Central venous-to-arterial carbon dioxide difference as a useful complementary goal of fluid resuscitation for septic shock patients.

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Abstract

Introduction: Central venous oxygen saturation has inevitable limitation when it serves as a goal of fluid resuscitation. The objective of this study was to assess the capacity of central venous-to-arterial carbon dioxide difference (P(cv-a)CO$_2$) as a complementary marker to guide fluid resuscitation when ScvO$_2$ has reached its threshold in septic shock patients.

Methods: This is a singel-central, observational study of septic shock patient. Patients were randomly divided into two groups with ScvO$_2$ normalized and both ScvO$_2$ and P(cv-a)CO$_2$ normalized as a target of fluid resuscitated respectively. Compared the variables at the beginning of study (T0) and 6 h after fluid resuscitated (T6) for both groups. Lactate clearanc were calculated, and dose of vasoactive drugs, duration of mechanical ventilation and ICU stay and 28-day mortality were recorded.

Results: 68 septic shock patients were included in study. At T0, no defference were found between the two groups. Heart rate and lactic acid decreased significantly at T6 in both groups, but lactate clearance rate of ScvO$_2$+P(cv-a)CO$_2$ group (30.1 ± 17.2) were significantly higher than ScvO$_2$ group (21.6 ± 14.3) (p<0.05). Mechanical ventilation time and duration of ICU stay of ScvO$_2$+P(cv-a)CO$_2$ group were shorter than ScvO$_2$ group (11.7 ± 4.9 days *vs.* 14.7 ± 6.2 days and 9.3 ± 4.4 days *vs.* 13.2 ± 6.2 days respectively). No significant difference was observed in 28-days mortality for the two groups.

Conclusion: P(cv-a)CO$_2$ is a valuable complementay goal to guide the fluid resuscitation for septic shock patients. The inclusion of P(cv-a)CO$_2$ into resuscitation protocol would be a safely and effectively practice. But P(cv-a)CO$_2$ may not availably enough to serve as a predictor of prognosis and mortality.

Introduction

Severe sepsis and septic shock is a life-threatening condition with an incidence of 300 per 100000, and still a common cause of death for patients of intensive care unit (ICU) [1,2]. Promoted practice for septic shock therapy is largely based on a study by Rivers et al. which developed a protocol known as early goal-direeted therapy (EGDT) [3]. EGDT is the key to early treatment of septic shock, which could maintain effective circulating blood volume and improve tissue perfusion. According to Rivers et al. several predefined resuscitation end point should be achieved in EGDT: CVP 8-12 mmHg, MAP 65-90 mmHg, urine output >0.5 mL/kg/hr, mixed venous oxygen saturation (SvO$_2$)>65% or central venous oxygen saturation (ScvO$_2$)>70%, haematocrit>30% [3].

Among those parameters, SvO$_2$ or ScvO$_2$ has been considered as a reliable and sensitive indicator to reflect systemic oxygen supply and demand relationship in septic shock patients, low SvO$_2$ or ScvO$_2$ always indicated unbalance state of tissue oxygen delivery and consumption, and always associated with increased postoperative complications [4,5]. But SvO$_2$ or ScvO$_2$ serves as an estimate of oxygen delivery/uptake relationship are not sufficiently precise to detect tissue hypoxia thus may not efficacious to improve tissue perfusion and metabolism [6,7]. Several studies have reported that EGDT goals achieved and ScvO$_2$ over 70% cannot rule out hypoxic tissue metabolism and hemodynamic abnormalities [8,9]. Recently, some multicenter studies also failed to demostrate ScvO$_2$>70% was effective in septic shock therapy [10,11]. These finding triggers the discussion if ScvO$_2$ alone is accurate enough to guide fluid resuscitation and vasoatctive drugs application effectively. To address the limitation of ScvO$_2$, some candidate parameters such as tissue oxygen saturation [12], lactate clearance [13] and carbon dioxide partial pressure [14] have been investigated as substitutable or complementary target to guide fluid resuscitation.

