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Combined milrinone and enteral metoprolol therapy in patients with septic myocardial depression

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ABSTRACT

Introduction: The multifactorial etiology of septic cardiomyopathy is not fully elucidated. Recently, high catecholamine levels have been suggested to contribute to impaired myocardial function.

Methods: This retrospective analysis summarizes our preliminary clinical experience with the combined use of milrinone and enteral metoprolol therapy in forty patients with septic shock and cardiac depression. Patients with other causes of shock or cardiac failure, patients with beta-blocker therapy initiated >48 hrs after shock onset and patients with pre-existent decompensated congestive heart failure were excluded. In all study patients, beta blockers were initiated only after stabilization of cardiovascular function (17.7±15.5 hrs after shock onset or intensive care unit admission) in order to decrease heart rate <95 bpm. Hemodynamic data and laboratory parameters were extracted from medical charts and documented before, 6, 12, 24, 48, 72, and 96 hours after the first metoprolol dosage. Adverse cardiovascular events were documented. Descriptive statistical methods and a linear mixed-effects model were used for statistical analysis.

Results: Heart rate control (65-95 bpm) was achieved in 97.5% of patients (n=39) within 12.2±12.4 hrs. Heart rate, central venous pressure, norepinephrine, arginine vasopressin and milrinone dosages decreased (all p<0.001). Cardiac index and cardiac power index remained unchanged, while stroke volume index increased (p=0.002). In two patients (5%) metoprolol was discontinued because of asymptomatic bradycardia. Norepinephrine and milrinone dosages were increased in nine (22.5%) and six (15%) patients, respectively. PH increased (p<0.001), while arterial lactate (p<0.001), serum C-reactive protein (p=0.001) and creatinine levels (p=0.02) decreased during the observation period. Twenty-eight day mortality was 33%.

Conclusions: Low doses of enteral metoprolol in combination with phosphodiesterase inhibitors are feasible in patients with septic shock and cardiac depression but no overt heart

failure. Future prospective controlled trials on the use of beta blockers for septic cardiomyopathy and their influence on pro-inflammatory cytokines are warranted.

INTRODUCTION

Septic cardiomyopathy refers to myocardial injury with or without lowered cardiac output in patients with sepsis [1, 2]. In contrast to earlier beliefs concerning the frequency of septic cardiomyopathy, a recent prospective trial in 67 adult septic shock patients without previous cardiac disease reported an overall hypokinesia rate (left ventricular ejection fraction <45%) of 60% [3]. As compared to patients able to maintain hyperdynamic circulation, survival is significantly compromised in septic shock patients with low systemic blood flow [4]. Even if cardiac output can be preserved, myocardial injury as indicated by increased plasma levels of troponin [5] or natriuretic peptides [6-8], is associated with poor outcome in septic shock.

The etiology of septic cardiomyopathy is multifactorial. Throughout the last decades several pathogenetic mechanisms including bacterial toxins, cytokines, nitric oxide, and reactive oxygen species were identified [2, 9]. Recently, the contributory role of adrenergic stress and catecholamine-induced toxicity has been suggested [2]. Similarities have been drawn between catecholamine-induced myocardial stunning [10, 11] and septic cardiomyopathy [12]. Sepsis was found to be an important risk factor for development of the left ventricular apical ballooning syndrome [13], originally known as Tako-Tsubo cardiomyopathy [14].

In view of the growing evidence for an association between beta adrenergic stress and the pathogenesis of septic cardiomyopathy [15], the administration of beta-blocking agents could be beneficial. Although at first glance it appears counterproductive to administer a potentially negative inotropic drug to a patient with myocardial depression, beta-blocker therapy improved myocardial oxygen utilization, decreased TNF-alpha production and preserved cardiac function in a septic animal model [16]. Similarly, Gore *et al.* found that a continuous esmolol infusion reduced heart rate by 20%, but did not compromise systemic oxygen delivery or organ blood flow in six hemodynamically stable patients with sepsis [17].

