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Metabolic effects of beta-blockers in critically ill patients: A retrospective cohort study

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ABSTRACT

Background: Beta-blockers have potential protective features during critical illness. Heart rate reduction, with limited effect on blood pressure and beneficial effects on metabolism, organ function and inflammation have been reported. We examined metabolic effects of beta-blockers among ICU patients, to address the effect on the estimated energy expenditure, measured by carbon dioxide production (VCO_2). Furthermore, we investigated effects on organ function and inflammation.

Methods: A retrospective study in adult patients admitted to our 17-beds mixed medical-surgical ICU from January 2013 to March 2016. Mechanically ventilated patients who commenced beta-blockers were eligible for inclusion. Exclusion criteria were: beta-blocker therapy in the 7 previous days, treatment duration <48 h, therapeutic hypothermia, and no VCO_2 measurements.

Outcome parameters were obtained at 6 different time points from 24 h before until 48 h after beta-blocker commencement. Linear mixed models were used to evaluate trends.

Results: In total 58 patients were included. Various types of beta-blockers were administered, with a median equivalent daily dose to metoprolol of 50.0 mg (IQR 25.0–62.5). The mean heart rate decreased from 103 ± 20 to 91 ± 19 beats per minute after 48 h ($p < 0.001$), with unaltered blood pressures. Metabolic and other parameters did not show significant differences over time, or parameter changes were due to trends that had already started before beta-blocker commencement.

Conclusions: No changes in VCO_2 after beta-blocker commencement were demonstrated suggesting no alterations in energy expenditure. Heart rates significantly decreased with unaltered blood pressures. Other parameters did not show trends that could be attributed to beta-blockers effects.

Introduction

Acute critical illness is associated with massive stimulation of the sympathetic nervous system and enhanced release of catecholamines. In the intensive care unit (ICU), this marked endogenous release is often further increased by exogenous stimulation due to the infusion of vasopressor agents. Enhanced catecholamine release may be essential to preserve blood pressure and organ perfusion, but the overwhelming stimulation in critically ill patients may surpass the benefits.[1,2] Among other effects caused by sympathetic stimulation, hypermetabolism has been described, resulting in an increased resting energy expenditure (REE) and catabolic state.[3,4] This catabolic response is associated with muscle wasting, which is more marked in those patients with multi-organ failure compared with those with only single organ failure.[5] When nutritional intake does not meet the metabolic demands, energy deficit may occur, which has been shown to be associated with an increased risk of complications, such as infections, prolonged length of stay and even mortality.[6]

Concerning the concept of adrenergic toxicity, there is a growing interest in the potential protective effects of beta-blockers in critically ill patients. Beneficial cardiovascular effects of beta-blockers have been shown in cardiac patients, who have been treated with beta-blockers since the 1960s in order to treat arrhythmias and prevent

Abbreviations: APACHE-II, acute physiology and chronic health evaluation II score; BMI, body mass index; bpm, beats per minute; cmH_2O, centimeter of water; CRP, C-reactive protein; g, gram; H^+, hydrogen; ICU, intensive care unit; IQR, interquartile range; kcal, kilocalorie; kg, kilogram; kPA, kilopascal; L, liter; m^2, square meter; min, minute; mg, milligram; mL, milliliter; mmHg, millimeter of mercery; mmol, millimole; N, sample size; NS, non-significant; NUTRIC, nutrition risk in critically ill; P/F-ratio, ratio of arterial oxygen tension to fraction of inspired oxygen; PDMS, patient data management system; REE, resting energy expenditure; SAPS-II, simplified acute physiology II score; SD, standard deviation; SOFA, sequential organ failure assessment score; VCO_2, carbon dioxide production; μg, microgram; μmol, micromole

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myocardial infarction.[4] More recently, various studies investigated different effects of beta-blockers in (septic) critically ill patients. Reduction of the heart rate may be considered as expected. Moreover, it is striking and possibly counterintuitive that beta-blockers during critical illness do not lead to reductions in blood pressure[7–12] and that use of even lower vasopressor and inotropic requirements have been reported.[7–9]

Recently, in a randomized controlled landmark trial among 144 critically ill, septic patients, performed by Morelli et al., positive hemodynamic effects of esmolol were shown. In addition, they observed beneficial metabolic effects, such as higher arterial pH and base excess, and lower plasma lactate levels in esmolol treated patients. Moreover, they showed favourable effects on organ function, with an improved ratio of arterial oxygen tension to fraction of inspired oxygen (P/F-ratio), lower partial pressure of carbon dioxide, and improved glomerular filtration rates, and a decreased inflammatory response, depicted by lower C-reactive protein (CRP) levels.[7] However, this study also has been criticized for the high mortality in the control group of 80.5%, compared with a mortality of 49.5% in the intervention group. These observations fuelled the debate on the fact that possibly the poor outcome in the control group was a major determinant in the reported observations.

More information on metabolic effects of beta-blockers would be of great value before a broader uptake of this strategy can be recommended and to administer these drugs intentionally, especially in patients with hypermetabolic conditions. Therefore, the objective of this study is to investigate metabolic changes in critically ill patients after beta-blocker commencement.

We hypothesized that beta-blockers would significantly decrease REE in critically ill patients.

Materials and methods

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of Gelderse Vallei Hospital. The need for informed consent was waived because of the retrospective nature of the study using coded and anonymized data obtained from routine care.

