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The Influence of Breathing Exercises on Regional Ventilation in Healthy and Patients with Chronic Obstructive Pulmonary Disease

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ABSTRACT
We hypothesized that the respiratory exercises have uniform effects on ventilation in healthy subjects but the effects varied in patients with chronic obstructive pulmonary disease (COPD). In this study, a total of 30 healthy volunteers and 9 patients with COPD were included. Data were recorded continuously during (1) diaphragmatic breathing; (2) pursed lip breathing with full inhalation; (3) pursed lip combining diaphragmatic breathing. The sequence of the three breathing exercises was randomized using machine generated random permutation. Spatial and temporal ventilation distributions were evaluated with electrical impedance tomography. Results showed that, tidal volume was significantly larger during various breathing exercises compared to quiet tidal breathing, in both healthy and COPD ($p < 0.01$). However, for other EIT-based parameters, statistical significances were only observed in healthy volunteers, not in patients. Diaphragmatic breathing alone might not be able to decrease functional residual capacity in COPD and the effect varied largely from patient to patient (6:3, decrease vs. increase). Ventilation distribution moved toward ventral regions in healthy during breathing exercises ($p < 0.0001$). Although this trend was observed in the COPD, the differences were not significant. Ventilation became more homogeneous when diaphragmatic breathing technique was implemented ($p < 0.0001$). Again, the improvements were not significant in COPD. Regional ventilation delay was relatively high in COPD and comparable in various breathing periods. In conclusions, the impact of pursed lip and diaphragmatic breathing varied in different patients with COPD. Breathing exercise may need to be individualized to maximize the training efficacy with help of EIT.

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Respiratory exercises; chronic obstructive pulmonary disease; electrical impedance tomography; regional ventilation

Introduction

Chronic obstructive pulmonary disease (COPD) is a prevalent lung disease associated with high mortality [1]. Patients with COPD have chronic and mostly irreversible air flow limitation that is progressive and they can be allocated to different severity stages using the GOLD and the ABCD classification schemes [2]. Although these classifications are established, reliable predictions of health-related outcomes and mortality do not always coincide with the classifications [3]. Breathing exercises, as part pulmonary rehabilitation, is important for patients with COPD to improve their quality of life [4]. Pursed lip breathing and diaphragmatic breathing are two common breathing techniques that help ease the COPD symptoms and improve lung functions [5]. Although these breathing techniques have been widely used in COPD pulmonary rehabilitation programs, the effects on regional ventilation were unclear. Besides, individualized breathing exercises might be beneficial, but few techniques are available to assess the efficiency of the respiratory muscle training.

Electrical impedance tomography (EIT) is a bedside non-invasive imaging modality that assesses the ventilation distribution and flow limitations [6]. It was proposed to assess the respiratory muscle training [7]. To date, the number of clinical studies exploring the performance of EIT in identifying airway obstruction in COPD is still rather limited. In contrast with the relatively broad interest in EIT applications in mechanically ventilated patients [8], there are only a few studies investigating the use of EIT in COPD (e.g. [9–11]). In view of the scarce research results in this field, we have initiated a study with the intention to examine the home

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breathing exercise effects on ventilation inhomogeneity in patients with COPD and the potential to optimize rehabilitation program for such patient group. Unfortunately, due to the limited number of previous studies in this field, the sample size calculation to power the study was uncertain. Therefore, we conducted this proof-of-concept study in order to explore (1) whether any differences in the effect of breathing exercises on ventilation could be observed in healthy? If yes, (2) would a similar trend show in COPD? With these findings we hoped to obtain the prior knowledge to calculate the sample size for further validation study. We hypothesized that the respiratory exercises have uniform effects on ventilation in healthy subjects but the effects varied in patients with COPD. The differences in spatial and temporal ventilation distribution between healthy and COPD were investigated previously [12] so that it was not the main objective of the current study (explored and summarized in the online supplement).

Methods

Subjects and measurements

The prospective observational study was approved by the ethics committee of the Fourth Military Medical University (KY20224101-1). The study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all subjects prior to the study. A total of 30 healthy volunteers and 9 patients with COPD were included (demographic summarized in Table 1). Four patients were GOLD-2, 3 were GOLD-3 and 2 were GOLD-4 (pulmonary function forced vital capacity was summarized in Table S1 in the supplement). A belt with 16 equidistantly fixed conductive rubber electrodes was placed around the chest in one transverse plane at the level of the 5th intercostal space at the parasternal line. Raw EIT data were acquired with VenTom-100 (MidasMED Biomedical technology, Suzhou, China) at a scan rate of 20 images/s using excitation currents of 1 mArms 50 kHz applied through opposite electrodes. Image reconstruction was accomplished by the GREIT algorithm [13]. The baseline for image reconstruction was obtained individually for each subject during quiet tidal breathing.

