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The level of partial pressure of carbon dioxide affects organ perfusion in respiratory failure patients undergoing pressure support ventilation with venovenous extracorporeal membrane oxygenation: a prospective study

Yuankai Zhou[1], Liangyu Mi[1], Shengjun Liu[1], Yingying Yang[1], Na Cui[1], Xiaoting Wang[1], Huaiwu He[1] and Yun Long[1,2*]

Abstract

Background We evaluated the influence of different partial carbon dioxide pressure ($PaCO_2$) levels on organ perfusion in patients with respiratory failure receiving pressure-support ventilation with veno-venous extracorporeal membrane oxygenation (V-V ECMO).

Methods In this twelve patients prospective study, ECMO gas-flow was decreased from baseline ($PaCO_2 < 40$ mmHg) until $PaCO_2$ increased by 5–10 mmHg (High-CO_2 phase). Resistance indices of gut, spleen, and snuffbox artery, the peripheral perfusion index (PPI), and heart rate variability were measured at baseline and High-CO_2 phase.

Results When $PaCO_2$ increased from 36 (36–37) mmHg at baseline to 42 (41–43) mmHg in the High-CO_2 phase ($p < 0.001$), PPI decreased significantly ($p = 0.026$). The snuffbox artery ($p = 0.022$), superior mesenteric artery ($p = 0.042$), and spleen ($p = 0.012$) resistance indices increased significantly. The root mean square of successive differences (RMSSD) decreased from 19.5(18.1–22.7) to 15.9(14.4–18.6) ms ($p = 0.034$), and the ratio of low-frequency to high-frequency components(LF/HF) increased from 0.47 ± 0.23 to 0.70 ± 0.38 ($p = 0.013$).

Conclusions High $PaCO_2$ might cause decreased peripheral tissue and visceral organ perfusion through autonomic nervous system in patients with respiratory failure undergoing PSV with V-V ECMO.

Keywords $PaCO_2$, Peripheral perfusion, Visceral perfusion, Heart rate variability, Extracorporeal membrane oxygenation.

*Correspondence:
Yun Long
ly_icu@aliyun.com
[1]Department of Critical Care Medicine, Peking Union Medical College Hospital, Beijing, China
[2]Department of Critical Care Medicine, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing 100730, China

Background

Respiratory drive and effort are commonly increased in patients with respiratory failure [1], even after receiving veno-venous extracorporeal membrane oxygenation (V-V ECMO) support, due to low pulmonary compliance or high systemic inflammation [2].Excessive respiratory effort may cause inspiratory muscle injuries and self-inflicted lung injury (SILI) [3–5], as well as worsening of extrapulmonary organ perfusion [6]. An elevation in the partial pressure of carbon dioxide in the arterial blood ($PaCO_2$) stimulates the respiratory center [3] and triggers an excitatory response. Increased sympathetic nervous system activity is frequently accompanied by hyperexcitation of the respiratory center and autonomic nervous system(ANS) [7, 8]. As a result, this sympathetic hyperactivity induces alterations in cardiac output and vascular resistance, which ultimately has an effect on the perfusion of visceral organs and peripheral tissues.

Different levels of extracorporeal carbon dioxide removal in patients with respiratory failure undergoing V-V ECMO has been shown to alter respiratory drive and effort [9, 10]. This study sought to investigate the impact of different CO_2 levels on ANS and organ perfusion in a cohort of patients with respiratory failure undergoing pressure-support ventilation (PSV) with V-V ECMO.

Methods

This study was authorized by the Peking Union Medical College Hospital's ethical committee(K24C0020). Before enrollment, written informed consent was obtained from all patients or their next of kin.

Patients

This trial was conducted in a 30-bed adult intensive care unit (ICU). The enrolment period was between December 2022 and November 2023.

The inclusion criteria were as follows: (1) age > 18 years; (2) patients with respiratory failure who received V-V ECMO and PSV via tracheal intubation; and (3) $PaCO_2$ < 40mmHg, peak airway pressure < 25 cmH_2O, and respiratory rate < 25 bpm; (4) sinus rhythm.

