Sarcoidosis; Fatigue and Exercise

Anita Grongstad

PhD thesis

Department of Pulmonary Rehabilitation, LHL Hospital Gardermoen

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Scientific environment

This doctoral thesis was carried out in the period 2016-2019. The doctoral project was anchored at the Department of Research and Development at LHL Hospital Gardermoen, which was the venue for the interventions and where I had my office. Scientifically, the doctoral project was affiliated to the Institute of Health and Society, Faculty of Medicine at the University of Oslo. The doctoral project was funded by the Dam Foundation and LHL Hospital Gardermoen.

The dedicated team of supervisors and important contributors to this doctoral thesis has included:

Anne Edvardsen, PhD/researcher, LHL Hospital Gardermoen, Norway
Principal Supervisor

Prof. **Nina Vøllestad,** Prof. at Inst of Health and Society, University of Oslo, Norway
Co-supervisor

Prof. **Martijn A. Spruit,** Dep of Research and Education, CIRO, The Netherlands.
Co-supervisor

Prof. **Line M. Oldervoll**, Researcher, LHL Clinics, Trondheim and Department of Public Health and Nursing, Norwegian University of Technology and Science (NTNU), Trondheim, Norway.
Co-author and research associate

Anita Grongstad, Physiotherapist, MSc in Exercise Physiology/Sports Sciences, LHL Hospital Gardermoen, Norway
PhD candidate

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The first seed for the present work was sown back in 2003, when I met patients with sarcoidosis at our rehabilitation clinic for the first time. They had this diffuse symptom of fatigue and reduced exercise capacity, and as a physiotherapist I was struggling to find the balance between improving their exercise capacity without worsening the fatigue. My clinical curiosity has therefore been an important motivating factor for this ph.d.-project.

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Articles in the thesis

Paper I

Grongstad A, Vøllestad N.K., Oldervoll L.M., Spruit M.A., Edvardsen A.

The effects of High *versus* Moderate Intensity Exercise on Fatigue in Sarcoidosis.

J Clin Med. 2019 Apr 5;8(4).

Paper II

Grongstad A, Vøllestad N.K., Oldervoll L.M., Spruit M.A., Edvardsen A.

The acute effects of Resistance Training on Fatigue in patients with Pulmonary Sarcoidosis.

Manuscript submitted May 2020

Paper III

Grongstad A, Spruit M.A., Vøllestad N.K., Oldervoll L.M., Edvardsen A. **Pulmonary Rehabilitation in Patients with Pulmonary Sarcoidosis: impact on exercise capacity and fatigue.**

Respiration 2020;99(4):289-297

Update

Since this thesis was approved by the evaluation committee, revised version of Paper II have been published:

Grongstad A, Vøllestad N.K., Oldervoll L.M., Spruit M.A., Edvardsen A.

The acute impact of Resistance Training on Fatigue in patients with Pulmonary Sarcoidosis.

Chronic Respiratory Disease 2020;17:1-10.

Summary

Sarcoidosis is a rare disease under the umbrella of interstitial lung disease (ILD), affecting rather young people and where the cause is unknown, prognosis is unpredictable and treatment strategies are not yet fully known. The disease can affect all organs, with 90% of cases having lung involvement. The most common and debilitating symptom is sarcoidosis-related fatigue, often experienced as an extreme feeling of exhaustion that may persist even in the remission of sarcoidosis. Exercise training is a core component in the treatment strategy of this patient group as reduced exercise capacity is one of the first clinical features observed and reduced peripheral muscle strength is highly prevalent. Since the impact of high-intensity exercise training on sarcoidosis-related fatigue has not been explored, exercise training with moderate-intensity has commonly been advised. In addition, pulmonary rehabilitation (PR) is recommended for patients with ILD, but few studies have studied the impact of PR in the specific group of patients with sarcoidosis only. Therefore, this thesis aims to understand how exercise training with different intensities affects sarcoidosis-related fatigue. First, to investigate the impact on fatigue following one single session of high-intensity exercise training compared to one single session of moderate-intensity exercise training, for both endurance and resistance training. Thereafter, to evaluate the impact on fatigue following a 4-week inpatient interdisciplinary PR program, where the high-intensity exercise protocols were included. Three papers are included in this thesis, all including the same sample of 41 patients with pulmonary sarcoidosis.

In *Paper I*, a crossover study design was used to investigate whether one single endurance session with high-intensity interval training affected fatigue differently compared to one single session with moderate-intensity continuous training. In *Paper II*, a randomized crossover study design was used to investigate whether one single session of high-intensity resistance training with high loads/few repetitions affected fatigue differently than one single session of moderate-intensity resistance training with low loads/many repetitions. *Paper III* was a pre-post study evaluating the impact of a 4-week inpatient PR program on exercise capacity and fatigue. In addition, we examined the relationship between baseline fatigue and changes in maximal exercise capacity following the PR program.

To assess the main outcome of fatigue, the Visual Analogue Scale-Fatigue was used in Papers I and II, while the Fatigue Assessment Scale was used in Paper III. Exercise capacity in Paper III was expressed as peak oxygen uptake ($\dot{V}O_{2peak}$).

Paper I showed that one session of high-intensity interval training did not affect the development of fatigue more than one session of moderate-intensity continuous training. No statistically significant difference was seen in fatigue development between the two sessions. In *Paper II*, a statistically significant difference in fatigue development was seen immediately after the high-intensity and moderate-intensity resistance training sessions, where an increased fatigue was observed after the moderate-intensity resistance training session only. However, the fatigue development did not reach a clinically relevant level. *Paper III* demonstrated that a 4-week inpatient, interdisciplinary PR program improved maximal exercise capacity significantly. There was a statistically significant decrease in fatigue scores. A moderate relationship was observed between baseline fatigue and change in maximal exercise capacity. Interestingly, a higher level of baseline fatigue was associated with a larger improvement in exercise capacity. Nevertheless, baseline fatigue was only a partial predictor for change in maximal exercise capacity following PR.