Study design and participants

We conducted a retrospective observational study using data from patients admitted to our 17-beds mixed medical-surgical ICU, at Gelderse Vallei Hospital, in Ede, the Netherlands. All invasive mechanically ventilated patients in the period of January 1st, 2013 to March 1st, 2016, who had beta-blocker therapy commenced during ICU stay were eligible and screened for inclusion. Beta-blockers were started for clinical reasons, such as persistent sinus tachycardia, hypertension and atrial fibrillation, at the discretion of the attending physician; there is no formal protocol to start this therapy during mechanical ventilation in specific patient groups routinely.

Inclusion criteria were age $\geq$18 years and invasive mechanical ventilation from at least 24 h before until at least 6 h after the start of beta-blocker therapy. Patients were excluded if they received previous beta-blocker therapy in the 7 days before beta-blocker commencement in the ICU, if they received beta-blockers for a duration less than 48 h, if they were treated with therapeutic hypothermia between 24 h before and 6 h after beta-blocker commencement, and if there was no VCO_2 measured during at least one time point before and one time point after the start of beta-blocker therapy. In case of multiple eligible ICU admissions during the study period, only the first admission was included.

Data collection

Variables were obtained from the Patient Data Management System (PDMS; iMDsoft MetaVision®, Tel Aviv, Israel).

Patient characteristics

For all patients we collected the following data at ICU admission: age; gender; body mass index (BMI); Acute Physiology and Chronic Health Evaluation-II score and predicted mortality (APACHE-II); Simplified Acute Physiology-II Score (SAPS-II); the Nutrition Risk in Critically ill score (NUTRIC); admission type, categorized as medical, elective surgical and emergency surgical, defined by the Dutch National Intensive Care Evaluation (NICE)[13]; sepsis diagnosis; and previous beta-blocker therapy. In addition, we collected the following clinical outcome parameters: duration of invasive mechanical ventilation in days; renal replacement therapy in days; length of ICU stay in days; length of hospital stay in days; ICU mortality; and hospital mortality.

As the primary outcome is not related to mortality or cardiovascular morbidity, but related to the effect of beta-blocker therapy on metabolism, inflammation and organ function, we did not collect the specific admission diagnosis. This is less relevant as compared to the acuity of acute disease expressed by the different scores, as well as the fact whether patients were medical or surgical.

Therapy characteristics

Concerning beta-blocker therapy, we recorded the type of beta-blocker; route of administration, categorized as enteral, intravenous, or combined; mean daily dose over the first 48 h; and duration of ICU stay until beta-blocker commencement in days. We calculated the equivalent daily dose to metoprolol, following the suggested conversion by Shalansky et al. and Huckleberry et al.[14,15]

Outcome measurements

Unless stated otherwise, outcome measurements were collected at 6 different time points before and after beta-blocker commencement within a predetermined range: −24 h (range −36 to −12 h); baseline (range −0.02 to −12 h); +6 h (range +3 to +6 h); +12 h (range +6 to +18 h); +24 h (range +18 to + 36 h); and +48 h (+36 to +60 h).

We addressed metabolic effects of beta-blockers primarily by detecting changes in REE. Therefore, we used the recently published indicator by Stapel et al. as primary endpoint: [carbon dioxide production (VCO_2)*8.19] as a reflection of the total daily energy expenditure.[16] VCO_2 data was collected using Hamilton-S1 ventilators (Hamilton Medical AG, Bonaduz, Switzerland) with mainstream capnography.

Secondary metabolic outcome parameters were: temperature; plasma glucose; insulin requirement in units/hour; caloric intake per 24 h, calculated by [total nutritional calories and non-nutritional calories (glucose, propofol and citrate) over the last 2 h*12], following our protocol recently published by Bousie et al.[17]; arterial pH and lactate in arterial blood; plasma potassium, plasma sodium, plasma phosphate and plasma magnesium. In addition, we recorded the route of feeding at baseline, categorized as enteral, parenteral or combined.

To evaluate hemodynamic changes we obtained data from heart rate; systolic arterial blood pressure; diastolic arterial blood pressure; mean arterial pressure; vasopressor use; inotrope use; and cardiac index, computed by pulse contour and thermodilution technique (PiCCO system; Pulsion Medical Systems SE, Feldkirchen, Germany). Respiratory status was assessed at baseline with ventilation mode; respiratory frequency; minute ventilation; tidal volume; fraction of inspired oxygen; and positive end expiratory pressure. Additionally,

partial pressure of carbon dioxide and partial pressure of oxygen obtained from arterial blood, peripheral capillary oxygen saturation measured by pulse oximetry; and P/F-ratio were collected at all time points. To assess organ function we collected: plasma creatinine; diuresis, calculated by [average hourly urine production over the last 2 h/2]; and bilirubin. Sequential Organ Failure Assessment (SOFA) scores were collected on ICU admission, 1 day before beta-blocker commencement (baseline), and 1, 2 and 3 days after beta-blocker commencement. CRP, white blood cell count, and albumin were collected to assess the immune response.

Statistical analysis

Baseline characteristics

Categorical variables are expressed as numbers and percentages. All descriptive data were tested for normality using Shapiro–Wilk test ($p < 0.05$ = normal distribution). Data with normal distributions are reported as mean and standard deviation (SD) and data without a normal distribution as median and interquartile range (IQR, 25–75).