In recent years, some studies have reported the inverse correlation between mix venous to arterial carbon dioxide differnce (P(v-a)CO$_2$) and cardiac index (CI) in septic patient or non-septic circulatory failure patients [15-17]. Carbon dioxide produced by peripheral tissues is removed by venous blood, therefore the reduced of blood flow and development of anaerabic metabolism could be indicated by elevated P(v-a)CO$_2$, experimental studies has suggested P(v-a)CO$_2$ could be

used as a marker of tissue hypoxia [18,19]. Unfortunately, the measurement of $P(v-a)CO_2$ requires pulmonary artery catherter insertion, which is seldom utilized in clinic today [20]. Central venous-to-arterial carbon dioxide difference $(P(cv-a)CO_2)$ as an estimate of $P(v-a)CO_2$, is derived from the insertion of central venous catheter that has been applied to most patients with septic shock [20]. As $P(v-a)CO_2$ potentially represents a more accessible parameter than $P(v-a)CO_2$, $P(v-a)CO_2$ have also been investigated of its possiblility to assess tissue hypoperfusion, Cushieri et al. showed a strong agreement between $P(v-a)CO_2$ and $(P(cv-a)CO_2)$, and found $(P(cv-a)CO_2)$ and CI also present a negative correlation [21].

Therefore, we aim to investigate the possibility of $P(cv-a)CO_2$ as a useful complementary marker to guide fluid resuscitation when $ScvO_2$ has reach its threshold in septic shock patients, and assess its potential to evaluate the severity of the disease and prognostic of patients in present study.

Materials and Methods

Patients

Patients with septic shock admitted to ICU of Xiangya Hospital Center of Zhongnan University from September 2010 to September 2011 were studied. All patients were diagnosed following the criteria defined by 2001 SCCM/ESICM/ ACCP/ATS/SIS International Sepsis Definitions Conference [22]. All recruitted patients required tracheotomy and assisted breathing with ventilator to improve hypoxia condition. Exclusion creteria were: age under 18, dying or predict death within 24 h; the presence of irreversible underlying disease; underlying heart disease or acute myocardial infarction, cardiogenic shock; patient or family members refused to have the operation; history of renal insufficiency and hemodialysis. All patients were randomly divided into two groups according to different fluid resuscitated goals, $ScvO_2$ group and $ScvO_2+P(cv-a)CO_2$ group; and all resuscitated prectice were following the international guidelines for management of severe sepsis and septic shock in 2008 [4].

Resuscitation protocol and hemodynamic management

The fluid resuscitated targets of $ScvO_2+P(cv-a)CO_2$ group as follow: CVP8~12 mmHg (12~15 mmHg with mechanical ventilation) , MAP $\geq$ 65 mmHg, urine volume $\geq$ 0.5 mL/kg/h, $ScvO_2>70\%$ and $P(cv-a)CO_2<6$ mmHg; and goals of $ScvO_2$ group were the same as $ScvO_2+P(cv-a)CO_2$ group except $P(cv-a)CO_2$ was not monitored and controlled.

When a patient was included in the study, a central venous catheter was inserted with right internal jugular or right subclavian vein approach and a pulse indicator continous cardiac output (PiCCO) catheter was placed in the same time for continuous central venous pressuer (CVP) and $ScvO_2$ monitoring. Blood pressure after invasive and noninvasive opration and arterial blood gas analysis were also monitered. In $ScvO_2+P(cv-a)CO_2$ group, $P(cv-a)CO_2$ was calculated every hour. Cultivate blood and/or hematuria and/or phlegm before antibiotics administered. Isotonic crystalloid was administered first to target CVP achieved 8~12 mmHg, if systolic blood pressure less than 80 mmHg, vasoactive drug would be administered at the same time. In any case of CVP decreased, retitration treatment would be adopted, and do not need to deal with the case of CVP higher than upper limit. Second, if CVP achieved 8~12 mmHg but MAP<65 mmHg, 2~20 μg/kg/min dopamine would be administered, and 0.1~2 μg/kg/min norepinephrine would be administered if blood pressure still cannot maintain. Fanally, if CVP achieved 8~12 mmHg and MAP achieved 65~90 mmHg, urine volume $\geq$ 0.5 mL/kg/h, but $ScvO_2$ still lower than 70%, following treatment would be conduct: (1) blood transfusion until haematoerit (HCT)>30%; (2) if HCT>30% but $ScvO_2<70\%$, combined with dobutamine (start dose is 3 μg/kg/min, increase by 1~2 μg/kg/min every 10 min, stop admitted when heart rate>150/min); (3) if $ScvO_2$ still cannot reach 70% by increase oxygen supply, treatment that such as cooling, sedative and analgesic could be adopted to lowering oxygen consumption. All goals must be achieved for a maximum of 6 h. For $ScvO_2+P(cv-a)CO_2$ group, when $P(cv-a)CO_2<6$ mmHg, CVP achieved 8~12 mmHg and MAP achieved 65~90 mmHg, urine volume $\geq$ 0.5 mL/kg/h, $ScvO_2>70\%$ should maintained in 6 h, if $P(cv-a)CO_2 \geq 6$ mmHg, adopt retitration therapy.

