Pulmonary Rehabilitation Improves Cardiovascular Response to Exercise in COPD

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Key Words

Rehabilitation · Exercise · Cardiopulmonary interactions · COPD

Abstract

Background: Pulmonary rehabilitation (PR) has emerged as a recommended standard of care in symptomatic COPD. **Objectives:** We now studied whether PR may affect cardiovascular response to exercise in these patients. **Methods:** Twenty-seven patients (9 females aged 69 ± 8 years) with moderate-to-severe airflow obstruction admitted to a 9-week PR course performed a pre-to-post evaluation of lung function test and symptom-limited cardiopulmonary exercise test (CPET). Oxygen uptake (VO_2), tidal volume (V_T), dyspnea and leg fatigue scores were measured during CPET. Cardiovascular response was assessed by means of oxygen pulse (O_2Pulse), the oxygen uptake efficiency slope and heart rate recovery at the 1st min. **Results:** A significant increase in peak VO_2 and in all cardiovascular parameters ($p < 0.05$) was found following PR when compared to baseline. Leg fatigue ($p < 0.05$), but not dyspnea, was significantly reduced after PR. When assessed at metabolic and ventilatory iso levels [$\% \text{VCO}_{2\text{max}}$ and $\% \text{minute ventilation } (V_{E\text{max}})$], O_2Pulse and V_T were significantly higher ($p < 0.05$) at submaximal exercise (75 and 50% of $\text{VCO}_{2\text{max}}$ and $V_{E\text{max}}$) after PR when com-

pared to baseline. V_T percent changes at 75% $\text{VCO}_{2\text{max}}$ and 75% $V_{E\text{max}}$ after PR significantly correlated with corresponding changes in O_2Pulse ($p < 0.01$). **Conclusions:** In COPD patients, a PR training program improved the cardiovascular response during exercise at submaximal exercise independent of the external workload. This change was associated with an enhanced ventilatory function during exercise.

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Introduction

In patients with COPD, the ventilatory constraints occurring during exercise have the potential to determine significant effects on cardiovascular function. In patients with severe COPD [1], dynamic hyperinflation on exertion was associated with lower oxygen pulse (O_2Pulse), an estimator of stroke volume during exercise [2]. This finding has been recently confirmed and extended by our group [3] in COPD patients with a wide range of airflow obstruction, by showing a significant relationship between dynamic hyperinflation and a battery of noninvasive measures of cardiovascular function during exercise.

Pulmonary rehabilitation (PR) is a nonpharmacologic treatment of proven efficacy in terms of both functional capacity, quality of life and perceived symptoms in patients with COPD [4]. PR programs allow COPD patients to tolerate a greater amount of restrictive dynamic ventilatory defect during exercise, by reducing the intensity of dyspnea without substantially modifying its descriptors [5]. Notably, a standard PR program can reduce dyspnea on exertion by lowering the ventilatory demand during exercise, resulting in the prolongation of the expiration time and, in turn, in the reduction of dynamic hyperinflation [6]. Interestingly, the reduction of pulmonary hyperinflation in COPD patients following lung volume reduction surgery may significantly improve the stroke volume during exercise, as assessed by O_2 Pulse [7, 8].

Therefore, we hypothesized that in COPD patients, a PR program could improve the cardiovascular response to exercise, by enhancing the ventilatory function during exercise. In order to test this hypothesis, we assessed the pre-to-post cardiovascular response to maximal exercise in a group of patients admitted to a PR program.

Methods

Subjects

We enrolled patients diagnosed for having COPD, defined according to the GOLD criteria [9], and referred for a course of PR. Eligibility criteria were: no clinical history of concomitant cardiac heart failure or anemia and the ability to perform a symptom-limited cycle ergometry cardiopulmonary test (CPET) with a peak of respiratory exchange ratio ≥ 1.05 in order to exclude poor motivation. All procedures and their risks were explained to the patients, who gave their informed consent to enter the study. The protocol was approved by the ethical review committee at the University Hospital of Parma.

