



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

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Anita Grongstad^{1,2} , Nina Kørpke Vøllestad²,
Line Merethe Oldervoll^{3,4}, Martijn Arthur Spruit^{5,6,7}
and Anne Edvardsen¹

Abstract

Fatigue is the most prevalent symptom among patients with sarcoidosis, and skeletal muscle dysfunction is a common clinical feature, making resistance training (RT) a recommended treatment strategy. Despite lacking knowledge regarding whether high-intensity RT will aggravate fatigue, low to moderate-intensity is routinely used even if the evidence for this protocol to improve muscle strength is inconclusive. This study aimed to investigate whether one single session of high-intensity RT induces a higher increase in fatigue than one single session of moderate-intensity RT. In this randomized crossover study, 41 patients with pulmonary sarcoidosis (age: 53 ± 11 yr) were recruited. They randomly performed one single session of high-intensity RT, 4 sets \times 5 repetitions maximum (5RM), and one single session of moderate-intensity RT, 2 sets \times 25 RM. Fatigue was assessed with the Visual Analogue Scale (0–100 mm) immediately before (T0), immediately after (T1) and 24 hours after (T2) each exercise session. 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), $p = 0.147$. The high-intensity 5RM session did not induce a larger increase in fatigue than the moderate-intensity 25RM session. RT appears feasible and safe in patients with pulmonary sarcoidosis irrespective of the intensity. Thus, the long-term effects of high-intensity RT on fatigue should be explored in a RT programme of longer duration.

Keywords

Sarcoidosis, muscle strength training, resistance training, sarcoidosis-related fatigue, exercise training

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¹ LHL Hospital Gardermoen, Jessheim, Norway

² Department of Interdisciplinary Health Sciences, University of Oslo, Oslo, Norway

³ LHL Clinics, Trondheim, Norway

⁴ Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, Norwegian University of Technology and Science (NTNU), Trondheim, Norway

⁵ Department of Research & Development, CIRO, Horn, The Netherlands

⁶ Department of Respiratory Medicine, Maastricht University Medical Centre, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht, The Netherlands

⁷ REVAL–Rehabilitation Research Center, BIOMED–Biomedical Research Institute, Faculty of Rehabilitation Sciences, Hasselt University, Diepenbeek, Belgium

Corresponding author:

Anita Grongstad, LHL Hospital Gardermoen, Ragnar Strøms veg 10, 2067 NO Jessheim, Norway.

Email: anita.grongstad@lhl.no



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Introduction

Sarcoidosis is a multisystem granulomatous disorder which can affect any organ but with the lung involvement in more than 90% of cases.¹ Sarcoidosis-related fatigue is a highly prevalent symptom in patients with sarcoidosis being reported in up to 85% of the population.² Sarcoidosis-related fatigue differs from exercise-induced muscle fatigue. The latter is a normal physiological response following exercise, while sarcoidosis-related fatigue is a perceived symptom that cannot be objectively measured and where the underlying cause remains unclear.³ Reported cofactors of fatigue are depression and anxiety as well as reduced physical and social functioning.^{2,4} In addition, lower-limb muscle weakness is a frequently reported condition in patients with sarcoidosis,^{5,6} and is related to exercise intolerance and fatigue, which in turn affect health related quality of life negatively.⁴⁻⁶ Therefore, the rationale for resistance training (RT) is strong, given its ability to counteract muscle weakness.⁷

Previous studies of exercise training in patients with sarcoidosis have focused on endurance training or combined endurance training and RT.⁸⁻¹¹ The existing RT protocols in those studies have consisted of low to moderate-intensity exercises with a medium to high number of repetitions, and where the improvements in muscle strength vary. This is particularly seen in exercises for the upper limbs, where studies have reported no significant improvement⁹ or equal improvements between the exercise group and the non-exercising control group.⁸ We assume the low to moderate-intensity protocols can explain the non-significant or small improvements in these existing studies. Our assumption is supported by Marcellis et al.,⁹ who concluded that their low-intensity protocol led to the small progression of muscle strength. The rationale for applying the lower intensity RT protocols has been to avoid the aggravation of fatigue, which the authors assumed could occur by higher RT intensity.⁹

