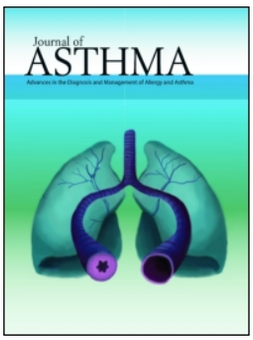

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Outpatient pulmonary rehabilitation for severe asthma with fixed airway obstruction: Comparison with COPD

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ABSTRACT

Background: The benefit of exercise has been demonstrated in asthma, but the role of pulmonary rehabilitation (PR) in people with severe asthma, especially with airway obstruction, has been less investigated. The activity limitation mechanisms differ in asthma and COPD, so the effect of a PR program not specific to asthma is unclear. *Methods:* We retrospectively compared the effect of an ambulatory PR program in nonsmoking patients with severe asthma and airway obstruction (FEV1/FVC ratio <70% and FEV1 < 80% measured twice, not under an exacerbation) and sex-, age-, FEV1-, and BMI-matched COPD controls. *Results:* We included 29 patients, each with asthma and COPD. Airway obstruction was moderate (median FEV1 57% [44–64]). VO_2 at peak was higher for asthma than COPD patients (19.0 [15.7–22.2] vs 16.1 [15.3–19.6] $ml.min^{-1}.kg^{-1}$, $p = 0.05$). After PR, asthma and COPD groups showed a significant and similar increase in constant work cycling test of 378 [114–831] s and 377 [246–702] s. Changes in Hospital Anxiety and Depression Scale (HAD) total score were similar (–2.5 [–7.0 to 0.0] vs –2.0 [–5.0 to 2.0], $p > 0.05$). Quality of life on the St. George's Respiratory Questionnaire (SGRQ) was significantly improved in both groups (–14.0 [–17.7 to –2.0], $p < 0.005$ and –8.3 [–13.0 to –3.6], $p < 0.0001$). *Conclusion:* Outpatient PR is feasible and well tolerated in patients with severe asthma with fixed airway obstruction. A nondedicated program strongly improves HAD and SGRQ scores and constant work-rate sub-maximal cycling, with similar amplitude as with COPD.

Abbreviations: Cis: confidence intervals; COPD: chronic obstructive pulmonary disease; CPET: cardiopulmonary exercise test; CWCT: constant work cycling test; $\Delta HR/\Delta VO_2$: HR response; DLCO: diffusing capacity of the lungs for carbon monoxide; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; HAD: hospital anxiety and depression scale; HR: heart rate; IQR: interquartile range; ORs: odds ratios; PA-aO2: alveolar–arterial difference for oxygen pressure; PR: pulmonary rehabilitation; RV: residual volume; SGRQ: St. George's Respiratory Questionnaire (SGRQ); 6-MWT: 6-min walking test; TLC: total lung capacity; VAS: visual analog scale; VO_2: oxygen uptake; VR: ventilatory reserve

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Asthma; pulmonary rehabilitation; physical activity; feasibility; ambulatory care

Introduction

Pulmonary rehabilitation (PR) is a multidisciplinary and comprehensive intervention with major components of exercise training and self-management education. It is advised for patients with chronic respiratory diseases who are symptomatic and have decreased daily life activities. PR can improve symptoms, exercise capacity, and quality of life, especially in patients with chronic obstructive pulmonary disease (COPD) [1,2].

Recently, the role of exercise training, alone, or rarely as a part of a PR program, has been mainly investigated in young patients [3–5] with mild asthma [6–11], sometimes combined with a dietary intervention in obese and nonobese patients [12,13]. In people with asthma, exercise significantly improves quality of

