Critical Care

BRIEF REPORT

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Effects of airway pressure release ventilation on lung physiology assessed by electrical impedance tomography in patients with early moderate-to-severe ARDS

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Abstract

Objective The aim of this study was to investigate the physiological impact of airway pressure release ventilation (APRV) on patients with early moderate-to-severe acute respiratory distress syndrome (ARDS) by electrical impedance tomography (EIT).

Methods In this single-center prospective physiological study, adult patients with early moderate-to-severe ARDS mechanically ventilated with APRV were assessed by EIT shortly after APRV (T0), and 6 h (T1), 12 h (T2), and 24 h (T3) after APRV initiation. Regional ventilation and perfusion distribution, dead space (%), shunt (%), and ventilation/perfusion matching (%) based on EIT measurement at different time points were compared. Additionally, clinical variables related to respiratory and hemodynamic condition were analyzed.

Results Twelve patients were included in the study. After APRV, lung ventilation and perfusion were significantly redistributed to dorsal region. One indicator of ventilation distribution heterogeneity is the global inhomogeneity index, which decreased gradually [0.61 (0.55–0.62) to 0.50 (0.42–0.53), $p < 0.001$]. The other is the center of ventilation, which gradually shifted towards the dorsal region (43.31 ± 5.07 to 46.84 ± 4.96%, $p = 0.048$). The dorsal ventilation/perfusion matching increased significantly from T0 to T3 (25.72 ± 9.01 to 29.80 ± 7.19%, $p = 0.007$). Better dorsal ventilation (%) was significantly correlated with higher PaO_2/FiO_2 (r = 0.624, $p = 0.001$) and lower $PaCO_2$ (r = -0.408, $p = 0.048$).

Conclusions APRV optimizes the distribution of ventilation and perfusion, reducing lung heterogeneity, which potentially reduces the risk of ventilator-induced lung injury.

Keywords Acute respiratory distress syndrome, Airway pressure release ventilation, Electrical impedance tomography, Heterogeneity, Ventilation/perfusion matching, Ventilator-induced lung injury

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Introduction

Airway pressure release ventilation (APRV) is a highly effective strategy improving lung recruitment and oxygenation in clinical studies, but its effects on lung injury and mortality is debatable [1, 2]. Animal studies revealed that APRV could normalize post-injury heterogeneity and reduce the risk of ventilator-induced lung injury (VILI) [3, 4]. However, the physiological effects of APRV on patients with acute respiratory distress syndrome (ARDS) have yet to be thoroughly investigated due to the unavailability of point-of-care evaluation method.

Electrical impedance tomography (EIT), a noninvasive, bedside, and radiation-free technique, has been proposed as a valid method monitoring lung ventilation and perfusion [5]. To uncover the underlying physiological mechanism, we assessed the impact of APRV on lung ventilation and perfusion in patients with early moderate-to-severe ARDS by EIT.

Methods

Study design

We conducted a prospective, observational study in the general ICU of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, from March 2022 to June 2022. The study was approved by the Institutional Research and Ethics Committee of Union Hospital (NO. 2022–0048). Written informed consents were obtained from the patients' legal representatives. The study was registered before enrollment at chictr.org.cn (ChiCTR2200057638).

Patients

The inclusion criteria were moderate-to-severe ARDS patients (defined as PaO_2/ $FiO_2 \leq 200$ mmHg with positive end-expiratory pressure ≥ 5 cmH_2O according to the Berlin definition [6]), endotracheal mechanical ventilation ≤ 48 h before enrollment, and expected to require continuous invasive mechanical ventilation ≥ 72 h. The exclusion criteria are provided in Additional file 1: Table S1.

Study protocol

We screened all adult, mechanically ventilated patients. Those patients who fulfilled the criteria for ARDS were submitted to a stabilization phase during which they were ventilated with volume-controlled, assist/control mode in accordance with the recommendations of the ARDS Network [7] (detailed procedures refer to Additional file 1). At the end of this stabilization period, patients were included if they met the inclusion and exclusion criteria, and baseline respiratory mechanics were measured. Then all patients were ventilated in APRV mode (C500 Infinity ventilator, Dräger, Germany). Patients were deeply sedated and, if necessary, paralyzed to abrogate spontaneous breathing if $PaO_2/FiO_2 < 150$ mmHg, whereas spontaneous breathing was permitted in patients with $PaO_2/FiO_2 \geq 150$ mmHg, respiratory rate less than 35 bpm, and no significant patient-ventilator asynchrony [8, 9]. Every patient maintained normovolemia during APRV.