To summarize, both high-intensity, interval training and resistance training appears to be well tolerated by patients with pulmonary sarcoidosis. Our sample was able to safely perform one single session of high-intensity endurance and resistance training without a worsening of fatigue, as the fatigue development was comparable to that observed following the moderate-intensity endurance and resistance training sessions. Further, a 4-week interdisciplinary PR program improved maximal exercise capacity and decreased fatigue in a sample of patients with sarcoidosis. However, the decreased fatigue was not clinically significant. Baseline fatigue only partly predicted change in maximal exercise capacity following PR, and surprisingly a high baseline fatigue score was related to a higher improvement in maximal exercise capacity following PR. The results from this thesis will provide physiotherapists and patients with sarcoidosis reassuring knowledge that exercise training with high-intensity is feasible, well tolerated and does not worsen/aggravate fatigue.

Abbreviations

6MWT	Six-minute walk test
6MWD	Six-minute walk distance
ATS/ERS	American Thoracic Society/European Respiratory Society
BMI	Body mass index
COPD	Chronic obstructive pulmonary disease
CPET	Cardiopulmonary exercise test
DLCO	Diffusion capacity of the lung for carbon monoxide
FAS	Fatigue assessment scale
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
HIIT	High-intensity interval training
HR	Heart rate
ILD	Interstitial lung disease
MCID	Minimal clinically important difference
MICT	Moderate intensity continuous training
PR	Pulmonary rehabilitation
PROMS	Patient-reported outcome measures
REK	Regional ethical committee
RT	Resistance training
RM	Repetition maximum
SD	Standard deviation
T0	Time point: Immediately before exercise session

T1	Time point: Immediately after exercise session
T2	Time point: 24 hours after exercise session
TLC	Total lung capacity
VAS-F	Visual analogue scale - fatigue
V̇O2peak	Peak oxygen uptake

1. Introduction

In the western world, physical exercise is considered to be part of a healthy lifestyle, by increasing aerobic capacity and muscle strength and thereby physical wellbeing (1-3). The significance of exercise training as a medical treatment and primary prevention in several chronic diseases is well documented (1, 4). Sarcoidosis is a rare disease, and is naturally not mentioned in global recommendations or reviews of the benefits of exercise training. However, the prevalence of poor exercise intolerance and reduced peripheral muscle strength in patients with sarcoidosis is substantial (5-7). This makes exercise training and pulmonary rehabilitation (PR), where exercise training is a core component, a recommended treatment strategy for this group of patients as well (8-10). Causes of sarcoidosis-related fatigue is not known and treatment strategies are still lacking (11). This makes both patients suffering from fatigue and health-care professionals uncertain regarding the provision of exercise training to improve exercise capacity, but without worsening fatigue. High-intensity exercise training has been shown to be superior to moderate-intensity exercise training regarding improvement in aerobic exercise capacity and maximal muscle strength in healthy subjects (12, 13). Due to the lack of studies of high-intensity exercise training in sarcoidosis, moderate-intensity exercise training is commonly used (14, 15). Therefore, we chose to investigate the impact on fatigue following one single session of high-intensity exercise training as a reasonable starting point, before introducing high-intensity exercise training into an exercise-based PR program of longer duration.

1.1 Sarcoidosis

1.1.1 Definition and etiology

Sarcoidosis is one of about 200 different diseases under the umbrella term interstitial lung diseases (ILD) (16). The most severe forms of ILD might lead to gradual loss of lung function, respiratory failure and eventually death, while sarcoidosis is one of the less severe forms of ILD in this regard (16). Variable degrees of inflammation are essential in all ILD, where sarcoidosis is characterized by non-caseating granulomatous (knot-like inflammations) (17). Almost any organ may be affected, but pulmonary sarcoidosis, with affection of the lungs and thoracic lymph nodes, is present in more than 90% of the cases (18). Other often reported affected organs are the eyes, skin, nervous system, heart, liver, spleen and bones

(17), and multi-organ involvement has been reported in up to 50% of patients with sarcoidosis (19). Even though sarcoidosis was first described as a disease almost 150 years ago, the etiology is still unknown (20). Today, it is assumed that its occurrence is contributed by a combination of genetic and environmental factors, where the triggering antigen varies depending on individual genetic background, ethnicity and geographic location (21). The peak age onset of sarcoidosis seems to have changed from between 20 and 40 years reported in a previous statement (17), to ages between 30 and 55 years in recent reviews (20, 22). Suggested explanations for the peak age shift has been better diagnostics, an ageing population and a change in exposure to environmental factors over the last decades (22).

1.1.2 Diagnosis

Sarcoidosis is for several reasons challenging to diagnose. Manifestation in different organs gives different symptoms that reflect different causes, in addition to the lack of sensitive and specific diagnostic tests (22). Further, the onset of sarcoidosis might be acute, with symptoms like low-grade fever and reduced general condition, or develop over time where symptoms like weight loss, dyspnea, fatigue, cough and chest pain are more common (18). Essential for the diagnosis, is a clinical observation and histologic demonstration of the characteristic non-caseating granulomas, followed by an exclusion of other diseases producing the same clinical and histologic picture (17). Due to the high prevalence of pulmonary involvement, chest radiographs, high-resolution computer tomography, bronchoscopy and tissue biopsy specimen to reveal non-caseating epithelioid granulomas are recommended to confirm the diagnosis of sarcoidosis (17, 20). The most common lung function impairments on spirometry is a reduction of volumes, particularly forced vital capacity (FVC), while the most frequent respiratory impairment on lung function tests is a reduction of diffusing capacity of the lung for carbon monoxide (DLCO) (23). However, the severity of pulmonary sarcoidosis varies from asymptomatic patients to patients with sarcoidosis that is refractory to treatment (20). In addition, a delay of 3 months is often seen from onset of symptoms until correct diagnosis of pulmonary sarcoidosis is given. This is due to the fact that pulmonary sarcoidosis mimics symptoms of alternative diagnosis, such as asthma and bronchitis with dry cough, chest discomfort and dyspnea, such as those diagnoses are often considered first (17, 24). Therefore, it is important that alternative diagnoses have been rigorously excluded, and that

the results of diagnostic evaluation and the clinic radiologic features are consistent with sarcoidosis before setting a diagnosis.