We excluded patients who had undergone abdominal surgery involving the digestive tract, descending thoracic, or abdominal aortic operations; who had coronary heart disease, renal artery stenosis, or severe mesenteric stenosis; or who had low-quality ultrasound imaging.

Typically, A 21-Fr cannula was used to venous access, and a 17-Fr cannula was used to venous return. The ECMO sweep gas flow (GF) was 2–10 L/min, and the blood flow was 3.0–4.0 L/min in order to preserve arterial oxygenation and normocapnia.

Measurements

Indices of peripheral perfusion

Peripheral blood flow was assessed using two clinical indices: peripheral perfusion index (PPI), and resistance index (RI) of the snuffbox artery (SBRI).

The PPI is an index obtained from the photoelectric plethysmographic output of a pulse oximeter. It was assessed using an A Viridia/56S monitor (Philips Medical Systems, Hamburg, Germany) to determine the proportion of the plethysmographic waveform that is pulsatile compared to non-pulsatile.

The SBRI was measured at a depth of 1 cm in the radial artery of the snuffbox using a 3–10 MHz linear probe and evaluated by Doppler ultrasound (Portable Doppler Ultrasound System, M10, Mindray, Shenzhen, China), as described in a previous study [11]. The RI was defined as the peak systolic velocity minus the end diastolic velocity (EDV) divided by the peak systolic velocity. It was obtained by waveform analysis in B-mode.

Indices of visceral perfusion

Doppler indices were assessed twice independently by two skilled doctors, and the mean of the two measurements were then calculated. The doctors have at least three years' critical care experience and have been trained by the China Critical Care Ultrasound Study Group.

The RI, as a Doppler ultrasound indicator, reflects the blood flow velocity variations. The lower values of RI indicated the lower vascular tension [12–15]. The visceral Doppler measurements were measured with a 2–5 MHz convex probe.

The RI values of the spleen and intestine were taken by identifying the most significant artery in each organ (spleen: subbranch of the splenic artery; intestine: initial part of the superior mesenteric artery) using colour Doppler mode. Three regions of the spleen were measured (inferior pole/posterior pole, superior pole/anterior pole and interpole) and averaged.

The superior mesenteric artery RI (SMA-RI) was assessed 1 cm proximal to the abdominal aort.

Heart rate variability

Heart rate variability(HRV) is considered to be a sensitive indicator of ANS function and was calculated during consecutive electrocardiogram (ECG) recordings over 5 min (Philips Medical Systems, Hamburg, Germany). The root mean square of successive difference between heart beats(RMSSD) and the frequency domain indices were obtained as HRV parameters. RMSSD quantifies vagal activity and is the main time-domain measure used for this purpose. The frequency domain indices used were the low-frequency power (LF, 0.04- to 0.15-Hz) and high-frequency power (HF, 0.15- to 0.4-Hz) and the

ratio of LF and HF (LF/HF). LF/HF indicates the balance between sympathetic and parasympathetic activity [16].

Blood gas analysis and hemodynamics

The mechanical ventilation parameters, heart rate (HR), mean arterial pressure were recorded. A Radiometer ABL800 FLEX analyser (Radiometer Medical ApS, Copenhagen, Denmark) was used for blood gas analysis, which was calibrated daily to ensure accurate measurements. The Pv-aCO_2 was calculated by subtracting $PaCO_2$ from central venous carbon dioxide tension.

All patients underwent mechanical PSV and had end-tidal carbon dioxide ($etCO_2$) monitoring with a CAPNOSTAT M2501A CO_2 sensor (Philips, The Netherlands).

Study protocol

Once the patient was enrolled, ECMO GF was adjusted to achieve stable baseline conditions, defined as peak airway pressure < 25 cmH_2O, respiratory rate < 25 bpm, and $PaCO_2$ < 40 mmHg. Before commencing the study, sedative medications were adjusted to achieve Richmond agitation-sedation scale scores ranging from −3 to −2, and the PSV mode was performed.

