Central venous pressure value can assist in adjusting norepinephrine dosage after the initial resuscitation of septic shock

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Abstract

Background: New definitions for sepsis and septic shock (Sepsis-3) were published, but the strategy to adjust vasopressors after the initial guidelines is still unclear. We conducted a retrospective observational study to explore dosing strategy of norepinephrine (NE).

Methods: A retrospective observational study in the 15-bed mixed intensive care unit of a tertiary care university hospital. The study was performed on septic shock patients after 30 mL/kg fluid resuscitation and mean arterial pressure (MAP) levels reached >65 mmHg requiring NE. We divided patients into NE dosage increase and decrease groups, and collected hemodynamic and tissue perfusion parameters before (T1) and after (T2) adjusting NE dosage.

Results: In both NE increase and decrease groups, central venous pressure (CVP) and pressure difference between usual MAP and MAP (dMAP) at the T1 time point were associated with lactate clearance. In groups LC HM (CVP <10 mmHg, dMAP >0 mmHg) and HC HM (CVP ≥10 mmHg, dMAP >0 mmHg), decrease in NE dosage decreased lactate level, while in group HC LM (CVP ≥10 mmHg, dMAP ≤0 mmHg), both increase and decrease in NE dosage led to increase lactate level.

Conclusions: After patients with septic shock (Sepsis-3) resuscitated to reach the initial recovery target goals, combination of CVP and MAP refer to usual levels can help doctors make the next decision to make the correct choice of increase NE dosage or decrease NE dosage.

Keywords: Septic shock; Vasopressors; Central venous pressure; Hemodynamics

Introduction

According to the new definitions published in The Third International Consensus Definitions for Sepsis and Septic Shock, sepsis is now defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection.[1,2] The criteria for septic shock included persistent hypotension requiring vasopressors to maintain mean arterial pressure (MAP) ≥65 mmHg and elevated lactate levels. The new guidelines imply that increased lactate levels (≥2 mmol/L) represent tissue hypoperfusion associated with tissue dysfunction in critically ill patients.[2,3] Thus, optimal initial hemodynamic management is a key component of the treatment of septic shock, as hypotensive patients have twice as much mortality compared with patients whose hypotension can be corrected with fluids and vasopressors.[4-6] This is substantiated by the fact that increasing the MAP to normal levels is associated with improved microcirculation in hypertensive septic shock patients.[7] Although high dosage of norepinephrine (NE) may be required to correct hypotension in severe cases, high dosage of exogenous NE may lead to myocardial injury, oxidative stress, or reduced hypoperfusion.[8-10]

Thus, if initiated, dosage of vasopressor should be titrated based on its effect on perfusion.

A recent study has shown that the patient’s usual MAP is a good reference for improving microcirculation in septic shock.[11] However, after achieving the initial MAP target of 65 mmHg and the later recommendation of using normal lactate as the resuscitation target, it is unclear as to how the dosage of NE can be adjusted to improve tissue perfusion. MAP is the driving pressure of tissue perfusion, but targeting high MAP (85 mmHg) results in a significantly higher risk of arrhythmias. Also, patients with previously diagnosed chronic hypertension had a reduced need for renal replacement therapy.[2] Thus, previous history of the patient is important to determine individual targets for patients with septic shock. We investigate the strategy of further adjusting the vasoactive agents after the initial fluid resuscitation of 30 mL/kg is provided and MAP of 65 mmHg is achieved. We conducted a retrospective
observational study to explore the association of NE dosage adjustment and change in the tissue perfusion by lactate levels reaction.

Methods

Ethical approval

The retrospective study was exempt from review and approval of the Local Ethics Committee of the Peking Union Medical College Hospital, Beijing, China, which waived the need for informed consent.

Patients

Patients admitted in the Department of Critical Care Medicine in Peking Union Medical College Hospital from June 2013 to June 2017 were eligible for participation in the study. Since the laboratory tests and data collected in this study were part of routine clinical practice. Patients with septic shock were managed according to an early resuscitation protocol modified from the Surviving Sepsis Campaign, with the aim of achieving the following: (1) at least 30mL/kg of intravenous crystalloid fluid be given within 3h after the diagnosis of septic shock, (2) MAP should reach above 65mmHg in patients requiring vasopressors NE, and (3) MAP targets be individualized and the dosage of NE be adjusted. We did not include patients with fluid challenges, changes in inotropes dosage or type, transfused blood products, changes in mechanical ventilation strategy, sedation and analgesia strategy, or dosage changes between study intervals.