Avoidance of worsening fatigue is a concern noted in other conditions associated with fatigue as chronic fatigue syndrome (CFS).¹² Most studies exploring fatigue following exercise training have focused on endurance training only, as in the latest Cochrane reviews of exercise therapy in both interstitial lung diseases and CFS.^{13,14} However, two recent studies have demonstrated that one single session of high-intensity endurance training did not worsen fatigue more than one single session of moderate-intensity endurance training in patients with sarcoidosis¹⁵ and chronic fatigue

syndrome.¹⁶ In addition, high-intensity RT (3–5 repetition maximum, RM) has been shown to be superior to low to moderate-intensity RT (10–30 RM) in relation to improved maximal muscle strength.¹⁷ Studies with high-intensity RT over a longer duration have also reported a reduction in fatigue among other patient groups suffering from fatigue, such as people with breast cancer and multiple sclerosis (MS).^{18,19}

The impact of high-intensity RT compared to moderate-intensity RT on fatigue in patients with sarcoidosis has not been studied, and recommendations regarding RT intensity for patients with sarcoidosis are in demand.²⁰ Increased knowledge regarding whether high-intensity RT aggravates fatigue needs to be explored before introducing high-intensity RT in a programme of longer duration. Therefore, the main aim of this study was to investigate whether acute fatigue changes differently between one single session of high-intensity RT and one single session of moderate-intensity RT immediately after and 24 hours after the sessions.

Methods

This randomized crossover study was approved by the Norwegian Regional Committee for Medical and Health Research Ethics (2014/2020), and informed consent was obtained from all individual participant included in the study. The study was registered at the ClinicalTrials.gov (NCT02735161) before the first patient was included.

Study design and subjects

The participants were recruited from a sample of patients with pulmonary sarcoidosis who were already admitted to a 4-week inpatient pulmonary rehabilitation (PR) programme at a national PR clinic in Norway (LHL Hospital Gardermoen) between April 2016 and June 2017. This study had a randomized crossover design, and the two RT sessions were performed during the first week of the PR programme. To avoid, as far as possible, the patients being prevented from participating in the regular PR programme due to restrictions from the study (described in detail in the section 'Resistance training protocols'), two of the individual exercise sessions in the PR programme were replaced with the two RT sessions in this study. Eligible participants (>18 years old) were diagnosed with pulmonary sarcoidosis prior to attending the PR in accordance with accepted guidelines.¹ 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.

Background variables

On the first day of the PR programme, information about the patient's medical history was collected from the pulmonary physician's 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 guidelines²¹ and reference values.²² Submaximal exercise capacity was assessed by the 6-minute walk test (6MWT) in accordance with standard criteria.²³ Maximal muscle strength was tested twice by the patients performing one-repetition maximum (1RM) on a leg press machine (Technogym, Italy) with the highest value being reported. Baseline sarcoidosis-related fatigue was assessed using the Fatigue Assessment Scale (FAS). The FAS is validated in patients with sarcoidosis^{24,25} and consists of 10-items: 5 questions reflecting physical fatigue and 5 questions reflecting mental fatigue ('how you usually feel'). The total score range is from 10 to 50 points where the cut-off for fatigue is >22 points. Scores between 22 and 34 points indicate mild-to-moderate fatigue, while scores >34 indicate severe fatigue.^{24,26} During the first or second day of the 4-week PR programme all background data were collected, the questionnaires were completed before the physical tests were performed.

Resistance training protocols

The RT protocols consisted of one single session of high-intensity RT (high load/few repetitions with four sets of 5RM) and one single session of moderate-intensity RT (low load/many repetitions consisting of two sets of 25RM). The patients were randomized to perform either the 5RM session or the 25RM session first, and the second session with the opposite protocol was performed at least 2 days later to avoid carry-over effects. In addition, to avoid carry-over effects of fatigue from other exercise sessions in the ordinary PR-programme, restrictions were set in relation to physical activity; the patients were not allowed

