Chapter 5

Benefits of physical training in patients with idiopathic or end-stage sarcoidosis-related pulmonary fibrosis: a pilot study

B Strookappe, M Elfferich, J Swigris, A Verschoof, J Verschakelen, T Knevel, M Drent

Sarcoidosis Vasc Diffuse Lung Dis 2015;32:43-52

Abstract

Background

The natural history of disease in patients with stage IV (fibrotic) sarcoidosis may mirror that of patients with idiopathic pulmonary fibrosis (IPF). Both are bothered by progressive dyspnea, exercise limitation and fatigue. The objective of this study was to establish whether patients suffering from pulmonary fibrosis might benefit from a physical training program.

Methods

Twenty-four eligible patients referred to the out-patient clinic of the ild care expertise team of Hospital Gelderse Vallei, Ede, The Netherlands between November 2012 and November 2013 were included in this observational pilot study of a 12-week physical training program. Outcomes, including exercise capacity, skeletal muscle strength and symptoms were assessed at two time points: 1) baseline; and 2) after completion of a 12-week physical training program.

Results

At baseline, the percentage predicted DLCO, FVC, FEV_1 and exercise capacity (assessed by six-minute walking distance (6MWD) or maximal oxygen uptake) was reduced in both groups. After program completion, exercise capacity improved (>10% improvement 6MWD) in 13 subjects (54.2%): 7 with IPF and 6 with sarcoidosis subjects. Other secondary endpoints, including pulmonary function tests and patient-reported outcome measures improved in some subjects.

Conclusion

A 12-week physical training program improved or maintained exercise capacity in patients with IPF (despite disease progression) or fibrotic sarcoidosis. The results from this pilot study could be used to design prospective studies aimed at answering lingering questions about exercise training in patients with these progressive, incurable conditions.

Introduction

The interstitial lung diseases (ILD) are a heterogeneous group of lung disorders characterized by physiologic restriction and impaired gas exchange. They induce hypoxemia and activity-limiting dyspnea that often lead to physical deconditioning.[1-4]

In sarcoidosis, morbidity and mortality are driven by the pulmonary aspects of the disease. However, the clinical presentation and disease course of pulmonary sarcoidosis are highly variable.[5,6] The natural history of stage IV sarcoidosis (by chest radiograph) can mimic idiopathic pulmonary fibrosis (IPF), with a progressive course and early mortality.[7,8] Complicating matters, some patients with sarcoidosis will develop pulmonary hypertension, and in patients not responding to currently available medical treatment, lung transplantation is considered.[6,9]

IPF is a chronic, progressive and fatal ILD characterized by pulmonary restriction, diminished exercise capacity and symptoms of exertional dyspnea, dry cough and disabling fatigue. Periods of transient clinical stability may occur, however disease progression is the rule. In IPF, lung transplantation is the only therapeutic modality shown to reliably improve survival.[10] Although IPF is not curable, the results of two recently conducted trials reveal that slowing disease progression is an achievable goal for some patients.[11,12]

In patients with fibrotic sarcoidosis or IPF (as well as other fibrotic ILDs), diminished exercise capacity is demonstrated by reduced oxygen uptake (as measured during a maximal cardiopulmonary exercise test) or a shorter-than-predicted distance covered during a six-minute walk test (6MWD).[13-15] Although fibrotic ILD – regardless of cause – is incurable and often refractory to drug therapy, limited data suggest that pulmonary rehabilitation – the backbone of which is an exercise program that most often includes a combination of aerobic and resistance training – is a safe and effective intervention[1-4] that improves symptoms, physical functioning and quality of life (QOL).[3,16]

The aim of this study was to expand the data on whether and how patients suffering from sarcoidosis or IPF benefit from a tailored physical training program, as delivered in pulmonary rehabilitation.

Methods

Subjects

Twenty-four consecutive patients referred to the out-patient clinic of the ILD care expertise team of Hospital Gelderse Vallei, Ede, The Netherlands between November

2012 and November 2013 were included as subjects in this study. Diagnoses were confirmed by the multidisciplinary ILD care expertise team in accordance with accepted guidelines.[10,17]

Study design

In this observational pilot study, there were two time points at which outcome variables were collected: 1) baseline; and 2) after completion of a 12-week physical training program. At our center, assessments of muscle strength and exercise capacity are routinely performed as part of the initial evaluation and follow-up of patients with ILD. Within subject, these assessments are made by the same tester at baseline and after 3 months.

