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Critical hemodynamic therapy oriented resuscitation helping reduce lung water production and improve survival

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Abstract

Background: Increased extravascular lung water (EVLW) in shock is common in the critically ill patients. This study aimed to explore the effect of cardiac output (CO) on EVLW and its relevant influence on prognosis.

Methods: The hemodynamic data of 428 patients with pulse-indicated continuous CO catheterization from Department of Critical Care Medicine, Peking Union Medical College Hospital were retrospectively collected and analyzed. The patients were assigned to acute respiratory distress syndrome group, cardiogenic shock group, septic shock group, and combined shock (cardiogenic and septic) group according to their symptoms. Information on 28-day mortality and renal function was also collected.

Results: The CO and EVLW index (EVLWI) in the cardiogenic and combined shock groups were lower than those in the other groups (acute respiratory distress syndrome group $vs.$ cardiogenic shock group $vs.$ septic shock group $vs.$ combined shock group: CO, 5.1 [4.0, 6.2] $vs.$ 4.7 [4.0, 5.7] $vs.$ 5.5 [4.3, 6.7] $vs.$ 4.6 [3.5, 5.7] at 0 to 24 h, $P = 0.009$; 4.6 [3.8, 5.6] $vs.$ 4.8 [4.1, 5.7] $vs.$ 5.3 [4.4, 6.5] $vs.$ 4.5 [3.8, 5.3] at 24 to 48 h, $P = 0.048$; 4.5 [4.1, 5.4] $vs.$ 4.8 [3.8, 5.5] $vs.$ 5.3 [4.0, 6.4] $vs.$ 4.0 [3.2, 5.4] at 48 to 72 h, $P = 0.006$; EVLWI, 11.4 [8.7, 19.1] $vs.$ 7.9 [6.6, 10.0] $vs.$ 8.8 [7.4, 11.0] $vs.$ 8.2 [6.7, 11.3] at 0 to 24 h, $P < 0.001$; 11.8 [7.7, 17.2] $vs.$ 7.8 [6.3, 10.2] $vs.$ 8.7 [6.6, 12.2] $vs.$ 8.0 [6.6, 11.1] at 24 to 48 h, $P < 0.001$; and 11.3 [7.7, 18.7] $vs.$ 7.5 [6.3, 10.0] $vs.$ 8.8 [6.3, 12.2] $vs.$ 8.4 [6.4, 11.2] at 48 to 72 h, $P < 0.001$. The trend of the EVLWI in the septic shock group was higher than that in the cardiogenic shock group ($P < 0.05$). Moreover, there existed some difference in the pulmonary vascular permeability index among the cardiogenic shock group, the septic shock group, and the combined shock group, without statistical significance ($P > 0.05$). In addition, there was no significant difference in tissue perfusion or renal function among the four groups during the observation period ($P > 0.05$). However, the cardiogenic shock group had a higher 28-day survival rate than the other three groups [log rank (Mantel-Cox) = 31.169, $P < 0.001$].

Conclusion: Tissue-aimed lower CO could reduce the EVLWI and achieve a better prognosis.

Keywords: Extravascular lung water; Cardiac output; Tissue perfusion; Organ function; Prognosis

Introduction

Critical hemodynamic therapy (CHT) concept and the oxygen-flow-pressure (OFP) targets for the resuscitation of critically ill patients have been established by our team and used in the clinical setting.[1,2] More and more evidences have proven that it was correct and useful in the daily clinical practice. This study used a retrospective cohort to reveal one pathophysiology mechanism of CHT, which helps reduce lung water production and improves survival through lowering the cardiac output (CO).

Extravascular lung water (EVLW) is the amount of water that exists in the lung interstitial.[3] Many recent researches have addressed EVLW in the fields of critical care and acute respiratory distress syndrome (ARDS). EVLW is a pathological factor that can damage lung compliance and gas diffusion function when ARDS and lung edema occur. Besides, many experiments have proved that EVLW was high not only in acute lung injury/ARDS but also in sepsis and septic shock.[4-6] Furthermore, an increase in EVLW during the first 48 h of ARDS may reduce the 28-day survival.[7] It has been repeatedly confirmed that increased EVLW was life-threatening and correlated with organs dysfunction and mortality in many critically ill patients.[8]

EVLW may develop mainly due to pulmonary capillary permeability increasing during the systemic inflammatory response (typically in acute lung injury/ARDS) or increased pulmonary capillary hydrostatic pressure.[9] In ARDS and sepsis/septic shock), the pulmonary microvascular permeability increases, and the outward fluid filtration from

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microvessels is greater. The pulmonary vascular permeability index (PVPI) is an indicator that has been shown to reflect the pulmonary microvascular permeability[10] and has been evaluated to determine the type of edema.[11] In the clinic, clinicians can use transpulmonary thermodilution techniques to measure both EVLW index (EVLWI) and PVPI. In hydrostatic edema, fluid overload is the main mechanism that associates with the damage of the lung: excess fluid is removed from the pulmonary vessels to the interstitial tissue because of the hydrostatic pressure. In many critical diseases, the alveolar fluid clearance mechanism is impaired, thus contributing to the accumulation of EVLW.[12] Interestingly, in clinical work, we have occasionally found that cardiogenic shock patients had a lower EVLW than ARDS or septic shock patients, which could not be explained by cardiogenic pulmonary edema mechanism. We suspected that EVLW stemmed not only due to permeability and hydrostatic pressure but possibly also from high CO. In this study, we selected pulse-indicated continuous cardiac output (PICCO) data from patients with ARDS, septic shock, cardiogenic shock, or combined shock to explore the association between CO and EVLW under the CHT frame.

