International Journal of Chronic Obstructive Pulmonary Disease Dovepress
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ORIGINAL RESEARCH

Benefits of different intensities of pulmonary rehabilitation for patients with moderate-to-severe COPD according to the GOLD stage: a prospective, multicenter, single-blinded, randomized, controlled trial

This article was published in the following Dove Press journal:
International Journal of Chronic Obstructive Pulmonary Disease

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Purpose: Pulmonary rehabilitation (PR) is essential to manage patients with COPD. The aim of this study was to investigate the appropriate intensity of PR exercise training for patients with moderate-to-severe COPD.

Patients and methods: A prospective multicenter randomized controlled trial was conducted from January 2014 to October 2018. The subjects were randomly assigned to three groups with different intensities of PR, according to their maximum oxygen uptake percentage determined by cardiopulmonary exercise testing. After 20 weeks of exercise training, the effects of low-, moderate-, and high-intensity exercise interventions on patients were compared to determine the most appropriate PR prescription.

Results: For patients with moderate COPD, all the measured parameters were significantly improved in the moderate- and high-intensity PR groups ($P<0.01$), while there was no significant difference in the frequency of acute exacerbations and the mMRC questionnaire after 20 weeks of PR exercise in the low-intensity PR group. For patients with severe COPD, all variables were also improved in the high-intensity PR group ($P<0.05$), while the mean differences of pre- and post-PR were lower than those in patients with moderate COPD. Moreover, the Hamilton Anxiety Scale and body mass index showed no significant difference in low-intensity PR group ($P>0.05$).

Conclusion: High-intensity PR exercise is helpful for patients with moderate to severe COPD. Moderate COPD patients need to receive intensive PR training; the improvement degrees from PR intervention were higher than those of the severe COPD patients. For patients with severe COPD, high-intensity PR exercise may be more beneficial if patients can tolerate it.

Keywords: chronic obstructive pulmonary disease, cardiopulmonary exercise testing, exercise therapy, pulmonary rehabilitation

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Introduction

COPD is a common disease, seriously endangering the public health.[1] Pulmonary rehabilitation (PR) has been proved to be beneficial for patients with COPD; however, its application is currently in development phase worldwide.[2] In addition, PR is a comprehensive intervention, involving exercise training, counseling, instructional training, and behavioral change tailored to each patient.[2,3] Improving the COPD

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http://doi.org/10.2147/COPD.S214836

patients' quality of life is of great significance,[4] and the purpose of PR is basically to reduce symptoms and improve exercise tolerance and functional capacity.[4] However, the essential amount of PR is seriously underestimated by general practitioners and patients.[5] Moore et al reported that 69,089 (64%) COPD patients in their cohort were eligible for PR, while only 6436 (9.3%) cases had been referred for rehabilitation.[6] Another study demonstrated that if there is no targeted effort, the rate of early PR referrals for patients with COPD is extremely low.[7]

The 2019 GOLD report emphasized on the prominent role of PR in COPD management.[8,9] The conclusions of the updated meta-analysis presented a strong argument that PR is beneficial for improving the subjective impact of symptoms and health status.[10,11] However, lack of research data hampers progress on the specific frequency intensity of exercise, the degree of supervision, and the appropriate duration of PR exercise. Aerobic exercise is the core of lung rehabilitation, while a limited number of studies have recommended specific exercise intensities for indicating an optimal duration of PR to achieve the most promising results for patients with different severities of COPD.[12,13] Although the new GOLD strategy provides the most appropriate exercise training program, it is based on the resources being available at each rehabilitation location and the patients' specific capabilities. Therefore, the appropriate intensity of PR interventions to improve the patients' quality of life with different severities of COPD remains elusive. To the best of our knowledge, there is no report concerning the comprehensive PR effect of patients with COPD based on the GOLD staging. It is noteworthy that most COPD patients with a high degree of severity (GOLD 4) require noninvasive positive pressure ventilation during daily activities, which might be extremely severe to tolerate high-intensity exercises. Therefore, we administered a 20-week PR exercise training for patients with moderate (GOLD 2)-to-severe (GOLD 3) COPD to compare exercise capacity (BODE) index, acute exacerbation (AE) of COPD (AECOPD), the psychological features of anxiety, and depression. We also discussed how to select an appropriate PR intervention in accordance with severity of COPD patients.

Materials and methods

Design

This is a prospective, multicenter, single-blinded, randomized controlled trial (Figure 1) conducted at five medical centers, including the Fourth Rehabilitation Hospital (Shanghai, China), Ruijin Hospital Affiliated to Shanghai Jiaotong University Medical College (Shanghai, China), the Second Affiliated Hospital of Suzhou University (Suzhou, China), West-Nanjing Road Community Health-care Center of Shanghai (China), and Caojiadu Community Health Service of Shanghai (China) from January 2014 to October 2018. Briefly, COPD patients who met the inclusion criteria were first contacted by visiting them in the inpatient room. Those who agreed to participate were provided with an explanation of rehabilitation program at the medical centers mentioned above and invited to sign written informed consent forms. All those patients were free to withdraw from the study at any time with no negative consequences. The performance testing was conducted in the same order at baseline (before randomization) and at 20 weeks.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of The Fourth Rehabilitation Hospital (Shanghai, China, Approval No. SP2015001), and written informed consent was obtained from each participant.

