Effects of norepinephrine on hemodynamics, vascular elasticity, cardiac pump function, and inflammatory factors in patients with septic shock

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Abstract
The effects of norepinephrine on hemodynamics, vascular elasticity, cardiac pump function, and inflammatory factors in patients with septic shock remained unknown. In this study, we included 124 cases of severe septic shock patients in our hospital. The patients were randomly divided into control group (treated with dopamine) and experimental group (treated with dopamine plus norepinephrine), while the hemodynamic index (heart rate (HR)), blood vessel elasticity index, heart pump function, and inflammatory factor index were recorded. After 12 h of treatment, both groups showed decreased HR, increased levels of cardiac index (CI), mean arterial pressure (MAP), central venous pressure (CVP), peripheral vascular resistance index (PVRI), and vascular elasticity ($P<0.05$). To date, lower HR, higher levels of CI, MAP, CVP, and PVRI were observed in the experimental group ($P<0.05$). Furthermore, the vascular elastic coefficient, stiffness index, arterial compliance, and the precursors of plasma amino-terminal brain natriuretic peptide were also significantly higher in the experimental group than those in the control group ($P<0.05$). However, inflammatory cell tumor necrosis factor alpha factor test group (TNF alpha), interleukin-1 (IL-1), and interleukin-6 (IL-6) concentrations were significantly lower than the control group ($P<0.05$), compared to experimental group ($P<0.05$). This research indicates that phenylephrine could significantly improve hemodynamics in patients with severe septic shock, by maintaining blood vessel elasticity, improving heart pump function, and reducing the inflammatory factors' activities, and this method could be used as a line of vascular tension of the medications used in patients with septic shock.

Keywords
heart pump function inflammation factor, hemodynamics, norepinephrine, septic shock, vascular elasticity

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Introduction
The incidence of septic shock is gaining an increase of about 9.0% per year. As known to all, septic shock is a sepsis syndrome caused by the products of microorganisms and their toxins. Among these inducers, Gram-negative bacteria are most likely to cause septic shock. The blood circulation would be invaded by the microorganisms and their toxins in the affected parts, and then, the host's various cells and humoral systems are to be activated. The cytokines and mediators are rapidly produced afterwards and thus affecting the blood reperfusion by influencing the tissues, organs, and systems, thereby leading to the ischemia hypoxia as well as metabolic dysfunction. Organ failure is the most severe periods in the process of septic shock.
Septic shock is usually accompanied by abnormal tissue and organ perfusion. Maintaining the normal blood pressure is the key to treating such diseases. In addition, vasoactive drugs should be used to maintain the vascular elasticity to maintain the normal physiological functions of blood vessels. Many unfavorable effects might be brought about once the vascular elasticity has been decreased, such as reducing the capacity of the vascular system to pump blood to the heart. The precursor of brain natriuretic peptide (BNP) is the amino-terminal pro-brain natriuretic peptide precursor (NT-pro BNP), and the NT-pro BNP is more sensitive than BNP in body. At present, during the early clinical treatment of septic shock, the main choices are involved with boosting pressure and ensuring organ perfusion. The first choice for severe septic shock is noradrenaline, but its safety and clinical efficacy are controversial. In this study, the effects of norepinephrine on hemodynamics, vascular elasticity, cardiac pump function, and inflammatory factors in patients with septic shock were studied. The details were roughly shown as follows.

### Data and method

#### Subjects

A total of 124 cases of patients with severe septic shock enrolled from September 2016 to September 2017 were randomly divided into the control group and experimental group according to the method of random number table, with 62 cases in each group. There were 20 females and 42 males in the experimental group, aged from 26 to 80 (65.13 ± 3.42 years). However, 18 females and 44 males were involved in the control group, whose ages were ranged from 24 to 79 (66.09 ± 2.19 years). There was no significant difference in the general data such as gender and age between the two groups (P > 0.05), indicating that this study was comparable (Table 1). To date, all subjects gave informed, signed consent to participate in the study, or in the case of children or deceased, informed written consent was given by the family or guardian.

#### Inclusion and exclusion criteria

**Inclusion criteria.** All patients should have a history of infection and be accompanied with fever, whose systolic blood pressure should be lower than 90 mmHg. Besides, disorders in the tissue microcirculation should be clearly diagnosed. Namely, the criteria for the diagnosis of septic shock in the Guidelines for Treatment of Severe Sepsis and Septic Shock in China should be met. The patients were all adults with independent decision-making ability. An informed consent form should be signed. Besides, the subjects should be treated according to the agreed experimental protocol after gaining the agreement from their family members and themselves. The whole treatment process was approved and supervised by the Medical Ethics Committee of our hospital.

**Exclusion criteria.** Patients who were diagnosed with diabetes, autoimmune diseases, and liver and kidney dysfunction as well as those who were diagnosed with aplastic anemia or leukemia and other hematological diseases were excluded. Apart from this, those who were diagnosed with malignant tumors and multiple organ failure and patients with poor function, myocardial infarction as well as poor compliance were all excluded.

