Supplementary File 1

Supplementary Detailed Methods

1. The Breathing Exercise Movements, Safety, and Effectiveness of LHP's RRPF

1.1 Breathing Exercise Movements of LHP's RRPF (Registration No.: 2015-V-00432628)

LHP's RRPF includes the following 3 consecutive sets of movements (*Figure S1*):

(1). Deep breath of the whole lung.

Patients stood upright, separated the two feet at the shoulder width, and placed both arms on the outer thighs. Then, patients raised both arms outward slowly and inhaled deeply till both hands closed over the top of the head. Subsequently, patients lowered both arms slowly and exhaled deeply till both arms returned to their original position. Patients repeated these movements 4 to 6 times within one minute (*Figure S1A*).

(2). Deep breath of unilateral lower lung.

Patients stood upright, separated the two feet at the shoulder width, and placed both arms on the outer thighs. Then, patients raised the right arm outward slowly, bended the torso leftward to approximately 30-60° angle, and inhaled deeply. Subsequently, patients exhaled deeply and lowered the right arm to its original position. Patients repeated the movements using the left arm. These movements were repeated 4 to 6 times within one minute (Figure S1B).

(3). Deep breath of the upper lung.

Patients stood upright, separated the two feet at the shoulder width, and placed both arms on the outer thighs. Then, patients crossed the two hands at the back of the neck, bended the head and neck forward, and exhaled deeply. Subsequently, patients kept the two hands crossed at the back of the neck, moved both arms backward, raised the head and neck slowly, and inhaled deeply. These movements were repeated 4 to 6 times within one minute (Figure S1C).

During the breathing exercises, patients should make sure that the movements are done properly, but they should avoid overdoing the exercises. The exercises should be done step by step but not cause fatigue or exhaustion. If patients experience over- ventilation during the breathing exercises, then oxygen inhalation should be allowed. If cough increases during the breathing exercises, antitussive drugs should be administered.

1.2 Lung Ventilation Efficiency Test

Vibration Response Imaging (VRI) (VRIxp, DEEPBREEZE) can measure lung function during breathing at resting state. Compared with conventional methods, VRI has substantial advantages. VRI can monitor the dynamic changes in lung volume and identify lesions directly, rapidly, and accurately. It can also discover abnormal breathing sounds in the lung with a high sensitivity and clearly illustrate the changes in lung volume in different regions (maximum energy frame, MEF). VRI has no impact on patient's condition. Thus, it is a safe and reliable method to evaluate the effectiveness of breathing exercises. The principle of operation of VRI is displayed in Figure S2. The lung volume and MEF during the breathing exercises were compared with those at resting state. VRI system divides the bilateral lung into upper, middle, and lower sections, calculates the percentage of each section, and configures the percentage quantitative lung data (QLD) map. Patients' maximal forced vital capacity (FVC) was used by the VRI system to estimate the lung volume of each lung section.

1.3 Safety and Effectiveness of LHP's RRPF in Healthy Individuals

Twenty healthy volunteers aged 40 to 50 years (10 men and 10 women) completed the breathing exercises of LHP's RRPF. VRI was performed before and after the breathing exercises to determine the effectiveness of LHP's RRPF on lung ventilation. The subject rested for one minute before and after each set of movement. Blood oxygen saturation and electrocardiogram were measured 3 times to determine the safety of LHP's RRPF.

2. Safety and Effectiveness of LHP's RRPF in Patients with IPF

2.1 Patient Inclusion and Exclusion Criteria

Inclusion criteria: 1) patients were diagnosed with IPF (definite UIP) according to the 2013 and 2018 ATS/ERS/JRS/ALAT guidelines [14, 15], and their IPF condition was stable for at least one month; 2) 40 to 80 years of age, male or female; 3) were able to tolerate the breathing exercises; 4) at stable state, arterial blood gas PO_2 >60mmHg and PCO_2 <50mmHg; 5) 6MWD ≥100 meters; 6) had good compliance with the study protocol; 7) were fully informed of study aims, methods, and potential adverse reactions,

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agreed to participate in the trial, and signed the informed consent form.

Exclusion criteria: 1) patients were unable to tolerate the breathing exercises; 2) had obvious lung infection that required anti-infection treatment (patients had respiratory infection or systemic infection within 4 weeks of the enrollment); 3) had malignant tumors 5 years before the enrolment; 4) participated in other clinical trials within 3 months of the enrolment; 5) had severe systemic diseases and organ dysfunction; 6) were pregnant, nursing, planning for pregnancy, or unable to use effective contraceptive; 7) had medical conditions that were considered unsuitable for the trial by the investigators.

The screening and single-blind randomization were completed at the Department of Respiratory Medicine, Shanghai Pulmonary Hospital, Tongji University. The study has been approved by the Institutional Review Board of Shanghai Pulmonary Hospital (Approval No.: K14-156). The clinical trial has been registered at http://www.chictr.org.cn/enindex.aspx. (Trial registration No.: ChiCTR-OOC-15005818).

Patients' baseline data were collected and are presented in *Table 1*. Baseline data included gender, age, BMI, disease duration, SGRQ score, FVC, FEV1, DLCO, 6MWD, and lung volume calculated based on chest X-ray results.

