Original Article

The influence of metoprolol in patients with sepsis-induced cardiomyopathy

A retrospective study

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ABSTRACT

الأهداف: للتركيز على تقييم التأثير السريري للميتوبرولول على اعتلال عضلة القلب الناجم عن الإنتان (SICM).

المنهجية: تم تسجيل ما مجموعه 90 مريضًا مصابًا باعتلال SICM في الفترة من ديسمبر 2018 إلى فبراير 2021 وتم تقسيمهم إلى مجموعتين وفقًا لاستخدام الميتوبرولول أثناء الإقامة في مستشفى بلدية سوتشو في سوتشو، الصين. قمنا بمقارنتها مع وظيفة القلب، ودرجة تقييم فشل الأعضاء المتتابعة، والنتائج السريرية.

النتائج: بين المجموعتين، كانت مؤشرات الأوكسجين ومقياس غلاسكو للغيبوبة في مجموعة الميتوبرولول أعلى في اليوم الأول من العلاج، مع مقياس غلاسكو للغيبوبة أعلى في اليوم الثالث من العلاج. ومع ذلك، فإن جرعات النورإبينفرين في المرضى الذين يعانون من الميتوبرولول لم تظهر أي فروق ذات دلالة إحصائية مع المجموعة الضابطة. كانت الوفيات الناجمة عن جميع الأسباب عند 28 يومًا في مجموعة الميتوبرولول أقل، كما اختلف بشكل كبير وقت الإزالة من دعم جهاز التنفس الصناعي وكذلك عدد الأعضاء الفاشلة بين المجموعتين.

الخلاصة: يمكن أن يقلل الميتوبرولول معدل الوفيات لمدة 28 يومًا ويقصر مدة التهوية الميكانيكية في SICM. بالإضافة لذلك يمكنه تقليل عدد حالات فشل الأعضاء وتحسين مؤشر الأوكسجين ومقياس غيبوبة غلاسكو لهؤلاء المرضى. وفي الوقت نفسه، لم يؤثر الميتوبرولول على جرعة النورإبينفرين في المرضى الذين يعانون من SICM.

Objectives: To focus on evaluating the clinical influence of metoprolol on sepsis-induced cardiomyopathy (SICM).

Methods: A total of 90 patients with SICM was enrolled from December 2018 to February 2021 and divided into 2 groups according to the use of metoprolol during hospitalization in Suzhou Municipal Hospital in Suzhou, China. We compared them with the cardiac function, sequential organ failure assessment score, and clinical outcomes.

Results: Between the 2 groups, the oxygenation indices and Glasgow coma scale in the metoprolol group were higher on the first day of treatment, with Glasgow coma scale higher on the third day of treatment. However, the doses of norepinephrine in patients with metoprolol showed no significant differences with the control group. The all-causemortality at 28 days in the metoprolol group was lower, and the time of removing from ventilator support as well as the number of failured organs also significantly differed between the 2 groups.

Conclusion: Metoprolol can reduce the 28-day mortality and shorten the duration of mechanical ventilation in SICM. It can also reduce the number of organ failures and improve the oxygenation index and Glasgow coma scale of these patients. Meanwhile, metoprolol did not affect the norepinephrine dose in patients with SICM.

Keywords: sepsis-induced cardiomyopathy, metoprolol, organ function, 28-day mortality

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Sepsis, as a life-threatening inflammatory reaction, often complicates organ dysfunction and manifests physiologic, pathologic, as well as biochemical abnormalities.[1-3] As a subset of sepsis, septic shock can occur with severe disorders in circulation, cell, and metabolism, the mortality of which is higher than sepsis alone.[1] As one of the frequent complications accompanying sepsis, sepsis-induced cardiomyopathy (SICM) has an incidence varying from 13.8-64% and the mortality ranging from 24.1-90%.[4]

The hemodynamics of patients with sepsis are characterized by high output and low resistance. As the first-line treatment for sepsis, aggressive resuscitation in early stage and vasoconstrictors are extremely important for maintaining the perfusion pressure of vital organs. However, myocardial injury appears in the early period of sepsis, and excessive fluid resuscitation as well as the continued stimulation of adrenergic receptors may lead to the deterioration of cardiac function.[5,6] Therefore, the earlier identification of SICM and the earlier prevention of progressive myocardial damage are particularly important for improving the prognosis of sepsis.