Apart from these studies, an increasing number of reports have been published suggesting advantageous effects of beta blockers in the acute critical illness. Although recently challenged [18, 19], perioperative beta blockade has repeatedly been shown to reduce cardiac complications and improve survival in high-risk surgery patients [20, 21]. Similarly, preliminary data on the use of beta blockers in critically ill patients with severe trauma [22], traumatic brain injury[23], or burns[24] indicate a beneficial influence on morbidity and mortality.

In an effort to reduce tachycardia in patients with septic shock requiring inotropic therapy we have cautiously started to use beta blockers. First, this therapeutic intervention was restricted to patients with chronic beta-blocker therapy in order to attenuate rebound tachycardia and decrease the risk of perioperative myocardial ischemia, but was later also used in patients without chronic beta-blocker treatment in an attempt to decrease high heart rate and economize cardiac function. This retrospective analysis summarizes our preliminary clinical experience with the combined use of milrinone and enteral metoprolol therapy in forty patients with septic shock and cardiac depression. Our hypothesis was that metoprolol would reduce heart rate without destabilizing cardiovascular function.

PATIENTS AND METHODS

The retrospective protocol was approved by the Ethics Committee of the Krankenhaus der Barmherzigen Schwestern in Ried im Innkreis. In view of the retrospective study design, written informed consent was waived. From January 1, 2005 to February 28, 2008, all medical records of an eight-bed multidisciplinary intensive care unit (ICU) were reviewed for patients with the admission diagnosis of septic shock as defined by the American College of Chest Physicians and the Society of Critical Care Medicine [25]. All patients with septic shock and cardiac depression who were treated with enteral metoprolol within 48 hrs after onset of shock or admission to the ICU were included in the analysis. Cardiac depression was defined as central venous oxygen saturation <65% despite adequate fluid resuscitation, oxygenation and hematocrit, and/or a cardiac index (CI) <2.5L/min/m² requiring inotropic therapy. Patients <18 years, patients with any cause of low cardiac output other than sepsis (*e.g.* myocardial ischemia), patients with pre-existent decompensated congestive heart failure (New York Heart Association Classification III and IV), patients with septic shock who did not require inotropic support or in whom cardiac output was not measured, and patients who first received beta blockers >48 hours after onset of shock or ICU admission were excluded.

Hemodynamic and General Treatment

All septic shock patients were invasively monitored with an arterial and a central venous catheter, as well as a transpulmonary thermodilution device to assess cardiac output (PICCO®, Pulsion Medical, Munich, Germany). Hemodynamic resuscitation was performed according to an institutional protocol (Figure 1) that served as a recommendation for the attending physician. During shock, all patients were mechanically ventilated and sedated with a midazolam/fentanyl infusion. Continuous veno-venous hemofiltration with a minimum filtration rate of 35 mL/min was commenced for renal indications only (*n*=28, 70%). Nutrition

was initiated *via* the parenteral route on ICU day 2 and gradually substituted with enteral nutrition starting on ICU day 3 or when cardiovascular function was stabilized.

Beta Blocker Therapy

In an effort to decrease heart rate to <95 bpm, compassionate use of metoprolol was started as considered indicated by the physician in charge. First, metoprolol was restricted to patients with chronic beta-blocker therapy in order to attenuate rebound tachycardia and decrease the risk of perioperative myocardial ischemia, but after one-third of the observation period was also used in patients without chronic beta-blocker treatment in an attempt to treat tachycardia and economize cardiac function. In all patients, beta blockers were initiated only after cardiovascular function had been stabilized. A retard formulation of metoprolol (Seloken retard®, Astra Zeneca; Vienna, Austria) was used at 25-47.5 mg *via* the enteral route. Based on response in heart rate, stroke volume or CI and arterial blood pressure, metoprolol was gradually increased to reach a targeted heart rate of 65-95 bpm. Metoprolol was transiently stopped or completely withdrawn if heart rate dropped to <60 bpm.