Outcome variables

Body composition

Height, weight, body mass index (BMI) and fat-free mass (FFM) were measured as reported previously.[18] FFM was calculated using the Lukaski formula.[19] To assess the degree of functional tissue depletion, FFM was adjusted for body size by calculating the FFM index (FFMI, FFM/ height^2 (kg.m^{-2})). Muscle atrophy was defined as FFMI <15 kg/m^2 for women and <17 kg/m^2 for men corresponding to <10th percentile of current reference values established in a large Caucasian group of healthy subjects.[20]

Lung function tests

Forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) were measured with a pneumotachograph (Masterlab, Jaeger, Würzburg, Germany). The diffusing capacity of the lung for carbon monoxide (DLCO) was measured using the single-breath method (Masterlab, Jaeger, Würzburg, Germany). Values were expressed as percentage of the predicted value (i.e., FVC%, FEV_1%, and DLCO% respectively).

Muscle strength

Maximal inspiratory pressure (PImax) was assessed with the MicroRPM (Micro Medical Ltd., Rochester, England) as previously described.[21,22] The maximal isometric grip strength of the dominant hand was measured with the Jamar dynamometer (Fabrication Enterprises Inc., Irvington, NY, USA) and expressed in kilograms (kgs).[23] Percentage of predicted was calculated using normative data of Mathiowetz and colleagues.[24]

Quadriceps strength was assessed during knee extension with the microFET (Biometrics, Almere, The Netherlands), an electronic hand-held dynamometer. The 'break' method was used to measure the maximal peak force of the dominant arm or leg in Newton (N). The highest value of at least two measurements was recorded.[25]

Exercise capacity

Maximal oxygen uptake – and other commonly collected variables – were measured during a cardiopulmonary exercise test using the Steep Ramp Test (SRT) protocol on a cycle ergometer.[26] After a two-minute unloaded warm-up, the intensity was increased by 25 watts every 10 seconds, with the subject pedaling at a rate of 70-80 rpm. The test was terminated when the subject indicated they could no longer continue or if the revolutions per minute fell below 60. Intermittent, standardized encouragement was given to the subject throughout the entire test. The six-minute walk test (6MWT) was administered according to the American Thoracic Society Guidelines.[27] Predicted 6MWD values were calculated according to Gibson and colleagues.[28]

Patient-reported outcome instruments

Fatigue was measured with the 10-item Fatigue Assessment Scale (FAS). Each item uses a 5-point rating scale, so the total score range is 10 to 50. Scores below 22 indicate no fatigue; scores of 22-34 indicate mild-moderate fatigue; and scores of 35 or more indicate extreme fatigue. In sarcoidosis, the FAS has acceptable psychometric properties.[29] The minimal clinically important difference in sarcoidosis is 4 points or a 10% change.[30]

The Borg Rating of Perceived Exertion (RPE) Scale was used to assess perceived exertion. Scores range from 6 to 20, where 6 means "no exertion at all" and 20 means "maximal exertion." The Borg Scale was used to determine the RPE during the 6MWT.

Average breathlessness intensity over a 2-week period was assessed with an 8-point, modified Borg scale (from 0 to 7), for which higher scores connote greater breathlessness.[31] Subjects also ticked a box to indicate whether their breathlessness was brief, periodic or continuous.

Intervention

In accordance with American Thoracic Society standards, the exercise program consisted of two major components: aerobic endurance training (stationary cycling, treadmill) and peripheral muscle strengthening.[32] The program consisted of 24 sessions over 12 weeks. Each session lasted 60 minutes, and both training components were performed at each session.

The aerobic endurance component was started at a level of 50-60% of peak work achieved during the SRT.[26] An interval protocol was used while subjects exercised continuously with a goal time of more than 30 minutes. After a 10 minute warm-up period, subjects completed alternating exercise intervals of 40 seconds at high resistance and 60 seconds at low resistance. After completing 10 intervals, subjects cooled down for five minutes. Intensity and duration were gradually increased (both

within sessions and over time) to build tolerance and confidence. During each session, the targeted exercise intensity was 13-15 on the Borg RPE Scale.[33] Pulse-oxymetry was used to monitor peripheral oxygen saturation levels during exercise, and supplemental oxygen use during training was commensurate with current prescriptions.

The strength training component consisted on exercises using *Life Fitness Circuit Series* equipment (Life Fitness, Barendrecht, The Netherlands). During each training sessions, subjects performed three sets of 15-20 repetitions of 6-8 different exercises – some lower- and some upper-body. At least two lower body exercises were performed each training session. The resistance level was individualized for each patient (according to patient preference) and reassessed and adjusted after every session using the Borg Score. The targeted exercise intensity was between 13-15 on the Borg score.[33]

Statistical analysis

Deviation from normality was tested for each continuous variable using the Kolmogorov-Smirnov test. Comparisons between baseline and follow-up values were performed using the paired *t*-test if data were normally distributed or the Mann-Whitney rank test if data were not normally distributed. Categorical variables were compared using Chi-square or Fisher's exact test as appropriate. Associations between the pulmonary function tests, 6MWD, FFMI and fatigue of the studied group were calculated using Pearson's correlations. We considered $p<0.05$ to represent statistical significance. All statistical analyses were performed using SPSS statistical software (version 19.0.0 for Windows) (SPSS Inc., Chicago, IL, USA). Descriptive statistics were generated for baseline characteristics.