Methods

Ethical approval

The study was conducted in accordance with the *Declaration of Helsinki* and was approved by the Institutional Research and Ethics Committee of the Peking Union Medical College Hospital (PUMCH-S351). This was a retrospective study, and all patients authorized us to use the clinical data.

Participants

The Critical Care Self-Built Database of Peking Union Medical College Hospital (PUMCH-CCSD) was built in 2013. This database integrates patient basic information, clinical monitoring, laboratory information, treatment information, nursing information, and many other aspects. We retrospectively collected data of patients undergoing PICCO monitoring and treatments in the Department of Critical Care Medicine, PUMCH, from August 2013 to December 2016. When the patients needed PICCO cauterization, the patients or their family members were totally informed of the various matters and signed informed consent.

The patients were included if they met the following criteria: (1) age ≥18 years; (2) continuous hemodynamic monitoring after intensive care unit (ICU) admission ≥24 h; and (3) survival time after shock ≥72 h. The patients were excluded if they met the following criteria: (1) cardiogenic pulmonary edema, as proven by the X-ray combined cardiogenic etiology suggested by hemodynamic evidence and patients who have normal right ventricular function but left ventricular dysfunction according to the critical ultrasound at bedside; (2) continuous hemodynamic monitoring <48 h or ≥2 time surveillance data points absent; and (3) abandoned treatment during ICU hospitalization. The patients were assigned to ARDS group, cardiogenic shock group, septic shock group, and combined shock (cardiogenic and septic) group according to their symptoms. The ARDS (moderate to severe) was defined as bilateral pulmonary infiltration with partial pressure of oxygen (PaO_2)/fraction of inspiration O_2 (FiO_2) <200 mmHg and positive end expiratory pressure (PEEP) >5 mmHg based on the Berlin Definition 2012.[13] The cardiogenic shock, in which lactate levels were ≥2 mmol/L, was defined as having inadequate CO due to primary failure of the heart, and continuously needing vasoactive and inotropic drugs, for example, adrenaline, dobutamine, milrinone, and cardiac glycosides. Septic shock was defined as a sepsis patient requiring a vasopressor to maintain blood pressure after fluid resuscitation and lactate ≥2 mmol/L based on Sepsis 3.0.[14] The combined shock was defined as having septic shock combined with cardiac dysfunction. On the basis of the 28-day mortality, all of the patients were divided into survivors or nonsurvivors.

Hemodynamic monitoring

Using a central venous catheter in the internal jugular or subclavian vein, a pressure sensor (Philips, Boeblingen, Germany) was connected to the monitor to show central venous pressure (CVP). CO, cardiac index (CI), EVLWI, PVPI, and other hemodynamic data were detected using the thermodilution method by the femoral PICCO catheter (Pulsion Medical Systems, Munich, Germany).

Data collection

Basic clinical characteristics were collected, including age, gender, heart rate, mean arterial pressure, acute physiology and chronic health evaluation II and sequential organ failure assessment scores; tissue perfusion-related index [central venoarterial carbon dioxide difference (P(v-a) CO_2), central venous oxygen saturation ($ScvO_2$), and lactate]; organ function index [serum creatinine (SCr), blood urea nitrogen (BUN)]; respiratory parameters (FiO_2%, PaO_2/FiO_2, PEEP); other hemodynamic parameters (global end-diastolic volume index) and systemic vascular resistance index; continuous renal replacement therapy (CRRT); and 28-day prognosis after PICCO initiation. For quantitative data, all the monitoring data for the relevant day (0–24 h, 24–48 h, and 48–72 h) were recorded.

Statistical analysis

The continuous variables with normal distributions were shown as mean ± standard deviation. Student's *t*-test and analysis of variance were used to compare variables with normal distribution between groups. The continuous variables that were not normally distributed were shown as medians (Q1, Q3) and were compared using nonparametric tests. Quantitative data with abnormal distribution were compared using the rank-sum test. The qualitative variables were compared using Chi-square test. Survival curves up to day 28 were estimated using the Kaplan-Meier method, and the log rank (Mantel-Cox) test. Repeated-measure analysis of variance was used to describe the dynamic changes of CO, EVLWI, PVPI, CVP, P(v-a)CO_2,

ScvO$_2$, lactate, and renal function among different groups at different time points after PICCO catheterization (24, 48, and 72 h). Data were analyzed using SPSS version 16.0 software (SPSS Inc., Chicago, IL, USA). A $P < 0.05$ was considered statistically significant.

Results

Patients characteristics

In this study, 428 patients were subjected to PICCO during the observation period. The 176 patients did not meet the criteria and were excluded. Ultimately, 252 patients were included in final analysis and were assigned to ARDS group ($n = 45$), cardiogenic shock group ($n = 79$), septic shock group ($n = 71$), and combined shock group ($n = 57$) [Figure 1]. The demographic and clinical characteristics of the included patients at the initial PICCO are summarized in Table 1.

Among the four groups, the ARDS group had the lowest PaO$_2$/FiO$_2$% and highest PEEP, EVLWI, and PVPI (all $P < 0.05$). In addition, there were no statistically significant differences in age, gender, acute physiology and chronic health evaluation II and sequential organ failure assessment scores, HR, MAP, CVP, CO, CI, global end-diastolic volume index, systemic vascular resistance index, P(v-a)CO$_2$, ScvO$_2$, lactate, SCr, BUN, and CRRT among four groups.