Outcome measurements

Shapiro–Wilk test was used for normality testing, following visual evaluation when *p*-values were 0.05 of higher. Means and SDs were calculated for each time point for all outcome variables. Outcome data were analyzed by using linear mixed models for repeated measures with maximum likelihood estimation to examine trends over time. For repeated covariance type Autoregressive Heterogeneous[1] was selected and time was set as a fixed effect. *F*-tests were calculated to define if time had a significant effect ($p < 0.05$). If this was the case, estimated marginal means at all time points were compared with baseline to assess changes over time. Effect of beta-blocker treatment was considered if analysis showed significant changes after beta-blocker commencement without similar significant trends before starting. Furthermore, if significant differences were displayed before baseline and those tendencies did not continue, effect of treatment was considered.

We divided the study population into two subgroups: septic and non-septic patients. We analyzed the data in septic and non-septic patients using linear mixed models for both the primary and secondary outcome measures, for only those parameters with *p*-values <0.10 in the linear mixed models analysis of the whole group of patients.

IBM SPSS Statistics for Windows, version 22.0 (IBM Corporation, released 2013, Armonk, New York, USA), was used for statistical analysis. For all tests we accepted the $P < 0.05$ significance level.

Results

Study participants

During the study period, there were 3083 adult patient admissions to our ICU, 1179 of them receiving invasive mechanical ventilation. Of these, 361 patients (31%) were treated with beta-blockers. We identified 151 patients with invasive mechanical ventilation from at least 24 h before until at least 6 h after the start of beta-blocker therapy eligible for inclusion. Of these, 64 patients were excluded due to beta-blocker treatment ≤7 days before reintroduction of beta-blocker treatment in the ICU, and 29 patients were excluded because they received beta-blockers for a total duration of less than 48 h. No patients were excluded for therapeutic hypothermia or lacking VCO_2 measurements. There were no multiple admissions. Finally, a total of 58 unique patients were eligible for analysis. Fig. 1 shows the flow chart depicting the patient selection process.

Baseline characteristics

Characteristics of study participants are displayed in Table 1. The study population comprised 31 males (53.4%) and 27 females (46.6%)

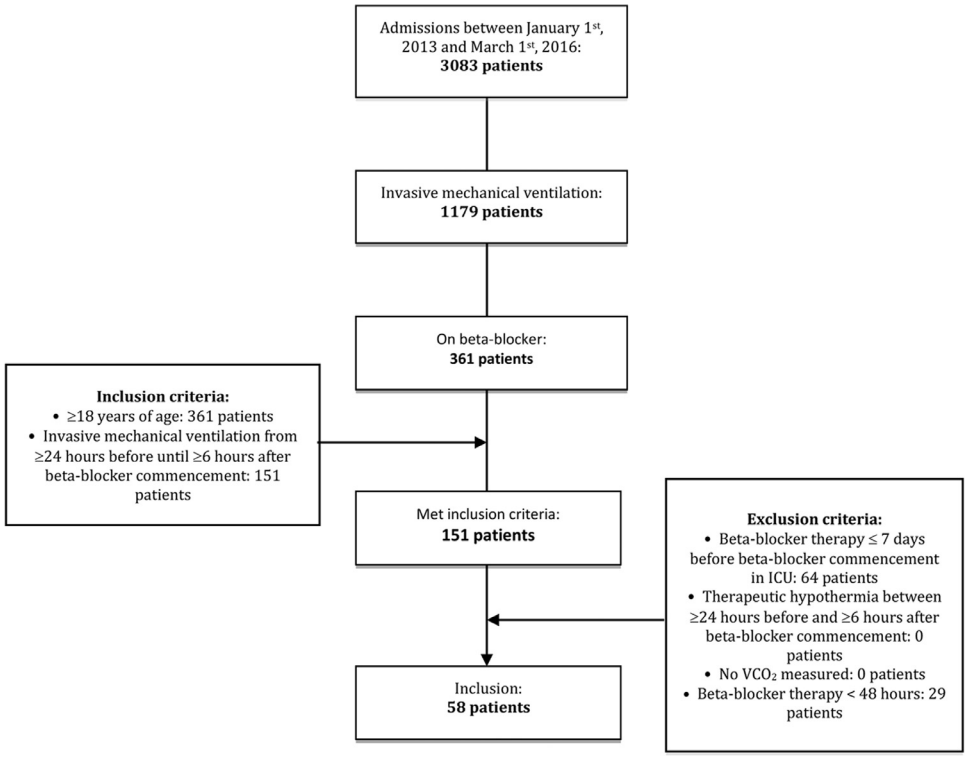

Fig. 1. Inclusion flow chart. Abbreviations: ICU: intensive care unit; VCO_2: carbon dioxide production.

Table 1
Characteristics on ICU admission and clinical outcomes of study participants