Results

All 24 training sessions were completed by 24 subjects: 12 with IPF and 12 with end-stage, refractory sarcoidosis. Baseline and post-training data are summarized in Table 5.1. A total of 9 subjects used supplemental oxygen during the training program: 6 with IPF and 3 with sarcoidosis.

Lung function tests

At baseline, FVC%, FEV_1% and DLCO% were decreased in both groups. Compared to the sarcoidosis subjects, IPF subjects had a significantly lower DLCO ($p=0.001$) and FEV_1 (0.003), but the FVC was not different ($p=0.294$). The 6MWD ($p<0.0001$), and the SRT (Watt; $p=0.002$) were significantly lower in IPF subjects compared with the sarcoidosis subjects. HGF did not differ between IPF and sarcoidosis subjects ($p=0.991$; Table 5.1 and Figure 5.1). At baseline 15 subjects (6 sarcoidosis and 9 IPF, $p=0.223$ for difference) had fatigue (FAS scale score >22). Mean FAS scores were similar between groups (26.8

± 2.7 vs. 28.5 ± 5.6, p=0.527). The majority of subjects in each group desaturated during a 6MWT at baseline (Figure 5.1).

Table 5.1 Summary of the demographic, clinical and physical characteristics of studied subjects with idiopathic or end-stage sarcoidosis-related pulmonary fibrosis at baseline and after a 12-weeks training program.

	Sarcoidosis subjects at baseline	Sarcoidosis subjects at follow-up	IPF subjects baseline	IPF subjects follow-up
Demographics				
Subjects, n	12		12	
Women/men, n	1/11		3/9	
Age, yrs	53.2 ± 11.7#		67.3 ± 11.3	
Time since diagnosis, yrs	10.0 ± 8.2#		3.5 ± 6.3	
Nonsmokers/smokers, n	12/0		12/0	
Body composition				
BMI, kg/m^2	27.8 ± 5.1		28.3 ± 4.6	
FFMI, kg/m^2	17.9 ± 1.8		17.4 ± 2.1	
Medication				
Prednisone use yes/no, n	5/7	4/8	7/5	7/5
Methotrexate use yes/no, n	1/11	8/3*	0	0
Anti-TNF-α use yes/no, n	1/11	3/9	0	0
Pirfenidone	0	0	0	3
Dyspnea measure				
Borg scale	4.0 ± 2.6	3.8 ± 1.9	4.6 ± 2.0	5.3 ± 2.1
Borg RPE scale	12.8 ± 3.0	12.0 ± 1.9	12.5 ± 3.0	13.9 ± 2.6
Fatigue measure				
FAS-score	21.9 ± 5.4#	20.7 ± 5.7	25.1 ± 5.6	25.9 ± 9.9
Physical functions				
SRT, Watt	270 ± 69#	286 ± 65	180 ± 71	190 ± 68
Oxygen saturation, start, %	96.6 ± 1.3	97.0 ± 1.1	96.6 ± 1.3	93.3 ± 2.7
Oxygen saturation, finish, %	92.3 ± 3.9#	92.2 ± 4.5#	86.9 ± 7.1	86.9 ± 6.4
Muscle force				
HGF, % predicted	89.3 ± 14.8	99.9 ± 5.8*	89.2 ± 14.7	97.4 ± 17.4
Pi, max, % predicted	102.5 ± 28.8	111.6 ± 30.7	80.0 ± 30.5	87.3 ± 27.3

Data are expressed as mean ± standard deviation (SD) or absolute numbers (n). IPF = Idiopathic pulmonary fibrosis; BMI = body mass index; FFMI = fat-free mass index; TNF = tumor necrosis factor; RPE = ratings of perceived exertion; FAS = Fatigue Assessment Scale; SRT = Steep Ramp Test; HGF= hand grip force; QPT: quadriceps peak torques; Pi, max = maximal inspiratory pressure. # all p's <0.05 sarcoidosis vs IPF; all p's <0.05 sarcoidosis baseline compared with 3 months later (after the training program) *p<0.05 sarcoidosis subjects (n=12) at baseline versus follow-up.

