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Effectiveness of pulmonary rehabilitation in severe asthma: a retrospective data analysis

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ABSTRACT

Background: Pulmonary Rehabilitation (PR) is a multimodal treatment that is still poorly investigated in severe asthma where respiratory symptoms remain “uncontrolled” despite intensive pharmacological therapy. Bronchiectasis and obstructive sleep apnea (OSAS) are common comorbidities which may worsen asthma control.

Aim: Aim of the present study is to investigate the effectiveness of PR on functional exercise, dyspnea, and muscle fatigue in patients with severe asthma.

Methods: A total of 317 patients affected from severe asthma according to GINA guidelines who underwent a multidisciplinary 3 weeks rehabilitation program with an adherence of >80% to PR and able to complete a Six Minute Walking Test (6MWT) were retrospectively included in the analysis. Pulmonary rehabilitation included endurance training, educational meetings, chest physiotherapy, breathing exercises, and psychological support. Six-minute walking distance and Borg scale for dyspnea and muscle fatigue were recorded before and after the rehabilitation.

Results: A total of 371 patients were analyzed, 39 had bronchiectasis (10.5%), 163 (43.9%) OSAS and 17 had both (4.6%). PR significantly improved 6MWT distance, Borg dyspnea and muscle fatigue (p value < 0.0001 for all outcomes) and mean SpO₂ recorded during 6MWT (p value < 0.0001). Median (IQR) delta 6 minute walking distance was 33 (14–60) m. 6MWT distance (p < 0.0001) and the oxygen saturation (p < 0.01) significantly improved in severe asthma with bronchiectasis and/or OSAS.

Conclusions: Our study provides evidence for the first time on a large sample of patients with severe asthma that a multidisciplinary PR program is effective in terms of exercise capacity and symptoms. In addition, exercise capacity improved in the presence of bronchiectasis and/or OSAS.

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Introduction

Several chronic respiratory conditions are known to reduce the physical performance of affected patients, as they fear it might trigger and/or worsen their symptoms (1–4).

A common consequence of reducing physical activity is a downward spiral leading to muscle deconditioning, progressive reduction of the capacity to manage daily activities with psychological distress and impaired quality of life (QoL) (1–4).

There is growing evidence that exercise training and other non-pharmacological interventions within pulmonary rehabilitation (PR) programs are able to improve physical fitness with positive effects on symptoms and psychosocial outcomes (1).

Much of what is known on PR derives from PR in COPD (Chronic Obstructive Pulmonary Disease) patients, while evidence is scanty in other chronic conditions like tuberculosis (5–8) and asthma (1–4).

Asthma is a complex condition characterized clinically by respiratory symptoms (cough, wheezing,

dyspnea, chest tightness), biologically by chronic inflammation (9–11) and functionally by obstruction (which can be transient) and bronchial hyperresponsiveness (1–4). The medical approach is based on the use of inhaled steroid and bronchodilators, eventually combined by PR.

The scanty evidence, mainly available on COPD patients, suggests that PR can reduce dyspnea, anxiety, rescue medications (thus reducing potential adverse events) while lowering hospital admissions (including emergency services) and sick leave (1–4). It was demonstrated that asthmatic patients can be absent from work for a mean of 37 days per year, while a subgroup of them (18.2%) have really much prolonged absence (>80 days) (3).

Recently a small out-patient cohort (49 patients) suggested that PR for 8 week is particularly effective on patients with uncontrolled asthma and on females (who are more likely to have this condition) (4). The study demonstrated a significant improvement of perceived dyspnea, pulmonary function tests, arterial blood gases, QoL and psychosocial symptoms on the overall cohort.

The ProKAR study demonstrated on an in-patient cohort of 201 asthmatics with mild to severe asthma (57% with step 3–4 severity as per Global Initiative for Asthma-GINA classification) that a PR “package” of 3 weeks was be effective and maintain the results achieved in the medium term (at the 12 months follow-up) (3). In particular, asthma control improved with slightly positive effects on the pulmonary function on the 6 minute walking test (6MWT- although the minimal improvement of clinical significance or MIC has never been defined in asthmatics) and QoL (3).