Blood glucose control within 6~8.3 mmol/L, volume replacement was performed with ringer's solution and hydroxyethyl starch as appropriate, some patient required to infuse concentrated red blood cells and albumin with crystalloid ratio at 3-4: 1.

Data collection

General information of patient includes sex, age, basic desease, type of disease, Acute Physidogy and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score were collected. Patient's heart rate, respiration, invasive and noninvasive blood pressure, pulse oximetry, OI, CVP, hourly urine output, arterial blood gas analysis, central venous blood gas analysis and other indicators were monitored hourly. Blood lactate concentration, CI, EVLWI, liquid qeuilibrium state were determined in T0 (at the start of the study) and T6 (6 h after inclusion) and calculated lactate clearance by following formula: lactate clearance=(blood lactate at T0-blood lactate at T6)/(blood lactate at T0). Dose of vasoactive drugs (integral dose of norepinephrine and dobutamine) comparison within 6 h, duration of mechanical ventilation, 28 day mortality and ICU stay were also recorded.

Statistical analysis

The data were analyzed using SPSS17.0, all results are presented as mean ± standard deviation. Pairwise comparision of geometric mean were used SNK-q test (student newmankeula, SNK method), analysis of attribute data used chi-square test, P<0.05 was considered statistically significant.

All data were checked by normality test and homogeneity of variance test.

Result

During the study period, a total of 128 patients with septic shock were admitted into the ICU of Xiangya hospital center of Zhongnan University. Among those patient, 60 were excluded according to the following criteria: septic shock over 24 h when enter ICU (n=28), refusal of PiCCO catheter placement (n=12), death within 24 h (n=12), $ScvO_2 < 70\%$ after fluid resuscitation (n=8). Finally, 68 patients were eligible for this study. No patients were found complications such as bleeding, infection, pneumothorax, air embolism in puncture site. Basic information was shown in Table 1.

Table 1. Baseline characteristics of patients.

	ScvO$_2$ group (n=30)	ScvO$_2$+P(cv-a)CO$_2$ group (n=38)	P value
Sex (male/fermale)	16/14	22/16	p>0.05
Age (years)	54.1 ± 15.0	53.6 ± 14.0	p>0.05
Infection site			
Lung	12	14	p>0.05
Enterocoelia	12	14	p>0.05
Urinary tract	3	5	p>0.05
Other	3	5	p>0.05
Basic deseases			
COPD	8	10	p>0.05
Hematological malignancy	8	10	p>0.05
Autoimmune disease	8	8	p>0.05
Diabetes	3	5	p>0.05
Hypertension	5	6	p>0.05

Table 2. Effect evaluation indices of fluid resuscitation at T0 and T6.

