Pulmonary Rehabilitation Improves Cardiovascular Response to Exercise in COPD

Sara Ramponi, Panagiota Tzani, Marina Aiello, Emilio Marangio, Enrico Clini, Alfredo Chetta

Respiratory Disease Unit, Clinical and Experimental Medicine, University Hospital, Parma, and Department of Oncology, Haematology, Respiratory Diseases and Ospedale Villa Pineta di Gaiato, Pavullo (MO), University of Modena-Reggio Emilia, Modena, Italy

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 (VO₂), tidal volume (Vₜ), dyspnea and leg fatigue scores were measured during CPET. Cardiovascular response was assessed by means of oxygen pulse (O₂Pulse), the oxygen uptake efficiency slope and heart rate recovery at the 1st min. Results: A significant increase in peak VO₂ and in all cardiovascular parameters (p < 0.05) was found following PR when compared to baseline. Vₜ percent changes at 75% VCO₂max and 75% Vₑmax after PR significantly correlated with corresponding changes in O₂Pulse (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.

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 (O₂Pulse), 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 O₂ 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 (FEV₁) and FEV₁/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, FEV₁ 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 pedal 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 (VO₂; in l/min), carbon dioxide production (VCO₂; in l/min), tidal volume (V₅; in liters), respiratory rate (RR; in bpm) and minute ventilation (VE; 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 (SaO₂) ≤84%.

Peak workload and peak VO₂ were recorded as the mean value of watts and VO₂ during the last 20 s of the test. Peak VO₂ 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-
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, VASdys and VASfat, 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 ± 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 (FEV₁/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 characteristics 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 (FEV₁ ≥50%) and 13 patients (1 female, mean age 69 ± 10 years) were GOLD III–IV (FEV₁ <50%). Patients were receiving inhaled long-acting β₂-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 VO₂ (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 O₂Pulse peak (r = 0.291, p = 0.148).

When assessed at metabolic (% VCO₂max) and ventilatory (% V₄max) iso levels, O₂Pulse and VT values were significantly higher and RR values were significantly lower.
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

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

<table>
<thead>
<tr>
<th></th>
<th>Before PR</th>
<th>After PR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO₂ peak, l/min</td>
<td>1.007 ± 0.237</td>
<td>1.133 ± 0.323</td>
<td>0.001</td>
</tr>
<tr>
<td>VO₂ peak, ml/kg/min</td>
<td>13.2 ± 3.0</td>
<td>14.8 ± 4.1</td>
<td>0.001</td>
</tr>
<tr>
<td>AT, ml/kg/min</td>
<td>9.6 ± 2.0</td>
<td>10.8 ± 3.1</td>
<td>0.003</td>
</tr>
<tr>
<td>AT, %</td>
<td>41 ± 12</td>
<td>47 ± 15</td>
<td>0.002</td>
</tr>
<tr>
<td>Workload peak, W</td>
<td>72 ± 25</td>
<td>85 ± 31</td>
<td>0.001</td>
</tr>
<tr>
<td>Vₑ peak, l/min</td>
<td>38 ± 13</td>
<td>40 ± 14</td>
<td>0.052</td>
</tr>
<tr>
<td>Vₜ peak, l/min</td>
<td>1.29 ± 0.45</td>
<td>1.37 ± 0.47</td>
<td>0.057</td>
</tr>
<tr>
<td>RR, bpm</td>
<td>30 ± 7</td>
<td>30 ± 6</td>
<td>0.92</td>
</tr>
<tr>
<td>O₂Pulse peak, ml/bpm</td>
<td>8.9 ± 2.1</td>
<td>9.7 ± 2.6</td>
<td>0.002</td>
</tr>
<tr>
<td>OUES, l/min</td>
<td>1.09 ± 0.36</td>
<td>1.19 ± 0.38</td>
<td>0.039</td>
</tr>
<tr>
<td>HRR, bpm</td>
<td>10.1 ± 7.9</td>
<td>13.5 ± 8.1</td>
<td>0.011</td>
</tr>
<tr>
<td>VASdys</td>
<td>90 (80–90)</td>
<td>90 (0–100)</td>
<td>0.208</td>
</tr>
<tr>
<td>VASfat</td>
<td>85 (80–90)</td>
<td>80 (70–85)</td>
<td>0.016</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th></th>
<th>Before PR</th>
<th>After PR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>50% VO₂VT, liter</td>
<td>0.96 ± 0.28</td>
<td>1.07 ± 0.42</td>
<td>0.006</td>
</tr>
<tr>
<td>RR, bpm</td>
<td>21 ± 4</td>
<td>19 ± 5</td>
<td>0.007</td>
</tr>
<tr>
<td>O₂Pulse, ml/bpm</td>
<td>6.80 ± 1.76</td>
<td>7.28 ± 2.24</td>
<td>0.010</td>
</tr>
<tr>
<td>75% VO₂VT, liter</td>
<td>1.15 ± 0.39</td>
<td>1.25 ± 0.44</td>
<td>0.002</td>
</tr>
<tr>
<td>RR, bpm</td>
<td>25 ± 5</td>
<td>23 ± 5</td>
<td>0.008</td>
</tr>
<tr>
<td>O₂Pulse, ml/bpm</td>
<td>8.03 ± 1.95</td>
<td>8.58 ± 2.41</td>
<td>0.006</td>
</tr>
<tr>
<td>100% VO₂VT, liter</td>
<td>1.29 ± 0.45</td>
<td>1.31 ± 0.43</td>
<td>0.956</td>
</tr>
<tr>
<td>RR, bpm</td>
<td>30 ± 7</td>
<td>28 ± 6</td>
<td>0.080</td>
</tr>
<tr>
<td>O₂Pulse, ml/bpm</td>
<td>8.92 ± 2.1</td>
<td>9.20 ± 2.49</td>
<td>0.167</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD.