to perform strenuous exercise training (endurance, RT or aerobic group sessions) from 48 hours before or until 24 hours after the RT sessions for the study. Both sessions consisted of four exercises using weight machines (Technogym): Latissimus pull down, leg press, chest press and low row. To set the target intensity for each of the four RT machines, the patients had an introduction to all four machines, combined with a direct measure of 5RM and 25RM test 2 days before the first session was performed. The 5RM and 25RM protocols were designed to be approximately equal in volume (repetitions \times sets \times load). Both sessions included a 6-minute warm-up on a treadmill and patients had the same rest time of 2 minutes between sets in both protocols. To make the patients distinguish between sarcoidosis-related fatigue (main outcome) and exercise-induced muscle fatigue the Borg CR10 was used to grade the latter.²⁷ The patients were asked during both sessions to grade their self-perceived exertion on the Borg CR10 scale in terms of 'how exhausting they felt it was to execute the RT exercise' immediately after each of the four resistance exercises. The sessions were supervised by a physiotherapist/project coordinator to ensure that the correct loading and execution was done. The rationale for the two different protocols was that 5RM is superior to 25RM in relation to improving muscle strength,¹⁷ while 25RM has been used in previous exercise studies in sarcoidosis patients and is also the protocol patients generally report they have been recommended by health care professionals.^{8,10}

Outcome variables

Primary outcome: We considered the FAS to be unsuitable for capturing acute changes in fatigue following a single exercise session, as the FAS items refer to 'how you usually feel'. Therefore, the Visual Analogue Scale-Fatigue (VAS-F) which ranges from 0 to 100 mm was used, where 0 indicates no fatigue and 100 indicates extreme fatigue. The VAS-F has shown good reliability over 1–2 days²⁸ and good sensitivity to change in patients with interstitial lung disease.²⁹ As the minimal clinically important difference (MCID) for the VAS-F for patients with sarcoidosis had not been established when this study was planned and when the power calculation performed, we chose that a change in 10 mm on the VAS-F would be considered relevant as this was well established as the MCID in patients with rheumatoid arthritis.³⁰ Fatigue was recorded immediately before the RT sessions