Baseline variables	Mean ± SD, median (IQR), or number (%)	
Age (years)	70	(65–75)
Sex, no. (%)		
Male	31	(53.4)
Female	27	(46.6)
Body mass index (kg/m^2)	26.1	(23.1–29.5)
Primary ICU admission diagnosis, no. (%)		
Medical	41	(70.7)
Elective surgical	7	(12.1)
Emergency surgical	10	(17.2)
Sepsis present at admission, no. (%)	29	(50.0)
APACHE-II score	24.3	±0.9
APACHE-II predicted mortality (%)	51.5	(29.9–70.4)
SAPS-II	53.0	±1.7
SOFA score	7.9	±0.4
NUTRIC score	6.0	(4.8–7.0)
Enteral nutrition at baseline	55	(94.8)
Enteral and parenteral nutrition at baseline	3	(5.2)
Ventilator settings at baseline		
Ventilation mode, no. (%)		
Adaptive support	11	(19.0)
Pressure control	3	(5.2)
Pressure support	44	(75.9)
FiO_2 (%)	34	(30–41)
PEEP (cmH_2O)	8	(6–10)
Respiratory frequency (breaths/min)	21	(71–28)
Inspiratory tidal volume (mL)	529	±22
Minute ventilation (L/min)	11.5	±0.4
Previous beta-blocker therapy, no. (%)	14	(24.1)
Outcome variables		
Length of ICU stay (days)	18	(11–30)
Length of hospital stay (days)	32	(21–49)
ICU mortality, no. (%)	5	(8.8)
Hospital mortality, no. (%)	13	(23.2)
Invasive mechanical ventilation days (days)	12	(7–20)
Renal replacement therapy, no. (%)	17	(29.3)
Renal replacement therapy days (days)	6	(4–12)

Abbreviations: APACHE-II: Acute Physiology and Chronic Health Evaluation II; cmH_2O: centimetre of water; FiO2: fraction of inspired oxygen; ICU: intensive care unit; IQR: interquartile range; L: liter; min: minute; mL: milliliter; PEEP: positive end expiratory pressure; SAPS-II: simplified acute physiology II score; SD: standard deviation.

with an overall median age of 70 years [65–75]. Median BMI was 26.1 kg/m^2 [23.1–29.5]. In total 41 medical (70.7%), 7 elective surgical (12.1%) and 10 emergency surgical (17.2%) patients were included. Mean APACHE-II score was 24.3 (0.9) with a median predicted mortality of 51.5% [29.9–70.4]. Mean SAPS-II and median NUTRIC scores were 53.0 (±1.7) and 6.0 (4.8–7.0), respectively. At baseline, all patients received enteral feeding, and 3 patients (5.2%) received supplemental parenteral nutrition.

For ventilation at baseline pressure support ventilation was used in 44 patients (75.9%), adaptive support ventilation in 11 patients (19.0%) and pressure control ventilation in 3 patients (5.2%). The median fraction of inspired oxygen was set at 0.34 [0.30–0.41] and the median positive end expiratory pressure at 8 cm H_2O [6–10]. The median respiratory frequency was 21 breaths per minute [71–28], the mean tidal volume 529 mL (±22) and the mean minute ventilation 11.5 L/min (±0.4).

Previous beta-blocker therapy was reported in 14 patients (24.1%).

Clinical outcomes

The median duration of mechanical ventilation was 12 days [7–20]. In total 17 patients received renal replacement therapy with a median duration of 6 days [4–12]. At the moment of analysis one patient was still in the ICU, and one patient was still in the hospital. Overall, median ICU length of stay was 18 days [11–30] with a median hospital stay of 32 days [21–49]. ICU and hospital mortality rates were 8.8% and 23.2%, respectively. (Table 1).

Table 2
Beta-blocker treatment

Variable	Median (IQR), or number (%)	
Beta-blocker, no. (%)		
Bisoprolol (enteral)	7	(12.1)
Labetolol (intravenous)	1	(1.7)
Metoprolol (enteral)	41	(70.7)
Metoprolol (enteral and intravenous)	5	(8.6)
Metoprolol (intravenous)	3	(5.2)
Sotalol (enteral)	1	(1.7)
Equivalent daily dose to metoprolol (mg)	50.0	(25.0–62.5)
Days in ICU until beta-blocker commencement (days)	7.0	(3.7–10.0)

Abbreviations: ICU: intensive care unit; IQR: interquartile range; mg: milligram.

Therapy characteristics

Treatment details are depicted in Table 2. The median time in ICU until the start of beta-blocker therapy was 7.0 days [3.7–10.0]. Beta-blockers examined in this study were enteral bisoprolol (12.1%), intravenous labetolol (1.7%), enteral metoprolol (70.7%), combined enteral and intravenous metoprolol (8.6%), intravenous metoprolol (5.2%), and enteral sotalol (1.7%). The median equivalent daily dose to metoprolol was 50.0 mg [25.0–62.5].

Primary end point: metabolic outcome parameters

Table 3 displays metabolic variables. The REE prior to beta-blocker initiation was 2242 (±654) and decreased to 2220 (±574) by 48 h. This change was not significant. Mean caloric intake was comparable at all time points. Although temperature showed a significant *F*-test, suggesting an association of time and temperature, no clear change from baseline was detected. Plasma glucose and insulin requirements did not change. Arterial pH showed an increase over time, already detectable before baseline, with unchanged arterial lactate levels. Plasma sodium, phosphate, potassium, and magnesium levels did not show significant differences. Subgroup analysis did not show differences between sepsis and non-sepsis patients.

Secondary outcome parameters

Cardiovascular and respiratory variables are displayed in Tables 4 and 5, respectively. Mean heart rate decreased significantly after beta-blocker commencement from 103 bpm (±20) to 91 bpm (±19) after 48 h ($p < 0.001$) (Fig. 2). Systolic, diastolic and mean arterial blood pressure were preserved, without significant changes in vasopressor (norepinephrine) or inotrope (enoximone) medication requirements. Cardiac index was measured in nine patients and no significant differences were shown over time. Peripheral capillary oxygen saturation, partial pressure of oxygen, partial pressure of carbon dioxide, and P/F-ratio did not show significant change over time.