Patients with severe asthma (GINA classification severity step 4–5) (2) are of particular importance as they are more likely to be admitted at emergency services and to be absent from work (3).

In summary, no study has reported on the PR outcomes of patients with severe asthma and showed if, after PR, in this population: a) the symptom score (Modified Borg scale) improves; and b) the oxygen saturation increases. Furthermore, the outcomes of PR among patients with severe asthma and co-morbidities were never investigated previously.

Aim of the present study is to investigate the effectiveness of a multidisciplinary PR program on functional exercise, dyspnea, and muscle fatigue on a large cohort of patients with severe asthma and, in about half of them, co-morbidities.

Our hypothesis is that a multidisciplinary PR program improves one or more of the parameters mentioned above in patients with severe asthma.

Methods

Study design and enrollment criteria

The study included patients with severe asthma (GINA classification severity step 4–5) (2) admitted from January 2007 to June 2017 at Istituti Clinici Scientifici Maugeri of Tradate, Italy, a reference institution specialized in PR.

All medical records of consecutive patients meeting the inclusion criteria were retrospectively analyzed, to complement available records in the Hospital Informatics System (implemented to support clinical and research activities but not including all the necessary variables to answer the clinical question set for the present study).

The Ethics Committee of Istituti Clinici Scientifici Maugeri approved the study protocol (Number 2219, 19/07/2018).

The inclusion criteria were as follows: subjects aged 18 years or more; diagnosis of severe asthma according to current GINA guidelines (step 4–5) (2); pharmacological treatment of asthma as per GINA guidelines over the previous 12 months; adherence of at least 80% of the activities of the PR program (described below) (12); ability to perform and complete a 6MWT.

Exclusion criteria included presence of co-morbidities that could hamper the PR intervention and concomitant diagnosis of COPD (1,13).

The PR program

The three-week inpatient PR program was managed by a multidisciplinary team (chest physician, nurse, respiratory therapist, psychologist, nutritionist), and was tailored to the patients’ individual needs. During the PR, pharmacological and non-pharmacological therapy was also optimized.

Patients were evaluated before (T0) and after (T1) the PR interventions with the following examinations:

T0: lung function tests (static and dynamic volumes according to American Thoracic Society) (14), performed by trained staff in a lung function laboratory with body plethysmograph (Masterlab Body Jaeger); blood gas analysis (automatic analyzer ABL 820 Radiometer Medical); chest radiography; T0 and T1: 6MWT (15), respiratory symptoms (using the Modified Borg scale) (16).

The PR intervention included endurance training, educational support and optional components such as breathing strategies (breathing retraining or pursed-lips breathing if dynamic hyperinflation or dyspnea

Table 1. Pulmonary rehabilitation program.

Pulmonary rehabilitation components		
Endurance training (cycle ergometer)	30 minutes (5 minutes warm up, 20 minutes training, and 5 minutes warm-down) at constant load (starting from the 50–70% of theoretical watt max, (25), and adjusted on subject's tolerance (26).	15 sessions 1/day 5 days/week
Educational program	Optimization of inhalation techniques Peak expiratory flow monitoring Characteristics of asthma and Asthma Action Plan Lifestyle, physical activity, and maintenance programs	2 individual sessions Individual daily session 2 "face to face" sessions 2 group sessions
Optional components		
Respiratory exercises	30 minutes	1 session per day
Airways clearance techniques	30 minutes	1/2 session per day
Psychological support relaxation technique	30/60 minutes	3 sessions per week
	Progressive Muscles Relaxation, Jacobson Method, 30 minutes	5 sessions per week
Nutritional counseling	30/60 minutes	2 sessions

Note. Each session or exercise was supervised by a respiratory therapist.

limiting exercise capacity) and airways clearance techniques (if retained secretions). Moreover, according to individual needs, other interventions were added: psychological support, relaxation techniques (if illness emotional impact at the psychological assessment, i.e., anxiety state or depressive symptoms) (17–19) and nutritional counseling (in case of obesity, diabetes or other metabolic problems) to design a personalized diet. Further details are available in Table 1.