Relationship between CO, EVLWI, and PVPI

Figure 2 shows the dynamic changes of CO, EVLWI, and PVPI. The CO of the septic shock group was higher than that of the other three groups at 0 to 24 h, 24 to 48 h, and 48 to 72 h. At the 0 to 24 h time point, the CO of ARDS and septic shock groups had no statistical significance, whereas at the other two points, CO of ARDS and septic shock groups had statistical significance (ARDS group vs. cardiogenic shock group vs. septic shock group vs. combined shock group: 5.1 [4.0, 6.2] vs. 4.7 [4.0, 5.7] vs. 5.5 [4.3, 6.7] vs. 4.6 [3.5, 5.7] at 0–24 h, $P = 0.009$; 4.6 [3.8, 5.6] vs. 4.8 [4.1, 5.7] vs. 5.3 [4.4, 6.5] vs. 4.5 [3.8, 5.3] at 24–48 h, $P = 0.048$; and 4.5 [4.1, 5.4] vs. 4.8 [3.8, 5.5] vs. 5.3 [4.0, 6.4] vs. 4.0 [3.2, 5.4] at 48–72 h, $P = 0.006$). With the progress of the treatment and infection control, the CO of the septic shock group gradually decreased ($P < 0.05$). The ARDS groups had the highest EVLWI and PVPI compared with the other groups at different time points, with statistical significance ($P < 0.05$). Furthermore, the EVLWI of the septic shock group was higher than that of the cardiogenic shock group (ARDS group vs. cardiogenic shock group vs. septic shock group vs. combined shock group: 11.4 [8.7, 19.1] vs. 7.9 [6.6, 10.0] vs. 8.8 [7.4, 11.0] vs. 8.2 [6.7, 11.3] at 0–24 h, $P < 0.001$; 11.8 [7.7, 17.2] vs. 7.8 [6.3, 10.2] vs. 8.7 [6.6, 12.2] vs. 8.0 [6.6, 11.1] at 24–48 h, $P < 0.001$; and 11.3 [7.7, 18.7] vs. 7.5 [6.3, 10.0] vs. 8.8 [6.3, 12.2] vs. 8.4 [6.4, 11.2] at 48–72 h, $P < 0.001$). However, there was no significant difference in PVPI between the septic and cardiogenic shock groups. Moreover, although there were no significant differences in the EVLWI and PVPI between the septic shock and combined shock groups ($P > 0.05$), the trends of EVLWI in the combined shock group were lower than those in the septic shock group. The detailed data of the CO, EVLWI, and PVPI are listed in Table 2.
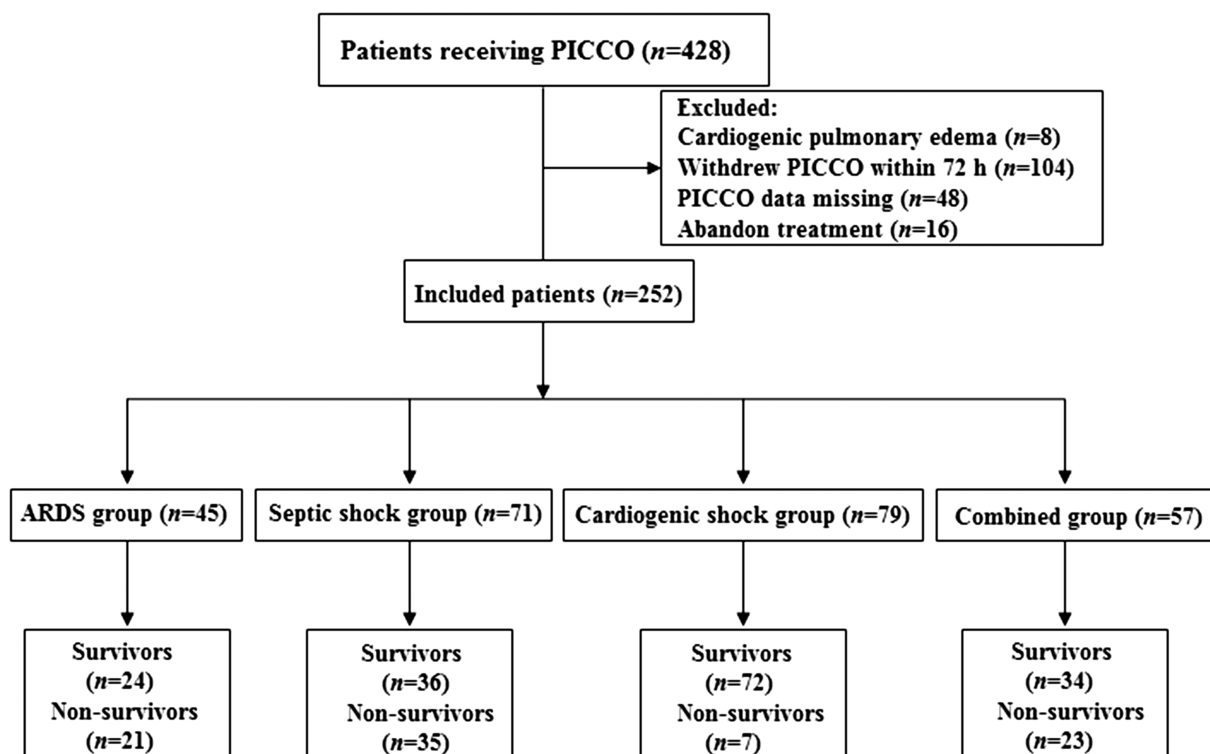

Figure 1: Flow chart of this study. ARDS: Acute respiratory distress syndrome; PICCO: Pulse-indicated continuous cardiac output.