Settings of APRV were standardized for all patients as follows. (1) Initially, high airway pressure (P_{High}) was set at the plateau pressure from volume control ventilation not to exceed 30 cmH_2O and low airway pressure (P_{Low}) was set at 0 cm H_2O. The release time (T_{Low}) was set at 0.3 to 0.6 s with I:E ratio 9:1 and adjusted to achieve an end-expiratory flow rate equal to 50–75% of the peak expiratory flow rate. (2) If patients develop $SpO_2 < 90\%$, three options are available (detailed method refer to Additional file 1): increase P_{High} by 2 cmH_2O until a maximum of 30 cmH_2O, increase the time of high airway pressure (T_{High}) by 0.5 s (with an unaltered T_{Low}, increased T_{High} implied an increased I:E ratio and a decreased respiratory rate), and increase FiO_2. (3) If patients develop $PaCO_2 > 60$ mmHg, T_{High} can be decreased to achieve greater mandatory respiratory rate, or P_{High} can be increased by 2 cmH_2O until a maximum of 30 cmH_2O. (4) If the PaO_2/FiO_2 does not improve or remains below 150 mmHg, prone positioning will be considered. (5) If refractory hypoxemia persists, recruitment maneuver and extracorporeal membrane oxygenation will be considered.

EIT assessment (detailed procedures refer to Additional file 1, Figure S1) was administered shortly after APRV (T0), and 6 h (T1), 12 h (T2), and 24 h (T3) after APRV initiation. Parameters of ventilator, respiratory mechanics, and hemodynamics were also recorded at T0, T1, T2, and T3 before EIT assessment. Arterial blood gases analysis was recorded at T0 and T3.

Study outcomes

The primary endpoint of the study was regional tidal volume distribution after 24 h of APRV. The second endpoints were global inhomogeneity (GI) index, center of ventilation (CoV), regional perfusion distribution, dead space-EIT (%), shunt-EIT (%), Ventilation/perfusion (V/Q) matching (%), and clinical variables related to respiratory and hemodynamic condition.

Statistical analysis

Statistical analyses were computed with GraphPad Prism 9.0 (GraphPad Software, San Diego, CA, USA). Continuous variables were summarized as mean ± standard deviation or median (25–75th), as appropriate. A paired t-test was used to compare the paired data. Repeated measures ANOVA or Friedman test was applied with post-hoc

Bonferroni's or Dunn's multiple comparisons to compare the data obtained at each time points, as appropriate. Correlation between continuous variables was assessed by the nonparametric Spearman correlation. A level of p value less than 0.05 (two-tailed) was considered as statistically significant.

Results

Twelve ARDS patients (9 male, 3 female) were included in the study. Mean age was 53.67 ± 12.37 years. There were 5 (42%) patients with severe ARDS and 7 (58%) patients with moderate ARDS. More detailed clinical characteristics of the study population were presented in Additional file 1: Table S2. During APRV, no patient developed barotrauma (pneumothorax, mediastinal emphysema, or subcutaneous emphysema), and all patients were in supine position.

Data from EIT-based measurements showed that the regional lung ventilation and perfusion significantly redistributed from the ventral to dorsal region following ARPV application (Table 1). The median GI index of ventilation progressively decreased [0.61 (0.55–0.62) to 0.50 (0.42–0.53), $p < 0.001$], and CoV gradually changed towards dorsal regions (43.31 ± 5.07 to 46.84 ± 4.96%, $p < 0.05$). Patients trend to have an increased global V/Q matching (%) (63.41 ± 13.47 to 68.58 ± 11.70%) and decreased shunt-EIT (%) (13.80 ± 7.53 to 8.39 ± 5.18%) from T0 to T3, but not significantly; however, the dorsal V/Q matching (%) increased significantly (25.72 ± 9.01 to 29.80 ± 7.19%, $p = 0.007$) (Fig. 1). In subgroup analysis, patients with moderate ARDS had a significant increase in global V/Q matching (%) (58.88 ± 14.34 to 67.60 ± 12.75%, $p = 0.019$) and a decrease in global functional shunt (16.78 ± 7.81 to 9.16 ± 5.92%, $p = 0.040$), whereas patients with severe ARDS had no improvement (Fig. 1).

