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Central Venous-to-Arterial Carbon Dioxide Difference ($Pcv\text{-}aCO_2$ gap) Guided Resuscitation in Patients with Septic Shock: A Pilot Randomized Controlled Trial

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Research Article

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ABSTRACT

Objective: The treatment approach for septic shock patients with elevated $Pcv\text{-}aCO_2$ and no volume response is controversial. This study aimed to explore the use of inotropes to reduce $Pcv\text{-}aCO_2$ and improve tissue perfusion.

Method: Single-center, open-label, randomized clinical trial. $Pcv\text{-}aCO_2$ was measured 3 hours after ICU admission, and eligible patients were randomly assigned to the milrinone or conventional therapy group. Milrinone patients without volume responsiveness received milrinone intervention, while the conventional therapy group received treatment per 2016 SSC guidelines, using other inotropes if necessary.

Results: 51 Patients were analyzed. At 6h post-ICU admission, 46.15% (12/26) of milrinone patients had $Pcv\text{-}aCO_2 \geq 6$ mm Hg, compared to 80% (20/25) in the conventional therapy group. There was a significant difference between the groups (p=0.012). The $Pcv\text{-}aCO_2$ levels were 6.07 ± 2.11 mm Hg and 7.25 ± 1.80 mm Hg in the milrinone and conventional therapy groups, respectively, with a significant difference (p=0.037). Milrinone patients exhibited higher cardiac output (4.38 L/min (3.98-5.28) *vs*. 3.98 L/min (3.46-4.72), p=0.043) and a higher lactate clearance rate compared to the conventional therapy group.

Conclusion: Early intervention with milrinone in septic shock patients with no fluid responsiveness after adequate fluid resuscitation can increase cardiac output and lactate clearance rate, and reduce levels of inflammatory factors.

Keywords: Septic shock; $Pcv\text{-}aCO_2$; Tissue perfusion; Mortality; Milrinone

Abbreviations: SOFA: Sequential Organ Failure Assessment; APACHE II: Acute Physiology and Chronic Health Evaluation II; MAP: Mean Arterial Pressure: CVP: Central Venous Pressure; CK-MB: Creatine Kinase Isoenzyme; Pcv-Aco_2: Central Venous-To-Arterial Carbon Dioxide Difference; $Scvo_2$: Central Venous Oxygen Saturation; LVEF: Left Ventricular Ejection Fraction; Lac: Lactic Acid; IL-6: Interleukin-6; ICU: Intensive Care Unit; MV: Mechanical Ventilation; CRRT: Continuous Renal Replacement Therapy; IL-6: Interleukin-6; CO: Cardiac Output; CI: Cardiac Index; SV: Stroke Volume; SVI: Stoke Volume Index; CFI: Cardiac Function Index; MAP: Mean Arterial Pressure; SVRI: Systemic Vascular Resistance Index; GEDVI: Global End Diastolic Volume Index; EVLWI: Extravascular Lung Water Index.

INTRODUCTION

Sepsis is a life-threatening organ dysfunction caused by impaired host response to infection [1]. Septic shock is the most serious type of sepsis and is the fourth leading cause of death worldwide [2]. Septic shock is associated with insufficient tissue perfusion due to ischemia and hypoxia. Therefore, active fluid resuscitation, increase in cardiac output, and improvement of tissue perfusion are crucial interventions for patients with septic shock.

Currently, one of the clinical treatment options for patients with septic shock is aggressive fluid therapy, which aims to restore normal tissue perfusion [2]. In 2021, Rivers et al., proposed the concept of "early goal-directed therapy" [3]. Since then, central venous oxygen saturation ($ScvO_2$) has been utilized as one of the indicators of adequate tissue perfusion in patients with septic shock. However, correction of $ScvO_2$ to the normal range does not guarantee the absence of tissue hypoperfusion [4,5]. To improve the monitoring of tissue perfusion in patients with septic shock, the central venous-to-arterial carbon dioxide difference (Pcv-aCO_2) has been suggested as an indicator of tissue perfusion following resuscitation intervention [6]. The arteriovenous difference in the partial pressure of carbon dioxide represents the disparity between central venous and arterial carbon dioxide levels, which is typically <6 mm Hg under normal physiological conditions [7]. The arteriovenous carbon dioxide partial pressure difference has been linked to the development of microcirculatory disorders [8]. In patients with septic shock undergoing early fluid resuscitation, a persistently elevated arteriovenous carbon dioxide partial pressure difference suggests a poor prognosis [9,10].

Furthermore, according to the Fick principle, Pcv-aCO_2 values can reflect the circulating blood volume and tissue perfusion of the body [11]. A study comparing the effects of hypoxic hypoxia and hematogenous hypoxia on Pcv-aCO_2 levels demonstrated that Pcv-aCO_2 increased under ischemic conditions but not under hypoxic conditions [12]. In addition, several studies have shown that Pcv-aCO_2 is negatively correlated with Cardiac Output (CO) and can serve as a marker of adequate cardiac output in patients with severe sepsis [6,10] Reduced cardiac output, inadequate effective circulating blood volume, and CO_2 stagnation can also lead to elevated Pcv-aCO_2 levels. Anaerobic metabolism under hypoxia leads to the production of acidic products, which further decreases myocardial contractility. These acidic byproducts can also weaken myocardial contractility, exacerbating microcirculatory disorders and increasing Pcv-aCO_2 levels. Therefore, Pcv-aCO_2 levels can reflect not only cardiac output and tissue microcirculatory perfusion but also the balance of tissue oxygen supply and demand, thus objectively indicating the status of tissue oxygen metabolism. During resuscitation from septic shock, it has been shown that Pcv-aCO_2 levels are closely correlated with Cardiac Index (CI). Notably, Pcv-aCO_2 levels can be reduced by changing cardiac output [13]. According to the septic shock guidelines, early fluid resuscitation is the primary treatment to improve the metabolic state and tissue cell perfusion and to correct microcirculatory disorders and abnormal blood flow distribution. However, the current treatment options for septic shock patients with elevated Pcv-aCO_2 and no response to aggressive fluid resuscitation remain controversial. Our study aimed to guide the use of positive inotropic drugs in patients with septic shock based on Pcv-aCO_2 levels, to provide a new treatment option for septic shock patients who are not volume-responsive and have inadequate perfusion.

