Original Article

Awake prone positioning and ventilation distribution as assessed by electric impedance tomography in patients with non-COVID-19 acute hypoxemic respiratory failure: A prospective physiology study

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ABSTRACT

Background: Awake prone positioning (APP) can reportedly reduce the need for intubation and help improve prognosis of patients with acute hypoxemic respiratory failure (AHRF) infected with COVID-19. However, its physiological mechanism remains unclear. In this study, we evaluated the effect of APP on lung ventilation in patients with moderate-to-severe AHRF to better understand the effects on ventilation distribution and to prevent intubation in non-intubated patients.

Methods: The prospective study was performed in the Department of Critical Care Medicine at Shanghai General Hospital, China, from January 2021 to November 2022. The study included patients with AHRF (partial pressure of oxygen [PaO_2]/inspired oxygen concentration [FiO_2] <200 mmHg or oxygen saturation [SpO_2]/FiO_2 <235) treated with high-flow nasal oxygen. Electrical impedance tomography (EIT) measurements including center of ventilation (COV), global inhomogeneity (GI) index, and regional ventilation delay (RVD) index were performed in the supine position (T_0), 30 min after the start of APP (T_1), and 30 min returning to supine position after the APP (T_2). Clinical parameters like SpO_2, respiratory rate (RR), FiO_2, heart rate (HR), and ROX (the ratio of SpO_2 as measured by pulse oximetry/FiO_2 to RR) were also recorded simultaneously at T_0, T_1, and T_2. To evaluate the effect of the time points on the variables, Mauchly's test was performed for sphericity and repeated measures analysis of variance was applied with Bonferroni's *post hoc* multiple comparisons.

Results: Ten patients were enrolled. The PaO_2/FiO_2 ratio was (111.4±33.4) mmHg at the time of recruitment. ROX showed a significant increase after initiation of APP {median (interquartile range [IQR]): T_0: 7.5 (6.0–10.1) *vs.* T_1: 7.6 (6.4–9.3) *vs.* T_2: 8.3 (7.2–11.0), *P*=0.043}. RR (*P*=0.409), HR (*P*=0.417), and SpO_2/FiO_2 (*P*=0.262) did not change significantly during prone positioning (PP). The COV moved from the ventral area to the dorsal area (T_0: 48.8%±6.2% *vs.* T_1: 54.8%±6.8% *vs.* T_2: 50.3%±6.1%, *P*=0.030) after APP. The GI decreased significantly after APP (T_0: median=42.7 %, [IQR: 38.3%–47.5%] *vs.* T_1: median=38.2%, [IQR: 34.6%–50.7%] *vs.* T_2: median=37.4%, [IQR: 34.2%–41.4%], *P*=0.049). RVD (*P*=0.794) did not change after APP.

Conclusions: APP can improve ventilation distribution and homogeneity of lung ventilation as assessed by EIT in non-intubated patients with AHRF.

Trail Registration Chinese Clinical Trial Registry Identifier: ChiCTR2000035895.

Introduction

Since the 1970s, prone positioning (PP) has been used to treat severe hypoxemia in patients with acute respiratory distress syndrome (ARDS) and has been shown to improve the survival rate of ARDS patients.[1,2] Patients with ARDS have a more uniform distribution of gas-to-tissue ratio along the ventral-dorsal axis from supine to PP, as well as a more uniform distribution of lung stress and strain.[3,4] Improving oxygenation and reducing mortality are the main reasons for adopting the PP in ARDS patients.

Changes in PP are often accompanied by significant improvements in arterial blood gases, primarily due to reduced overdistension of ventral lung regions and reduced periodic opening and closing of dorsal lung regions, resulting in an overall better ventilation-perfusion match.[5–8] However, although these physiological findings are widely recognized, they are mostly derived from animal models, with limited evidence obtained in patients given the lack of proper non-invasive assessment methods in the past decades.

Traditional PP is mainly used for mechanically ventilated patients. Awake prone positioning (APP) has become widely used after the COVID-19 pandemic.[9–11] Recent studies have found that APP reduces the need for intubation in patients with acute hypoxemic respiratory failure (AHRF) infected with COVID-19, especially in those with moderate-to-severe AHRF requiring advanced respiratory support and intensive care.[9,12] Additionally, there is a significant reduction in intubation risk with APP in patients receiving advanced respiratory support.[13] Although the clinical significance of PP has been demonstrated, the relevant physiological mechanisms are yet to be confirmed. Previous studies evaluating the physiological mechanisms during APP were only performed in patients with COVID-19.[14,15] The effect and mechanism of APP in patients with non-COVID-19 AHRF remain unclear.

