The acute effects of resistance training on fatigue in patients with pulmonary sarcoidosis

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Abstract

Introduction: Sarcoidosis-related fatigue and skeletal muscle dysfunction are frequent symptoms in patients with sarcoidosis. Despite lacking knowledge whether high-intensity resistance training (RT) will worsen fatigue, low to moderate intensity is commonly recommended. This study aimed to investigate whether a single session of high-intensity RT will induce a larger acute increase in fatigue than a single RT session of moderate-intensity.

Methods: In this crossover study, 41 patients with pulmonary sarcoidosis (age: 53 ± 11 yr) were recruited. They randomly performed one session of high-intensity, 4 sets x 5 repetitions maximum (5RM), and one session of moderate-intensity, 2 sets x 25 RM. Fatigue was assessed with the Visual Analogue Scale (0-100 mm) before (T0), immediately after (T1) and 24 hours after (T2) each exercise session.

Results: Fatigue development from T0 to T1 was significantly lower after 5RM (– 3 ± 18 mm) than after 25RM (5 ± 15 mm), p = 0.004. No difference was seen from T0 to T2 between 5RM (0 ± 17 mm) and 25RM (6 ± 18 mm), p = 0.147.

Conclusion: Since the 5RM session did not induce a larger increase in fatigue than the 25RM session, a single session of RT thus appears feasible and safe in patients with pulmonary sarcoidosis irrespective of the RT intensity. The long-term effects of high-intensity RT on fatigue should be explored in a RT program of longer duration.

Introduction

Sarcoidosis is a multisystem granulomatous disorder affecting any organ but the lungs are affected in more than 90% of the cases [1]. Sarcoidosis-related fatigue is highly prevalent in patients with sarcoidosis, reported in up to 85% [2]. The underlying causes of fatigue remains unclear, but reported cofactors are depression and anxiety as well as reduced physical and social functioning [2, 3]. In addition, lower-limb muscle weakness is a frequently reported condition in patients with sarcoidosis [4, 5], and is related to exercise intolerance and fatigue, which in turn affect the health related quality of life negatively [3–5]. Therefore, the rationale for resistance training (RT) is strong, given its ability to counteract muscle weakness [6].

Previous studies of exercise training and fatigue in sarcoidosis have focused on endurance training or combined endurance and RT, with RT protocols consisting of low- to moderate-intensity with a medium to high number of repetitions [7–10]. The rationale to apply these protocols has been to avoid aggravation of fatigue which may occur when relatively high-intensity RT is performed [8]. However, high-intensity RT (3–5 repetition maximum, RM) has shown to be superior to low- to moderate-intensity RT (10–30 RM) in relation to improve maximal muscle strength [11]. Recent studies of other patient groups suffering from fatigue, such as breast cancer and multiple sclerosis (MS), showed that high-intensity RT programs of 12–16 weeks reduced fatigue [12, 13].

To our knowledge, no studies have explored the effects of high-intensity RT on fatigue in patients with sarcoidosis. Thus, both patients and health care professionals express reservations in relation to high-intensity RT for patients with sarcoidosis suffering from fatigue. Therefore, the main aim of this study was to investigate whether a single session of high-intensity RT will induce a larger acute increase in fatigue than a single session of moderate-intensity RT.

Methods

STUDY DESIGN AND SUBJECTS.

The study had a randomized crossover design with a convenience sample of patients with pulmonary sarcoidosis recruited from a national pulmonary rehabilitation (PR) clinic in Norway (LHL Hospital Gardermoen). Patients (> 18 years) with pulmonary sarcoidosis diagnosed in accordance with accepted guidelines [1], who attended a 4-week inpatient PR program between April 2016 and June 2017, were eligible for the study. Patients were excluded if they 1) had a concurrent and predominant diagnosis of other significant respiratory disorders (asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, or lung carcinoma); 2) unstable cardiovascular disease; and/or 3) were not able to perform the required physical tests and exercise training sessions due to co-morbidities. All patients were in a stable phase of the disease and those on medication used their standard medication. The Regional Committee for Medical and Health Research Ethics approved the study (2014/2020), and informed consent was obtained from all individual participant included in the study.