The inspired oxygen fraction, PEEP, PSV, norepinephrine dose, sedative and analgesic doses, and ECMO blood flow remained constant during the protocol. Peripheral perfusion and ultrasound parameters were measured immediately, and HRV and hemodynamic parameters were collected. All data collection was completed within 10 min.

After stabilization of baseline parameters, the protocol was initiated. Initially, the ECMO GF was adjusted to 50% of the baseline value, and subsequent changes in $etCO_2$ levels were closely monitored. Adjustments to the ECMO GF were made at 5-minute intervals, either increasing or decreasing by 0.5 L/min, until the $etCO_2$ stabilized at a level 5–10 mmHg above the baseline value. Once the $etCO_2$ had stabilized, all parameters were re-measured 20 min later to capture the effects of the intervention at high $PaCO_2$ levels. The time between two tests should not exceed one hour to avoid the possibility of interference from other factors (Fig. 1).

Statistical analysis

Descriptive statistics were calculated. All data are expressed as mean±standard deviation or median (25–75% interquartile range). The normality of the data distribution was assessed using the Shapiro–Wilk test. Variables were compared between the baseline and High-CO_2 phases using Student's paired t-test or paired-samples Wilcoxon signed-rank test. Linear correlations were analyzed using Pearson's test. The sample size was larger than that used in previous studies on patients with respiratory failure who received V-V ECMO [9, 10, 17]. All comparisons were two-tailed, and $p<0.05$ was required to reject the null hypothesis. SPSS version 25.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis.

Results

Twelve respiratory failure patients on V-V ECMO support were enrolled in this prospective study. Basic patient characteristics and demographics are shown in Table 1. Eleven patients received V-V ECMO with internal jugular-femoral vein access, and one patient received a double-lumen neck cannula. The study protocol was successfully completed by all enrolled patients.

All patients were male and had a mean age of 72±10 years. Upon enrollment in the study, the mechanical ventilation (MV) time was 19(9–25) days, the Sequential Organ Failure Assessment (SOFA) score was 12±2, and the mean ECMO time was 11(7–18) days (Table 1).

Our results showed that ECMO GF was down-regulated from 5.3±1.4 L/min in the baseline phase to 3.0±1.0 L/min in the High-CO_2 phase. Consequently, the $PaCO_2$ increased from 36(36–37) mmHg during the baseline phase to 42(41–43) mmHg during the High-CO_2 phase (Table 2).

Regarding peripheral perfusion indicators, we observed a significant decrease in PPI (from 1.5±0.5 in the baseline phase to 1.1±0.4 in the High-CO_2 phase, $p=0.026$). The SBRI increased from 0.89±0.10 during the baseline phase to 0.99±0.13 during the High-CO_2 phase, $p=0.022$. Concerning indices of visceral perfusion, the SMA-RI ($p=0.042$) and spleen-RI ($p=0.012$) increased significantly from the baseline phase to the High-CO_2 phase (Table 3; Fig. 2).

Furthermore, HRV parameters changed significantly with elevation in $PaCO_2$. The RMSSD decreased from 19.5(18.1–22.7) to 15.9(14.4–18.6) ms ($p=0.034$), and the LF/HF increased from 0.47±0.23 to 0.70±0.38 ($p=0.013$) (Table 3; Fig. 2).

Discussion

This study explored the correlation between $PaCO_2$ and organ perfusion in respiratory failure patients undergoing PSV with V-V ECMO, which has not been reported previously. The results of this study indicated that, in patients with respiratory failure undergoing PSV with V-V ECMO, an increase in $PaCO_2$ levels from <40 mmHg to >40 mmHg was accompanied by a decline in peripheral perfusion indices (PPI and SRBI) and visceral perfusion indices (SMA-RI and spleen-RI), and may associated with sympatho-excitation and parasympatho-inhibition of the ANS.