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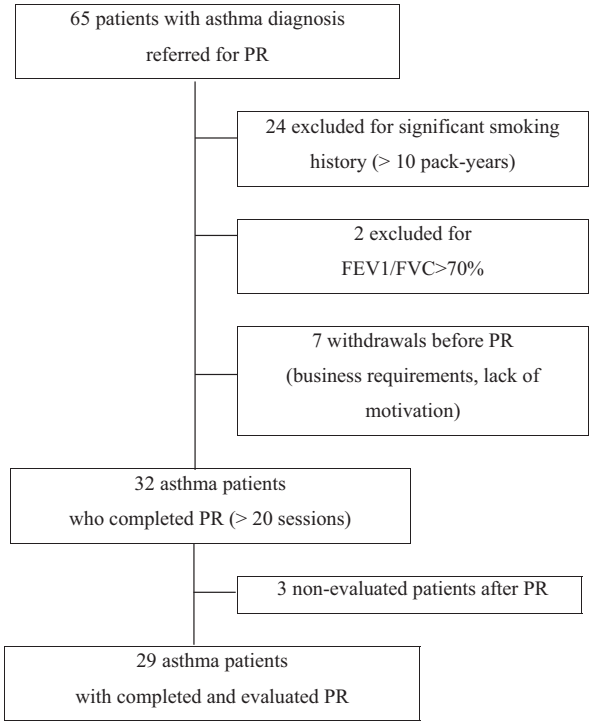

Figure 1. Flow of asthma patients in the study.

life and exercise capacity [14]. Some studies found a positive impact on forced expiratory volume in 1 s (FEV1), asthma control, bronchial hyperresponsiveness, exercise-induced bronchoconstriction, airway inflammation, anxiety and depression, and weight or body composition [8,9,15,16].

However, the role of PR in people with severe asthma, especially those with impaired lung function, has been poorly investigated [17,18]. Yet, these individuals, like COPD patients, frequently report a limitation in daily activities [19], which suggests that asthma and COPD patients might have the same ability to reduce exertional dyspnea and improve exercise capacity. However, the mechanisms leading to exercise limitation may differ in COPD and severe asthma. For example, alveolar gas transfer is well preserved in asthma [20]. Therefore, exercise-induced oxygen desaturation is less likely to occur [21]. In contrast, some COPD patients desaturate during exercise because of impaired gas transfer, which contributes to exercise limitation by increasing ventilatory load and reducing oxygen transport to muscles. The prevalence of steroid-induced myopathy, involving respiratory and/or peripheral muscles, may also differ between patients with severe asthma and COPD [22]. Thus, exercise programs designed initially for COPD may not be appropriate for asthma patients. Some recent studies suggest the need for an asthma-tailored rehabilitation program, especially to improve adherence [23].

In the Paris area, practitioners may prescribe outpatient PR through a multidisciplinary network coordinating programs designed mainly for people with COPD but also, as recommended, all chronic respiratory diseases. We hypothesized that asthma patients may experience different benefits from PR than COPD patients, because of different exercise limitations mechanisms. The aim of this retrospective study was to compare the effects and tolerance of an outpatient PR program in patients with severe asthma, with fixed airway obstruction, and in sex-, age-, body mass index (BMI)- and FEV1-matched COPD patients referred to this regional network.

Material and methods

Patients

This study is based on a retrospective analysis of patients included in a regional network coordinating a multidisciplinary PR program since 2006. Approximately 200 patients are included every year. Their consent is required to enter their clinical data into a database. Patients with severe asthma were selected from this database.

First, asthma diagnosis was confirmed by 1 junior (WG) and 2 senior (AB and CT) pulmonologists by reviewing the medical file, according to the history of respiratory symptoms (wheezing, shortness of breath, chest tightness, and cough that varies over time and

intensity) and documented bronchodilator reversibility and/or variable expiratory airflow limitation in the medical history. To avoid an overlap population, smokers and ex-smokers (>10 pack-years) were excluded (Figure 1). Mention of any CT scan abnormality (bronchiectasia, emphysema, etc.) inconsistent with an asthma diagnosis led to exclusion from the study. Second, patients with severe asthma were identified according to ATS-ERS guidelines [24], having received at least a high dose of inhaled steroids and long-acting beta agonists during the previous year or systemic corticosteroids for at least 50% of the previous year. Then, fixed airflow obstruction was defined as a FEV1/forced vital capacity (FEV1/FVC) ratio <70% and FEV1 < 80% at least twice, not under an asthma exacerbation [24]. Finally, patients who did not participate in a sufficiently effective PR program (<20 PR sessions) were excluded.