Data Documentation

Where available, the following variables were extracted from routinely performed measurements documented in the medical charts: demographic data, preexistent diseases, chronic beta-blocker therapy, source of infection, need for renal replacement therapy, length of stay at the ICU, as well as 28-day mortality. The Simplified Acute Physiology Score II [26] and a modified Goris multiple organ dysfunction syndrome score [27] were calculated from most aberrant clinical and laboratory variables during the first 24 hours after admission or during the ICU stay, respectively. Hemodynamic data were documented at shock onset; before, 6, 12, 24, 48, 72, and 96 hours after the first metoprolol dosage and included heart rate (HR), mean arterial pressure (MAP), central venous pressure (CVP), central venous oxygen

saturation ($ScvO_2$), cardiac index (CI) and stroke volume index (SVI), as well as norepinephrine, arginine vasopressin, and milrinone requirements. The cardiac power index (CPI), an index of cardiac contractility strongly correlated with outcome in acute and chronic heart failure [28], was calculated as the product of simultaneously measured MAP and CI [CPI (W/m^2) = MAP x CI x 0.0022]. Systemic vascular resistance was calculated according to the standard formula. Also documented were the time elapsed between shock onset and initiation of metoprolol therapy, as well as the time between initiation of metoprolol therapy and attainment of the targeted heart rate range. Serum concentrations of creatinine, aspartate and alanine aminotransferase, total bilirubin, troponin I, C-reactive protein, and the PaO_2/FiO_2 quotient were recorded before, 24, 48, 72, and 96 hours after start of metoprolol. PH and arterial lactate levels were documented before, 6, 12, 24, 48, 72, and 96 hours after the first metoprolol dosage.

Definition of Adverse Events

In order to evaluate the incidence of adverse events during the 96-hour observation period, the following definitions were retrospectively applied. A decrease in arterial blood pressure was considered a >20% reduction in MAP as compared to baseline values or a MAP <65 mmHg at two or more time points, both requiring an increase in norepinephrine support. A decrease in CI, stroke volume index, or central venous oxygen saturation was similarly defined as a >20% reduction as compared to baseline values at two or more time points, requiring an increase in inotropic support and/or withdrawal of metoprolol therapy. Bradycardia was defined as a drop in heart rate to <60 bpm and was considered to be symptomatic if it resulted in a MAP <65 mmHg or CI <2.5 $L/min/m^2$.

Statistical Analysis

The primary endpoint was to assess the clinical course and hemodynamic parameters during combined milrinone and metoprolol therapy. The secondary endpoint was to evaluate changes in laboratory and organ function parameters.

The SPSS® 12.0.1. software package was used for statistical analysis (SPSS Inc, Chicago, IL). Kolmogorov Smirnov tests were used to verify normal distribution of study variables, which was approximately given for all variables except serum liver enzymes and total bilirubin concentrations, as well as arterial lactate levels. After *ln* transformation, the normality assumption was achieved for these variables, too. Descriptive statistical methods were applied to present demographic and clinical data, and to evaluate the incidence of adverse events. Changes in hemodynamic or laboratory parameters during metoprolol therapy were assessed with a linear mixed-effects model. In contrast to conventional tests such as the analysis of variance, this method can evaluate changes over time despite the fact that some patients dropped out because they died during the observation period [29]. If changes over time were significant, comparisons *vs.* baseline values were performed using the same model and applying Bonferroni corrections. *P* values <0.05 were considered to indicate statistical significance. All variables are given as mean values±SD, if not indicated otherwise.

RESULTS

During the review period, 174 patients with septic shock were treated at the ICU. Forty patients thereof were treated with a milrinone infusion and received enteral metoprolol during the first 48 hrs after shock onset or ICU admission (17.7±15.5 hrs) (Table 1). Seven patients died during the observation period.