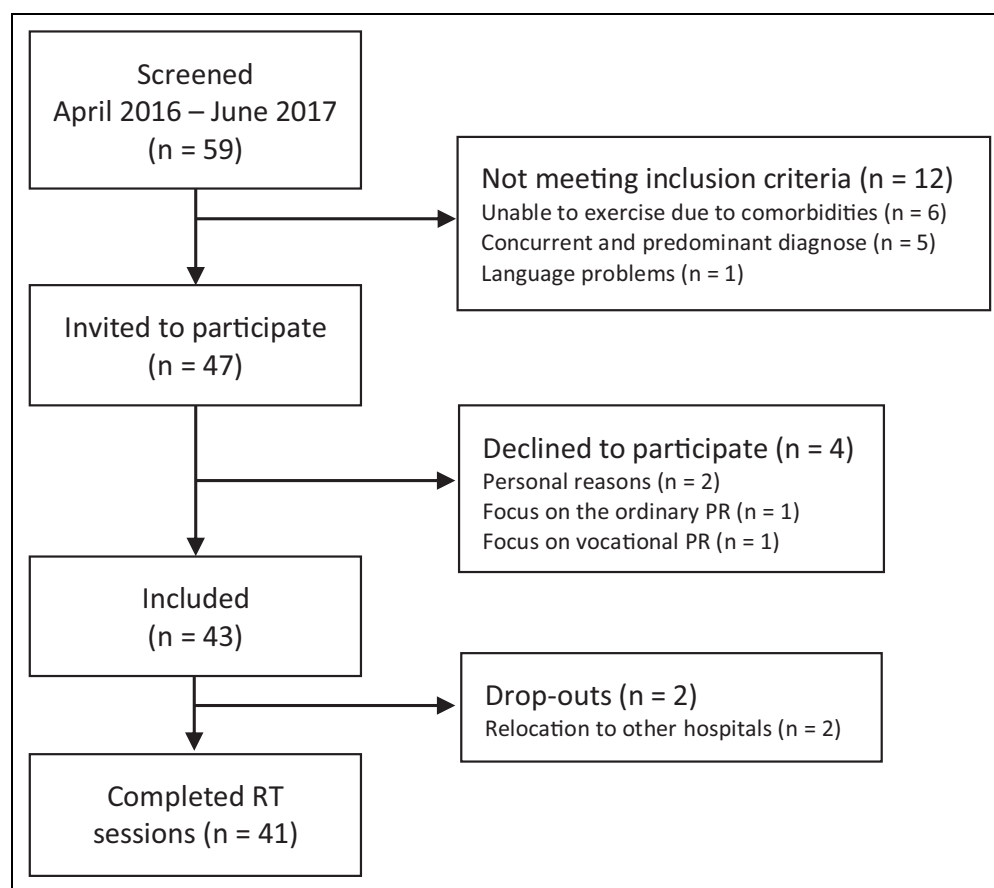


Figure 1. Flowchart of recruitment, inclusion and dropouts. PR, pulmonary rehabilitation; RT, resistance training.

(T0), immediately after the sessions were completed (T1), and again 24 hours after the sessions were completed (T2). Measure point T2 was included because patients often report a delayed onset of fatigue the day after an exertion (physically or mentally). The patients were asked to grade their sarcoidosis-related fatigue ('How would you grade your self-perceived fatigue right now?') by putting a line between 0 and 100 mm on a blank VAS-F scale directly at all the three measure points, and thereby not being exposed to their previous scores.

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

Statistical analyses

A power calculation was performed based on a change in VAS-F of 10 mm and SD of 22 mm³⁰ with an alpha-value of 0.05 and power of 0.8. Based on the

power calculation, 40 participants required to be included in the study. 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. A mixed ANOVA was conducted to assess the impact of 5RM and 25RM on the patients' scores of fatigue, across three time periods (immediately before the RT sessions, immediately after and 24 hours after the sessions). All statistical analyses were performed using SPSS version 22 (SPSS Inc.).

Results

Of the 59 patients diagnosed with pulmonary sarcoidosis who attended PR at the LHL Hospital during the recruitment period, 47 met the inclusion criteria (Figure 1). Four declined to participate and 2 were excluded due to relocation to other hospitals for further medical investigations, leaving 41 patients being included in the final analysis.

Table 1. Baseline characteristics of the patients with pulmonary sarcoidosis, $n = 41$.^a

Characteristic	Mean (SD)	n (%)
Age, yrs	53 ± 11	
Sex, female		21 (51)
BMI, kg/m ²	30 ± 6	
FVC, % pred.	93 ± 21	
FEV ₁ , % pred.	82 ± 22	
FEV ₁ /FVC	72 ± 11	
TLC, % pred.	93 ± 18	
DLCO, % pred.	76 ± 16	
6MWD, m	580 ± 81	
Leg press, 1RM, kg	171 ± 50	
Fatigue, FAS, points	30 ± 6	
Medication		
Prednisolon, patients		11 (27)
Methotrexate, patients		6 (15)

^aData are presented as mean (SD) or n (%).

BMI: Body Mass Index; FVC % pred.: Forced Vital capacity in percent of predicted; FEV₁ % pred.: forced expiratory volume in 1 second in percent of predicted; TLC % pred.: Total lung capacity in percent of predicted; DLCO % pred.: Diffusing capacity of the lung for carbon monoxide in percent of predicted; 6MWD: 6-minute walking distance; 1RM: One repetition maximum (of leg muscle strength); FAS: Fatigue Assessment Scale.

The sample happened to be evenly distributed between female and male. They were obese with normal to mildly impaired lung function and normal functional capacity (6MWD) (Table 1). Mean fatigue score on the FAS at baseline was 30 points, distributed into 33 patients (80%) with mild to moderate fatigue, 6 (15%) with severe fatigue, and 2 (5%) had FAS score of 18 points.

All patients completed both RT sessions without any adverse events. The main effect comparing fatigue development following one session of 5RM and one session of 25RM was not significant, $F = .06, p = .804$. There was no significant interaction between the two different types of RT and time, Wilks Lambda = .93, $p = .069$. Neither no effect for time, Wilks Lambda = .97, $p = .356$ with both 5RM and 25RM showing no significant changes in fatigue scores across the three measure times (Table 2). The individual variation is visualized in Figure 2.