MATERIALS AND METHODS

Trial design and participants

The study was a prospective, open-label, randomized trial. We conducted the study from December, 2020 to December, 2021 in the intensive care medicine department of Northern Jiangsu People's Hospital, Yangzhou, China. According to the definition of septic shock in Sepsis 3.0, it is characterized by persistent hypotension requiring vasopressor therapy to maintain a mean arterial pressure (MAP) ≥ 65 mmHg and a serum lactate level>2 mmol /L despite adequate volume resuscitation. Patients diagnosed with septic shock were resuscitated following the "Surviving Sepsis Campaign (SSC) guidelines of 30 ml/kg crystalloid. Pcv-aCO_2 was measured at 3 hours after admission to the ICU, and adult patients aged 18 years and older with Pcv-aCO_2 greater than 6 mmHg were eligible for inclusion in the study. The exclusion criteria were: Diagnosis of septic shock more than 6 hours before ICU admission, Pregnant women, a non-resuscitable terminal condition or predicted death within 24 hours, Chronic cardiac insufficiency (NYHA cardiac function class III and above), severe valvular stenosis and obstructive hypertrophic cardiomyopathy, and patient or family members who refused to participate in the trial. Criteria for withdrawal and termination included the occurrence of drug-related serious adverse events, such as drug allergy or severe arrhythmia.

Randomization and interventionsy

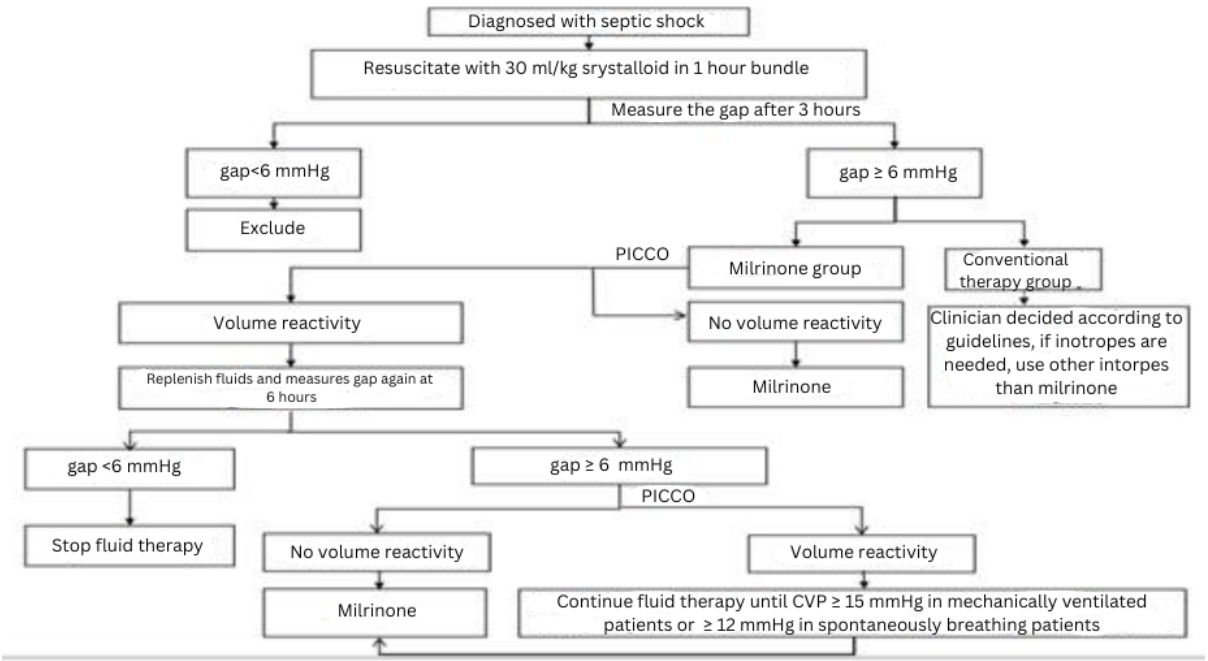
Patients were randomized in a 1:1 ratio into the milrinone group and the conventional therapy group. We stratified the randomization based on a computer-generated table of random numbers. Throughout the study, patients and researchers remained blinded to the assigned therapy.

Patients diagnosed with septic shock received initial fluid resuscitation following the SSC 2016 guidelines, which involved administering a 30 ml/kg crystalloid solution within a 1-hour bundle. If a target Mean Arterial Pressure (MAP) of 65 mmHg cannot be achieved, norepinephrine should be initiated during or after 1-hour fluid resuscitation within the first hour of hypotension. The Pcv-aCO_2 was measured after 3 hours and patients with Pcv-aCO_2 ≥ 6 mm Hg were randomized into two groups. A Pulse Indicator Continous Cardiac Output (PICCO) was inserted in all patients upon enrollment to evaluate fluid responsiveness. A 15% increase in Stroke Volume (SV) after a rehydration test (500ml of saline administered intravenously over 15 minutes) was considered fluid-responsive. Patients in the milrinone group were assessed for volume responsiveness. For patients who did not exhibit fluid responsiveness, the phosphodiesterase inhibitor milrinone (0.3 ug/kg/min-0.5 ug/kg/min) was administered.