Electrical impedance tomography (EIT) is a new non-invasive, non-radiative, and easily operable technology that can be used to monitor regional ventilation dynamically at the bedside.[16,17] The ability of EIT to determine gravity-related changes has long been demonstrated.[18] Therefore, EIT has been used to monitor the lung physiology response to changes in body position. In traditional ARDS, the pleural pressure gradient is increased because of poor compliance of the lungs, resulting in severe compressive atelectasis in dependent lung regions (dorsal area) and local overdistension in non-dependent lung regions (ventral area).[19,20] Furthermore, owing to the technical characteristics of EIT, it is feasible to capture the changes of ventilation redistribution after APP, which may guide clinical treatment.

In this study, we evaluated the effect of APP on regional lung ventilation in patients with moderate-to-severe AHRF in an attempt to better understand the underlying physiological changes that lead to improvement of oxygenation during APP.

Methods

Study design and population

This prospective study was performed in the Department of Critical Care Medicine at Shanghai General Hospital, China, from January 2021 to November 2022, and the study was approved by the Institutional Ethics Committee. All recruited patients provided written informed consent. This study is registered with the Chinese Clinical Trial Registry (ChiCTR2000035895).

Patients who fulfilled the following inclusion criteria were enrolled: those with moderate-to-severe AHRF, defined as (1) percutaneous arterial oxygen saturation (SpO_2) <90% or arterial partial pressure of oxygen (PaO_2) <60 mmHg without oxygen inhalation and (2) inhaled oxygen concentration (FiO_2) ≥40%; PaO_2/FiO_2 <200 mmHg or SpO_2/FiO_2 <235.[6]

The exclusion criteria were: age <18 years, AHRF caused by COVID-19 (all patients underwent confirmatory reverse transcription polymerase chain reaction), no more than a 48-h interval since diagnosis of AHRF and initiation of APP, severe hemodynamic instability, pregnancy, duration of PP <1 h, respiratory rate (RR) >40/min, partial pressure of carbon dioxide in arterial blood ($PaCO_2$) >60 mmHg, pH <7.20, hemodynamic instability, decreased level of consciousness, Glasgow coma scale (GCS) <10, severe nasal obstruction, failure of or unable to wear high-flow nasal cannula (HFNC), HFNC intolerance, or contraindication to EIT monitoring.

Baseline assessment and data collection

The following data on the baseline characteristics of patients were collected at enrollment: sex, height, body mass index (BMI), acute physiology and chronic health evaluation II (APACHE II) score at intensive care unit (ICU) admission, etiology of AHRF, and the arterial partial oxygen pressure to the fraction of inspired oxygen (PaO_2/FiO_2) ratio. Thoracic computed tomography (CT) was performed as a routine exam during ICU admission, and the findings were collected. The following clinical events and outcomes were also recorded: intubation and hospital mortality.

Study protocol

All patients admitted to the ICU for AHRF met the treatment requirements for HFNC (Optiflow™, Fisher & Paykel, Shanghai, China), titrated at high-flow settings, adjusted FiO_2, targeted SpO_2 ≥92%, and adjusted airflow velocity; the set temperature ensured that the patient could tolerate the HNFC well and the target SpO_2 was maintained. EIT measurements were performed in the supine position (T_0), 30 min after the start of APP (T_1), and at 30 min returning to the supine position after the APP (T_2). SpO_2, RR, and inspired oxygen concentration including heart rate (HR) were also recorded simultaneously at T_0, T_1, and T_2. The ROX (the ratio of SpO_2 as measured by pulse oximetry/FiO_2 to RR) index was calculated simultaneously using the following formula: ROX=SpO_2/FiO_2/RR.[21] While the patients were prone more than once, we used the first two or three measurements. If the indication for intubation was reached during the PP, the supine position was restored immediately and the patient prepared for invasive mechanical ventilation.