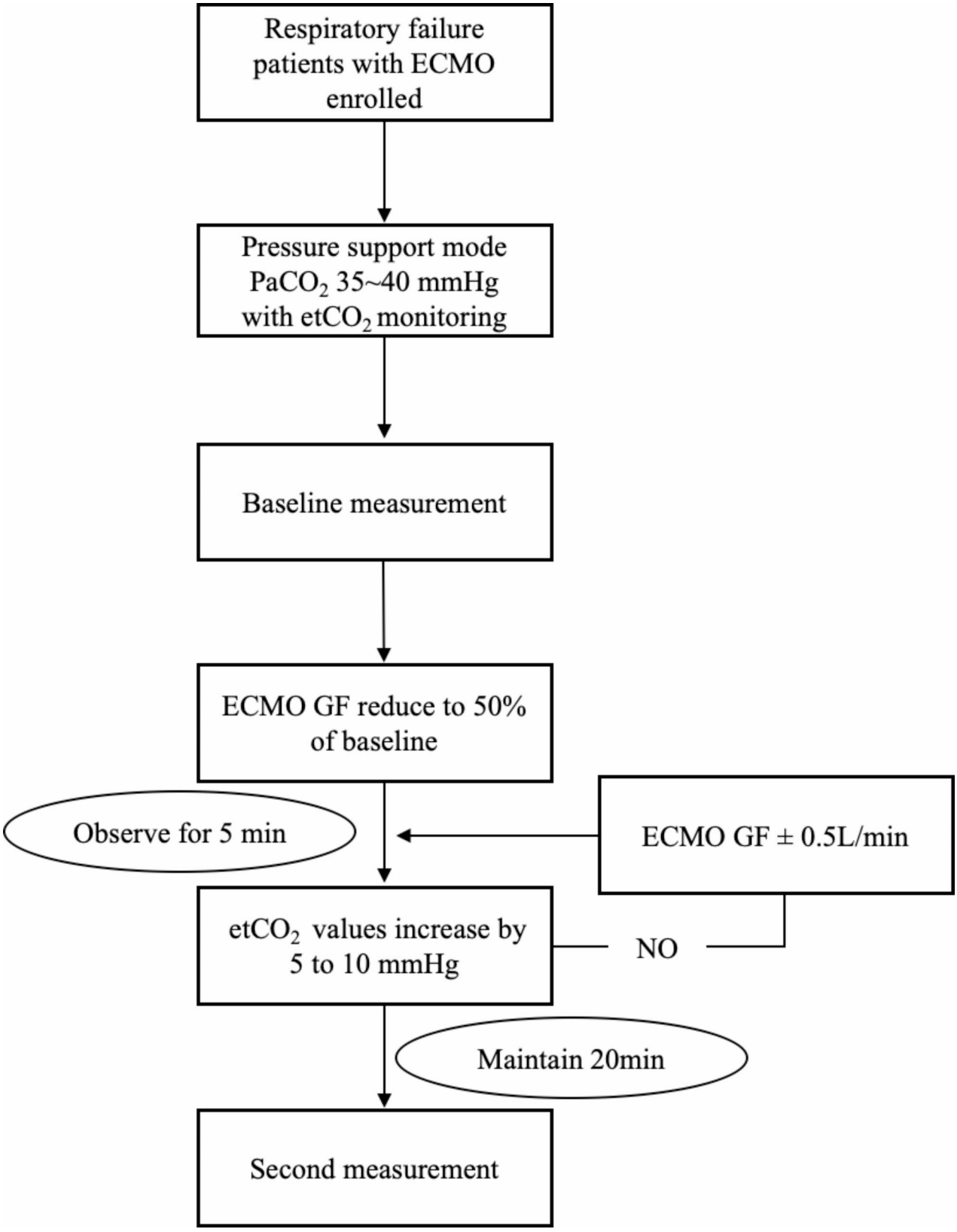

Fig. 1 Study protocol. ECMO: extracorporeal membrane oxygenation; PSV: pressure support ventilation; $etCO_2$: end tidal carbon dioxide; GF: gas flow