Rehydration was continued for patients who showed volume response and reevaluated at 6 hours after ICU admission. If the patient's Pcv-aCO_2 was<6 mmHg, fluid therapy was discontinued. If the Pcv-aCO_2 remained ≥ 6 mmHg and there was no volume responsiveness, milrinone was added. If the patient is volume responsive, fluid therapy is continued until the Central Venous Pressure (CVP) is ≥ 15 mmHg for mechanically ventilated patients or ≥ 12 mmHg for spontaneously breathing patients (at which point the patient is considered to be at maximum fluid capacity).

Patients in the milrinone group were discontinued after discontinuation of norepinephrine. For the conventional therapy group, the clinician decided on the treatment method following the SSC 2016 guidelines (Figure 1).

Figure 1. Study protocol and intervention.



Outcomes

The primary outcome included cardiac output and lactate clearance rate. Secondary outcomes were: ICU mortality, ICU length of stays, total length of stays, duration without Mechanical Ventilation (MV), Continuous Renal Replacement Therapy (CRRT) rate, intensity of vasoactive drug usage, fluid usage within 3 hours of enrollment (T3), Interleukin-6 (IL-6), and changes in hemodynamic indices.

Statistical analysis

Sample size calculation based on Wang et al., studies [14]. Our hypothesis is that the cardiac index of the conventional therapy group is 3.0 ± 0.8 L/min·m^2 and that it will increase to 3.6 ± 0.8 L/min·m^2 in the milrinone group. With the type I error of 5% and the type II error of 20%, we have calculated that each group will require 28 cases. To accommodate for potential data loss, the sample size will be increased by 10%, resulting in a total sample size of approximately 64 cases. Statistical analysis of the data was performed using the statistical software SPSS 26.0. For measurement data, the Shapiro-Wilk test was used to test the normality of the data. Data were considered to be normally distributed if $p>0.05$. Data that conformed to normal distribution were expressed as mean ± standard deviation ($x \pm s$). An Independent sample t-test was used to compare the two groups. Data that did not obey the normal distribution were expressed as the median (interquartile range) (M(IQR)), and the nonparametric rank-sum test (Mann-Whitney U test) was used to compare the two groups. The Chi-square test was used to compare rates between the two groups. A two-tailed $p<0.05$ was considered statistically significant.

Ethical consideration

All participants provided written informed consent. The study was conducted following the principles of the Declaration of Helsinki. The RCT protocol was approved by the ethics committee of the Northern Jiangsu People's Hospital (2021ky026), and granted on 26 February, 2021. The study protocol was also submitted to the China Clinical Trial Registry (registration number ChiCTR2100044523: 23 March, 2021) before the beginning of the trial. Written

informed consent to use clinical data without disclosing personal information was obtained from each patient. The study adhered to the CONSORT guidelines [15].

RESULTS

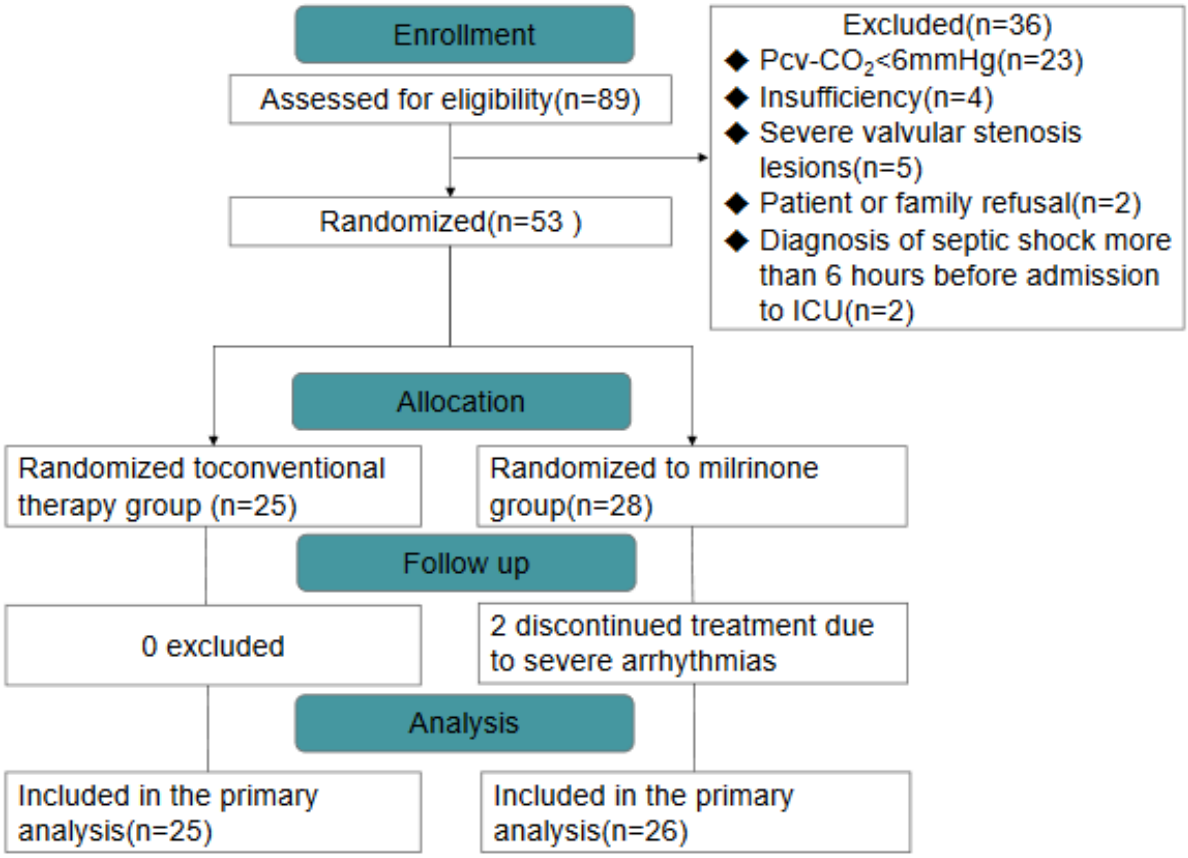
During the study period, 89 patients were assessed for eligibility. Of these, 36 patients were excluded. Ultimately, 53 patients were included in the study, with 28 patients randomly assigned to the milrinone group and 25 patients randomly assigned to the conventional therapy group. Two patients in the milrinone group withdrew from the study due to severe arrhythmias, resulting in 51 patients being included in the final analysis. The patient characteristics are displayed in Table 1. The study population consisted of 58.8% male, median age of 69 years. Abdominal infection was identified as the primary source of infection. The baseline characteristics such as age, gender, Sequential Organ Failure Assessment (SOFA) score, Acute Physiology and Chronic Health Evaluation (APACHE II) score, and lactates showed no differences between the groups (P>0.05) (Table 1) as shown in Figure.2