1.1.3 Epidemiology

The prevalence and incidence of sarcoidosis vary greatly. Remarkably, the highest prevalence and incidence rates are reported in ethnic groups of African Americans and northern European (22). An estimated prevalence of 0.16% with an incidence of 11.5 per 100 000 per year has been reported in a Swedish study and 0.14% with an incidence of 17.8 per 100 000 among African Americans in the United States of America (25, 26). In contrast, the prevalence amongst Caucasians in the USA was 0.05% and the incidence 8.1 per 100 000 (26), which was in line with southern European, with a French study showing a prevalence of 0.03% and incidence of 4.9 per 100 000 per year in a population of Greater Paris (27). There are currently no existing epidemiological studies of patients with sarcoidosis in Norway. An annual incidence of 790 new cases was estimated based on the incidence in Sweden from 1984 (28), translated to the Norwegian population at the same period of time (29). Due to different methods used during the last decades from population screenings, where the possibility of discovering cases by chance increases to register-based studies to date, a real estimate of the prevalence and incidence of sarcoidosis is difficult to establish.

1.1.4 Prognosis

The clinical course and prognosis of sarcoidosis largely remains difficult to predict. In a few cases the disease is silent or asymptomatic, while in approximately two-thirds of patients the disease "burns-out" with a spontaneous remission within 2 years following presentation (18). A chronic progressive course is seen in approximately 25% of affected persons (20). Sarcoidosis might also be life-threatening, where pulmonary sarcoidosis accounts for most diseases-related deaths reported in < 5% of cases (17). Who gets a spontaneous remission and who gets a chronic course of the disease is difficult to predict. However, it seems that patients with an acute onset more often have a spontaneous remission, whilst a chronic prognosis is mostly characterized by a slow progressive course with multi-organ involvement, large individual variations and almost constant lung involvement (18) .

1.1.5 Clinical features

The most common and debilitating symptom among patients with sarcoidosis is sarcoidosis-related fatigue (described in detail in chapter 1.2). Sleep disturbance, poor quality of life and depression are other well documented clinical features, where as depression is more common in patients suffering from all day fatigue compared to milder forms of fatigue (30-34). Compared to age-matched healthy subjects, patients with sarcoidosis show reduced maximal exercise capacity ($\dot{V}O_{2peak}$), reduced functional capacity (6-minute walk distance, 6MWD) and reduced peripheral maximal muscle strength (5-7). In addition, patients with pulmonary sarcoidosis report symptoms such as dry cough, chest discomfort and dyspnea (17).

1.2 Fatigue

Fatigue is a common complaint amongst patients with many different chronic diseases such as rheumatoid arthritis, chronic obstructive pulmonary disease (COPD), cancer, multiple sclerosis and Parkinson's disease among others, hence the term disease-related fatigue (35, 36). Fatigue may also be a result of medication or medical treatment, such as chemotherapy (37). There exists no formal accepted definition of fatigue, but it is described as an overwhelming sustained sense of tiredness and exhaustion, followed by a decreased capacity for physical and mental work that cannot be relieved by rest (30, 38).

Sarcoidosis-related fatigue is the most frequently and burdensome symptom in sarcoidosis, reported in up to 90% of patients (30, 32). The etiology of sarcoidosis-related fatigue is still not known, but it is suggested to be multifactorial (30). Active inflammation and systemic treatment with corticosteroids, reduced quality of life, depressive symptoms, sleep disturbance, pain, and extrapulmonary involvement are all associated with fatigue (30, 32). Fatigue in patients with sarcoidosis is extremely heterogeneous. The intensity varies from no symptoms/mild complaints to severe fatigue, and the frequency varies from all day fatigue, to intermittent fatigue that varies during the day as morning or afternoon fatigue (39, 40). The onset of fatigue is also a mystery, as patients have reported onset of fatigue both acute, and several hours after or the following day after a given physical or mental activity. Remarkably, sarcoidosis-related fatigue may persist even if objective signs of disease activity have disappeared (41). Due to its subjective nature fatigue is still ignored and underestimated amongst clinicians (36).

It is important to distinguish between sarcoidosis-related fatigue, which is a disease-related fatigue, and physiological fatigue. Sarcoidosis-related fatigue is a subjective symptom perceived by the patient, while physiological fatigue is a physiological response caused by tiredness following exercise or work, mental stress and sleep deprivation amongst other things. Physiological fatigue can be relieved by rest, as opposed to sarcoidosis-related fatigue (38).

1.2.1 Assessment of fatigue

Even though fatigue is a prominent symptom in many chronic diseases, no laboratory tests or objective markers have been identified to measure disease-related fatigue (42-44). Since fatigue is a subjective symptom, patient-reported outcome measures (PROMS), both generic and disease-specific, are commonly used to assess fatigue (44). Some unidimensional fatigue outcome measures are related to severity only, while others are served as screening tools to capture different facets of fatigue or to evaluate interventions or causality (45). In sarcoidosis, the Fatigue Assessment Scale (FAS) is the most widely used PROMS, and so far the only self-reported questionnaire that is validated for patients with sarcoidosis (46). FAS is suitable for assessing and determining the severity of fatigue, as well as to assess changes in fatigue following an intervention (47). However, FAS was not considered suitable to assess the immediate changes in fatigue related to one single exercise session, as the statements in FAS refer to "how you usually feel". For this purpose, the visual analogue scale (VAS) was considered more suitable for assessing fatigue perceived "here and now", and thereby able to capture changes in fatigue following one single exercise session. In addition, the VAS has commonly been used to assess fatigue, regardless of diagnosis, termed as visual analogue scale fatigue (VAS-F) (45). More detailed information about FAS and VAS is described in chapter 3.5.1.

1.3 Management

The management of sarcoidosis is challenging, due to the huge variability in organs manifested and the unpredictable prognosis, in addition to limited numbers of treatment studies (20). Most patients require no treatment, and to date there exist no treatments that cure sarcoidosis (20).

1.3.1 Pharmacological treatment

Pharmacological treatment aims to suppress the granulomatous inflammation and prevent the progression of persistent chronic organ damage (20). The first-line therapy is corticosteroids, either topical steroid (skin or eye lesions) or systemic therapy. Second-line therapy is introduced if patients do not respond or are not able to tolerate corticosteroids, where the most common alternative is cytotoxic drugs, such as methotrexate (20). In recent years, biological drugs have been suggested as a third-line therapy for sarcoidosis, where anti-TNF agents have shown to be effective in patients with some conditions, such as those with a FVC < 70% of predicted (48). For selected patients with end-stage disease, lung transplantation might be a treatment option (17).

1.3.2 Non-pharmacological treatment

Pulmonary rehabilitation

Pulmonary rehabilitation (PR) defined as *"... a comprehensive intervention based on a thorough patient assessment followed by patient tailored therapies that include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors"*.