Table 1 Characteristics of twelve spontaneously breathing respiratory failure patients with venovenous extracorporeal membrane oxygenation enrolled

Patients Number	Age (year)	Sex	SOFA	ARDS Etiology	Days on ECMO before Enrolment	Days on MV before Enrolment	Cst (ml/cm H2O)	PEEP (cm H_2O)	PSV Level (cm H_2O)	ECMO BF (L/min)	In-hospital Survival
1	62	male	11	virus pneumonia	18	6	22	8	11	4	S
2	79	male	10	virus pneumonia	10	12	18	10	8	3.5	D
3	80	male	12	virus pneumonia	7	18	20	8	8	3.2	S
4	68	male	11	virus pneumonia	11	23	17	8	12	4	D
5	78	male	14	virus pneumonia	10	23	16	10	8	3.2	S
6	75	male	12	virus pneumonia	59	60	13	10	8	4	D
7	78	male	12	virus pneumonia	17	25	18	8	10	3.1	S
8	66	male	14	virus pneumonia	7	8	17	8	12	3.6	S
9	86	male	12	virus pneumonia	17	30	8	8	12	3	D
10	59	male	15	virus pneumonia	8	13	22	8	10	3.5	D
11	84	male	9	virus pneumonia	4	8	21	8	12	3.5	S
12	59	male	13	diffuse alveolar hemorrhage	18	19	24	6	12	3.3	S
*Total	72 ± 10	-	12 ± 2	-	11(7–18)	19(9–25)	18 ± 4	8(8–10)	11(8–12)	3.5 ± 0.4	7S/5D

*Values are given as mean + standard deviation or median (interquartile range)

SOFA: sequential organ failure assessment; ARDS: acute respiratory distress syndrome; ECMO: extracorporeal membrane oxygenation; MV: mechanical ventilation; Cst: static lung compliance; PEEP: positive end expiratory pressure; PSV: pressure support ventilation; BF: blood flow

Table 2 Variations in the breathing pattern between baseline phase and High-CO_2 phase in respiratory failure patients undergoing pressure support ventilation with venovenous extracorporeal membrane oxygenation

Characteristic	Baseline	High-CO_2	*p* value
ECMO GF (L/min)	5.3 ± 1.4	3.0 ± 1.0	< 0.001
RR(bpm)	13 ± 2	15 ± 2	0.012
MVe (L/min)	3.8 ± 1.4	5.5 ± 1.9	< 0.001
Vt (ml/kg)	4.2 ± 1.2	5.4 ± 1.4	< 0.001
pH	7.44 ± 0.05	7.42 ± 0.04	0.014
$PaCO_2$ (mmHg)	36(36–37)	42(41–43)	< 0.001
PaO_2 (mmHg)	97(88–129)	94(87–108)	0.182
HCO_3^-(mmol/L)	26.1 ± 2.0	26.6 ± 2.5	0.612
Arterial Lactate(mmol/L)	1.5 ± 0.4	1.7 ± 0.5	0.215
HR(bpm)	82 ± 13	87 ± 13	0.008
MAP(mmHg)	88 ± 11	91 ± 10	0.147
NE(ug/kg/min)	0.06(0.01–0.15)	0.06(0.01–0.15)	> 0.999
Fentanyl (ug/h)	58 ± 15	58 ± 15	> 0.999
Propofol (mg/h)	65(60–95)	65(60–95)	> 0.999
Midazolam(mg/h)	2.6 ± 2.4	2.6 ± 2.4	> 0.999

Values are given as mean + standard deviation or median (interquartile range)

ECMO: Extracorporeal Membrane Oxygenation; GF: gas flow; RR: respiratory rate; MVe: minute volume expiration; Vt: tidal volume; $PaCO_2$: partial pressure of carbon dioxide in arterial blood gas; PaO_2: Oxygen partial pressure of arterial blood gas; HR: heart rate; MAP: mean arterial pressure; NE: norepinephrine

