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Original article

Long-term effects of pulmonary rehabilitation on daily life physical activity of patients with stage IV sarcoidosis: A randomized controlled trial

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ABSTRACT

Introduction. – Pulmonary rehabilitation (PR) is known to improve exercise tolerance, mood, and quality of life in patients with chronic respiratory diseases. The aim of this work was to determine whether PR provides long-term benefits in increasing daily life physical activity in patients with chronic sarcoidosis.
Methods. – This randomized prospective study (registered ClinicalTrials.gov NCT02044939) of 38 patients with stage IV chronic sarcoidosis was performed between 2012 and 2016. Patients were assigned to participate in a 2-month PR program ($n = 20$) or receive counseling ($n = 18$). Assessments were performed at baseline, 2 months (end of the PR program), 6 months, and 12 months, and included daily life physical activity parameters (measured for 5 consecutive days), exercise tolerance, dyspnea, anxiety, depression, fatigue, and quality of life. The primary outcome was the 12-month change in time spent in activities above an estimated energy expenditure of 2.5 metabolic equivalents (METs). Secondary daily life physical activity outcomes included number of steps per day, total daily energy expenditure, and total energy expenditure above 2.5 METs.
Results. – The primary outcome did not differ between the two groups; mean between-group differences were −13.2 min (95% confidence interval [CI]: −76.3 to 49.8) at 6 months and −18.1 min (95% CI: −55.7 to 19.4) at 12 months. Although PR had no effect on secondary daily life physical activity outcomes, it did significantly increase exercise tolerance at 6 and 12 months and decrease the dyspnea score at 6 months and the fatigue score at 12 months.
Conclusion. – This trial failed to demonstrate a beneficial effect of PR on daily life physical activity in sarcoidosis patients, suggesting that long-term behavioral programs may be necessary to complement PR.

1. Introduction

Sarcoidosis is a systemic disease of unknown cause that can affect many organs, but the lungs are most frequently affected (90%–95% of cases) [1]. Sarcoidosis is usually classified into five stages (0–IV) based on radiological findings [2], and approximately 5% of patients with pulmonary sarcoidosis have the chronic fibrosing form of the disease (stage IV). Patients with stage IV disease gradually develop exercise-associated dyspnea [1] leading to a progressive reduction in daily life physical activity [3–6].

Pulmonary rehabilitation (PR), defined as an "evidence-based, multidisciplinary and comprehensive intervention for patients with chronic respiratory disease who are symptomatic and often have decreased daily life activities" [7], is an appropriate treatment for many patients with chronic respiratory diseases. Although a considerable body of evidence supports the benefits of PR for patients with chronic obstructive pulmonary disease (COPD), relatively little is known about its effects in patients with sarcoidosis [7–9]. Most studies of PR in patients with interstitial lung diseases (ILDs) have been performed with mixed patient populations, but in general, they have confirmed that PR is safe and improves exercise tolerance, quality of life, and dyspnea, at least in the short term [10]. Indeed, two recent studies of patients with sarcoidosis by

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Lingner et al. [11] and Naz et al. [12] demonstrated that 3-week and 3-month PR programs, respectively, resulted in improved 6-minute walk test (6MWT) performance and self-reported dyspnea, depression, anxiety, and quality of life ratings at the end of the program. Along these lines, two studies also reported that physical training improves exercise capacity and fatigue among sarcoidosis patients [13,14]. However, although rehabilitation improves exercise tolerance, it is not known whether daily life physical activity is also improved in sarcoidosis patients. We report here the results of a multicentric randomized controlled trial of a 2-month PR program in patients with chronic stage IV sarcoidosis to evaluate the long-term (12 months) beneficial effects of PR on daily life physical activity.

2. Patients and methods

2.1. Patients

This study was an open-label multicenter randomized controlled trial conducted in patients with stage IV chronic sarcoidosis to evaluate the efficacy of a 2-month PR program on daily life physical activity (National PHRC 2012-A00347-36 "Respiratory rehabilitation in chronic fibrotic sarcoidosis (stage IV): a randomized therapeutic trial"). The study was retrospectively registered with ClinicalTrials.gov (NCT02044939) and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. All patients gave written informed consent before randomization. The study protocol was approved by an independent Ethical Committee (decision CPP Northwest 15-05-2012).