BACKGROUND VARIABLES

On the first day of the PR, information about the patient`s medical history was collected from the pulmonary physician medical report, and a set of background and baseline measures were obtained. Body mass index was calculated and lung function tests (MasterScreen BodyDiffusion RT, Germany) were performed according to international guidelines [14] and reference values [15]. Submaximal exercise capacity was assessed by the 6-min walk test (6MWT) in accordance with standard criteria [16] and predictive values was calculated [17]. Maximal muscle strength was tested twice performing the one-repetition maximum (1RM) on a leg press machine (Technogym, Italy), and the highest value was reported. Baseline sarcoidosis-related fatigue was assessed using the Fatigue Assessment Scale (FAS). FAS is validated in patients with sarcoidosis [18, 19] and consist of 10-items: five questions reflecting physical fatigue and five mental fatigue. The total score range is from 10 to 50 points where cut-off for fatigue is > 22 points. Score between 22 and 34 indicate mild-to-moderate fatigue, and score > 34 indicate severe fatigue [18, 20]. All background data and questionnaires were collected before the physical tests were performed.

RESISTANCE TRAINING PROTOCOLS

During the first week of the ordinary PR program, all patients performed the two supervised RT sessions in random order; a high-intensity session with high load/low repetitions consisting of four sets of five repetitions maximum (5RM) and a moderate-intensity session with low load/many repetitions consisting of two sets of 25 repetitions maximum (25RM). Both sessions consisted of four exercises using weight machines (Technogym): Latissimus pull down, leg press, chest press and low row. The two protocols were designed to be approximately equal in volume (repetitions x sets x load). To determine the 5RM and 25RM intensity, the patients had an introduction to all four machines, combined with a 5RM test. The intensity for the 25RM session for each machine was then calculated based in the 5RM load (5 reps x 4 sets x 5RMkg/25 reps x 2sets). The familiarization and test were performed at least two days before the first session. Both sessions had a 6 min warm-up on treadmill and rest between the sets were 2 min. Self-perceived exertion was regularly graded during the sessions using the Borg CR10 scale [21]. To avoid carry-over effects of fatigue from other exercise sessions in the PR-program, the patients were not allowed to perform strenuous exercise 48 h before and 24 h after both sessions. The rationale for the two different protocols was that 5RM is superior 25RM in relation to improving muscle strength [11], while 25RM is used in previous exercise studies in sarcoidosis and is also the protocol patients report they have been recommended by health care professionals [7, 9]. The RT sessions were supervised by a physiotherapist/project coordinator.

OUTCOME VARIABLES.

Primary outcome: To measure changes in sarcoidosis-related fatigue as an acute response after one single RT session, the Visual Analogue Scale (VAS Fatigue; VAS-F) ranging from 0 to 100 mm was used, where 0 indicated no fatigue and 100 extreme fatigue. The VAS scale has shown good reliability over 1-2 days [22] and good sensitivity for changes in patients with interstitial lung disease [23]. A change of 10 mm is well established as the minimal clinically important difference (MCID) [24]. Fatigue was recorded one minute before the RT sessions (T0), one minute after the sessions were completed (T1) and 24 h after the sessions were completed (T2). Measure point (T2) was included because patients often report the onset of fatigue on the day after an activity. The patients were asked to grade their fatigue by putting a line on a blank VAS-F scale directly at all measure points, and thereby not being exposed to any previous scores.

Secondary outcome: As an objective indicator of exertion, blood lactate was assessed in samples drawn by capillary puncture from the finger tip and was taken at T0, T1 and T2 for both sessions, and immediately analysed with a blood gas analyser (ABL 800 Flex, Radiometer).

STATISTICAL ANALYSES

Power calculation was based on a change in VAS-F of 10 mm and SD of 22 mm [24] with an alfa-value of 0.05 and power 0.8. Based on the power calculation, 40 participants needed to be included. P-values of < 0.05 were considered as statistically significant. All relevant variables were tested for normal distribution by visual inspection of histograms, Q-Q plots and test of normality. Due to the cross-over design, paired sample t-tests were used to detect statistically significant changes in fatigue from T0 to T1 and from T0 to T2, both within and between the 5RM and the 25RM session. All statistical analysis were performed using SPSS version 22 (SPSS Inc).

Results

Forty-seven of 59 patients with pulmonary sarcoidosis who attended PR during the recruitment period met the inclusion criteria (Figure 1). Four declined to participate and 43 patients were included. Two patients were excluded after one week due to relocation to other hospitals for further medical investigations, leaving 41 patients for the final analysis.

The sample was evenly divided between female and male; obese, normal to mildly impaired lung function and normal functional capacity (6MWD) (Table 1). Baseline fatigue score (FAS) showed 33 patients (80%) with mild to moderate fatigue, six (15%) had severe fatigue, and two (5%) had FAS score of 18 points.