Heart rate was reduced to the targeted range of 65-95 bpm in 97.5% of the patients (*n*=39) within 12.2±12.4 hrs. Of the 36 patients treated with arginine vasopressin, 31 received arginine vasopressin before baseline measurements, while five patients were started on arginine vasopressin therapy during the observation period (within 6 hrs, *n*=4; within 24 hrs, *n*=1). While heart rate and central venous pressure significantly decreased, stroke volume index increased during the observation period. At the same time, norepinephrine, arginine vasopressin and milrinone dosages were significantly reduced (Table 2). A significant increase in pH as well as a decrease in arterial lactate, serum creatinine concentrations and C-reactive protein levels was seen during the observation period (Table 3).

Metoprolol therapy was discontinued in two patients, because asymptomatic bradycardia occurred and heart rate remained within the lower targeted limits after one and two metoprolol dosages, respectively. The incidence of adverse events during the observation period is presented in Table 4.

DISCUSSION

After cardiovascular stabilization, heart rate and central venous pressure decreased and stroke volume index increased in this study population during combined milrinone and enteral metoprolol therapy. Simultaneously, vasopressor and inotropic drug support was reduced. Except for an increase in pH as well as a decrease in arterial lactate, serum creatinine and C-reactive protein levels, organ function variables remained unchanged.

Pathophysiologically, septic cardiomyopathy is defined as an inadequately increased cardiac output in relation to the lowered systemic vascular resistance in sepsis and does not necessarily imply that cardiac output is absolutely decreased [1, 2]. Indeed, overt cardiac failure as known from patients with cardiogenic shock is rare and has been observed in a maximum of 10%-15% of septic shock patients [30]. More commonly, the clinical picture of septic cardiomyopathy is characterized by a variable degree of myocardial depression which can be detected echocardiographically or biochemically through elevated troponin levels in ≥50% [3, 31] and >40% [5], respectively, of sepsis patients. Independently of the presence of overt cardiac failure, the grade of myocardial depression correlates with poor prognosis in sepsis [2, 4]. In our analysis, all patients suffered from septic shock with considerably impaired cardiac pump function requiring infusion of an inotropic agent. Even though moderately elevated troponin I serum concentrations in 92.5% of the study patients (n=37) further underline the presence of septic cardiomyopathy, the lack of echocardiography data limits the detailed investigation of cardiac dysfunction in our analysis.

Despite the growing evidence that beta blockers can be safely and probably beneficially administered in acute critical illness, current use of beta-blocking agents in patients with septic shock and cardiomyopathy must definitely be considered experimental. In an attempt to reduce tachycardia in patients with chronic beta-blocker therapy in whom rebound tachycardia was suspected [32], we have initiated enteral metoprolol therapy for the first time. The results of a study of the favourable effects of

perioperative beta-blockade[33] then prompted us to also employ beta blockers in patients without previous chronic beta-blocker therapy. Nonetheless, in all patients, this was done compassionately and as considered indicated by the treating physician, starting cautiously with low metoprolol dosages and under tight control of cardiac output and central venous oxygen saturation.

A selective beta-1 instead of a non-selective beta-blocker was chosen to prevent inhibition of potentially beneficial beta-2 effects [34]. Since in our clinical experience esmolol infusion was associated with frequent and rapid decreases in heart rate and cardiac output, metoprolol was applied *via* the enteral route. Accordingly, Gore *et al.* observed a 20% decrease in CI during esmolol infusion in hemodynamically stable sepsis patients [17]. Since heart rate is a major determinant of myocardial oxygen consumption [35], it was used to dose metoprolol. In cardiovascular high-risk patients, a heart rate of 95 bpm was shown to be the critical threshold at which myocardial oxygen demand outstripped coronary supply and myocardial ischemia was likely to occur [36, 37].

Instead of beta-agonists, a phosphodiesterase III inhibitor was applied as an inotropic agent in all our patients. Although this does not correspond to current recommendations [38], milrinone has been used in patients with septic shock at our institution throughout the last decade. Positive inotropic effects of milrinone are mediated through inhibition of the breakdown of cyclic adenosine monophsophate (cAMP) by phosphodiesterases [39] and act independently of beta-1 receptors. In view of differences in cAMP-independent actions [40] and compartmentation of cAMP-mediated signaling [41], the combination of milrinone and metoprolol may hold potential benefits for myocardial function [39].