Study Protocol

The study was an observational prospective trial. Outcome measures were taken at baseline and after the completion of PR. All measurements were performed and recorded under the supervision of personnel not aware of the study purposes. Comparisons were made between times, with each patient serving as his/her own control.

PR Program

Patients were referred to PR according to the American Thoracic Society/European Respiratory Society statement and recommendations [10]. Patients reached the rehabilitation clinic and performed activities during a half-day session. The program consisted of 3-hour sessions 3 times a week. A minimum of 21 sessions was the required number for program completion; each session was conducted as previously reported [11]. Briefly, the rehabilitation program included instructions for compensatory breathing

techniques, energy conservation, stress management and symptoms control and optimization of the drug therapies. Each session included the following: (1) supervised incremental exercise on a cycloergometer; the training modality consisted of both progressively increasing load (up to 70–80% of the maximal load reached on the incremental test carried out at admission) and time (up to 30 consecutive min starting from a minimum of 10 min), (2) abdominal and upper and lower limb muscle strength activities, lifting weights (300–500 g) and circling shoulders and full arms, (3) disease-related education and (4) nutritional and psychosocial counseling, when appropriate.

Strategies to perform structured exercise programs at home were not implemented. During the study period, patients were only encouraged to perform their usual daily-life activities. Physiotherapists involved in this program were instructed to homogenize the type and duration of all activities.

Measurements

Pulmonary Function Testing

Pulmonary function tests were performed according to the international recommendations [12–14]. A flow-sensing spirometer and a body plethysmograph connected to a computer for data analysis (Vmax 22 and 6200; Sensor Medics, Yorba Linda, Calif., USA) were used for these measurements. Total lung capacity (TLC), vital capacity (VC), inspiratory capacity (IC), forced expiratory volume at 1st second (FEV_1) and FEV_1/VC and IC/TLC ratios were recorded. Lung diffusion capacity for carbon monoxide (TLCO) was measured by the single breath method using a mixture of carbon monoxide and methane. TLC, VC, IC, FEV_1 and TLCO were expressed as a percentage of the predicted values, which were obtained from the regression equations by Quanjer et al. [15] and Cotes et al. [16].

Cardiopulmonary Exercise Test

CPET was performed according to a standardized procedure [17]. Briefly, the exercise protocol started with an initial 3 min of rest, followed by unloaded cycling for another 3 min and a subsequent increment of 5–15 W each minute, depending on the anthropometric data and the degree of the individual's functional impairment, with the aim of performing a total exercise time with a range 8–12 min. Patients were asked to maintain a pedaling frequency of 60 rpm indicated by a digital display placed on the monitor of the cycle ergometer (Corival PB, Lobe Bv, Groningen, The Netherlands). Breath-by-breath oxygen uptake (VO_2 ; in l/min), carbon dioxide production (VCO_2 ; in l/min), tidal volume (V_T ; in liters), respiratory rate (RR; in bpm) and minute ventilation (V_E ; in l/min) were collected during the test (CPX/D; Med Graphics, St. Paul, Minn., USA). Patients were continuously monitored by a 12-lead ECG (Welch Allyn CardioPerfect, Delft, The Netherlands) and a pulse oximeter (Pulse Oximeter 8600; Nonin Medical Inc., MPLS, Minn., USA). Blood pressure was measured in mm Hg at 2-min intervals. Stopping criteria consisted of symptoms such as unsustainable dyspnea or leg fatigue, chest pain, ECG-significant ST-segment depression, a drop in systolic blood pressure or oxygen saturation (SaO_2) $\leq 84\%$.

Peak workload and peak VO_2 were recorded as the mean value of watts and VO_2 during the last 20 s of the test. Peak VO_2 was expressed both as absolute value (l/min) and in terms of ml/kg/min. Anaerobic threshold (AT) was noninvasively determined by both V-slope and ventilatory equivalents methods ('dual method ap-

proach') and was expressed in ml/kg/min and as percent of predicted peak VO_2 [2].