Selected severe asthma patients were then matched 1:1 with COPD patients from the same database who performed effective PR during the same period. COPD was defined by a history of progressive chronic obstruction of lung airflow (FEV1/FVC ratio <70%) that interferes with normal breathing, with no reversibility after bronchodilator test. Patients were matched to COPD patients on sex, age, BMI, and FEV1. These criteria were chosen because of their prognostic value in lung diseases and their eventual impact on PR results. The matching was achieved for the criteria in a respective range to have the nearest value between an asthma patient and a COPD patient: FEV1 ± 11%, in the same COPD GOLD stage (for the asthma and paired COPD patient), age (±5 years), and BMI (±3 kg/m^2).

PR program

The regional network gathers a hundred physiotherapists, >30 dieticians and >30 psychologists, all working in private practice in the Paris area. The PR program is prescribed by lung specialists or general practitioners. The patient's physical and educational needs and objectives in the program are evaluated by an individual interview.

All patients had to have no exacerbations in the previous 4 weeks when beginning PR. Contraindications for PR, such as uncontrolled ischemic heart disease, uncontrolled systemic hypertension, and neuromuscular or rheumatologic impairment, were checked by the medical coordinator in charge of the program. Patients gave informed consent to participate in the PR program and signed a therapeutic partnership agreement.

Each patient followed a PR program of 20–30 ambulatory training sessions, 2 or 3 per week, with a physiotherapist trained by the network. Every session lasted 1–1.5 h and combined physical training and educational sessions. The physical training included endurance on an ergo cycle with an objective of a minimum of 30 minutes' duration. Training conditions such as heart rate (HR) target and oxygen need were fixed by a medical coordinator based on initial functional evaluation (see below). Endurance work rate was adapted to the HR target, leading most of the time to increased work rate over the sessions. Depending on patients' needs, the program included strengthening of muscles—particularly limb muscles—proprioception, flexibility, relaxation, and learning breathing strategies during exercise. Training in airway clearance techniques could be added if needed. Educational sessions focused on patient needs and objectives: skills and knowledge acquisition for asthma or COPD, inhaled device techniques, exacerbation management and unsupervised physical activity in developing action plans with each patient.

When necessary, the patient was also referred to a psychologist, dietician, or a stop-smoking consultant. The health professionals interacting with a patient were chosen so as to be as close as possible to the patient's home or workplace and their availability. At all times, health professionals, especially physiotherapists, might refer to medical or physiotherapist coordinators of the network.

Functional evaluation

Initial functional evaluation included arterial blood gas measurement, spirometric tests and a cardiopulmonary exercise test (CPET). CPET, performed according to recommendations [25], was used to assess the safety of exercise, define the factors contributing to exercise limitation, and identify a suitable exercise prescription (HR target of endurance training, need for oxygen). Various parameters were identified or calculated: ventilatory threshold, slope of oxygen uptake (V_{O2}) versus work rate ($\Delta V_{O2}/\Delta WR$), ventilatory reserve, HR reserve, and HR response ($\Delta HR/\Delta V_{O2}$) (as defined in 22). Arterialized ear lobe blood samples at rest and exercise peak were analyzed for PO_2 and PCO_2 in 22 asthma patients and 28 COPD patients, with the alveolar–arterial difference for oxygen pressure ($PA\text{-}aO_2$) calculated.

Two submaximal exercise tests, a 6-min walking test (6-MWT) [26] and a constant work cycling test (CWCT) were performed at enrollment and within 2

months after the end of the program to assess the effect of exercise training. For all exercise tests, dyspnea and lower-limb fatigue were evaluated by patients on a 0–100 mm visual analog scale (VAS). The constant load of CWCT was determined for each patient at 80% of peak work load measured by the initial CPET and reached in 30 s, without warm-up time or verbal encouragement. HR and pulse oxyhemoglobin saturation (SpO_2) were continuously monitored and recorded minute by minute, as were dyspnea and fatigue scores. Cycling above a minimal rate (>50 rounds/min) was maintained as much possible by the patient, until severe lower-limb fatigue and/or severe dyspnea.