2.2 Study Design and Randomization

This was a single center, single blind randomized control trial. The random numbers were generated in SAS by the biostatisticians from Tongji University. The randomized results were concealed in opaque sealed envelopes prepared and shuffled before the start of the study by an independent person unrelated to the study protocol. The study schedule is displayed in *Figure S3*. Patients were screened, enrolled, and randomized. During the trial, patients were scheduled to have clinic visits at the 6^{th} and / or 12^{th} month. If patients developed IPF exacerbation during the trial, then the patients were withdrawn from the trial and treated immediately.

2.3 Frequency and Management of the Breathing Exercise of LHP's RRPF

Patients in the exercise group repeated the breathing exercise 3 times daily (4 to 6 minutes each time) and rested for one minute after each time. Two weeks before the trial started, patients assigned to the exercise group underwent breathing exercise training twice per week (at outpatient clinic or in hospital). The training was provided by the study investigators. The study investigators made sure that patients fully understood and learned the breathing exercises. After the trial started, patients in the exercise group provided video recording of their exercise to the investigators once per month. The investigators re-trained the patients if they found the patients did not execute the movements correctly. In each clinic visit, the investigators examined patients' breathing exercise, corrected movements, or re-trained the patients to make sure that the patients performed the breathing exercise correctly. Patients in the control group did not perform the breathing exercise and only came to the two clinic visits. Every patient wrote a diary following the study protocol during the trial. Patients continued their existing therapies during the trial at least for one year. Clinic visits were scheduled at the 6^{th} month and 12^{th} month of the trials. Some patients did not come to the 6^{th} month clinic visit and only returned to the 12^{th} month clinic visit.

3. Effectiveness and Safety Assessment

3.1 Primary Endpoints

The study primary endpoints were changes in FVC and lung volume. Lung function was determined according to the 2005 ATS/ERS Guidelines [16]. Changes in FVC after the breathing exercises was used to estimate the effectiveness of LHP's RRPF. Chest X-ray was performed at the beginning and end of the trial. Lung volume was determined by the position of the left and right transverses relative to the position of the posterior rib on the X-ray image. Changes in lung volume after the breathing exercises was measured.

3.2 Secondary Endpoints

The study secondary endpoints included 6MWD, quality of life score (St. George's Respiratory Questionnaire, SGRQ score), forced expiratory volume in one second (FEV1), and diffusing capacity of the lungs for carbon monoxide (DLCO). 6MWD was determined according to the ATS Guidelines [17] in the study site. On the flat ground, patient walked back and forth along a 40-meter straight line for 6 minutes, and the walking distance was measured. 6MWD represents patient heart and lung function and physical activity endurance. The standard SGRQ [18] was used to assess the impact of the breathing exercise on the quality of life (QOL) of patients. FEV1 was determined according

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to the 2005 ATS/ERS Guidelines [16]. FEV1 represents airway ventilation function. DLCO represents oxygen exchange capacity and was used to estimate the effectiveness of LHP's RRPF.

3.3 Safety Measurement

Electrocardiogram (EKG) was performed to assess the effect of the breathing exercise on cardiac function. Patients underwent EKG at the beginning of the trial and the 6th and 12th month clinic visits.

4. Statistical Analyses

Paired t-test was used to compare the heart rate and blood oxygen saturation of healthy volunteers before the breathing exercise, right after the exercise, and one minute after the end of the exercise. Paired t-test was also used to compare the lung volume of healthy volunteers when doing the exercise versus when breathing calmly at the rest state (mean QLD%).

Independent sample t-test was used to analyze the baseline data of enrolled patients, including age, BMI, gender, disease duration, SGRQ score, 6MWD, FVC, FEV1, DLCO, and lung volume (left and right).

FVC, SGRQ, 6MWT, FEV1, and DLCO were measured at the beginning of the trial and the 6th and 12th month clinic visits. Of the 82 enrolled patients, 12 only had baseline data; 20 did not have the 6th month clinic visit data; 11 did not have the 12th month clinic visit data; 39 had complete data. The data value differences between the 6th month clinic visit and the baseline and between the 12th month clinic visit and the baseline were considered as effectiveness variables. The effectiveness variables were analyzed using linear mixed effect model. In this model, missing data were allowed; random data loss was assumed; the missing data were not imputed. Unstructured covariance matrix was used in the linear mixed effect model (likelihood-ratio is the minimal), $P<0.05$ was considered significantly different. The statistical analysis software IBMSPSS24 was used.

A diary book was handed out to every study participant. All the study participants recorded the frequency, onset time, severity, and description of adverse events during the trial. Safety analysis was descriptive.

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Figure S1 Illustration of breathing exercise of LHP's RRPF. (A) Deep breath of the whole lung. Patients raised both arms outward slowly and inhaled deeply till both hands closed over the top of the head. Subsequently, patients lowered both arms slowly and exhaled deeply till both arms returned to their original position. (B) Deep breath of unilateral lower lung. Patients raised one arm outward slowly, bended the torso toward the opposite direction to the arm to approximately 30-60° angle, and inhaled deeply. Subsequently, patients exhaled deeply and lowered the arm to its original position. (C) Deep breath of upper lung. Patients crossed the two hands at the back of the neck, bended the head and neck forward, and exhaled deeply. Subsequently, patients kept the two hands crossed at the back of the neck, forced both arms backward, raised the head and neck slowly, and inhaled deeply.