The cardiovascular response to exercise was expressed by the following parameters: O_2Pulse , the oxygen uptake efficiency slope (OUES), i.e. the relation between oxygen uptake and ventilation [18] and the heart rate recovery at peak of exercise (HRR) [19]. O_2Pulse (ml/bpm) was calculated by dividing instantaneous oxygen uptake by heart rate (HR) [2] and was measured at rest and at peak of exercise. The OUES describes the relationship between VO_2 and V_E during incremental exercise, via a log transformation of V_E , and was expressed in l/min as the gradient of the linear relationship of $\log_{10}\text{V}_E$ to VO_2 [18]. OUES thus represents the absolute rate of increase in oxygen uptake per 10-fold increase in minute ventilation. HRR in bpm was defined as the reduction in the HR from the peak exercise level to the rate 1 min after the end of exercise [19].

In order to match metabolic and ventilatory workloads during the two CPETs at the baseline and after PR [8], ventilatory and cardiovascular parameters, i.e. V_T , RR and O_2Pulse , were measured in each patient at the metabolic and ventilatory iso levels, expressed as % $\text{VCO}_{2\text{max}}$ and % $\text{V}_{E\text{max}}$ obtained during the baseline CPET, i.e. at 100% $\text{VCO}_{2\text{max}}$, 75% $\text{VCO}_{2\text{max}}$ and 50% $\text{VCO}_{2\text{max}}$ and at 100% $\text{V}_{E\text{max}}$, 75% $\text{V}_{E\text{max}}$ and 50% $\text{V}_{E\text{max}}$, respectively.

Dyspnea and Muscle Fatigue

Daily-life activity-related dyspnea was evaluated with the Italian version of the Medical Research Council (MRC) 5-point scale modified by the ATS [20]. Dyspnea and muscle fatigue induced by CPET were measured at the end of the incremental exercise by a visual analog scale (VAS; VAS_{dys} and VAS_{fat}, respectively, in mm) [21]. The VAS scale consisted of a horizontal line with the word 'none' placed at the left end of the scale and the word 'very severe' at the right end. The VAS was scored from 0 to 100, but the subjects were unaware of the numbers.

Statistical Analysis

Data are reported as mean $\pm$ standard deviation (SD), unless otherwise specified. The distribution of variables was assessed by means of the Kolmogorov-Smirnov goodness-of-fit test. Values before and after rehabilitation were compared using the Student *t* test or the Wilcoxon signed-rank test, when appropriate. Relationships among study variables were then assessed by the Pearson's correlation coefficient (*r*) and linear regression analysis. A *p* value <0.05 was considered significant.

Results

Twenty-seven ex-smoker COPD patients (9 females, mean age 69 ± 8 years and mean BMI 27 ± 4) were consecutively recruited. Their lung function characteristics are shown in table 1. Overall, a wide range of airway obstruction (FEV_1/VC from 36 to 69%), lung hyperinflation (IC/TLC ratio from 14 to 60%), diffusing capacity (TLCO from 29 to 106%) and daily-life activity-related dyspnea (MRC scale 1–4) were found among the functional char-

Table 1. Lung function data before and after the PR program of 27 COPD patients

	Before PR	After PR	p value
VC, %pred	77 $\pm$ 18	79 $\pm$ 22	0.45
VC, liter	2.55 $\pm$ 0.67	2.70 $\pm$ 0.96	0.38
FEV_1 , %pred	50 $\pm$ 14	52 $\pm$ 22	0.27
FEV_1 , liter	1.29 $\pm$ 0.44	1.35 $\pm$ 0.56	0.37
FEV_1/VC , %	51 $\pm$ 10	51 $\pm$ 11	0.93
TLC, %pred	112 $\pm$ 24	115 $\pm$ 21	0.41
TLC, liter	6.75 $\pm$ 1.83	6.95 $\pm$ 1.81	0.46
IC, %pred	81 $\pm$ 19	80 $\pm$ 18	0.71
IC, liter	2.24 $\pm$ 0.62	2.33 $\pm$ 0.71	0.53
IC/TLC, %	35 $\pm$ 13	33 $\pm$ 9	0.50
TLCO, %pred	67 $\pm$ 21	66 $\pm$ 18	0.40