The CWCT as performed again at the end of PR at the same workload, with censure time of 30 min if substantial progression was observed. During this second testing, HR, fatigue, and dyspnea were recorded after the same duration as the first testing, to compare variation in these parameters at isotime values and to assess the chronotropic negative effect and the symptom improvement after PR.

The Hospital Anxiety Depression Scale (HAD) was used to evaluate psychological distress in all patients. Health status was evaluated by the St. George's Respiratory Questionnaire (SGRQ), a self-reporting questionnaire validated for evaluating quality of life in both COPD [27] and asthma [28]. The total score is expressed as a percentage, from 0%, no impairment of life quality, to 100%, maximal impairment. In cohort studies, a minimal change in 4 points for the total score was considered clinically significant [29].

Statistical analysis

Data are summarized as proportions for categorical variables and median [interquartile range (IQR) 58.0–74.0] for continuous variables. All associations between the COPD and asthma matched groups were analyzed by univariate conditional logistic regression, estimating odds ratios (ORs) and 95% confidence intervals (CIs). HAD scale, SGRQ scores and results of PR were compared between baseline and post-intervention by paired Wilcoxon test in each group (COPD and asthma). Type I error was set at 0.05. All analyses involved using SAS v.9.4 (SAS Inst., Cary, NC, USA).

Results

Clinical and functional characteristics at baseline

From 2006 to 2015, 65 patients with asthma were referred to the network for PR; 32 patients responded to the criteria defined in methods. Three patients did not have a final evaluation after a complete PR program, which led to matching 29 asthma patients (Figure 1), each with a patient selected among more than 800 COPD patients who had completed a PR program during the same period. The study populations represented mainly middle-aged nonobese females with moderate airway obstruction (median FEV1 57% [44–64]) (Tables 1 and 2).

Table 1. Baseline characteristics of patients with asthma and chronic obstructive pulmonary disease (COPD).

	Asthma ($n = 29$)	COPD ($n = 29$)
Demographics		
Age (years)	66.0 [58.0–74.0]	64.0 [55.0–71.0]
Female	20 (69)	20 (69)
BMI (kg/m^2)	23.1 [20.6–27.7]	23.3 [20.8–27.2]
Active smoker	0 (0)	7 (24)
Comorbidities		
Allergy	8 (28)	2 (7)
Nasal polyposis	2 (7)	0 (0)
Cardiovascular disease	6 (21)	8 (28)
Diabetes	3 (10)	3 (10)
Gastroesophageal reflux	5 (17)	6 (21)
Depression	3 (10)	7 (24)
Obstructive sleep apnea	3 (10)	1 (3)
Osteoporosis	2 (7)	2 (7)
Dyslipidemia	5 (17)	9 (31)
Treatments		
Home oxygen therapy	0 (0)	2 (7)
Inhaled corticosteroids	29 (100)	24 (83)
Daily inhaled steroids dose (μg/d)	1000 [640–1320]	1000 [500–1000]
Long-acting muscarinic agonist	11 (38)	22 (76)*
Long-acting beta agonist	29 (100)	28 (97)
Daily oral corticosteroids	6 (21)	2 (7)
Leukotriene receptor antagonist	7 (24)	0 (0)
Theophylline	3 (10)	1 (3)
Omalizumab	2 (7)	0 (0)

Data are median [interquartile range] or *n* (%).
BMI, body mass index.
*$p < 0.005$.

As expected, matched COPD patients differed from asthma patients by smoking status, allergy, and treatments. COPD patients were mostly heavy smokers or ex-smokers. COPD patients were more frequently prescribed long-acting muscarinic agonists than asthma patients; the use of other inhaled treatments did not significantly differ (Table 1). At the time of inclusion, bronchial reversibility was less frequent in COPD than asthma patients (14 vs 38%) (Table 2), even though all asthma patients had a positive bronchial dilation test documented in their file. Transfer alveolar-gas anomalies were more frequent in COPD than asthma patients (77% predicted [59–93] vs 65% predicted [55–73]; OR 1.1 [95% CI 1.0–1.1], $p = 0.04$) (Table 2) and rest and exercise hypoxemia was more pronounced, although not significantly (Table 2 and 3). These discrepancies between the two groups provide some evidence for distinct obstructive lung disease in the two groups. No data concerning blood or

Table 2. Pulmonary function test and resting blood gas analysis at inclusion.