Table 3 Parameters between baseline phase and High-CO_2 phase in respiratory failure patients undergoing pressure support ventilation with venovenous extracorporeal membrane oxygenation

		Baseline	High-CO_2	*p* value
peripheral perfusion parameters	PPI	1.5 ± 0.5	1.1 ± 0.4	0.026
	SBRI	0.89 ± 0.10	0.99 ± 0.13	0.022
splanchnic perfusion parameters	SMA-RI	0.80 ± 0.04	0.82 ± 0.05	0.042
	Spleen-RI	0.64 ± 0.05	0.68 ± 0.07	0.012
heart rate variability parameters	RMSSD(ms)	19.5(18.1–22.7)	15.9(14.4–18.6)	0.034
	LF(ms^2)	51.4(23.2-120.2)	69.5(41.43–178.9)	0.110
	HF(ms^2)	115.4(77.5-206.1)	117.8(90.1-175.1)	0.850
	LF/HF	0.47 ± 0.23	0.70 ± 0.38	0.013

Values are given as mean + standard deviation or median (interquartile range)

PPI: Peripheral perfusion index; SBRI: resistance index of snuffbox artery; SMA-RI: resistance index of superior mesenteric artery; Spleen-RI: resistance index of spleen; RMSSD: the root mean square of successive differences; LF: low-frequency; HF: high-frequency; LF/HF: the ratio of LF to HF components

Effect of PaCO2 on respiratory center and ANS

It has been demonstrated that elevated $PaCO_2$ could increase respiratory effort in patients with respiratory failure undergoing PSV with V-V ECMO [10]. $PaCO_2$ changes are the main factor exciting the respiratory center in humans, and its effect on the respiratory center is mainly achieved through two pathways. One is the central chemoreceptor located in the medulla oblongata, which is very sensitive to changes in $PaCO_2$ levels (note that CO_2 effects on the central chemoreceptor is mainly achieved through changes in H^+), and a ventilation-enhancing response occurs when $PaCO_2$ increases by 2 mmHg. The other pathway indirectly affects the excitability of the respiratory center by peripheral chemoreceptors, but the sensitivity is much lower. Consequently, the respiratory center is stimulated when $PaCO_2$ is elevated, causing an increase in the respiratory drive sent through the respiratory center, which then leads to increased respiratory effort.

