doi.org/10.36721/PJPS.2026.39.3.REG.12881.1

Protective effect of pituitrin combined with norepinephrine on cardiopulmonary injury in patients with septic shock diagnosed by critical care ultrasound evaluation

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Abstract: **Background**: Septic shock is a life-threatening complication of sepsis, often accompanied by cardiopulmonary dysfunction, which significantly increases the mortality of patients. Norepinephrine (NE) is a commonly used vasopressor in the treatment of septic shock, but single-drug therapy may not fully achieve cardiopulmonary protection. Antidiuretic hormone (ADH) has potential regulatory effects on hemodynamics and inflammation, but its combined efficacy with NE in cardiopulmonary protection for septic patients remains to be further verified. **Objectives**: This study aims to investigate the effectiveness of ADH combined with NE in providing cardiopulmonary protection for septic patients. **Methods**: A total of 100 patients with septic shock admitted to our hospital from March 2022 to March 2023 were enrolled in this study. They were randomly divided into an observation group and a control group, with 50 patients in each group. The observation group was treated with ADH combined with NE, while the control group received NE monotherapy. Relevant indicators of the two groups were dynamically monitored and compared. **Results**: Statistical analysis showed that tumor necrosis factor-α (TNF-α), cardiac troponin I (cTnI), and brain natriuretic peptide (BNP) had significant differences in group effect, time effect, and interaction effect (P<0.05). Interleukin-1 (IL-1) and interleukin-6 (IL-6) only showed significant time effect (P<0.05), but no significant group effect or interaction effect (P>0.05). Arterial partial pressure of oxygen (PaO_2) and PaO_2/fraction of inspired oxygen (P/F ratio) exhibited significant time effect and group effect (P<0.05), but no significant interaction effect (P>0.05). After treatment (T3), compared with the control group, the observation group had significantly lower levels of TNF-α, IL-1, IL-6, cTnI, BNP, and creatine kinase isoenzyme MB (CK-MB) (P<0.05), and significantly higher PaO_2 and P/F ratio (P<0.05). **Conclusion**: ADH combined with NE can effectively improve the inflammatory response, cardiac and pulmonary function indexes of septic patients, and exert significant cardiopulmonary protection effects. It is a viable and effective therapeutic strategy for septic patients.

Keywords: Critical care ultrasound; Norepinephrine; Pituitrin; Septic shock

Submitted on 15-05-2024 – Revised on 01-11-2024 – Accepted on 01-11-2024

INTRODUCTION

Septic shock is an extremely severe inflammatory disease, typically triggered by infection (Gavelli *et al*., 2021). It is characterized by the onset of systemic inflammatory response syndrome accompanied by multi-organ dysfunction (Oczkowski *et al.,* 2022), which can even be fatal (Srzić *et al.,* 2022). In recent years, the mortality rate of septic shock has declined, yet the medical community faces significant challenges in protecting cardiopulmonary function (Shields *et al.,* 2021). The treatment of septic shock requires comprehensive consideration of multiple factors, including prompt control of the infection source (Teja *et al.,* 2023), suppression of inflammatory responses and support of organ function (Bougouin *et al.,* 2022). The cardiopulmonary system is one of the organ systems most susceptible to impairment in septic shock (Hellman *et al.,* 2021). Dysfunction of the heart and lungs can lead to hemodynamic instability and inadequate oxygenation, thereby affecting overall survival rates. Therefore, the development of more effective cardiopulmonary protection strategies is crucial for the recovery of septic shock patients. Antidiuretic hormone (ADH) plays a vital role in maintaining fluid balance, regulating blood volume and blood pressure (Chu *et al.,* 2021). Norepinephrine (NE) is an important neurotransmitter that belongs to the sympathetic nervous system (Gaskill, 2022). NE influences overall blood circulation and blood pressure by regulating heart function and peripheral vascular tone (Weinberger *et al.,* 2021). Thus, this study endeavors to explore the impact of ADH in conjunction with NE on cardiopulmonary function among severe septic shock patients and assess its protective potential against cardiopulmonary injury. Utilizing ultrasound assessments and other methods, we aim to elucidate the therapeutic value of this combined approach in modulating cardiopulmonary function and enhancing the prognosis of septic shock patients. These findings aim to offer fresh insights and substantial evidence supporting the management of septic shock, offering a potential avenue for tailored treatments based on individual needs.