	Asthma ($n = 29$)	COPD ($n = 29$)
FEV1 (% predicted)	57 [44–64]	58 [49–69]
FEV1/FVC ratio	50 [44–58]	47 [37–51]
FEV1 reversibility**	8 (38)	4 (14)
with FEV1 gain	19 [17–23]	24 [18–36]
RV (% predicted)	123 [94–150]	137 [121–162]
RV/TLC ratio (% predicted)	125 [105–146]	116 [110–134]
DLCO (% predicted)	77 [59–93]	65 [55–73]*
pH	7.44 [7.42–7.45]	7.43 [7.41–7.45]
PaCO2 (mmHg)	39.3 [36.8–40.8]	39.1 [36.4–41.8]
PaO2 (mmHg)	77.4 [71.5–81.6]	71.0 [67.7–75.4]

*$p = 0.04$ of conditional logistic regression between the matched groups.
**FEV1 reversibility was defined as gain of more than 12% and 200 ml of baseline FEV1 after bronchodilator administration and expressed by *n* (%) patients. Only 21 asthma patients and 28 COPD patients were tested.
FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; DLCO, diffusion capacity of the lungs for carbon monoxide.

Table 3. Cardiopulmonary exercise test before pulmonary rehabilitation program (PR).

	Asthma ($n = 29$)	COPD ($n = 29$)
Maximal work load (watts)	70 [59–98]	63 [52–80]
Maximal oxygen uptake (V_{O2}) (ml/min/kg)	19.0 [15.7–22.2]	16.1 [15.3–19.6]*
Ventilatory threshold (ml/min/kg)	12.0 [9.8–15.6]	10.9 [9.9–12.0]
(watts)	30 [20–50]	31 [24–39]
(%V_{O2} max predicted)	50 [42–69]	53 [42–61]
V_{O2}—workload slope ($ml.min^{-1}.W^{-1}$)	11.2 [10.0–12.3]	10.8 [10.0–11.8]
Ventilatory reserve (%)	2 [9–16]	9 [−2 to 17]
Heart rate reserve (%)	10 [2–13]	15 [7–25]
Heart rate response ($beats.ml^{-1}$)	63 [40–79]	60 [38–73]
Peak arterialized P_{O2} (mmHg)	82 [74–90]	76 [65–84]
Peak-resting PA-aO_2 (mmHg)	0.7 [−1.5 to 7.1]	2.5 [−0.3 to 13.4]

*$p = 0.05$ of conditional logistic regression between the matched groups.
PA-aO_2, alveolar–arterial difference for oxygen pressure.

sputum eosinophilia were available in the database. Conversely, asthma and COPD patients did not differ in comorbidities; cardiovascular diseases were frequent in both groups (21 and 28%, respectively) (Table 1).

During CPET, median V_{O2} at peak was higher for asthma than COPD patients (19.0 [IQR 15.7–22.2] vs 16.1 [15.3–19.6] $ml.min^{-1}.kg^{-1}$, $p = 0.05$) (Table 3). Also, median maximal workload was higher but not significantly for asthma patients (70 W [59–98] vs 63 W [52–80], $p = 0.06$). All other parameters, such as ventilatory threshold and V_{O2}-workload slope, were similar for the groups. Exercise limitations did not differ, although ventilatory and HR reserves were lower for asthma than COPD patients (2% [9–16] vs 9% [2–17], $p = 0.1$ and 10% [2–13] vs 15% [7–25], $p = 0.06$).

Walking distance during the 6MWT and cycling time during the CWCT were similar before PR (Table 4). During the walking test and CPET, blood oxygenation during exercise was more preserved but not significantly for asthma than COPD patients: 29% of asthma patients had a significant oxygen saturation decrease (≥4%) between rest and the last 3 walking minutes, versus 48% of COPD patients ($p > 0.05$). Similarly, alveolar–arterial oxygen pressure difference between rest and peak exercise was lower but not significantly for asthma than COPD patients (0.7 [−1.5 to 7.1] vs 2.5 [−0.3 to 13.4] mmHg, $p = 0.06$) (Table 3).