Outcome measures

The following data were collected in an electronic database:

Subjects' characteristics (age, sex); co-morbidities; smoking history (pack/years); asthma severity (severity classification was based on current medications, lung function and clinical assessment by chest physician over the 10-year study period, according to the GINA guidelines); respiratory function (Forced Expiratory Volume in the first second-FEV1; %, Forced Vital Capacity-FVC; %, FEV1/FVC; Residual Volume %-RV); partial pressure of Oxygen (PaO₂, in mmHg); partial pressure of carbon dioxide (PaCO₂, in mmHg); pH; Arterial Oxygen Saturation (SaO₂, before PR-T0); 6MWT (walking distance and % predicted); Heart Rate (HR); Peripheral Oxygen Saturation (SpO₂); perceived dyspnea and muscle fatigue before and after the test (measured with the Modified Borg scale-T0; after PR-T1).

The analysis was performed on the whole cohort, comparing the different variable pre-versus post-PR and comparing patients with step 4 versus step 5 severe asthma.

Furthermore, we performed a sub-analysis of 56 patients with severe asthma and bronchiectasis versus 315 without this co-morbidity, and the 180 patients with severe asthma and OSAS (Obstructive Sleep Apnea Syndrome) versus those without the co-

morbidity. Both diagnosis were made by a chest physician based on CT scan for bronchiectasis and on nocturnal cardio-respiratory monitoring for OSAS.

Statistical analysis

Qualitative variables were described with absolute and relative frequencies, whereas quantitative variables with means (standard deviations) or medians (inter-quartile ranges) based on their normal distribution, respectively. In-between comparisons for qualitative and quantitative variables were performed with the chi-squared or Fisher exact test when appropriate, and Student t or Mann-Whitney test in case of parametric or nonparametric distribution, respectively. Within group comparisons of quantitative variables pre-post PR were assessed with Wilcoxon signed-rank test. *P* values less than 0.05 was considered statistically significant. Stata 15 (StataCorp LLC, Texas USA) was used for every statistical analysis.

Results

A descriptive analysis of the cases enrolled is summarized in Table 2.

Out of 517 clinical records of patients with bronchial asthma reviewed, 371 patients with severe asthma were recruited, 358 (96.5%) with step 4 and 13 with step 5 (GINA classification), the vast majority being stable (84.8%). Stability was assessed through medical history and respiratory symptoms at the time of admission. Pharmacological therapy was also optimized when needed. In fact, drug-therapy was modified in 141 (38%) out of 371 patients under PR: 39% (55/141) due to asthma exacerbation, 44.7% (63/141) due to uncontrolled asthma and in 16.3% (23/141) the number of drugs was reduced.

The median (IQR) age of the cohort was 66 years (57–72), 35.9% were male.

The majority of patients (227, 61.5%) never smoked, while 114 (30.9%) stopped smoking and 28 (7.6%) were still active smokers. Overall 95 patients (27.1%) smoked 10 pack-years or more.

The baseline mean (SD) FEV1% of predicted was 79.6% (22.8) and the median (IQR) FEV1/FVC was 66.6% (54.4–73.7) (Table 2).

Among the 371 patients analyzed, 39 had bronchiectasis (10.5%), 163 (43.9%) OSAS, and 17 both the co-morbidities (4.6%).

Out of 180 diagnosed OSAS patients, 106 (58.9%) were diagnosed with OSAS before PR while 74 (41.1%) were diagnosed during PR. They were treated as follows: 89 (49.5%) with Continuous Positive Airway Pressure (CPAP); 22 (12.2%) with night supplemental oxygen; 60 (33.3%) with mild OSAS were

put on a diet program and the remaining 9 (5%) refused to be treated.