Metoprolol plays an important role in many cardiovascular diseases. Although metoprolol can improve the imbalance of cardiac oxygen supply and oxygen consumption by lowering the mortality of sepsis, its effect on the abnormal hemodynamic state of high output and low resistance remains controversial due to its negative inotropic.[7,8] Given the recent advancements in our understanding of decatecholamine, metoprolol may improve the prognosis of sepsis by inhibiting adrenergic reactions.[6,9,10] Recent researches have shown that β-blockers do not affect the hemodynamic status and tissue perfusion in the premise of reducing heart rate and cardiac oxygen consumption in septic shock and sepsis.[11] The meta-analysis and randomized trials have shown that β-blockers can contribute to reducing 28-day mortality in sepsis.[12,14,15] Meanwhile, the safety of β-blockers was verified without exacerbation of cardiac dyfunction in septic shock.[16-19] However, the efficacy of β-blockers in SICM still needs to be explored. Thus, this study focuses on this controversial content and provides evidence for clinical treatment strategies for SICM.

Methods. This study retrospectively analyzed patients with SICM and divided them into 2 groups according to the use of metoprolol which was produced by Yantai Juxian Pharmaceutical in China. From December 2018 to February 2021, 90 inpatients with SICM who were hospitalized in our institute were included in this study. The treatment group received long-term oral metoprolol treatment during hospitalization and the target dose maintained the heart rate within the normal range. Exclusion criteria included: acute coronary syndrome, acute cerebrovascular disease (acute cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage), and acute pulmonary embolism.

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The ethics committee of Suzhou Municipal Hospital in Suzhou, China, approved our study (approval no.: KL901336) and the principles of Helsinki declaration was implemented in the whole research process.

General clinical data included: age, gender, weight, hypertension (HT), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), previous cerebral infarction, as well as infection site. Cardiac-related indicators included: cTNI, NT-proBNP, left ventricular ejection fraction (LVEF), left atrial diameter (LAD), left ventricular end diastolic diameter (LVEDD), pulmonary artery systolic pressure (PASP), and stroke volume (SV). The indexes of sequential organ failure assessment (SOFA) were acquired on the first and third days of treatment. Clinical outcome related indicators included: the duration time of ventilator support, continous renal replacement therapy (CRRT), the number of organ dysfunctions, the residence time of Intensive care unit (ICU), and the 28-day mortality.

Although the relationship between SICM and sepsis has been relatively clear, consensus on the definition of SICM is lacking. Most scholars believe that it can be defined as reversible myocardial dysfunction secondary to sepsis. Related studies have proposed the following definitions of SICM: I) a clear history of sepsis; II) an LVEF lower than 0.55; III) a dilated left ventricle; and IV) the return of cardiac function indices (such as cardiac output and LVEF) to normal after sepsis is under control, a process that is reversible.[20]

Statistical analysis. The study adopted the Statistical Package for the Social Sciences, version 22.0, for Windows (IBM Corp., Armon, NY, USA) as well as Graphpad Prism 8.0 for statistical analysis. The measurement data were presented as mean±standard deviation (SD) and carried out with the Kolmogorov-Smirnov normality test. T-test and Mann-Whitney-U test were used for normally and abnormally distributed independent samples. The counting data are represented as the number of cases and percentage. Fisher's exact test, pearson's and continuous correction Chi-squared test were carried out based on the total sample size and minimum theoretical frequency. Kaplan-Meier plots and Mantel-Cox regression can be used to describe Time-to-event data.