A 10-min training session of the breathing exercises was conducted for all subjects. An investigator performed subjective quality control on the performance based on the movements of the lips, chest and abdomen. The EIT examinations were performed while the subjects were seated and instructed not to speak or to move their upper torso during the data acquisition. Data were recorded continuously during a period of quiet tidal breathing followed by (1) diaphragmatic breathing, a smooth and deep inspiration with anterior displacement of the abdominal region, which emphasizes the action of the diaphragm; (2) pursed lip breathing with full inhalation, soft exhalation performed for 4 to 6 s against the resistance of partially closed lips and clenched teeth; (3) pursed lip combining diaphragmatic breathing, combination of deep inspiration with anterior displacement of the abdominal region and soft exhalation against the resistance. The sequence of the three breathing exercises was randomized using machine generated random permutation. A 5-min break was given between the exercises.

Table 1. Subjects' demographics.

	Age (years)	Height (cm)	Weight (kg)
Healthy volunteers	25.8 ± 0.7	176.9 ± 5.8	74.8 ± 11.7
Patients with COPD	68.7 ± 9.7	170.1 ± 7.2	68.0 ± 10.7

EIT data analysis

EIT data were analyzed offline with MATLAB R2015a (The MathWorks Inc., Natick, MA, USA).

Functional EIT (fEIT) - tidal variation (TV) was calculated by subtracting the end-expiration from the end-inspiration image, which represents the variation during tidal breathing. Averaging results of the last five breaths was conducted to increase signal-to-noise ratio (same for the rest of the EIT-based parameters).

$$TV_i = \frac{1}{N}\sum_{n=1}^{N}\left(\Delta Z_{i,Ins,n} - \Delta Z_{i,\exp,n}\right) \quad (1)$$

where TV_i is the pixel i in the fEIT image; N is the number of breaths within the analyzed period, which was 5 in the present study; $\Delta Z_{i,Ins}$ and $\Delta Z_{i,Exp}$ are the pixel values in the raw EIT image at the end-inspiration and end-expiration, respectively. Zero was assigned to TV_i if $TV_i < 0$. The TV in each breathing exercise period was normalized to the one during quiet tidal breathing (in %). Besides, the changes of TV during various breathing exercises were assessed by calculating the slope of TV over time.

$$TV_{slope}\left(m\right) = am + b, m \in \left[1,2,\ldots,10\right] \quad (2)$$

where m is the number of breaths, a is the slope and b is the intercept. The larger the TV is, the larger the tidal volume for gas exchange occurs during the breathing exercises.

Change of end-expiratory lung impedance (EELI) reflects the change of end-expiratory lung volume (or functional residual volume). During the breathing exercises, the larger the decrease of EELI is, the larger the expiratory residual volume and less air trapping. All changes of EELI were referred to the quiet tidal breathing period.

$$\Delta EELI_{be} = {(EELI_{be} - EELI_{qu})}\big/{TV_{qu}} \quad (3)$$

where $EELI_{be}$ is the $EELI$ level of certain breathing excise, $EELI_{qu}$ is the level of quiet tidal breathing period. The changes of $EELI$ within various breathing exercise periods were assessed by calculating the slope of $EELI$ over time and denoted as $EELI_{slope}$.

Center of ventilation (CoV) depicts ventilation distribution influenced by gravity (relative impedance value weighted with location in anteroposterior co-ordinate) [14]:

$$CoV = \sum\left(y_i \times TV_i\right) \Big/ \sum TV_i \times 100\% \quad (4)$$

where TV_i is the impedance change in the fEIT image for pixel i, and y_i is the pixel height and of pixel i scaled so the bottom of the image (dorsal) is 100% and the top (ventral) is 0%. The changes of CoV within various breathing exercise periods were assessed by calculating the slope of CoV over time and denoted as CoV_{slope}. CoV may also indirectly reflect the diaphragm activity.