The intended equal volume for each of the four machines between the 5RM and 25RM session was achieved (Table 3). There was no statistically significant difference in lactate level between the 5RM and the 25RM sessions at T0, while there was a statistically significant increase of the lactate level within both the 5RM and the 25RM sessions from T0 to T1,

$p < 0.001$. However, the increase was significantly higher at T1 following the 25RM session than the 5RM session, $p < 0.001$ (Table 3).

Discussion

This is to our knowledge the first study examining the changes in sarcoidosis-related fatigue as a response to two single RT sessions, with high-intensity and moderate-intensity respectively, 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.⁹ This theory was not supported by our findings as there was no significant increase in fatigue development following the high-intensity 5RM session, both immediately after the session nor 24 hours later. Our results suggest that RT, irrespective of the intensity, did not aggravate fatigue in patients with sarcoidosis, which is clinically relevant both for clinicians who are prescribing exercise programmes for patients with sarcoidosis and the patients themselves. The individual variation in fatigue development, is presented in Figure 2.

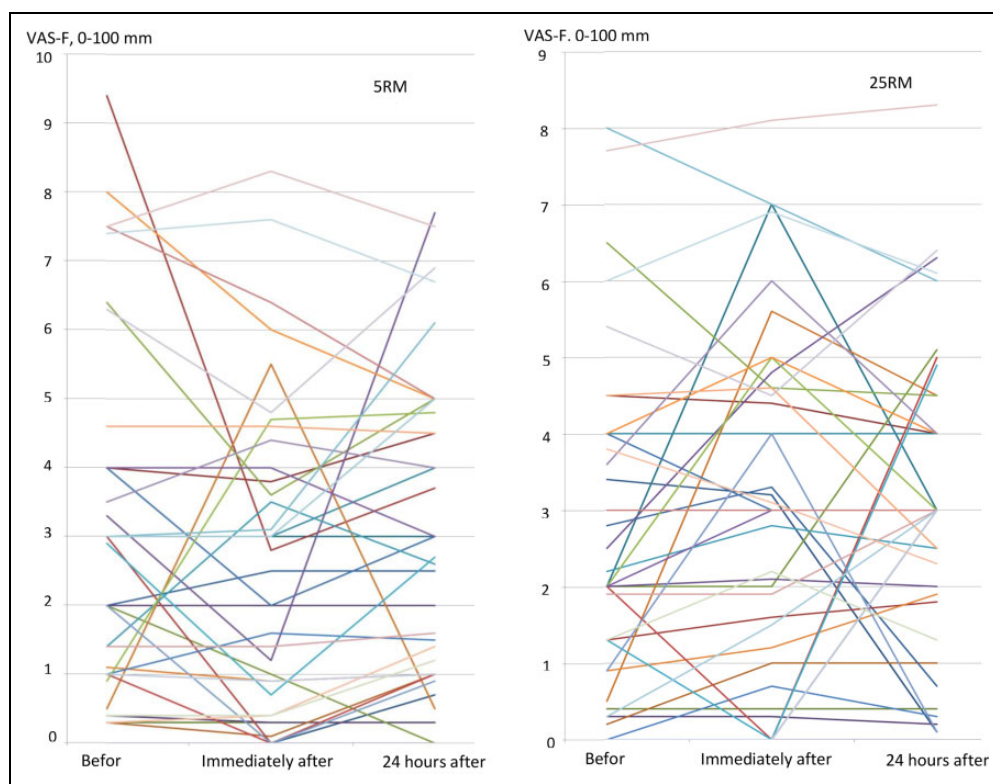
As the results in the current study are based on one session only, we cannot predict fatigue development as a response to high-intensity RT of longer duration in patients with sarcoidosis. Interestingly, our findings were supported by a recently published study by Kullberg and colleagues.³¹ They reported a significant increase in muscle strength and less fatigue in patients with sarcoidosis following high-intensity RT. Even if their sample reported a baseline fatigue score of 30 points, which was below the cut-off for fatigue of 36 points for the fatigue severity scale (FSS), they concluded that high-intensity RT seemed to be safe and well tolerated. Significant improvements were seen in both muscle strength and fatigue following 12 weeks high-intensity RT and persisted after 5 month follow-up. In addition, results from other RT studies of patients suffering from disease-related fatigue support high-intensity RT protocols. Patients with MS showed both significant and clinical improvements in fatigue after 12 weeks of high-intensity RT.¹⁹ A randomized controlled study of breast cancer survivors,¹⁸ showed significant improvement in fatigue after 16 weeks of high-intensity RT compared to the control group.¹⁸ To our knowledge no comparable