From T0 to T3, median respiratory system static compliance after APRV application increased from 32.15 (27.11–42.30) to 37.95 (36.00–44.25) mL/cmH_2O ($p = 0.030$). Additionally, PaO_2/FiO_2 increased from 109.5 ± 36.44 to 222.2 ± 58.46 mmHg significantly ($p < 0.001$), and $PaCO_2$ decreased from 44.27 ± 8.58 to 36.78 ± 4.20 mmHg significantly ($p = 0.032$). Better dorsal ventilation (%) was significantly correlated with higher PaO_2/FiO_2 (r = 0.624, $p = 0.001$) and lower $PaCO_2$ (r = -0.408, $p = 0.048$) (Fig. 1). No significant difference was identified in hemodynamic variables.

Discussion

To the best of our knowledge, this is the first study using EIT to assess the physiological effects of APRV on lung ventilation and perfusion distribution, and V/Q matching in patients with early moderate-to-severe ARDS.

This study showed that dorsal region recruited after 24 h of APRV; moreover, the lung ventilation became more homogenous according to the results of GI index and CoV, suggesting that APRV has the potential to reduce the risk of VILI. Interestingly, we observed that ventilation redistributed prior to perfusion redistribution, implying that optimized ventilation facilitated in perfusion improvement. Dorsal alveolar recruitment reduced pulmonary vascular resistance, facilitating significant improvement of dorsal perfusion and V/Q matching. On the contrary, if lung inflation caused overexpansion rather than alveolar recruitment, an increase in pulmonary vascular resistance in hyperinflated regions would also direct perfusion toward nonaerated dorsal regions, ultimately leading to increased functional shunt and dead space [10].

The number of unmatched regions is associated with ARDS severity and the risk of VILI, as well as being an independent predictor of mortality [11]. Our study showed that V/Q matching improved and functional shunt decreased significantly in the moderate ARDS subgroup after 24 h APRV. Unfortunately, no significant improvement in V/Q matching was observed in severe ARDS, which could be attributed to the lack of significant improvement in perfusion redistribution (Additional file 1: Table S3). Pulmonary microvascular thrombosis, endothelial swelling and damage, and abnormal vasoconstraction could lead to significant local hypoperfusion or even vascular occlusion, resulting in increased dead space [12]. In this situation, in addition to alveolar recruitment, inhaled pulmonary vasodilators, anti-inflammatory, or anticoagulation might be used as adjunctive therapy, but the evidence is limited, necessitating additional research [13].

There are several limitations in our study. First, the sample size was limited. Second, we didn't focus on the effects of spontaneous breathing on APRV. The effects of APRV with or without spontaneous breathing on ARDS patients are still being debated [14]. Third, EIT only provides a cross-sectional lung-region analysis, which may differ from whole-lung evaluation. Forth, cardiac output was not measured in this cohort. Fifth, we didn't measure end expiratory lung volume to assess any variation induced by APRV. Finally, there was no control group. Future research should focus on these issues.

Conclusions

APRV is a strategy based on pathophysiology that provides lung recruitment, stabilization, and homogeneity, potentially protecting injured lungs in patients with early moderate-to-severe ARDS.