Inclusion and exclusion criteria

All subjects were included in the study based on the following criteria: 1) age ≥40 years; 2) clinical features of COPD and moderate-to-severe COPD, an FEV_1/FVC ratio <0.70, and an FEV_1 measurement between 30% and 80% with respect to the theoretical value based on post-bronchodilator spirometry (GOLD 2 and GOLD 3); 3) no clinical features of asthma and/or evidence of bronchodilator responsiveness on spirometry; and 4) stable COPD with no recent history of exacerbation requiring hospitalization during the last 3 months. In order to minimize inaccuracy of diagnosis, COPD diagnosis was reviewed for each participant at baseline prior to enrolment and in accordance with GOLD strategies.[14] Exclusion criteria were 1) coexisting active pulmonary tuberculosis, pulmonary fibrosis, pneumothorax, or lung cancer; 2) physically illness or mental incapacitation that prevented participation; 3) active microbial infections; and 4) lack of medical records; 5) clinical examinations consistent with coronary artery disease (eg, coronary angiography with stenting, coronary artery bypass grafting, myocardial infarction, admission to coronary care unit (CCU), etc.) or congestive heart failure; 6) neuromuscular, orthopedic and/or medical diseases precluding exercise testing; and 7) undergoing a

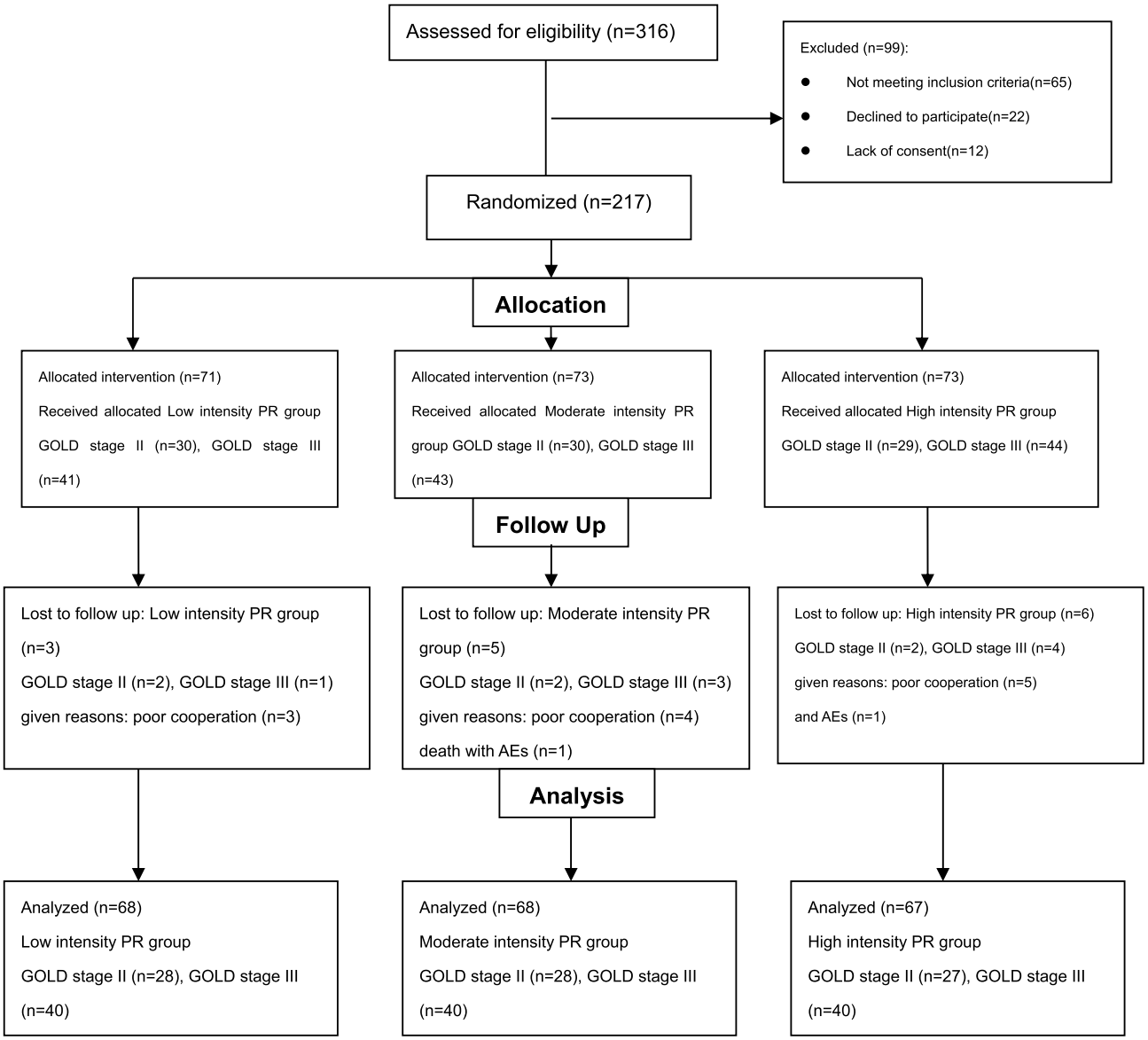

Figure 1 Flowchart of the randomized controlled trial.
Abbreviations: PR, pulmonary rehabilitation; AECOPD, acute exacerbation of COPD.

cardiopulmonary rehabilitation program within the last year. The patients were followed-up for 24 months after active participation in a PR program.

Exacerbations of COPD

Exacerbations of COPD are defined as[14] an acute worsening of respiratory symptoms, which result in additional therapy. Exacerbations of COPD play a substantial role in the rehabilitation of patients because they negatively impact health status, rates of hospitalization and readmission, and disease progression. Exacerbations of COPD are also complex events typically associated with increased airway inflammation, enhanced mucus production, and remarkable gas trapping. These changes may contribute to amplify dyspnea, which is a key symptom of an exacerbation. Other symptoms include increased sputum purulence and volume, together with increased cough and wheeze.

They are classified as follows:

1. Mild (treatment with short-acting bronchodilators only, SABDs)
2. Moderate (treatment with SABDs plus antibiotics and/or oral corticosteroids) or
3. Severe (patients requiring hospitalization or visiting the emergency room). Severe exacerbations may be associated with acute respiratory failure as well.