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MATERIALS AND METHODS

General data

This study adopts a retrospective case-control trial. From October 2022 to March 2023, the patients admitted with septic shock in the hospital's ICU were enrolled in the study. These patients were randomly divided into two groups adhering to block randomization principles: a treatment group and a control group, each consisting of 50 cases. The sample size calculation formula $n=\left(\frac{z_{1-\alpha/2}+z_{1-\beta}}{\delta/\sigma}\right)^2$, with α set at 0.05, β at 0.20, the expected effect size δ at 1.0 and the standard deviation σ at 1.5, yields an n of approximately 97. To ensure an adequate sample size, we have chosen a sample size of 100.

Inclusion criteria

(a) Patients with septic shock aged between 18 and 65; (b) Patients diagnosed with septic shock as evaluated by critical care ultrasound; (c) During admission to the ICU, patients with persistent hypotension (systolic blood pressure <90mmHg or mean arterial pressure <65mmHg) accompanied by elevated blood lactic acid levels (>2mmol/L) required vasoactive drugs to maintain stable circulation (Font *et al.,* 2020); (d) The patient provided informed consent and the study was approved by the ethics committee of our hospital, the ethical batch number is 2024 (17th).

Exclusion criteria

(a) Pregnant or lactating women; (b) Patients with a known history of ADH or NE allergy; (c) Patients with known cardiovascular diseases such as severe arrhythmia, heart failure, and serious myocardial infarction; (d) Patients with known diseases related to NE secretion, such as adrenomedullary tumors and pheochromocytoma; (e) Patients with known severe thyroid dysfunction to avoid interfering with the efficacy ADH; (f) Patients who have been treated with drugs used in similar studies to treat septic shock; (g) Patients who havestable circulation and do not need to continue treatment after receiving cardiopulmonary resuscitation or vasoactive drugs; (h) Patients who have received high-dose epinephrine or ADH without significant effect; (i) Patients known to have severe hepatic impairment or hepatic failure.

Methods

Both groups received standard cluster therapy involving fluid resuscitation and prudent antibiotic administration. Upon admission, the control group underwent treatment with NE administered intravenously via NE Bitartrate Injection (Shanghai Hefeng Pharmaceutical Co., Ltd., H31021177, strength: 1ml: 2mg) at a dosage ranging between 5-15 mg/min. The dosage was adjusted as needed to sustain patients' mean arterial pressure within the range of 65-75 mmHg. Based on the control group, ADH was used in combination with intravenous injection (Chengdu Haitong Pharmaceutical Co., Ltd., H51022068, specification: 1 ml: 6 IU) at a dosage of 0.01-0.03 U/min in the observation group.

Observation indicators

Serum inflammatory, myocardial injury and blood gas analysis indices were assessed at specific intervals: upon admission (T0), at 3 days (T1), 1 week (T2), and 15 days (T3) post-treatment. (a) Serum inflammatory markers: TNF-α, IL-1 and IL-6 plasma levels were measured using fasting venous blood samples collected in the morning. (b) Myocardial injury indicators: CK-MB, cTnI, and BNP concentrations were evaluated. (c) Blood gas analysis indicators: Arterial blood was drawn for analysis to measure lung injury markers, encompassing PaO_2, $PaCO_2$, and the oxygenation index (P/F). Adverse events of patients are directly recorded in electronic health records. Upon receiving an adverse event report, immediate measures should be taken to mitigate any ongoing harm to the patient and prevent similar events from occurring in the future.

Statistical analysis

SPSS 25.0 software facilitated the analysis of data. Measurement data, represented as "$\bar{x}$ ±s" for mean and standard deviation, underwent group t-tests to assess differences between the groups. Count data, including gender and underlying diseases, were expressed as n (%) and compared using the Chi-square test. Two-way analysis of variance (ANOVA) was employed to examine variations in myocardial injury, inflammation and blood gas parameters before and after treatment within and between the groups. In instances where a group or time interaction emerged in the two-way ANOVA, subsequent pairwise comparisons were conducted to identify specific groups or time points displaying differences. Statistical significance was established at $P<0.05$.