Table 1: Baseline of the patients' characteristics at the initial of PICCO.

Characteristics	ARDS group (n=45)	Cardiogenic shock group (n=79)	Septic shock group (n=71)	Combined shock group (n=57)	Statistical values	P
Age (years)	57.8 ± 20.2	59.4 ± 16.4	54.6 ± 16.5	58.5 ± 16.2	1.104[*]	0.348
Gender					4.737[†]	0.192
Male	28 (62.2)	42 (53.2)	39 (54.9)	40 (70.2)		
Female	17 (37.8)	37 (46.8)	32 (45.1)	17 (29.8)		
APACHE II score	28.3 ± 9.4	23.0 ± 8.1	26.4 ± 8.3	26.1 ± 8.9	4.056[*]	0.008
SOFA score	13.5 ± 4.0	12.2 ± 3.3	12.6 ± 3.7	12.5 ± 3.2	1.384[*]	0.248
Heart rate (beats/min)	107.1 ± 24.3	104.5 ± 18.7	111.8 ± 17.2	105.3 ± 16.0	2.124[*]	0.098
Mean arterial pressure (mmHg)	88.7 ± 12.0	89.3 ± 10.5	88.1 ± 10.7	85.1 ± 10.6	1.796[*]	0.149
CVP (mmHg)	12.0 (10.0, 14.0)	10.7 (9.2, 12.7)	10.8 (9.0, 10.3)	10.0 (8.0, 13.5)	5.923[‡]	0.115
CO (L/min)	5.3 ± 2.0	5.0 ± 2.1	5.7 ± 2.2	4.7 ± 2.1	2.212[*]	0.087
CI (L/min/m^2)	3.0 ± 1.1	2.9 ± 1.1	3.2 ± 1.2	2.7 ± 1.1	2.467[*]	0.063
EVLWI (mL/kg)	14.4 ± 7.2	8.7 ± 3.1	9.6 ± 4.0	9.6 ± 4.1	16.203[*]	<0.001
PVPI	2.3 (1.7, 3.6)	1.6 (1.3, 2.1)	1.8 (1.4, 2.4)	1.8 (1.4, 2.4)	26.382[‡]	<0.001
GEDVI (mL/m^2)	740.5 ± 162.8	755.8 ± 181.6	695.4 ± 162.5	690.6 ± 119.8	2.303[*]	0.078
SVRI (dyn·s·cm^{-5}·m^{-2})	2242.2 ± 714.0	2197.3 ± 898.5	2169.4 ± 730.1	2369.6 ± 1150.4	0.714[*]	0.714
P(v-a)CO$_2$ (mmHg)	4.7 (3.0, 6.6)	5.2 (3.7, 7.9)	4.8 (2.9, 6.3)	6.1 (3.9, 8.0)	6.555[‡]	0.088
ScvO$_2$ (%)	73.5 ± 10.5	73.1 ± 9.7	73.8 ± 10.9	70.0 ± 11.9	1.435[*]	0.233
Lactate (mmol/L)	3.8 (2.2, 8.0)	3.1 (1.8,6.8)	3.2 (2.0,6.2)	3.7 (1.9, 6.2)	5.923[‡]	0.442
FiO$_2$%	48.9 (40.0, 58.8)	42.9 (40.0, 60.0)	40.0 (35.0, 50.0)	37.0 (30.0, 46.2)	29.457[‡]	<0.001
PaO$_2$/FiO$_2$	115.0 (98.0, 125.8)	291.0 (229.1, 343.3)	220.1 (175.2, 306.8)	284.7 (215.5, 355.1)	7.514[‡]	<0.001
PEEP (cmH$_2$O)	11.7 (5.0, 18.0)	7.0 (5.0, 8.9)	7.7 (5.0, 10.0)	5.0 (5.0, 8.3)	11.851[‡]	0.008
CRRT	16 (35.6)	44 (55.7)	39 (54.9)	31 (54.4)	5.661[†]	0.129
SCr (μmol/L)	146.5 (101.0, 216.5)	134.0 (88.0, 178.0)	139.0 (95.8, 300.5)	128.0 (88.0, 183.0)	3.727[‡]	0.292
BUN (mmol/L)	13.6 (9.4, 19.3)	9.2 (6.3, 13.6)	11.6 (8.7, 15.7)	10.4 (7.2, 15.2)	8.881[‡]	0.031
Mortality	21 (46.7)	7 (8.9)	35 (49.3)	23 (40.4)	33.831[†]	<0.001