The COPD patients received information required to highlight the importance of understanding of exacerbation symptoms and time of seeking professional health care for therapy. In addition, all patients were trained under the supervision of physiotherapists. Once dyspnea and sputum volume were intensified in a patient, a doctor attempted to report those symptoms.

Grouping

Initially, all subjects were assigned to GOLD 2 and GOLD 3 based on the criteria of GOLD.[14] The participants were randomly assigned to the following groups: 1) low-intensity PR group, 2) moderate-intensity PR group, and 3) high-intensity PR group. Participants were allocated to each group on a random basis, which was defined by a computerized generator and was independent of the control of the principal investigator. The allocation sequence of the 89 participants of GOLD 2 and 128 participants of GOLD 3 was defined through a computer generator prior to the start of the study. After the generation of this sequence, 217 envelopes were created, numbered in the appropriate order, and contained the result of the allocation. The order of the envelopes' number was defined based on the order of participants' enrolment. The principal investigator was not aware of the information contained within the envelopes, thereby maintaining a minimization randomization process. To ensure the accuracy of the use of the envelopes, the documents inside the envelope were signed by the Data Safety Monitoring Board (DSMB) and were returned by the researchers after participants' allocation.

Evaluation

Data related to the history and the current status of the disease, current medications, smoking history, and general physical examination were collected. At this stage, exclusion was still possible, in case of any inability or incapacity. Eventually, the patients underwent the following assessments.

Primary endpoint

Primary outcome of COPD patients was assessed at baseline and at 20th week using the BODE index.[15,16] The BODE index, a multidimensional scale that predicts the risk of death, was accordingly calculated. It consisted of the following variables: body mass index (BMI) (B), obstruction (O, ie, FEV1), dyspnea (D, measured using the mMRC questionnaire), and exercise (E; meters walked in 6-min walk test, 6MWT). The participants' BMI was calculated as body weight (kg)/height (m^2). We also used the mMRC questionnaire to measure the intensity of dyspnea during daily activities. The 6MWT is widely used for testing functional capacity and physical exercise tolerance based on the distance walked in 6 mins. None of the participants used oxygen during the test. At the beginning and end of the test, blood pressure, heart rate, respiratory rate, Borg Dyspnea Scale, fatigue in the legs, and oxygen saturation were measured. The 6MWT was undertaken in accordance with the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines. The variables were assigned to points as follows: BMI (>21 kg/m^2=0 point, ≤21 kg/m^2=1 point), FEV_1% predicted (≥65%=0 point, 50–64%=1 point, 36–49%=2 points, and ≤35%=3 points), mMRC questionnaire (0–1=0 point, 2=1 point, 3=2 points, and 4=3 points), and 6MWD (≥350 m=0 point, 250–349 m=1 point, 150–249 m=2 points, and <149 m=3 points), and the points were summed to determine score of the BODE index. The scores ranged between 0 and 10 points, and higher scores represented a greater risk of death.

Secondary endpoint

Frequent exacerbations were defined as moderate or severe exacerbations or one or more hospitalization due to exacerbation of COPD in the previous 12 months. The COPD patients received information required to highlight COPD exacerbation symptoms and were interviewed every 3 months as well. An investigator recorded the patients' vital status and the frequency of AECOPD with or without hospitalization. The Hamilton Rating Scale for Depression (HRSD) was used to assess the patients' depression,[17] and the Hamilton Anxiety Scale (HAMA) was employed to identify the patients' anxiety.[18]

Other variables collected at baseline

Pack-years of smoking were calculated as follows: number of cigarette/cigarettes packs smoked/day × number of years smoked (where a bidi pack was calculated as the number of cigarette/cigarettes/20).[19]

Sample size

Using values of the BODE index in COPD patients with similar severity as reference,[20] we estimated that 168 patients (28 patients in each group) were recruited to detect a statistically significant difference of 1 point between groups, with assumption of a common SD of 2 points in the index, two-sided significance level (α) of 5%, statistical power (1-β) of 80%, and a common dropout rate

of 10%. It has been shown that the difference in 1 point in the BODE index had clinical relevance and was also associated with an increased risk of mortality of 33%.

Measurements

Pulmonary function tests

Spirometry, plethysmography, and diffusion test were carried out (Master Screen, Care Fusion Germany 234 GmbH, Höchberg, Germany) by trained personnel in a quiet room. Each test was performed three times, and the best result for each test was recorded and used to obtain the FVC, FEV_1, and the FEV_1/FVC ratio. Spirometry was repeated 20 mins after inhaling 200 μg of salbutamol to obtain the PB FVC, FEV_1, and FEV_1/FVC ratios. All patients with an FEV_1/FVC ratio <70% and fixed airway obstruction on spirometry (improved PB FEV_1<200 mL or improved FEV_1/FVC <12%) were included in the present study, while those patients with a history of wheezing, chest tightness, and allergies affecting the eyes, nose, or skin; those suffering from osteoarthritis; and those with oxygen saturation <90% were excluded from the study as well.

Cardiopulmonary exercise testing

In the present study, the intensity of PR was determined by cardiopulmonary exercise testing as follows: ≥70% of maximal oxygen uptake, which was defined as high-intensity PR exercise, 50~70% was defined as moderate-intensity PR exercise, and <50% was defined as low-intensity PR exercise. The cutoff values were based on the prognostic importance of maximal oxygen uptake in COPD patients as reported in a previous study.[20]