Table 6 shows organ function and inflammatory parameters. SOFA scores decreased over time. Creatinine levels, diuresis and bilirubin remained unchanged. A declining trend was visible for CRP starting before baseline, with no changes in white blood cell counts. *F*-test for albumin interactions with time was significant, but no clear trends were detectable from baseline. Subgroup analysis in septic and non-septic patients did not demonstrate significant differences between the two groups.

Table 3
Metabolic variables of study participants

Variable		N	Mean ± SD	Mean change from baseline	*P*-value *F*-test	*P*-value pairwise comparison with baseline
Estimated REE* (kcal/day)	−24 h	58	2093 ± 468	−150	0.299	–
	Baseline	58	2242 ± 654	–		–
	6 h	58	2151 ± 475	−91		–
	12 h	57	2233 ± 582	−10		–
	24 h	56	2205 ± 487	−37		–
	48 h	44	2220 ± 574	−23		–
Caloric intake (kcal/day)**	−24 h	58	1796 ± 520	66	0.342	–
	Baseline	58	1730 ± 565	–		–
	6 h	58	1761 ± 492	31		–
	12 h	58	1858 ± 438	128		–
	24 h	58	1705 ± 644	−25		–
	48 h	57	1735 ± 549	5		–
Temperature (°C)	−24 h	58	37.3 ± 0.7	−0.1	0.012	0.056
	Baseline	58	37.4 ± 0.7	–		–
	6 h	58	37.3 ± 0.8	−0.1		0.320
	12 h	58	37.6 ± 0.8	0.2		0.116
	24 h	58	37.5 ± 0.7	0.1		0.473
	48 h	57	37.4 ± 0.7	0.0		0.679
Serum glucose (mmol/L)	−24 h	58	7.8 ± 1.7	0.3	0.238	–
	Baseline	58	7.5 ± 1.5	–		–
	6 h	58	7.4 ± 1.6	−0.1		–
	12 h	57	7.3 ± 1.4	−0.3		–
	24 h	58	7.3 ± 1.4	−0.3		–
	48 h	58	7.8 ± 2.1	0.3		–
Insulin requirement (units/h)	−24 h	58	2.3 ± 2.0	−0.2	0.320	–
	Baseline	58	2.4 ± 1.9	–		–
	6 h	58	2.4 ± 1.8	−0.1		–
	12 h	58	2.2 ± 1.9	−0.2		–
	24 h	57	1.9 ± 1.5	−0.5		–
	48 h	55	1.9 ± 1.7	−0.5		–
Arterial pH (-log10 [H^+])	−24 h	57	7.41 ± 0.06	−0.02	0.001	0.002
	Baseline	48	7.42 ± 0.04	–		–
	6 h	25	7.43 ± 0.06	0.00		0.011
	12 h	46	7.43 ± 0.05	0.01		0.053
	24 h	49	7.44 ± 0.05	0.02		0.005
	48 h	56	7.44 ± 0.05	0.01		0.031
Lactate (mmol/L)	−24 h	57	1.4 ± 0.9	0.0	0.412	–
	Baseline	48	1.4 ± 1.0	–		–
	6 h	23	1.2 ± 0.4	−0.2		–
	12 h	46	1.2 ± 0.4	−0.2		–
	24 h	47	1.2 ± 0.4	−0.2		–
	48 h	55	1.2 ± 0.3	−0.2		–
Serum sodium (mmol/L)	−24 h	57	143 ± 5	0	0.102	–
	Baseline	48	144 ± 5	–		–
	6 h	21	146 ± 5	2		–
	12 h	46	144 ± 5	0		–
	24 h	47	145 ± 5	1		–
	48 h	56	144 ± 5	0		–
Serum potassium (mmol/L)	−24 h	58	4.0 ± 0.4	0.0	0.700	–
	Baseline	50	4.0 ± 0.4	–		–
	6 h	31	4.0 ± 0.4	0.0		–
	12 h	51	4.1 ± 0.4	0.0		–
	24 h	52	4.0 ± 0.3	0.0		–
	48 h	56	4.0 ± 0.3	−0.1		–
Serum phosphate (mmol/L)	−24 h	43	1.08 ± 0.41	0.07	0.139	–
	Baseline	28	1.01 ± 0.45	–		–
	6 h	14	0.87 ± 0.30	−0.15		–
	12 h	25	0.96 ± 0.34	−0.05		–
	24 h	26	1.05 ± 0.27	0.03		–
	48 h	27	0.97 ± 0.19	−0.04		–
Serum magnesium (mmol/L)	−24 h	43	0.87 ± 0.17	0.05	0.110	–
	Baseline	24	0.82 ± 0.16	–		–
	6 h	12	0.78 ± 0.15	−0.04		–
	12 h	22	0.81 ± 0.12	−0.02		–
	24 h	23	0.82 ± 0.15	0.00		–
	48 h	28	0.79 ± 0.14	−0.03		–

* Estimated REE: [8.19*VCO_2].

** Caloric intake: [energy uptake over last 2 h*12].Abbreviations: °C: degrees Celsius; H^+: hydrogen; h: hour; kcal: kilocalorie; L: liter; min: minute; mmol: millimole; N: sample size; REE: resting energy expenditure; SD: standard deviation.