Results. The study finally included 90 inpatients with SICM, the average age of which was 76.77±13.05 years. A total of 42 (46.7%) patients received long-term oral metoprolol treatment. Age, gender, HT (after comparison between 2 groups), DM, CKD, COPD,

cerebral infarction, and the source of infection showed no statistic differences, as shown in Table 1.

To further evaluate of cardiac structural changes in patients with SICM, the cardiac color doppler ultrasound indices are compared in Table 2. After comparison, the LVEDD (51.39±6.11 vs. 48.32±5.88, p=0.018) and LAD (41.12±5.05 vs. 37.89±7.10, p=0.016) group were significantly larger in the metoprolol. However, other indicators, such as LVEF, SV, and PASP did not show statistic differences between the 2 groups. The comparative results of cTnI and NT-proBNP were the same as above (p>0.05).

After the comparison between the 2 groups, patients with the metoprolol on the first day of treatment had higher oxygenation index and lower respiratory SOFA scores (269.13±110.80 vs. 215.37±120.14, p=0.034; 1.85±1.21 vs. 2.43±1.17, p=0.027, Figure 1 & Table 3). By comparing between the first and third days of treatment, the counts of platelet decreased in patients without metoprolol and it showed no differences in patients with metoprolol (155.00±103.83 vs. 105.96±81.94, p=0.013; 158.80±116.36 vs. 119.88±77.65, p=0.083; Figure 1). The GCS of the metoprolol group was higher on the first and third days of treatment in the metoprolol group (10.25±4.53 vs. 8.21±4.21, p=0.023; 9.85±4.32 vs. 7.77±5.05, p=0.044; Figure 1). However, the neurological SOFA scores in the metoprolol group were lower only on the first day (1.88±1.70 vs. 2.64±1.47, p=0.029; Table 3). In terms of the circulatory system, the MAP level of patients with metoprolol was higher on these 2 days of treatment (73.29±11.77 vs. 67.96±11.56, p=0.037; 77.84±12.64 vs. 70.15±13.48, p=0.007; Figure 1), whereas the significant differences of SOFA scores in the 2 groups shows only on the first day (2.70±1.36 vs. 3.26±0.85, p=0.028; Table 3). The dosage of epinephrine in the metoprolol group was not statisitically different from control group. The total score of SOFA in patients with metoprolol showed a lower significant on the first day of treatment (8.83±3.70 vs. 11.02±3.00, p=0.004; Table 3).

Table 1 - Clinical baseline characteristics.

Parameters	Control group (n=48)	Metoprolol group (n=42)	*P*-values
Age (years)	75.29±15.04	78.45±10.22	0.242
Female	38 (79.2)	29 (69.0)	0.336
Weight (kg)	56.96±12.61	57.0±9.52	0.852
HT	32 (66.7)	25 (59.5)	0.517
DM	16 (33.3)	19 (45.2)	0.283
CKD	13 (27.1)	11 (26.2)	1.000
COPD	11 (26.2)	7 (16.7)	0.599
Cerebral infarction	13 (27.1)	15 (35.7)	0.494
The source of infection			
Lung	44 (91.7)	40 (95.2)	0.681
Abdomen	13 (21.7)	7 (16.7)	0.311
Skin soft tissue or catheter	5 (10.4)	8 (19.0)	0.368
other	4 (8.3)	2 (4.8)	0.799

Values are presented as numbers and precentages (%) or mean ± standard deviation (SD). HT: hypertension, DM: diabete mellitus, CKD: chronic kidney disease, COPD: chronic obstructive pulmonary disease

Table 2 - Cardiac structure and functions.

