the treatment of patients with sepsis. Additionally, several departments of the hospital take care of patients with sepsis and severe sepsis on their intermediate care units. Only in cases of further deterioration patients are transferred to the ICU.

The acute phase of severe sepsis and septic shock was defined narrowly from two days before until three days after sepsis onset. Consequently, it cannot be excluded that patients in the discontinued group received their beta-blocker medication after this period. At first sight, this appears to represent a limitation, because beta-blockers might not have been discontinued during the complete phase of sepsis. However, even interrupting chronic beta-blocker therapy for only a few days was associated with a significantly worse outcome.

Conclusions

These data suggest that discontinuation of a pre-existing chronic beta-blockade during severe sepsis and septic shock is associated with increased mortality. Conversely, continuing chronic beta-blockade in the acute phase of severe sepsis and septic shock might be associated with decreased mortality rates up to 90 days. These results are hypothesis-generating and require verification in prospective trials.

Authors' contributions

Study design/planning: M.G., S.W., C.F., S.-O.K.
Study conduct: S.W., C.F., C.S.
Data analysis: S.W., C.F., M.G., S.R., K.M., M.V.

Writing paper: M.V., S.R., C.F.
Revising paper: all authors

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

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Declaration of interest

In 2013, C.F. and S.-O. K. attended a "simulator training for therapy with anti-infectives: diagnosis and therapy of infectious diseases in critical ill patients" organized and paid by Pfizer Pharma GmbH, Berlin, Germany.
In 2015, C.S. and C.F. received travel funding for DIVI from Astellas Pharma GmbH, Germany. C.S. received lecture fees from Dräger GmbH and Radiometer GmbH.
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