	T0	T6
MAP		
ScvO$_2$ group	53.0 ± 4.9	74.7 ±5.3[*]
ScvO$_2$+P(cv-a)CO$_2$ group	50.6 ± 5.6	73.6 ± 13.9[*]
Heart rate		
ScvO$_2$ group	122.5 ± 18.6	108.4 ± 12.5[*]
ScvO$_2$+P(cv-a)CO$_2$ group	125.3 ± 15.3	113.0 ± 11.9[*]
APACHE II score		
ScvO$_2$ group	20.0 ± 6.0	15. 3 ± 4.9[*]
ScvO$_2$+P(cv-a)CO$_2$ group	19. 5 ± 5.9	13.9 ± 5.6[*]
SOFA score		
ScvO$_2$ group	8.1 ± 1.0	5.3 ± 1.8[*]
ScvO$_2$+P(cv-a)CO$_2$ group	7.7 ± 1.2	5.0 ± 1.2[*]
CVP		
ScvO$_2$ group	3.3 ± 1.9	10.1 ± 2.8[*]
ScvO$_2$+P(cv-a)CO$_2$ group	4.3 + 2.4	11.8 + 2.4 [*#]
ScvO$_2$		
ScvO$_2$ group	52.3 ± 8.0	72.6 ± 3.0[*]
ScvO$_2$+P(cv-a)CO$_2$ group	51.6 ± 10.0	83.2 ± 11.0[*#]
Lactate		
ScvO$_2$ group	5.3 ± 1.6	4.3 ± 1.5[*]
ScvO$_2$+P(cv-a)CO$_2$ group	5.9 ± 1.7	4.1 ± 1.5[*]
Lactate clearance		
ScvO$_2$ group		21.6 ± 14.3
ScvO$_2$+P(cv-a)CO$_2$ group		30.1 ± 17.2[#]
OI		
ScvO$_2$ group	132.3 ± 26.5	151.4 ± 25.3[*]
ScvO$_2$+P(cv-a)CO$_2$ group	126.0 ± 22.4	150.9 ± 20.4[*]
CI		
ScvO$_2$ group	4.3 ± 0.8	4.5 ± 0.6
ScvO$_2$+P(cv-a)CO$_2$ group	4.2 ± 0.7	5.3 ± 1.0[*#]
EVLWI		
ScvO$_2$ group	4.9 ± 2.9	7.3 ± 3.4[*]
ScvO$_2$+P(cv-a)CO$_2$ group	4.7 ± 2.7	7.6 ± 3.3[*]

[*]Significant difference between T0 and T6 in the same group, P<0.05

[#]Significant difference between ScvO2+P(cv-a)CO2 group and ScvO2 group, P<0.05

Comparison between patients in ScvO$_2$ group and ScvO$_2$+P(cv-a)CO$_2$ group at T0

Demographic and clinical characteristics such as sex, age, basic desease and infection site at baseline were similar in the two groups (p>0.05). Before fluid resuscitation practice, there are no significantly defferent in heart rate, MAP, CVP, ScvO$_2$, APACHE II score, SOFA score between the two groups either. As shown in Table 2, lactic acid level of patients in ScvO$_2$+P(cv-a)CO$_2$ group was slightly higher than ScvO$_2$ group patients, but no statistical difference was found between the two groups. Mean arterial pressure of all patients were lower than 60 mmHg, OI lower than 200, CI in both groups were high normal, and MAP, OI, CI, EVLWI and SOFA score have no difference between the two groups (p>0.05).

Comparison between patients in ScvO$_2$ group and ScvO$_2$+P(cv-a)CO$_2$ group at T6

After fluid resuscitation 6 h, heart rate and lactic acid decreased significantly in both ScvO$_2$+P(cv-a)CO$_2$ and ScvO$_2$

group, and CYP, MAP and $ScvO_2$ increase significantly (p<0.05), but no statistically significant were observed between the two groups (p>0.05). Lactate clearance rate of $ScvO_2+P(cv-a)CO_2$ group (30.1 ± 17.2) were higher than $ScvO_2$ group(21.6 ± 14.3) (p<0.05). After 6 h, liquid equilibrium state of $ScvO_2+P(cv-a)CO_2$ group (3011 ± 1198) mL were higher than $ScvO_2$ group (2415 ± 680) mL (p<0.05), but vasoactive drug dose were significantly less than $ScvO_2$ group (dose of dobutamine and norepinephrine were (87.8 ± 40.1) mg *vs.* (111.7 ± 45.1) mg and (13.1 ± 5. 7) mg *vs.* (16.8 ± 6.0) mg respectively) (p<0.05). After 6 h, CVP and CI of $ScvO_2+P(cv-a)CO_2$ group were also higher than $ScvO_2$ group (p<0.01), but incidence of pulmonary edema and EVLWI (12/30) *vs.* (l4/38) between the two group have no significant difference (p>0.05). After recovery, oxygenation index in both groups were significantly improve, but no difference were found between two groups (p>0.05).