Parameters	Control group (n=48)	Metoprolol group (n=42)	*P*-values
cTNI (ng/ml)	1.82±2.76	4.71±2.06	0.136
NT-proBNP (pg/ml)	13183.79±12315.85	16393.33±11126.90	0.200
LVEF (%)	46.71±7.08	44.22±7.57	0.113
LVEDD (mm)	48.32±5.88	51.39±6.11	0.018*
LAD (mm)	37.89±7.10	41.12±5.05	0.016*
SV (ml)	53.50±18.72	60.37±23.16	0.389
PASP (mmHg)	38.00±10.16	34.56±10.03	0.119*

Values are presented as mean ± standard deviation (SD). *p<0.05. LVEF: left ventricular ejection fraction, LVEDD: left ventricular end-diastolic dimension, LAD: left atrial diameter, SV: stroke volume, PASP: pulmonary artery systolic pressure

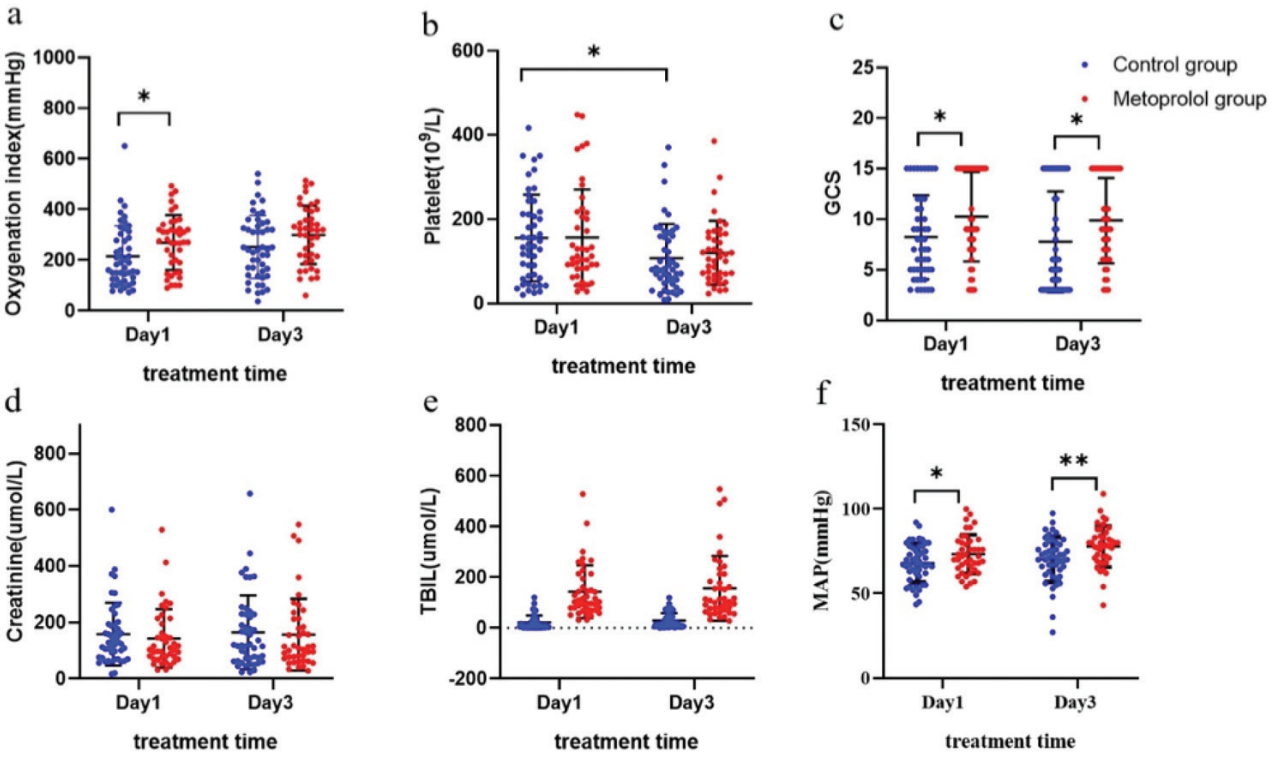

Figure 1 - Scatter dot plot depicting sequential organ failure assessment score associated indexes on the first and third days of treatment. Sequential organ failure assessment score associated indexes included: **a**) oxygenation index(mmHg); **b**) platelet count(109/L); **c**) GCS; **d**) creatinine (umol/L); **e**) TBIL (umol/L); and **f**) MAP (mmHg). **P*-value of <0.05. ***P*-value of <0.01. Scatter dot plot displayed mean and standard deviation. GCS: glasgow coma scale, TBIL: total bilirubin, MAP: mean arterial pressure

Table 3 - Sequential organ failure assessment score of corresponding organ system.