A decrease in heart rate together with an increase in stroke volume index given an unchanged CI can be interpreted as an economization of cardiac work and oxygen consumption. Reduced heart rates lower the risk of myocardial ischemia [21, 36, 37], particularly in patients with obstructive coronary artery disease [42]. In light of diminishing

milrinone support, these observations may even reflect improved cardiac pump function in our study patients. Moreover, a decrease in central venous pressure as observed during metoprolol therapy often follows amelioration of myocardial performance [28]. The observation that organ function variables remained unchanged during beta-blocker therapy strengthens the assumption that metoprolol therapy did not reduce systemic blood flow or limit organ oxygen supply. Similarly, organ blood flow (extremity and hepatic blood flow) was not overtly affected during esmolol infusion in six hemodynamically stable sepsis patients [17]. Since metoprolol therapy was commenced 17.7±15.5 hrs after onset of shock and initiation of standard hemodynamic therapy, it is unlikely that cardiovascular changes simply resulted from fluid therapy, vasopressor or milrinone infusion. However, because of the uncontrolled design, our study cannot prove a causative relationship between the observed hemodynamic changes and metoprolol therapy.

In view of the preference of milrinone over dobutamine and the frequent use of a supplementary arginine vasopressin infusion, the hemodynamic effect during enteral metoprolol therapy can be interpreted only in the context of our institutional hemodynamic protocol. For example, infusion of arginine vasopressin in 95.6% of the study patients could have interfered with the hemodynamic effects of metoprolol therapy. Likewise, a decrease in heart rate as well as a mild increase in CI was reported during supplementary AVP infusion in patients with advanced vasodilatory shock and hypodynamic circulation[43]. Although in most patients (89%) AVP was started before metoprolol therapy, we cannot determine the extent to which this influenced the hemodynamic course during the observation period.

Response to metoprolol in this study population was not entirely homogeneous. Whereas overall MAP and CI did not decrease, nine and seven patients exhibited a decrease in MAP and CI, respectively, requiring an increase in norepinephrine or milrinone dosages during the observation period. It cannot be proven that the observed changes reflect beneficial or adverse effects of metoprolol. It is conceivable that without beta-blocker therapy stroke

volume index would have increased even more and milrinone infusion could have been withdrawn earlier. Similarly, the decrease in MAP and CI in some patients may have resulted from the course of the underlying disease process instead of being related to metoprolol therapy.

Data from experimental and clinical studies suggest that several beta-blocker effects such as heart rate control[44], antagonization of catecholamine-induced stunning of the myocardium [11, 45, 46], and reduction of myocardial inflammation [47, 48] may be beneficial in patients with septic myocardial depression. Although data are still conflicting [49], beneficial effects of beta blockers were reported to also include attenuation of an overshooting immune response. Adult trauma patients treated with a continuous beta-blocker infusion exhibited lower serum interleukin 6 levels than did controls receiving standard of care [22]. Reduced pro-inflammatory cytokine production was also illustrated during esmolol infusion in rats with septic cardiomyopathy [16]. Interestingly, serum C-reactive protein levels decreased during metoprolol therapy in our study. Although it could be hypothesized that metoprolol reduced interleukin 6 levels and thus C-reactive protein levels [50], many other factors such as focus control [38], adequate antibiotic therapy [38], and hemodynamic stabilization[51] are likely to have caused the decrease of C-reactive protein levels in our analysis.

In addition to the uncontrolled study design, other important limitations need to be noted when interpreting the results of our analysis. First, this is a retrospective study and it entails potential difficulties because of missing values in individual patients. Furthermore, patient enrolment was not performed according to a strict protocol as in a prospective trial but at the discretion of the attending physician. Therefore, some patients who would have been eligible for metoprolol therapy according to our treatment scheme may have been missed. Second, although a hemodynamic protocol that served as a recommendation for resuscitation of septic shock patients was available, we cannot be sure whether the attending physicians

strictly adhered to the protocol during resuscitation of all study patients. Third, forty patients are too small a population for adequately evaluating the safety profile of metoprolol therapy in patients with septic shock and cardiac depression.