Table 1. Baseline characteristics.

Characteristics	Milrinone group (n=26)	Conventional therapy group (n=25)	P
Age (years)	70.5 (67,78)	66 (59,74)	0.053
Gender male, n (%)	16 (61.5)	14 (56.0)	0.688
source of infection, n (%)			0.473
Respiratory	5 (19.2)	7 (28.0)	
Intra-abdominal	13 (50.0)	13 (52.0)	
Urogenital	6 (23.1)	2 (8.0)	
others	2 (7.7)	3 (12.0)	
Combined underlying disease, n (%)			0.537*
Arterial hypertension	9 (34.6)	12 (48.0)	
Diabetes	4 (15.4)	2 (8.0)	
Coronary artery atherosclerotic heart disease	1 (3.8)	2 (8.0)	
others	13 (50.0)	11 (44.0)	
qSOFA	2.5 (2,3)	2 (2,3)	0.196
SOFA	10.5 (8,12)	10 (9,13)	0.924
APACHE II	19 (14,22)	18 (14,25)	0.932
basic vital signs			
Temperature (℃)	36.7 (36.2,37.6)	36.5 (36.1,38.0)	0.887
MAP (mmHg)	79.2 (70.3,87.5)	77.3 (70.3,89.3)	0.637
Respiratory rate (times/min)	19.5 (18.0,25.0)	20.0 (19.0,25.5)	0.441
Heart rate (beats/min)	100.35 ± 23.43	96.84 ± 23.53	0.596
CVP(mmHg)	8.69 ± 2.75	8.20 ± 2.94	0.54
Laboratory metrics			
Hemoglobin (g/L)	107.19 ± 19.18	116.32 ± 24.72	0.146
White blood cells (109/L)	6.33 (3.19,11.89)	13.01 (8.19,19.63)	0.065
Blood platelets (109/L)	138.5 (66.0,239.7)	146.0 (78.0,289.0)	0.287
Albumin (g/L)	24.92 ± 7.03	25.14 ± 6.39	0.904
Creatinine (μmol/L)	104.1 (75.5,162.0)	85.3 (59.2,169.6)	0.522
Urine volume (ml)	1376.41 ± 856.63	1446.40 ± 994.66	0.789
Troponin (ng/ml)	0.04 (0.02,0.11)	0.06 (0.02,0.27)	0.359
CK-MB (ng/ml)	2.11 (1.23,3.91)	1.87 (0.69,9.66)	0.985
Myoglobin (ng/ml)	497.7 (128.3,690.7)	292.3 (134.9,891.4)	0.836
Pcv-aCO_2 (mmHg)	9.1 (7.2,11.0)	8.1 (7.0,10.5)	0.295
$ScvO_2$	68.47 ± 8.98	67.77 ± 7.71	0.765
LVEF	52.42 ± 8.41	54.72 ± 4.36	0.23

3-hour cardiac output (L/min)	3.63 ± 0.54	3.36 ± 0.42	0.069
Lac (mmol/L)	4.5 (2.4,8.4)	3.9 (2.4,6.0)	0.44
IL-6 (pg/ml)	330 (276,416)	318 (223,356)	0.122
Note: *Inclusion of coronary artery disease in other analysis.			

Figure 2. Flow diagram of randomization of the study population.



Positive inotropic drug use and safety evaluation

At 3 hours of ICU admission, the Pcv-aCO_2 levels were similar in the two groups [mmHg; 9.1 (IQR 7.2, 11.0) *vs* 8.1 (IQR 7.0, 10.5); P=0.295). With 23.07% (6/26) showing no volume reactivity and receiving milrinone for intervention in the milrinone group.