Data collection

Intensive care unit (ICU) data were collected retrospective-ly from the electronic patient data monitoring system and hospital administration database. Time 1 (T1) was set before NE dosage was adjusted and Time 2 (T2) was set after NE dosage was adjusted; the interval between T1 and T2 was <6h. We divided patients into NE dosage increase and decrease groups, and collected hemodynamic and tissue perfusion parameters before T1 and after T2 adjusting NE dosage. Arterial and central venous blood samples were drawn for analysis at time points T1 and T2 where the time interval between arterial and central venous blood gas was <5min. The blood pressure level was recorded based on the medical record.

We collected demographic information, serial blood gas parameters, and relevant variables for calculation of daily sequential organ failure assessment (SOFA) score and acute physiology and chronic health evaluation (APACHE) II score where the worst values of the physiological parameters were used to calculate the SOFA score and the APACHE II score. Hemodynamic parameters, including heart rate (HR), blood pressure, and central venous pressure (CVP), were recorded at T1 and T2. The arterial and central venous blood samples were withdrawn simultaneously to record the following variables (SEM PREMIER 3000): arterial oxygen saturation (SaO2), arterial oxygen tension (PaO2), arterial carbon dioxide tension (PaCO2), standard base excess (SBE), arterial blood lactate, central venous oxygen tension (PvO2), central venous carbon dioxide tension (PvCO2), and central venous oxygen saturation (SvO2). The central venous-to-arterial carbon dioxide difference was calculated as follows: Pcv-a CO2 =PvCO2 – PaCO2.

The ratio of P(v-a)CO2/C(a-v)O2 was calculated using the following formula: Ratio=P(v-a) CO2/(CaO2 – CvO2).

Statistical analysis

Statistical analysis of the data was performed using SPSS 16.0 (IBM, Somers, NY, USA). Descriptive statistics were computed for all study variables. To verify the normality of the distributions of continuous variables, histograms, and normal quantile plots were examined and the Kolmogorov-Smirnov test was used. Continuous variables were presented as mean ± standard deviation, and variables not normally distributed variables are presented as median (25–75% interquartile range) if not normally distributed. Categorical variables are presented as number and percentage. Linear regression model was used to determine the association between baseline characteristics and changes in lactate (linear correlation between the indicators at T1 and the lactate clearance changes [before and after the NE dosage change]), before linear regression analysis, each factor analyzed by Student’s t test. The Mann-Whitney U test was used for comparisons when appropriate. A P < 0.05 was considered to be statistically significant.

Results

Baseline characteristics

During the study period 1560 patients whose diagnostic criteria were in accordance with the septic shock (Sepsis-3) were admitted to the ICU. One hundred and fifty patients were excluded as <30mL/kg fluid was given 3h after the diagnosis of septic shock. Eleven patients were excluded as MAP was <65mmHg; 178 patients were excluded as the therapy strategy changed between T1 and T2, which include 32 cases of fluid challenges, 24 cases of changes in inotropes dosage or type, 42 cases of transfused blood products, 20 cases of changes in mechanical ventilation strategy, 23 cases of changes in sedation and analgesia strategy, or dosage changes between study intervals. Thirty-seven patients were excluded because the data were incomplete or there was an inability to acquire the usual level of MAP at T1 or T2. The general and clinical characteristics of the remaining 1184 patients are displayed in Table 1. A total of 600 patients were included in NE dosage increase group, while 584 patients were included in NE dosage decrease group. The general characteristics between NE dosage increase group and NE dosage decrease group are shown in Table 2.