PR is a core component of the management of patients with chronic pulmonary diseases, and emerging evidence support PR for patients with ILD (8, 9, 49, 50). PR in patients with ILD shows promising improvements in exercise capacity, symptoms and health-related quality of life immediately after PR, while little evidence is available regarding the long-term effects. Most PR studies are largely based on other ILDs than sarcoidosis, or where the sample of patients with sarcoidosis is limited to a small number in mixed groups of ILDs (8, 9, 49). To our knowledge, only one study has explored the effects of PR in a sample of patients with sarcoidosis only, suggesting PR to be an effective therapy in improving exercise capacity and the symptom burden of sarcoidosis (51).

Exercise training

Exercise training is described as a cornerstone in PR (50). But while PR is defined as "*a comprehensive intervention that include, but are not limited to exercise training…"*, exercise training is defined as a "*planned, structured, and repetitive bodily movement done to improve and/or maintain one or more components of physical fitness"* (52). However, the two terms are often used interchangeably, making the comparison of studies challenging. An important aim of exercise training in sarcoidosis is to improve exercise capacity and muscle strength; hopefully without worsening fatigue. But the optimal exercise program in relation to intensity, frequency and duration has not been defined for patients with sarcoidosis (10). Despite that deconditioning is a hallmark and exercise training is recommended as a treatment strategy in patients with sarcoidosis, a limited numbers of exercise training studies are available (10). To our knowledge, four exercise studies (14, 15, 53, 54) and one exercise-based PR study are published (51). All five studies showed significant improvements in exercise capacity and muscle strength, and promising improvements with reduction in fatigue (14, 15, 51, 53, 54). The overall benefits of exercise training are numerous. It can be performed almost everywhere, outside, inside, organized by a company or in voluntary groups, performed with friends, peers or alone. Exercise is almost completely without side effects, if performed as recommended. No matter where and how, the main components in an exercise program should include endurance training and resistance training. In accordance to the ATS/ERS statement, exercise training in PR should include a combination of endurance and resistance training (50).

Endurance training

The individual goals of endurance training will differ between subjects. In general, the overall goal is to improve cardiorespiratory fitness to increase daily function and physical activity, and thereby delay all-cause mortality (12, 50). The two main methods of endurance training are moderate-intensity continuous training (MICT) with a fixed or constant intensity for a certain period of time, or as repeated intervals, with a combination of periods with high-intensity interspersed with periods with lower intensity or rest periods. The latter is often termed as high-intensity interval training (HIIT) (12, 55). The recommended intensity for endurance training in PR is > 60% of maximal work rate (50), and emerging evidence supports high-intensity exercise training to be superior over moderate-intensity training to improve exercise capacity in both healthy persons and people with cardio vascular diseases

(56-58). However, the reported intensity among the current existing studies of endurance exercise training in patients with sarcoidosis have used lower intensities, varying from 50-60% of maximal work rate (14, 15, 53) to 60-80% of peak speed based on a six-minute walk test (6MWT) (51, 54). There are no existing studies exploring the impact of high-intensity interval training on fatigue in patients with sarcoidosis (8). To our knowledge, only one study with sarcoidosis patients has used an interval protocol, but the intensity was low to moderate (50% of max work rate) (14).

Resistance training

"Overload" is the main principle for gaining improvements in muscle strength, where the effectiveness is dependent on several factors such as sets, repetitions and load/intensity, amongst others, where load/intensity is the most crucial variable (59). In the absence of an optimal resistance training (RT) prescription for patients with chronic respiratory diseases, included patients with ILD and sarcoidosis, the latest statement for PR follow the guidelines from the American College of Sports Medicine (50). The recommendation for RT is 1-3 sets of 8-12 repetitions with initial loads equivalent to either 60-70% of 1RM, or loads that evoke muscular fatigue after 8-12 repetitions (49, 50). In general, growing evidence indicates that high-load training (≥ 70% of 1RM or 3-5RM) is superior to low-load training (≤ 70% of 1RM or 20-28 RM) in relation to improved maximal muscle strength in healthy subjects (13, 60).

1.3.3 Management of fatigue

There is limited evidence available for treatment strategies of sarcoidosis-related fatigue. Identification of reversible causes of fatigue is essential at an initial phase, such as depression, anxiety, sleep deprivation or metabolic disturbance (61). Pharmacological treatment with anti-TNF-α therapy and neurostimulants have been shown to improve fatigue, but due to short duration trials, small sample sizes and observational studies without placebo or control groups, no conclusions have been drawn (11, 61). Non-pharmacological treatment such as cognitive behavioral therapy could be considered, but the recommendations are based on studies treating patients with chronic fatigue syndrome and not sarcoidosis (30, 61). Exercise training has on a group level showed promising results in improvements in fatigue. However, a high number of patients do not improve fatigue levels following exercise training, indicating

that exercise training might not be beneficial in all patients with sarcoidosis-related fatigue in terms of improvements in fatigue levels (10, 11).

2. Aims

The objective of this thesis was to investigate whether one single session of high-intensity exercise training would affect sarcoidosis-related fatigue differently than one single session of moderate-intensity exercise training, both in endurance and resistance training. Thereafter to evaluate the impact of a 4-week inpatient PR program including high-intensity exercise training in terms of exercise capacity and fatigue. In addition, the aim was to explore whether there was any associations between baseline fatigue and changes in exercise capacity. The scientific issues were addressed in three papers.

Research questions

Paper I

- The main aim of this study was to investigate whether a single session of HIIT would affect sarcoidosis-related fatigue differently than a single session of MICT. The second aim was to evaluate the feasibility of a HIIT session in patients with sarcoidosis.

Paper II

- 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.

Paper III

- The main aim of this study was to examine the changes in exercise capacity, defined as V̇O2peak, and fatigue following a 4-week inpatient exercise-based PR program in patients with pulmonary sarcoidosis. The secondary aim was to examine the association between baseline fatigue and change in V̇O2peak following PR.

3. Materials and methods

3.1 Study organization, approval and registration

This project has involved several dedicated people who have contributed more or less on each part. The study protocol was prepared in collaboration with the former head of the research and development department, Morten Ryg, my main supervisor, Anne Edvardsen, and co-supervisors Martijn A. Spruit and Nina K. Vøllestad, along with myself. The project was approved by the Norwegian Regional Committee for Medical and Health Research Ethics (REK) in 2014 (2014/2020). The application for financial support was approved by the Norwegian ExtraFoundation for Health and Rehabilitation (Dam Foundation from 2019) in the fall 2015 (2016/FO76163), and the project was then registered at the ClinicalTrials.gov website (NCT02735161).