Table 2. The mean fatigue scores within and between the 5RM and the 25RM session, n = 41.^a

	VAS-F			VAS-F from T0 to T1		VAS-F from T0 to T2	
	T0 Mean (SD)	T1 Mean (SD)	T2 Mean (SD)	Mean change Mean (SD)	Δ Group diff. Mean (SD)	Mean change Mean (SD)	Δ Group diff. Mean (SD)
5RM	27 \pm 26	24 \pm 23	27 \pm 23	-3 \pm 18		0 \pm 17	
25RM	24 \pm 22	29 \pm 23	29 \pm 21	5 \pm 15	8 \pm 18	6 \pm 18	6 \pm 25

VAS-F: Visual Analogue Scale–Fatigue, 0–100 mm; T0: immediately before training session; T1: immediately after training session; T2: 24 hours after training session; Group diff.: Group difference; 5RM: 4 sets \times 5 repetitions maximum; 25RM: 2 sets \times 25 repetition maximum.

^aAll data presented as mean (SD).

**Figure 2.** Individual changes in fatigue (VAS 0-100 mm) following the 5RM and the 25RM sessions.

high-intensity RT studies of patients with CFS exist. Nevertheless, a randomized pilot trial comparing 4 weeks of low to moderate-intensity RT and graded endurance training showed that RT was equally effective as endurance training in improving fatigue severity.¹² It is possible that the mechanisms behind fatigue in cancer, CFS and MS may differ from fatigue in sarcoidosis such as these studies are not directly transferable to the sarcoidosis population. However, inflammation is a key mechanism of fatigue in cancer,³² and it has been suggested that fatigue in MS and sarcoidosis is at least partially mediated through elevated levels of pro-inflammatory cytokines.^{33,34} As it

is well known that endurance training of long enough duration and exercise training of sufficient intensity have a general anti-inflammatory effect,³⁵ this supports exercise training as a core treatment component in patients suffering from fatigue.³⁵

To ensure that the patients had an awareness of the difference between sarcoidosis-related fatigue and exercise-induced fatigue, the Borg CR10 scale was used to measure the latter.¹⁵ 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

Table 3. Exercise volume and lactate responses, n = 41.^a

Exercise machines	5RM		25RM		p Value
	Load (kg)	Volume (reps × sets × load)	Load (kg)	Volume (reps × sets × load)	
Leg press	145 ± 43	2907 ± 869	58 ± 18	2913 ± 876	0.476 ^b
Lat machine	37 ± 11	742 ± 225	15 ± 4	741 ± 222	0.776 ^b
Chest press	41 ± 17	817 ± 333	16 ± 7	814 ± 337	0.511 ^b
Low row	18 ± 16	353 ± 325	7 ± 6	352 ± 318	0.778 ^b
Lactate	mmol-L		mmol-L		
T0	2.2 ± 1.0		2.0 ± 0.7		.297
T1	6.0 ± 2.2 ^c		9.5 ± 3.5 ^c		< .0001

T0: before training session; T1: immediately after training session; T2: 24 h after training session.

^aAll data presented as mean (SD).

^bBetween volume 5RM and 25RM, $p < 0.001$.

^cFrom T0–T1 within each session, $p < 0.001$.

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 reporting a low sarcoidosis-related fatigue by the VAS-F scale during a high-intensity interval session.¹⁵ In this study, measures of blood lactate concentration were taken as an objective indicator of exertion, where a significantly increase in blood lactate was observed immediately after both sessions. This revealed that even though the patients performed RT with high metabolic stress, with lactate levels of 6.0 mmol/L (5RM) and 9.5 mmol/L (25RM), they reported a low sarcoidosis-related fatigue score of 24 mm and 29 mm on the VAS-F, respectively. This supports the clinical experience that the patients manage to differentiate between sarcoidosis-related fatigue and exercise-induced fatigue.