SOFA scores	Day 1 of treatment			Day 3 of treatment		
	Control group	Metoprolol group	*P*-values	Control group	Metoprolol group	*P*-values
Respiratory	2.43±1.17	1.85±1.21	0.027*	2.02±1.277	1.53±1.132	0.060
Blood coagulation system	1.15±1.25	1.23±1.14	0.769	1.68±1.25	1.38±1.10	0.234
Nervous system	2.64±1.47	1.88±1.70	0.029*	2.62±1.73	2.00±1.60	0.088
Kidney	1.04±1.02	0.83±1.04	0.328	1.15±1.20	1.00±1.24	0.571
Liver	0.57±0.90	0.35±0.74	0.205	0.85±0.96	0.52±0.91	0.118
The dosage of NE (ug/kg.min-1)	10.62±8.08	10.50±8.51	0.951	10.70±9.16	12.23±9.17	0.499
Cardiovascular system	3.26±0.85	2.70±1.36	0.028*	3.07±0.85	2.78±1.53	0.291
Total SOFA score	11.02±3.00	8.83±3.70	0.004*	10.79±3.21	9.05±4.01	0.031*1

Values are presented as mean ± standard deviation (SD). **p*<0.05. Sequential organ failure assessment (SOFA) were evaluated with the function of 6 organ system with the range from 0-24. NE: norepinephrine

Compared with control group, the time of weaning from ventilator for patients with metoprolol was shorter (8.00±9.62 vs. 8.04±8.39, *p*=0.042. Meantime, the study group with the metoprolol showed lesser failured organs (2.98±1.66 vs. 3.81±1.35, *p*=0.014). Moreover, the incidence of CRRT and the resident time of ICU did not have significant differences in study population (Table 4).

The metoprolol group had a 28-day mortality of 61.9% while the control group had a 28-day mortality of 85.4% (*p*=0.015). A 28-day survival analysis were showed as Kaplan-Meier curves in Figure 2. After comparison between the 2 groups, the adjusted mortality hazard ratio in patients with the metoprolol was 0.55 (95% CI: [0.34-0.89]; *p*=0.011).

Table 4 - Clinical outcomes of patients in 2 groups.

Parameters	Control group (n=48)	Metoprolol group (n=42)	*P*-values
Duration of mechanical ventilation	8.04±8.39	8.00±9.62	0.042*
CRRT	23 (47.9)	15 (35.7)	0.288
Number of organ faliure	3.81±1.35	2.98±1.66	0.014*
Length of ICU stay	11.21±10.08	16.21±13.86	0.0581

Values are presented as mean ± standard deviation (SD) or numbers and percentages (%). *$p<0.05$. Renal failure was over stage 3 in acute kidney injury and other organ failures were based on sequential organ failure assessment score over 3 points, except cardiovascular failure. CRRT: continuous renal replacement therapy, ICU: intensive care unit

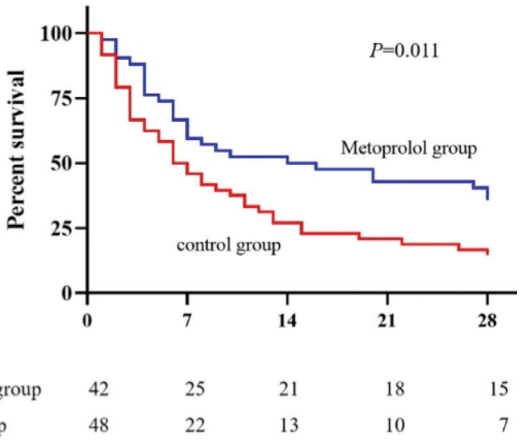

Figure 2 - The adjusted mortality hazard ratio in patients with the metoprolol of 0.55 (95% CI: [0.34-0.89]; p=0.011).