Table 4
Cardiovascular variables of study participants

Variable		N	Mean ± SD	Mean change from baseline	*P*-value *F*-test	*P*-value pairwise comparison with baseline
Heart rate (bpm)	−24 h	58	100 ± 17	−3	<0.001	0.069
	Baseline	58	103 ± 20	–		–
	6 h	58	96 ± 19	−7		<0.001
	12 h	58	95 ± 18	−8		<0.001
	24 h	58	95 ± 19	−8		0.003
	48 h	58	91 ± 19	−12		<0.001
Systolic blood pressure(mmHg)	−24 h	58	136 ± 25	−10	0.052	–
	Baseline	58	145 ± 30	–		–
	6 h	58	141 ± 28	−4		–
	12 h	58	141 ± 31	−4		–
	24 h	58	146 ± 31	1		–
	48 h	58	146 ± 30	1		–
Diastolic blood pressure(mmHg)	−24 h	58	60 ± 13	−4	0.115	–
	Baseline	58	64 ± 11	–		–
	6 h	58	61 ± 14	−3		–
	12 h	58	60 ± 13	−4		–
	24 h	58	61 ± 13	−3		–
	48 h	58	61 ± 12	−3		–
MAP (mmHg)	−24 h	58	84 ± 18	−6	0.166	–
	Baseline	58	90 ± 16	–		–
	6 h	58	87 ± 18	−3		–
	12 h	58	87 ± 18	−4		–
	24 h	58	89 ± 19	−1		–
	48 h	58	88 ± 16	−2		–
Cardiac index (L/min/m^2)	−24 h	12	3.3 ± 0.9	0.0	0.469	–
	Baseline	9	3.3 ± 0.8	–		–
	6 h	8	3.4 ± 0.8	0.1		–
	12 h	8	3.4 ± 0.5	0.1		–
	24 h	8	3.5 ± 0.6	0.2		–
	48 h	5	3.1 ± 0.7	−0.2		–
Enoximone dosage (μg/kg/min) in patients on enoximone at baseline	−24 h	9	0.86 ± 0.75	−0.29	0.222	–
	Baseline	9	1.15 ± 0.47	–		–
	6 h	9	1.11 ± 0.62	−0.04		–
	12 h	9	1.05 ± 0.65	−0.10		–
	24 h	9	0.67 ± 0.47	−0.47		–
	48 h	9	0.69 ± 0.65	−0.45		–
Norepinephrine dosage (μg/kg/min) in on norepinephrine at baseline	−24 h	6	0.10 ± 0.11	0.03	0.184	–
	Baseline	6	0.07 ± 0.04	–		–
	6 h	6	0.03 ± 0.03	−0.04		–
	12 h	6	0.03 ± 0.03	−0.04		–
	24 h	6	0.01 ± 0.02	−0.06		–
	48 h	6	0.01 ± 0.02	−0.06		–
Enoximone dosage (μg/kg/min) in all patients	−24 h	58	0.29 ± 0.69	0.12	0.478	–
	Baseline	58	0.18 ± 0.45	–		–
	6 h	58	0.19 ± 0.48	0.01		–
	12 h	58	0.20 ± 0.51	0.03		–
	24 h	58	0.15 ± 0.40	−0.03		–
	48 h	58	0.12 ± 0.37	−0.05		–
Norepinephrine dosage (μg/kg/min) in all patients	−24 h	58	0.03 ± 0.08	0.02	0.380	–
	Baseline	58	0.01 ± 0.02	–		–
	6 h	58	0.01 ± 0.02	0.00		–
	12 h	58	0.01 ± 0.02	0.00		–
	24 h	58	0.01 ± 0.03	0.00		–
	48 h	58	0.01 ± 0.02	0.00		–

Abbreviations: bpm: beats per minute; kg: kilogram; L: liter; m^2: square meter; MAP: mean arterial pressure; min: minute; mmHg: millimeter of mercury; N: sample size; SD: standard deviation; μg: microgram.

Discussion

Our retrospective, single-center study demonstrates that low dose beta-blockers in critically ill mechanically ventilated ICU patients did not induce reductions in REE as reflected by VCO_2 measurements. This is inconsistent with previous research. Herndon et al. investigated the effects of the non-selective beta-blocker propranolol on catabolism in a randomized trial among children with severe burns. The intervention group (13 children) showed lower REEs, measured with indirect calorimetry, and less decrease in lean body mass.[10] Also other metabolic effects of beta-blockers, like an increase in potassium, and improvements of pH, lactate and base excess after introduction of beta-blockers could not be reproduced in our ICU population.[7,8,10] These effects on REE were also not reproducible in a small trial among 6 septic patients, who received the selective beta-blocker esmolol. A significant reduction in heart rate with preservation of blood pressure was reported, but REE, was not affected.[11] Together with other conflicting results,[12] this may indicate that we have to value positive findings on the impact of beta-blockers on metabolism with caution.

However, inconsistent results and our present findings could also be explained by differences in patient and treatment characteristics.