Values are expressed as mean $\pm$ SD.

acteristics at study entry. According to the GOLD classification [9], 14 patients (7 females with a mean age of 70 ± 6 years) were GOLD I–II ($\text{FEV}_1 \geq 50\%$) and 13 patients (1 female, mean age 69 ± 10 years) were GOLD III–IV ($\text{FEV}_1 < 50\%$). Patients were receiving inhaled long-acting β_2 -agonists (81%), corticosteroids (78%) and tiotropium (67%). All patients completed the rehabilitation program and performed 26 ± 4 sessions over 9 (range 7–10) consecutive weeks. No exacerbations were referred during the course.

Eighteen (8 females) out of 27 patients (67%) suffered from arterial hypertension and were taking diuretics (61%), ACE-inhibitors (33%), Ca-antagonists (33%), beta-blockers (44%) and sartans (44%). There was no change in any medication over the study period.

As expected, lung function did not change across the PR (table 1). Exercise data comparisons, measured before and after the PR, are reported in table 2. A significant increase in peak VO_2 ($p = 0.0001$) as well as in AT ($p = 0.003$), and in the maximal workload ($p = 0.0001$) were found following PR. All cardiovascular parameters measured after PR changed significantly compared to those reported before PR ($p < 0.05$ for all comparisons). The perception of leg fatigue ($p = 0.016$), but not of dyspnea, reduced significantly following PR. The change in OUES correlated significantly with change in AT ($r = 0.437$, $p = 0.019$) (fig. 1) but not with change in O_2Pulse peak ($r = 0.291$, $p = 0.148$).

When assessed at metabolic (% $\text{VCO}_{2\text{max}}$) and ventilatory (% $\text{V}_{E\text{max}}$) iso levels, O_2Pulse and V_T values were significantly higher and RR values were significantly lower

Table 2. Exercise data before and after the PR program of 27 COPD patients

	Before PR	After PR	p value
VO ₂ peak, l/min	1.007±0.237	1.133±0.323	0.001
VO ₂ peak, ml/kg/min	13.2±3.0	14.8±4.1	0.001
AT, ml/kg/min	9.6±2.0	10.8±3.1	0.003
AT, %	41±12	47±15	0.002
Workload peak, W	72±25	85±31	0.001
V _E peak, l/min	38±13	40±14	0.052
V _T peak, l/min	1.29±0.45	1.37±0.47	0.057
RR, bpm	30±7	30±6	0.92
O ₂ Pulse peak, ml/bpm	8.9±2.1	9.7±2.6	0.002
OUES, l/min	1.09±0.36	1.19±0.38	0.039
HRR, bpm	10.1±7.9	13.5±8.1	0.011
VASdys	90 (80–90)	90 (0–100)	0.208
VASfat	85 (80–90)	80 (70–85)	0.016

Values are expressed as mean ± SD or median (25th–75th percentile).

Table 3. V_T, RR and O₂Pulse measured at metabolic iso levels before and after the PR program of 27 COPD patients

		Before PR	After PR	p value
50% VCO ₂	V _T , liter	0.96±0.28	1.07±0.42	0.006
	RR, bpm	21±4	19±5	0.007
	O ₂ Pulse, ml/bpm	6.80±1.76	7.28±2.24	0.010
75% VCO ₂	V _T , liter	1.15±0.39	1.25±0.44	0.002
	RR, bpm	25±5	23±5	0.008
	O ₂ Pulse, ml/bpm	8.03±1.95	8.58±2.41	0.006
100% VCO ₂	V _T , liter	1.29±0.45	1.31±0.43	0.956
	RR, bpm	30±7	28±6	0.080
	O ₂ Pulse, ml/bpm	8.92±2.1	9.20±2.49	0.167

Values are expressed as mean ± SD.