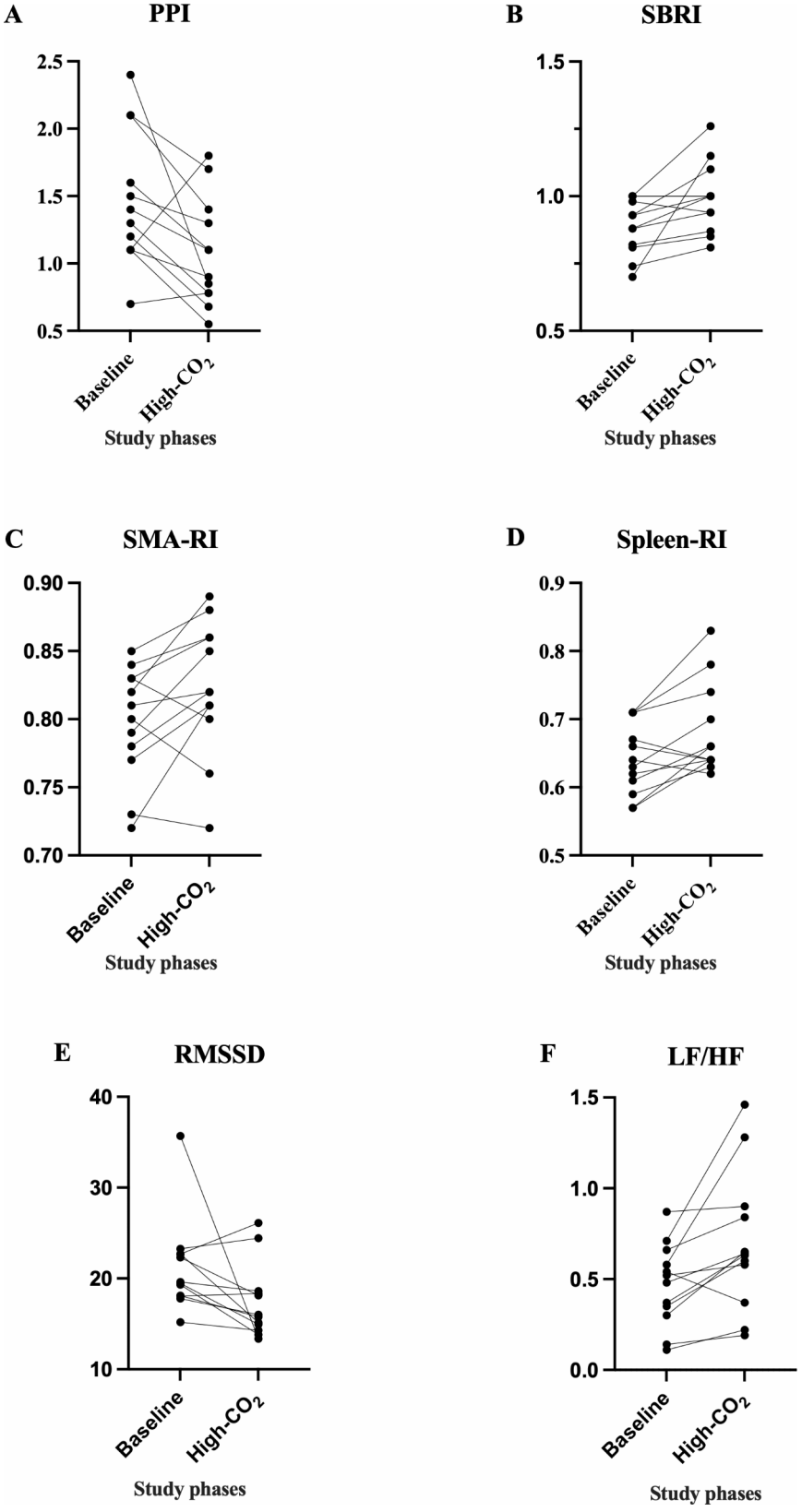

Fig. 2 Baseline phase vs. High-CO_2 phase. PPI: Peripheral perfusion index; SBRI: resistance index of snuffbox artery; SMA-RI: resistance index of superior mesenteric artery; Spleen-RI: resistance index of spleen; RMSSD: the root mean square of successive differences; LF/HF: the ratio of low-frequency to high-frequency components

As the respiratory center of the body, the pre-Bötzinger complex (preBötC) also has a direct influence on ANS and systemic haemodynamics. The preBötC participates directly in the regulation of cardiovascular activity. Pre-BötC neurons project directly to vascular pre-sympathetic and parasympathetic neurons, thereby influencing the vascular tone in various organs. This has also been demonstrated in animal studies [18]. Inhibition of pre-BötC neurons in rats modulates the activity of cardiac parasympathetic neurons, whereas excitation of preBötC neurons modulates the activity of sympathetic vasomotor neurons, which produce oscillations in heart rate and blood pressure in phase with respiratory rhythms.

HRV parameters could reflect the state of the ANS [19]. RMSSD is thought to reflect parasympathetic activity and is also considered to be a major indicator of vagal-mediated HRV [20]. Some studies suggest an correlation of the LF/HF with the sympathetic and parasympathetic balance of the ANS [21], and elevated LF/HF suggests increased sympathetic excitation. In the present study, it was found that an increase in $PaCO_2$ led to a decrease in RMSSD and an increase in LF/HF. The decrease in patients' HRV values during the High-$PaCO_2$ phase has suggested an alteration in ANS, possibly confirming the effects on the ANS when the respiratory drive of the pre-BötC is increased.