3.2 Location

The localization for all three papers was the LHL Hospital Gardermoen. The hospital offers a 4-week inpatient interdisciplinary exercise-based PR program, where the patients attending our hospital have to be referred by their general practitioner or pulmonary physician. The program consists of a standard activity plan with educational sessions and group exercise sessions (Appendix I), where seven different health-care disciplines are represented. All patients receive an individually tailored exercise program including resistance- and endurance training as prescribed by a physiotherapist at baseline. Additional individual appointments with relevant health-care professional are given based on initial assessments, the referral physician's requests and the patients' own aims for the PR. The LHL Hospital Gardermoen receives patients from all Norwegian regions, and the annual number of patients admitted to PR is about 1,400 patients (> 18 years old) where the majority have COPD (about 65%). The LHL Hospital Gardermoen is the only hospital in Norway offering a customized PR program for patients with pulmonary sarcoidosis. Statistics up to 2016 showed that the annual number of sarcoidosis patients attending PR at the LHL Hospital was approximately 30 patients.

3.3 Participants

Inclusion criteria were patients (>18 years old) with pulmonary sarcoidosis. They had to be in a stable phase of the disease, and those on medication continued using their standard medication (steroids and methotrexate). Exclusion criteria were 1) had a concurrent and predominant diagnosis of another significant respiratory disorder (asthma, COPD, cystic fibrosis, or lung carcinoma); 2) had unstable cardiovascular disease; 3) were not able to perform the required physical tests and exercise training sessions because of co-morbidities.

From a population of 59 eligible patients with pulmonary sarcoidosis attending the LHL Hospital Gardermoen between April 2016 and June 2017, 12 did not meet the inclusion criteria and four declined to participate in the study due to personal reasons (*n* = 2), focus on ordinary PR (n = 1) or vocational PR (*n* = 1). Forty-three patients were included, two dropped out due to relocation to other hospitals for further medical investigations, leaving 41 patients completing the 4-week PR program. The diagnosis of pulmonary sarcoidosis was confirmed before attending PR in accordance with accepted guidelines (17). The sample of 41 participants was included in all the three papers, where characteristics are presented in Table 1.

Table 1: Characteristics of the sample, *n* = 41

Characteristic	Mean ± SD	*n* (%)
Age, years	53 ± 11	
Gender, female		21 (51)
Time since diagnosis, years	8 ± 10	
Sarcoidosis in other organs		
Eye		3 (7)
Liver		2 (5)
Skin		1 (2)
Neurologic		1 (2)
Multiorgan		1 (2)
Comorbidities		
Hypertension		3 (7)
Type II diabetes		2 (5)
Asthma		2 (5)
Atrial fibrillation		2 (5)
Depression		1 (2)
Polyneuropathy		1 (2)
Chronic pancreatitis		1 (2)
FVC, % pred.	93 ± 21	
FEV_1, % pred.	82 ± 22	
TLC, % pred.	93 ± 18	
DLCO, % pred.	76 ± 16	
Fatigue, FAS 10-50 points	30 ± 6	
< 22		2 (5)
22-34		33 (80)
>34		6 (15)

Medication	
Prednisolon	11 (27)
Methotrexate	6 (15)

Data presented as mean (SD) or *n* (%). FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 sec; TLC: total lung capacity; DLCO: diffusion capacity of the lung for carbon monoxide; FAS: fatigue assessment scale; < 22: no fatigue, 22-34: mild to moderate fatigue, > 34: severe fatigue.

3.4 Design

All patients included in the study were referred to PR, and the impact on exercise capacity and fatigue after the 4-week PR program is presented in Paper III. In addition, we wanted to investigate the impact of high-intensity versus moderate-intensity exercise training on fatigue which is presented in Papers I and II. As our sample primarily included participants in the ordinary PR program, the interventions in our project were organized to avoid intervening too much from the patients' primary PR program. Therefore, the four different exercise sessions in Paper I and Paper II were performed within the first two weeks, and the sessions were carefully scheduled and adjusted to compliment the regular PR program (Figure 1).

Paper I was a crossover study to compare fatigue development between two endurance sessions with different intensities; one single session of HIIT and one session of MICT. Fatigue was assessed using the VAS-F. Baseline fatigue was assessed immediately before each session, and change in fatigue was calculated from the baseline score in relation to both fatigue score assessment immediately after the exercise session and 24 hours later. The patients performed the HIIT session in the first week, as this protocol was a part of their personally customized exercise program, and it was therefore important to introduce it to them as early as possible. The MICT was performed within the second week (Figure 1). To avoid influence of daily fluctuation of fatigue, the HIIT and MICT sessions were performed at the same time of the day, either in the morning (between 8:00am-11:30am), or in the afternoon (between 13:00pm-17:00pm), with half of the subjects in each group. The sessions and assessments of fatigue were supervised and administered by me.

Paper II was a randomized crossover study to compare fatigue development between two RT sessions of different intensity/load. The patients were randomized by a lottery, whether to perform the first RT session of high-intensity (5RM) or moderate-intensity (25RM) (Figure 1). Both RT sessions were performed during the first week and at the same time of the day. The protocol of the three fatigue assessments (VAS-F) described in Paper I was also used in

Paper II. The RT sessions in Paper II were performed at different times of the day compared to the endurance sessions in Paper I. If the endurance sessions (Paper I) were performed before lunchtime, the resistance sessions (Paper II) were performed after lunchtime, and vice versa. The RT sessions and assessments of fatigue were supervised and administered by me.

Paper III had a pre-post design. Fatigue was assessed using the FAS, and all participants completed the FAS on the first day and the last day of the PR program. Exercise capacity, defined as peak oxygen uptake ($\dot{V}O_{2peak}$), was measured by a cardiopulmonary exercise test (CPET) and performed on the first or second day of the PR program and within the last days of the 4-week PR program (Figure 1). The pre and post CPET was scheduled to be performed at the same time of the day to avoid daily fluctuations of fatigue influencing the results. The CPETs were administered by experienced technicians.