PR intervention

The intervention provided a 20-week supervised inpatient PR program, included 10 education sessions delivered by a multidisciplinary team, comprising medical care, respiratory therapy, education, nutritional and psychological counseling, and chest physiotherapy. The patients underwent conventional exercise training 5 days per week for 40 mins, with 10 mins of warm-up before training, as well as 10 mins of relaxation exercises after training. The exercise component of warm-up incorporated an individualized exercise program consisting of various types of interval endurance training, such as walking and functional strength exercises. Moreover, relaxation exercises included stretching and walking. The exercise program consisted of 20 mins of stationary cycling using an upper limb and lower limb coordination exercise machine (Jiangsu Tianrui Medical Equipment Co., Ltd., Nanjing, China), starting at 50% of the maximal load achieved during an exercise test. The load was progressively increased by 10 W, if the patient's heart rate and oxygen saturation were stable and the exercise was well tolerated. The sessions were ended with the help of relaxation techniques. Electrocardiogram (ECG) signals and blood-oxygen saturation level were monitored during the exercise session and within 1 hr after the exercise. To ensure patient's safety, if the blood-oxygen saturation was <85%, blood pressure was >200/100 mmHg (1 mmHg=0.133 kPa), or the heart rate reached 85% of the maximum value during the cardiopulmonary exercise testing, the exercise was stopped. Furthermore, once a patient had severe shortness of breath and could not tolerate exercise subjectively, the physiotherapist attempted to report the case. Patients were given a 5-min rest before continuing their training as well. The duration of exercise training was defined as the sum of the time to reach the target intensity. Patients, who were repeatly unable to tolerate rehabilitation training for more than three times, were removed from this study.

In this study, 3 patients in the low-intensity PR group, 4 patients in the moderate-intensity PR group, and 5 patients in the high-intensity PR group were lost the follow-up because of poor cooperation.

Adverse events (AEs)

Definition

AEs occurred after patients received rehabilitation training, while they were not necessarily causally related to rehabilitation intervention. Thus, an AE can be an undesirable and unexpected physical sign (eg, including laboratory abnormalities, etc.), a symptom, or a time-related illness during training, regardless of whether there is a causal relationship with training.

Serious AE (SAE) refers to any event during rehabilitation training, that requires hospitalization, prolonged hospitalization, disability, impact on workability, or endangers life or death.

Determination of the severity of AEs

1. Mild: A patient can endure it, without influencing continuation of treatment, with no need for special treatment, and no impact on COPD patient's clinical conditions;

2. Moderate: A patient is unbearable and needs to stop taking the medicine or do special treatment, containing a direct impact on COPD patient's clinical conditions;
3. Severe: An event endangering patient's life, disability, or death; thus, the patient must stop that event immediately or do an emergency treatment.

AEs' handlers

Any AEs, eg, patients' subjective discomfort in training and abnormal laboratory testing, should be effectively treated seriously and carefully analyzed; besides, corresponding measures should be taken immediately, and patients should be examined on time according to their clinical conditions.

Management of anticipated AEs

AEs included shortness of breath, dyspnea, arrhythmias, increased heart rate that reached 85% of the maximum value during the cardiopulmonary exercise test, fingertip blood-oxygen saturation of less than 85%, and blood pressure <200/100 mmHg (1 mmHg=0.133 kPa), which were closely followed to observe the outcomes of events or suspension training. Generally, if mild acute exacerbations occur during rehabilitation, the patient needs to suspend scheduled intensity training for 4 weeks, and to be treated with short-acting, drug dosing adjustment, and receive symptomatic treatment as indicated by the protocol.

Management of serious AEs

When severe AEs are basically judged, corresponding treatment or rescue measures shall be immediately taken according to the clinical manifestations and clinical treatment standards. If acute exacerbations (moderate or severe) occur during rehabilitation, a patient has to stop scheduled intensity training. During resting at bed, a patient performs some active exercises being consistent with his/her conditions, in which the patient lost the follow-up (Figure 1).

Follow-up for unmitigated AEs

All AEs should be tracked until they are properly resolved or stable.

In this study, one patient of GOLD 3, who allocated to moderate-intensity PR group, with multiple comorbidities died due to AEs. Besides, one patient of GOLD 3, who allocated to high-intensity PR group, was withdrawn from the study because of AEs.

Adherence

Adherence was defined in accordance with the prescribed regimen of PR classes. To monitor adherence in each group, we quantified the activity on a self-reported card registered by the patients, and attendance in the scheduled visits was every 3 months with physician over the 1-year follow-up. Moreover, an investigator recorded the patients' vital status and the frequency of AECOPD with or without hospital admission.

Statistical analysis

Data were analyzed by using SPSS 22.0 software (IBM, Armonk, NY, USA). Prior to statistical analysis, the Kolmogorov–Smirnov test and the Shapiro–Wilk test were carried out to assess the normality of continuous data. Descriptive statistics (mean ± SD) were used to determine the participants' characteristics. Normally distributed baseline demographic variables were compared by one-way ANOVA. Non-normally distributed variables were compared by using the Kruskal–Wallis test, with an alpha level of significance of 0.05. In addition, Δ expressed the mean difference between before and after PR treatment in the same group of patients. The outcomes of each variable were measured. If the one-way ANOVA showed a significant interaction for each variable, Bonferroni's post hoc test was performed to identify the specific mean differences. An unconditional logistic regression analysis was applied to assess the influence of PR. For all analyses, $P<0.05$ (2-tailed) was considered statistically significant.

Results

Participants' characteristics

Of the 316 patients with moderate-to-severe COPD who were referred to respiratory services for PR, a total of 217 patients were eventually randomized into three groups, 14 of whom lost follow-up (rate of losing the follow-up =6.45%). Among those patients who lost the follow-up, one in moderate-intensity PR group died due to acute exacerbations, one in high-intensity PR group died due to acute exacerbations, and 12 were due to poor cooperation. The distribution of participants is shown in Figure 1. Baseline characteristics are documented in Table 1. The subjects' mean age was 65.3±6.2 years. No significant difference was found in FEV_1, BODE index, and other baseline characteristics obtained at admission in the three groups.