Determining factors related to changes in lactate levels

We performed linear regression analysis in both NE dosage increase and decrease group patients to find several characteristics at T1 independently related to changes in lactate between T2 and T1 (dLac=LacT2–LacT1).
In the NE dosage increase group, the correlation coefficient for CVP at T1 was 0.132 (\(P<0.0005\)), while that of pressure difference between usual MAP and MAP (dMAP) was -0.021 [Table 3]. In the NE dosage decrease group, the correlation coefficient for CVP at T1 and dMAP was 0.083 (\(P<0.0005\)) and -0.013 (\(P=0.002\)) [Table 3]. We also looked at other tissue perfusion parameters, such as pulse pulsation index, pH, ScvO2, Pcv-aCO2, and SBE and their relation to dLac [Table 3]. We found that in NE dosage increase and decrease group, CVP and dMAP at T1 were positively correlated to dLac [Figure 1]. CVP at T1 was significantly related to dLac (\(n=1184\), \(R=0.18, P<0.001\)), while the linear regression equation was \(dLac=0.108CVP (T1)+1.073\). If the dLac reached <0, then the CVP at T1 reached <10mmHg.

**Grouping of patients**

In our study, patients were resuscitated to reach the goals recommended by the international guidelines for septic shock such that at least 30mL/kg of intravenous crystalloid fluid was given and MAP reached 65mmHg. After administering the recommended fluid levels, we observed the values of CVP and MAP and divided patients into four groups based on CVP and dMAP values at T1: (1) group LC HM (low CVP, high MAP): CVP <10mmHg, dMAP >0mmHg, (2) group HC HM (high CVP, high MAP): CVP ≥10mmHg, dMAP >0mmHg, (3) group LC LM (low CVP, low MAP): CVP <10mmHg, dMAP ≤0mmHg, and (4) group HC LM (high CVP, low MAP): CVP ≥10mmHg, dMAP ≤0mmHg. Each of these four groups was further sub-divided into NE increase and NE decrease group. We compared dLac in each group increasing and decreasing the NE dosage group. Significant differences existed in group LC HM (\(P<0.001\)), group HC HM (\(P=0.001\)), and group HC LM (\(P<0.001\)) [Figure 2]. In group LC HM, decrease in NE dosage reduced the patient’s lactate removing more than NE dosage increase group (\(P<0.001\)). In group HC HM, NE dosage decrease group reduced the patient’s lactate removing more than NE dosage increase group (\(P=0.001\)). In group LC LM, the lactate removal was similar between the two teams (\(P=0.5\)). In group HC LM, both teams had increased lactate and no removal, while the effect was more severe in the NE dosage increase group (\(P<0.001\)). We also measured other parameters in these four groups, including differences in the levels of ScvO2, Pcv-aCO2, HR, MAP, CVP at time points T1 and T2 [Table 4].

**Discussion**

We performed a retrospective cohort study on patients with septic shock after the recommended guidelines of providing 30mL/kg fluid resuscitation and MAP reaching

### Table 1: General characteristics of all patients with septic shock (\(n=1184\)).

| Variables                              | Results         |
|----------------------------------------|-----------------|
| Age (years)                            | 59.3 ± 15.8     |
| Male, n (%)                            | 751 (63.4)      |
| APACHE II score                        | 28.1 ± 9.6      |
| SOFA, day 1                            | 12.8 ± 3.6      |
| Fluid infusion before the study for    | 1710.2 ± 698.3  |
| septic shock resuscitation (mL)        |                 |
| Source of infections, n (%)            |                 |
| Pneumonia                              | 483 (40.8)      |
| Abdominal                              | 277 (23.4)      |
| Blood                                  | 245 (20.7)      |
| Urinary                                | 112 (9.5)       |
| Soft tissue                            | 15 (1.3)        |
| No specific site                       | 52 (4.4)        |
| Comorbidities, n (%)                   |                 |
| Chronic hypertension                   | 403 (34.0)      |
| Diabetes                               | 177 (15.9)      |
| Chronic renal failure                  | 156 (13.2)      |
| Chronic heart failure                  | 107 (9.0)       |
| Usual MAP acquired from previous       | 89.2 ± 10.8     |
| medical records (mmHg)                 |                 |
| Mechanical ventilation, n (%)          | 923 (78.0)      |
| Length of ICU stay (h)                 | 300.1 ± 277.3   |
| ICU mortality, n (%)                   | 284 (24.0)      |

Data are expressed as n (%) or mean ± standard deviation. APACHE: Acute physiology and chronic health evaluation; ICU: Intensive care unit; MAP: Mean arterial pressure; SOFA: Sequential organ failure assessment.