All patients completed both RT sessions without any serious adverse events. The acute fatigue development, measured with VAS-F, from baseline (T0) to immediately after (T1), was decreased after the 5RM session compared to increased after the 25RM session, with a statistically significant difference, p = 0.004 (Table 2). Between the two sessions, no statistically significant difference in fatigue development was seen from baseline (T0) to 24 h after (T2), p = 0.147 (Table 2). Within each session, there was a statistically significant change in fatigue development after the 25RM session only, both immediately after, p = 0.038, and 24 h after, p = 0.047 (Table 2).

The intended equal volume for each of the four machines between the 5RM and 25RM session was achieved (Table 3). No statistically significant difference in lactate level at T0 or T2 between 5RM and 25RM, while 25RM showed a statistically significant higher lactate level at T1 than 5RM, $p < 0.001$. Within each session there was a statistically significant increase in lactate level from T0 to T1, $p < 0.001$ (Table 3).

Discussion

This is to our knowledge the first study examining the acute changes in sarcoidosis-related fatigue following two RT sessions with high-intensity respectively moderate-intensity with matched volume in patients with sarcoidosis. The main finding is that one session of high-intensity RT (5RM) did not induce a larger increase in fatigue than one session of moderate-intensity RT (25RM).

One of the main arguments for not prescribing high-intensity RT for patients with sarcoidosis has been the fear of aggravating fatigue [8]. This fear was not supported by our findings as there was no significantly worsening in fatigue development following the high-intensity 5RM session, neither immediately after nor 24 h after. Contrary to previous assumptions of high-intensity aggravating fatigue [8], a statistically significant change in fatigue was only seen following the moderate-intensity 25RM session with a worsening in fatigue both immediately after and 24 h after. The increase in fatigue immediately after the 25RM sessions was statistically significant higher than the 5RM session. However, the statistically significant changes both within the 25RM session, and the difference of 8 mm between the 5RM and 25RM immediately after, did not reach the MCID of 10 mm [24]. Our results showed that RT irrespective of the intensity did not aggravate fatigue in patients with sarcoidosis, which is clinically relevant for both patients and clinicians.

As the results in the current study are based on one session only, we cannot predict fatigue development as a response to high-intensity RT of longer duration in sarcoidosis. However, results from other RT studies of patients suffering from disease-related fatigue support high-intensity RT protocols. Patients with MS showed both significantly and clinically improvement in fatigue after 12 weeks of high-intensity RT [13]. A randomised controlled high-intensity RT study of breast cancer survivors [12], showed significantly improvement in fatigue after 16 weeks RT compared to the control group [12]. The mechanisms behind fatigue in cancer and MS may differ from fatigue in sarcoidosis. Anyhow, inflammation is a key mechanism of fatigue in cancer [25], and fatigue in MS and sarcoidosis are suggested to at least partially be mediated through elevated levels of pro-inflammatory cytokines [26, 27]. Because it is well known that exercise training with long enough duration and of sufficient intensity have an anti-inflammation effect in general [28], it supports exercise training as a core treatment component in patients suffering from fatigue [28].

To ensure and make the patients aware to differentiate between sarcoidosis-related fatigue and exercise-induced fatigue, that normally follows RT with loads to failure, the Borg CR10 scale was used for the latter [21]. During both sessions the patients regularly graded their self-perceived exertion on the Borg CR10 scale (data not shown). Our clinical experience is that patients with sarcoidosis-related fatigue clearly manage to distinguish between these two aspects of fatigue. This was also in accordance with findings in a previous study where patients with sarcoidosis reported a high self-perceived exertion using Borg CR10, while they reported a low sarcoidosis-related fatigue by the VAS-F scale during a high-intensity interval session [29]. In this study, measures of blood lactate concentration was used as an objective indicator of exertion, where a statistically significant increase in blood lactate immediately after was seen in both sessions. This revealed that even though the patients performed RT with high metabolic stress, with lactate levels of 6.0 (5RM) and 9.5 mmol/L (25RM), they reported a low sarcoidosis-related fatigue score of 24 and 29 mm, respectively. This support the clinical experience that the patients managed to differentiate between sarcoidosis-related fatigue and exercise-induced fatigue.