Additionally, there were no significant differences in comorbidities between patients with moderate and severe

Table 1 Baseline characteristics of the participants

Variables	Low-intensity PR group (n=68)	Moderate-intensity PR group (n=68)	High-intensity PR group (n=67)	*P*-value
Age (years)	65.9±6.8	65.3±5.4	64.6±6.4	0.496
Male/female	40/28	37/31	38/29	0.874
FEV_1% predicted	49.56±11.98	48.65±12.03	48.70±12.43	0.887
GOLD 2, n (%)	28 (41%)	28 (41%)	27 (40%)	0.993
GOLD 3, n (%)	40 (59%)	40 (59%)	40 (60%)	0.993
6MWD (m)	274.0±70.5	267.2±61.3	267.9±66.6	0.806
mMRC	2.10±0.76	2.07±0.69	2.07±0.75	0.966
BMI	20.87±3.58	21.51±3.66	21.04±3.57	0.558
BODE index	4.60±1.69	4.60±1.57	4.58±1.65	0.996
HRSD	20.24±4.68	20.38±4.53	20.97±4.57	0.618
HAMA	18.13±3.85	17.38±3.75	18.69±3.25	0.114
Frequency of AECOPD	2.01±0.91	2.10±1.00	2.24±1.06	0.417
Number of smokers, n (%)	28 (41%)	31 (46%)	27 (40%)	0.800
Pack-years smoked	18.57±5.06	21.16±4.27	19.00±4.89	0.083
Coronary heart disease, n (%)	23 (34%)	20 (29%)	25 (37%)	0.622
Diabetes mellitus, n (%)	17 (25%)	20 (29%)	22 (33%)	0.603
Chronic renal failure, n (%)	2 (3%)	3 (4%)	3 (4%)	0.911
Noncirrhotic liver disease, n (%)	3 (4%)	1 (1%)	3 (4%)	0.637

Note: Measurement data are presented as mean ± SD.
Abbreviations: PR, pulmonary rehabilitation; 6MWT, meters walked in the 6-min walk test; BMI, body mass index; HRSD, Hamilton Rating Scale for Depression; HAMA, Hamilton Anxiety Scale; AECOPD, acute exacerbation of COPD; BODE index, body mass index, airflow obstruction, dyspnea, and exercise capacity index.

COPD (coronary heart disease: 34% vs 33%, diabetes mellitus: 25% vs 32%, chronic renal failure: 2% vs 5%, noncirrhotic liver disease: 2% vs 4%, respectively).

Table 2 summarizes the changes in BMI, lung function, and other parameters after three interventions. The 6MWD, mMRC, BODE index, and HRSD were improved, while the frequency of AECOPD was significantly decreased among all the groups after 20-week of PR exercise training. However, FEV_1, BMI, and HAMA were notably increased only in moderate- and high-intensity PR groups ($P<0.05$). The comparison analysis between groups showed that the 6MWD, BODE index, and HRSD were improved in parallel with the increase of PR exercise intensity. Compared with low- and moderate-intensity PR groups, the FEV_1 was remarkably higher and frequency of AECOPD was markedly decreased after 20 weeks of high-intensity PR exercise training. Compared with the mild PR group, the mMRC of the high-intensity PR group was significantly higher, and the HAMA of the moderate-intensity PR group and high-intensity PR group was notably improved as well.

PR intervention for GOLD 2 COPD patients

The changes between pre- and post-PR intervention of three different intensive exercise training programs for moderate COPD patients (GOLD 2) are summarized in Table 3. All variables improved in the high-intensity PR group between preintervention and postintervention. Significant differences were also found in all parameters except for FEV_1 and HAMA in the moderate-intensity PR group. Besides, 6MWD and frequency of AECOPD were improved in low-intensity PR group after 20 weeks of PR intervention.

The comparison analysis between groups showed that significant differences were found in the improved degrees of 6MWD and BODE index among the three groups (Δ6MWD: 54.5 vs 25.8 vs 10.3, ΔBODE index: 1.6 vs 0.8 vs 0.0, respectively; Table 3). Additionally, FEV_1, HRSD, HAMA, and frequency of AECOPD were significantly improved in high-intensity PR group compared with moderate-intensity PR group and low-intensity PR group (ΔFEV_1: 3.2 vs 0.3 vs 0.8, ΔHRSD: 3.3 vs 1.5 vs 0.4, ΔHAMA: 2.3 vs 0.0 vs 0.2, frequency of AECOPD 1.2 vs 0.7 vs 0.6, respectively). Compared with the low-intensity PR group, the mMRC of the high-intensity PR group and the moderate-intensity PR group (ΔmMRC: 1.4 vs 0.9 vs 0.0) was remarkably improved. Compared with the low-intensity PR group (ΔBMI: 1.2 to 0.4), the BMI of the high-intensity PR group was notably increased.

Table 2 Comparison of parameters before and after different intensities of PR among all the participants