Peripheral muscle weakness has been suggested to be a contributor to both fatigue and exercise intolerance in patients with sarcoidosis,³⁶ making the rationale for RT strong. Still, RT for sarcoidosis patients has received relatively little attention. To date the numbers of exercise studies including RT in sarcoidosis are limited to four studies, all with protocols including a combination of both endurance and resistance training.^{8–11} The results regarding improvements in peripheral muscle strength in these studies did not reveal compelling results; three of the studies showed no significant improvements in hand grip strength^{8,10} or elbow flexors strength.⁹ Further, the significant improvements of lower-limb muscle strength seen in the study of Marcellis et al.⁹ and Naz

et al.¹¹ 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 were 8–10 repetitions of 40% calculated from an initial test⁹ and 15–20 repetitions where loads were individualized according to the patient's preference or tolerance.^{8,11} As high-intensity RT (3–5RM) has shown to be more effective in improving maximal muscle strength compared to 9–11RM and 20–28RM,¹⁷ the high-intensity protocol used in this study of 5RM (86% of 1RM) might be a more effective protocol to improve maximal muscle strength in patients with sarcoidosis. One study using a similar 5RM protocol showed significant improvements in maximal muscle strength after 8 weeks of RT in patients with COPD.³⁷ Although the current 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 programme for sarcoidosis patients.²⁰

Strengths and limitations

The sessions were supervised and all participants were closely controlled to assure they followed 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 for facilitating

the patients' compliance to avoid strenuous activities 48 hours before and 24 hours after each session, and in turn to avoid affecting the fatigue level. A possible limitation was the T2 measure time point of post-exercise VAS-F, 24 hours post exercise. This time point might have been too early to detect onset of fatigue as delayed muscle soreness tend to peak 24–72 hours post exercise and fatigue development has been reported up to 72 hours post-exercise in patients with sarcoidosis³⁸ and CFS.¹⁶ Adding a T3 time point in 48–72 hours post-exercise might have been advantageous to fully detect the fatigue development. However, as our patients were participants in a 4-week PR programme, we felt it was impractical and unethical to deny them performing exercise training both 48 hours before each session and beyond the 24 hours after each session as described in the protocol. It is worth noting that our sample of patients with a minor impaired lung function and functional capacity might be a limitation regarding generalizing of our results. However, the descriptive data of lung function, functional capacity (6MWD) and the level of fatigue (FAS) are comparable with previous studies of patients with sarcoidosis.^{5,8,9,39} At the same time, the patients investigated in this study had normal or near normal exercise capacity and fatigue. The results may therefore not be comparable in cohort of patients with more severe disease. Nevertheless, our sample included 70% of all patients with pulmonary sarcoidosis who attended LHL Hospital Gardermoen during the inclusion period, which is the only hospital offering PR for patients with pulmonary sarcoidosis in Norway. Clearly, the design with only one session of 5RM and 25RM is a limitation for predicting the long-term impact of high-intensity RT on fatigue.

Conclusion

As the 5RM session did not induce a larger increase in fatigue than the 25RM session, we conclude that a single session of RT thus appears feasible and safe in patients with pulmonary sarcoidosis irrespective of the exercise intensity. Thus, the effects of high-intensity RT on fatigue, as well as muscle strength, should be explored in a RT programme of longer duration.

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Authors' note

This work was attributed to LHL Hospital Gardermoen, Norway.

Author contributions

Conceptualization: AG, MAS and AE; methodology: AG, NKV, LMO, MAS, and AE; validation: AG, NKV, LMO, MAS, and AE; formal analysis: AG, NKV, LMO, MAS, and AE; investigation: AG; data curation: AG and AE; writing – original draft preparation: AG and AE; writing – review and editing: AG, NKV, LMO, MAS, and AE; visualization: AG; supervision: AE, NKV, LMO and MAS; project administration: AG and AE; funding acquisition: AG and AE.


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ORCID iD

Anita Grongstad  <https://orcid.org/0000-0002-0582-3431>

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