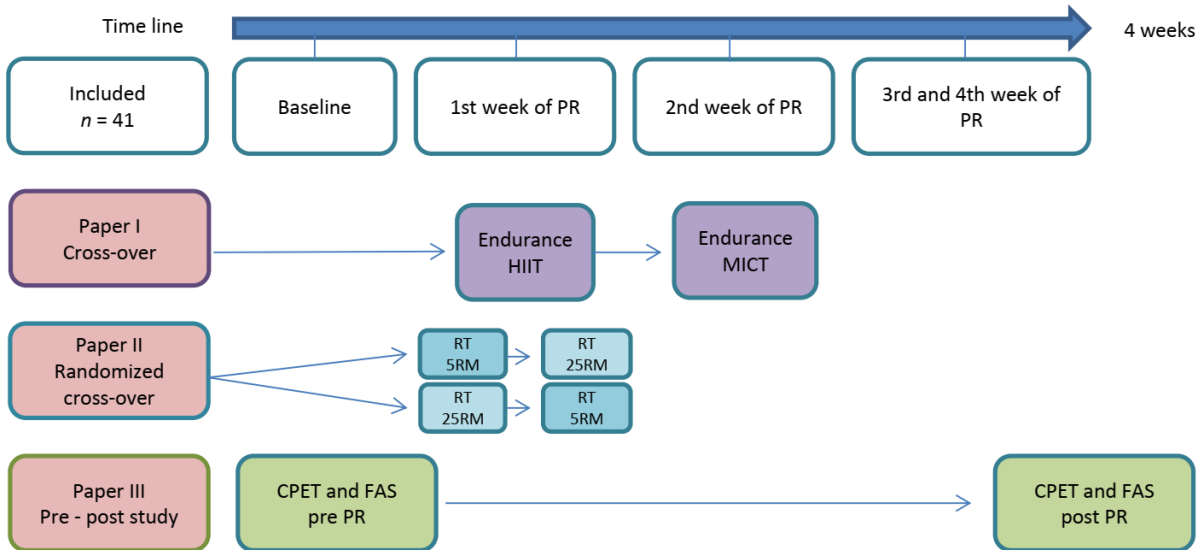


Figure 1. An overview of the timeline of interventions during the 4-weeks inpatient PR program.

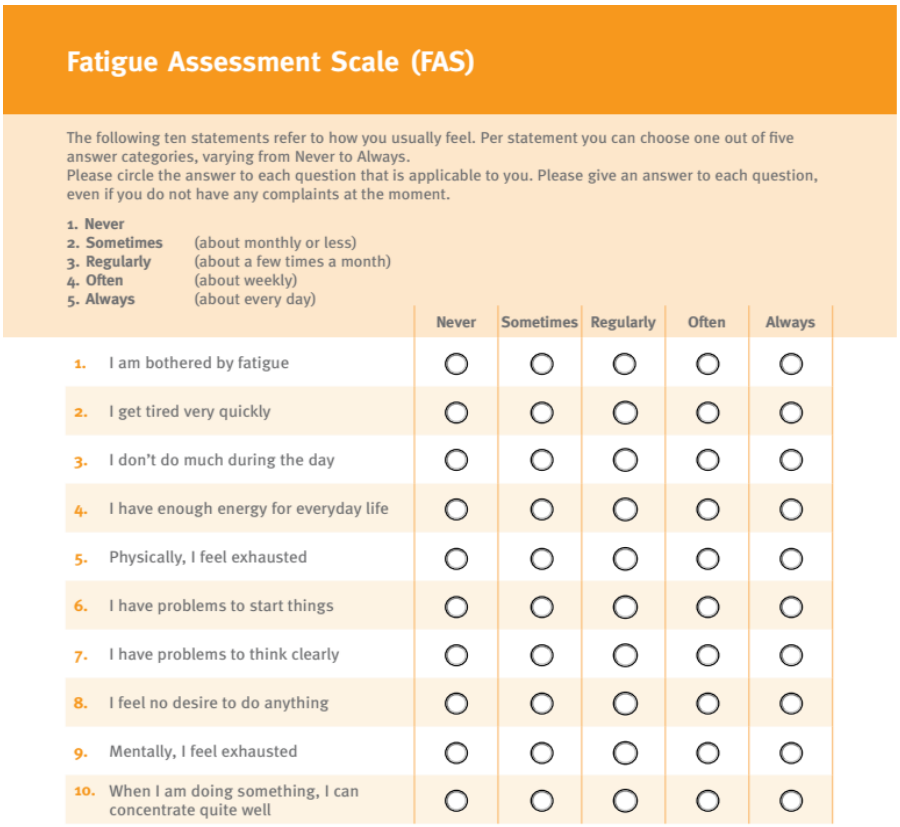
3.5 Outcome measures and assessment tools

3.5.1 Assessment of fatigue

Fatigue assessment scale (FAS)

The FAS was used as a background measure of fatigue in all the three papers, and as a primary outcome measure in Paper III. The patients completed the FAS on the first and last days of PR. FAS is the most common and widely used validated tool to assess fatigue in

patients with sarcoidosis (46, 62). Although the FAS includes 10 items divided into two aspects of fatigue reflecting physical and mental fatigue, it is considered as a unidimensional scale. The FAS with the 10 items and the five-point Likert response scale is shown in Figure 2.



Fatigue Assessment Scale (FAS)

The following ten statements refer to how you usually feel. Per statement you can choose one out of five answer categories, varying from Never to Always.
Please circle the answer to each question that is applicable to you. Please give an answer to each question, even if you do not have any complaints at the moment.

1. **Never**
2. **Sometimes** (about monthly or less)
3. **Regularly** (about a few times a month)
4. **Often** (about weekly)
5. **Always** (about every day)

	Never	Sometimes	Regularly	Often	Always
1. I am bothered by fatigue	○	○	○	○	○
2. I get tired very quickly	○	○	○	○	○
3. I don't do much during the day	○	○	○	○	○
4. I have enough energy for everyday life	○	○	○	○	○
5. Physically, I feel exhausted	○	○	○	○	○
6. I have problems to start things	○	○	○	○	○
7. I have problems to think clearly	○	○	○	○	○
8. I feel no desire to do anything	○	○	○	○	○
9. Mentally, I feel exhausted	○	○	○	○	○
10. When I am doing something, I can concentrate quite well	○	○	○	○	○

Figure 2. Fatigue Assessment Scale

The score range is 10 to 50 points, where the cut-off for fatigue is > 21 points. FAS scores may also be divided into three groups: 10 to 21 as no fatigue, 22 to 34 as mild to moderate fatigued, and 35 to 50 as severely fatigued (63). A change of four points or more indicates a clinically meaningful change in fatigue (47). The Norwegian version of FAS, developed by the ILD care foundation (www.ildcare.nl) was used (Appendix II).