EIT data

EIT measurements were performed using a PulmoVista500 (Dräger Medical, Lübeck, Germany), with an EIT belt containing 16 electrodes placed around the chest wall in the fourth or fifth intercostal space and connected to an EIT monitor. The EIT measurements were recorded continuously at 20 Hz, while the patient was in a relatively stable state. The ventral and dorsal regions were defined as the upper and lower parts of the axis from the sternum to the vertebrae, respectively. Based on the measurements of the EIT data, the following parameters were calculated:

(1) The percentage of ventilation in the respective region, four regions of interest (ROIs) are divided horizontally with equal height from the ventral side to the dorsal side (ROI 1, ROI 2, ROI 3, and ROI 4).

(2) After identifying the tidal variations (the difference in impedances between end-inspiration and end-expiration) within a predefined lung area, the global inhomogeneity (GI) index is calculated based on the difference between the tidal variation in each pixel and the median value of all pixels in the lung regions.[16,22]

$$GI = \frac{\Sigma(\text{pixel differences from median})}{\Sigma(\text{pixels}) \text{ where } \Sigma(\text{pixels})} \times 100\ \%$$
$$= \Sigma(\Delta Zj), \text{ and } \Sigma(\text{pixel differences from median}) \times 100\ \%$$
$$= \Sigma(\Delta Zj - \Delta Z\text{median}) \times 100\ \%$$

(3) The center of ventilation (COV) is a measure of the anteroposterior distribution of tidal volume (VT) and is computed by the following formula. COV yields a value between 0% and 100%, where 0% indicates all image amplitude at the ventral region and 100% indicates all amplitude at the dorsal region.[16,23]

$$COV\ [\%] = \frac{(\text{Height weighted pixel sum})}{(\text{Pixel sum}) \text{ where } (\text{Pixel sum})}$$
$$= \Sigma(\Delta Zj), \text{ and } (\text{Height} - \text{weighted pixel sum})$$
$$= \Sigma(yj \times \Delta Zj)$$

(4) The regional ventilation delay (RVD) parameter defines the extent of the temporal delay of the regional inspiration (derived from the regional impedance waveform) compared with the global inspiration (derived from the global impedance waveform) for every pixel within the contour of the ventilated area.[24,25] The RVD ratio (%), which indicates the ratio of the number of pixels affected by the RVD (NRVD) to the total number of pixels within the ventilated area (NV), is calculated as the second RVD parameter. The RVD ratio is calculated as follows:

$$RVD = \frac{NRVD}{NV} \times 100\ \%$$

Statistical analysis

Statistical analysis was performed using SPSS 26.0 (IBM Corporation, Armonk, NY, USA) and Prism 8 (GraphPad Software, San Diego, CA, USA). To test the effect of the time points on the variables, Mauchly's test was used for sphericity, and repeated measures analysis of variance was applied with *post hoc* Bonferroni's multiple comparisons. When the violation of sphericity occurred (i.e., Mauchly's test $P < 0.05$), the Greenhouse–Geisser method was used for correction. Correlation between continuous variables was assessed by Pearson's regression coefficient. All statistical tests were two-tailed, and $P < 0.05$ was considered to indicate statistically significant differences. We used a convenience sample size of 10 patients. We performed a correlation analysis on EIT data and changes in clinical parameters such as $\Delta T_{GI1} = GI_{T1} - GI_{T0}$, $\Delta T_{GI2} = GI_{T2} - GI_{T0}$, $\Delta T_{RVD1} = RVD_{T1} - RVD_{T0}$, $\Delta T_{RVD2} = RVD_{T2} - RVD_{T0}$, $\Delta T_{ROX1} = ROX_{T1} - ROX_{T0}$, and $\Delta T_{ROX2} = ROX_{T2} - ROX_{T0}$.
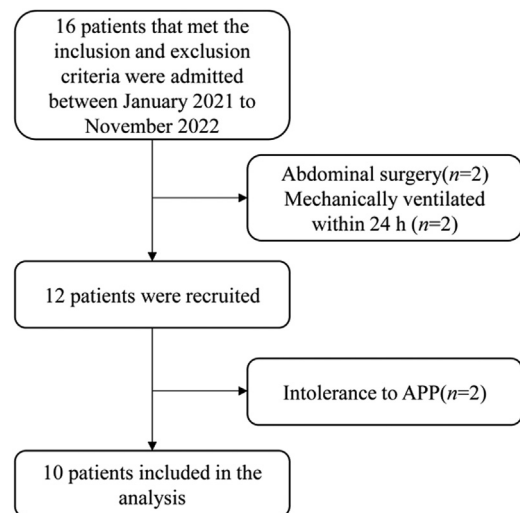

Figure 1. Flow diagram of the study. APP, Awake prone positioning.