After completion of the training program, in subjects with sarcoidosis, the mean improvement in FVC% (Δ=9.7 ± 11.4, p=0.075), FEV_1% (Δ=7.9 ±9.6; p=0.145) and DLCO% (Δ=5.1 ± 4.5; p= 0.460) were unchanged from baseline. In subjects with IPF, FVC% (Δ=-5.3 ± 7.8; p=0.386), FEV_1% (Δ= -9.0 ± 7.1; p=0.186) were also unchanged from baseline. There was a trend toward decline for DLCO% (Δ=-6.8 ± 12.0; p=0.163) among subjects with IPF. A greater proportion of subjects with sarcoidosis had improvements (>10% change from baseline) in pulmonary function tests (Figures 5.2 and Table 5.2).

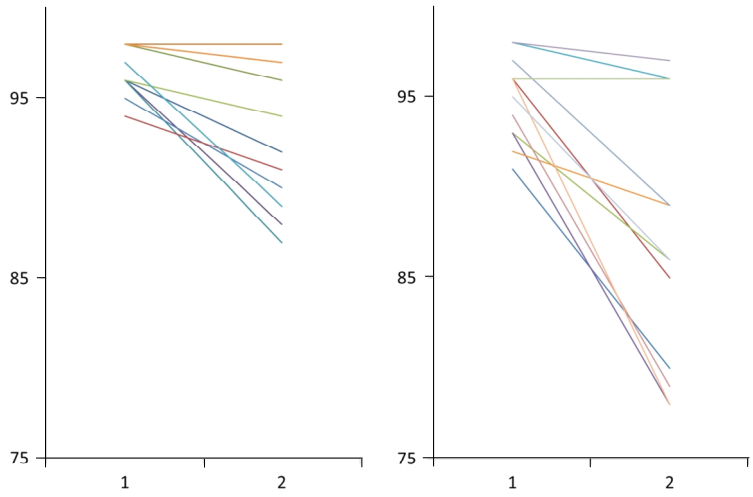

Figure 5.1 Individual changes of the oxygen saturation before and after the six minute walking test at baseline of the studied sarcoidosis (A: n=12) and idiopathic pulmonary fibrosis (IPF) subjects (B: n=12).

Table 5.2 Pulmonary function tests and 6 minute walking distance (6MWD) at baseline and after a 12-weeks training program of the studied subjects with idiopathic or end-stage sarcoidosis-related pulmonary fibrosis.

	Sarcoidosis patients at baseline	Sarcoidosis patients at follow-up		IPF patients baseline	IPF patients follow-up	
Lung function tests			p-value			p-value
DLCO, % predicted	62.7 ± 16.4#	67.8 ± 16.7#	0.460	40.9 ± 12.6	34.1 ± 10.5	0.163
ΔDLCO		5.1 ± 8.5			-6.8 ± 12.0	0.01*
FVC, % predicted	71.3 ± 12.3#	81.0 ± 13.0#	0.075	77.0 ± 13.4	71.7 ± 14.9	0.368
ΔFVC		9.7 ± 11.4			-5.3 ± 7.8	0.001*
FEV_1, % predicted	63.0 ± 14.2#	70.9 ± 11.2#	0.145	83.7 ± 16.1	74.7 ± 16.2	0.186
Δ6MWD		7.9 ± 9.6			-9.0 ± 7.1	<0.001*
6MWD, meter	513 ± 102#	565 ±122#	0.278	305 ± 137	335 ± 125	0.588
Δ6MWD, meter		51.3 ± 33.3			29.4 ± 73.6	0.358*
6MWD, % predicted	64.8 ± 9.4#	70.9 ± 11.5#	0.198	46.0 ± 18.6	50.0 ± 15.7	0.706
Δ6MWD, %		9.5 ± 5.4			9.45 ± 19.4	0.990*

Data are expressed as mean ± standard deviation (SD). IPF = Idiopathic pulmonary fibrosis; DLCO = diffusing capacity of the lung for carbon monoxide; FVC = forced vital capacity; FEV_1 = forced expiratory volume in one second; 6MWD = six-minute walking distance; Δ difference between follow-up and baseline. #p<0.05: sarcoidosis subjects (n=12) at baseline and follow-up vs IPF subjects (n=12) at baseline and follow-up *p Δ sarcoidosis vs IPF

Muscle strength

The HGF of the dominant hand increased by at least 10% over the baseline values in 12 subjects (7 with sarcoidosis vs. 5 with IPF). There was a trend toward improvement in mean HGF values in the sarcoidosis group (p=0.081) but not in the IPF group (p=0.247). Muscle atrophy was present at baseline in a total of 10 subjects (all were male; 5 with sarcoidosis and 5 with IPF). Only one subject was cachectic (BMI<20). At baseline, quadriceps strength was less than 80% of predicted in one subject with sarcoidosis and six with IPF. Quadriceps strength improved in the subject with sarcoidosis (by 10%, from 74 to 84%) and in three subjects with IPF (76% to 90%, 74% to 111%, and 70% to 82%). It remained unchanged in the other three IPF subjects.