### Table 2: General baseline hemodynamics between NE dosage increase and NE dosage decrease group.

| Variables                              | NE dosage increase (\(n=600\)) | NE dosage decreases (\(n=584\)) | \(t\)  | \(P\)  |
|----------------------------------------|-------------------------------|---------------------------------|-------|-------|
| Age (years)                            | 62 (53, 71)                   | 59 (52, 72)                     | 1.331 | 0.128 |
| Male, n (%)                            | 380 (63.3)                    | 371 (63.5)                     | 0.161 | 0.952 |
| APACHE score                           | 13.0 (11.0, 15.0)             | 13.0 (11.0, 16.0)              | -0.288| 0.801 |
| HR at T1 (beats/min)                   | 111.4 ± 20.6                  | 109.5 ± 21.9                   | 1.352 | 0.125 |
| Fluid infusion volume at T1 (mL)       | 1713.8 ± 25.6                 | 1698.6 ± 23.7                  | 1.226 | 0.134 |
| CVP at T1 (mmHg)                       | 11.0 (9.0, 14.0)              | 11.0 (9.0, 13.0)               | 0.942 | 0.347 |
| MAP at T1 (mmHg)                       | 82.2 ± 14.9                   | 89.7 ± 16.6                    | -3.643| <0.001|
| Time interval between T1 and T2 (h)    | 4.0 (2.9, 5.1)                | 4.2 (3.0, 5.1)                 | -1.053| 0.238 |
| NE dosage change between T1 and T2 (\(\mu g/kg\) per minute) | 0.41 (0.28, 0.73)          | -0.35 (-0.26, -0.56)          | 3.678 | <0.001|
| Infusion fluid volume between T1 and T2 (mL) | 550 (344, 810)             | 548 (371, 779)                 | 1.511 | 0.111 |

Data are expressed as n (%) or mean ± standard deviation or median (25–75% interquartile range). Time 1 (T1) was set before norepinephrine dosage was adjusted and Time 2 (T2) was set after norepinephrine dosage was adjusted. HR: Heart rate; CVP: Central venous pressure; MAP: Mean arterial pressure; NE: Norepinephrine; SOFA: Sequential organ failure assessment.
above 65 mmHg was fulfilled in patients requiring vasopressors including NE. We show that in both NE dosage increase and decrease groups, CVP level was negatively correlated with the clearance of lactate with septic shock, while dMAP was positively correlated with the clearance of lactate with septic shock. We also found that among the four groups divided based on their CVP and dMAP values; group LC HM and group HC HM had reduced lactate level when the NE dosage was decreased. Although both increase and decrease in the NE dosage showed increased lactate level in group HC LM, the effect was more severe upon increase in NE dosage.

Sepsis is characterized by a complex combination of cardiovascular derangements, including vasodilatation, hypovolemia, myocardial depression, and altered microvascular flow. [11,12] Vasopressors are used to improve tissue perfusion pressure, while avoiding excessive vasoconstriction in sepsis and septic shock. [13,14] NE is a commonly used vasopressor agent in septic shock. Its strong alpha-adrenergic properties make it a very effective vasopressor agent, and is considered the first vasopressor of choice. [15,16] It is also a key vasoactive agent recommended for restoring MAP in the treatment of septic shock, and it not only performs as a vasopressor but also affects pre-load and tissue perfusion. [17,18]

Increasing the dosage of NE significantly augments cardiac output by 11% to 17%, suggesting that NE might recruit blood from the large venous unstressed volume as a method of "endogenous fluid challenge." [19]

Studies show that increasing the dosage of NE is associated with increases in cardiac output, oxygen delivery, and SvO2. [20] During sepsis, which is characterized by relative cardiac depression, the increase in cardiac output could be explained by the beta-1 adrenergic action of NE. [21,22] Although some studies do not show improved outcome when a higher blood pressure is achieved, other studies show that a lower mean blood pressure is associated with a higher incidence of renal failure. [4,23] However, it is unclear if vasoconstriction is deleterious for microcirculation. In addition, our results expand previous knowledge by addressing the variation in the usual blood pressure target in individuals.