The global inhomogeneity (GI) index is calculated from the tidal EIT images to summarize the ventilation heterogeneity [15].

$$GI = \sum_{l \in lung}\left|TV_l - Median\left(TV_{lung}\right)\right| \Big/ \sum_{l \in lung} TV_l \quad (5)$$

where TV denotes the value of the differential impedance in the tidal images; TV_l is the pixel in the identified lung area; Pixel l is considered as lung region if TV_l > 10% × max(TV). TV_{lung} are all the pixels representing the lung area. High GI index implies high variation among pixel tidal impedance values. The changes of GI within various breathing exercise periods were assessed by calculating the slope of GI over time and denoted as GI_{slope}.

The regional ventilation delay (RVD) index characterizes the regional ventilation delay as pixel impedance rising time compared to the global impedance curve [16], which may assess tidal recruitment/derecruitment.

$$RVD_l = t_{l,40\%} \Big/ T_{inspiration,global} \times 100\% \quad (6)$$

where $t_{l,40\%}$ is the time needed for pixel l to reach 40% of its maximum inspiratory impedance change. $T_{inspiration,global}$ denotes the inspiration time calculated from the global impedance curve. To assess the distribution of RVD, Muders et al. proposed to use standard deviation of the pixel values [16]:

$$RVD_{SD} = \sqrt{\frac{1}{L}\sum_{l \in lung}\left(RVD_l - mean\left(RVD_{lung}\right)\right)^2} \quad (7)$$

where L is the total number of pixels identified as lung area. Since the RVD various largely during spontaneous breathing [17], the slope of RVD during each period was not calculated.

Statistical analysis

Data analyses were performed using Matlab R2015a (The MathWorks Inc., Natick, USA). The Lilliefors test was used for normality testing. After confirming that the data were normally distributed, results were expressed as mean ± standard deviation. Repeated measures one-way ANOVA was used to compare the EIT-based parameters among different breathing exercises and quiet tidal breathing. For statistically significant parameters, paired t-test was used to further compare the differences between each breathing exercise and quiet tidal breathing. A *p*value <0.05 was considered statistically significant. Significance levels were corrected for multiple comparisons using Holm's sequential Bonferroni method.

The differences in various parameters between healthy and COPD were compared and summarized in the online supplement. Between-Subjects one-way ANOVA was used to analyze the differences between groups.

Results

TV was significantly larger during various breathing exercises compared to quiet tidal breathing, in both healthy volunteers and patients with COPD (Figure 1). However, for other EIT-based parameters, statistical significances were only observed in healthy volunteers, not in patients (Figures 2–5). Diaphragmatic breathing alone might not be able to decrease EELI in COPD and the effect varied largely from patient to patient (Figure 2, right). Ventilation distribution moved toward ventral regions in healthy during breathing exercises (Figure 3, left). Although this trend was observed in the COPD, however, the differences were not significant. Ventilation became more homogeneous when diaphragmatic breathing technique was implemented (Figure 4, left). Again, the improvements were not significant in COPD. Pursed lip breathing technique introduced the highest RVD in healthy (Figure 5, left). On the other hand, RVD_{SD} was relatively high in COPD and comparable in various breathing periods (Figure 5, right; Table S2 in the supplement). The TV and RVD maps of typical subjects are illustrated in the online supplement (Figures S1 and S2). Besides the amplitude, TV maps showed no differences among various breathing exercises. For RVD maps, the exercises involving diaphragm (DB, PL + DB) introduced early inflation in the dorsal regions in both healthy and COPD.

Discussion

In the present study, we demonstrated the influences of breathing exercises on regional ventilation in healthy volunteers and subjects with COPD. The influences in healthy volunteers were systematic. On the other hand, the effects of breathing exercises varied in patients with COPD with considerable inter-subject variations based on the small sample size.