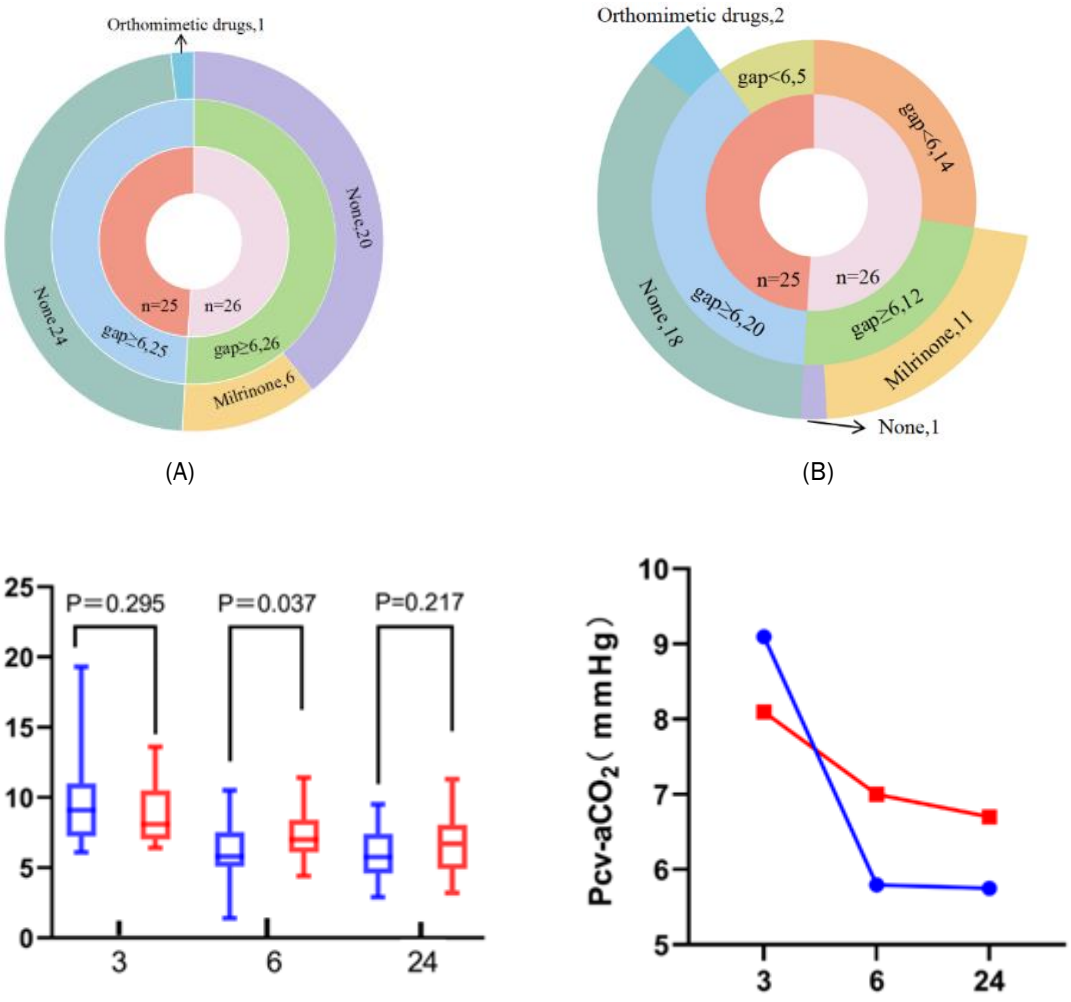
In the conventional therapy group, with 4% (1/25) receiving positive inotropic drugs. At 6 hours of admission to the ICU, Pcv-aCO_2 was measured again in both groups, revealing that 46.15% (12/26) of patients in the milrinone group still had Pcv-aCO_2 levels higher than 6mmHg, with 91.67% (11/12) of these patients undergoing intervention with milrinone.

In the conventional therapy group, 80% (20/25) of patients had Pcv-aCO_2 levels higher than 6mmHg, with 10% (2/20) of these patients using positive inotropic drugs. Compared to patients in the conventional therapy group, patients in the milrinone group received significantly lower Pcv-aCO_2 levels (mmHg; 6.07 ± 2.11 *vs.* 7.25 ± 1.80, p=0.037).

At 24 hours of ICU admission, 38.46% (10/26) of patients in the milrinone group had Pcv-aCO2 above 6 mmHg and 64% (16/25) of patients in the conventional therapy group had Pcv-aCO_2 levels above 6mmHg. Patients in both

groups had a decrease in Pcv-aCO_2 levels compared to admission. Pcv-aCO_2 levels did not differ between groups (mmHg; 5.75 (IQR 4.6, 7.4) *vs* 6.7 (IQR 4.9, 8.1), P=0.217) (Figure 3).

Figure 3. Pharmacologic interventions and changes in Pcv-aCO_2. (A) Pcv-aCO_2 elevation and drug use at 3 hours of ICU admission in both groups. (B) Pcv-aCO_2 elevation and drug use at 6 hours of ICU admission in both groups. (C) Changes in Pcv-aCO_2 after admission to ICU in both groups. **Note:** ( ) Milrinone group; ( )Conventional therapy group; ( )Milrinone group; ( ) Conventional therapy group ; ( ) Milrinone group; ( ) Conventional therapy group.



(c) Enrollment time (hours)