Table 4. V_T, RR and O₂Pulse measured at ventilatory iso levels before and after the PR program of 27 COPD patients

		Before PR	After PR	p value
50% V _E	V _T , liter	0.89±0.32	1.01±0.47	0.013
	RR, bpm	22±4	19±4	0.007
	O ₂ Pulse, ml/bpm	6.39±2.02	6.82±2.31	0.033
75% V _E	V _T , liter	1.15±0.41	1.23±0.44	0.025
	RR, bpm	25±5	23±4	0.004
	O ₂ Pulse, ml/bpm	7.82±2.06	8.47±2.33	0.001
100% V _E	V _T , liter	1.30±0.45	1.351±0.48	0.199
	RR, bpm	30±6	28±6	0.029
	O ₂ Pulse, ml/bpm	8.97±2.1	9.24±2.51	0.182

Values are expressed as mean ± SD.

Fig. 1. Relationship between the percent change in OUES values after the PR program, expressed as percent of baseline, and the corresponding change in AT in 27 COPD patients.

at submaximal exercise (75 and 50% of VCO₂max and V_Emax) after PR ($p < 0.05$ for each comparison) (tables 3, 4; fig. 2, 3). After PR, the V_T changes (% of values measured before PR) at 75% VCO₂max and at 75% V_Emax significantly correlated with the corresponding O₂Pulse changes ($r = 0.494$, $p = 0.0012$ and $r = 0.471$, $p = 0.0151$) (fig. 4).

The pre-to-post PR change of metabolic, cardiovascular and ventilatory variables, including VO₂ peak, maximal workload, V_E, V_T, RR, O₂Pulse, OUES and HRR, was similar in the subgroup of the normotensive and hypertensive patients as well as in the subgroup of the patients GOLD I–II and GOLD III–IV.

Discussion

The main finding of this study is that a PR program may improve the cardiovascular response to exercise in COPD patients. We found that this increase was independent of external workload at submaximal exercise and that, at this level, it was related to an enhancement in ventilatory response. Moreover, our study shows that PR results in improved aerobic capacity, both at peak of exercise and at the anaerobic threshold, and also improved maximal sustainable workload and reduced limb muscle fatigue at maximal exercise.

In patients with COPD, the influence of respiration on venous return to the heart has been investigated. Unlike

Fig. 2. Mean values of O₂Pulse (a) and V_T (b) before and after PR at metabolic iso levels (% VCO₂max) in 27 COPD patients. ** p < 0.01.

Fig. 3. Mean values of O₂Pulse (a) and V_T (b) before and after PR at ventilatory iso levels (% V_Emax) in 27 COPD patients. * p < 0.05; ** p < 0.01.

in normal subjects who show an increase in venous return during inspiration, in patients with pulmonary emphysema, the flow was found to be maximal in expiration and markedly reduced or completely arrested during inspiration [22]. When evaluated by magnetic resonance tech-

nique, both left and right ventricular performance results were impaired because of the small end-diastolic dimensions in patients with severe emphysema [23]. In these patients, the decrease in biventricular preload was attributed to the intrathoracic hypovolemia following lung hy-

Fig. 4. Relationship between the percent change in V_T values after the PR program, expressed as percent of baseline at submaximal exercise (at 75% V_{CO_2max}), and the corresponding change in O_2Pulse values in 27 COPD patients.

perinflation. In a recent population-based study, a greater extent of emphysema on CT scanning was related to impaired left ventricular filling, reduced stroke volume and lower cardiac output [24].

In COPD patients, the exercise-related changes in lung mechanics are closely associated with the cardiovascular response to exercise. The dynamic hyperinflation occurring during exercise was related to O_2Pulse with heavy hyperinflators showing a significantly lower O_2Pulse at peak of exercise than mild-to-moderate hyperinflators [1, 3]. On the other hand, lung volume reduction surgery has been shown to improve stroke volume during exercise in patients with advanced emphysema [7, 8]. It is conceivable that dynamic hyperinflation during exercise may progressively reduce left-ventricle stroke volume since it increases intrathoracic pressures and, consequently, decreases the preload by reducing both venous return and the volume of the left ventricle. Thus, a reduced filling of the left ventricle and a reduced cardiac output may occur. Therefore, in COPD patients, a better or improved ventilation is likely associated to a better or improved stroke volume during exercise. In this study, we have further strengthened this conclusion.