MAP is a surrogate for systolic and diastolic blood pressures and systemic vascular resistance. An adequate MAP is typically essential to restore effective perfusion pressure and organ perfusion in septic shock patients. On the contrary, CVP is surrogate for volume status and right ventricular function. Thus, we selected these two parameters together as a guide to further set the reference standard for patients.

Table 3: Linear regression for the baseline characteristics to the changes in lactate.

| Variables at T1         | NE dosage increase group |               |               |               | NE dosage decreases group |               |               |               |
|-------------------------|--------------------------|---------------|---------------|---------------|---------------------------|---------------|---------------|---------------|
|                         | Coefficient             | 95% CI        | P             | Coefficient   | 95% CI                    | P             |               |               |
| CVP                     | 0.132                    | 0.075 to 0.190| 0.000         | 0.083         | 0.048 to 0.118            | 0.000         |
| Heart rate              | 0.007                    | -0.003 to 0.18| 0.172         | 0.001         | -0.006 to 0.007           | 0.777         |
| SAP                     | -0.018                   | -0.028 to -0.009| 0.000         | -0.008        | -0.014 to -0.002          | 0.007         |
| MAP                     | -0.035                   | -0.049 to -0.021| 0.000         | -0.012        | -0.018 to -0.006          | 0.000         |
| DAP                     | -0.032                   | -0.048 to -0.016| 0.000         | -0.017        | -0.027 to -0.007          | 0.001         |
| dMAP                    | -0.021                   | -0.033 to -0.008| 0.001         | -0.013        | -0.017 to -0.009          | 0.002         |
| ScvO2                   | -0.029                   | -0.044 to -0.013| 0.000         | -0.011        | -0.022 to 0.000           | 0.035         |
| Pcv-aCO2                | 0.046                    | 0.007 to 0.084| 0.019         | 0.012         | -0.011 to 0.035           | 0.315         |
| PI                      | -0.452                   | -0.719 to -0.185| 0.001         | -0.002        | -0.086 to 0.082           | 0.964         |
| pHa                     | -0.2478                  | -4.580 to -0.375| 0.021         | -4.269        | -5.934 to -2.604          | 0.000         |
| SBE                     | -0.043                   | -0.077 to -0.009| 0.012         | -0.026        | -0.050 to -0.002          | 0.031         |
| Cv-aCO2/Da-vO2 ratio    | 0.056                    | -0.033 to 0.145| 0.217         | 0.000         | -0.028 to 0.026           | 0.959         |

CVP: Central venous pressure; Cv-aCO2/Da-vO2 ratio: The venous-to-arterial CO2 to arterial-venous O2 content difference ratio; DAP: Diastolic arterial pressure; dMAP: Difference between usual MAP and MAP; MAP: Mean arterial pressure; Pcv-aCO2: The central venous-to-arterial CO2 partial pressure difference; PI: Pulse pulsation index; SAP: Systolic arterial pressure; SBE: Standard base excess; ScvO2: Central venous oxygen saturation.
Our research differs from previous studies in that we did not focus on the specific hemodynamic targets of septic shock resuscitation, such as CVP, ScvO₂, and MAP. The purpose of our research was how to make the next recovery decision based on the values of the hemodynamic parameters. As specific target parameter values cannot help us to make the correct treatment choice, some studies obtain the MAP target values only through adjusting the NE dosage. The Surviving Sepsis Campaign guidelines do not provide clinicians with clear recommendations on MAP, CVP targets, parameter-specific numerical reference values to guide recovery, and improve prognosis.