Feasibility and tolerance of the PR program

The program course was similar for asthma and COPD patients, particularly in number and duration

Table 4. Submaximal exercise tests before and after PR.

	Asthma		COPD	
6-min walk test	Pre-PR	Post-PR	Pre-PR	Post-PR
Distance (m)	492 [400–570]	509 [440–569]	510 [455–541]	510.0 [456–558]
delta (pre- vs post-PR)		0.0 [−31.0 to 34.0]		7.0 [−27.0 to 21.0]
Dyspnea (VAS)	4.0 [1.8–6.5]	5.0 [4.0–8.0]	5.0 [3.0–7.0]	3.3 [2.3–6.5]
delta (pre- vs post-PR)		1.0 [−1.0 to 3.0]		−1.0 [−3.0 to 1.3]**
Constant work-rate cycling test				
Time (s)	300 [240–408]	660 [360–1173]*	252 [234–318]	690 [486–1200]*
delta (pre- vs post-PR)		378 [114–831]		377 [246–702]
Distance (km)	1.7 [1.5–2.4]	3.3 [2.6–8.1]*	1.4 [1.2–1.8]	3.8 [2.2–7.0]*
delta (pre- vs post-PR)		1.7 [0.6–6.3]		1.8 [1.1–3.4]
Heart rate	138 [124–145]	121 [117–140]*	125 [114–137]	121 [107–130]*
delta (pre- vs post-PR)		−14 [−19 to −1]		−7 [−14 to 0]
Dyspnea	9.0 [6.8–9.0]	4.0 [2.0–6.5]*	8 [7–9]	4.0 [3.0–6.0]*
delta (pre- vs post-PR)		−3.0 [-5.0 to −1.0]		−4.0 [−6.0 to −3.0]
Fatigue	9.0 [5.5–10.0]	5.0 [1.5–6.5]*	8 [7–9]	4.0 [3.0–5.3]*
delta (pre- vs post-PR)		−3.0 [−5.0 to −1.0]		−4.0 [−6.0 to −3.0]

*$p = 0.034$ of conditional logistic regression between the matched groups.
**$p = 0.1$ of conditional logistic regression between the matched groups.
Heart rate, dyspnea and fatigue at post-PR CWCT were isotime values

Table 5. Baseline and post-PR Hospital Anxiety Depression Scale (HAD) and St. George's respiratory questionnaire (SGRQ) scores.

	Asthma		COPD	
	Pre-PR	Post-PR	Pre-PR	Post-PR
HAD				
Total score	15.0 [12.0–18.0]	11.0 [8.0–14.0]*	15.0 [10.0–18.0]	11.0 [6.0–17.0]*
delta (pre- vs post-PR)		−2.5 [−7.0 to 0.0]		−2.0 [−5.0 to 2.0]
Anxiety domain	9.5 [8.0–12.0]	8.0 [6.0–10.0]*	8.0 [6.0–10.0]	7.0 [4.0–9.0]
delta (pre- vs post-PR)		−2.0 [−3.0 to 0.0]		−1.0 [−2.0 to 1.0]
Depression domain	6.5 [4.0–7.0]	3.0 [1.0–6.0]*	6.0 [3.0–8.0]	4.0 [2.0–7.0]
delta (pre- vs post-PR)		−2.0 [−4.0 to 1.0]		0.0 [−3.0 to 1.0]
SGRQ				
Total	47.0 [39.0–60.0]	32.0 [26.0–39.0]*	44.5 [34.6–54.0]	33.4 [23.0–43.5]*
delta (pre- vs post-PR)		−14.0 [−17.7 to −2.0]		−8.3 [−13.0 to −3.6]

*Significant difference between before and after PR.
**Significant difference between asthma and COPD patients.

of sessions: 30 sessions in both groups over the same period (122 days [112–147] and 116 days [93–132], respectively, $p < 0.05$). The progression in endurance cycling power between the first and last session was also similar for asthma and COPD patients (increase in 15 W [5–25] and 38% of the initial power [8–75] and increase in 10 W [6–20] and 29% of the initial power [20–59], respectively, $p > 0.05$).