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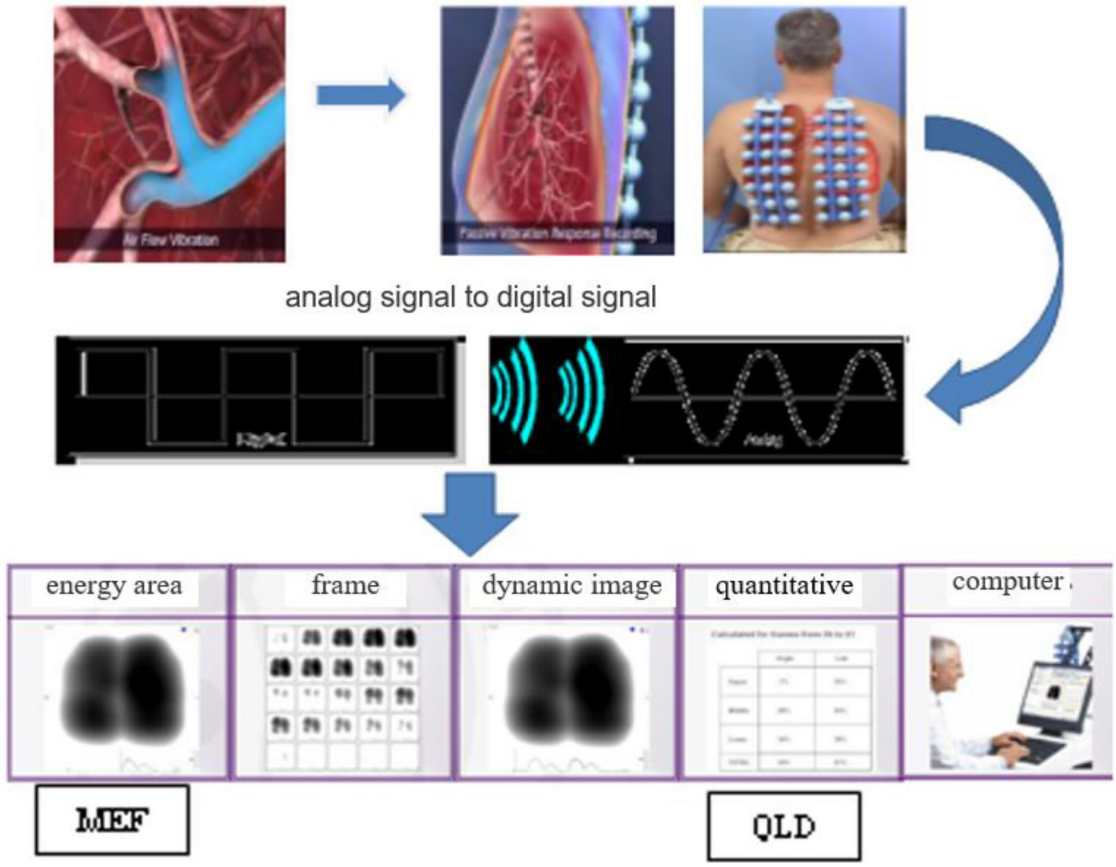

Figure S2 The principle of operation of vibration response imaging (VRI). The airflow distributed along the bronchial tree generates vibrations, which propagate through the soft tissue of the lungs and chest wall to the surface of the chest. The vibrational energy is captured by multiple acoustic sensors-microphones, and the captured energy is recorded as an analog signal. Through a specific algorithm-filtering, sampling, time division, and interpolation, data were used to create a real-time energy distribution plot and digital signals during breathing. MEF, maximum energy frame; QLD, quantitative lung data.

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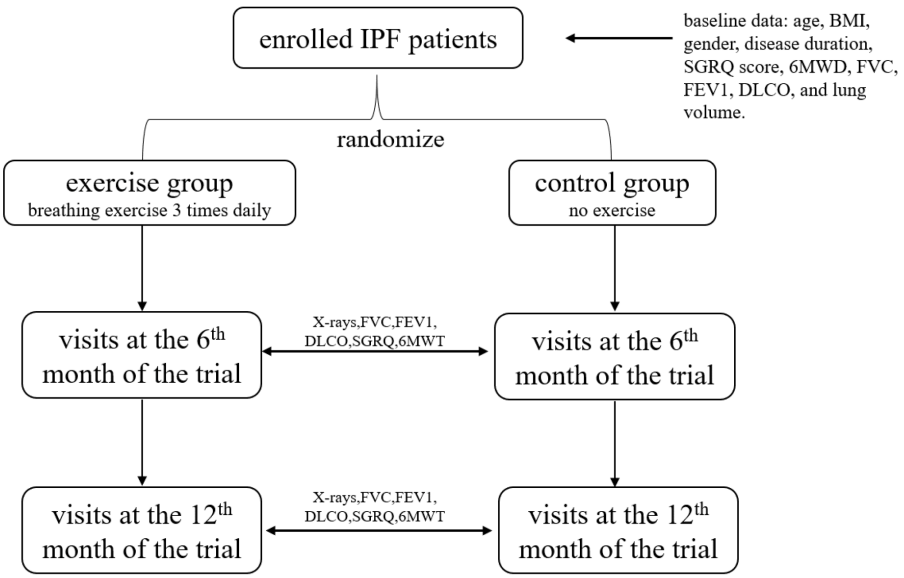

Figure S3 Study design and procedure. Enrolled patients with IPF were randomized to the exercise group and control group. Patients in both groups returned to clinic visits at the 6th and 12th month of the trial. Clinical data were collected during the clinic visits, and the data were compared with the baseline data.