After the initial resuscitation, we divided the septic shock patients based on their CVP values and the difference between usual MAP and the MAP at T1 into four subgroups. We then compared the effect of increasing or decreasing the NE dosage strategy. In group LC HM, CVP was <10 mmHg and MAP was higher than usual. Here, decrease in NE dosage decreased lactate level accompanied by a significant decrease in HR, while the ScvO₂ decreased in NE increase group. In Group HC HM, CVP was higher than 10 mmHg and MAP was higher than usual. Here, decrease in NE dosage decreased lactate level, HR, and CVP. Thus based on these results in the above two conditions, decreased NE dosage could be employed. In group LC LM, CVP was lower than 10 mmHg and MAP lower than usual. In this subgroup, neither increase nor decrease in NE dosage dictated dLac. In this condition, more parameters are needed to help determine the next recovery decision. In group HC LM, CVP was higher than 10 mmHg and MAP lower than usual. In this subgroup, both increase and decrease in NE dosage led to increase in lactate, but the increase was more severe in the NE increase dosage group. Thus, increasing NE dosage in this condition could worsen the patient condition. We use emoticons as markers to make a schematic of the results [Supplementary Figure, http://links.lww.com/CM9/A36].

Although we sampled a relatively large cohort, but it was a single center retrospective design, and all patients followed similar basic treatment based on local protocol concerning antibiotics, steroids, and mechanical ventilation. Based on the guidelines, we chose lactate removal as an indication of improvement in tissue perfusion, as a sepsis is associated with difference in microcirculation. However, we need to perform prospective studies to monitor changes in microcirculation to confirm our conclusions.

Conclusions

In this observational retrospective study, we found that after patients with septic shock (Sepsis-3) were resuscitated to reach the initial recovery target goals, CVP and the difference between usual MAP and the MAP at T1 were significantly related to dLac. Thus, CVP and MAP levels can help the doctors to make the next decision regarding the correct choice to increase or decrease NE dosage.
Table 4: Change in the variables in between NE dosage increase and NE dosage decrease groups.