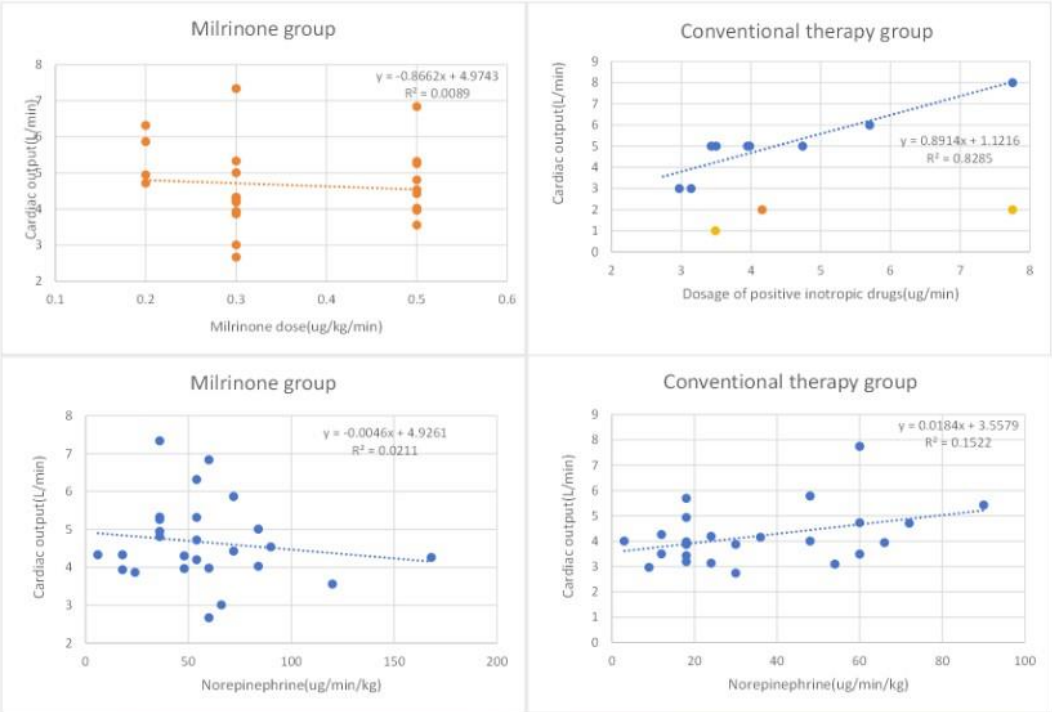
We used the occurrence of arrhythmia to assess safety. We observed that paroxysmal atrial fibrillation (lasting less than 1 hour) was present in 38.46% (10/26) of patients in the milrinone group and 12% (3/25) of patients in the conventional therapy group, none of which required intervention with antiarrhythmic drugs.

Primary outcome

The primary outcome indicators were cardiac output and lactate clearance rate. At 6 hours post-ICU admission, the cardiac output was 4.38 L/min (IQR 3.98-5.28) in the milrinone group and 3.98 L/min (IQR 3.46-4.72) in the conventional therapy group, indicating a significant difference between the two groups (p=0.043). In addition, we specifically described vasoactive drug usage at 6 hours in both patient groups (Figure 4). The vasoactive drug intensity

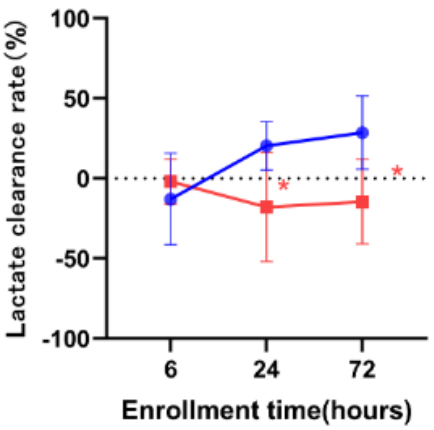
for the milrinone group and conventional therapy group was 58 ug/min (IQR 36-80) and 24 ug/min (IQR 18-42), respectively (p=0.001).

Figure 4. Administration of vasoactive drugs in both groups at 6 hours. **Note:** (■) dopamine; (■) neosynephrine; (■) vasopressin.



Furthermore, we analyzed the lactate clearance rate at 6 hours, 24 hours, and 72 hours. The results showed that at 24 hours and 72 hours after enrollment, the lactate clearance rate of patients in the milrinone group was significantly higher compared to that of patients in the conventional therapy group (P;0.037 and 0.014). At 6 hours after enrollment, the lactate clearance rate in the conventional therapy group (9.09 (-20.19, 18.18)) was higher than that in the milrinone group (0 (IQR -14.26, 24.50)), but the difference was not significant (P=0.49) (Figure 5).

Figure 5. The lactate clearance rate in the two groups. **Note:** Statistically significant difference in lactate clearance between the two groups. (●) milrinone group; (■) conventional therapy group.



Secondary outcome

The secondary outcome measures are displayed in Table 2. The levels of the inflammatory factor IL-6 were 215 pg/ml (IQR 107-438) in the milrinone group and 373 pg/ml (IQR 274-509) in the conventional therapy group, indicating a significant difference between them (p=0.02). The hemodynamic indexes of the two groups were analyzed, and the results showed that the Cardiac Function Index (CFI) of patients in the milrinone group was higher than those in the conventional therapy group (L/min; 6.45 (5.69, 7.92) *vs.* 5.55(5.17, 6.34), P=0.007) (Table 3). There were no significant differences between other secondary outcomes as shown in Table 2 and 3.

Table 2. Secondary outcome.

	Milrinone group (n=26)	Conventional therapy group (n=25)	p
ICU mortality, n (%)	6 (23.1)	6 (24)	0.938
Length of ICU stay (days)	6.5 (4.8,14.0)	14.0 (5.0,18.5)	0.119
Total length of stay (days)	15.5 (7,20.86)	18 (12.5,35.5)	0.157
Length of time without MV (hours)	93 (33,144)	82 (39,267.5)	0.515
CRRT rate, n (%)	11 (42.3)	8 (32)	0.447
3-hour liquid volume (ml)	2424.81 ± 829.91	2230.20 ± 993.47	0.451
IL-6 (pg/ml)	215 (107,438)	373 (274,509)	0.02

Table 3. Changes in hemodynamic parameters at 6 hours.