Regional ventilation captured by EIT may identify the change of lung function. Scaramuzzo et al. conducted a follow-up study on COVID-19 patients and found that regional information provided by EIT was more sensitive compared to pulmonary function test [18]. Other two studies using regional ventilation distribution to evaluate the disease status in patients with COPD [11] and idiopathic pulmonary fibrosis [19]. Ma and colleagues evaluated the effect of rehabilitation in COPD [20]. Although these studies

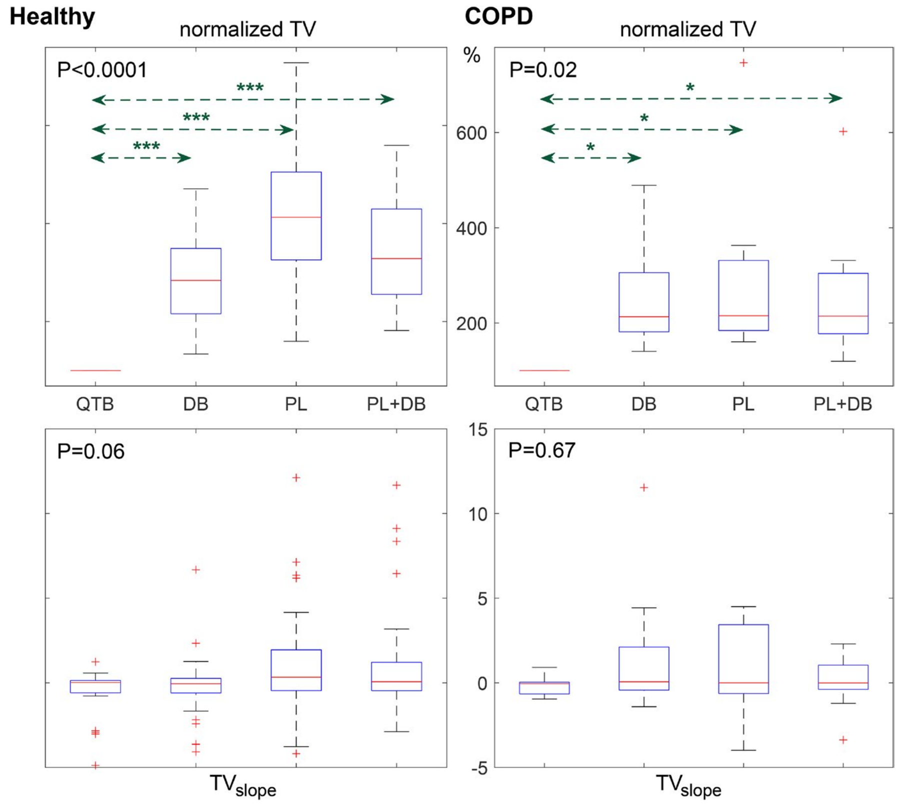

Figure 1. Boxplots of tidal variation (TV) at different breathing exercises. Left column is data from healthy volunteers and right column is from the patients with COPD. QTB, quiet tidal breathing; DB, diaphragmatic breathing; PL, pursed lip breathing; PL+DB, pursed lip combining diaphragmatic breathing. The boxes mark the quartiles while the whiskers extend from the box out to the most extreme data value within 1.5*the interquartile range of the sample. Red pluses are samples outside the ranges. *$p < 0.013$; ***$p < 0.0001$ compared to QTB.