We found that our patients following a PR program showed an enhanced ventilatory capacity during exercise, i.e. a deeper and slower breathing pattern compared to the same level of ventilatory demand of baseline. In this study, we did not measure the IC changes during exercise

that would have allowed to insight the true mechanical constraints on V_T . Accordingly, we cannot infer any conclusion concerning the mechanisms leading to these changes in breathing pattern. Importantly, several studies have previously shown that PR programs with high-intensity training modalities, either on treadmill [25] or on a cycloergometer [6, 26–28], were able to induce a deeper and slower breathing pattern in COPD patients. The enhancement in breathing pattern was associated to reduced dynamic hyperinflation and improved tolerance to exercise [6, 28], and so far, it has been mainly attributed to an improved force and ventilatory muscle endurance [26, 28]. The question whether the enhancement in breathing pattern following PR may be due to other factors, such as exercise-induced changes in catecholamine release profile [29] or in sensorial inputs [30], requires further study.

In this study, we found that O_2Pulse at peak of maximal exercise significantly increased after PR compared to baseline. Although the O_2Pulse does not directly measure the stroke volume, it may be considered as a reliable surrogate marker, when arterial oxygen content can be assumed as normal [2]. In healthy subjects, exercise stroke volume may be estimated simply as 5 times the slope of the linear oxygen uptake-HR relationship [31]. The study was noninvasively performed and, therefore, we did not measure the true arterial oxygen content in the patients. However, patients with concomitant anemia were excluded and the resting oxygen saturation of the included patients was quite normal and its change at peak exercise was statistically, but not clinically, significant (data not shown).

Our study suggests that in COPD patients, PR acts on exercise stroke volume by enhancing the ventilatory response independent of the external workload. Interestingly, this was found at the submaximal level of exercise, how most activities are performed in daily life. In our patients, O_2Pulse and V_T measured after PR significantly increased and RR significantly decreased at the metabolic and ventilatory iso levels (i.e. 75 and 50% of V_{CO_2max} and V_{Emax}) compared to the baseline values. Furthermore, although association does not imply causality, we also found a significant correlation between the percent change of baseline value in V_T after PR, as assessed both at 75% V_{CO_2max} and at 75% V_{Emax} , and the change in O_2Pulse . We cannot exclude that at peak of exercise O_2Pulse was proportionally increased due to the higher workload performed after the PR course.

In this study, we provided the evidence that COPD patients, after a substantial period of participation in a stan-

dard PR program, showed a significant change not only in ventilatory function and in O₂Pulse, but also in OUES and HRR values. The OUES represents the rate of increase of oxygen uptake in response to a given 1-min ventilation during incremental exercise, indicating how effectively oxygen is extracted and taken into the body [32]. From a physiological point of view, the OUES can be affected by several factors, such as lactic acidosis onset, muscle mass, oxygen delivery and extraction and the dead space of ventilation. Therefore, OUES is considered as an objective measure of cardiorespiratory and muscular fitness that integrates the functional capacities of several organ systems during exercise [33]. It is of note that OUES was found to be sensitive enough to the effects of physical training in patients with cardiac disease [34]. In this study, we have found that OUES increased by 9.2% after a PR program and that this increase was related to the change in oxygen uptake at the anaerobic threshold, but not to the change in oxygen pulse. Taken together, these findings demonstrate that in COPD patients, a given oxygen uptake was achieved after PR at lower ventilatory cost, and they also suggest that the increase in OUES was likely due to a delay in the onset of metabolic acidosis occurring during exercise, rather than to the cardiac adaptations and oxygen delivery. We cannot, however, exclude that some changes in the oxidative function of skeletal muscles may also have contributed to an increase of OUES.