	Milrinone group (n=26)	Conventional therapy group (n=25)	p
CO (L/min)	4.38（3.98-5.28）	3.98（3.46-4.72）	0.043
CI (L/(min.m^2))	2.52 (2.28,3.0)	2.26 (2.0,2.62)	0.061
SV (ml)	53.08 (40.67,58.64)	48.50 (40.97,56.18)	0.386
SVI (ml/m^2)	29.21 ± 7.87	28.24 ± 8.60	0.679
CFI (L/min)	6.45 (5.69,7.92)	5.55 (5.17,6.34)	0.007
MAP (mmHg)	81.24 ± 9.81	83 ± 13.08	0.589
Heart rate (beats/min)	92.5 ± 16.97	88.36 ± 21.73	0.451
SVRI (dyn.sec.m^2.cm-5)	2337.85 ± 632.83	2616.54 ± 649.13	0.127
GEDVI (ml/m^2)	687.54 ± 67.64	708.04 ± 65.81	0.278
EVLWI (ml/kg)	6.0 (4.75,11)	6.0 (5.0,9.0)	0.79

DISCUSSION

Our findings indicate that intervention with milrinone in patients with septic shock who are non-volume-responsive and still have high Pcv-aCO_2 after adequate fluid resuscitation effectively increases cardiac output, enhances lactate clearance, improves tissue perfusion, and reduces inflammatory factor levels.

To meet the tissue perfusion needs of patients in septic shock, enrolled patients underwent fluid resuscitation at 30 ml/kg within 3 hours of admission to the ICU, and Pcv-aCO_2 measurements were completed immediately at 3 hours with randomized grouping and interventions. To minimize the impact on the outcome of discontinuation of positive inotropic drugs due to the occurrence of atrial fibrillation, antiarrhythmic drugs were avoided if atrial fibrillation in enrolled patients was paroxysmal or did not affect hemodynamic stability. Our results showed that Pcv-aCO_2 tended to decrease after systematic anti-shock treatment without milrinone administration. In the conventional therapy group, Pcv-aCO_2 levels returned to the normal range within 72 hours of admission, but the addition of milrinone shortened the time to achieve Pcv-aCO_2, thereby achieving tissue perfusion promptly and shortening the time of tissue ischemia and hypoxia.

Our study showed a significantly higher lactate clearance rate at 24 hours and 72 hours in the milrinone group of patients compared to the conventional therapy group [16]. Demonstrated that lactate clearance was significantly associated with decreased levels of pro-inflammatory factors, which is consistent with our findings. In addition to lactate clearance, milrinone has been shown to reduce the expression of inflammatory factors in sepsis [17]. Phosphodiesterase inhibitors have been found to suppress the release of various inflammatory mediators and cytokines, downregulate the expression of *IL-4* and *IL-5* genes in TH_2 cells, inhibit leukocyte activation and wandering, and modulate the expression of leukocyte adhesion factors, as well as stimulate the release of endogenous hormones and catecholamines [18].

Further analysis revealed that the Pcv-aCO_2 levels in the milrinone group normalized first at the outset, and there was no disparity in mortality rates between the two groups for the following reasons. Firstly, this outcome may be linked to the early implementation of a standardized fluid management protocol for patients with septic shock. Early aggressive fluid resuscitation may have minimized the variation in microcirculatory perfusion between the two patient groups. Secondly, the Pcv-aCO_2 levels decreased earlier in the milrinone group than in the conventional therapy group, but this difference was not substantial enough to impact mortality rates. Thirdly, our study had a small sample size and did not yield statistically significant differences. Fourthly, guidelines recommend the use of vasoactive drugs to maintain a mean arterial pressure of>65 mm Hg in patients in shock, with norepinephrine being recommended as a first-line agent. High doses of norepinephrine stimulate cardiac β-receptors, leading to increased myocardial contraction, which may lead to the same increase in cardiac output in conventional therapy group patients, thereby reducing the disparity between the two groups. Additionally, we observed that the rate of mechanical ventilation and CRRT use, as well as the length of ICU stay, and the total length of stay, were lower in the milrinone group compared to the conventional therapy group, although these differences were not statistically significant. The results may be constrained by the small sample size of our study.

Enhanced tissue perfusion strategies are crucial in the treatment of septic shock, and the main objective of using positive inotropic drugs is to elevate cardiac output and enhance tissue oxygen delivery. In septic shock, the patient's hemodynamics are typical of the high-cardiac output and low-systemic vascular resistance type, but many septic shock patients often experience cardiac insufficiency [19,20], leading to a shift in the patient's hemodynamics towards low-cardiac output type. Guidelines recommend adding dobutamine to norepinephrine or epinephrine alone in adults with septic shock and concurrent cardiac insufficiency in cases of persistent hypoperfusion despite adequate volume and arterial blood pressure [21]. However, studies have indicated that the use of epinephrine and dopamine, which strongly agonize beta receptors, is associated with a higher risk of morbidity and mortality compared to norepinephrine [22]. Furthermore, Ryota, et al., also demonstrated that the use of epinephrine and dobutamine was associated with increased in-hospital morbidity and mortality in high-risk sepsis patients with lactate>4 mmol/L [23]. Milrinone, through the inhibition of phosphodiesterase, increases intracellular calcium levels, enhancing myocardial contractility and exerting positive inotropic effects [24,25]. Another study showed that epinephrine and dobutamine increased the rates of hospital death and atrial fibrillation, while milrinone had no significant effect on hospital death rates [23]. It does not impact mean arterial pressure and heart rate, nor does it increase myocardial oxygen consumption [24,25]. The results of a retrospective unit study showed that the administration of milrinone in patients with septic shock did not increase in-hospital morbidity and mortality when compared with epinephrine and dobutamine [23]. In our study, we observed that the intensity of vasoactivity was higher in the milrinone group than in the conventional therapy group, which may be related to the hypotension caused by milrinone in patients. Milrinone

increasing cyclic Guanosine Monophosphate (cGMP) in vascular smooth muscle causes vasodilation, leading to a decrease in blood pressure [26].