Results

Patient characteristics

The study included 10 patients (7 male and 3 female; mean age: 68.5 (59.0, 73.8) years; BMI: 22.9 ± 4.5 kg/m^2) with AHRF (Figure 1). They received 17 times of APP with an average duration of 2 h (interquartile range [IQR]: 2.0–4.5 h), some of the patients received the APP more than once. The mean APACHE II score at ICU admission was (9.7 ± 6.3) points. Severe AHRF occurred in three (30%) patients and moderate AHRF occurred in seven (70%) patients. One patient was intubated during their ICU stay and died at the end of the study period (Table 1).

Table 1
Baseline of patient characteristics (*n*=10).

Variable	Data
Sex (male)	7
Age (years)	68.5 (59.0, 73.8)
BMI (kg/m^2)	22.9 ± 4.5
MAP (mmHg)	99.9 ± 12.5
HR (beats/min)	91.2 ± 10.2
RR (breaths/min)	21.0 ± 4.9
ROX	8.1 ± 2.4
Gas flow rate of HFNC (L/min)	40 (40, 40)
AHRF etiology	
Pneumonia	9
Pancreatitis	1
Intubated	1
Mortality	1
PaO$_2$/FiO$_2$ (mmHg)	111.4 ± 33.4
GCS	15 (14, 15)
APACHE II score at ICU admission	9.7 ± 6.3
The interval from AHRF diagnosis to APP initiation (day)	17.2 ± 3.6
APP duration (h)	2 (2.0, 4.5)

Data are expressed as median(interquartile range) or mean ± standard deviation. APACHE II: Acute physiology and chronic health evaluation II; APP: Awake prone positioning; AHRF: Acute hypoxemic respiratory failure; BMI: Body mass index; FiO$_2$: Inspired fraction of O$_2$ ratio; GCS: Glasgow coma scale; HFNC: High-flow nasal cannula; HR: Heart rate; ICU: Intensive care unit; MAP: Mean arterial pressure; PaO$_2$: Arterial partial pressure of O$_2$; RR: Respiratory rate; ROX: The ratio of SpO$_2$ as measured by pulse oximetry/FiO$_2$ to RR.
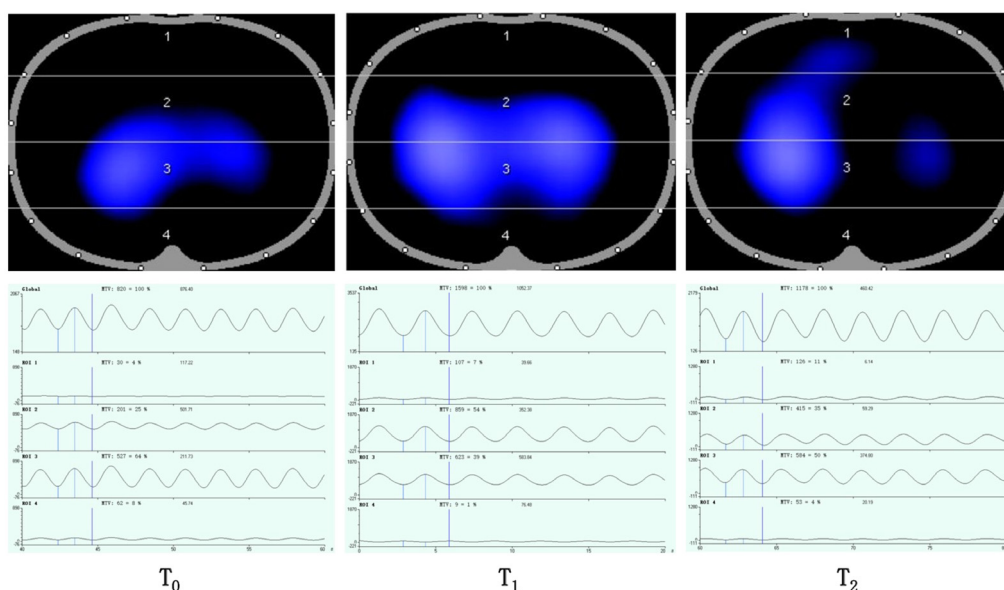
Figure 2. Representative images and waveforms of EIT.

EIT: Electrical impedance tomography; T_0: Supine positioning; T_1: After 0.5 hour in awake prone positioning; T_2: After returning to the supine positioning for 0.5 hour.