HRR is a marker of the cardiac autonomic function and it is a powerful predictor of mortality in the general population, independent of the workload and the change of HR during exercise [19]; 12 bpm or less is considered an abnormal value [19]. A low HRR is a common finding in patients with impaired spirometry [35] and is associated with a decreased survival in COPD patients [36]. In these patients, the autonomic nervous dysfunction, such as the increase of sympathetic tone and/or the reduction of the parasympathetic tone, is attributed to the increased work of breathing and it would represent a compensatory mechanism to promote a wider airway caliber [36]. In this study, we found that HRR significantly increased after PR (from 10.1 to 13.5 bpm as the mean values). Notwithstanding, the question whether the enhancement in ventilatory function following PR may contribute to HRR increases requires further studies.

In summary, 9 weeks of PR provided the chance to improve the cardiovascular response during exercise in COPD patients. This improvement in cardiovascular response found after PR was then associated with an enhancement of ventilatory function upon exercise. The results of this study further support the importance of PR in the management of COPD patients. Other studies are now required to define the duration of positive effects of PR on the cardiovascular function during exercise in these patients.

References

- 1 Vassaux C, Torre-Bouscoulet L, Zeineldine S, et al: Effects of hyperinflation on the oxygen pulse as a marker of cardiac performance in COPD. *Eur Respir J* 2008;32:1275–1282.
- 2 Wasserman K, Hansen JE, Sue DY, et al: Normal values. *Principles of Exercise Testing and Interpretation*. Philadelphia, Lippincott Williams & Wilkins, 1994, pp 143–162.
- 3 Tzani P, Aiello M, Elia D, et al: Dynamic hyperinflation is associated with a poor cardiovascular response to exercise in COPD patients. *Respir Res* 2011;12:150.
- 4 Casaburi R, ZuWallack R: Pulmonary rehabilitation for management of chronic obstructive pulmonary disease. *N Engl J Med* 2009;360:1329–1335.
- 5 Bianchi R, Gigliotti F, Romagnoli I, et al: Impact of rehabilitation program on dyspnea intensity and quality in patients with chronic obstructive pulmonary disease. *Respiration* 2011;81:186–195.
- 6 Porszasz J, Emtner M, Goto S, Somfay A, Whipp BJ, Casaburi R: Exercise training decreases ventilatory requirements and exercise-induced hyperinflation at submaximal intensities in patients with COPD. *Chest* 2005;128:2025–2034.
- 7 Benditt JO, Lewis S, Wood DE, Klima L, Albert RK: Lung volume reduction surgery improves maximal O₂ consumption, maximal minute ventilation, O₂pulse and dead space-to-tidal volume ratio during leg cycle ergometry. *Am J Respir Crit Care Med* 1997;156:561–566.
- 8 Lammi MR, Ciccolella D, Marchetti N, Kohler M, Criner GJ: Increased oxygen pulse after LVRS is associated with reduced dynamic hyperinflation. *Eur Respir J* 2012;40:837–843.
- 9 Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS, GOLD Scientific Committee: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *Am J Respir Crit Care Med* 2001;163:1256–1276.
- 10 Nici L, Donner C, Wouters E, et al: American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. *Am J Respir Crit Care Med* 2006;173:1390–1413.
- 11 Rossi G, Florini F, Romagnoli M, et al: Length and clinical effectiveness of pulmonary rehabilitation in outpatients with chronic airway obstruction. *Chest* 2005;127:105–109.
- 12 Miller MR, Hankinson J, Brusasco V, et al: ATS/ERS Task Force standardisation of spirometry. *Eur Respir J* 2005;26:319–338.
- 13 Wanger J, Clausen JL, Coates A, et al: Standardisation of the measurement of lung volumes. *Eur Respir J* 2005;26:511–522.
- 14 Macintyre N, Crapo RO, Viegi G, et al: Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J* 2005;26:720–735.
- 15 Quanjer PH, Tammeling GJ, Cotes JE, et al: Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official statement of the European Respiratory Society. *Eur Respir J Suppl* 1993;6:5–40.