Peripheral muscle weakness have been suggested to be a contributor to both fatigue and exercise intolerance [30], makes the rationale for RT strong. Still, RT has received relatively little attention. To date

the numbers of exercise studies including RT in sarcoidosis are limited to four studies, all with a combination of endurance and resistance training [7–10]. They all showed a statistical significant improvement in fatigue after 3-months exercise training, while the MCID of 4 points improvement varied from 74.4% [7] to 33% of the patients [8, 9]. In addition, the improvements of peripheral muscle strength in the above mentioned studies did not reveal compelling results; three of the studies showed no significant improvements in hand grip strength [7, 9] or elbow flexors strength [8]. Further, the significant improvements of lower-limb muscle strength seen in the study of Marcellis et al. [8] and Naz et al. [10] might, as discussed by the authors themselves, be influenced by the endurance training which mainly concentrated on lower limb muscles (treadmill walking and cycling). We believe the use of low- to moderate-intensity protocols may explain the lack of compelling improvements in maximal muscle strength in the above mentioned sarcoidosis studies. The target loads was 8–10 repetitions of 40% calculated from an initial test [8] and 15–20 repetitions where loads were individualized according to the patient's preference or tolerance [7, 10]. As high-intensity RT (3–5RM) has shown to be more effective to improve maximal muscle strength compared to 9–11RM and 20–28RM [11], the high-intensity protocol used in this study of 5RM (86% of 1RM) might be an effective protocol to improve maximal muscle strength in patients with sarcoidosis. One study using a similar 5RM protocol showed significantly improvements in maximal muscle strength after 8 weeks in patients with COPD [31]. Although this study was not designed to measure effects on maximal muscle strength, the absence of adverse events and the non-aggravation of fatigue following our high-intensity RT protocol, might be a step towards defining the most optimal RT program for sarcoidosis patients [32].

All participants were closely controlled to follow the protocol (intensity of RM, sets and pauses) on all four machines, as a quality assurance of the results. The inpatient PR-setting was also beneficial to facilitate the patient's compliance to avoid strenuous activities 48 h before and 24 h after each session, and in turn to avoid affecting the fatigue level. Clearly, the design with only one session of 5RM and 25RM is a limitation predicting the long-term effects of high-intensity RT on fatigue.

Conclusion

Since the 5RM session did not induce a larger increase in fatigue than the 25RM session, a single session of RT thus appears feasible and safe in patients with pulmonary sarcoidosis irrespective of the RT intensity. However, the long-term effects of high-intensity RT on fatigue should be explored in a RT program of longer duration.

Declarations

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*Conflict of Interest:*The authors declare that they have no conflict of interest.

Trial registry: ClinicalTrials.gov; No.: NCT02735161

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Tables

Table 1 Patients baseline characteristics *n* = 41

Variables	Mean (SD)	*n* (%)
Age, yrs	53 ± 11	
Sex, female		21 (51)
BMI, kg/m2	30 ± 6	
FVC, % pred.	93 ± 21	
FEV1, % pred.	82 ± 22	
TLC, % pred.	93 ± 18	
DLCO, % pred.	76 ± 16	
6MWD, m	580 ± 81	
6MWD, % pred.	97 ± 17	
Leg press, 1RM, kg	171 ± 50	
Fatigue, FAS 10-50 points	29.8 ± 5.8	
Medication		
Prednisolon, patients		11 (27)
Methotrexate, patients		6 (15)

Data are presented as mean (SD) or n (%). *BMI* Body Mass Index, *DLCO % pred.* Diffusing capacity of the lung for carbon monoxide in percent of predicted, *FAS* Fatigue Assessment Scale, *FEV_1 % pred.* Forced expiratory volume in 1 s in percent of predicted, *FVC % pred.* Forced vital capacity in percent of predicted, *TLC % pred.* Total lung capacity in percent of predicted, *1RM* One repetition maximum (of leg muscle strength), *6MWD* 6-minute walk distance.

Table 2 Acute changes in fatigue within and between 5RM and 25RM, *n* = 41

	VAS-F			VAS-F from T0 to T1			VAS-F from T0 to T2		
	T0	T1	T2	Mean change	ΔGroup diff.		Mean change	ΔGroup diff.	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	*p*-value	Mean (SD)	Mean (SD)	*p*-value
5RM	27 ± 26	24 ± 23	27 ± 23	-3 ± 18			0 ± 17		
25RM	24 ± 22	29 ± 23	29 ± 21	5 ± 15*	8 ± 18	0.004	6 ± 18*	6 ± 25	0.147

All data presented as mean (SD). *Group Diff*. Group difference, *T0* Before training session, *T1* Immediately after training session, *T2* 24 h after training session, *VAS-F* Visual Analogue Scale–Fatigue 0-100 mm, *5RM* 4 sets x 5 repetitions maximum, *25RM* 2 sets x 25 repetition maximum, *$p < 0.05$.