RESULTS

Comparison of general data

The analysis indicated no significant differences in age, weight, gender distribution, or history of hypertension and diabetes between the controlgroupand observation group ($P>0.05$).For more detailed insights, please refer to Table1.

Comparison of serum inflammatory indicators at different time points between the controlgroupand observation group

In the comprehensive analysis, TNF-α displayed significance concerning time and group interaction ($P<0.05$), whereas IL-1 and IL-6 exhibited significant differences over time ($P<0.05$). However, there were no significant differences observed in time or interaction between groups for IL-1 and IL-6 ($P>0.05$). Within-group comparisons highlighted notably reduced levels of TNF-α, IL-1, and IL-6 in both groups post-treatment compared to pre-treatment levels ($P<0.05$). In terms of between-group comparisons, the observation group consistently showed

Table 1: Comparison of general data [(x + s), n (%)]

Item	Control group (n=50)	Observationgroup (n=50)	χ^2/t	*P*
Age	50.99±9.54	49.47±9.00	0.819	0.415
Weight	43.2±8.34	44.93±9.34	0.977	0.331
Sex				
Male	25(50.0)	27(54.0)	0.160	0.689
Female	25(50.0)	23(46.0)	0.160	0.689
History of hypertension	24(48.0)	25(40.0)	0.040	0.841
History of diabetes	29(58.0)	30(60.0)	0.041	0.839

Table 2: ANOVA results of differences in serum inflammatory indicators between the control group and observation group ($\bar{x}$+s)

Group	Number of cases	TNF-α(ng/L)			
		T0	T1	T2	T3
Observation group	50	50.65±9.39	33.38±5.19[a]	24.71±4.67[ab]	20.39±4.72[abc]
Control group	50	50.22±8.59	43.67±5.56[ad]	41.23±4.56[abd]	35.37±4.83[abcd]
F inter group, P inter group		274.143, <0.001			
F Time, P Time		240.531, <0.001			
F Interactivity, P Interactivity		14.080, <0.001			
Group	Number of cases	IL-1(ng/L)			
		T0	T1	T2	T3
Observation group	50	30.87±7.52	25.55±7.28[a]	20.47±7.43[ab]	18.57±7.4[ab]
Control group	50	28.93±7.98	25.6±7.69[a]	23.34±7.08[a]	21.33±6.99[ab]
F inter group, P inter group		1.565,0.212			
FTime, PTime		34.385, <0.001			
F inter activity, P inter activity		0.902,0.515			
Group	Number of cases	IL-6(ng/L)			
		T0	T1	T2	T3
Observation group	50	31.1±8.16	25±8.68[a]	18.02±8.94[ab]	17.02±8.86[ab]
Control group	50	28.22±8.39	25.87±8.69	20.77±9.08[ab]	19.69±9.12[ab]
F inter group, Pinter group		0.938,0.333			
F Time, PTime		36.433, <0.001			
F inter activity, P inter activity		0.840,0.567			

Note: a, b and c indicate that $P<0.05$ compared with T0, T1 and T2 within the same group, respectively; d indicates that $P<0.05$ compared between groups in the same period.

significantly lower TNF-α levels than the control group at T1, T2, and T3 ($P<0.05$). However, there were no significant disparities between the control and observation groups for IL-1 and IL-6 levels at each time point ($P>0.05$). For more detailed insights, please refer to Table 2 and Fig. 1.

Comparison of myocardial injury indicators at different time points between the control group and observation group

In the comprehensive analysis, cTnI and BNP showed significant variations concerning both time and group interaction ($P<0.05$), while CK-MB displayed significant differences over time and in the interaction between the control group and observation group ($P<0.05$). However, there was no notable variance in the interaction between groups for CK-MB ($P>0.05$). Within each group, CK-MB levels notably decreased with the extension of treatment duration ($P<0.05$). Conversely, cTnI and BNP levels exhibited a significant increase after T1, T2, and T3 compared to pre-treatment levels ($P<0.05$). When comparing between the control group and observation group, the observation group consistently demonstrated significantly lower levels of CK-MB, cTnI and BNP than the control group at T1, T2, and T3 ($P<0.05$). For more detailed insights, please refer to Table 3 and Fig. 2.