CONCLUSIONS

Low doses of enteral metoprolol in combination with phosphodiesterase inhibitors are feasible in patients with septic shock and cardiac depression but no overt heart failure. Future prospective controlled trials on the use of beta blockers for septic cardiomyopathy and their influence on pro-inflammatory cytokines are warranted.

KEY MESSAGES

- Heart rate significantly decreased during combined milrinone infusion and enteral metoprolol therapy in patients with septic shock and cardiac depression.
- In 97.5% of patients, targeted heart rates of 65-95 bpm were achieved.
- Enteral metoprolol therapy appears to have no major adverse effects on cardiovascular or organ function.
- Mean arterial blood pressure increased despite decreasing norepinephrine, arginine vasopressin and milrinone dosages.
- Cardiac function economized, resulting in a maintained cardiac index with a lower heart rate and a higher stroke volume index.

LIST OF ABBREVIATIONS

cAMP	cyclic adenosine monophosphate
CI	cardiac index
CPI	cardiac power index
ICU	intensive care unit
MAP	mean arterial blood pressure

COMPETING INTERESTS

The author(s) declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

CAS made substantial contributions to acquisition, analysis and interpretation of data, was involved in drafting the manuscript and gave final approval of the version to be published. MWD made substantial contributions to concept and design, acquisition, analysis and interpretation of data, was involved in drafting the manuscript and gave final approval of the version to be published. MH made substantial contributions to acquisition of data, critically revised the manuscript for important intellectual content and gave final approval of the version to be published. HU performed the statistical analysis, critically revised the manuscript for important intellectual content and gave final approval of the version to be published. GL made substantial contributions to acquisition of data, critically revised the manuscript for important intellectual content and gave final approval of the version to be published. CT made substantial contributions to acquisition of data, critically revised the manuscript for important intellectual content and gave final approval of the version to be published. SJ made substantial contributions to acquisition of data, critically revised the manuscript for important intellectual content and gave final approval of the version to be published. WRH made substantial contributions to concept and design, was involved in drafting the manuscript, and gave final approval of the version to be published.

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FIGURE LEGENDS

Figure 1. **Institutional Hemodynamic Protocol.**

*, fluid resuscitation using crystalloids to cover basal fluid demands (~30 mL/kg/d) and colloids for further fluid loading (guided by responses in stroke volume and cardiac index, arterial and central venous pressure, heart rate as well as clinical signs). As colloids hydroxyethylstarch (molecular weight, 130.000; Voluven® 130/0.4; Fresenius Kabi, Graz, Austria) with a dose limitation of 30 mL/kg/d based on the manufacturer's instructions) and gelatine (molecular weight, 22.600; Gelofusin®; B Braun, Melsungen, Germany) without a dose limitation were used.

#, new-onset tachyarrhythmias, progressive tachycardia >110 beats/min despite adequate fluid resuscitation, pulmonary arterial hypertension with new signs of right heart dysfunction, new-onset hyperglycemia (blood sugar >130 mg/dL) resistant to insulin dosages >5 IU/h, new increase in troponin serum concentrations, or progressive deterioration of diastolic or systolic ventricular function.

RBC, red blood cells; $ScvO_2$, central venous oxygen saturation; SVI, stroke volume index; CI, cardiac index; MAP, mean arterial blood pressure; NE, norepinephrine.