Variable		Low-intensity PR group (n=68)	Δ (95% CI)	P_1 value	Moderate-intensity PR group (n=68)	Δ (95% CI)	P_1 value	High-intensity PR group (n=67)	Δ (95% CI)	P_1 value	P_2 value
BODE index	Pre-PR Post-PR	4.6±1.7 4.0±1.4	−0.6 (−2.0,1.6)	<0.001	4.6±1.6 3.6±1. 5	−1.0 (−3.0,1.0)	<0.001	4.6±1.7 3.1±1.6	−1.5 (−3.0,0.0)	<0.001	<0.001[a,b,c]
FEV_1% predicted	Pre-PR Post-PR	49. 6±12.0 49. 7±12.0	0.1 (−5.0,4.0)	0.752	48.7±12.0 49.1±12.0	0.4 (−3.0,2.0)	0.014	48.7±12.4 51.2±13.3	2.5 (−1.6,8.0)	<0.001	<0.001[b,c]
6MWD (m)	Pre-PR Post-PR	274.0±70.5 286.7±73.9	12.7 (−27.1,40.0)	<0.001	267.2±61.3 291.3±63.7	24.2 (−12.0,63.7)	<0.001	267.9±66.6 309.2±72.8	41.3 (12.0,83.2)	<0.001	<0.001[a,b,c]
mMRC	Pre-PR Post-PR	2.1±0.8 1.7±0.8	−0.5 (−2.0,1.6)	0.001	2.1±0.7 1.3±0.9	−0.8 (−2.0,1.0)	0.001	2.1±0.8 1.0±0.7	−1.1 (−3.0,1.0)	<0.001	0.003[b]
BMI	Pre-PR Post-PR	20.9±3.6 21.4±3.0	0.5 (−4.0,3.0)	0.061	21.5±3.7 22.0±3.6	0.5 (−2.0,2.0)	<0.001	21.0±3.6 22.0±2. 8	1.0 (−2.0,4.0)	<0.001	0.137
HRSD	Pre-PR Post-PR	20.2±47 21.4±6.0	1.1 (−4.6,7.0)	0.013	20.4±4.5 18.0±4.8	−2.3 (−7.0,1.0)	<0.001	21.0±4.6 17.1±5.1	−3.9 (−10.0,0.6)	<0.001	<0.001 [a,b,c]
HAMA	Pre-PR Post-PR	18.1±3.9 18.3±4.7	0.2 (−4.0,6.0)	0.553	17.4±3.8 16.0±4.0	−1.4 (−6.1,3.0)	<0.001	18.7±3.3 16.7±4.0	−2.0 (−6.6,2.6)	<0.001	<0.001[a,b]
Frequency of AECOPD	Pre-PR Post-PR	2.0±0.9 1.5±0.7	−0.5 (−2.0,1.0)	<0.001	2.1±1.0 1.2±0.7	−0.9 (−3.0,1.0)	<0.001	2.2±1.1 1.0±0.8	−1.3 (−3.0,0.0)	<0.001	<0.001[b,c]

Notes: Measured data were presented as mean ± SD. [a]Significant differences between low-intensity PR group and moderate-intensity PR group; [b]Significant differences between low-intensity PR group and high-intensity PR group; [c]Significant differences between moderate-intensity PR group andhigh-intensity PR group.

Abbreviations: Δ, the mean difference between pre-PR and post-PR groups; P_1, differences between pre-PR and post-PR groups; P_2, differences among the three groups before and after PR intervention; PR, pulmonary rehabilitation; BMI, body mass index; HRSD, Hamilton Rating Scale for Depression; HAMA, Hamilton Anxiety Scale; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; BODE index, body mass index, airflow obstruction, dyspnea, and exercise capacity index.

Table 3 Comparison of parameters before and after different intensities of PR in the COPD patients with GOLD 2

Variable		Low-intensity PR group (n=28)	Δ (95% CI)	P_1 value	Moderate-intensity PR group (n=28)	Δ (95% CI)	P_1 value	High-intensity PR group (n=27)	Δ (95% CI)	P_1 value	P_2 value
BODE index	Pre-PR Post-PR	3.3±1.2 3.3±1.6	0.0 (−2.0,2.6)	1.000	3.4±1.2 2.6±1.1	−0.8 (−2.6,0.6)	<0.001	3.4±1.2 1.9±0.9	−1.6 (−3.0,0.0)	<0.001	<0.001[a,b,c]
FEV_1% predicted	Pre-PR Post-PR	61.0±9.5 60.3±10.0	−0.8 (−5.0,2.0)	0.070	60.2±9.5 60.5±9.7	0.3 (−2.7,2.0)	0.229	60.9±9.5 64.1±9.7	3.2 (−1.2,8.0)	<0.001	<0.001[b,c]
6MWD (m)	Pre-PR Post-PR	292.8±68.0 303.0±72.7	10.3 (−29.3,29.1)	0.003	277.3±62.4 303.1±66.7	25.8 (−8.4,63.7)	<0.001	271.7±62.1 326.2±64.5	54.5 (25.6,88.0)	<0.001	<0.001[a,b,c]
mMRC	Pre-PR Post-PR	1.8±0.8 1.8±0.9	0.0 (−2.0,2.0)	0.879	1.9±0.8 1.0±0.9	−0.9 (−1.0,2.0)	0.001	1.9±0.8 0.5±0.5	−1.4 (−3.0,0.0)	<0.001	<0.001[a,b]
BMI	Pre-PR Post-PR	20.8±3.2 21.1±3.4	0.4 (−2.6,2.0)	0.213	21.5±4.2 22.2±4.3	0.6 (−1.0,3.0)	0.002	21.0±3.3 22.2±2.7	1.2 (−2.6,3.6)	<0.001	0.039[b]
HRSD	Pre-PR Post-PR	18.6±5.1 18.2±6.1	−0.4 (−5.0,6.1)	0.537	17.9±4.8 16.5±5.2	−1.5 (−4.0,2.1)	<0.001	20.0±4.8 16.7±5.4	−3.3 (−9.6,1.0)	<0.001	0.001[b,c]
HAMA	Pre-PR Post-PR	17.6±4.2 17.8±5.0	0.2 (−3.0,5.0)	0.602	17.2±3.6 17.2±3.8	0.0 (−4.0,5.0)	1.000	18.7±2.5 16.4±3.5	−2.3 (−8.0,2.6)	<0.001	<0.001[b,c]
Frequency of AECOPD	Pre-PR Post-PR	1.8±0.7 1.1±0.6	−0.6 (−2.0,1.0)	0.001	1.7±0.7 1.0±0.6	−0.7 (−2.0,0.6)	<0.001	1.7±0.7 0.5±0.5	−1.2 (−2.6,0.0)	<0.001	0.012 [b,c]

Notes: Measured data were presented as mean ± SD. [a]Significant differences between low-intensity PR group and moderate-intensity PR group; [b]Significant differences between low-intensity PR group and high-intensity PR group; [c]Significant differences between moderate-intensity PR group and high-intensity PR group.