The data were shown as mean ± SD, median (Q1, Q3), or n (%). [*]F values. [†]χ^2 values. [‡]Z values. ARDS: Acute respiratory distress syndrome; APACHE II: Acute physiology and chronic health evaluation II; BUN: Blood urea nitrogen; CI: Cardiac output index; CO: Cardiac output; CRRT: Continuous renal replacement therapy; CVP: Central venous pressure; EVLW: Extravascular lung water; EVLWI: Extravascular lung water index; GEDVI: Global end-diastolic volume index; PEEP: Positive end expiratory pressure; PICCO: Pulse-indicated continuous cardiac output; PVPI: Pulmonary vascular permeability index; P(v-a)CO$_2$: Central venoarterial carbon dioxide difference; ScvO$_2$: Central venous oxygen saturation; SCr: Serum creatinine; SD: Standard deviation; SOFA: Sequential organ failure assessment score; SVRI: Systemic vascular resistance index.
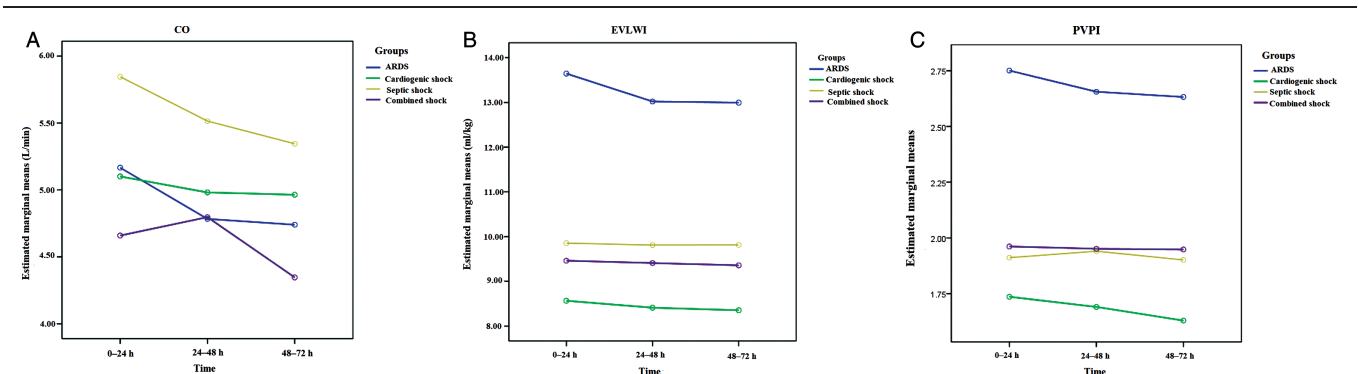

Figure 2: Dynamic changes in CO (A), EVLWI (B), and PVPI (C) at 0–24, 24–48, and 28–72 h. ARDS: Acute respiratory distress syndrome; CO: Cardiac output; EVLWI: Extravascular lung water index; PVPI: Pulmonary vascular permeability index.

Tissue perfusion index and renal function

Figure 3 shows the dynamic changes in the tissue perfusion index and the renal function. The CVP and SCr of these four groups showed a significant downward trend. However, there was no significant difference among the four groups at different time points. At the last time point (48–72 h), the cardiogenic shock, septic shock, and combined shock groups had a lower CVP than the ARDS group (P < 0.05). Regarding the ScvO$_2$, the trends in the four groups did not change significantly with time. However, the combined shock group was lower than the other three groups. The lactate showed a significant decreased trend in all four groups, but there were no clear trends for P(v-a)CO$_2$ and BUN. The detail data of the tissue perfusion index and the renal function are listed in Table 2.

Table 2: Dynamic changes in hemodynamic parameters, the tissue perfusion index, and renal function during the treatment process.