Table 5
Respiratory variables of study participants

Variable		N	Mean ± SD	Mean change from baseline	*P*-value *F*-test
SpO_2 (%)	−24 h	58	97 ± 2	0	0.350
	Baseline	58	97 ± 2	–	
	6 h	58	98 ± 2	0	
	12 h	58	97 ± 3	0	
	24 h	58	98 ± 2	0	
	48 h	58	97 ± 2	0	
pO_2 (kPa)	−24 h	57	11.8 ± 2.3	−0.3	0.149
	Baseline	48	12.1 ± 2.9	–	
	6 h	25	12.5 ± 2.3	0.4	
	12 h	46	11.3 ± 1.9	−0.8	
	24 h	49	11.5 ± 2.1	−0.6	
	48 h	56	11.3 ± 2.0	−0.8	
pCO_2 (kPa)	−24 h	57	5.4 ± 1.2	0.2	0.730
	Baseline	48	5.3 ± 1.0	–	
	6 h	25	5.4 ± 1.2	0.1	
	12 h	46	5.3 ± 1.0	0.1	
	24 h	49	5.3 ± 1.1	0.1	
	48 h	56	5.4 ± 1.2	0.1	
PF ratio (mmHg)	−24 h	57	259.2 ± 85.8	−8.8	0.581
	Baseline	50	268.0 ± 87.7	–	
	6 h	27	270.7 ± 82.7	2.7	
	12 h	44	269.4 ± 74.2	1.4	
	24 h	49	276.0 ± 80.5	8.0	
	48 h	57	273.8 ± 67.4	5.8	

Abbreviations: IQR: interquartile range; kPa: kilopascal; N: sample size; pO_2: partial pressure of oxygen; pCO_2: partial pressure of carbon dioxide; PF ratio: ratio of arterial oxygen tension to fraction of inspired oxygen; SD: standard deviation; SpO2: saturation of peripheral oxygen.

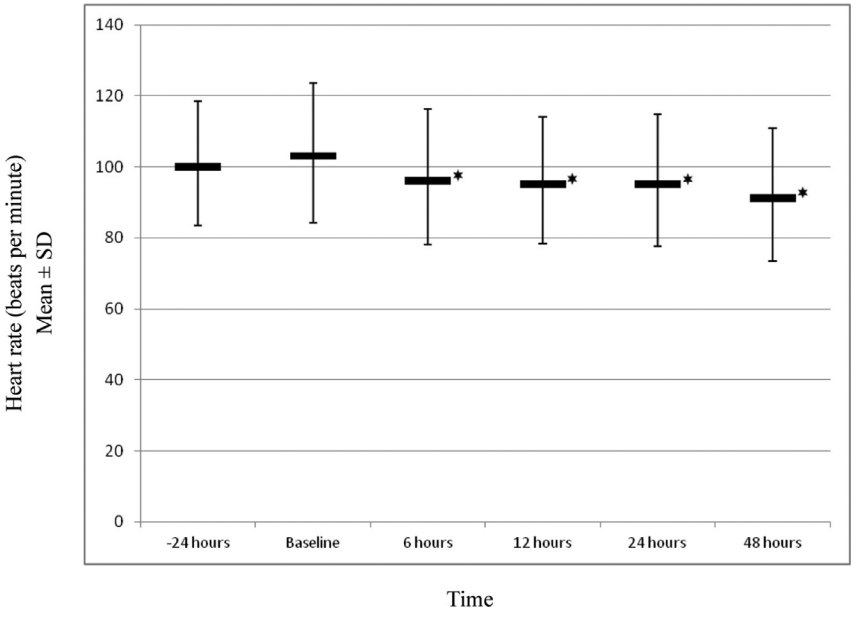

Fig. 2. Changes in heart rate. * Significant change from baseline.

We studied adults, while Herndon at al. investigated the effects among children. We report use of various selective and non-selective beta-blockers, with a median equivalent daily dose to metoprolol of 50 mg per day with a mean reduction in heart rate of 12 bpm (12%). All patients in the study of Herndon received the non-selective beta-blocker propranolol and a larger decrease in heart rate was seen (20%). Morelli et al. administered a median esmolol dosage of 100 mg per hour and reported a larger reduction in heart rate (28 bpm). Although the reduction in heart rate seen in our population clearly shows effect of the administered beta-blockers, the less impressive decrease in heart rate could indicate that our patients received lower dosages and as a consequence the metabolic effects only may be seen when larger dosages are used. Furthermore, it is possible that Herndon et al. overestimated metabolic effects due to the small intervention group of only 13 children or that effects among patients with burns, patients known to have marked increases in metabolic rate, are better detectable. In addition, their study outcome parameters were obtained two weeks after beta-blocker commencement, whereas we collected variables in our population only up to 48 h after beta-blockers were started. Potentially we would have seen metabolic changes at later time points. This assumption is supported by prior research showing that long-term beta-blocker therapy decreases lactate levels in septic patients.[18] Inconsistent results with Morelli et al. could potentially be explained by overestimation of