Ventilation distribution

The changes of ventilation distribution at the T_0, T_1, and T_2 time points are shown in Figure 2. The EIT-based measured values and the comparison of the changes among the time points T_0, T_1, and T_2 are listed in Figure 3 and Table 2. Lung ventilation distribution decreased in ventral ROI 1 (T_0: median=13.0%, [IQR: 9.5%–16.0%] *vs.* T_1: median=4.0%, [IQR: 2.0%–12.5%] *vs.* T_2: median=12.0%, [IQR: 9.5%–16.5%], *P*=0.026). COV moved from the ventral area to the dorsal area (*P*=0.030) (Table 2 and Figure 4A).

Clinical respiratory parameters

Clinical parameters regarding RR at T_0, T_1, and T_2 were assessed and compared (Table 2). Our study found that ROX showed a significant increase after initiation of PP (T_0: median=7.5, [IQR: 6.0–10.1] *vs.* T_1: median=7.6, [IQR: 6.4–9.3]
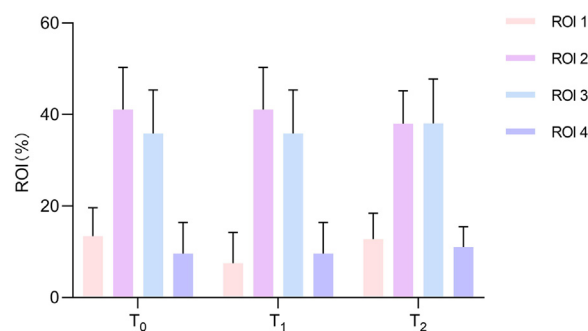

Figure 3. Ventilation distribution in the horizontal ROI by EIT.

EIT: Electrical impedance tomography; ROIs: Regions of interest; T_0: Supine positioning; T_1: After 30 min in awake prone positioning; T_2: After returning to the supine positioning for 30 min.

vs. T_2: median=8.3, [IQR: 7.2–11.0], *P*=0.043, Figure 4B). RR (*P*=0.409, Figure 4C), HR (*P*=0.417), and SpO_2/FiO_2 (*P*=0.262, Figure 4D) did not change significantly during PP treatment.

Table 2

Clinical parameters and EIT data.

Items	T_0	T_1	T_2	*P*-value
GI (%)	42.7 (38.3, 47.5)	38.2 (34.6, 50.7)	37.4 (34.2, 41.4)[†]	0.049
COV (%)	48.8±6.2	54.8±6.8*	50.3±6.1	0.030
RVD (%)	5.0 (2.0, 8.0)	3.0 (1.0, 7.0)	3.0 (1.0, 6.0)	0.794
RR (breaths/min)	20.0 (18.0, 23.0)	22.0 (18.0, 23.0)	20.0 (18.0, 22.0)	0.409
ROX	7.5 (6.0, 10.1)	7.6 (6.4, 9.3)	8.3 (7.2, 11.0)[†]	0.043
SpO_2/FiO_2	170.0±28.3	170.1±34.00	173.5±32.8	0.262
HR (beats/min)	91.2±10.2	88.9±13.4	87.7±11.8	0.417
ROI 1 (%)	13.0 (9.5, 16.0)	4.0 (2.0, 12.5)*	12.0 (9.5, 16.5)	0.026
ROI 2 (%)	41.1±9.3	38.7±16.4	38.0±7.2	0.598
ROI 3 (%)	35.9±9.5	43.2±14.8	38.1±9.7	0.204
ROI 4 (%)	8.0 (4.5, 13.0)	8.0 (5.0, 6.5)	10.0 (7.5, 14.5)	0.716

Data are expressed as mean ± deviation, median (interquartile range).

COV: Center of ventilation; EIT: Electrical impedance tomography; FiO_2: Inspired fraction of O_2 ratio; GI: Global inhomogeneity; HR: Heart rate; ROI: Region of interest; ROX: $SpO_2/FiO_2/RR$; RR: Respiratory rate; RVD: Regional ventilation delay; SpO_2: Percutaneous arterial oxygen saturation; T_0: Supine positioning; T_1: After 0.5 hour in awake prone positioning; T_2: After returning to the supine positioning for 0.5 hour.