Out of 56 patients diagnosed with bronchiectasis, 11 (18.6%) were diagnosed during PR while the remaining ones before PR. They all underwent 30 minute bronchial disobstruction physiotherapy sessions once or twice daily

A comparative analysis of the different variables analyzed is summarized in Table 3.

PR significantly improved their 6 minute walking distance as well as the Borg dyspnea and muscle fatigue scores (p values < 0.0001 for all outcomes). Moreover, PR significantly improved basal and mean SpO2 recorded during 6MWT (p values < 0.0001).

The median (IQR) delta at 6 minute walking distance was 33 (14–60) meters.

A comparative analysis of the variables analyzed in patients with GINA classification grade 4 and 5 is summarized in Table 4.

Patients with grade 5 had a worse functional status, lower PaO2, and a lower performance at the 6MWT (% predicted) but the total distance was not significantly different.

After PR both patients with severe asthma and co-morbidities (bronchiectasis and OSAS) significantly improved the distance covered at the 6MWT ($p < 0.0001$) and the oxygen saturation ($p < 0.01$).

The median distance gain (delta) in meters post-versus pre PR was 30.5 for patients with severe asthma and bronchiectasis and 42 for those without this co-morbidity; it was 20 for patients with severe asthma and OSAS and 48 for those without the co-morbidity.

Table 2. Descriptive analysis.

Variables	<i>n</i> = 371
Males, <i>n</i> (%)	133 (35.9)
Median (IQR) age, years	66 (57–72)
Smoke, <i>n</i> (%)	
Non smoker	227 (61.5)
Active smoker	28 (7.6)
Former	114 (30.9)
Pack/year > 10	95 (27.1)
Median (IQR) pack/year	0 (0–12)
Median (IQR) FEV1, L	1.7 (1.3–2.2)
Mean (DS) FEV1, %	79.6 (22.8)
Median (IQR) FVC, L	2.6 (2.0–3.1)
Median (IQR) FVC%	94.5 (82–106)
Median (IQR) FEV1/FVC	66.6 (56.4–73.7)
Median (IQR) RV%	136.4 (117.0–156.9)
Mean (SD) PaO2	76.8 (8.6)
Mean (DS) PaCO2	36.6 (3.6)
Median (IQR) pH	7.4 (7.4–7.4)
Median (IQR) SaO2 %	95.9 (94.8–96.8)
Therapy, <i>n</i> (%)	
LABA/ICS (high dose)	342 (96.6)
Oral steroid	11 (3.1)
Monoclonal/Anti Ige	1 (0.3)
GINA scale, <i>n</i> (%)	
4	358 (96.5)
5	13 (3.5)

Note. FEV1: Forced Expiratory Volume in the first second; FVC: Forced Vital Capacity; RV: Residual Volume; PaO2: partial pressure of Oxygen; PaCO2: partial pressure of carbon dioxide; SaO2: Arterial Oxygen Saturation; LABA: Long-acting beta-agonists; ICS: inhaled corticosteroid; GINA: Global Initiative for Asthma

Discussion

Aim of the present study is to investigate the effectiveness of a multidisciplinary PR program on functional exercise, dyspnea, muscle fatigue and oxygen saturation on a large cohort of patients with severe asthma

Table 3. Comparison of 6MWT pre and post-pulmonary rehabilitation.

	Pre	Post	<i>p</i> value
Median (IQR) 6MWT meters	455 (397–516)	496 (440–553)	< 0.0001
Median (IQR) 6MWT % predicted	100 (85–111)	107 (95–118)	< 0.0001
Median (IQR) basal HR, bpm	78 (71–85)	77 (70–85)	< 0.0001
Median (IQR) mean HR, bpm	104 (93–112)	106 (97–114)	0.0001
Median (IQR) max HR, bpm	114 (102–124)	117 (107–128)	< 0.0001
Median (IQR) basal SpO2	95 (94–96)	96 (94–97)	< 0.0001
Median (IQR) mean SpO2	94 (92–96)	95 (93–96)	< 0.0001
Median (IQR) min SpO2	92 (91–94)	93 (91–94)	0.0002
Median (IQR) basal Borg dyspnea	1 (0–2)	0 (0–1)	< 0.0001
Median (IQR) final Borg dyspnea	3 (2–4)	3 (1–3)	< 0.0001
Median (IQR) basal Borg leg fatigue	0 (0–1)	0 (0–1)	< 0.0001
Median (IQR) final Borg leg fatigue	3 (1–4)	2 (1–3)	< 0.0001