Table 3: Results of analysis of variance for differences in myocardial injury indicators between the control group and observation group ($\bar{x}$+s).

Group	Numbe rof cases	CK-MB (U/L)			
		T0	T1	T2	T3
Observation group	50	43.43±11.69	30.6±11.61[a]	22.65±11.59[ab]	17.66±11.47[abc]
Control group	50	45±10.8	35.02±10.83[ad]	30.16±10.94[abd]	28.26±10.95[abd]
F inter group, P inter group		28.362, <0.001			
F Time, P Time		68.297, <0.001			
F Interactivity, P Interactivity		1.112,0.354			
Group	Number of cases	cTnI (ug/L)			
		T0	T1	T2	T3
Observation group	50	1.12±0.32	2.09±0.57[a]	2.6±0.57[ab]	1.12±0.33[bc]
Control group	50	1.04±0.29	3.04±0.59[ad]	4.05±0.59[abd]	2.04±0.31[abcd]
F inter group, P inter group		298.236, <0.001			
F Time, P Time		457.896, <0.001			
F inter activity, P inter activity		17.520, <0.001			
Group	Number of cases	BNP (ug/L)			
		T0	T1	T2	T3
Observation group	50	1.05±0.22	3.66±0.7[a]	3.08±0.6[ab]	2.07±0.6[abc]
Control group	50	0.98±0.22	4.92±0.67[ad]	3.98±0.63[abd]	2.97±0.63[abcd]
F inter group, P inter group		173.094, <0.001			
F Time, P Time		620.769, <0.001			
F inter activity, P inter activity		9.463, <0.001			

Note: a, b and c indicate that $P<0.05$ compared with T0, T1 and T2 within the same group, respectively; d indicates that $P<0.05$ compared between groups in the same period.

Comparison of blood gas analysis indicators at different time points between the control group and observation group

The comprehensive analysis revealed no significant differences in $PaCO_2$ concerning time or group interaction ($P>0.05$). However, significant variations emerged over time and in group interaction for PaO_2 and P/F ($P<0.05$), although lacking such distinctions in group interaction ($P>0.05$). PaCO2 levels within each group remained stable across different time points ($P>0.05$). Notably, PaO_2 decreased significantly after T1 and T2 compared to pre-treatment levels ($P<0.05$), yet remarkably increased after T3 ($P<0.055$).

Conversely, the control group displayed a significant decrease in P/F after T1, T2, and T3 ($P<0.05$). Contrastingly, the observation group showed a significant drop after T1, no significant change after T2, but a substantial rise after T3. The inter group comparison highlighted that the PaO2 levels in the observation group were significantly higher than those in the control group at T1, T2, and T3 ($P<0.05$). However, no significant differences emerged in $PaCO_2$ and P/F between the two groups at each time point ($P>0.05$). Additional details are available in Table 4.

DISCUSSION

Septic shock stands as a severe infectious condition marked by the continued presence of systemic inflammatory response syndrome (Sedhai*et al*., 2022), often leading to multiple organ dysfunction. Sepsis often stems from bacterial, fungal, or other microbial infections (Fage *et al*., 2023). This triggers an exaggerated immune system response, leading to the release of diverse inflammatory mediators within the body. Consequently, this cascade of inflammatory responses induces severe abnormalities in the circulatory system and damage to organ functions (Ling *et al*., 2021). Septic shock is a serious complication of sepsis, manifested as hypotension (Ge *et al*., 2021), heart failure, multiple organ dysfunction and other symptoms (Fitzgerald, 2021). Its condition deteriorates rapidly (Kang *et al*., 2022), and it is a life-threatening disease state. The escalating incidence of sepsis is thought to correlate with several factors, including widespread antibiotic misuse (Garcia *et al*., 2022), rising microbial resistance (Yue *et al*., 2022), and prolonged periods of immobility (Garbero*et al*., 2021). Due to its multifaceted pathogenesis and symptoms mirroring other illnesses, diagnosing and treating sepsis pose considerable challenges.