Exercise capacity

Maximal work achieved (Watts from the SRT: 10% over baseline) improved in 10 subjects (6 with sarcoidosis and 4 with IPF). Mean values for change from baseline were unchanged (sarcoidosis group p=0.488 and IPF group p=0.534). The 6MWD increased by 10% over the baseline value in half of the subjects (6/12 with sarcoidosis and 6/12 with IPF). There was no between-group difference in mean change in 6MWD (% of predicted value) from baseline to post-program (Δ=9.5 ± 5.4% for sarcoidosis vs. 9.5 ± 19.4% for IPF; p=0.990 for comparison; Table 5.2 and 5.3). As defined by a >10% increase from baseline in raw value, 6MWD improved in 13 subjects (54.2%): 6 with sarcoidosis (6/12 or 50%) and 7 with IPF (7/12 or 54.2%).

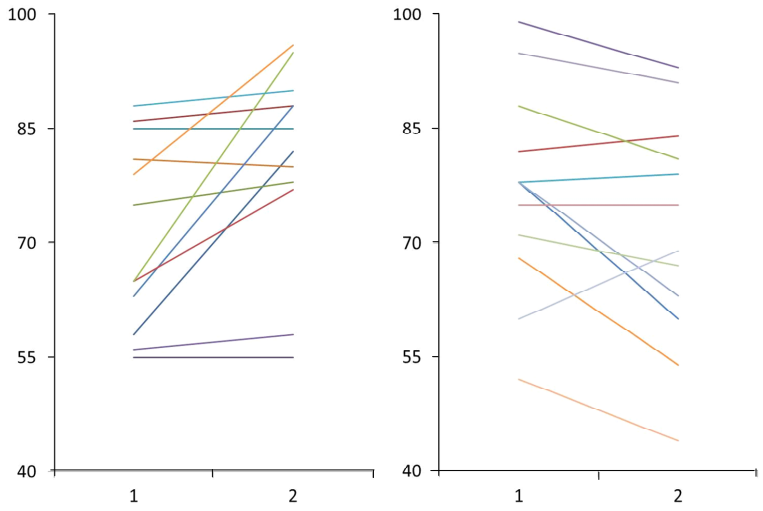

Figure 5.2 Individual changes in forced vital capacity (FVC), percentage predicted after a 12-weeks training program compared to baseline of studied sarcoidosis (A: n=12) and idiopathic pulmonary fibrosis (IPF) subjects (B: n=12).

Table 5.3 Change of pulmonary function tests (DLCO and FVC, percentage of predicted) and 6 minute walking distance (6MWD, percentage of predicted) as well as the Steep ramp test (SRT), Watt; Hand grip force (HGF, percentage predicted) of ≥10% (improvement); between -10% and 10 % (stable) and ≥ 10% deterioration) between baseline and a 12-weeks training program of the studied subjects with idiopathic or end-stage sarcoidosis-related pulmonary fibrosis.

	improvement		stable		deterioration	
DLCO, % predicted	6		11		7	
	5 Sarcoidosis	1 IPF	6 Sarcoidosis	5 IPF	1 Sarcoidosis	6 IPF
FVC, % predicted	6		14		4	
	5 Sarcoidosis	1 IPF	7 Sarcoidosis	7 IPF	0 Sarcoidosis	4 IPF
6MWD, % predicted	13		11		2	
	6 Sarcoidosis	7 IPF	6 Sarcoidosis	3 IPF	0 Sarcoidosis	2 IPF
SRT, Watt	10		12		2	
	6 Sarcoidosis	4 IPF	6 Sarcoidosis	6 IPF	0 Sarcoidosis	2 IPF
HGF, % predicted	12		9		3	
	7 Sarcoidosis	5 IPF	3 Sarcoidosis	6 IPF	2 Sarcoidosis	1 IPF

IPF = Idiopathic pulmonary fibrosis; DLCO = diffusing capacity of the lung for carbon monoxide; FVC = forced vital capacity; 6MWD = six-minute walking distance; SRT = Steep Ramp Test; HGF= hand grip force.

Patient-reported outcome instruments

Of the 15 subjects with an abnormally increased FAS score at baseline, 8 improved (4 with sarcoidosis vs. 4 with IPF), 5 remained stable and 2 deteriorated. Breathlessness did not change in either group.