TABLES, FIGURES AND CAPTIONS

Table 1. Characteristics of the Study Population		
n		40
Age	(years)	71 ± 13
Male Sex	*n* (%)	21 (53)
BMI	(kg/m²)	28 ± 7
Premorbidities	*n* (%)	
cAHT		23 (58)
oCAD		10 (25)
CHF		12 (30)
COPD		8 (20)
CRI		14 (35)
CLD		4 (10)
Neoplasm		3 (8)
Chronic Beta-Blocker Therapy	*n* (%)	15 (38)
Source of Infection	*n* (%)	
Liver/Abdomen		21 (53)
Lung		10 (25)
Skin/Soft Tissue		3 (8)
Joint/Bone		2 (5)
Catheter/Device		1 (3)
Urogenital Tract		1 (3)
Unknown Origin		2 (5)
CVVHF	*n* (%)	28 (70)
MODS Score (12)	(points)	9.9 ± 2.3
SAPS II	(points)	53 ± 16
ICU LOS	(days)	15 ± 11
28-day Mortality	*n* (%)	13 (33)

BMI, body mass index; cAHT, chronic arterial hypertension; oCAD, obstructive coronary artery disease; CHF, compensated congestive heart failure; COPD, chronic obstructive pulmonary disease; CRI, chronic renal insufficiency; CLD, chronic liver disease; CVVHF, continuous veno-venous hemofiltration; MODS, multiple organ dysfunction syndrome; SAPS, simplified acute physiology score; ICU, intensive care unit; LOS, length of stay.

Data are given as mean values±SD, if not indicated otherwise.

Table 2. Hemodynamic Variables at Shock Onset and during the Observation Period.

		ICU Admission[§]	Baseline	6 hrs	12 hrs	24 hrs	48 hrs	72 hrs	96 hrs	*p*-value
Patients	*(n)*	40	40	40	39	37	37	35	33	
HR	*(bpm)*	110 ± 19	101 ± 18	84 ± 17[#]	84 ± 14[#]	84 ± 13[#]	83 ± 13[#]	79 ± 13[#]	78 ± 14[#]	<0.001*
MAP	*(mmHg)*	59 ± 19	85 ± 23	82 ± 15	85 ± 18	87 ± 15	90 ± 20	91 ± 20	90 ± 21	0.16
CVP	*(mmHg)*	14 ± 4	12 ± 3	12 ± 4	12 ± 3	11 ± 3	11 ± 3[#]	10 ± 3[#]	9 ± 3[#]	<0.001*
CI	*(L/min/m²)*	1.9 ± 0.6	3.1 ± 1.1	3.2 ± 1.0	3.3 ± 0.9	3.4 ± 0.9	3.4 ± 1.0	3.5 ± 1.0	3.5 ± 0.8	0.56
SVI	*(mL/beat/m²)*	18 ± 7	32 ± 12	40 ± 14	40 ± 12	42 ± 12[#]	42 ± 13[#]	42 ± 10[#]	44 ± 9[#]	0.002*
CPI	*(W/m²)*	0.24 ± 0.14	0.61 ± 0.32	0.57 ± 0.22	0.60 ± 0.17	0.65 ± 0.18	0.68 ± 0.30	0.71 ± 0.25	0.68 ± 0.23	0.27
$ScvO_2$	*(%)*	64 ± 12	71 ± 10	72 ± 6	72 ± 11	74 ± 9	77 ± 8	73 ± 11	72 ± 11	0.35
SVRI	*(dyne*sec*cm^{-5}/m²)*	2041 ± 1181	2114 ± 825	1918 ± 897	1913 ± 777	1895 ± 647	2014 ± 800	2060 ± 852	1824 ± 569	0.78
NE	*(µg/kg/min)*	0.12 ± 0.25 (n=18)	0.17 ± 0.11	0.18 ± 0.11	0.18 ± 0.11	0.17 ± 0.13	0.13 ± 0.13	0.09 ± 0.08[#]	0.06 ± 0.07[#]	<0.001*
AVP	*(IU/h)*	n.a.	2.0 ± 1.6	2.2 ± 1.3	2.1 ± 1.3	2.1 ± 1.2	1.9 ± 1.3	1.3 ± 1.3	0.8 ± 1.1[#]	<0.001*
Mil	*(µg/kg/min)*	0.24 ± 0.19 (n=6)	0.31 ± 0.16	0.34 ± 0.17	0.33 ± 0.16	0.30 ± 0.17	0.24 ± 0.18	0.21 ± 0.19	0.12 ± 0.13[#]	<0.001*
Meto	*(mg)*	n.a.	47 ± 19	n.a.	n.a.	47 ± 41	52 ± 42	51 ± 42	54 ± 37	n.a.