Table 1 Electrical impedance tomography data analysis of selected physiologic variables, respiratory parameters, and hemodynamic parameters at the four different time points

Variables	T0	T1	T2	T3	*P* value
EIT data					
Ventilation distribution, ventral (%)	68.87 ± 10.94	61.04 ± 12.80[a]	58.66 ± 12.51[a]	55.83 ± 13.48[a]	< 0.001
Ventilation distribution, dorsal (%)	31.13 ± 10.94	38.96 ± 12.80[a]	41.34 ± 12.51[a]	44.17 ± 13.48[a]	< 0.001
Ventilation distribution, ROI 1 (%)	16.01 (9.93–22.39)	10.99 (7.40–16.66)[a]	12.95 (9.13–15.35)	12.05 (7.30–15.68)[a]	0.009
Ventilation distribution, ROI 2 (%)	52.12 ± 5.54	48.81 ± 9.34	46.07 ± 8.73	42.88 ± 9.24[a]	0.002
Ventilation distribution, ROI 3 (%)	26.62 ± 10.21	33.42 ± 9.37	36.56 ± 10.75[a]	35.51 ± 11.11[a]	0.001
Ventilation distribution, ROI 4 (%)	4.52 ± 3.58	5.56 ± 6.40	4.78 ± 5.57	8.66 ± 5.32[a]	0.027
Perfusion distribution, ventral (%)	57.75 (53.81–67.97)	56.20 (52.72–61.52)	57.37 (47.63–63.24)	49.62 (46.80–58.74)[a]	0.013
Perfusion distribution, dorsal (%)	42.25 (32.03–46.19)	43.80 (38.48–47.28)	42.63 (36.76–52.37)	50.38 (41.26–53.20)[a]	0.013
Perfusion distribution, ROI 1 (%)	15.86 ± 8.62	12.61 ± 4.54	12.54 ± 5.10	13.11 ± 4.91	0.405
Perfusion distribution, ROI 2 (%)	46.76 ± 9.18	44.43 ± 4.83	42.87 ± 5.64	38.99 ± 6.00[a]	0.009
Perfusion distribution, ROI 3 (%)	36.32 (27.99–39.37)	37.82 (29.37–42.87)	36 (30.81–42.19)	39.47 (33.76–43.95)[a]	0.037
Perfusion distribution, ROI 4 (%)	5.93 ± 3.16	6.45 ± 3.04	7.40 ± 3.71	9.00 ± 3.29[a b]	0.005
GI index-ventilation	0.61 (0.55–0.62)	0.54 (0.51–0.61)	0.53 (0.47–0.55)[a]	0.50 (0.42–0.53)[a]	< 0.001
Center of Ventilation (%)	43.31 ± 5.07	45.09 ± 4.88	46.05 ± 4.63	46.84 ± 4.96[a]	0.048
Shunt (%)	13.80 ± 7.53	10.15 ± 3.34	12.39 ± 8.37	8.39 ± 5.18	0.059
Shunt, ventral (%)	4.29 (1.94–7.03)	2.87 (1.07–5.66)	3.39 (1.79–6.62)	2.30 (1.02–3.57)	0.348
Shunt, dorsal (%)	7.38 (4.99–13.01)	6.41 (4.94–8.75)	5.60 (3.00–10.49)	4.80 (2.80–8.38)	0.458
Dead space (%)	23.92 (14.71–31.43)	25.54 (15.37–29.57)	18.19 (15.02–28.31)	26.81 (19.34–31.08)	0.777
Dead space, ventral (%)	8.30 ± 2.40	8.49 ± 2.45	9.25 ± 2.67	7.13 ± 2.06	0.906
Dead space, dorsal (%)	6.99 (4.70–9.13)	7.95 (4.60–10.64)	7.26 (4.40–9.86)	8.67 (6.27–13.02)	0.552
V/Q matching (%)	63.41 ± 13.47	69.13 ± 10.18	67.76 ± 13.25	68.58 ± 11.70	0.258
V/Q matching, ventral (%)	35.89 (30.51–43.33)	38.28 (34.23–42.30)	34.07 (27.65–43.14)	34.43 (31.38–36.78)	0.682
V/Q matching, dorsal (%)	25.72 ± 9.01	31.13 ± 6.62	33.14 ± 8.95[a]	29.80 ± 7.19	0.007
Respiratory parameters					
PaO_2	75.16 ± 17.19	–	–	116.1 ± 41.24	0.004
$PaCO_2$	44.27 ± 8.58	–	–	36.78 ± 4.20	0.032
PaO_2/FiO_2	109.5 ± 36.44	–	–	222.2 ± 58.46	< 0.001
Mean airway pressure (cmH_2O)	20.83 ± 2.21	20.75 ± 2.30	20.83 ± 2.13	20.50 ± 1.78	0.448
Total minute ventilation (L/min)	5.88 ± 0.90	6.14 ± 0.99	6.55 ± 1.19[a]	7.53 ± 1.22[abc]	< 0.001
Tidal volume (mL/kg PBW)	6.90 ± 0.68	7.19 ± 0.74	7.66 ± 0.74[a]	8.82 ± 0.84[abc]	< 0.001
Tidal volume (mL)	442.5 ± 32.86	461.3 ± 36.15	491.8 ± 38.8[a]	567.5 ± 60.93[abc]	< 0.001
*Driving pressure (cmH_2O)	11.93 ± 1.73	11.40 ± 1.61	10.86 ± 2.15	10.30 ± 1.97	0.090
*Crs (mL/cmH_2O)	32.15 (27.11–42.3)	32.40 (29.63–39.98)	38.45 (30.15–45.53)	37.95 (36.00–44.25)	0.030
Hemodynamic parameters					
Systolic blood pressure (mmHg)	118.3 ± 17.83	125.1 ± 16.18	125.4 ± 28.22	130.8 ± 26.98	0.624
Diastolic blood pressure (mmHg)	62 ± 9.42	64.75 ± 8.76	61.33 ± 13.9	65.67 ± 11.62	0.734
Heart rate (bpm)	103 ± 19.24	93.92 ± 17.71	90.67 ± 90.67	89.17 ± 12.48	0.185
Norepinephrine dose (μg/kg/min)	0 (0–0.246)	0 (0–0.17)	0.05 (0–0.15)	0 (0–0.15)	0.968