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A

calm breathing both arms flatting both arms raising

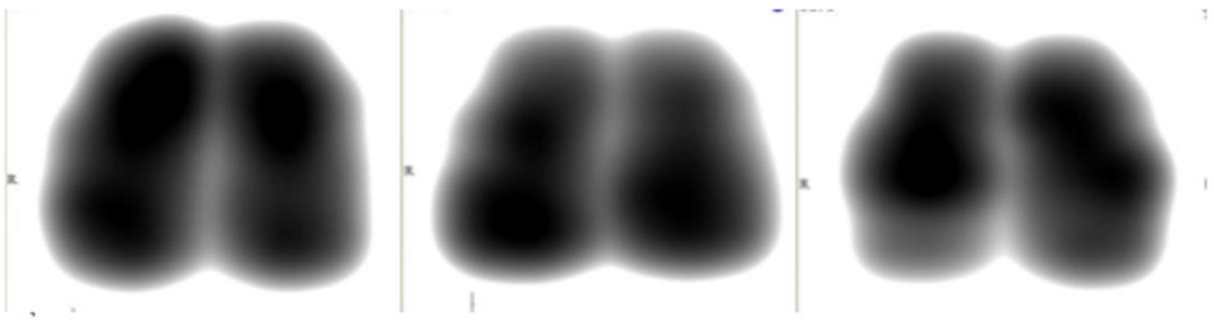
Comparison	The left lung	Mean% During exercise	Mean% at rest	*P*	The right lung	Mean% During exercise	Mean% at rest	*P*
Both arms parallel to the ground	Upper	9.25 ±3.3	11.5 ±2.9	0.032	Upper	8.2 ±4.4	9.2 ±4.4	0.41
	Middle	18.3 ±4.4	19.0 ±4.7	0.332	Middle	18.8 ±5.1	17.8 ±4.6	0.271
	Lower	22.5 ±4.2	21.6 ±5.3	0.553	Lower	23.0 ±6.3	20.9 ±6.3	0.103
Both arms upward	Upper	8.4 ±3.3	11.5 ±2.9	0.001	Upper	6.6 ±2.5	9.2 ±4.4	0.019
	Middle	19.5 ±4.8	19.0 ±4.7	0.544	Middle	18 ±4.2	17.8 ±4.6	0.796
	Lower	23.9 ±5.6	21.6 ±5.3	0.083	Lower	23.7±7.4	20.9 ±6.3	0.133

B

calm breathing left arm raising right arm raising

Comparison	The left lung	Mean% During exercise	Mean % at rest	*P*	The right lung	Mean% During exercise	Mean% at rest	*P*
The left arm was raised.	Upper	8.7 ±3.3	11.5 ±2.9	0.004	Upper	9.1 ±4.0	9.2 ±4.4	0.934
	Middle	19.5 ±4.3	19.0 ±4.7	0.527	Middle	17.1 ±3.6	17.8 ±4.6	0.588
	Lower	23.6±6.6	21.6 ±5.3	0.309	Lower	21.6 ±5.8	20.9 ±6.3	0.594
The right arm was raised.	Upper	11.7 ±3.7	11.5 ±2.9	1.000	Upper	7.7 ±3.5	9.2 ±4.4	0.055
	Middle	20.2 ±5.3	19.0 ±4.7	0.259	Middle	15.5 ±3.6	17.8 ±4.6	0.071
	Lower	22.0 ±6.0	21.6 ±5.3	0.800	Lower	23.0±6.3	20.9 ±6.3	0.176

C



calm breathing bended the head and neck forward bended the head and neck backward

Comparison	The left lung	Mean% During exercise	Mean% at rest	*P*	The right lung	Mean% During exercise	Mean% at rest	*P*
The head and neck were bended forward	Upper	12.9±3.2	11.5 ±2.9	0.458	Upper	11.4±4.8	9.2 ±4.4	0.168
	Middle	18.9±5.0	19.0 ±4.7	0.684	Middle	15.7±5.2	17.8 ±4.6	0.248
	Lower	21.3±7.4	21.6 ±5.3	0.397	Lower	20.3±7.1	20.9 ±6.3	0.846
The head and neck were stretched backward.	Upper	13.7±3.4	11.5 ±2.9	0.122	Upper	11.3±1.2	9.2 ±4.4	0.116
	Middle	19.9±5.3	19.0 ±4.7	0.383	Middle	18.3±3.1	17.8 ±4.6	0.581
	Lower	20.5±6.1	21.6 ±5.3	0.107	Lower	16.5±7.0	20.9 ±6.3	1.000