| Items | NE dosage increase | NE dosage decrease | t     | P    |
|-------|--------------------|--------------------|-------|------|
| Group LC HM |                    |                    |       |      |
| n     | 47                 | 109                |       |      |
| dLac (mmol/L) | 0.2 (–0.2, 0.6)    | –0.2 (–0.6, 0.1)  | 3.367 | <0.001 |
| ScvO₂(T2-T1) (%) | –1.9 (–9.0, 2.7)   | 0.0 (–5.0, 3.5)   | –2.228 | 0.031 |
| Pcv-aCO₂(T2-T1) (mmHg) | –1.0 (–3.5, 3.4)  | 0.0 (–1.9, 2.2)  | –1.030 | 0.213 |
| PI(T2-T1) | –6.8 (–7.0, –6.2) | –6.6 (–7.0, –5.4) | –1.324 | 0.109 |
| Ratio(T2-T1) | –0.01 (–0.08, 0.01) | 0.02 (–0.00, 0.05) | –0.312 | 0.723 |
| HR(T2-T1) (beats/min) | –6.0 (–3.0, 11.0) | –4.0 (–11.0, 3.0) | 2.762 | 0.012 |
| MAP(T2-T1) (mmHg) | –4.0 (–17.0, 0.0) | –3.0 (–12.0, 3.0) | –0.412 | 0.611 |
| CVP(T2-T1) (mmHg) | 0.0 (–1.0, 2.0) | 0.0 (–1.0, 2.0) | 0.912 | 0.366 |
| Group HC HM |                    |                    |       |      |
| n     | 131                | 186                |       |      |
| dLac (mmol/L) | 0.0 (–0.5, 0.9)    | –0.2 (–1.0, 0.2)  | 3.668 | 0.001 |
| ScvO₂(T2-T1) (%) | –0.7 (–7.0, 6.5)   | 2.0 (–5.4, 8.5)   | –1.189 | 0.287 |
| Pcv-aCO₂(T2-T1) (mmHg) | –0.1 (–3.0, 2.0)  | 0.0 (–3.0, 2.2)  | –1.478 | 0.128 |
| PI(T2-T1) | –7.0 (–7.1, –6.4) | –6.7 (–7.0, –6.1) | –3.984 | 0.001 |
| Ratio(T2-T1) | –0.01 (–0.05, 0.04) | 0.03 (0.00, 0.05) | –1.109 | 0.234 |
| HR(T2-T1) (beats/min) | 3.0 (–3.0, 10.0) | –3.0 (–11.0, 3.0) | 4.112 | <0.001 |
| MAP(T2-T1) (mmHg) | –9.0 (–18.0, –1.0) | –3.0 (–13.0, 5.3) | –4.098 | <0.001 |
| CVP(T2-T1) (mmHg) | 0.0 (–3.0, 1.0) | –1.0 (–3.0, 0.0) | 4.234 | <0.001 |
| Group LC LM |                    |                    |       |      |
| n     | 128                | 94                 |       |      |
| dLac (mmol/L) | –0.1 (–0.9, 1.2)   | –0.1 (–0.5, 0.4)  | 0.514 | 0.551 |
| ScvO₂(T2-T1) (%) | –1.3 (–8.8, 5.8)   | –0.5 (–8.2, 6.1)  | –1.326 | 0.159 |
| Pcv-aCO₂(T2-T1) (mmHg) | 0.0 (–2.0, 2.5)   | –0.6 (–3.0, 2.0)  | 1.293 | 0.171 |
| PI(T2-T1) | –6.9 (–7.1, –6.3) | –6.8 (–7.0, –6.0) | –0.542 | 0.569 |
| Ratio(T2-T1) | –0.01 (–0.04, 0.02) | 0.02 (–0.01, 0.05) | –0.172 | 0.842 |
| HR(T2-T1) (beats/min) | 5.0 (–1.8, 9.8)   | 0.0 (–14.3, 5.0)  | 4.105 | <0.001 |
| MAP(T2-T1) (mmHg) | 2.5 (–4.8, 11.0) | 10 (2.8, 15.0) | –3.239 | 0.002 |
| CVP(T2-T1) (mmHg) | 0.0 (–1.0, 2.0) | 0.5 (0.0, 1.0) | –1.092 | 0.274 |
| Group HC LM |                    |                    |       |      |
| n     | 294                | 194                |       |      |
| dLac (mmol/L) | 0.4 (–0.1, 2.0)    | –0.1 (–0.7, 0.5)  | 4.278 | <0.001 |
| ScvO₂(T2-T1) (%) | 1.4 (–6.0, 8.0)    | –0.5 (–6.0, 4.8)  | 1.721 | 0.093 |
| Pcv-aCO₂(T2-T1) (mmHg) | –0.8 (–3.3, 2.0)  | 0.0 (–2.0, 2.0)  | –0.931 | 0.393 |
| PI(T2-T1) | –7.0 (–7.2, –6.6) | –6.7 (–7.0, –6.0) | –4.387 | <0.001 |
| Ratio(T2-T1) | –0.01 (–0.06, 0.04) | 0.02 (–0.01, 0.06) | –1.165 | 0.215 |
| HR(T2-T1) (beats/min) | 3.0 (–7.0, 11.0) | –5.0 (–14.0, 3.0) | 4.441 | <0.001 |
| MAP(T2-T1) (mmHg) | –2.0 (–9.0, 9.0) | 5.0 (1.0, 13.3) | –4.780 | <0.001 |
| CVP(T2-T1) (mmHg) | 0.0 (–2.0, 0.0) | –1.0 (–2.0, 0.0) | 3.790 | 0.005 |

Group LC HM (low CVP, high MAP): CVP < 10 mmHg, dMAP > 0 mmHg; Group HC HM (high CVP, high MAP): CVP ≥ 10 mmHg, dMAP ≥ 0 mmHg; Group LC LM (low CVP, low MAP): CVP < 10 mmHg, dMAP ≤ 0 mmHg; Group HC LM (high CVP, low MAP): CVP ≥ 10 mmHg, dMAP < 0 mmHg. Time 1 (T1) was set before norepinephrine dosage was adjusted and Time 2 (T2) was set after norepinephrine dosage was adjusted; Ratio: Cv-aCO₂/Da-vO₂ ratio, the venous-to-arterial CO₂ to arterial-venous O₂ content difference ratio. CVP: Central venous pressure; HR: Heart rate; MAP: Mean arterial pressure; NE: Norepinephrine; PI: Pulse pulsation index; dLac: LactateT2 – lactateT1.

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Conflicts of interest
None.

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