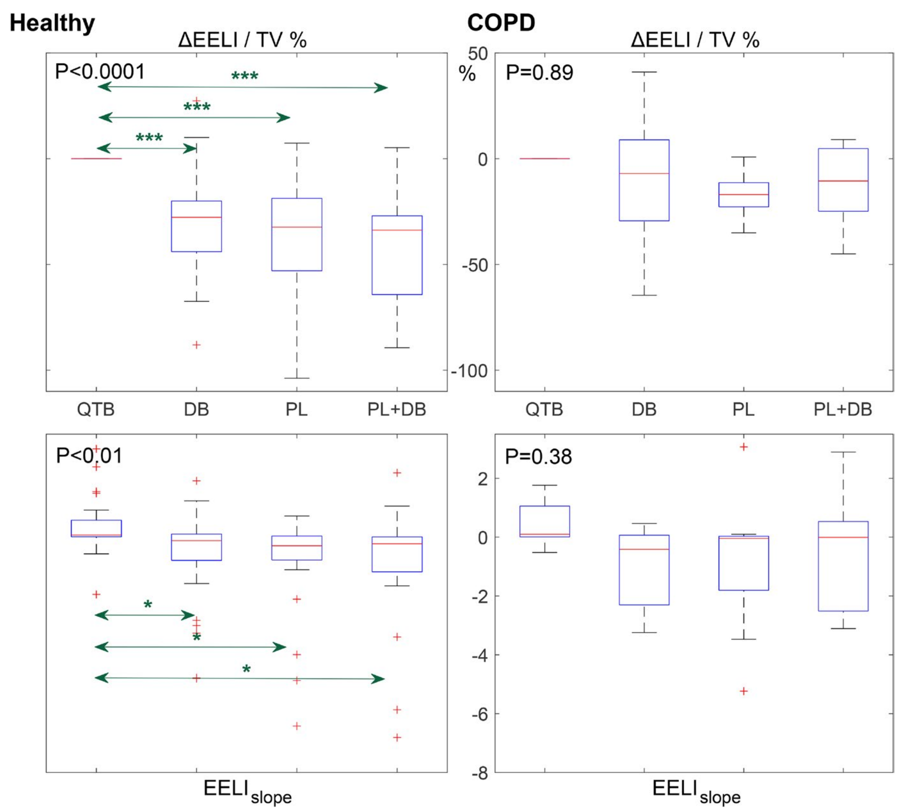

Figure 2. Boxplots of end-expiratory lung impedance (EELI) at different breathing exercises. Left column is data from healthy volunteers and right column is from the patients with COPD. QTB, quiet tidal breathing; DB, diaphragmatic breathing; PL, pursed lip breathing; PL+DB, pursed lip combining diaphragmatic breathing. The boxes mark the quartiles while the whiskers extend from the box out to the most extreme data value within 1.5*the interquartile range of the sample. Red pluses are samples outside the ranges. *$p < 0.01$; ***$p < 0.0001$ compared to QTB.