Table 3. Practice in fluid resuscitation and outcomes comparison between $ScvO_2+P(cv-a)CO_2$ group and $ScvO_2$ group.

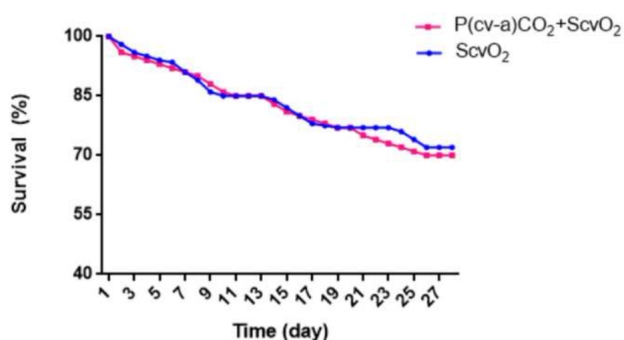|	ScvO$_2$ group	P(cv-a)CO$_2$+ ScvO$_2$ group	t/x^2	P value
Norepinephrine (mg)	16.8 ± 6.0	13.1 ± 5.7	0.011	P<0.05
Dobutamine (mg)	111.7 ± 4 5.1	87.8 ± 40.1	0.023	P<0.05
Fluid balance volume (mL)	2415 ± 680	3011 ± 1198	0.017	P<0.05
Pulmonary edema (%)	6/30 (20%)	8/38 (21%)	-	P>0.05
Mechanical ventilation time (day)	14.7 ± 6.2	11.7 ± 4.9	0.028	P<0.05
duration of ICU stay (day)	13.2 ± 6.2	9.3 ± 4.4	0.003	P<0.05
28 days mortality (%)	8/30 (27%)	11/38 (29%)		P>0.05

Figure 1. Survival Comparison between patients in $ScvO_2$ group and $ScvO_2+P(cv-a)CO_2$ group. The survival rate in $ScvO_2$ group and $ScvO_2+P(cv-a)CO_2$ group were 73% and 71% respectively at 28-days following. No statistically significant differences were observed in 28-days mortality and survival curves between the two groups.

P(cv-a)CO2 and outcome in 28-days following

Results of 28 days follow up shown in Table 3 and Figure 1. Mechanical ventilation time and duration of ICU stay of $ScvO_2$ group were significantly increased than $ScvO_2+P(cv-a)CO_2$ group (p<0.05). Eight of 30 patients in $ScvO_2$ group and 11 of 38 patient in $ScvO_2+P(cv-a)CO_2$ group death after 28 days, the mortality in 28 days and overall mortality in patients were very close, no significant difference were observed between the two groups. As Figure 1 shows, the survival curves of the two groups were also not found statistically significant difference (p>0.05).

Discussion

The main findings of present study are as follows: for fluid resuscitation in patients with septic shock, when $ScvO_2>70\%$ is achieved, the presence of $P(cv-a)CO_2$ within normal range is relevant to elevated CVP, CI; reduce dose of vasoactive drugs; correlate with higher lactate clearance; and less mechanical ventilation and ICU stay. Therefore $P(cv-a)CO_2$ may be a useful complementary target for EGDT.

$P(cv-a)CO_2$ with better CI and tissue perfusion

Sufficient tissue perfusion is an essential component of oxygenation for patients with septic shock. When oxygen delivery could not reach oxygen demand, it would trigger tissue hypoxia, eventually lead to organ failure [23]. Therefore, the use of early and efficient tool to identify and correct hypoperfusion state is the key for fluid resuscitation practice of patients with septic shock patients, and then improves outcomes. Since the landmark study by Rivers et al. [3], $ScvO_2$ was used as measurement of the balance of oxygen delivery and consumption, and serve as a goal for EGDT. But $ScvO_2$ alone has its limitation as it is measured downstream from tissue [5]. Oxygenation index (OI) basically independent of anaerobic metabolism, in septic condition, capillary shunting and mitochondrial damage will affect tissue oxygen extraction, but the heterogeneity of microcirculation may cover up low local oxygen venous saturation [24,25]. In that case, tissue hypoxia would present while $ScvO_2$ over its threshold, therefore $ScvO_2$ maybe an inaccuracies indicator to reflect the global tissue perfusion. Because the solubility of carbon dioxide is around 20 times than oxygen, carbon dioxide is more likely to spread out of ischemic tissue into veins, making it an extremely sensitive indicator of hypoperfusion [26]. Some studies have confirmed that the increase of CO_2 partial pressure is capable to reflect tissue perfusion than other normal indicator (eg, blood lactate) althought its pathophysiology is still unclear [27].