Figure S4 Healthy volunteers' QLD, MEF, and EVP. (A) VRI-MEF during deep breath of the whole lung. The 3 photos are maximum energy frames (MEF) during deep breathing using the whole lung when the Subject was at rest state, kept both arms parallel to the ground, and raised both arms upward, respectively. The table displays the mean quantitative lung data (QLD)% of bilateral lung volume when both arms were kept parallel to the ground and when both arms were raised upward. P values were calculated from statistical analyses. (The whole lung QLD is 100%, which is the total sum of the left upper, middle, and lower lung and the right upper, middle, and lower lung.). (B) VRI-MEF during deep breath of unilateral lower lung. The 3 photos are maximum energy frames (MEF) during deep breathing using unilateral lower lung when the subject was at rest state, raised the left arm, and raised the right arm, respectively. The table displays the mean quantitative lung data (QLD)% of bilateral lung volume when the subjects raised the left arm and when the subjects raised the right arm. P values were calculated from statistical analyses. (The whole lung QLD is 100%, which is the total sum of the left upper, middle, and lower lung and the right upper, middle, and lower lung.). (C) VRI-MEF during deep breath of upper lower lung. The 3 photos are maximum energy frames (MEF) during deep breathing using the upper lung when the subject was at rest state, bended the head and neck forward, and stretched the head and neck backward, respectively. The table displays the mean quantitative lung data (QLD)% of bilateral lung volume when the subjects bended the head and neck forward and stretched the head and neck backward. P values were calculated from statistical analyses. (The whole lung QLD is 100%, which is the total sum of the left upper, middle, and lower lung and the right upper, middle, and lower lung.).

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Table S1 Safety of LHP's RRPF in healthy volunteers

Parameters	Time of the measurement	Hear rate (mean ± standard deviation)	P
Heart rate	Right after the exercise/rest state	90.95±11.26/78.45±11.52	<0.001
	One minute after the exercise/rest state	79.05±11.21/78.45±11.52	0.447
Blood oxygen saturation	Right after the exercise/rest state	98.10±1.71/98.45±0.95	0.420
	One minute after the exercise/rest state	98.70±0.57/98.45±0.95	0.204

LHP's RRPF, LHP's respiratory rehabilitation for pulmonary fibrosis.