Data are mean ± SD or median (25–75th)

[*] The methods for calculating driving pressure and Crs are provided in Additional file 1

ROI, Region of Interest; GI, Global Inhomogeneity; V/Q, ventilation/perfusion; PaO_2/FiO_2, ratio of partial pressure arterial oxygen and fraction of inspired oxygen; Crs, respiratory system compliance

T0: shortly after APRV; T1, T2, and T3: 6 h, 12 h, and 24 h after APRV application

[a] vs. T0, $P < 0.05$

[b] vs. T1, $P < 0.05$

[c] vs. T2, $p < 0.05$

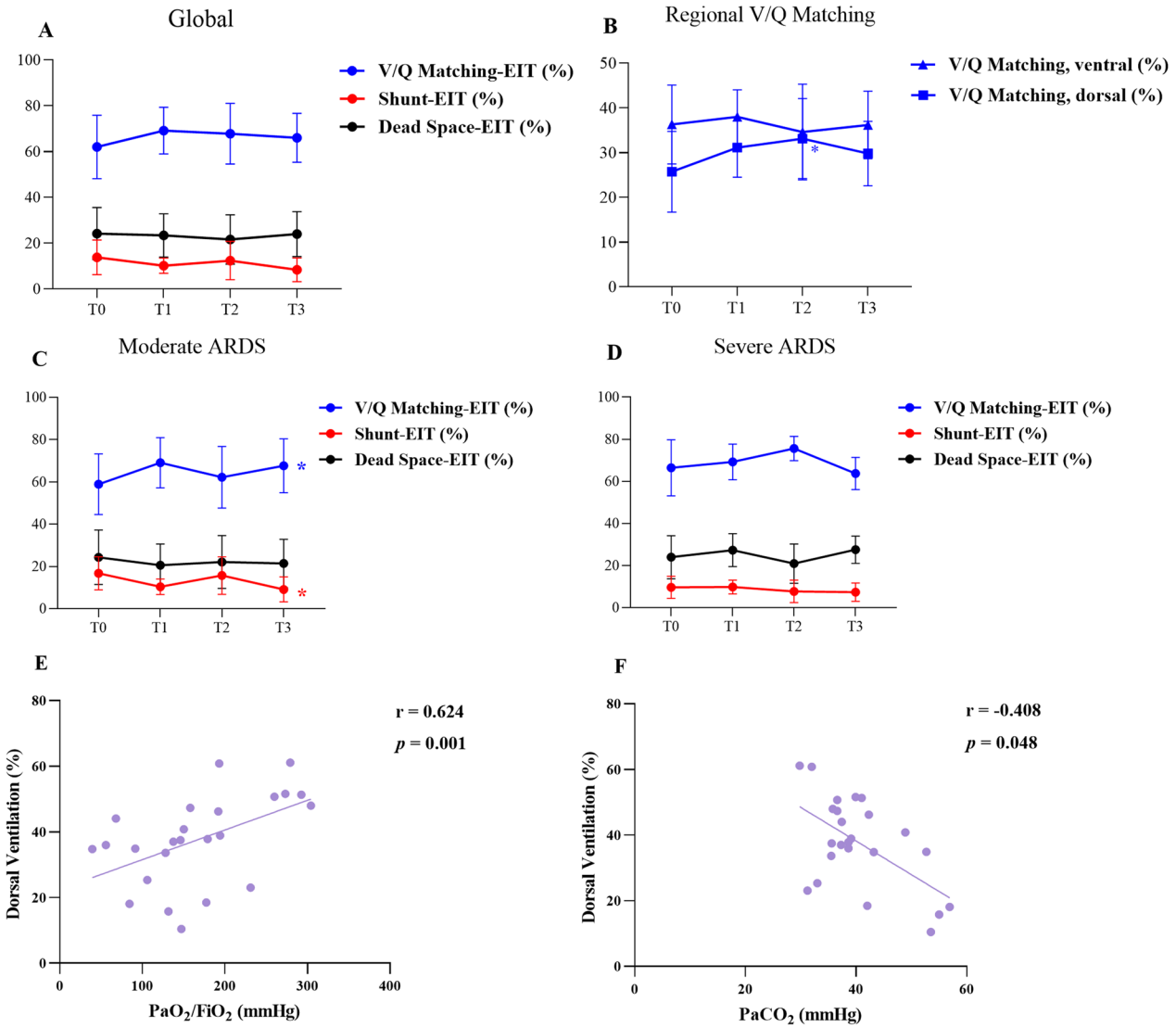

Fig. 1 Evolution of global shunt-EIT (%), dead space-EIT (%), and V/Q matching (%) at T0, T1, T2 and T3 (**A**). Evolution of V/Q matching (%) in ventral and dorsal region at T0, T1, T2 and T3 (**B**). Subgroup analysis of V/Q matching (%), shunt-EIT (%), and dead space-EIT (%) evolution at T0, T1, T2, and T3 (**C**, **D**). Patients were divided into two subgroups based on the severity of ARDS: moderate ARDS with seven patients (**C**) and severe ARDS with five patients (**D**). Better dorsal ventilation (%) was significantly correlated with higher PaO_2/FiO_2 (**E**) and lower $PaCO_2$ (**F**). V/Q, ventilation/perfusion; EIT, Electrical impedance tomography; ARDS, acute respiratory syndrome. T0: shortly after APRV; T1, T2, and T3: 6 h, 12 h, and 24 h after APRV application. *$p < 0.05$

Abbreviations

APRV	Airway pressure release ventilation;
VILI	Ventilator-induced lung injury
ARDS	Acute respiratory distress syndrome
EIT	Electrical impedance tomography
VCV	Volume-controlled ventilation
V/Q	Ventilation/perfusion
GI	Global inhomogeneity
CoV	Center of ventilation

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-023-04469-8.

Additional file 1. Methods. Table S1. Exclusion criteria. **Table S2.** Patients' main characteristics. **Table S3.** Subgroup analysis of ventilation and perfusion distribution evolution at T0, T1, T2, and T3. **Fig. S1.** Ventilation and perfusion measured by EIT in a representative patient at different time points.

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Author contributions
All authors met authorship criteria and participated significantly in the study. LY, XZ and YS were involved in the conception and design. All authors contributed to data collection or analysis. RL, YW, HZ, AW and XZ wrote the manuscript with supervision of LY, XZ and YS. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the Institutional Research and Ethics Committee of Union Hospital (NO. 2022–0048) and written informed consent was obtained from the patients' legal representatives.

Consent for publication
Not applicable.

Competing interests
ZZ receives consulting fee from Draeger Medical. The other authors declare no competing interests.

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