- 16 Cotes JE, Chinn DJ, Quanjer PH, Roca J, Yernault JC: Standardization of the measurement of transfer factor (diffusing capacity). Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official statement of the European Respiratory Society. *Eur Respir J Suppl* 1993;6:41–52.
- 17 ATS/ACCP: Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003;167:211–277.
- 18 Baba R, Nagashima M, Goto M, et al: Oxygen uptake efficiency slope: a new index of cardiorespiratory functional reserve derived from the relation between oxygen uptake and minute ventilation during incremental exercise. *J Am Coll Cardiol* 1996;28:1567–1572.
- 19 Cole CR, Blackstone EH, Pashkow FJ, Snader CE, Lauer MS: Heart-rate recovery immediately after exercise as a predictor of mortality. *N Engl J Med* 1999;341:1351–1357.
- 20 Brooks SM: Surveillance for respiratory hazards. *ATS News* 1982;8:12–16.
- 21 Tzani P, Piepoli MF, Longo F, et al: Resting lung function in the assessment of the exercise capacity in patients with chronic heart failure. *Am J Med Sci* 2010;339:210–215.
- 22 Nakhjavan FK, Palmer WH, McGregor M: Influence of respiration on venous return in pulmonary emphysema. *Circulation* 1966;33:8–16.
- 23 Jörgesen K, Müller MF, Nel J, Upton RN, Houltz E, Ricksten SE: Reduced intrathoracic blood volume and left and right ventricular dimensions in patients with severe emphysema. *Chest* 2007;131:1050–1057.
- 24 Barr GR, Bluemke DA, Ahmed FS, et al: Percent emphysema, airflow obstruction, and impaired left ventricular filling. *N Engl J Med* 2010;362:217–227.
- 25 Puente-Maestu L, Sanz ML, Sanz P, Cubillo JM, Mayol J, Casaburi R: Comparison of effects of supervised versus self-monitored training programmes in patients with chronic obstructive pulmonary disease. *Eur Respir J* 2000;15:517–525.
- 26 Casaburi R, Porszasz J, Burns MR, Carithers ER, Chang RS, Cooper CB: Physiologic benefits of exercise training in rehabilitation of patients with severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1997;155:1541–1551.
- 27 Vogiatzis I, Nanas S, Roussos C: Interval training as an alternative modality to continuous exercise in patients with COPD. *Eur Respir J* 2002;20:12–19.
- 28 Puente-Maestu L, Abad YM, Pedraza F, Sánchez G, Stringer WW: A controlled trial of the effects of leg training on breathing pattern and dynamic hyperinflation in severe COPD. *Lung* 2006;184:159–167.
- 29 Clark AL, Galloway S, MacFarlane N, Henderson E, Aitchison T, McMurray JJ: Catecholamines contribute to exertional dyspnoea and to ventilatory response to exercise in normal humans. *Eur Heart J* 1997;18:1829–1833.
- 30 Costes F, Roche F, Pichot V, Vergnon JM, Garet M, Barthelemy JC: Influence of exercise training on cardiac baroreflex sensitivity in patients with COPD. *Eur Respir J* 2004;23:396–401.
- 31 Whipp BJ, Higgenbotham MB, Cobb FC: Estimating exercise stroke volume from asymptotic oxygen pulse in humans. *J Appl Physiol* 1996;81:2674–2679.
- 32 Hollenberg M, Tager IB: Oxygen uptake efficiency slope: an index of exercise performance and cardiopulmonary reserve requiring only submaximal exercise. *J Am Coll Cardiol* 2000;36:194–201.
- 33 Akkerman M, van Brussel M, Hulzebos E, Vanhees L, Helder PJ, Takken T: The oxygen uptake efficiency slope: what do we know? *J Cardiopulm Rehabil Prev* 2010;30:357–373.
- 34 Defoor J, Schepers D, Reybrouck T, Fagard R, Vanhees L: Oxygen uptake efficiency slope in coronary artery disease: clinical use and response to training. *Int J Sports Med* 2006;27:730–737.
- 35 Seshadri N, Gildea TR, McCarthy K, Pothier C, Kavuru MS, Lauer MS: Association of an abnormal exercise heart rate recovery with pulmonary function abnormalities. *Chest* 2004;125:1286–1291.
- 36 Lacasse M, Maltais M, Poirier P, et al: Post-exercise heart rate recovery and mortality in chronic obstructive pulmonary disease. *Respir Med* 2005;99:877–886.