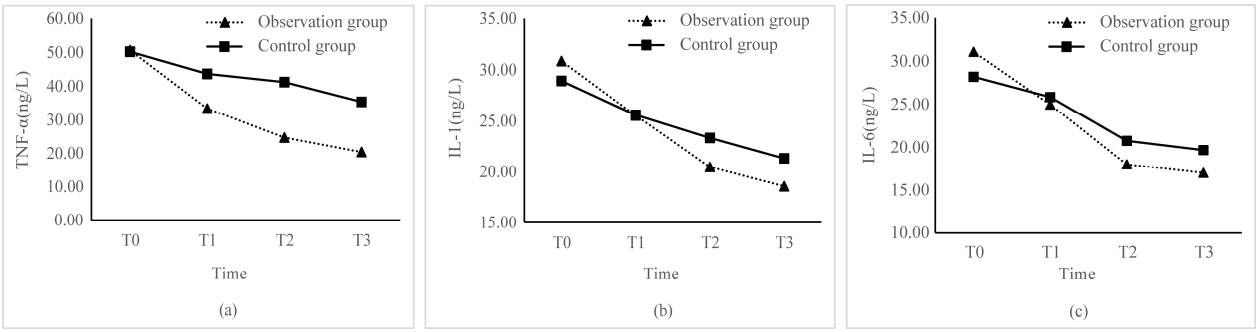

Fig.1: Changes of serum inflammatory indicators
Note: Figure 1(a) represents TNF-α level, (b) represents IL-1 level and (c) represents IL-6 level.

Table 4: Results of variance analysis for differences in blood gas analysis indicators between the two groups ($\bar{x}$+s)

Group	Number of cases	PaO2(mmHg)			
		T0	T1	T2	T3
Observation group	50	70.45±9.06	60.41±9.98a	65.58±10.27ab	75.64±10.31abc
Control group	50	67.52±8.87	56.09±9.79ad	60.16±10.47abd	68.05±10.45bcd
F inter group, P inter group		25.752,<0.001			
F Time, P Time		37.436,<0.001			
F inter activity, P inter activity		0.364,0.939			
Group	Number of cases	PaCO2(mmHg)			
		T0	T1	T2	T3
Observation group	50	39.89±8.63	39.89±8.85	41.82±8.49	40.36±9.4
Control group	50	40.61±8.26	39.62±8.39	42.56±8.1	38.25±8.84
F inter group, P inter group		0.070,0.791			
F Time, P Time		2.139,0.095			
F inter activity, P inter activity		0.223,0.987			
Group	Number of cases	P/F(mmHg)			
		T0	T1	T2	T3
Observation group	50	231.61±48.02	201.46±48	221.15±48.32	251.56±47.85
Control group	50	235.4±49.55	180.21±36.05	202.68±48.18	215.49±65.59
F inter group, P inter group		13.047,<0.001			
F Time, P Time		16.848,<0.001			
F inter activity, P inter activity		1.022,0.419			

Note: a, b and c indicate that P<0.05 compared with T0, T1 and T2 within the same group, respectively; d indicates that P<0.05 compared between groups in the same period.

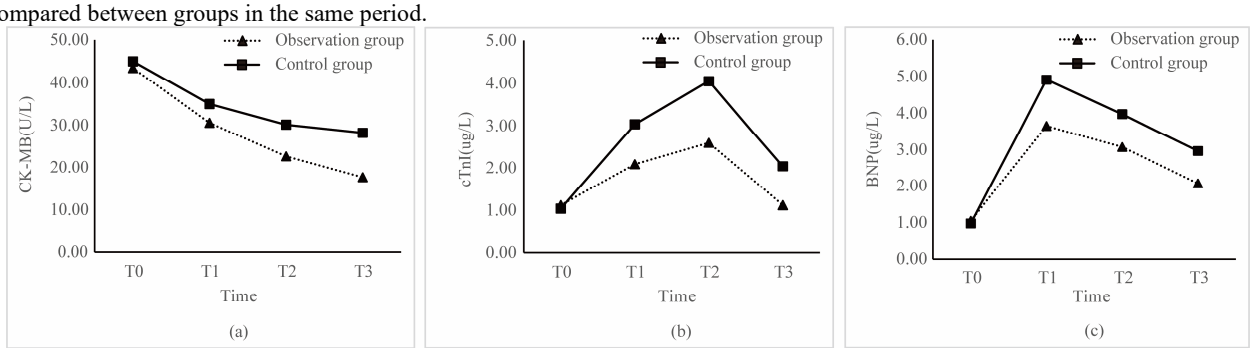

Fig. 2: Changes of myocardial injury indicators
Note: Figure 2(a) shows CK-MB level, (b) cTnI level and (c) BNP level.