Characteristics	0–24 h	24–48 h	48–72 h	P
CO (L/min)				
ARDS group	5.1 (4.0, 6.2)	4.6 (3.8, 5.6)	4.5 (4.1, 5.4)	0.067
Cardiogenic shock group	4.7 (4.0, 5.7)	4.8 (4.1, 5.7)	4.8 (3.8, 5.5)	0.381
Septic shock group	5.5 (4.3, 6.7)	5.3 (4.4, 6.5)	5.3 (4.0, 6.4)	0.027
Combined shock group	4.6 (3.5, 5.7)	4.5 (3.8, 5.3)	4.0 (3.2, 5.4)	0.118
P	0.009	0.048	0.006	0.001[*], 0.013[†], 0.506[‡]
EVLWI (mL/kg)				
ARDS group	11.4 (8.7, 19.1)	11.8 (7.7, 17.2)	11.3 (7.7, 18.7)	0.340
Cardiogenic shock group	7.9 (6.6, 10.0)	7.8 (6.3, 10.2)	7.5 (6.3, 10.0)	0.617
Septic shock group	8.8 (7.4, 11.0)	8.7 (6.6, 12.2)	8.8 (6.3, 12.2)	0.990
Combined shock group	8.2 (6.7,11.3)	8.0 (6.6, 11.1)	8.4 (6.4, 11.2)	0.902
P	<0.001	<0.001	<0.001	0.236[*], <0.001[†], 0.817[‡]
PVPI				
ARDS group	2.2 (1.7, 3.6)	2.2 (1.8, 3.3)	2.4 (1.8, 3.5)	0.609
Cardiogenic shock group	1.7 (1.3, 2.0)	1.6 (1.3, 2.0)	1.5 (1.4, 1.8)	0.046
Septic shock group	1.8 (1.5, 2.2)	1.8 (1.3, 2.4)	1.8 (1.3, 2.5)	0.769
Combined shock group	1.9 (1.4, 2.2)	1.8 (1.4, 2.1)	1.8 (1.4, 2.1)	0.968
P	<0.001	<0.001	<0.001	0.230[*], <0.001[†], 0.845[‡]
CVP (mmHg)				
ARDS group	11.9 (10.0, 13.3)	10.9 (8.9, 12.3)	10.2 (8.4, 12.6)	0.022
Cardiogenic shock group	10.5 (9.1, 11.7)	10.1 (8.8, 11.9)	9.3 (8.3, 10.9)	0.001
Septic shock group	10.5 (8.7, 12.2)	9.8 (7.9, 11.8)	9.1 (7.7, 11.6)	<0.001
Combined shock group	10.5 (9.2, 12.7)	9.9 (8.6, 12.0)	9.0 (7.9, 10.9)	0.003
P	0.142	0.583	0.080	<0.001[*], 0.188[†], 0.745[‡]
P(v-a)CO$_2$ (mmHg)				
ARDS group	4.6 (3.5, 5.6)	4.4 (3.0, 5.6)	4.9 (3.3, 7.0)	0.019
Cardiogenic shock group	5.6 (4.3, 6.8)	4.8 (3.9, 6.1)	5.4 (4.2, 7.0)	0.019
Septic shock group	4.0 (3.1, 5.6)	4.3 (2.5, 7.0)	5.1 (3.9, 7.2)	0.008
Combined shock group	5.7 (4.3, 7.1)	5.4 (3.8, 6.7)	5.8 (3.8, 7.7)	0.893
P	0.020	0.251	0.979	0.003[*], 0.012[†], 0.386[‡]
ScvO$_2$ (%)				
ARDS group	72.4 ± 6.8	73.7 ± 6.7	73.3 ± 7.0	0.254
Cardiogenic shock group	73.0 ± 6.9	73.6 ± 6.0	72.0 ± 7.4	0.121
Septic shock group	75.0 ± 9.4	75.2 ± 9.6	73.2 ± 10.3	0.111
Combined shock group	71.2 ± 8.5	70.4 ± 8.6	70.6 ± 8.3	0.823
P	0.165	0.025	0.333	0.135[*], 0.041[†], 0.461[‡]
Lactate (mmol/L)				
ARDS group	4.1 (2.6, 6.3)	2.9 (1.4, 5.2)	2.3 (1.2, 3.8)	0.008
Cardiogenic shock group	2.4 (1.5, 4.5)	1.5 (1.1, 2.0)	1.2 (0.9, 1.5)	<0.001
Septic shock group	3.2 (1.9, 5.6)	2.1 (1.5, 3.7)	1.7 (1.2, 2.9)	<0.001
Combined shock group	2.8 (1.7, 4.7)	1.9 (1.4, 3.2)	1.7 (1.3, 2.7)	<0.001
P	0.002	0.001	<0.001	<0.001[*], <0.001[†], 0.790[‡]
SCr (μmol/L)				
ARDS group	133.5 (94.7, 189.8)	119.0 (78.3, 176.4)	119.5 (73.2, 149.8)	0.003
Cardiogenic shock group	127.7 (85.0, 183.7)	124.5 (87.0, 176.0)	117.2 (76.0, 163.9)	0.147
Septic shock group	130.5 (81.4, 269.3)	133.4 (73.3, 215.3)	130.1 (69.0, 184.4)	0.028
Combined shock group	121.7 (91.5, 173.3)	115 (85.3, 166.3)	104.3 (79.0, 164.0)	0.585
P	0.029	0.368	0.440	<0.001[*], 0.183[†], 0.057[‡]
BUN (mmol/L)				
ARDS group	12.3 (8.7, 17.5)	9.5 (6.9, 15.8)	10.5 (6.8, 15.6)	0.072
Cardiogenic shock group	8.9 (6.2, 13.3)	9.0 (6.2, 12.6)	8.6 (5.5, 15.3)	0.411
Septic shock group	11.4 (7.9, 15.9)	11.4 (7.6, 14.4)	11.0 (8.0, 14.4)	0.379
Combined shock group	10.6 (7.3, 16.2)	9.8 (6.6, 13.1)	8.5 (5.4, 14.8)	0.191
P	0.094	0.784	0.913	0.052[*], 0.530[†], 0.281[‡]