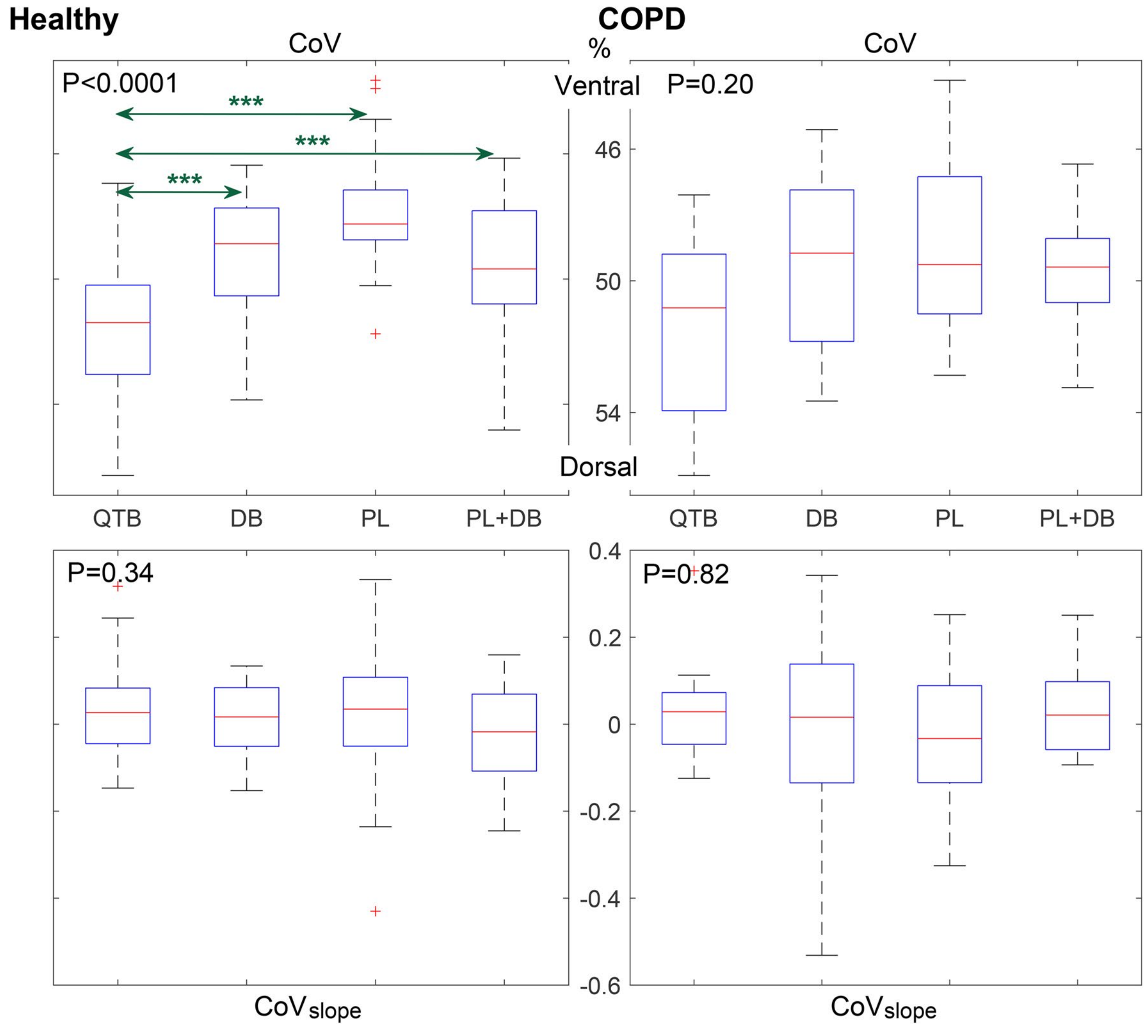

Figure 3. Boxplots of Center of ventilation (CoV) at different breathing exercises. Left column is data from healthy volunteers and right column is from the patients with COPD. QTB, quiet tidal breathing; DB, diaphragmatic breathing; PL, pursed lip breathing; PL + DB, pursed lip combining diaphragmatic breathing. The boxes mark the quartiles while the whiskers extend from the box out to the most extreme data value within 1.5*the interquartile range of the sample. Red pluses are samples outside the ranges. ***$p < 0.0001$ compared to QTB.

proved that EIT can be used to assess the lung status, we still missed the real-time information about the treatment itself. Recently, Li et al. have summarized their experience in using EIT to guide the physiotherapy, in which regional ventilation distribution was assessed in real-time to adjust the therapy strategies [21]. Similarly, in the current study, we calculated the regional information during the breathing exercises and aimed to use such information to guide the therapy in the future.

Pursed lip breathing and diaphragmatic breathing techniques are easy to learn, and patients can practice at home to ease the symptoms [22]. In the control cohort, we found that these breathing exercises can increase lung ventilation through active inhalation and exhalation (*TV* and *EELI*). Besides, ventilation redistributed toward ventral regions (*CoV*) and introduce a slightly higher temporal ventilation difference (*RVD*). Diaphragmatic breathing improves ventilation homogeneity while pursed lip breathing does not (*GI*). The impacts of breathing exercises were relatively consistent on the healthy subjects examined in the study. Although similar trends were observed in the patients with COPD, the variation of impacts of breathing exercises was much larger, which led to statistically insignificant results. TV among various breathing exercises was similar in COPD (Figure 1, right). We suspect that without extending the expiration time, the breathing exercises would not increase the tidal volumes as much as the healthy volunteers due to the flow limitation. To prove our hypothesis, we would need to setup one more exercise with much longer expiration time, which was not explored in the current study. Some patients benefited from diaphragmatic breathing and were able to lower their functional residual capacity while the others not (Figure 2, right). Pursed lip breathing on the other hand was able to lower the functional residual capacity but not necessary the ventilation homogeneity. The variation of impacts on patients with COPD could be due to individual pathological status. It was demonstrated in a previous study that regional ventilation responses to bronchodilator were different in various patients with COPD. Early studies evaluating the effects of breathing techniques also