PR was well tolerated by asthma patients: short-acting beta agonists were required during exercise for only three asthma and five COPD patients. During the PR program, only one asthma patient presented a moderate exacerbation between two sessions, with no need to temporarily stop the program. Bronchitis occurred in 34% asthma patients versus 21% COPD patients; muscular or articular minor trauma was seen in 10% asthma versus 31% COPD patients, with no need for more supplementary medical visits (10 vs 24%) or emergency care. Hospitalization related to the bronchial illness occurred in one patient in each group.

Functional characteristics after PR

After PR, results for pulmonary function test or 6-MWT did not change in either group. Only 16% of asthma patients and 7% of COPD patients increased their walking distance by at least 50 m after PR (Table 4).

Both asthma and COPD patients had a significant and similar increase in endurance during the CWCT (Table 4): median increase in exercise time 378 s [IQR 114–831] and 377 s [246–702], respectively, accounting for more than twice the initial time (2.5 [1.4–3.7] and 2.4 [1.9–3.3], respectively). This increase was largely above the minimal clinically significant difference of 105 s or 33% observed in COPD cohort studies [30]. This difference was reached in 75% of asthma patients and 90% of COPD patients. Isotime measures during the second test were always lower after PR (Table 4) and similar in the asthma and COPD groups: isotime HR (−14.5 [−19.5 to −1.5] vs −7.0 [−14.0–0.0], $p > 0.05$), isotime dyspnea (−3.0 [−5.0 to −1.0] vs −4.0 [−6.0 to −3.0], $p > 0.05$) and isotime fatigue (−3.0 [−5.0 to −1.0] vs −4.0 [−6.0 to −3.0], $p > 0.05$).

HAD and SGRQ

Before the program, HAD and SGRQ scores did not differ significantly between the asthma and COPD groups (Table 5). After PR, changes in HAD total score were similar in the two groups. The same proportion of patients showed 4 or more points' improvement in total score (43 and 40%). However, asthma patients showed significant improvement in all determinants of HAD and anxious and depressive elements, but COPD patients showed improvement in only total HAD score, with a less marked and more inconsistent effect.

After PR, the respiratory impact on quality of life evaluated by the SGRQ significantly decreased for both asthma and COPD patients, with a similar change in median total SGRQ score (−14.0 [IQR −17.7 to −2.0], $p < 0.005$, and −8.3 [−13.0 to −3.6], $p < 0.0001$, respectively) (Table 5). This variation was largely clinically significant (a decrease of ≥4 points) in 68% asthma patients and 72% COPD patients ($p > 0.05$). Overall, the impact was important but more heterogeneous for asthma than COPD patients.

Discussion

In this retrospective study, we demonstrate that patients with severe asthma and impaired lung function can benefit from a safe ambulatory nondedicated PR program to the same extent as COPD patients.

Activity limitation is a prognostic factor in COPD, accelerated by exacerbations [31], but it is also frequently reported in patients with severe asthma,

especially those with high-intensity activities [32] and contributes to poor asthma control [32], low quality of life, and global asthma burden. This limitation can be related to several mechanisms, including exertional dyspnea, muscular deconditioning, or obesity. The mechanism of exertional dyspnea is complex in asthma and can be usefully assessed by a CPET [33]. Dyspnea can result from a mixture of exercise-induced bronchoconstriction, mechanical limitations due to dynamic lung hyperinflation, decreased respiratory muscle strength, psychological factors, nasal obstruction, or hyperventilation syndrome [34], all contributing to symptoms to varying degrees [33]. Exercise training improves exertional dyspnea mainly by improving peripheral muscle conditioning but also by improving emotional well-being and modification of dyspnea perception. In severe asthma, the level of sedentary behavior is associated with increased airway inflammation [32], but exercise training could reduce levels of airway and systemic inflammatory molecules in some studies [35], thereby helping to improve asthma control.