Note. 6MWT: Six Minute Walking Test; HR: Heart Rate; SpO2: Peripheral Oxygen Saturation

Table 4. Comparison of variables at baseline according to GINA scale classification.

Variables	Step 4 (n = 358)	Step 5 (n = 13)	p value
Males, n (%)	130 (36.3)	3 (23.1)	0.39
Median (IQR) age, years	66 (58–72)	55 (52–58)	<0.05
Smoke, n (%)			
Non smoker	216 (60.7)	11 (84.6)	0.43
Active smoker	28 (7.9)	–	
Former	112 (31.5)	2 (15.4)	
Pack/year > 10	94 (27.7)	1 (8.3)	0.19
Median (IQR) pack/year	0 (0–13)	0 (0–0)	0.13
Median (IQR) FEV1, L	1.7 (1.3–2.2)	1.2 (0.9–2.0)	<0.05
Mean (DS) FEV1, %	80.2 (22.2)	62.3 (33.0)	<0.05
Median (IQR) FVC, L	2.6 (2.0–3.1)	2.6 (1.4–3.2)	0.63
Median (IQR) FVC%	94.8 (82.1–106.0)	84.1 (54.5–111)	0.28
Median (IQR) FEV1/FVC	66.7 (56.4–73.9)	61.7 (28.6–73.7)	0.35
Median (IQR) RV%	136.1 (117.0–156.8)	152.1 (121.2–182.0)	0.38
Mean (SD) PaO2	77.0 (8.5)	71.7 (11.5)	<0.05
Mean (DS) PaCO2	36.6 (3.6)	36.4 (3.2)	0.81
Median (IQR) pH	7.4 (7.4–7.5)	7.4 (7.4–7.5)	0.22
Median (IQR) SaO2 %	96 (94.9–96.8)	94.6 (93.0–96.7)	0.09
Therapy, n (%)			
LABA/ICS (high dose)	342 (100.0)	0 (0.0)	<0.0001
Oral steroid	0 (0.0)	11 (91.7)	
Monoclonal/Anti Ige	0 (0.0)	1 (8.3)	
Median (IQR) 6MWT meters	454.5 (399–516)	455 (384–495)	0.57
Median (IQR) 6MWT % predicted	100 (86–112)	89 (65–92)	<0.05
Mean (SD) basal HR, bpm	78.5 (11.0)	72.8 (11.1)	0.08
Mean (SD) mean HR, bpm	103.3 (13.5)	96.6 (14.8)	0.09
Mean (SD) max HR, bpm	113.5 (15.4)	108.9 (14.0)	0.31
Median (IQR) basal SpO2	95 (94–96)	93.5 (92.5–96.0)	0.19
Median (IQR) mean SpO2	94 (92–96)	93 (90–95)	0.26
Median (IQR) min SpO2	92 (91–94)	91 (88.5–93.5)	0.16
Median (IQR) basal Borg dyspnea	1 (0–2)	1 (0–2)	0.59
Median (IQR) final Borg dyspnea	3 (2–4)	4 (3–5)	0.14
Median (IQR) basal Borg leg fatigue	0 (0–1)	0 (0–1)	0.77
Median (IQR) final Borg leg fatigue	3 (1–4)	3 (2.0–3.5)	0.87

Note. FEV1: Forced Expiratory Volume in the first second; FVC: Forced Vital Capacity; RV: Residual Volume; PaO2: partial pressure of Oxygen; PaCO2: partial pressure of carbon dioxide; SaO2: Arterial Oxygen Saturation; 6MWT: Six Minute Walking Test; HR: Heart Rate; SpO2: Peripheral Oxygen Saturation

(GINA step 4 and 5); 59% of them had co-morbidities (OSAS and/or bronchiectasis).