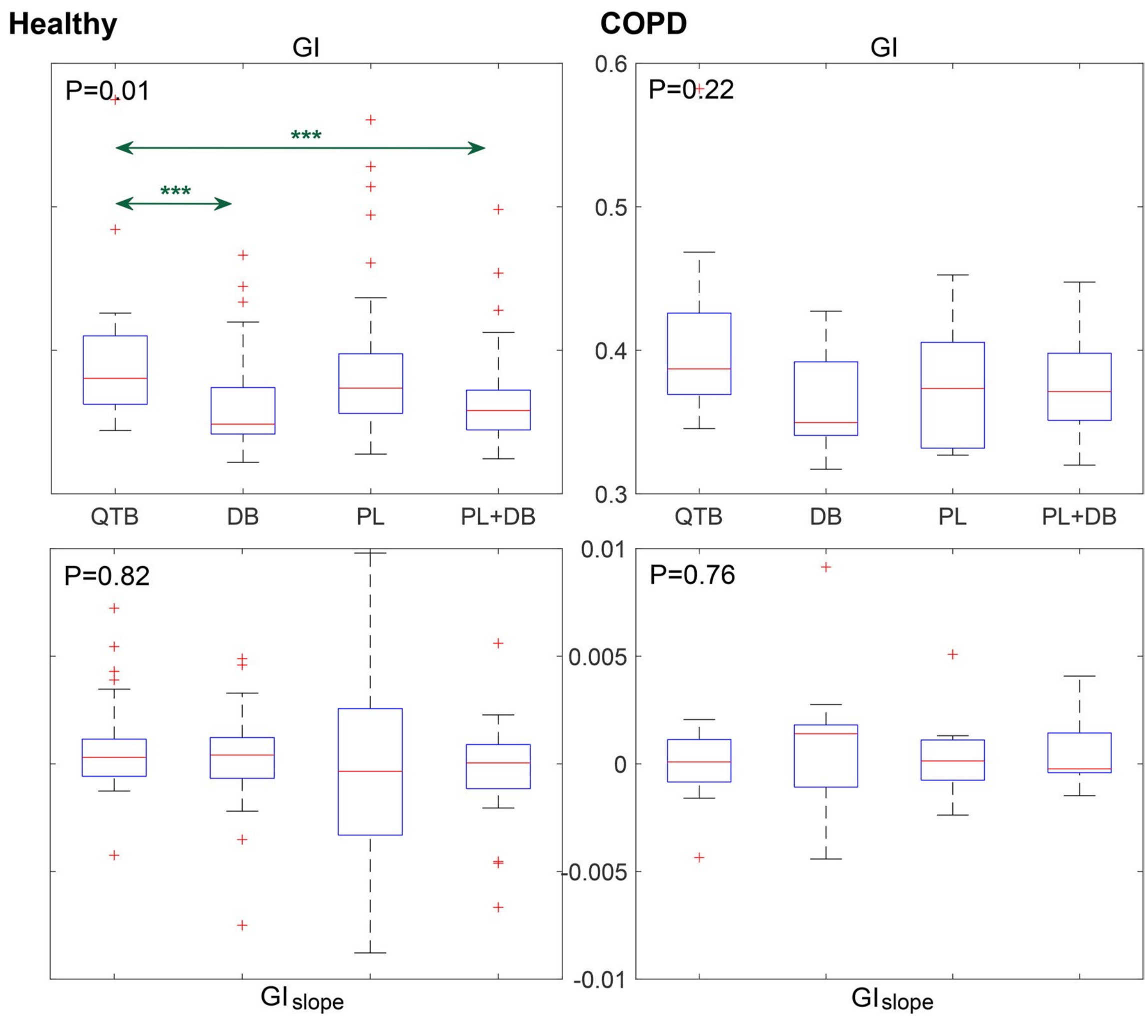

Figure 4. Boxplots of the global inhomogeneity (GI) index at different breathing exercises. Left column is data from healthy volunteers and right column is from the patients with COPD. QTB, quiet tidal breathing; DB, diaphragmatic breathing; PL, pursed lip breathing; PL + DB, pursed lip combining diaphragmatic breathing. The boxes mark the quartiles while the whiskers extend from the box out to the most extreme data value within 1.5*the interquartile range of the sample. Red pluses are samples outside the ranges. ***$p < 0.0001$ compared to QTB.