There are several limitations in this study. Firstly, the study had an open design, which may have led to a certain degree of bias. Secondly, there are no standardized criteria for the administration of positive inotropic drugs to enhance tissue perfusion in patients with septic shock. Thirdly, due to the impact of COVID-19, the trial was forced to pause for three months and, as a result of the limited time for the researchers to complete the study, the final sample size was smaller than the estimated sample size. Larger studies will be needed in the future to validate these results.

CONCLUSION

The use of milrinone in patients with septic shock, whose Pcv-aCO_2 remains high after adequate fluid resuscitation, is effective in increasing cardiac output and lactate clearance, as well as reducing inflammatory factor levels. Although it does not reduce mortality, future larger studies are needed to validate this result.

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ETHICAL COMMITTEE CONSENT

This study was approved by the ethics committees of Northern Jiangsu People's Hospital. All patients enrolled in this study provided written informed consent. The research process was carried out following the requirements of the Ethics Committee.

INFORMED CONSENT STATEMENT

Informed consent was obtained from all subjects involved in the study at the time of enrollment.

DATA AVAILABILITY STATEMENT

The data supporting that support the findings of this study are available from Northern Jiangsu People's Hospital but, restrictions apply to the availability of these data, which were used under license for the current study and so are not publicly available. Data, however, available from the authors upon reasonable request and with the institution’s permission.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Singer M, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). Jama.2016;315:801.

2. Wittayachamnankul B, et al. The role of central venous oxygen saturation, blood lactate, and central venous-to-arterial carbon dioxide partial pressure difference as a goal and prognosis of sepsis treatment. J Crit Care. 2016; 36:223-229.
3. Rivers E, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001;345:1368-1377.
4. Van Beest PA, et al. The incidence of low venous oxygen saturation on admission in the ICU: A multicenter observational study in the Netherlands. Crit Care. 2008;12: R33.
5. Bellomo R, et al. The pursuit of a high central venous oxygen saturation in sepsis: Growing concerns. Crit Care. 2008;12:130.
6. Van Beest PA, et al. Central venous-arterial pCO_2 difference as a tool in resuscitation of septic patients. Intensive Care Med. 2013;39:1034-1039.
7. Gutierrez G. A mathematical model of tissue–blood carbon dioxide exchange during hypoxia. Am J Respir Crit Care Med. 2004;169:525-533.
8. Ospina-Tascón GA, et al. Can venous-to-arterial carbon dioxide differences reflect microcirculatory alterations in patients with septic shock? Intensive Care Med. 2016;42:211-221.
9. Ospina-Tascón GA, et al. Persistently high venous-to-arterial carbon dioxide differences during early resuscitation are associated with poor outcomes in septic shock. Crit Care. 2013;17: R294.
10. Mallat J, et al. Central venous-to-arterial carbon dioxide partial pressure difference in early resuscitation from septic shock: A prospective observational study. Eur J Anaesthesiol. 2014;31:371-380.
11. Raghunathan K, et al. Association between initial fluid choice and subsequent in-hospital mortality during the resuscitation of adults with septic shock. Anesthesiology. 2015;123:1385-1393.
12. Vallet B, et al. Venoarterial CO_2 difference during regional ischemic or hypoxic hypoxia. J Appl Physiol. 2000;89:1317-1321.
13. Monnet X, et al. Lactate and venoarterial carbon dioxide difference/arterial-venous oxygen difference ratio, but not central venous oxygen saturation, predict an increase in oxygen consumption in fluid responders. Crit Care Med. 2013;41:1412-1420.
14. Wang Z, et al. Combination therapy with milrinone and esmolol for heart protection in patients with severe sepsis: A prospective, randomized trial. Clin Drug Investig. 2015;35:707-716.
15. Falci, SG, et al. CONSORT: When and how to use it. Dental Press J Orthod. 2015; 20: 13-15.
16. Nguyen HB, et al. Early lactate clearance is associated with biomarkers of inflammation, coagulation, apoptosis, organ dysfunction and mortality in severe sepsis and septic shock. J Inflamm. 2010;7:6.
17. Fang XL, et al. Effect of fluid resuscitation on adhesion molecule and hemodynamics in patients with severe sepsis. Chinese Critical Care Medicine. 2006;18:539-541.
18. Dschietzig T, et al. Dexamethasone inhibits stimulation of pulmonary endothelins by proinflammatory cytokines: Possible involvement of a nuclear factor κB dependent mechanism. Intensive Care Med. 2001;27:751-756.
19. Chu M, et al. Circumferential strain rate to detect lipopolysaccharide-induced cardiac dysfunction: A speckle tracking echocardiography study. Quantitative Imaging in Medicine and Surgery. 2019;9:151-159.
20. Chu M, et al. Circumferential strain can be used to detect lipopolysaccharide-induced myocardial dysfunction and predict the mortality of severe sepsis in mice. Stover CM, ed. PLOS ONE. 2016;11:e0155346.

21. Dellinger RP, et al. Surviving sepsis campaign: International guidelines for the management of severe sepsis and septic shock: 2008. Crit Care Med. 2008;36:296-327.
22. Magda S, et al. Comparison of dopamine and norepinephrine in the treatment of shock. Mdica. 2010;5:69.
23. Sato R, et al. Effects of inotropes on the mortality in patients with septic shock. J Intensive Care Med. 2021;36:211-219.
24. Shipley JB, et al. Milrinone: Basic and clinical pharmacology and acute and chronic management. Am J Med Sci. 1996;311:286-291.
25. Mathew R, et al. Milrinone as compared with dobutamine in the treatment of cardiogenic shock. N Engl J med 2021; 385:516-552.
26. Hwang W, et al. The effect of milrinone on induced hypotension in elderly patients during spinal surgery: A randomized controlled trial. Spine J. 2014;14:1532-1537.