The trial was conducted in seven Pulmonology Departments in France. Inclusion criteria were:

- a sarcoidosis diagnosis according to the American Thoracic Society (ATS)/European Respiratory Society (ERS)/World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) statement [15];
- radiographic stage IV disease defined by patent advanced fibrosis with evidence of upper lobe volume loss with hilar retraction with or without masses, coarse linear bands, honeycombing, bullae, and emphysema;
- subjectively symptomatic despite optimized outpatient medical treatment.

A total of 38 patients were enrolled between July 2012 and April 2016 and were randomized to the control group ($n = 18$) or the PR group ($n = 20$). Follow-up visits were planned at 2 months (end of the PR program), 6 months, and 12 months after inclusion for the PR group and at 6 and 12 months after inclusion for the control group.

2.2. Randomization

Patients were randomly allocated in a 1:1 fashion to the control or PR program arms. The randomization sequence was provided by an independent statistician who did not take part in patient assessment using computer-generated random numbers with block sizes of four. Randomization was carried out using sequentially numbered, sealed, opaque envelopes containing allocated arm assignments. The patient was declared randomized when the seal was broken.

2.3. Interventions

Patients assigned to the PR group attended an outpatient PR program at least three times per week for 2 months, with each training session targeting a minimum duration of 30 min. At all locations, the programs included individual and group-based strengthening exercises, upper/lower limb training, and supervised endurance training. In addition, patients received training in resumption of daily life physical activity, therapeutic patient education, psychosocial support, and motivational communication, to facilitate health-related behavioral changes and self-management. All sessions were conducted individually with a multi-professional health-care team.

Patients assigned to the control group received oral counseling to increase their physical activity at home.

2.4. Outcome measures

2.4.1. Daily life physical activity

Subjects were equipped with a physical activity monitor (SenseWear Pro Armband with SenseWear software version 6.1; BodyMedia Inc., Pittsburgh, PA, USA) and instructed to wear the device continuously (except while showering or bathing) for 5 consecutive days, of which 2 were to be weekend days, as previously described [6]. Daily life physical activity was assessed by measuring four parameters: the number of steps per day (SPD), the total daily energy expenditure (EE, kcal/day), the EE above 2.5 metabolic equivalents (METs) (kcal/day), and the time (min/day) spent in activities requiring an EE of > 2.5 METs. The prespecified primary outcome was the 12-month change in time (min/day) spent in activities requiring EE > 2.5 METs. The prespecified secondary outcomes were (i) the 6-month change in EE > 2.5 METs and (ii) the 6-and 12-month change in other daily life physical activity parameters. Changes in exercise capacity and the following patient-reported outcomes were also assessed at 6 and 12 months as exploratory secondary outcomes.

2.4.2. Exercise capacity

Exercise tolerance was evaluated using a 6-min stepper test (6MST), as previously reported [16]. Arterial oxygen saturation and heart rate were measured continuously.

2.4.3. Patient-reported outcomes

Patients assessed dyspnea using the modified Medical Research Council (mMRC) self-administered questionnaire, which consists of five questions about perceived breathlessness and is scored on a scale from 0 (not troubled by breathlessness except during strenuous exercise) to 4 (very severe dyspnea: too breathless to leave the house or breathless when dressing or undressing) [17].

Fatigue was assessed using the Fatigue Assessment Scale (FAS) questionnaire. This scale contains 10 items with a maximum total score of 50 points. Scores of 22–34 indicate mild-to-moderate fatigue, and scores ≥ 35 indicate severe fatigue [18].

Patients indicated their overall quality of life using the Visual Simplified Respiratory Questionnaire (VSRQ). A score ≥ 80 (on a scale of 0–100) indicates a satisfactory quality of life [19].

Patients reported their psychological state using the Hospital Anxiety and Depression Scale (HADS), which was designed to identify and quantify the two most common forms of psychological disorders in medical patients [20]. For both subscales, a score of 8 to 10 (on a scale of 0–21) is indicative of uncertain symptoms, and a score ≥ 11 is indicative of clinically relevant symptoms.

2.4.4. Pulmonary function tests

Pulmonary function was evaluated at baseline and at the 12-month follow-up visit. Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), and total lung capacity (TLC) were measured by spirometry and plethysmography, and single-breath diffusing capacity of the lung for carbon monoxide (DLco, in mL CO/min/mmHg) was measured and corrected for hemoglobin concentration. Reference equations for lung volumes and DLco

were taken from the ERS guidelines [21,22]. The lower limits of normal were set at the 5th percentile (or the predicted value minus 1.64 standard deviations [SD]) of each reference population, according to the 2005 ATS/ERS guidelines [23]. The results are conventionally expressed as percent of the predicted values.