Visual analogue scale – fatigue (VAS-F)

In Paper I and Paper II, the aim was to assess the changes in fatigue following one single session of exercise training by capturing the intensity of fatigue at a single point. For this

purpose the VAS-F with a measuring unit 0-100 mm was used (0 = no fatigue and 100 = extreme fatigue) (Appendix III). The patients were asked to mark a line across the VAS-F line to describe their "here and now" perceived fatigue. Each time it was pointed out that it was the sarcoidosis-related fatigue they were to grade. Assessment points were immediately before each session (T0), immediately after each session (T1) and 24 hours after the session (T2). The patients received a new VAS-F scale at every measure point, and were therefore unable to see their previous fatigue scores.

The argument for including a measure point 24 hours after the sessions was primarily based on feedback from patients reporting the onset of fatigue the day after an activity. In addition, two other studies exploring development of fatigue in relation to exercise assessed fatigue scores both 24 hours post-exercise and several more days post-exercise (64, 65). Due to practical reasons, 24 hours post-exercise was chosen as the last measure point of fatigue in this project. This was to avoid too many restrictions regarding participation in exercise groups in the ordinary PR program. When planning this project, no studies had reported the minimal clinically important difference (MCID) of VAS-F in patients with sarcoidosis. Therefore, the MCID of 10 mm was used which has been established in patients with rheumatoid arthritis (66).

3.5.2 Assessment of exercise capacity

Exercise capacity was expressed as peak oxygen uptake ($\dot{V}O_{2peak}$), defined as the highest level of oxygen uptake that was measured during a CPET. The CPET was performed on the first or second day and the last day of the PR program.

The CPET is considered as the gold standard in providing an objective measure of exercise capacity (67). This is relevant in patients with pulmonary sarcoidosis where lung function tests often are normal and pulmonary gas exchange problems are not obvious at rest, but where gas exchange impairment and exercise limitations most often are discovered during maximal exercise tests (68, 69). The usefulness of a CPET was also demonstrated in our study, where two patients were excluded from the study and relocated for further medical investigations due to cardiac abnormalities during the CPET at baseline. A CPET is, in addition to be an objective and accurate measure of exercise capacity, becoming more widespread for evaluating the response to exercise-based rehabilitation in pulmonary and

cardiac diseases (67). Nevertheless, changes in $\dot{V}O_{2peak}$ has, to our knowledge, not been reported as an outcome measure in previous studies of patients with sarcoidosis.
The CPETs were performed on a treadmill under supervision of experienced technicians (Ganshorn Schiller CS-200 Switzerland /Vyntus CPX, Germany). The CPET protocol used at the LHL Hospital Gardermoen is a stepwise incremental test until exhaustion based on a modified Bruce protocol (70). The protocol starts with a 3 minutes rest phase in standing position. To optimize the test for each patient, there are four different levels where the walking speed starts at 1.2 km/hour, 2.4 km/hour, 3.6 km/hour or 4.8 km/hour. The first step of the chosen level is used as the 2 minutes warm-up. Then the speed increases every two minutes by 0.6 km/hour up to 5.4 km/hour. Thereafter the elevation is increased by 2% inclination every two minutes, starts at 4% and ends at a maximal of 8%. The last step is a further increase of speed of 0.6 km/hour every two minutes until test termination. The protocol ends with a 5 minutes recovery phase.

The patients were continuously monitored with a 12-lead electrocardiography (Schiller CS-200, Switzerland/Custo Med GmbH, Germany). Peak oxygen uptake ($\dot{V}O_{2peak}$, $mL \cdot kg^{-1} \cdot min^{-1}$), minute ventilation ($\dot{V}E$), breathing frequency (BF), oxygen pulse (O_2/HR) and respiratory exchange ratio (RER) were measured by breath-by-breath basis and averaged over 30 second intervals. Gas calibration was performed daily and volume calibration was performed before each test. Biological verification of the CPET-equipment were performed by protocol every 3rd month. $\dot{V}O_{2peak}$ was defined as the highest level that could be performed for a minimum of 30 seconds. Norwegian reference values for CPET were applied (71). Blood pressure (Tango M2, SunTech Medical, USA) was monitored at rest, every 2nd minute during the test and during the recovery phase. Oxygen saturation (SpO2) and heart rate (HR) were recorded (Model 3150 oximeter, NONIN Medical, USA) before test start, at the end of each two minute step and upon termination. Concurrently perceived exertion termed as breathlessness were assessed using the Borg CR10 Scale (72).

One of the participants during the CPET. Private photo with permission.

3.5.3 Other measures

Lung function testing

All lung function measurements were performed the first or second day of PR and were carried out by specialized personnel in accordance to international guidelines (73). Forced vital capacity (FVC), forced expiratory volume in 1 sec (FEV_1) and diffusion capacity of the lung for carbon monoxide (DLCO) were measured by pulmonary function equipment (Jaeger, MasterScreen PFT, Germany). Bodypletysmography was used to measure total lung capacity (TLC) (MasterScreen BodyDiff, CareFusion, Höchberg, Germany). Reference values were applied from the European Coal and Steel Community (74). The lung function equipment was calibrated daily and biological controls were performed monthly.

Functional capacity

The six-minute walk test (6MWT) was used to assess functional capacity. 6MWT is the most commonly used test of functional capacity in exercise studies of patients with sarcoidosis (14, 15, 51, 53, 54). The primary outcome from a 6MWT is the six-minute walked distance (6MWD). The 6MWT is a standardized test for all patients attending PR at our hospital and was administered by nurses who were specially trained in performing this test. The 6MWT was performed in accordance with standard criteria with two tests performed at baseline and the best distance reported, and again after 4 weeks of PR (75).

Blood lactate

Blood lactate by capillary puncture on a fingertip was used as an objective measure of physical exertion. Measurements were taken immediately before, immediately after and 24 hours after each of the exercise sessions in Papers I and II and CPETs, and immediately analyzed with a blood gas analyzer (ABL 800 Flex, Radiometer, Denmark).