The data were shown as mean ± SD, or median (Q1, Q3). [*]P value of main effect for times. [†]P value of main effect for groups. [‡]P value of crossover effect. ARDS: Acute respiratory distress syndrome; BUN: Blood urea nitrogen; CO: Cardiac output; CVP: Central venous pressure; EVLWI: Extravascular lung water index; PVPI: Pulmonary vascular permeability index; P(v-a)CO$_2$: Central venoarterial carbon dioxide difference; ScvO$_2$: Central venous oxygen saturation; SCr: Serum creatinine; SD: Standard deviation.
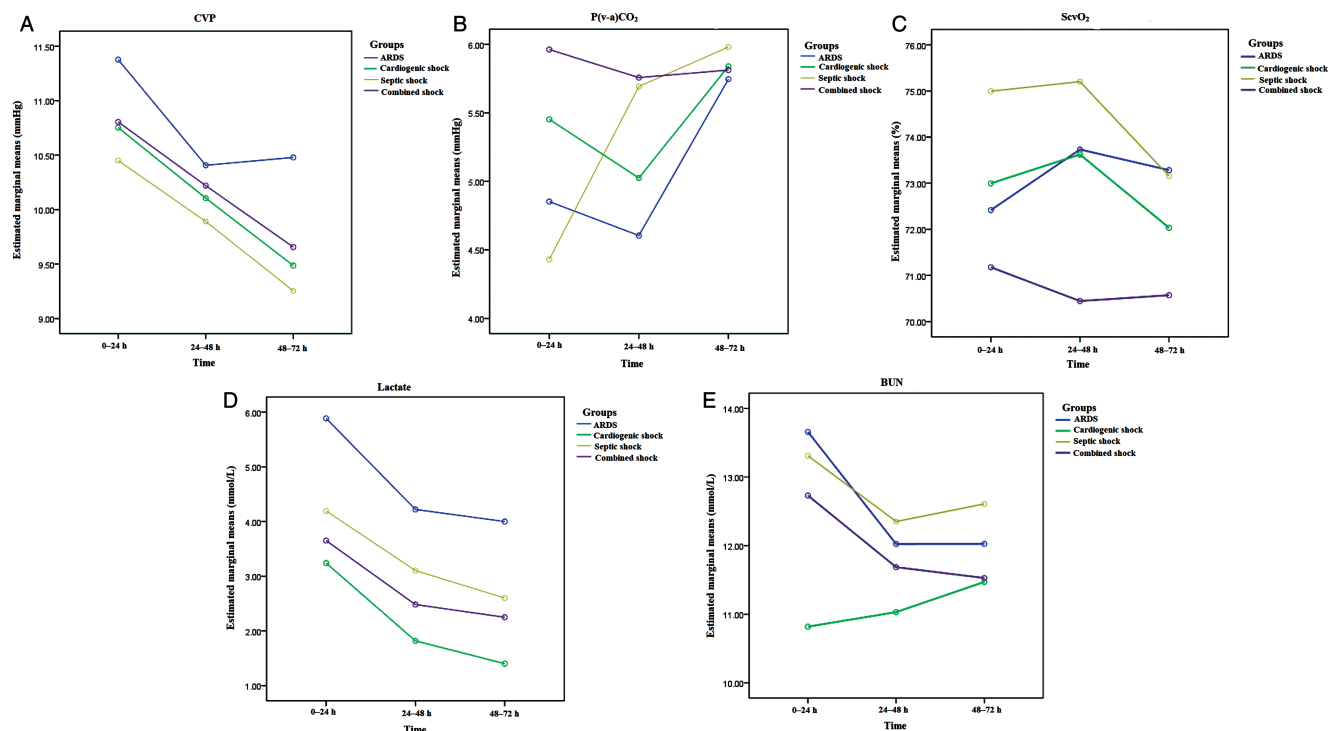
Figure 3: Dynamic changes in the tissue perfusion index (A–C) and renal function (D, E) at 0–24, 24–48, and 28–72 h. ARDS: Acute respiratory distress syndrome; BUN: Blood urea nitrogen; CVP: Central venous pressure; P(v-a)CO$_2$: Central venoarterial carbon dioxide difference; ScvO$_2$: Central venous oxygen saturation.
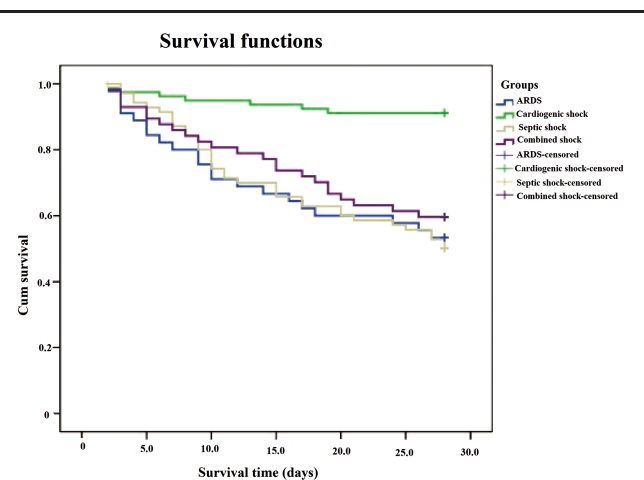

Figure 4: Kaplan-Meier analyses of the 28-day survival rates. ARDS: Acute respiratory distress syndrome.

Prognosis for 28-day survival

As depicted in Figure 4, post-hoc tests showed statistically significant differences in 28-day survival rates among the ARDS, cardiogenic shock, septic shock, and combined shock groups [log rank (Mantel-Cox) = 31.169, $P <$ 0.001]. The cardiogenic shock group had a higher 28-day survival rate than the other three groups, including ARDS, septic shock, and combined groups.

Discussion

This was a retrospective study exploring the relationship between EVLW and CO and revealing the potential

reasons behind CO for lung edema. The results of this study confirmed that the lower the CO, the smaller the tendency of EVLW formation. In addition, this study found that the moderate lower CO in the cardiogenic shock group did not affect the tissue perfusion and renal function. The cardiogenic shock group had the highest 28-day survival rate, which might indicate that less EVLW improved patients' survival rates.

Increased pulmonary microvascular hydrostatic pressure and increased permeability of the alveolo-capillary barrier could both result in interstitial EVLW.[15] The most pathophysiological hallmark of pulmonary edema is an increase in EVLW, especially in ARDS or other infectious diseases.[16] In this study, the results showed that EVLWI in ARDS was obviously higher than that in other groups in the previous studies. There is no doubt that pulmonary edema resulting from ARDS can be due to the high PVPI, which is also obviously higher than that in the other three groups. Regardless of the ARDS group, our results also suggested that among the remaining three groups, the EVLWI was apparently low in the lower CO groups such as the cardiogenic shock group and the combined shock group, whereas the PVPI in these three groups was nearly the same with no significant difference. According to the formation mechanism of lung water and the Starling principle, we could know the factors that can influence water in the lungs in light of the calculation formula: $Q_f = k_f [(p_v - p_i) - \Delta(\pi_v - \pi_i)]$ (Q_f, extravascular and intravascular lung water; k_f, vascular wall permeability index; Δ, reflow index; p, hydrostatic pressure; π, osmotic pressure; v, vascular; i, interstitial).[17,18] This meant that the formation of pulmonary edema could be divided into