#### Treatments

All the 124 patients involved in the trial were treated with correction of shock. Apart from this, anti-infection and low-flow oxygen therapy were combined as well. Furosemide injection (manufacturer: Guangdong Nanguo Pharmaceutical Co., Ltd.; batch number: national medicine permission number: H44022506) was to be applied
by intravenous drip if the patient was accompanied by edema. Close observation should be conducted, and the recovery condition of the blood volume should be evaluated. Besides, the infusion type and dose were adjusted according to electrolyte levels, and the results were obtained from the blood gas analysis. The specific protocol was as follows: the control group was treated with dopamine hydrochloride for injection (Jilin Jinsheng Pharmaceutical Co., Ltd.; National medicine permission number: H20040214) and was pumped by a central venous pump with an initial dose of 1 μg/kg/min. The dose was adjusted according to the patient’s blood pressure, with a largest dose to be 15 μg/kg/min. Patients in the experimental group were treated with micro-pumping of noradrenaline (manufacturer: Shandong Xinhua Pharmaceutical Co., Ltd.; batch number: national medicine permission number: H37020634) on the basis of the control group with an initial dose of 0.05 μg/kg/min, with a highest dose to be 15 μg/kg/min to maintain the normal status of the mean arterial pressure (MAP).

Clinical observation indexes

Hemodynamics

12 h after treatment, the main hemodynamic data in the supine respiratory positions were monitored before and after administration. Digital non-invasive hemodynamic monitoring system was applied, and the monitoring indicators included heart rate (HR), cardiac index (CI), MAP, peripheral vascular resistance index (PVRI), and central venous pressure (CVP).

Vascular elasticity

The Color Doppler Ultrasound Diagnostic System (XUZHOU Dawei Portable Color Doppler Ultrasound DW-PF522) was used to monitor the elasticity index of the carotid artery 12 h after treatment, including the arterial compliance (AC), stiffness index (β), as well as the elasticity modulus (Ep).

Cardiac pump function

The plasma NT-pro BNP levels were monitored using enzyme-linked immunosorbent assay (ELISA) 12 h after the treatment.

Inflammatory factors

12 h after treatment, various inflammatory markers, such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6), were measured.

Statistical analysis

SPSS 22.0 software was used to analyze the data. The enumeration data were presented as the percentage and the χ² test was used at the same time. However, the measurement data were expressed as x ± standard deviation (SD) and t-test was applied for these data. P < 0.05 was considered statistically significant.

Results

Comparison of the hemodynamics in patients of both groups

No significant difference was detected in the levels of HR, CI, MAP, CVP, and PVRI before treatment (P > 0.05). 12 h after treatment, the HR levels in both groups were decreased, and the levels of CI, MAP, CVP, and PVRI were all increased when compared with those before treatment, with the changes more obvious in the experimental group, and difference in the changes after treatment was statistically significant between the two groups (P < 0.05; see Table 2).

Comparison of the arterial vascular elasticity in patients of both groups

No significant difference was found in the arterial vascular elasticity before treatment (P > 0.05). Compared with the control group, the coefficient of vascular elasticity and the AC in the experimental group was significantly increased, and the arterial stiffness index was significantly decreased 12 h after treatment, the difference of which was statistically significant (P < 0.05; Table 3).

Comparison of the cardiac pump function in patients of both groups

12 h after the treatment, the cardiac pump function index was increased in both groups. The NT-proBNP level in the test group (5278.31 ± 1008.01) was higher than that in the control group (4787.31 ± 999.59) pg/mL, and the difference was statistically significant (P < 0.05; see Table 4).
Comparison of the inflammatory factors in patients in both groups

Results obtained 12 h after the treatment in the two groups showed that the TNF-α, IL-1, and IL-6 levels in the control group and the experimental group were decreased compared with those before treatment. Compared with the control group, the decrease in extent mediated by norepinephrine was more obvious than dopamine, indicating that both norepinephrine and dopamine can reduce the early cytokine levels in patients with sepsis shock. Besides, the ability of norepinephrine to improve the inflammatory cytokines was better than dopamine, and the difference was statistically significant ($P < 0.05$; see Table 5).

### Discussion

Septic shock refers to a systemic inflammatory response syndrome that is caused by a highly suspicious focus of infection. Bacteria, fungi, parasites, and viruses all can cause septic shock, but the presence and development of septic shock may not depend on the bacteria and toxins. It is generally believed that septic shock is mainly caused by

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### Table 2. Comparison of the HR, CI, MAP, CVP, and PVRI levels in both groups.