2.4.5. Cardiopulmonary exercise tests

At baseline, subjects completed a 6MWT and a triangular exercise test on a cycle ergometer (Ergometrics 800®; Ergoline, Bitz, Germany), with blood pressure and electrocardiographic monitoring (Medcard®; Medisoft, Sorrine, Belgium) according to a standardized protocol, as detailed previously [24]. We focused on aerobic capacity by assessing the maximal oxygen uptake (VO_2max), and the results are expressed as mL O_2/kg/min and the percentage of predicted values [25]. The 6MWT was performed in accordance with international recommendations [26].

2.5. Accident protocol

Patients were provided with PR agreement forms that included an accident protocol. An accident was defined as death, hospitalization, or emergency care for heart or orthopedic disease occurring at any time from baseline to the 12-month follow-up visit. The patient or the therapist could declare an accident. Patients were asked to interrupt physical activities if they experienced any abnormal sensation, especially chest or joint pain, and to contact both the rehabilitation team and the attending physician.

2.6. Statistical analysis

The initially planned trial was to enroll 150 patients (75 per arm), which we calculated would provide 80% power to detect a mean between-group difference of 30 min in the time spent in activities with EE > 2.5 METs from baseline to 12 months. This calculation was done with a two-sided type I error of 0.05, assuming a standard deviation of 69 min, and considering a correlation coefficient between baseline and 12-month values of 0.4 to account for the fact that the primary analysis was adjusted for baseline value.

Analyses were performed on all randomized patients in both groups (intention-to-treat analysis). In the PR program arm, we compared the outcome measures between baseline and 2 months (end of the PR program) using paired Student's *t*-tests or, for non-Gaussian distribution of within-subject differences, Wilcoxon's signed rank test. We estimated and compared the 6- and

Table 1
Baseline characteristics of patients.

Characteristic	Control group (n = 18)	PR group (n = 20)	*P*-value
Age (years)	57.5 (49.0–65.0)	57.5 (48.0–63.5)	0.92
Sex ratio (M/F)	7/11	10/10	0.49
Duration of sarcoidosis (years)	16.0 (7.5–26.0)	14.0 (9.0–29.0)	0.70
Patients taking prednisone, n (%)	9 (50)	12 (60)	0.66
Prednisone dose (mg/day)	5.0 (0.0–15.0)	5.0 (0.0–15.0)	0.75
Patients taking additional immunosuppressant drugs, n (%)	5 (27.7)	10 (50)	0.43
BMI (kg/m^2)	27.3 (23.4–31.2)	28.4 (23.7–31.1)	0.94
FVC, mean (SD)[a]	81.4 (18.2)	80.7 (18.2)	0.95
FEV_1, mean (SD)[a]	61.1 (16.9)	66.8 (20.2)	0.60
TLC, mean (SD)[a]	87.4 (18.2)	83.5 (13.7)	0.66
DLco, mean (SD)[a]	62.7 (18.5)	56.8 (15.9)	0.28
VO_2max (ml/kg/min)	17.0 (13.9–21.9)	15.3 (13.6–21.2)	0.56
VO_2max[a]	73.5 (62.0–81.0)	67.5 (59.5–80.0)	0.64
6MWT distance (m)	456 (380–510)	430 (372–505)	0.75
6MWT nadir SpO_2 (%)	94.5 (92.0–95.0)	92.0 (89.0–95.0)	0.06

Values are expressed as the median (IQR) unless otherwise indicated. 6MWT: 6-min walk test; BMI: body mass index; DL_{CO}: diffusing lung capacity for carbon monoxide; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 s; IQR: interquartile range; PR: pulmonary rehabilitation; TLC: total lung capacity.

[a] Percentage of predicted value.