Discussion. Whether metoprolol is suitable for sepsis or not is controversial in clinical practice because of its negative inotropic effect. However, a series of experiments showed that β-blockers did not affect cardiac output or blood supply to several vital organs in patients with sepsis.[14,21,22] Therefore, metoprolol is relatively safe for patients with sepsis after adequate fluid resuscitation in the early period. However, the safety and efficacy of metoprolol for SICM is controversial because of the unique state of cardiac function. This study found that metoprolol could reduce the 28-day mortality of SICM and make patients with SICM wean from mechanical ventilation earlier. The BEAST study also revealed that β-blockers could lower inpatient mortality and the incidence of invasive ventilation in sepsis, but it did not provide a subgroup analysis of SICM.[23] Therefore, our study focus on the influence of metoprolol in SICM.

At present, SICM involves a number of possible pathological mechanisms and may be a result of the interaction of them.[24] Among them, sympathetic hyperactivation is crucial in the pathogenesis of SICM. The release of catecholamines in the early stage of shock results in sustained activation of α and β adrenal receptors, which exacerbates myocardial damage by inducing cellular apoptosis and calcium overload.[25] The sympathetic hyperactivation in patients with SICM can affect myocardial diastolic function, aggravate myocardial ischemia, and induce tachyarrhythmia. Therefore, preventing the progressive damage to the myocardium caused by the sympathetic hyperactivation is crucial for SICM.

Metoprolol, as a selective β1 receptor blocker, contributes to decatecholaminization and improve the prognosis of sepsis by restricting the endogenous adrenergic response and exogenous catecholamine intake.[6,26] In several studies, β-blockers have been proven that they can reduce mortality in sepsis.[13,14,24] Theoretically, β-blockers can improve the state of overactivation in the β-adrenergic receptor, thus reducing myocardial oxygen consumption and increasing end-diastolic volume, which can ultimately improve the prognosis of SICM. This study also revealed that patients with metoprolol have lower 28-day mortality in SICM. Moreover, we found that metoprolol contributed to the recovery of respiratory and nervous system functions and could improve the SOFA score in SICM. Similar results were found in a study in which β-blockers had a better effect on the prognosis of patients with sepsis but had no effect on SOFA scores.[24] In terms of hemodynamic effects, this study showed that metoprolol did not increase the dosage of norepinephrine and even improve the MAP level in SICM. Fucsh et al[27] also revealed that β-blockers did not increase the dosage of catecholamines in septic shock. It may be explained by the fact that β-blockers can improve the down regulation of the vascular β1 receptor in patients with sepsis.[28] The study population in above experiments were all with sepsis, whereas our study further explored the effects of metoprolol on SICM. Above all, our study showed that metoprolol could improve some organ function without affecting hemodynamics, which may further explain why metoprolol could reduce the 28-day mortality of patients with SICM.

Study limitations. First, some data collected in

this experiment were based on the operator's personal evaluation, such as the GCS and SOFA scores, and they consequently exhibit certain inter-operator variability. Second, left ventricular diastolic function and right ventricular function were involved in patients with SICM, the patients of which were not enrolled in this study due to undefined criteria. Third, the cardiovascular effects of β-blockers are multifactorial, which makes it possible to inhibit myocardial contractility excessively and affect vital organ perfusion. Therefore, more clinical studies are needed to explore how to safely and effectively use β-blockers, such as the timing of application, dosage, target heart rate, comedication, and so on.[14,19,29,30]

In conclusion, this study indicated that metoprolol can improve the organ function of patients with SICM and reduce 28-day mortality. In addition to early and appropriate fluid resuscitation, this study provided relevant data that support improvements in the clinical prognosis of patients with SICM, and further studies will be devoted to some relevant prospective clinical studies in the future.

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