Effect of PaCO2 on organ perfusion

Based on the results of previous related studies [12, 14, 22, 23], the RI of the visceral and peripheral organs decreased significantly, indicating a reduction of organ perfusion.

The results of this study showed that, in patients with respiratory failure undergoing PSV with V-V ECMO, an increase in $PaCO_2$ was associated with a decline in visceral and peripheral perfusion indices.

As described above, elevated $PaCO_2$ leads to excitation of the respiratory center, which in turn causes sympatho-excitation and parasympatho- inhibition. It leads to micro-arterial constriction, with ensuing increased systemic vascular resistance, which may reduce blood flow to visceral organs, such as the intestine and spleen.

The innate neural network within the gastrointestinal tract, which includes the intestinal muscle plexus, submucosal plexus, and interstitial cells of Cajal, is mainly regulated by the sympathetic nervous system. This system regulates the gastrointestinal blood flow through nerve-dependent vasoconstriction.

Hyperexcitation of the respiratory center is commonly accompanied by hyperactivity of the sympathetic nerves, which alters cardiac output and vascular resistance. These alterations can affect the perfusion of the visceral organs and peripheral tissues.

Moreover, perfusion of peripheral tissue might be affected by blood alkalosis. Skin microcirculatory blood flow decreases markedly with alkalosis [24].

Impact of PaCO2 level on organ protection in V-V ECMO patients undergoing PSV

This study investigated the potential correlation between $PaCO_2$ level and visceral and peripheral organ perfusion in patients with respiratory failure undergoing PSV with V-V ECMO, which may be caused by the neurological stress response. This revelation underscores the need for subsequent, larger-scale, controlled trials to provide a more definitive assessment of the intervention's impact on organ perfusion dynamics and overall clinical outcomes.

Limitations

This study has some limitations: (1) A non-invasive, indirect measurement method was used. The RI indirectly measures vascular resistance. (2) The size of the sampled population was small, although the statistical outcome was satisfactory. (3) HRV is a useful index of ANS and can be measured easily. But many different physiological processes affect it, and the effect of patients of different ages and comorbidities may have hampered analysis. However, this study used a paired *t*-test analysis, which can reduce the effect of different ages and comorbidity states on our HRV analyses.

Conclusions

High level of $PaCO_2$ might lead to a decrease in peripheral tissue and visceral organ perfusion through ANS in patients with respiratory failure undergoing PSV with V-V ECMO.

Abbreviations

BF	blood flow
Cst	Static lung compliance
GF	gas flow
HF	high-frequency
HR	heart rate
LF	low-frequency
LF/HF	the ratio of LF to HF components
MAP	mean arterial pressure
MV	mechanical ventilation
MVe	minute volume expiration
NE	norepinephrine
$PaCO_2$	partial pressure of carbon dioxide in arterial blood gas
PaO_2	Oxygen partial pressure of arterial blood gas
PEEP	Positive end expiratory pressure
PPI	Peripheral perfusion index
PSV	pressure support ventilation
RMSSD	the root mean square of successive differences
RR	respiratory rate
SBRI	resistance index of snuffbox artery
SMA-RI	resistance index of superior mesenteric artery
SOFA	Sequential organ failure assessment
Spleen-RI	resistance index of spleen
Vt	tidal volume
V-V ECMO	veno-venous extracorporeal membrane oxygenation

Supplementary Information

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Supplementary Material 1

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Author contributions
Yuankai Zhou contributed to the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article, and final approval of the version to be published. Liangyu Mi, Shengjun Liu and Yingying Yang helped in data collection and data analysis; Xiaoting Wang helped to build up the research idea; Na Cui and Huaiwu He guided the discussion; Yun Long guided the whole research program and should be considered the correspondence author of this article.

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Data availability
Data is provided within supplementary information files(Additional file 1).

Declarations

Ethics approval and consent to participate
This study was authorized by the Peking Union Medical College Hospital's ethical committee(K24C0020). Before enrollment, written informed consent was obtained from all patients or their next of kin.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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