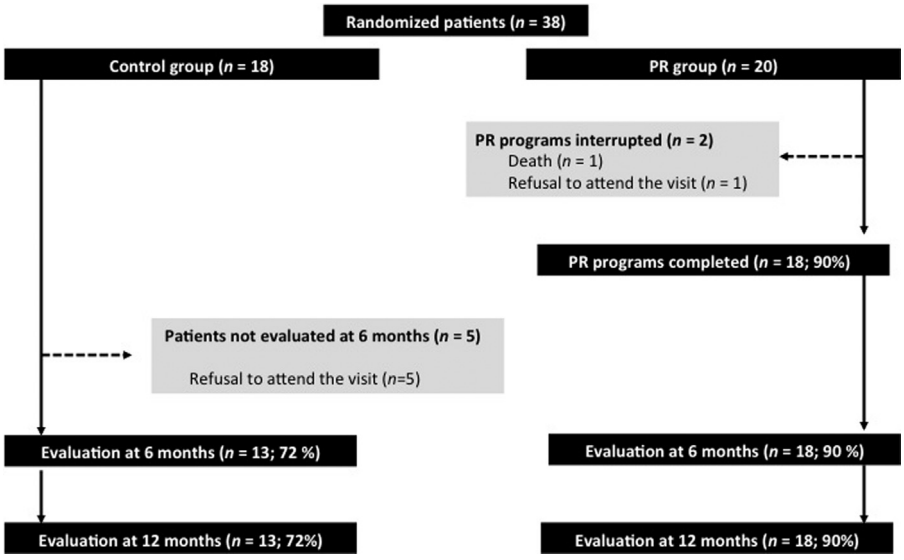

Fig. 1. Consort flow diagram.

Table 2
Within-patient changes in outcomes at the end of PR.

	Baseline	End of PR	Difference	*P*-value
Duration of physical activity > 2.5 METs, min/day	149 (125)	137 (75.4)	12.0 (87.3)	0.62
Number of steps per day	6263 (3937 to 10336)	6869 (5154 to 9162)	−190 (−3122 to 1919)	0.68
Total EE (kcal/day)	2343 (268)	2369 (390)	−26.0 (338)	0.78
EE > 2.5 METs (kcal/day)	572 (410)	571 (256)	0.7 (294)	0.99
6MST (strokes)	503 (150)	570 (117)	−66.4 (85.4)	0.012
HADS total score	14.5 (7.0)	14.5 (8.0)	0.9 (4.1)	0.39
HADS anxiety subscore	8.7 (4.3)	8.2 (5.0)	0.5 (2.9)	0.49
HADS depression subscore	6.7 (3.9)	6.3 (4.1)	0.4 (2.3)	1.00
FAS score (n = 17)	27.9 (8.0)	25.0 (5.5)	2.9 (6.9)	0.77
VSRQ (n = 17)	41.3 (12.7)	50.9 (15.1)	−9.6 (11.9)	0.007
MMRC score	2.0 (1.0 to 3.0)	1.0 (1.0 to 2.0)	0 (0 to 1.0)	0.016

Descriptive parameters were calculated for the patients with values at baseline and the end of PR (n = 18) unless indicated. Values are expressed as median (IQR) unless otherwise indicated. P values were calculated using paired Student's t-test, or Wilcoxon's signed rank test in the case of non-Gaussian distribution of the within-subject difference. 6MST: 6-min stepper test; EE: energy expenditure; FAS: Fatigue Assessment Scale; HADS: Hospital Anxiety and Depression Scale; METs: metabolic equivalents; mMRC: modified Medical Research Council questionnaire; PR: pulmonary rehabilitation; VSRQ: Visual Simplified Respiratory Questionnaire.

Table 3
Primary outcomes measures at baseline and 6 and 12 months after pr: daily life physical activity parameters.

	Control group (n = 18)		PR group (n = 20)		Difference in change from baseline adjusted to the baseline value[c]	
Parameter	n	Value, mean (SD)	n	Value, mean (SD)		*P*-value
Duration of physical activity > 2.5 METs, min/day[a]						
Baseline	18	151.9 (122.4)	20	158 (134)		
6 months	13	137.8 (130)	17	116 (83.1)	−13.2 (−76.3, 49.8)	0.67
12 months	13	145.7 (95)	18	112 (97.4)	−18.1 (−55.7, 19.4)	0.33
Number of steps per day, median (IQR)[a]						
Baseline	18	5396 (3522–8094)	20	6223 (3768–10616)		
6 months	13	5010 (3115–7538)	17	5323 (2826–6211)		
12 months	13	4219 (3457–6707)	18	3924 (2912–6199)		
Change, 0–6 months	13	556 (−720–3929)	17	915 (588–1618)		1.00 [b]
Change, 0–12 months	13	336 (−395–2417)	18	681 (−21–2566)		0.86 [b]
Total EE (kcal/day)						
Baseline	18	2630 (742)	20	2337 (389)		
6 months	13	2533 (740)	17	2239 (398)	20.0 (−260, 300)	0.89
12 months	13	2574 (609)	18	2246 (472)	−26.7 (−305, 251)	0.85
EE > 2.5 METs (kcal/day)						
Baseline	18	703 (639)	20	619 (499)		
6 months	13	671 (614)	17	450 (268)	−124 (−368, 151)	0.36
12 months	13	693 (500)	18	392.0 (298)	−180 (−371, 12.1)	0.065