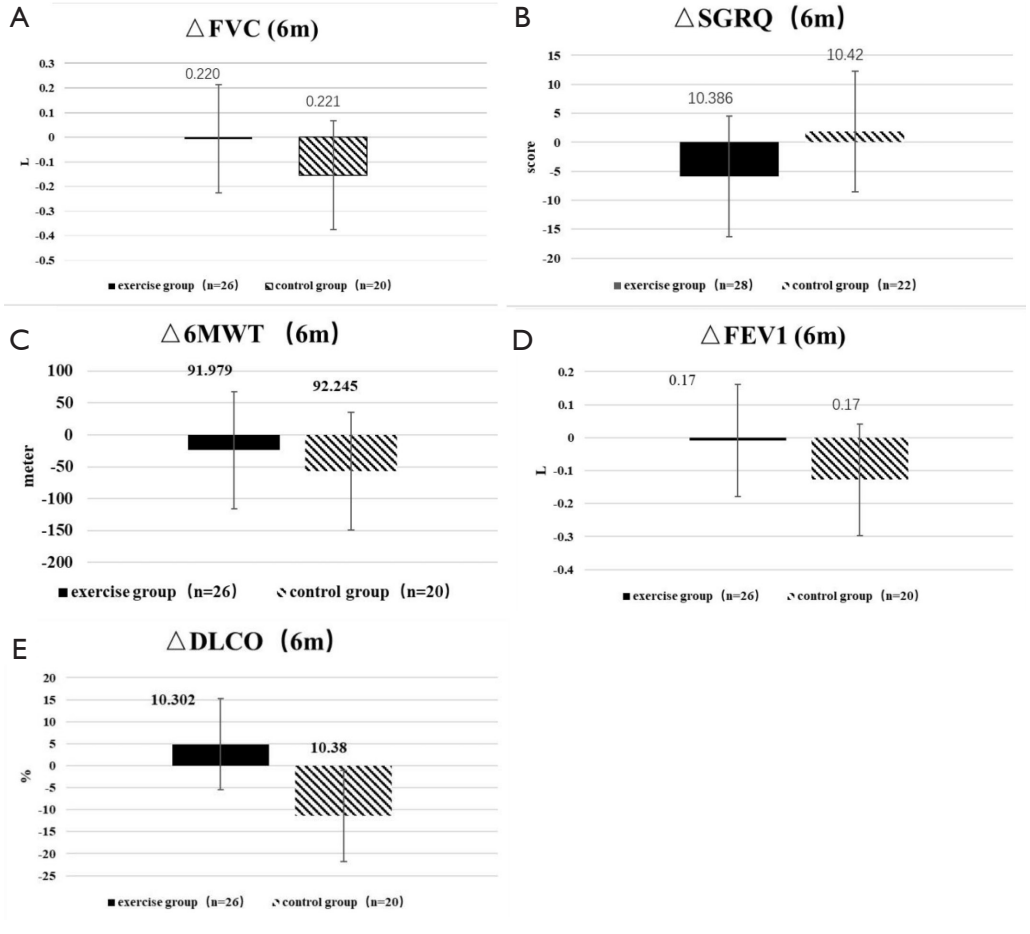

Figure S5 Comparison of ΔFVC, ΔSGRQ, Δ6MWD, ΔFEV1, and ΔDLCO at the 6th month (6m) Clinic Visit of the Exercise Group Versus the Control Group. (A) Comparison of ΔFVC at the 6th month (6m) Clinic Visit of the Exercise Group (n=26) Versus the Control Group (n=20) (P=0.023). The Y-axis represents changes in FVC (ΔFVC).ΔFVC = the FVC values at the 6th month clinic visit – FVC values at the baseline. The data are presented as mean ΔFVC ± standard deviation. (B) Comparison of ΔSGRQ at the 6th Month Clinic Visit of the Exercise Group (n=28) Versus the Control Group (n=22) (P=0.016). The Y-axis represents changes in SGRQ (ΔSGRQ). ΔSGRQ = the SGRQ values at the 6th month clinic visit – SGRQ values at the baseline. The data are presented as mean ΔSGRQ ± standard deviation. (C) Comparison of Δ6MWD at the 6th Month (6m) Clinic Visit of the Exercise Group (n=28) Versus the Control Group (n=22) (P=0.266). The Y-axis represents changes in 6MWD (Δ6MWD). Δ6MWD = the 6MWD values at the 6th month clinic visit – 6MWD values at the baseline. The data are presented as mean Δ6MWD ± standard deviation. (D) Comparison of ΔFEV1 at the 6th Month (6m) Clinic Visit of the Exercise Group (n=26) Versus the Control Group (n=20) (P=0.017). The Y-axis represents changes in FEV1 (ΔFEV1). ΔFEV1 = the FEV1 values at the 6th month clinic visit – FEV1 values at the baseline. The data are presented as mean ΔFEV1 ± standard deviation. (E) Comparison of ΔDLCO at the 6th Month (6m) Clinic Visit of the Exercise Group (n=26) Versus the Control Group (n=20) (P<0.001). The Y-axis represents changes in DLCO (ΔDLCO). ΔDLCO = the DLCO values at the 6th month clinic visit – DLCO values at the baseline. The data are presented as mean ΔDLCO ± standard deviation. SGRQ, St. George's Respiratory Questionnaire; 6MWD, six-minute walk distance; FVC, forced vital capacity; FEV1, forced expiratory volume in one second; DLCO, diffusing capacity of the lungs for carbon monoxide.

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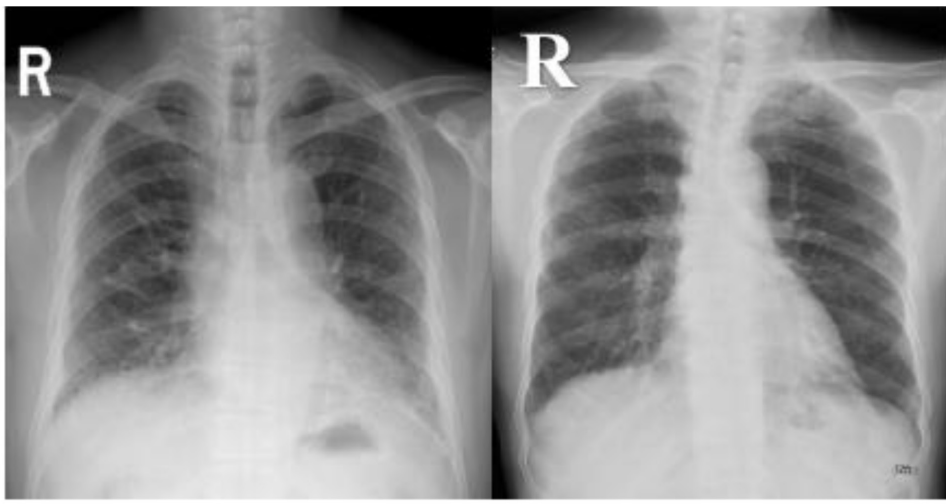
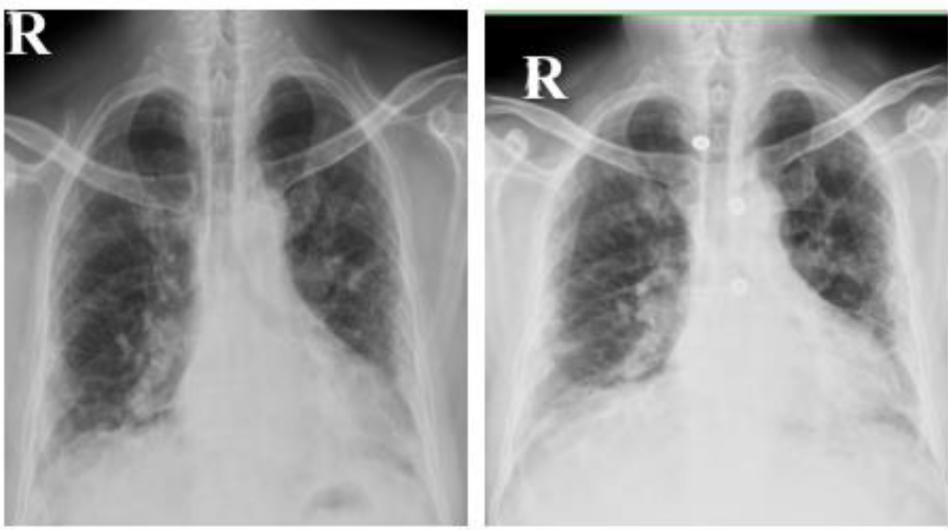
A



Left panel: Chest X-ray at the beginning of the trial
Right panel: Chest X-ra at the 12th month of the trial
The R on the figure means right side of the chest.