Hence, precise early diagnosis and prompt intervention hold paramount importance. The assessment through critical care ultrasound is notable for its significant benefits in both diagnosing and treating sepsis (Sweeney *et al*., 2021). Critical care ultrasound is used to observe and evaluate the condition of patients' internal organs through ultrasonic technology. It can quickly and non-invasively evaluate the function and structure of vital organs such as heart, lungs and blood vessels and provide real-time information (Lim *et al*., 2021). In patients with sepsis, critical care ultrasound evaluation can help physicians detect problems such as abnormal cardiac function, pulmonary effusion and hemodynamic disorders earlier, thus better guiding treatment and intervention (Kattan *et al*., 2022).

The real-time and dynamic capabilities of ultrasound technology enable ongoing monitoring of treatment effects and facilitate the prompt detection and management of potential complications. This technology's agility allows for timely responses, ensuring effective interventions as needed during treatment.

Septic shock is a serious infectious disease and its pathophysiological processes include the release of inflammatory factors, vasodilation, increased vascular permeability and disorders of the circulatory system. This series of reactions forms a waterfall chain reaction that leads to multiple organ impairment (Jozwiak, 2022). After treatment, the observation group displayed notably lower TNF-α levels compared to the control group (P<0.05). Additionally, there was a moderate reduction in IL-1 and IL-6 levels when compared to the control group. These findings indicate that the combination therapy of ADH and NE effectively suppresses inflammatory responses, ultimately improving the therapeutic results for patients with sepsis. Previous research has indicated that ADH can curb the inflammatory response through diverse mechanisms, such as hindering inflammatory cell activation and migration, as well as reducing the release of inflammatory mediators. Additionally, ADH can modulate immune cell function, notably reducing serum TNF-α expression levels (Kotani *et al*., 2023).NE can reduce the release of inflammatory mediators by reducing immune cell activation and cytokine production (Fanelli *et al*., 2021). In addition, NE may reduce the leakage of inflammatory cells through regulation of vascular tone and effectively lower the levels of IL-6 and IL-10.

Compared with NE alone, ADH (antidiuretic hormone, oxyvasopressin) has certain anti-inflammatory and immunomodulatory effects (Kattan *et al*., 2023), which can affect the release of immune cells and inflammatory factors through various pathways (Liu *et al*., 2022). ADH has been associated with inhibiting the production and release of inflammatory mediators such as TNF-α, IL-1, and IL-6. Its known ability to modulate immune cell activation and hinder the movement of inflammatory cells contributes to a potential decrease in inflammatory responses. In addition, it may regulate the function of immune cells by affecting cytokine production and cell surface receptor expression. The combination of ADH and NE produces synergistic effects in immune and inflammatory regulation (Guedes *et al*., 2022). The anti-inflammatory effect of ADH helps to reduce the release of inflammatory mediators, while NE can alleviate the over activation of immune cells. These pathways often work in tandem, potentially reinforcing one another's actions. Their combined effect tends to curb immune cell activation and limit the release of inflammatory mediators, collectively contributing to a decrease in the intensity of the inflammatory response (Pak *et al*., 2022).