P-values were calculated using a constrained longitudinal data analysis model except[b], which used the Mann–Whitney U–test. CI: confidence interval; EE: energy expenditure; IQR: interquartile range; METs: metabolic equivalents; PR: pulmonary rehabilitation; SD: standard deviation. [a]Prespecified primary outcome (change at 12 months). [b,c]Values are presented as the mean (SD) except [b]median (IQR), [c]mean (95% confidence interval).

12-month changes in outcome measures between the two arms using the constrained longitudinal data analysis model [27] [28]. In this model, the baseline and post-baseline values are both modeled as dependent variables using a linear mixed model, and the true baseline means are constrained to be the same for the two treatment groups to adjust for observed baseline differences. The between-group differences in change from baseline to time of interest (6 and 12 months) were estimated by the time-by-treatment group interaction. We visually inspected the normality of model residuals, and nonparametric analysis was used for deviations; absolute changes from baseline to time of interest were calculated and compared between the two treatment groups using Mann–Whitney U-tests. All statistical tests were two-sided and $P < 0.05$ was considered statistically significant. No adjustment for multiple testing was applied to the exploratory secondary outcomes. Data were analyzed using SAS software version 9.4 (SAS Institute, Cary, NC, USA).

3. Results

From July 2012 to April 2016, 38 patients with sarcoidosis were enrolled in the trial and randomized to participate in the PR program (n = 20) or to receive counseling about physical activity without the PR program (control group, n = 18). As shown in Table 1, the clinical and functional characteristics at baseline were well balanced across the two study groups. Only two patients (one in each group) presented with sarcoidosis localized to the heart. The disposition of patients at 12 months is summarized in Fig. 1. In the control group, five patients withdrew consent, and in the PR group, one patient died and one withdrew consent. The death was not considered attributable to the PR program or to exercise re-training. In total, 18 of the 20 patients completed all PR sessions.

Table 2 summarizes the outcome measures at baseline and the end of the 2-month program for the patients in the PR group. Exercise tolerance (6MST), quality of life (VSRQ score), and dyspnea

Table 4
Secondary outcomes measures at baseline and 6 and 12 months after PR: pulmonary function, exercise capacity, dyspnea, quality of life, anxiety, and depression.