B



Left panel: Chest X-ray at the beginning of the trial
Right panel: Chest X-ra at the 12th month of the trial
The R on the figure means right side of the chest.

Figure S6 Chest X-ray images at the 12th month (12 m) visit. (A) Increased lung volume of a patient from the exercise Group. (B) Reduced lung volume of a patient from the control group.

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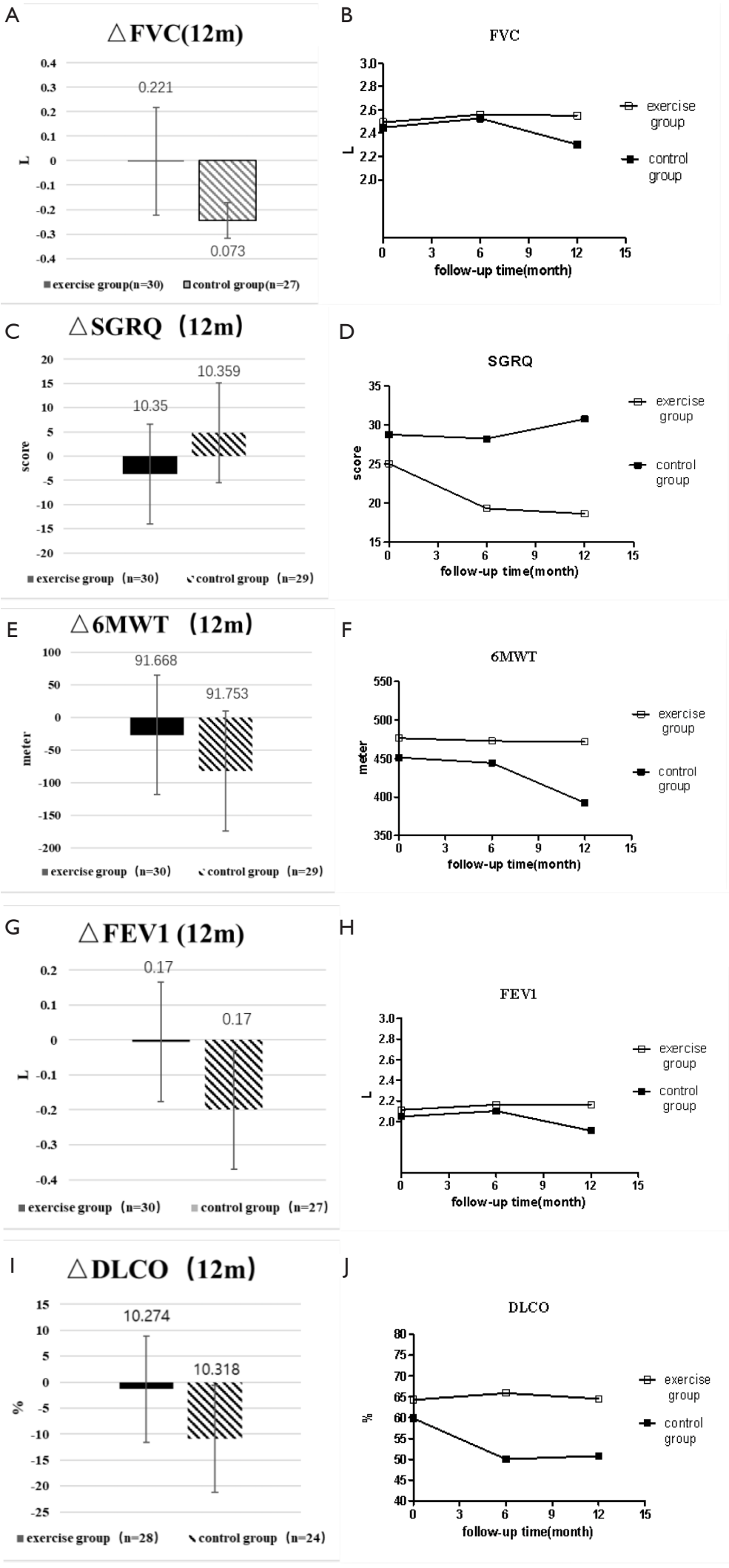