Abbreviations: Δ, the mean difference between pre-PR and post-PR groups; P_1, differences between pre-PR and post-PR groups; P_2, differences among the three groups before and after PR intervention; PR, pulmonary rehabilitation; BMI, body mass; HRSD, Hamilton Rating Scale for Depression; HAMA, Hamilton Anxiety Scale; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; BODE index, body mass index, airflow obstruction, dyspnea, and exercise capacity index.

PR intervention for GOLD 3 COPD patients

Table 4 summarizes the changes between preintervention to postintervention for patients of GOLD 3 within the three groups. All variables were significantly improved in the high-intensity PR group between preintervention and postintervention. Significant differences were also noted in all parameters in the low-intensity PR group except for BMI and HAMA. In addition, only BMI was not markedly increased in the moderate-intensity PR group.

The comparison analysis between the groups revealed that FEV_1 and 6MWD were considerably improved in the high-intensity PR group compared with the moderate-intensity PR group and low-intensity PR group (ΔFEV_1: 2.0 vs 0.6 vs 0.7, Δ6MWD: 32.4 vs 23.0 vs 14.5, respectively). Significantly higher improvement of frequency of AECOPD was only found in the high-intensity PR group compared with the low-intensity PR group (frequency of AECOPD 1.4 vs 0.5). Compared with the low-intensity PR group, HAMA was markedly decreased in the high-intensity PR group and moderate-intensity PR group (ΔHAMA 1.8 vs 2.4 vs 0.2). Significant differences were also found in the improved degree of HRSD among the three groups (ΔHRSD 4.3 vs 3.0 vs 2.2).

The effects of PR intervention

This study was conducted to assess the effects of PR. An unconditional logistic regression analysis was applied, in which the variables were selected by backward procedure. The results are presented in Table 5. It was revealed that age, intensity of PR, GOLD 2/GOLD 3, HRSD, and frequency of AECOPD were statistically significant ($P<0.05$), and ORs were 2.338, 10.339, 3.146, 1.114, and 2.701, respectively. Additionally, their corresponding 95% CIs) were (1.052,5.200), (3.215,33.244), (2.173,4.555), (1.030,1.205), and (1.503,4.854), respectively.

Discussion

To the best of our knowledge, this is the first study comparing the results of different intensive PR regimens in patients with moderate-to-severe COPD. The findings of the present study are summarized as follows: 1) it is recommended that patients with moderate COPD undergo moderate- and high-intensity PR exercises, especially high-intensity PR exercise, which may have higher physiological advantages; 2) for patients with severe COPD, high-intensity PR exercise may be more beneficial, although moderate- and low-intensity PR training programs can sufficiently decrease the frequency of AECOPD and could be helpful to significantly improve the symptoms of dyspnea and quality of life; 3) the improved degree of PR intervention for moderate COPD patients was higher than that of severe COPD patients.

The evaluation of COPD has shifted from spirometry to a focus on patients' overall health.[21] The BODE index and the frequency of AECOPD were major determinants of quality of life in COPD patients.[22] A previous study showed that the total BODE index converted by recentering is more promising in the prediction of mortality risk and quality of life than lung function, as well as being simple and feasible.[23] AECOPD also plays a substantial role in this disease because acute exacerbations can rapidly reduce patients' quality of life, aggravate their symptoms, accelerate the decline in lung function, and increase the social and economic burden of the family. Matsui et al[24] reported that early PR was associated with reduced 90-day readmission and shortened the length of stay in hospital (LOS) in patients with AECOPD. Our results showed that in all public health training groups, the BMI and frequency of AECOPD were improved, while the high-intensity PR group had a significantly higher level of benefit. Those results are in line with previously reported findings (eg, Moore et al[6]), demonstrating that PR can reduce hospital admissions for AECOPD. A number of researches[25–27] also showed a significant relationship between GOLD stages and the BODE index, and the capacity of exercise in patients was associated with the severity of COPD. It was confirmed that geriatric COPD rehabilitation in the setting of a nursing home may reduce hospital admissions in frail COPD patients and increase exercise tolerance as well.

Furthermore, COPD has significant extrapulmonary effects; the most important effect of these systemic manifestations is dysfunction of skeletal muscle, especially in the lower limb muscles involved in walking, leading to a progressive decline in daily activities. Studies[28,29] revealed that in a remarkable proportion of COPD patients, fatigue in skeletal muscle, rather than breathing difficulty, limits the patient's exercise capacity. Symptoms of fatigue and dyspnea may hinder patients to perform physical activities, set a vicious cycle of worsening muscle endurance, as well as further erosion of exercise tolerance. Moreover, PR is one of the most effective non-pharmacological management programs for patients with COPD. The majority of current PR guidelines recommend that higher intensity is a key component of any exercise program. However, in PR,

Table 4 Comparison of parameters before and after different intensities of PR in COPD patients with GOLD 3