	Control group ($n = 18$)		PR group ($n = 20$)		Difference in change from baseline adjusted to the baseline value[b]	
Parameter	*n*	Value, mean (SD)	*n*	Value, mean (SD)		*P*-value
FVC (% predicted)						
Baseline	18	81.4 (18.2)	20	80.7 (18.2)		
12 months	13	85.4 (21.6)	18	78.6 (19.4)	−2.3 (−7.3, 2.6)	0.35
FEV_1 (% predicted)						
Baseline	18	61.1 (16.9)	20	66.8 (20.2)		
12 months	13	61.3 (18.9)	18	65.0 (20.4)	3.0 (−1.8, 7.9)	0.21
TLC (% predicted)						
Baseline	18	87.4 (18.2)	20	83.5 (13.7)		
12 months	13	88.2 (22.3)	18	82.5 (12.4)	−0.9 (−6.5, 4.7)	0.75
DLco (% predicted)						
Baseline	18	62.7 (18.5)	20	56.8 (15.9)		
12 months	12	64.3 (18.6)	18	55.8 (18.4)	−2.8 (−10.2, 4.6)	0.44
FAS score						
Baseline	18	31.3 (14.9)	20	26.4 (7.4)		
6 months	13	24.4 (5.2)	17	23.1 (6.6)	−2.7 (−6.3, 0.9)	0.13
12 months	11	26.1 (7.2)	17	23.1 (7.1)	−4.2 (−8.4, −0.03)	0.048
6MST (strokes)						
Baseline	17	311 (81.8)	20	456 (185)		
6 months	13	273 (82.9)	17	545 (155)	155 (105, 206)	< 0.001
12 months	12	283 (133)	17	504 (148)	113 (51, 175)	< 0.001
HADS total score						
Baseline	18	10.7 (6.5)	20	14.8 (6.7)		
6 months	12	11.6 (5.9)	18	13.9 (7.1)	−0.4 (−4.1, 3.4)	0.85
12 months	12	12.6 (6.0)	18	13.2 (6.3)	−2.0 (−5.4, 1.4)	0.24
HADS anxiety subscore						
Baseline	18	6.7 (3.6)	20	8.3 (4.0)		
6 months	12	6.4 (2.7)	18	8.3 (4.8)	0.8 (−1.5, 3.1)	0.47
12 months	12	6.8 (2.8)	18	7.8 (4.4)	−0.05 (−2.1, 2.0)	0.95
HADS depression subscore						
Baseline	18	4.1 (3.4)	20	6.6 (3.8)		
6 months	12	5.2 (3.4)	18	5.4 (3.4)	−1.3 (−3.2, 0.6)	0.18
12 months	12	5.8 (3.6)	18	5.2 (3.7)	−2.1 (−4.4, 0.3)	0.082
VSRQ score						
Baseline	18	38.5 (21.4)	20	42.6 (14.2)		
6 months	13	44.0 (14.7)	17	45.6 (16.2)	2.7 (−8.7, 14.0)	0.63
12 months	12	50.2 (14.4)	17	48.9 (15.2)	1.0 (−9.0, 11.0)	0.84
mMRC score, median (IQR)[a]						
Baseline	17	1.0 (0.0–2.0)	20	2.0 (1.0–2.5)		
6 months	14	1.0 (1.0–2.0)	18	1.0 (1.0–2.0)		
12 months	14	1.0 (0.0–2.0)	18	1.0 (1.0–3.0)		
Change, 0–6 months	14	0 (0–0)	18	0 (0–1)		0.017[c]
Change, 0–12 months	14	0 (0–0)	18	0 (0–0)		0.35[c]

CI: confidence interval; DLCO: diffusing lung capacity for carbon monoxide; FAS: Fatigue Assessment Scale; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 s, HADS: Hospital Anxiety and Depression Scale; IQR: interquartile range; mMRC: Modified Medical Research Council questionnaire; PR: pulmonary rehabilitation, SD: standard deviation; TLC: total lung capacity; VSRQ: Visual Simplified Respiratory Questionnaire. [a,b]Values are presented as the mean (SD) except [a]median (IQR) and [b]mean (95% confidence interval). *P*-values were calculated using a constrained longitudinal data analysis model except[c], which used the Mann–Whitney U-test.

(mMRC score), were significantly improved at the end of the PR program compared with baseline, whereas none of the daily life physical activity parameters had changed.

After adjustment for the baseline values, there was no significant difference between the control and PR groups in the primary outcome (mean 12-month change in time spent in activities with EE > 2.5 METs) (Table 3). The mean between-group differences were −13.2 min (95% confidence interval [CI]: −76.3 to 49.8 min, $P = 0.67$) at 6 months and −18.1 min (95% CI: −55.7 to 19.4 min, $P = 0.33$) at 12 months. PR had no significant effects on other daily life physical activity parameters (SPD, total EE/day, EE > 2.5 METs/day) at 6 or 12 months (Table 3). There were no significant differences in the parameters between the end of PR (2 months) and 6 or 12 months (additional tables S1 and S2).

Analysis of the exploratory secondary outcome measures (Table 4) indicated that PR was associated with a significant increase in 6MST at 6 months (mean difference in change from baseline: 155 strokes, 95% CI: 105 to 206) and at 12 months (113 strokes, 95% CI: 51 to 175), and with a significant decrease in FAS score at 12 months (mean difference in change from baseline: −4.7, 95% CI: −9.4 to −0.05). The PR group also experienced a significant decrease in dyspnea compared with the control group between baseline and 6 months ($P = 0.017$). There were no clinical relapses during follow-up, and the BMI did not change significantly in either the PR group ($P = 0.95$) or the control group ($P = 0.67$). There were no changes in the doses of immunosuppressive drugs other than steroids, for which the doses were slightly reduced between baseline and 12 months for both groups (PR group: 5 mg/day [IQR

0–15] to 4 mg/day [0–12], $P = 0.09$; control group: 5 mg/day [0–15] to 4 mg/day [0–12], $P = 0.06$).