Discussion

In this study, we observed that patients suffering from IPF or severe fibrotic pulmonary sarcoidosis benefited from a 12-week, supervised exercise training program. Mean 6MWD improved in both groups, and 54.2% of subjects (N=13; 7 with IPF and 6 with sarcoidosis) experienced a >10% improvement in 6MWD. All the more impressive, despite trends toward decline in mean FVC% and DLCO% (and slightly less-so for FVC%), in subjects with IPF, mean 6MWD increased. Furthermore, mean values for FVC% and DLCO% in subjects with sarcoidosis improved, although differences from baseline did not meet statistical significance.

Peripheral muscle (particularly the quadriceps) weakness is common in patients with sarcoidosis or IPF. Quadriceps force is associated with exercise limitation as well as lung function impairment in IPF patients.[34-36] Similarly, sarcoidosis patients with reduced peripheral muscle strength (particularly the quadriceps) are more fatigued and more likely to have impaired lung function, 6MWT and QOL.[14] In our study, fatigue was associated with exercise capacity (as defined by SRT), but not muscle strength (data not shown).

Cremers and colleagues found that muscle atrophy was present in 34% patients with stage IV sarcoidosis.[18] Marcellis and co-investigators observed a trend toward lower levels of the FFM index (FFM adjusted for body size) in sarcoidosis patients with reduced leg muscle strength.[14] In the present study, 41.6% of subjects had muscle atrophy at base line. The FFMI did not correlate with pulmonary function test results nor with fatigue or the 6MWD (data not shown). Chura and colleagues assessed the use of different exercise tests, including the SRT, in patients with COPD.[37] They suggested that the SRT is a reliable, practical test of leg muscle anaerobic power, even in the setting of ventilatory limitation. In our study, peak work achieved (i.e., watts generated during the SRT) improved in 42% and remained stable in 50% of subjects, thus suggesting that the exercise program delivered in pulmonary rehabilitation has the potential to preserve or improve peripheral muscle strength. Limited data suggest that patients with pulmonary fibrosis have a limited capacity for muscle remodeling after exercise training; this could result from a complex interplay of several factors, including systemic inflammation, arterial and muscular hypoxia and cachexia. In cachectic patients, strengthening exercises may activate anabolic and catabolic pathways simultaneously, thereby limiting the magnitude of the training effect.[38]

Both IPF and fibrotic sarcoidosis create burdens in patients' lives. Symptoms of dyspnea induces exercise limitation, fatigue leads to physical inactivity, and the symptoms themselves, or the thought of living with a progressive, incurable condition, creates anxiety, mood disturbance and impairs emotional well-being.[39-44] Although less well-recognized than exertional dyspnea and dry cough, fatigue or exhaustion is very common in patients with IPF. As in sarcoidosis, fatigue is a frustrating symptom for IPF patients, perhaps as frustrating as shortness of breath.[42] Like Elfferich and colleagues, we observed that fatigue was more prevalent among subjects with IPF (9/12) than those with sarcoidosis (6/12).[41]

In both sarcoidosis and IPF, exercise capacity, as measured by 6MWD, is often reduced.[14,45,46] In both conditions, ventilatory impairment is the main factor contributing to exercise limitation, although gas exchange abnormalities also contribute.[14,45,46] Recently, Marcellis and colleagues reported that fatigue and 6MWD were associated with QOL in sarcoidosis. In particular, the most affected QOL domain – physical health – showed strong associations with fatigue and exercise capacity at baseline and follow-up in their study.[43] The same is true for IPF: 6MWD is associated with health-related QOL.[46] In our study, although physical training did not improve fatigue at the group level, among the 15 subjects with significant fatigue at baseline (as defined by FAS scores), 8 (53.3%) had significant improvement in fatigue after completion of the physical training program.

Although we cannot be certain, medical treatment was unlikely to have significantly influenced results: one subject in the sarcoidosis group had discontinued

prednisone by the end of the training session. Nine subjects with sarcoidosis started therapy during the training session: seven started MTX, and two started infliximab. The beneficial effects of these medications are not expected before three months.[47] In the IPF group, the number of subjects taking prednisone at baseline and at the end of the training session was the same. Although three subjects with IPF initiated treatment with pirfenidone during the training program, two discontinued it because of side effects. The one subject who remained on pirfenidone progressed and recently underwent lung transplantation.