ICU, intensive care unit; HR, heart rate; MAP, mean arterial blood pressure; CVP, central venous blood pressure; CI, cardiac index; SVI, stroke volume index; CPI, cardiac power index; ScvO2, central venous oxygen saturation; SVRI, systemic vascular resistance index; NE, norepinephrine requirements (n in parentheses indicates the number of patients who received norepinephrine already at intensive care unit admission); AVP, arginine vasopressin dosage; Mil, milrinone requirements (n in parentheses indicates the number of patients who received milrinone already at intensive care unit admission); Meto, metoprolol dosage; n.a., not administered.

*, significant time effect; #, significant effects vs. baseline; §, not included in the longitudinal mixed-effects analysis.

Data are given as mean values±SD.

Table 3. Organ Function Variables during the Observation Period.

		Baseline	**6 hrs**	**12 hrs**	**24 hrs**	**48 hrs**	**72 hrs**	**96 hrs**	***p*-value**
Patients	(n)	40	40	39	37	37	35	33	
pH		7.36 ± 0.09	7.37 ± 0.06	7.37 ± 0.1	7.38 ± 0.08	7.38 ± 0.07#	7.4 ± 0.06#	7.42 ± 0.07#	<0.001*
Lactate	(mg/dL)	22 ± 15	24 ± 14	29 ± 32	14 ± 10#	12 ± 8#	11 ± 7#	10 ± 5#	<0.001*
Creatinine	(mg/dL)	2.3 ± 1.3	…	…	2.0 ± 1.0	1.8 ± 0.7	1.7 ± 0.8	1.6 ± 0.7#	0.02*
ASAT	(IU/L)	230 ± 651	…	…	143 ± 253	166 ± 320	199 ± 474	153 ± 336	0.97
ALAT	(IU/L)	128 ± 435	…	…	78 ± 222	90 ± 225	101 ± 207	90 ± 157	0.78
Bilirubin	(mg/dL)	1.7 ± 1.4	…	…	1.6 ± 1.3	1.5 ± 1.1	1.5 ± 1.5	1.6 ± 2.2	0.60
C-reactive Protein	(mg/dL)	17.6 ± 8.7	…	…	17.8 ± 9.1	15.2 ± 9.3	11.6 ± 8.6	10 ± 8.2	0.001*
Troponin I	(µg/L)	8 ± 40	…	…	6 ± 21	3 ± 9	3 ± 7	2 ± 5	0.60
Platelets	(G/L)	145 ± 78	…	…	132 ± 88	130 ± 106	134 ± 112	133 ± 123	0.95
PaO_2/FiO_2		244 ± 129	…	…	243 ± 92	252 ± 102	238 ± 84	262 ± 89	0.87

ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; PaO2, arterial oxygen tension; FiO2, inspiratory oxygen tension; …, not measured.

*, significant time effect; #, significant effects vs. baseline.

Data are given as mean values±SD.

Table 4. Adverse Events during the Observation Period.	
	n (%)
Asymptomatic Bradycardia	2 (5)
Symptomatic Bradycardia	0 (0)
Increase in NE Dosage	9 (22.5)
Decrease in CI	7 (17.5)
Decrease in CI and $ScvO_2$	1 (2.5)
Decrease in SVI	2 (5)
Increase in Milrinone Dosage	6 (15)

NE, norepinephrine; CI, cardiac index; ScvO2, central venous oxygen saturation; SVI, stroke volume index.

Figure 1

Figure 1. **Institutional Hemodynamic Protocol.**