4. Discussion

The present study has two main findings: (i) as expected, a 2-month PR program significantly improved dyspnea, exercise tolerance, and quality of life for patients with sarcoidosis compared with baseline; and (ii) exercise tolerance, but none of the daily life physical activity measures, was improved in the short term (immediately post-PR) and long term (6 and 12 months) after PR. The mean values for FVC and DLco (% predicted) also showed no long-term improvement after PR.

Our study demonstrates that exercise conditioning (exercise bike, walking, climbing stairs) can be performed safely by patients with chronic sarcoidosis, confirming previous reports in patients with various ILDs [10]. Interestingly, we found that the significant PR-induced improvements in dyspnea and exercise tolerance observed in the short term (i.e., immediately after the PR program) were sustained long term (12 months). In a large-scale study of 296 patients with sarcoidosis, Lingner et al. [11] found that exercise tolerance, quality of life, mood, and fatigue were significantly improved after a 3-week inpatient PR program; however, longer-term effects were not reported. Similarly, in a retrospective observational study of 90 patients, Strookappe et al. observed that a supervised, 12-week, aerobic exercise and strength training program improved exercise performance, strength, and fatigue in patients with sarcoidosis [14]. In a small randomized controlled study of patients with stage III/IV sarcoidosis, Naz et al. [12] reported immediate benefits in exercise tolerance, quality of life, mood, and fatigue in the PR group ($n = 9$) immediately after a 3-month PR program [12], although this study also did not include follow-up assessments. Lastly, Marcellis et al. also reported improvement of exercise tolerance, fatigue, and quality of life in a short nonrandomized study of 18 patients [13]. Taken together, these results suggest that patients with advanced sarcoidosis would benefit from integrating exercise training and PR into the standard treatment approach.

Studies in patients with fibrotic idiopathic interstitial pneumonia and COPD have also failed to show significant beneficial effects of PR on daily life physical activity, despite evidence of increased exercise tolerance [29,30]. We previously reported that daily life physical activity was significantly impaired in patients with chronic stage IV sarcoidosis, as measured using a physical activity monitor [6]. Indeed, we expected that the patients would progressively improve their level of daily life physical activity after completion of the PR program. Why this did not occur, despite improvements in dyspnea, fatigue, and exercise capacity, is unclear. However, this finding does suggest that simply increasing the patient's exercise capacity through PR does not mean that they will take advantage of it in their daily life. A similar finding that improvements in exercise capacity after PR do not necessarily increase daily life physical activity was observed in COPD patients but remains controversial [30–33]. Fatigue is a frequent finding in sarcoidosis patients and is likely to influence the level of daily life physical activity [34]. In our study, PR had no effect on the mean fatigue (FAS) score of the entire cohort, but it did significantly reduce fatigue at 12 months for 8 subjects who had abnormal fatigue levels at baseline, despite the lack of effect on daily life physical activity. Collectively, these observations raise the possibility that complementary counseling to improve psychological and behavioral factors, such as the ability to cope with the disease, might allow patients to fully exploit the beneficial effects of PR in their daily lives.

Our study has several limitations. The sample size was small, with only 38 patients enrolled in this multicentric study over the 4-year period. In part, this was due to the homogeneity of sarcoidosis phenotypes, since stage IV chronic sarcoidosis is the least common form [1]. In addition, most patients with stage IV sarcoidosis were middle-aged and employed, and did not want to spend three half-days a week in a PR center. The previous randomized controlled study by Naz et al. [12] included 18 patients with chronic sarcoidosis. Lastly one cannot exclude that it might be necessary to perform such a PR program for at least 3 months to achieve a significant effect.

In conclusion, our study suggests that although improvements in functional capacity after PR are necessary to support increases in daily life physical activity, other facets of patient behavior are important in translating these gains into increased activities of daily living. Therefore, we propose that physicians should take a multifaceted, holistic approach to increasing daily life physical activity by complementing PR programs with other supportive measures, such as psychological and nutritional education.

Authorship statement

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The other authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.resmer.2019.10.003.

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