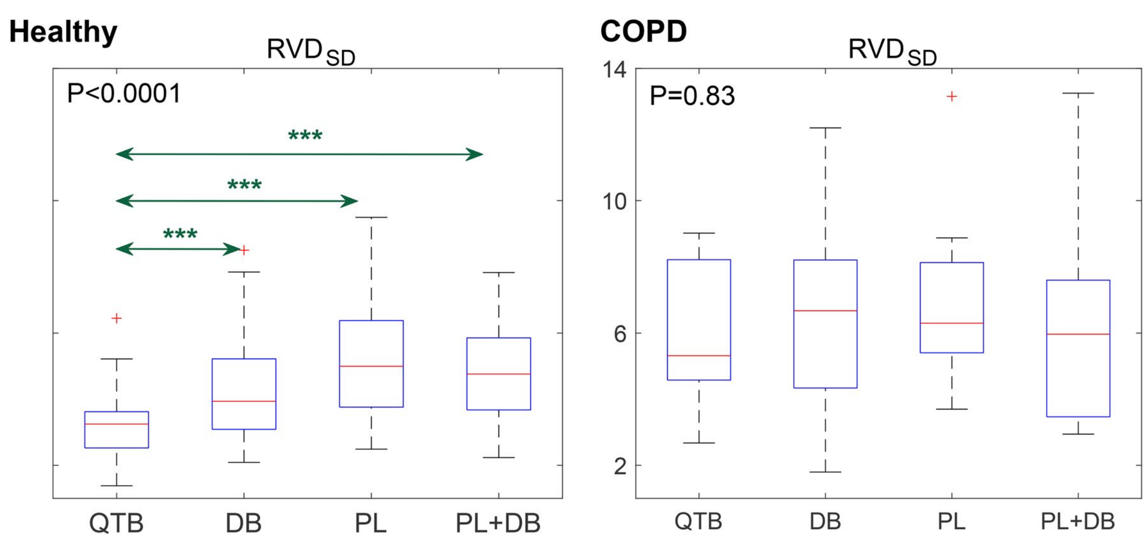

Figure 5. Boxplots of standard deviation of regional ventilation delay (RVD_{SD}) at different breathing exercises. Left column is data from healthy volunteers and right column is from the patients with COPD. QTB, quiet tidal breathing; DB, diaphragmatic breathing; PL, pursed lip breathing; PL + DB, pursed lip combining diaphragmatic breathing. The boxes mark the quartiles while the whiskers extend from the box out to the most extreme data value within 1.5*the interquartile range of the sample. Red pluses are samples outside the ranges. ***$p < 0.0001$ compared to QTB.

confirmed that the responses were different among patients [23, 24]. Therefore, our finding coincided with these previous studies that individualized monitoring of the training effect could be beneficial. In most of the studies that evaluated the effects of breathing exercises usually lasted for weeks and used lung function improvement as end point [25]. To date, few techniques can be used to assess the immediate effects of the breathing exercises. Mendes et al. used optoelectronic plethysmography (OEP) to assess the asynchrony between chest wall compartments [24]. Similarly, OEP was used to evaluate chest wall volumes in various diseases [26–28]. Although these studies were able to assess the effects of breathing techniques on chest wall, unlike EIT, no regional ventilation information could be observed. Mendes et al. also applied respiratory inductive plethysmography to teach the subjects how to better manage the breathing techniques. In our present study, only 10 min training time was given before the measurements were conducted. This could be a potential reason that some subjects with COPD were not able to completely manage the breathing technique. McGrath et al. have presented a protocol how to train subject through music [25]. While we are exciting to see such innovative attempt, we would like to point out the potential of EIT as visual feedback for the subject training. In a previous study, we demonstrated that EIT could be used to train pilots for their anti-gravity straining maneuver [29]. In the present, we have included a control group that showed systematic ventilation alteration patterns among breathing exercises. In the future study design, we would explore the subject training effect of breathing exercises with and without EIT.

Comparing the spatial and temporal ventilation distribution between healthy and COPD was not the main goal of the study. Nevertheless, we found significant differences in $\Delta EELI$ and RVD_{SD} (Table S2). Air trapping occur often in COPD and therefore during breathing exercise, they might not be able to exhale as much air as the healthy volunteers, which led to smaller $\Delta EELI$. For RVD_{SD}, we suspected that the heterogeneity in airway resistances was the main cause. Whether these information could be used to diagnose COPD requires further investigation.

We acknowledge a few limitations of the study: The number of patients was limited. In this proof-of-concept study, we observed that breathing exercises would introduce various regional ventilation distributions. We were not intended to compare the differences between healthy and patients with COPD. Therefore, the number of subjects was able to serve our purpose. Similarly, we acknowledge the age difference between healthy and COPD, but the influence on the findings might be limited. The performance of breathing exercises was controlled by one of the investigators, but we could not rule out the possibility that younger subjects had better understanding and management of the exercises. The break between exercises might not be sufficient for subjects especially COPD to recover. Besides, the levels of severity were scattered, and no outcome assessments were included. Further studies are warranted to confirm whether breathing exercise selected by EIT can help to improve training efficacy and outcomes.

Conclusions

The influences of breathing exercises on regional ventilation in healthy subjects were systematic. On the other hand, the effects of breathing exercises varied in COPD with larger inter-subject variations. Breathing exercise may be individualized to maximize the training efficacy with help of EIT.

Disclosure statement

No potential conflict of interest was reported by the authors.

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