* T_0 *vs.* T_1 *P* <0.05.
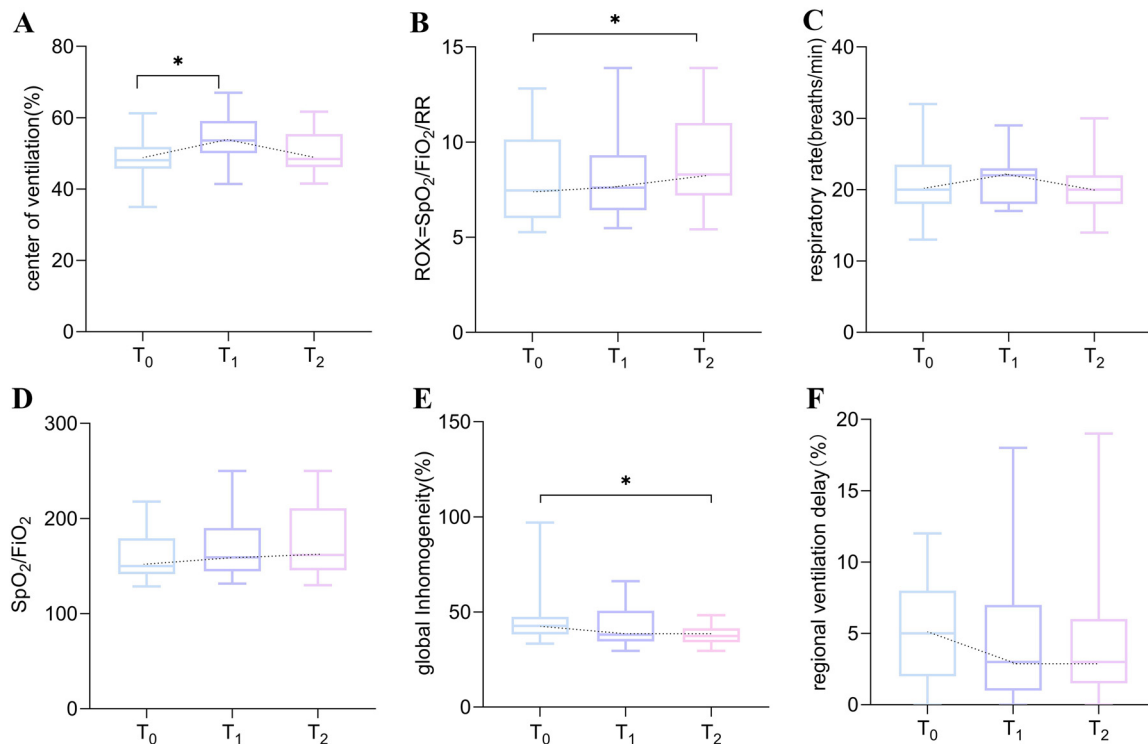† T_0 *vs.* T_2 *P* <0.05.

Figure 4. Bonferroni's multiple comparisons. A: Comparisons of COV. B: Comparisons of ROX=$SpO_2/FiO_2/RR$ (%). C: Comparisons of RR (breaths/min).Comparisons of SpO_2/FiO_2. D: Comparisons of SpO_2/FiO_2.E: Comparisons of GI. F: Comparisons of RVD. $^*P < 0.05$.
COV: Center of ventilation; FiO_2: Inspired fraction of O_2 ratio; GI: Global inhomogeneity; RR: Respiratory rate; ROX: The ratio of SpO_2 as measured by pulse oximetry/FiO_2 to RR; RVD: Regional ventilation delay; SpO_2: Percutaneous arterial oxygen saturation; T_0: Supine positioning; T_1: After 0.5 hour in awake prone positioning; T_2: After returning to the supine positioning for 0.5 hour.

Uniformity of ventilation

Based on the measurement of EIT and the analysis of results, GI decreased significantly after PP (T_0: median=42.7%, [IQR: 38.3%–47.5%] *vs.* T_1: median=38.2%, [IQR: 34.6%–50.7%] *vs.* T_2: median=37.4%, [IQR: 34.2%–41.4%], $P = 0.049$, Figure 4E). RVD (T_0: median=5.0%, [IQR: 2.0%–8.0%] *vs.* T_1: median=3.0% [IQR: 1.0%–7.0%] *vs.* T_2: median=3.0%, [IQR: 1.0%–6.0%], P=0.794, Figure 4F) showed a downward trend, but the effect was not obvious. Through correlation analysis, we found that there was no significant correlation between the GI change and ROX change (ΔT_{GI1} *vs.* ΔT_{ROX1}, P=0.299; ΔT_{GI2} *vs.* ΔT_{ROX2}, P=0.500). In addition, there was no significant correlation between changes in RVD and ROX (Figure 5).