Table 3 Exercise volumes and lactate responses $n = 41$

	5RM		25RM		
Exercise Machines	Load (kg)	Volume (reps x sets x load)	Load (kg)	Volume (reps x sets x load)	*p*-value 5RM vs 25RM
Leg press	145 ± 43	2907 ± 869	58 ± 18	2913 ± 876	0.476
Lat Machine	37 ± 11	742 ± 225	15 ± 4	741 ± 222	0.776
Chest Press	41 ± 17	817 ± 333	16 ± 7	814 ± 337	0.511
Low Row	18 ± 16	353 ± 325	7 ± 6	352 ± 318	0.778
Lactate	mmol·L		mmol·L		
T0	2.2 ± 1.0		2.0 ± 0.7		0.297
T1	6.0 ± 2.2*		9.5 ± 3.5*		<0.0001
T2	2.4 ± 1.2		2.3 ± 1.1		0.516

Data presented as mean (SD). *5RM* 4 sets x 5 repetitions maximum, *25RM* 2 sets x 25 repetition maximum, *T0* Before training session, *T1* Immediately after training session, *T2* 24 h after training session, *$p < 0.001$ from T0 - T1 within the 5RM and 25RM session.

Figures

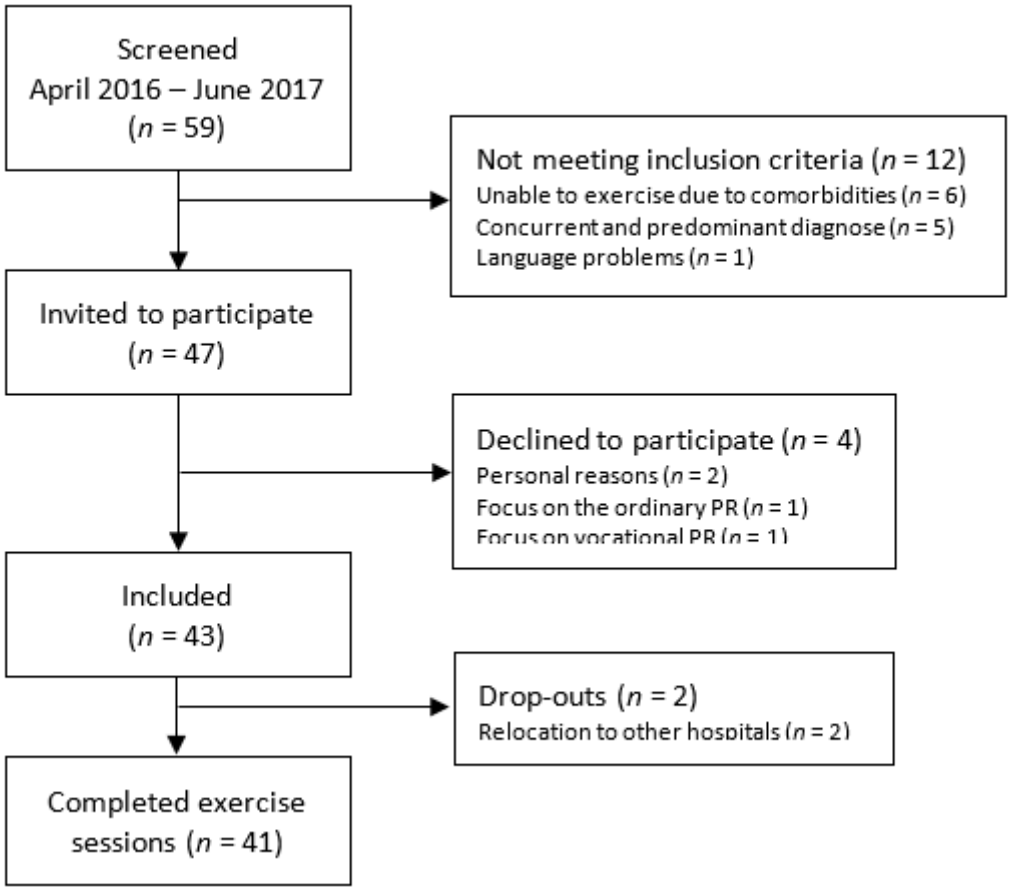

Figure 1

Flowchart of recruitment, inclusion and drop-outs. PR, Pulmonary Rehabilitation