Our study provides evidence for the first time on a large sample of patients with severe asthma that the symptom score (Modified Borg scale) improves and the oxygen saturation increases after PR.

Interestingly, the 6MWT at T0 is normal in the majority of these patients although dyspnea at rest and after exercise is present. This finding is rather new, and differs from what was reported in COPD patients (20) where the perception of dyspnea is affected by exercise capacity.

These findings suggest that, as asthma treatment is based on controlling signs and symptoms, PR would represent an added value in patients with severe asthma and dyspnea at rest.

In the Turner et al. (21) study 35 patients with mild to moderate asthma were studied, with similar findings as far as the baseline 6MWT at T0 was concerned in the presence of dyspnea at rest.

However, in this study dyspnea did not improve after PR (21).

Mendes (22) studied 101 patients with severe asthma, divided into two treatment groups. The

patients undergoing PR achieved a significant reduction of their asthma-related symptoms.

Although on a small sample of patients with severe asthma (7 cases), Barreiro (23) identified dyspnea as the main cause limiting exercise performance.

We have been able to provide for the first time evidence that PR improves the performances at the 6MWT and the oxygen saturation in patients with severe asthma and co-morbidities (bronchiectasis and OSAS).

However, quality studies are necessary to further describe the impact of bronchiectasis and OSAS in patients with severe asthma.

Furthermore, the results of our study support the rationale for PR in patients with severe asthma and dyspnea at rest. In these patients the priorities are represented by symptom control from one side, and evaluation of QoL as an additional gate to propose PR to the right patients from the other.

It is interesting to note that in Germany Ligner (3) reported 62% of patients having uncontrolled asthma.

Another important finding of our study is the contribution given to the assessment of the minimum improvement of the six minute walking distance after

PR. While in our study the overall post-PR improvement was 33 meters, in the Ligner's study it was 60 m. This difference can be explained by the different population involved.

Further studies are necessary to estimate this value, which is well established (25 m.) in COPD patients (24). In our study and in others (3) the model chosen to deliver the PR intervention was the in-patient one. The known advantages of this approach in patients with severe asthma include the easier organization of the PR program, the possibility to intervene more rapidly and efficiently on the medical treatment to rapidly improve the symptoms (while ensuring treatment adherence and providing real time education) and monitoring/treatment of the associated co-morbidities (OSAS and bronchiectasis in our study).

The main disadvantage in comparison with an out-patient model is essentially represented by the higher cost. In terms of acceptability to patients, while some patients prefer to stay at home and report daily to undergo the PR program others find it logistically easier to be hospitalized.

In our experience, the in-patient model worked well in patients with severe asthma, while the out-patient one is probably best suited for mild asthma.

The main strength of our study is represented by the large sample size, and the main limitation the impossibility to recover the QoL questionnaires from all the subjects studied.

In an unpublished report from our group, 37 cases from the same cohort were admitted again in 2017 and 2018 and underwent a QoL test (EuroQoL). 24 had both a pre- and post-PR EuroQoL with a mean basal score of 58.54 ± 18.14 and a final one of 75.20 ± 11.46 on a scale ranging from 0 to 100. Another limitation of this study is that, due to its retrospective nature, the analysis of co-morbidities was limited to those originally planned (bronchiectasis and OSAS) which did not include other co-morbidities or cardiovascular conditions.

Furthermore, the long study period considered (2007–2017) could be considered another limitation as over the years, there were relevant changes in drug therapy (e.g., introduction of tiotropium, and biological drugs).

Finally as there was no comparison group, no causal statements are possible

Conclusions

A multidisciplinary PR program is effective in improving symptoms and functional exercise capacity

in patients with severe asthma. In addition, exercise capacity also improved in presence of bronchiectasis and/or OSAS.

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Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper

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