In our study, we have investigatd the potential of $P(cv-a)CO_2$ as a complementary target in fluid resuscitation while $ScvO_2>70\%$. By maintaining $P(cv-a)CO_2$ within normal range in a group of septic shock patients that $ScvO_2$ already over 70%, and with another group of patients only normalize $ScvO_2>70\%$ s a control group, we found that both groups mean arterial pressure and CVP were significantly higher in T6, and

heart rate decrease significantly than T0, indicated fluid resuscitation is effective. But CI of patients in $ScvO_2+P(cv-a)CO_2$ group increased significantly than control group, which revealed that $P(cv-a)CO_2$ as a complementary target is beneficial to elevate cardiac output, then improve tissue perfusion.

The normal range of $P(cv-a)CO_2$ is 2~5 mmHg, over 6 mmHg would indicated inadequate cardiac output and tissue hypoperfusion [26]. Althought $ScvO_2$ were higher than 70% in all 30 cases of $ScvO_2$ group, but 12 (40%) patients have $P(cv-a)CO_2>6$ mmHg, which indicated tissue hypoperfusion of those patients. This is consistent with the reports of Varpuls, and in agreement with reports found that $P(cv-a)CO_2$ have a nagitive relationship with cardiac output [25,28]. And this may contributed to the higher CI of $ScvO_2+P(cv-a)CO_2$ group. In other research, patients whose $P(cv-a)CO_2$ over 6 mmHg always present great lactate level than whose $P(cv-a)CO_2$ less than 6 mmHg, and CI, $ScvO_2$ lower than patients that $P(cv-a)CO_2<6$ mmHg [29]. Insufficient CI would lead to hypoxia because of low flow state, and the shortage of blood flow cannot take CO_2 away from tissue, which would elevate $P(cv-a)CO_2$.

The signifacantly higher blood lactate clearance observed in $ScvO_2+P(cv-a)CO_2$ group also support patients in this group reach a better perfusion state. Arterial blood lactate is a sensitive indicator of tissue ischemia and hypoxia, so dynamic monitor of arterial blood lactate is importance for early diagnosis of shock and tissue hypoxia. Oxygen delivery restoration in resuscitation would be indicated by the reduction of blood lactate concentration [30]. Studies have found that a lactate clearance of 10% or more is evidence of adequate tissue oxygen delivery, and serve as an independent predictor of prognosis and survival from septic shock [7,31,32]. In this study, blood lactate in both groups were decrease signifacantly than previous, and lactate clearance of both groups were above 10%, but $ScvO_2+P(cv-a)CO_2$ group (30.1% ± 17.2%) have higher lactate clearance than $ScvO_2$ group(21.6% ± 14.3%), indicated $ScvO_2+P (cv-a)CO_2$ group could reach a better resuscitation state, and improve body tissue perfusion; while $ScvO_2$ group maybe just reach the lower limit of capacity requirements. Therefore, normalize both $P(cv-a)CO_2$ and $ScvO_2$ may be beneficial to patients with septic shock in aspect of cardiac output and tissue hypoperfusion improvement.

P(cv-a)CO_2 and fluid resuscitation practice

By fluid resuscitation, abundance crystal and colloid liquids may be use during early aggressive treatment, which may damage alveolar capillaries, resulting in pulmonary interstitial edema, increased lung damage and even lead to acute respiratory distress syndrome [33]. Extravascular lung water index (EVLWI) is a sensitive indicator of pulmonary oedema, was monitered by PiCCO to assess the degree of pulmonary edema during the early period of fluid resuscitation, reduce the incidence of lung injury. The balance fluid volume of $ScvO_2$ group and $ScvO_2+P(cv-a)CO_2$ group was 2415 ± 680 mL and 3011 ± 1198 mL respectively, data shows statistically