Discussion

This prospective study was performed on awake, non-intubated, spontaneously breathing patients with AHRF. The results provide some proof of concept regarding changes in ventilation distribution during PP in patients with AHRF using HFNC. The main findings can be summarized as follows: Compared with the supine position, the PP improved the ventilation distribution, decreased ventilation in the dorsal area, and moved the ventilation center from the ventral to the dorsal area. After

APP, the GI was reduced, which was likely mainly attributed to the improvement of synchronization and uniformity of lung ventilation.

Our study found that EIT captured the changes in lung ventilation distribution in real time. APP can increase COV significantly, and the ventilation distribution moved from the ventral area to the dorsal area. Grieco et al.[26] confirmed that PP can promote VT distribution toward dependent lung regions without affecting VT size, driving pressure (ΔPL), lung compliance, and pendelluft magnitude. Besides, in our study, GI showed that after returning to the supine position, the improvement in ventilation uniformity was significant. There was no correlation between the EIT data and the change value (T_2–T_0) between the clinical parameters and the baseline value (T_2–T_0) after returning to the supine position. Traditional methods of monitoring pulmonary ventilation (oxygenation index, blood gas analysis) can only reflect the overall condition of the lungs, but cannot intuitively reflect the changes in lung physiology. EIT provides real-time visualization of lung ventilation at the bedside, so it is an ideal monitoring system for PP. In PP, ventilation increased in the dependent area, while the hyperventilation state of the alveoli decreased in the non-dependent area. Such a favorable shift may result from promoting the homogeneous distribution of total stress. Previous studies have shown that prone position can reduce the risk of ventilator-induced lung injury (VILI) by reducing ventilation heterogeneity and alveolar hyperdilation
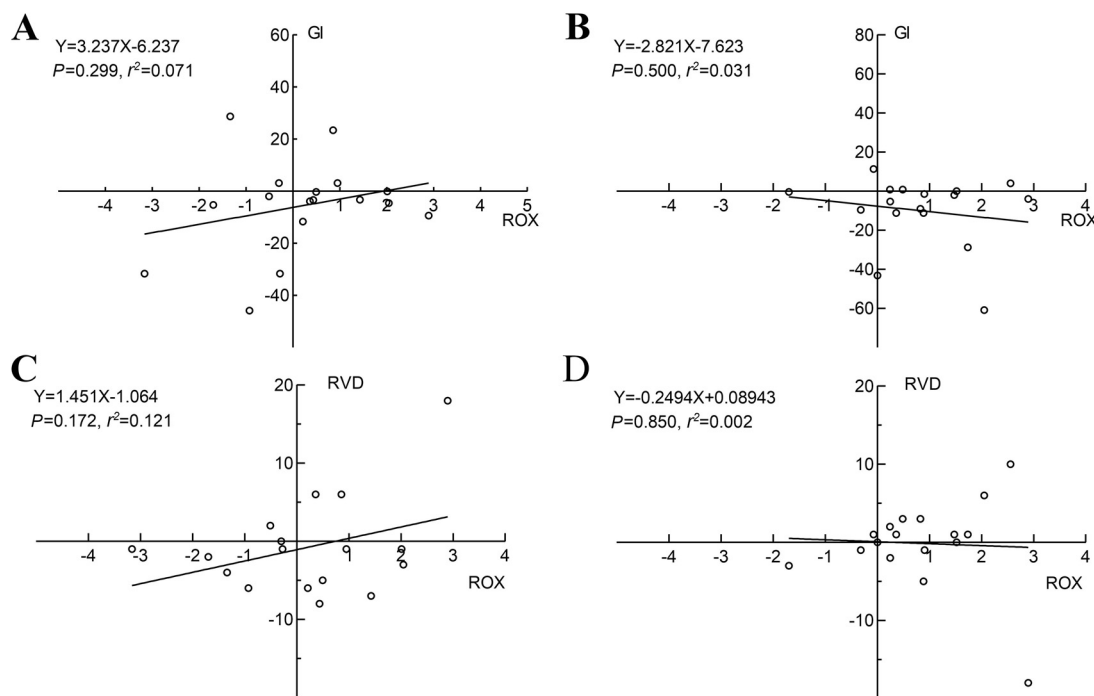
Figure 5. Correlation analysis. A: Correlations between $\Delta T_{GI1}(GI_{T1}-GI_{T0})$ and $\Delta T_{ROX1}(ROX_{T1}-ROX_{T0})$. B: Correlations between $\Delta T_{GI2}(GI_{T2}-GI_{T0})$ and $\Delta T_{ROX2}(ROX_{T2}-ROX_{T0})$. C: Correlations between $\Delta T_{RVD1}(RVD_{T1}-RVD_{T0})$ and $\Delta T_{ROX1}(ROX_{T1}-ROX_{T0})$. D: Correlations between $\Delta T_{RVD2}(RVD_{T2}-RVD_{T0})$ and $\Delta T_{ROX2}(ROX_{T2}-ROX_{T0})$. GI: Global inhomogeneity; ROX: The ratio of SpO_2 as measured by pulse oximetry/FiO_2 to RR; RVD: Regional ventilation delay.