"pressure type" or "permeability type" pulmonary edema. ARDS is a typical disease that can cause permeability-type edema, which was not the focus of this article. Similar to the other groups in this study, we should explore the other factors that made EVLW different as they had the same PVPI. It may be the first time to report in 1998 that overmuch vascular flow could aggravate lung injury and pulmonary edema.[19] Jozwiak et al[3] suggested that EVLW increased with volume expansion at the same permeability. A higher CO, which meant that there was more volume in the pulmonary vascular that could enhance the hydrostatic pressure, resulted in a high EVLW.[3] These views were in line with the results of this study. Another possible reason to explain our findings was the increased transvascular pressure. Regardless of the colloid osmotic pressure or capillary hydrostatic pressure, the key point of "pressure-type" pulmonary edema was the changing of transvascular pressure.[20,21] The interstitial edema is generated from the pulmonary capillary network around the alveoli. The capillary network and its surroundings are like a black box, as we cannot measure the luminal microvascular pressure and interstitial pressure at the bedside. Although there was no direct indicator in this study to confirm the relationship between CO and transvascular pressure, there was the possible reason that explained the clinical phenomenon. It is well established that typical hydrostatic pressure lung edema is the main clinical manifestation in heart failure patients.[22] However, in our study, we excluded these patients who presented with cardiogenic pulmonary edema at the initial PICCO. The results confirmed our hypothesis that a lower CO could cause a lower EVLW.

In this study, the lung could benefit from tissue-aimed lower CO, and there was no extra injury to organs and tissue perfusion. In the shock resuscitation stage, CO is usually increased by means of fluid treatment to improve oxygen delivery. However, many experiments have shown that excessive fluid therapy and a sustained high-capacity state could be harmful,[23,24] which was an independent risk factor in ICU patients.[25] Sakr et al[23] confirmed that a higher cumulative fluid balance at day 3 after ICU admission was independently associated with an increase in the hazard of death. Cunha et al[26] found that after recovery from shock, the fluid balance continued to rise. Patients who received more fluid treatment spent more time in the ICU and hospital. A clinical investigation designed by Sakr et al[27] revealed that nonsurvivors had a higher fluid balance during the first 4 days as well as cumulative fluid balance and a higher mean ICU stay than survivors in ARDS. During the ICU stay, a higher fluid balance was an independent risk contributing to a higher mortality in ARDS.[27] A multicenter European observational study confirmed that a positive fluid balance was associated with a worse outcome in patients with acute kidney injury.[28] All of the above studies have shown that excessive fluids might result in splanchnic congestion and cause damage to the organs. Thus, it is necessary to find the tissue-aimed lower CO and correspondent volume status for decreasing edema and injury. That means as long as the CO level meets the tissue perfusion and organ function levels, we do not need to increase it. In animal research, restrictive fluid resuscitation could improve oxygenation more than nonrestrictive fluid resuscitation in ARDS.[29] In the "fluids and catheters treatment trial,"[30] patients in the conservative strategy group showed a shorter duration of mechanical ventilation and significantly improved lung function without increasing other organ failures. Goal-directed fluid management, whether for septic shock or cardiogenic shock, could reduce vasopressor use and improve the prognosis.[31,32] Therefore, we hypothesized that the perfusion-aimed lowest CO was the most suitable CO for patients, and the results of this study might support this opinion.

This study revealed that the cardiogenic shock group had the lowest rate of deaths based on the 28-day survival. The most obvious difference between this group and the other three groups was that it had the lowest EVLW. This result at least indicated that lower EVLW was beneficial for patient prognosis, and this lower EVLWI was derived from perfusion-aimed lower levels of CO. To support this opinion, several studies have suggested that administration based on EVLW measurements was safe and effective,[32] reduced the duration of weaning from ventilation, decreased the fluid balance,[33] and improved ICU mortality.[33,34] In a retrospective study of ARDS patients, a decreased EVLW during the first week in ICU yielded a decrease in the day-28 mortality.[35] Except for ARDS patients, other patients with sepsis or septic shock but without ARDS had increased EVLW, possibly reflecting indirect lung injury,[36] as lower EVLW could improve the prognosis. Here, we provided evidence that a lower EVLWI was due to perfusion-aimed lower CO.

This study had several limitations. First, because this was a retrospective study, we did not measure the luminal microvascular and alveolar interstitial pressure. The mean pulmonary artery pressure and pulmonary capillary wedge pressure could be obtained by Swan-Ganz catheterization to assess the microvascular pressure. Esophageal pressure monitoring could be used to evaluate the interstitial pressure.[36] Therefore, prospective randomized control studies should be conducted in the future. Second, as a retrospective study, the number of patients included was small, so the results of this study could only provide a train of thought or possibility, and we still need large sample studies to reach high-quality conclusions. Third, urine output and fluid balance parameters were important for this study. Calculating the volume of liquid appears to be complicated and difficult due to a retrospective study involved a significant proportion of patients received CRRT.

In conclusion, through this retrospective study of the relationship between CO and EVLW under the CHT frame, we found that CHT-oriented resuscitation could reduce the production of EVLW and yield a good prognosis, which might be due to avoiding increasing the CO as soon as the patients' CO meets tissue perfusion and organ function levels. The most essential contribution leading to better prognosis of critically ill patients has been the cancellation or weakening of ineffective and potentially harmful treatments. We find that increased lung water from CO may be one of the possible mechanisms for an increased EVLW, and this study reveals how to prevent or reduce reinjury from our

treatments in clinical work. In the future, more investigations of precise and personalized CHT treatment involving hemodynamic therapy should be performed.

Conflicts of interest

None.

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