significant difference. Although patients in $ScvO_2+P(cv-a)CO_2$ group received more crystal and colloid fluid than did patients in the $ScvO_2$ group during early aggressive treatment, which may cause acute lung injury, but the slight increased of EVLWI in $ScvO_2+P(cv-a)CO_2$ group (7.6 ± 3.3) did not show any significant difference compare with control group (7.3 ± 3.4). The incidence of pulmonary edema in 28-days following (20% *vs.* 21%) also support more intravenous fluids received in patients of $ScvO_2+P(cv-a)CO_2$ group did not cause significant harm to the lungs than control group. In contrast, $ScvO_2+P(cv-a)CO_2$ group (11.7 ± 4.9 days) effectively reduce the duration of mechanical ventilation than control group (14.7 ± 6.2 days). This may be because patients in $ScvO_2+P(cv-a)CO_2$ group got adequately fluid resuscitation, cardiac output increased, body tissue perfusion improved effectively, lung perfusion and cell metabolism also improved, fanally shorten the duration of mechanical ventilation. Those datas indicated that normalize both $ScvO_2$ and $P(cv-a)CO_2$ in fluid resuscitation could be practiced safely by balance the demand of cardiac preload and the occur of pulmonary edema.

There are some patients in both group needed dobutamine because of $ScvO_2$ lower than 70%. Dobutamine is an strong agonist for β1 and β2 adrenergic receptor. The active effect to β1 receptor could improve cardiac index by 25% to 50%, and heart rate increase by 10% to 20% [7]. β2 receptor activation could reduce pulmonary wedge pressure and improve cardiac output then improve tissue perfusion [34]. Therefore, dobutamine can increase oxygen delivery but also increase myocardial oxygen consumption. In our study, patients of $ScvO_2+P(cv-a)CO_2$ group required less vasoactive drugs than $ScvO_2$ group after fluid resuscitation in 6 h. In consideration of more adequate resuscitation state were receives in patients of $ScvO_2+P(cv-a)CO_2$ group, they also enhanced cardiac preload to increase cardiac output, raised effective circulating volume, thereby reducing the amount of vasoactive drugs.

P(cv-a)CO_2 with prognosis and mortality

SOFA score and APACHE II score are scoring system commonly used in critically ill patients, for evaluating severity of patients with septic shock and predict prognosis or mortality [35]. Fabrice V point out SOFA score obvious decrease in low $P(cv-a)CO_2$ group patients in 24 h [29] and research from Emmanuel et al. have investigated the use of P (cv-a) CO_2 as an individualized goal to guide orientation treatment for 70 high-risk surgical patients, recording the patient's CI, CVP, and P (cv-a)CO_2, analyzed their prognosis, found that patients with complications have higher $P(cv-a)CO_2$ value than patients didn't have complications; for patients whose $ScvO_2 \geq 71\%$ and with complications, $P(cv-a)CO_2$ value is significantly higher than patients who without complications occur [36]. Bakker and other studies suggest that surviving septic shock patients have lower $P(cv-a)CO_2$ than the patients who died, although they have a very similar CI, oxygen supply and oxygen consumption values [28]. In this study, SOFA score and APACHE II score have no significant difference between two groups when enter the program, and SOFA score and APACHEII score decreased significantly in T6. But there are

also no significant difference in SOFA score and APACHEII score in T6 between the two groups. Although the length of stay in ICU was much shorter in ScvO$_2$+P(cv-a)CO$_2$ group (9.3 ± 4.4 days *vs.* 13.2 ± 6.2 days), no significant difference were observed in 28 days mortality for the two groups. The 28 days mortality rate in both groups were similar with previous studies [3,11], indicated that the resuscitation practice in our study is effective.

But as a singel-central preliminary research, the studied patients group is small, we may not get sufficient datas to indentify some significant finding. Further multi-center chlinical trials with larger sample are required to comfirm the effective of P(cv-a)CO$_2$ as a complementary goal to guide the fluid resuscitation.

Conclusion

P(cv-a)CO$_2$ is a valuable complementary goal to guide the fluid resuscitation for septic shock patients. The inclusion of P(cv-a)CO$_2$ into resuscitation protocol would be a safely and effectively practice. But P(cv-a)CO$_2$ may not availably enough to serve as a predictor of prognosis and mortality.

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