and optimizing recruitment maneuver.[27,28] Real-time monitoring of changes in lung ventilation distribution through EIT can provide a better understanding of the effectiveness of PP in individual patients, which may help optimize lung protection in APP.

Relevant studies have confirmed that APP under noninvasive ventilation is feasible in patients with AHRF in COVID-19 and can improve oxygenation and prognosis.[29,30] Several studies have used EIT to monitor patients with COVID-19 in PP,[14,15,26,31,32] but few studies have elucidated the effects of APP in AHRF patients who did not have COVID-19 infection. Brunelle et al.[15] showed that APP is not associated with a decrease of lung ventilation inhomogeneity assessed by EIT in spontaneously breathing and non-intubated COVID-19 patients with AHRF, despite an improvement in oxygenation. We found that in the study by Brunelle et al.[15] and Liu et al.,[14] the respiratory support at ICU admission was different. In our study, all patients used HFNC. This may be one of the reasons for the difference in results in GI, but more research is needed to validate these findings. However, our result is not significant despite SpO_2/FiO_2 showing a decreased trend. We believe this is likely because of the small sample size. It is necessary to conduct further research in the future with larger sample sizes. In our study, measurements were only performed 30 min after the start of APP; there have been some studies that suggested longer PP times.[33,34] We thought extending the measurement time to 60 min or more at APP may be due to positive results.

There are still many unresolved issues regarding the clinical application of APP, such as indications for APP patients switching to mechanical ventilation and indications for discontinuing PP. During APP, the tolerance level and symptoms of the patient need to be closely monitored to avoid delayed intubation owing to failure of PP. Since the severity of the disease and the effect on PP are not the same among different patients, more precise treatment is required to achieve the best therapeutic effect.

Our study has some limitations. First, the sample size is quite small on account of this being a preliminary study. Given the lack of *a priori* information, we were not able to calculate a suitable sample size. The findings of our study provide basic information for further studies. Second, only RVD was assessed, and the respiratory physiology during APP was explained from the ventilation perspective. Prone position also changes lung perfusion, which improves oxygenation.[14,32] Currently, EIT bedside perfusion measurement requires patients to hold their breath for >10 s, which is difficult to achieve in spontaneously breathing patients with severe AHRF, who have strong respiratory drive. In the future, more convenient EIT measurement methods are needed to explore the changes in blood flow in patients with APP to more comprehensively explain the physiological mechanism of APP.

Conclusions

EIT can be used to monitor changes in the distribution of lung ventilation in APP patients. APP improves oxygenation in non-intubated patients by improving spatial and temporal ventilation homogeneity.

CRediT Authorship Contribution Statement

Jingjing Wang: Writing – original draft, Supervision, Software, Methodology, Investigation, Formal analysis, Data curation. **Changxing Chen:** Investigation, Data curation. **Zhanqi Zhao:** Writing – review & editing, Software, Methodology. **Puyu Deng:** Data curation. **Chenchen Zhang:** Data curation. **Yu Zhang:** Data curation. **Hui Lv:** Data curation. **Daonan Chen:** Data curation. **Hui Xie:** Writing – review & editing, Methodology, Funding acquisition, Formal analysis, Data curation. **Ruilan Wang:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization.

Acknowledgment

Funding

Ethics Statement

All study procedures were in accordance with the ethical standards of the Research Ethics Committee of Shanghai General Hospital (No. [2020]74).

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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