Variable		Low-intensity PR group (n=40)	Δ (95% CI)	P_1 value	Moderate-intensity PR group (n=40)	Δ (95% CI)	P_1 value	High-intensity PR group (n=40)	Δ (95% CI)	P_1 value	P_2 value
BODE index	Pre-PR Post-PR	5.5±1.4 4.6±1.0	−1.0 (−3.0,1.0)	<0.001	5.5±1.2 4.3±1.3	−1.2 (−4.0,1.0)	<0.001	5.4±1.5 4.0±1.4	−1.4 (−4.0,0.0)	<0.001	0.301
FEV_1% predicted	Pre-PR Post-PR	41.5±4.8 42.2±6.3	0.7 (−4.9,5.0)	0.049	40.6±4.7 41.1±4.9	0.6 (−3.0,3.0)	0.034	40.5±5.4 42.5±6.5	2.0 (−2.0,7.9)	<0.001	0.003[b,c]
6MWD (m)	Pre-PR Post-PR	260.8±70.1 275.3±73.5	14.5 (−31.5,47.6)	<0.001	260.1±60.3 283.1±60.9	23.0 (−20.6,75.6)	<0.001	265.4±70.0 297.8±76.5	32.4 (−19.4,78.3)	<0.001	0.001[b,c]
mMRC	Pre-PR Post-PR	2.3±0.7 1.6±0.8	−0.8 (−2.0,1.0)	0.001	2.2±0.6 1.5±0.8	−0.7 (−2.0,1.0)	0.001	2.2±0.7 1.4±0.7	−0.9 (−3.0,1.0)	<0.001	0.798
BMI	Pre-PR Post-PR	21.0±3.9 21.6±2.7	0.6 (−5.9,4.0)	0.139	21.5±3.3 21.9±3.0	0.4 (−3.0,2.0)	0.073	21.1±3.8 22.0±2.9	0.9 (−2.0,4.0)	0.003	0.575
HRSD	Pre-PR Post-PR	21.4±4.1 23.6±4.9	2.2 (−4.0,8.0)	0.001	22.1±3.5 19.2±4.2	−3.0 (−7.0,0.9)	<0.001	21.6±4.3 17.3±4.9	−4.3 (−11.0,-0.1)	<0.001	<0.001[a,b,c]
HAMA	Pre-PR Post-PR	18.5±3.6 18.7±4.6	0.2 (−5.0,7.0)	0.701	17.5±3.9 15.1±3.8	−2.4 (−8.9,2.0)	<0.001	18.7±3.7 16.9±4.4	−1.8 (−6.0,3.90)	<0.001	<0.001[a,b]
Frequency of AECOPD	Pre-PR Post-PR	2.2±1.0 1.7±0.7	−0.5 (−3.0,1.0)	0.004	2.4±1.1 1.4±0.7	−1.0 (−4.0,2.0)	<0.001	2.6±1.1 1.3±0.8	−1.4 (−4.0,1.9)	<0.001	0.016 [b]

Notes: Measured data were presented as mean ± SD. [a]Significant differences between low-intensity PR group and moderate-intensity PR group; [b]Significant differences between low-intensity PR group and high-intensity PR group; [c]Significant differences between moderate-intensity PR group and high-intensity PR group.

Abbreviations: Δ, the mean difference between pre-PR and post-PR groups; P_1, differences between pre-PR and post-PR groups; P_2, differences among the three groups before and after PR intervention; PR, pulmonary rehabilitation; BMI, body mass index; HRSD, Hamilton Rating Scale for Depression; HAMA, Hamilton Anxiety Scale; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; BODE index, body mass index, airflow obstruction, dyspnea, and exercise capacity index.

Table 5 Univariate analysis for predicting the effects of pulmonary rehabilitation on COPD patients (BODE≤–1)

Variables	B	*P*	OR	95% CI
Age level (≤65/>65 years)	0.849	0.037	2.338	1.052~5.200
Intensity of PR		<0.001		
High/Low	2.336	<0.001	10.339	3.215~33.244
Moderate/Low	1.022	0.053	2.778	0.985~7.831
GOLD 2/GOLD 3	1.146	<0.001	3.146	2.173~4.555
HRSD	0.108	0.007	1.114	1.030~1.205
Frequency of AECOPD	0.994	0.001	2.701	1.503~4.854

Abbreviations: PR, pulmonary rehabilitation; HRSD, Hamilton Rating Scale for Depression.

the role of exercise intensity in improving athletic performance and extending athletic training outcomes remains elusive. The FEV_1 was significantly improved in this study, because the patients were not adequately stable at baseline, or PR improved respiratory muscle strength, which led to improvement of lung function.

Morris et al[20] found that there is insufficient evidence to suggest that high-intensity exercise training program provides additional benefits compared with the low-intensity exercise training, although they only compared high-intensity exercise training program with low-intensity one. Therefore, further efforts should be made to tailor specific therapeutic approaches to individuals' needs.[30] Our results demonstrated that severe-intensity PR exercise training results in a greater improvement in exercise capacity for GOLD 2 and GOLD 3 patients. Physical activity may increase the confidence and willingness of COPD patients to further participate in intense physical activities, and may serve as an intermediate target to increase uptake of PR.[31,32] One possible explanation for this effect is that high-intensity training extends the patient's movement time.[33] If the patients of GOLD 3 can tolerate hypopnea during PR, they may require high-intensity exercise and provide more physiological results. The better the lung function and the higher the exercise intensity, the more beneficial the exercise will be for the patient.

Anxiety and depression are major complications of COPD as well.[34] In addition, PR may help reduce anxiety and depression. Our results revealed that depression and anxiety were significantly improved in the PR-based groups, especially in the high-intensity PR group, which is consistent with previous studies.[35–37]

Several limitations should be taken in interpreting our results into account. First, this is a small sample size study; therefore, further well-designed, multicenter, prospective interventional clinical trials with PR treatment need to be conducted in the future. Second, the participants of the present study only confined to GOLD 2 and GOLD 3 patients, because the patients of GOLD 1 had no obvious symptoms, which resulted in poor compliance, while different rehabilitation strategies being consistent with their conditions for patients with GOLD 4 are highly required.

In summary, high-intensity PR exercise should be adopted for patients with moderate-to-severe COPD. Moderate COPD (GOLD 2) patients need to further receive intensive PR training; the improved degrees of PR intervention for the GOLD 2 patients were further considerable compared with those of GOLD 3 patients. For severe COPD (GOLD 3) patients, high-intensity PR exercise might be more beneficial if patients can tolerate it.

Acknowledgment

This study was financially supported by the Shanghai Health and Family Planning Commission (Grant No. 201540060), the Key Construction Projects of Shanghai Health and Family Planning on Weak Discipline (Grant No. 2015ZB0401), Health and Family Planning Commission of Jing'an District, Shanghai (Grant No. 2018MS21).

Disclosure

The authors declare that there are no conflicts of interest in this work.

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