In this study, we assessed the evolution of dyspnea after PR during the 6MWT and CWCT by comparing patients' dyspnea scores on a VAS at the same cycling time between the initial and final tests (isotime dyspnea). After PR, a decrease of 1–2 cm in VAS dyspnea score has been reported and associated with an increase in exercise capacity [36]. Dyspnea measured during the CWCT decreased by 3 cm for asthma patients and 4 cm for COPD patients at isotime, associated with a significant improvement in exercise capacity. However, during the 6MWT, dyspnea decreased to a lesser extent for COPD than asthma patients and did not significantly change for asthma patients. This finding could suggest that the mechanisms of exertional dyspnea and/or the effect of the PR on these mechanisms differed in our asthma and COPD patients, despite similar levels of obstruction and lung distension and similar BMI. VAS is a reliable tool to assess dyspnea [37] but may lack sensitivity to assess sensory dimensions of dyspnea, therefore underestimating some effects of PR in our patients. The use of questionnaires exploring both sensory and affective dimensions of dyspnea, such as the Multidimensional Dyspnea Profile Questionnaire [38,39], may be more appropriate to evaluate the effect of a PR program on all the dyspnea components.

Similarly, asthma and COPD patients showed improved quality-of-life scores on the SGRQ, which also evaluates dyspnea [28,40]. The significant improvement in total SGRQ score in our asthma patients (mean decrease by 14 points) was similar to that observed in a randomized clinical trial of mepolizumab in severe asthma [41], although we did not evaluate the effect of PR on asthma control or exacerbations. These data suggest that PR is a valuable and reasonably inexpensive treatment for severe asthma, especially when exertional dyspnea is a prominent symptom. In France, the cost of ambulatory physical and educative sessions in PR programs was recently added to coverage by health insurance schemes but only for COPD. These results are important to convince institutions to extend health cost coverage for other chronic lung diseases for which PR is recommended.

The PR has demonstrated benefit in COPD patients, but patients with severe asthma can face barriers in accessing community-based exercise programs. Healthcare professionals may perceive higher risks of PR for people with severe asthma [23], as suggested in our study by the very low number of patients referred for PR (65 during a 9-year period in a large urban area). The risk of exercise-induced bronchoconstriction is frequently argued as a limitation of PR for people with asthma. However, exercise-induced bronchoconstriction can be generally prevented by physical conditioning incorporating a warm-up before and a cool-down period after exercise. During PR, endurance training includes times of warming up and progressive recuperation, which explains why no exercise-induced bronchoconstriction was reported in our series.

Patients with asthma, especially those with severe disease, are more likely to think that physical activity should be avoided [42]. Participation in a PR program may also be limited by the jobs of younger patients, which is responsible for a high dropout rate, concerning 25% of severe asthma patients enrolled in a home-based program in France [17]. For these reasons, some authors suggest the design of asthma-tailored programs. In our study, the PR program was not customized for asthma patients: the same professional team was implicated, and similar physical training based on CPET results and an educational program as for COPD patients were proposed. Adherence, tolerance, and benefits were similar between asthma and COPD patients, which support the use of the same PR healthcare center or professional team for asthma patients as for COPD patients. However, the PR program is a patient-tailored therapeutic approach that needs to be based on an initial comprehensive physical and educative evaluation, even more so for asthma patients in whom mechanisms of exercise

limitation may be more heterogeneous than in COPD patients.

Our study has several limitations, due to retrospective design and the small number of asthma patients, regarding the high prevalence of the disease. We did our best to exclude an overlap population. The discrepancies in smoking use, allergy, transfer gas anomalies and treatments confirm that we studied two different populations with airflow limitation. Another limitation was the high number of different health professionals interacting with all the patients. Although they were all trained by the network and followed recommended procedures for the program, heterogeneity in the practice cannot be avoided. However, we demonstrated a strong positive effect of the program, similar to that observed in randomized trials.

In conclusion, we show that outpatient PR, even in a nondedicated program for asthma, is a safe and well-tolerated treatment in patients with severe asthma and fixed airway limitation. PR improves constant work-rate submaximal cycling exercise, with similar amplitude as for patients with COPD, with a great and significant improvement in HAD and quality-of-life scores. PR could be included in the therapeutic arsenal. Its place relative to drug therapies should be prospectively evaluated in randomized trials.

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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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