The findings of our study should be interpreted in the context of several limitations: first the sample size in this pilot study was small, and we did not include a control group; thus, the results should be interpreted as hypothesis-generating and used predominantly to help design larger, definitive studies. Although subjects used oxygen during training, if they used it at home, oxygen flow rates were not titrated (and oxygen was not initiated to prevent desaturation) during training sessions. Whether training would have a greater impact on improving outcomes if peripheral oxygen saturations were maintained >90% during exercise sessions is a question that merits investigation. Two retrospective studies have shown that ambulatory oxygen therapy may significantly improve 6MWT performance and dyspnea in patients with IPF.[48,49] Likewise, whether exercise training programs could or should be modified to better suit patients with IPF or fibrotic sarcoidosis is a topic in need of exploration.

In conclusion, a 12-week physical training program improved or maintained exercise capacity in patients with IPF (despite disease progression) or fibrotic sarcoidosis, and in certain subjects, other important outcomes improved. The results from this pilot study could be used to design prospective studies aimed at answering lingering questions about exercise training in patients with these progressive, incurable conditions.

References

1. Spruit MA, Thomeer MJ, Gosselink R, et al. Skeletal muscle weakness in patients with sarcoidosis and its relationship with exercise intolerance and reduced health status. Thorax 2005;60:32-38.
2. Holland A, Hill C. Physical training for interstitial lung disease. Cochrane Database Syst Rev 2008;(4): CD006322.
3. Swigris JJ, Brown KK, Make BJ, Wamboldt FS. Pulmonary rehabilitation in idiopathic pulmonary fibrosis: a call for continued investigation. Respir Med 2008;102:1675-1680.
4. Braam AW, de Haan SN, Vorselaars AD, et al. Influence of repeated maximal exercise testing on biomarkers and fatigue in sarcoidosis. Brain Behav Immun 2013;33:57-64.
5. Baughman RP, Lower EE, Gibson K. Pulmonary manifestations of sarcoidosis. Presse medicale 2012;41 (6 Pt 2):e289-302.
6. Valeyre D, Prasse A, Nunes H, Uzunhan Y, Brillet PY, Muller-Quernheim J. Sarcoidosis. Lancet 2014;383: 1155-1167.
7. Nardi A, Brillet PY, Letoumelin P, et al. Stage IV sarcoidosis: comparison of survival with the general population and causes of death. Eur Respir J 2011;38:1368-1373.
8. Patterson KC, Strek ME. Pulmonary fibrosis in sarcoidosis. Clinical features and outcomes. Ann Am Thorac Soc 2013;10:362-370.
9. Valeyre D, Nunes H, Bernaudin JF. Advanced pulmonary sarcoidosis. Curr Opin Pulm Med 2014;20: 488-495.
10. Travis WD, Costabel U, Hansell DM, et al. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 2013;188:733-748.
11. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med 2014;370:2071-2082.
12. King TE, Jr., Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med 2014;370:2083-2092.
13. Du Bois RM, Weycker D, Albera C, et al. Six-minute-walk test in idiopathic pulmonary fibrosis: test validation and minimal clinically important difference. Am J Respir Crit Care Med 2011;183:1231-1237.
14. Marcellis RG, Lenssen AF, Elfferich MD, et al. Exercise capacity, muscle strength and fatigue in sarcoidosis. Eur Respir J 2011;38:628-634.
15. Jackson RM, Gomez-Marin OW, Ramos CF, et al. Exercise limitation in IPF patients: a randomized trial of pulmonary rehabilitation. Lung 2014;192:367-376.
16. Holland AE, Hill CJ, Conron M, Munro P, McDonald CF. Short term improvement in exercise capacity and symptoms following exercise training in interstitial lung disease. Thorax 2008;63:549-554.
17. Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. Am J Respir Crit Care Med 1999;160:736-755.
18. Cremers JP, Drent M, Elfferich MD, et al. Body composition profiling in a Dutch sarcoidosis population. Sarcoidosis Vasc Diffuse Lung Dis 2013;30:289-299.
19. Lukaski HC, Bolonchuk WW, Hall CB, Siders WA. Validation of tetrapolar bioelectrical impedance method to assess human body composition. J Appl Physiol (1985) 1986;60:1327-1332.
20. Evans WJ, Morley JE, Argiles J, et al. Cachexia: a new definition. Clin Nutr 2008;27:793-799.
21. Black LF, Hyatt RE. Maximal respiratory pressures: normal values and relationship to age and sex. Am Rev Respir Dis 1969;99:696-702.
22. ATS/ERS Statement on respiratory muscle testing. Am J Respir Crit Care Med 2002;166:518-624.
23. Werle S, Goldhahn J, Drerup S, Simmen BR, Sprott H, Herren DB. Age- and gender-specific normative data of grip and pinch strength in a healthy adult Swiss population. J Hand Surg Eur Vol 2009;34:76-84.
24. Mathiowetz V, Wiemer DM, Federman SM. Grip and pinch strength: norms for 6- to 19-year-olds. Am J Occup Ther 1986;40:705-711.
25. Bohannon RW. Make tests and break tests of elbow flexor muscle strength. Physical therapy 1988;68: 193-194.
26. Meyer K, Samek L, Schwaibold M, et al. Physical responses to different modes of interval exercise in patients with chronic heart failure--application to exercise training. Eur Heart J 1996;17:1040-1047.

27. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111-117.
28. Gibbons WJ, Fruchter N, Sloan S, Levy RD. Reference values for a multiple repetition 6-minute walk test in healthy adults older than 20 years. J Cardiopulm Rehabil 2001;21:87-93.
29. Michielsen HJ, Drent M, Peros-Golubicic T, De Vries J. Fatigue is associated with quality of life in sarcoidosis patients. Chest 2006;130:989-994.
30. De Kleijn WP, De Vries J, Wijnen PA, Drent M. Minimal (clinically) important differences for the Fatigue Assessment Scale in sarcoidosis. Respir Med 2011;105:1388-1395.
31. Skevington SM, Pilaar M, Routh D, MaCleod RD. On the language of breathlessness. Psychology & health 1997;12:677-689.
32. Nici L, Donner C, Wouters E, et al. American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. Am J Respir Crit Care Med 2006;173:1390-1413.
33. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982;14:377-381.
34. Marcellis RG, Lenssen AF, de Vries GJ, et al. Is There an Added Value of Cardiopulmonary Exercise Testing in Sarcoidosis Patients? Lung 2013;191:43-52.
35. Marcellis RG, Lenssen AF, de Vries J, Drent M. Reduced muscle strength, exercise intolerance and disabling symptoms in sarcoidosis. Curr Opin Pulm Med 2013;19:524-530.
36. Nishiyama O, Taniguchi H, Kondoh Y, et al. Quadriceps weakness is related to exercise capacity in idiopathic pulmonary fibrosis. Chest 2005;127:2028-2033.
37. Chura RL, Marciniuk DD, Clemens R, Butcher SJ. Test-Retest Reliability and Physiological Responses Associated with the Steep Ramp Anaerobic Test in Patients with COPD. Pulm Med 2012;2012:653831.
38. Vogiatzis I, Simoes DC, Stratakos G, et al. Effect of pulmonary rehabilitation on muscle remodelling in cachectic patients with COPD. Eur Respir J 2010;36:301-310.
39. De Vries J, Drent M. Quality of life and health status in sarcoidosis: a review. Semin Respir Crit Care Med 2007;28:121-127.
40. Drent M, Lower EE, De Vries J. Sarcoidosis-associated fatigue. Eur Respir J 2012;40:255-263.
41. Elfferich MD, De Vries J, Drent M. Type D or 'distressed' personality in sarcoidosis and idiopathic pulmonary fibrosis. Sarcoidosis Vasc Diffuse Lung Dis 2011;28:65-71.
42. De Vries J, Kessels BL, Drent M. Quality of life of idiopathic pulmonary fibrosis patients. Eur Respir J 2001;17:954-961.
43. Marcellis RG, Lenssen AF, Drent M, De Vries J. Association between physical functions and quality of life in sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 2014;31:117-128.
44. De Vries J, Drent M. Relationship between perceived stress and sarcoidosis in a Dutch patient population. Sarcoidosis Vasc Diffuse Lung Dis 2004;21:57-63.
45. Swigris JJ, Wamboldt FS, Behr J, et al. The 6 minute walk in idiopathic pulmonary fibrosis: longitudinal changes and minimum important difference. Thorax 2010;65:173-177.
46. Verma G, Marras T, Chowdhury N, Singer L. Health-related quality of life and 6 min walk distance in patients with idiopathic pulmonary fibrosis. Can Respir J 2011;18:283-287.
47. Cremers JP, Drent M, Bast A, et al. Multinational evidence-based World Association of Sarcoidosis and Other Granulomatous Disorders recommendations for the use of methotrexate in sarcoidosis: integrating systematic literature research and expert opinion of sarcoidologists worldwide. Curr Opin Pulm Med 2013;19:545-561.
48. Visca D, Montgomery A, de Lauretis A, et al. Ambulatory oxygen in interstitial lung disease. Eur Respir J 2011;38:987-990.
49. Frank RC, Hicks S, Duck AM, Spencer L, Leonard CT, Barnett E. Ambulatory oxygen in idiopathic pulmonary fibrosis: of what benefit? Eur Respir J 2012;40:269-270.