| Groups                  | Case number | HR      | CVP     | MAP     | PVRI    | CI       |
|-------------------------|-------------|---------|---------|---------|---------|----------|
| The experimental group  | 62          |         |         |         |         |          |
| Before treatment        |             | 107.55 ± 12.29 | 6.05 ± 0.72 | 55.39 ± 5.72 | 8.29 ± 1.13 | 2.10 ± 0.22 |
| 12 h after treatment    |             | 85.39 ± 11.73  | 7.21 ± 0.85 | 78.29 ± 8.92  | 12.10 ± 1.41 | 3.28 ± 0.38 |
| t                       | –           | 10.270  | 8.199   | 17.902  | 16.602  | 21.164   |
| p                       | –           | 0.000   | 0.000   | 0.000   | 0.000   | 0.000    |
| The control group       | 62          |         |         |         |         |          |
| Before treatment        |             | 108.39 ± 12.54 | 6.02 ± 0.69 | 53.29 ± 5.80 | 8.26 ± 1.20 | 2.13 ± 0.29 |
| 12 h after treatment    |             | 95.34 ± 11.19 | 6.78 ± 0.82 | 59.20 ± 6.13 | 10.15 ± 1.8 | 2.77 ± 0.30 |
| t                       | –           | 6.113   | 0.533   | 5.514   | 6.879   | 12.077   |
| p                       | –           | 0.000   | 0.000   | 0.000   | 0.000   | 0.000    |

HR: heart rate; CI: cardiac index; MAP: mean arterial pressure; PVRI: peripheral vascular resistance index; CVP: central venous pressure.

### Table 3. Comparison of the coefficients of vascular elasticity, arterial stiffness index, as well as the arterial compliance in both groups.

| Group             | Case number | Ep (kPa)   | $\beta$    | AC (mm²/kPa) |
|-------------------|-------------|------------|------------|--------------|
| The experimental  | 62          | 110.39 ± 18.57 | 6.77 ± 1.02 | 0.71 ± 0.21  |
| t                 | –           | 135.12 ± 19.68  | 5.67 ± 0.89 | 6.398 ± 0.91 |
| p                 | –           | 0.000       | 0.000      | 0.000        |
| The control group | 62          | 126.42 ± 13.69 | 7.21 ± 0.56 | 0.60 ± 0.23  |
| t                 | –           | 135.22 ± 14.57 | 7.53 ± 0.78 | 0.75 ± 0.28  |
| p                 | –           | 3.465       | 2.624      | 3.259        |

AC: arterial compliance.

### Table 4. Comparison of the cardiac pump function in NT-proBNP levels in both groups.

| Group               | Case number | The experimental group | The control group |
|---------------------|-------------|------------------------|-------------------|
| Before treatment    | 62          | (4783.51 ± 999.59)     | (4325.21 ± 1 035.15) |
| 12 h after treatment| 62          | (5278.36 ± 1054.01)    | (4478.32 ± 1208.01) |
| t                   | –           | 2.682                  | 0.757             |
| p                   | –           | 0.008                  | 0.450             |

Comparison of the inflammatory factors in patients in both groups

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excessive inflammation owing to the body’s reactions, while bacteria and toxins are just the triggers of septic shock. Previously, noradrenaline was preferred to maintain the blood pressure. From the Septic Shock Guidelines published in 2014, emerging evidence suggest that norepinephrine could be the first choice as a vasoactive drug. Although no clear clinical guidelines suggest vasoactive drugs for septic shock’s treatment, studies have shown that norepinephrine could help to maintain the balance in the supply and demand of oxygen, which is the main reason why noradrenaline is the first picked medicine in the treatment of septic shock.10

Norepinephrine could not only induce vasoconstriction and increase blood pressure and coronary blood flow by agonizing alpha receptors (α-receptor) but also strengthen myocardial contractility and increase cardiac output by activating beta receptors (β-receptor). And its function depends on the drug dose. Studies have shown that norepinephrine has a protective effect on renal functions.11,12 Consistently, our study showed that norepinephrine can improve the hemodynamics in patients with severe septic shock, maintain the vascular elasticity, improve the cardiac pump functions, and improve the inflammatory factors as well. Furthermore, 124 patients with severe septic shock treated in our research were enrolled, and the hemodynamics, vascular elasticity, cardiac pump function as well as inflammatory factors were determined. Results have shown that norepinephrine was more effective in the treatment of patients with septic shock than dopamine, proving norepinephrine to be a first-choice vasoactive drug which is more suitable for the clinical treatment of septic shock.

### Table 5. Comparison of inflammatory factors in both groups.

| Group          | Case number | Status          | TNF-α        | IL-1         | IL-6         |
|----------------|-------------|-----------------|--------------|--------------|--------------|
| The experimental group | 62          | Before treatment| 48.12 ± 13.24 | 29.43 ± 8.32 | 32.45 ± 10.32 |
|                |             | 12 h after treatment | 42.43 ± 15.34 | 27.74 ± 7.26 | 28.58 ± 8.42 |
| t              | –           |                 | 2.211        | 1.205        | 2.287        |
| P              | –           |                 | 0.028        | 0.230        | 0.023        |
| The control group | 62          | Before treatment| 45.32 ± 14.85 | 30.73 ± 9.25 | 29.54 ± 9.48 |
|                |             | 12 h after treatment | 35.84 ± 14.63 | 25.76 ± 9.39 | 26.74 ± 9.24 |
| t              | –           |                 | 3.580        | 2.968        | 1.665        |
| P              | –           |                 | 0.000        | 0.003        | 0.098        |

TNF-α: tumor necrosis factor-α; IL-1: interleukin-1; IL-6: interleukin-6.

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