Figure S7 Comparison of ΔFVC, ΔSGRQ, Δ6MWD, ΔFEV1, and ΔDLCO at the 12th month (12m) Clinic Visit of the Exercise Group Versus the Control Group. (A,B). Comparison of ΔFVC at the 12th month (12m) Clinic Visit of the Exercise Group (n=30) Versus the Control Group (n=27) (P=0.001). (A) The Y-axis represents changes in FVC (ΔFVC); ΔFVC = the FVC values at the 12th month clinic visit – FVC values at the baseline; the data are presented as mean ΔFVC ± standard deviation. (B) X-axis is the time of the trial; Y-axis is FVC; the data are presented as mean FVC. (C,D) Comparison of ΔSGRQ at the 12th Month Clinic Visit of the Exercise Group (n=30) Versus the Control Group (n=29) (P=0.003). (C) The Y-axis represents changes in SGRQ (ΔSGRQ); ΔSGRQ = the SGRQ values at the 12th month clinic visit – SGRQ values at the baseline; the data are presented as mean ΔSGRQ ± standard deviation. (D) X-axis is the time of the trial; Y-axis is SGRQ score; the data are presented as mean SGRQ score. (E,F) Comparison of Δ6MWD at the 12th Month (12 m) Clinic Visit of the Exercise Group (n=30) Versus the Control Group (n=30) (P=0.041). (E) The Y-axis represents changes in 6MWD (Δ6MWD); Δ6MWD = the 6MWD values at the 12th month clinic visit – 6MWD values at the baseline; the data are presented as mean Δ6MWD ± standard deviation. (F) X-axis is the time of the trial; Y-axis is 6MWD; the data are presented as mean 6MWD. (G,H) Comparison of ΔFEV1 at the 12th Month (12m) Clinic Visit of the Exercise Group (n=30) Versus the Control Group (n=27) (P=0.001). (G) The Y-axis represents changes in FEV1 (ΔFEV1); ΔFEV1 = the FEV1 values at the 12th month clinic visit – FEV1 values at the baseline; the data are presented as mean ΔFEV1 ± standard deviation. (H) X-axis is the time of the trial; Y-axis is FEV1; the data are presented as mean FEV1. (I,J). Comparison of ΔDLCO at the 12th month (12m) Clinic Visit of the Exercise Group (n=28) Versus the Control Group (n=24) (P=0.003). (I) The Y-axis represents changes in DLCO (ΔDLCO); ΔDLCO = the DLCO values at the 12th month clinic visit – DLCO values at the baseline; the data are presented as mean ΔDLCO ± standard deviation. (J) X-axis is the time of the trial; Y-axis is DLCO; the data are presented as mean DLCO. Two patients from the exercise group and 5 from the control group did not have the 12th month DLCO. SGRQ, St. George's Respiratory Questionnaire; 6MWD, six-minute walk distance; FVC, forced vital capacity; FEV1, forced expiratory volume in one second; DLCO, diffusing capacity of the lungs for carbon monoxide.

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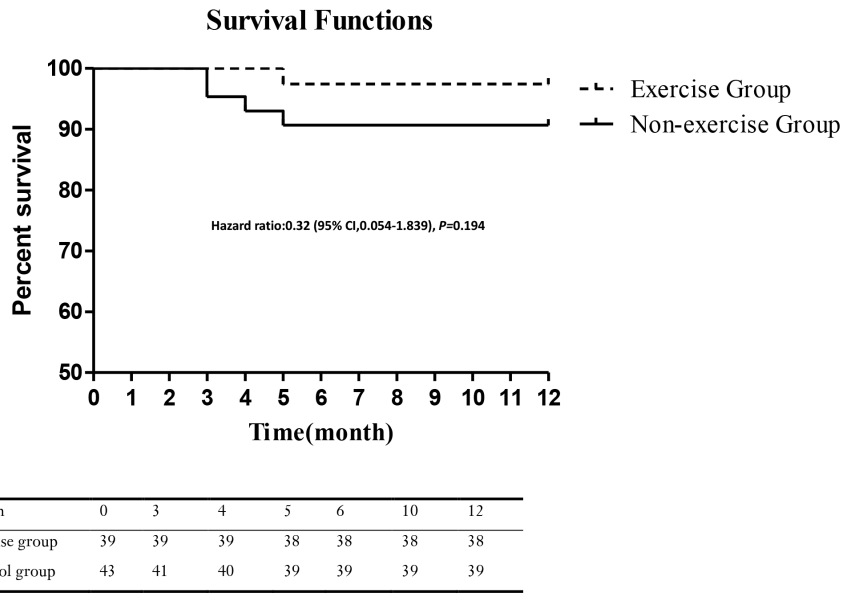
Table S2 The number of patients developed acute exacerbation during the trial

Group	With acute exacerbation	No acute exacerbation	Total
Exercise	3	36	39
Control	9	34	43
Total	12	70	82

χ^2 test P=0.090.



Month	0	3	4	5	6	10	12
Exercise group	39	39	39	38	38	38	38
Control group	43	41	40	39	39	39	39

Figure S8 The 12-month (12 m) survival curve of patients from the exercise and control groups (n=82). The X-axis is month, and the Y-axis is the percentage of survival. The table presents the number of the survived patients in each month.

Table S3 Mortality of the exercise and control groups

Cause of death	Time of death	Exercise group (n=39)	Control group (n=43)
Lumber fracture repair surgery	The 4th month		1
Acute exacerbation	The 2nd month		1
Acute exacerbation	The 5th month	1	
Acute exacerbation	The 3rd month		1
Acute exacerbation	The 4.5th month		1

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