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

<table>
<thead>
<tr>
<th></th>
<th>Before PR</th>
<th>After PR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>50% Vₑ VT, liter</td>
<td>0.89 ± 0.32</td>
<td>1.01 ± 0.47</td>
<td>0.013</td>
</tr>
<tr>
<td>RR, bpm</td>
<td>22 ± 4</td>
<td>19 ± 4</td>
<td>0.007</td>
</tr>
<tr>
<td>O₂Pulse, ml/bpm</td>
<td>6.39 ± 2.02</td>
<td>6.82 ± 2.31</td>
<td>0.033</td>
</tr>
<tr>
<td>75% Vₑ VT, liter</td>
<td>1.15 ± 0.41</td>
<td>1.23 ± 0.44</td>
<td>0.025</td>
</tr>
<tr>
<td>RR, bpm</td>
<td>25 ± 5</td>
<td>23 ± 4</td>
<td>0.004</td>
</tr>
<tr>
<td>O₂Pulse, ml/bpm</td>
<td>7.82 ± 2.06</td>
<td>8.47 ± 2.33</td>
<td>0.001</td>
</tr>
<tr>
<td>100% Vₑ VT, liter</td>
<td>1.30 ± 0.45</td>
<td>1.351 ± 0.48</td>
<td>0.199</td>
</tr>
<tr>
<td>RR, bpm</td>
<td>30 ± 6</td>
<td>28 ± 6</td>
<td>0.029</td>
</tr>
<tr>
<td>O₂Pulse, ml/bpm</td>
<td>8.97 ± 2.1</td>
<td>9.24 ± 2.51</td>
<td>0.182</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD.

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
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 technique, 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. 2. Mean values of O2Pulse (a) and VT (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 VT (b) before and after PR at ventilatory iso levels (% VEmax) in 27 COPD patients. * p < 0.05; ** p < 0.01.
perflation. 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$_2$Pulse with heavy hyperinflators showing a significantly lower O$_2$Pulse 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$_2$Pulse at peak of maximal exercise significantly increased after PR compared to baseline. Although the O$_2$Pulse 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$_2$Pulse 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 VCO$_2$max and VE max) 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% VCO$_2$max and at 75% VE max, and the change in O$_2$Pulse. We cannot exclude that at peak of exercise O$_2$Pulse 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 \( O_2 \)Pulse, 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 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