Table 6
Organ function and inflammatory variables of study participants

Variable		N	Mean ± SD	Mean change from baseline	*P*-value *F*-test	*P*-value pairwise comparison with baseline
SOFA score	Admission	58	7.9 ± 2.9	1.5	<0.001	<0.001
	Baseline	58	6.4 ± 2.9	–		–
	1 day	58	5.7 ± 2.9	−0.7		0.009
	2 days	58	5.1 ± 2.8	−1.3		<0.001
	3 days	58	4.4 ± 2.7	−2.0		<0.001
Creatinine (μmol/L)	−24 h	56	129 ± 113	17	0.071	–
	Baseline	41	112 ± 82	–		–
	6 h	12	128 ± 53	16		–
	12 h	37	84 ± 51	−28		–
	24 h	45	98 ± 52	−13		–
	48 h	56	94 ± 53	−18		–
Diuresis (mL/h)	−24 h	58	132.7 ± 95.7	−12.5	0.868	–
	Baseline	58	145.2 ± 102.4	–		–
	6 h	58	129.2 ± 89.8	−16.1		–
	12 h	58	137.3 ± 99.5	−7.9		–
	24 h	58	130.6 ± 90.1	−14.6		–
	48 h	57	134.8 ± 89.3	−10.5		–
Bilirubin (μmol/L)	−24 h	56	9.7 ± 12.7	−0.3	0.477	–
	Baseline	40	10.0 ± 15.5	–		–
	6 h	12	8.8 ± 8.0	−1.2		–
	12 h	36	11.2 ± 18.1	1.1		–
	24 h	44	8.4 ± 7.7	−1.7		–
	48 h	55	9.7 ± 13.3	−0.4		–
CRP (mg/L)	−24 h	56	133.3 ± 83.0	27.2	<0.001	0.002
	Baseline	39	106.1 ± 64.5	–		–
	6 h	12	102.2 ± 70.9	−4.0		0.224
	12 h	37	98.8 ± 80.8	−7.3		0.122
	24 h	45	95.3 ± 67.6	−10.8		0.003
	48 h	55	82.7 ± 68.5	−23.5		<0.001
WBC (10^9/L)	−24 h	56	14.1 ± 6.4	0.5	0.580	–
	Baseline	42	13.6 ± 6.7	–		–
	6 h	12	12.6 ± 5.2	−1.0		–
	12 h	40	13.2 ± 5.9	−0.4		–
	24 h	46	12.6 ± 5.2	−1.0		–
	48 h	55	13.3 ± 5.8	−0.3		–
Albumin (g/L)	−24 h	39	19.3 ± 6.0	−0.9	0.030	0.729
	Baseline	19	20.2 ± 5.4	–		–
	6 h	9	16.2 ± 2.8	−3.9		0.253
	12 h	16	18.8 ± 4.0	−1.3		0.604
	24 h	21	17.9 ± 4.9	−2.3		0.208
	48 h	25	19.2 ± 4.5	−1.0		0.055

Abbreviation: g: gram; h: hour; L: liter; mg: milligram; mmHg: millimeter of mercury; mL: milliliter; N: sample size; SD: standard deviation; SOFA: Sequential Organ Failure Assessment; WBC: white blood cell count; μmol: micromole.

effects of beta-blockers in their study. They showed large unexpected survival differences among their intervention group and control group. Mortality rates in the control group were uncommonly high, especially in the first few days, which may be due to unknown confounders. This could suggest that differences in outcome parameters among the intervention group and control group are possibly attributable to differences in mortality rates, rather than based on the beneficial effect of beta-blockers. As published previously, we also did not see reductions in blood pressure after beta-blocker commencement.[7,8,10,12] This contributes to the evidence that beta-blockers in critically ill patients have no or only limited negative effects on blood pressure, at least with the described dosages applied.

In our study, beta-blocker commencement did not induce significant changes in respiratory, organ-specific and inflammatory parameters that were not seen before baseline. However, we did see ongoing significant decreases in CRP, and SOFA-scores and an increase in arterial pH. Possibly, this is more related to the general recovery of patients from their critical illness than to effects of beta-blockade. Schmittinger et al. published significant drops in CRP in a retrospective research among 40 septic shock patients with sepsis induced cardiac depression, receiving combined therapy of milrinone, used as an inotrope with lusitrope effects, and enteral metoprolol. However, the lack of a control group and measurements before baseline to evaluate trends make their results difficult to interpret.[8] Morelli et al. showed a significant decrease in CRP levels in their intervention group that was not seen in their control group. As our retrospective study lacks a control group we cannot be confident that the better organ performance is due to beta-blocker effects.

Our study has several limitations and strengths to be considered. First, our study was performed retrospectively introducing risk of residual confounding, some missing variables, and the absence of a control group. Second, the relatively small sample size might have resulted in non-significant results, whereas trends could potentially have led to significant results in a larger population. Moreover, the limited sample size precludes extensive subgroup analyses for all baseline characteristics. Third, since all patients on beta-blockers were eligible for inclusion, we studied a heterogeneous population, combining effects of various types and doses of beta-blockers, and studied in different patients groups. This may have limited the internal validity, however it may increase external validity of results.

Strengths of our study include the many parameters we collected and analyzed. In addition, very few studies focused on this topic before, therefore our results may be seen as a contribution to a better understanding of the effects of beta-blockers on metabolism, organ function and inflammatory response.

Conclusions

In this retrospective single center study among mechanically ventilated, critically ill patients on beta-blocker therapy we did not observe significant changes in resting energy expenditure after beta-blocker commencement. Heart rate significantly decreased with preservation of blood pressure. Other metabolic, organ function and inflammatory parameters did not show trends over time that could clearly be attributed to the effect of beta-blockers. Conflicting results have been previously published and our data suggests that we have to interpret positive findings with caution. Still administering beta-blockers intentionally in critically ill patients to optimize hypermetabolism should be considered experimental and probably not effective using an equivalent daily dosage of 50 mg metoprolol. We recommend more prospective research to investigate metabolic, organ function and inflammatory effects of beta-blockers before more rigorous recommendations can be done.

Availability of data and material

The dataset analyzed during the current study is available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

ARHZ conceived the study. DAB extracted all information from the PDMS database. CHH collected additional data, performed the statistical analyses and drafted the manuscript. ARHZ made substantial contributions to the conception and design of the study and drafting of the manuscript. All authors read and approved the final version of the manuscript.

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Not applicable.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.hrtlng.2019.02.004.

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