Septic shock is a serious infectious disease, and its pathophysiological process can cause significant damage to the cardiopulmonary system. Septic shock can lead to a systemic inflammatory response, which affects the function of the cardiopulmonary system. Vasodilation and increased vascular permeability may cause circulatory problems such as hypovolemia and hypotension and affect the contractility and cardiac output of the heart (Ranjit *et al*., 2023). On the pulmonary side, inflammatory reactions may lead to lung tissue edema and imbalance of alveolar surfactants, which in turn affect gas exchange and respiratory function (Jouffroy *et al*., 2022). In septic shock, abnormalities of the circulatory system may lead to myocardial oxygen deficiency and cause cardiomyocyte damage, resulting in elevated cTnI and CK-MB levels. BNP is a cardiac hormone that is increased in release when the heart is damaged or stressed. In septic shock, disturbances of the circulatory system may lead to increased cardiac stress (Al-Husinat *et al*., 2023), thus triggering an increase in BNP reflecting cardiac functional impairment. In animal models, the application of ADH helps maintain cardiovascular stability, improve cardiac contractility and reduce pulmonary edema (Chua *et al*., 2022). NE's potential to enhance blood flow and maintain organ perfusion by increasing vascular tone has been noted (Xu *et al*., 2022). After treatment at T3, the study demonstrated significantly reduced levels of CK-MB, cTnI, and BNP in the observation group in contrast to the control group (P<0.05). These findings emphasize the effectiveness of combining ADH with NE in protecting myocardial health. Additionally, following T3 treatment, the observation group displayed notably elevated PaO2 and P/F levels compared to the control group, signifying the efficacy of ADH and NE in stabilizing blood gases and improving pulmonary function (P<0.05).

The Monnet study also pointed out that the combination of ADH and NE can effectively improve patients' lung function and reduce the 28 day mortality rate (Monnet *et al.,* 2023). Analyzing these findings, it's plausible that ADH and NE alleviate myocardial and pulmonary

damage by modulating inflammatory and immune responses. Their combined action may synergistically inhibit the release of inflammatory mediators and diminish immune cell activity, thereby reducing the severity of cardiopulmonary injury (Larsen *et al*., 2021). In addition, ADH may play a role by regulating body fluid balance and maintaining circulatory stability, while NE may maintain the circulatory system through increased vascular tone and cardiac output (Bakker, 2021). ADH and NE have different mechanisms of action in the cardiovascular and respiratory systems. The combined use of these two drugs may produce synergies that may help reduce the degree of myocardial and pulmonary damage. Thus, it protects the heart muscle and lungs more comprehensively.

CONCLUSION

The study findings support the effectiveness of combining ADH with NE in patients with severe septic shock, particularly in protecting against cardiopulmonary injury. The primary conclusions highlight: 1) the significant impact of this combination on stabilizing circulation, increasing cardiac index, reducing cardiopulmonary injury and alleviating organ damage; 2) ultrasound evaluation improves accurate cardiopulmonary diagnosis, enabling early treatment and enhancing recovery chances; 3) this treatment reduces immune-inflammatory response, organ dysfunction, and improves hemodynamic stability, lowering mortality. In summary, the combination of ADH and NE is a highly effective therapeutic approach for severe septic shock, particularly in fortifying cardiopulmonary protection, offering vital insights for clinical application. However, in actual clinical practice, the dosage, administration method, and timing of ADH and NE may vary depending on individual patient differences. Therefore, further research and large-scale clinical trials should be conducted to verify the long-term efficacy and safety of the combination therapy of ADH and NE, as well as its applicability in different patient populations.

Acknowledgments
We acknowledge the guidance provided by the Ethics Committee of Affiliated Hospital of Nantong University and Yancheng Dafeng People's Hospital regarding the ethical review of this study. We are grateful for the substantial support from all medical staff of the Department of Emergency, Affiliated Hospital of Nantong University, and the Department of ICU, Yancheng Dafeng People's Hospital, in patient recruitment, data collection and clinical sample processing. We also acknowledge the voluntary participation of all patients and their families in this study. Additionally, we appreciate the academic support provided by the graduate education team of the Medical School of Nantong University during the research process.

Authors' contributions
Henghao Cui was responsible for the conception and design of the study, data collection, statistical analysis, and drafting of the manuscript; Xiaochun Yuan participated in the performance of experiments, collection of clinical samples, and verification of experimental data; Kai Lu assisted with patient recruitment, sorting of clinical data, and preliminary data analysis; Wenxiao Yan conducted literature review, revision of the manuscript, and supplementary academic content; Zhongwei Huang supervised the entire research process, performed critical revision of the manuscript for important intellectual content, and gave final approval of the published version. All authors have read and approved the final manuscript.

Funding
This study received no specific funding from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability statement
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethical approval
Ethical Committee Yancheng Dafeng People's Hospital, Ethical approval Number 2024 ("17th")

Conflict of interest
The authors report there are no competing interests to declare.

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