Heart rate

Heart rate was monitored continuously during the endurance exercise sessions in Paper I using a sport watch (Polar V800, Polar Electro, Kempele, Finland).

Perceived breathlessness

The Norwegian version of the Borg CR10 scale was used to assess the subjective perception of breathlessness in relation to exercise intensity (72, 76). In Paper I, breathlessness was reported every minute during the HIIT session and every 3rd minute during the MICT session. The Borg CR10 was also used during the CPETs in Paper III as described in section 3.5.2.

3.6 Exercise sessions

In Papers I and II we wanted to investigate whether different exercise intensities would influence fatigue development differently. As the intensity was different, we aimed to equate other factors that could possibly influence fatigue development.

In Paper I, equal energy expenditure (kcal) was used to equate the HIIT and MICT sessions, estimated by a Polar V800 sport watch. The Polar V800 sport watch has shown to be the most accurate sport watch for estimating energy expenditure during aerobic activities in healthy individuals (77). The Polar V800 "Smart calories" function was used to estimate energy expenditure based on the following individual parameters: gender, date of birth, bodyweight, height, HR_{peak}, resting HR, $\dot{V}O2peak$, and a grading of how hard/often they usually exercise (hours per week). Values from baseline CPET and baseline procedure measures at the hospital were used for bodyweight, height, HR_{peak}, resting HR and $\dot{V}O2peak$. The individual kcal

expenditure after completing the HIIT was noted, and then the MICT session lasted until the patient had consumed the same amount of individual kcal as at the HIIT session.
The warm-up period was included in both sessions. The intensity of the MICT sessions of 70% of HR_{max}, was based on a combination of the intensity from previous exercise studies in sarcoidosis of 50-60% of max work rate/speed (14, 15, 54), and the American College of Sports Medicine defining moderate intensity as 64-76% of HR_{max} (12). The HIIT protocol of 4 intervals of 3 minutes was adopted and modified from previous studies of HIIT in patients with cardiovascular diseases of 85-95% of HR_{max} (57, 78, 79). The HIIT protocol of 4 x 3 minutes in Paper I has regularly been used at the LHL Hospital for years.

In Paper II, a familiarization combined with a 5RM and 25RM test was performed on all the four exercise machines in advance. Then the sessions were approximately equated by volume. The volume was calculated by multiplying the loads (kg) x sets x repetitions. The four RT exercise machines (leg press, chest press, latissimus pull down and low row) and the rest period of 2 minutes between each set was similar for the 5RM and the 25RM session. The 5RM and 25RM protocols were adopted and modified from diverse studies and clinical practice. A systematic review and meta-analysis of high-load and low-load RT, described 3-8RM as "high load" and 20-28RM as "low load" (60). In addition, the 25RM was based on two studies of patients with sarcoidosis which used protocols of 15-20 repetitions (14, 53), which was in accordance with the load/number of repetitions patients have reported being advised to follow by health-care professionals. The 5RM protocol was adopted from studies of patients with arterial disease and healthy men (13, 80), and years of clinical experience from our clinic.

3.7 Statistical analyses

A sample size calculation was performed for Papers I and II, and was based on the primary outcome of a change in VAS-F of 10 mm, assuming a standard deviation (SD) of 22 mm. With a power of 0.8 and an alpha-level set to 0.05, a sample size of 40 patients was required. Paper III was an explorative pre-post study, and no sample size calculations were performed. The data analyses were performed using IBM Statistic version 22 (SPSS Inc, USA), were continuous variables were reported as mean ± SD. Number (%) was used to describe

frequencies. Normal distribution of relevant variables was evaluated by Shapiro-Wilk test and by visual inspection of histograms and Q-Q plots.

Paper I-III: Descriptive statistics were used to characterize the study population.

Paper I-II: A paired sample t-test was used to compare differences in fatigue development (VAS-F) between two exercise sessions of different intensity in these two crossover trials.

Paper III: With a pre-post design without any control group, a paired sample t-test was used to compare the changes in fatigue (FAS) and exercise capacity ($\dot{V}O_{2peak}$) following a 4-week PR program. To examine potential predictors for change in $\dot{V}O_{2peak}$ after PR, bivariate and multivariate linear regression analyses were used. Investigated variables at baseline were age, sex, weight, height, FVC, FEV_1, TLC, DLCO, sarcoidosis in more than one organ, comorbidities, baseline $\dot{V}O_{2peak}$, baseline 6MWD and baseline fatigue. Variables were included in the multivariate analysis if p-value was <0.200 except for age and sex, and a backward regression model was used.

3.8 Ethical considerations

The study protocol was approved by the Norwegian Regional Committee for Medical and Health Research Ethics (2014/2020/REK), and the Declaration of Helsinki was followed. This study did not involve any potentially dangerous elements, only minor ethical issues which were two-sided. First, exposing patients who are initially fatigued to perform multiple tests and questionnaires in addition to the regular PR program was considered. And on the other hand, to put restrictions on exercise training on patients who finally had the opportunity and available facilities to exercise 24/7 for four weeks. We tried to preserve the first issue by replacing the patients individual exercise sessions with the exercise sessions in this study, and the second issue by performing all exercise sessions needed for Papers I and II within the first two weeks, so they were "free" to exercise as much as they wanted in the last weeks.

4. Summary of results

4.1 Paper I

The aim of this study was to investigate whether one single session of HIIT of ≥ 85% of HR_{max} would affect fatigue differently from one single session of moderate-intensity

continuous training (MICT) of 70% of HR_{max}, and to evaluate the feasibility of the HIIT session in patients with sarcoidosis.

Assessment of fatigue by the VAS-F 0-100 mm was done immediately before, immediately after, and 24 hours after the exercise sessions, where both calculations of change were based from the assessment done immediately before.

One of the participants performing the HIIT session.
Private photo with permission.

Fatigue development revealed that one single session of HIIT did not worsen fatigue more than one single session of MICT. The mean change in fatigue score from immediately before to immediately after the HIIT session was 3.6 ± 13.5 mm, compared to 1.4 ± 13.5 mm following the MICT session (p = 0.326). The mean change in fatigue score from immediately before to 24 hours after the session was 8.2 ± 17.0 mm following the HIIT session compared to 2.1 ± 17.1 mm following the MICT session (p = 0.106). The individual variations in fatigue development following the HIIT and the MICT sessions are shown in Figure 3.

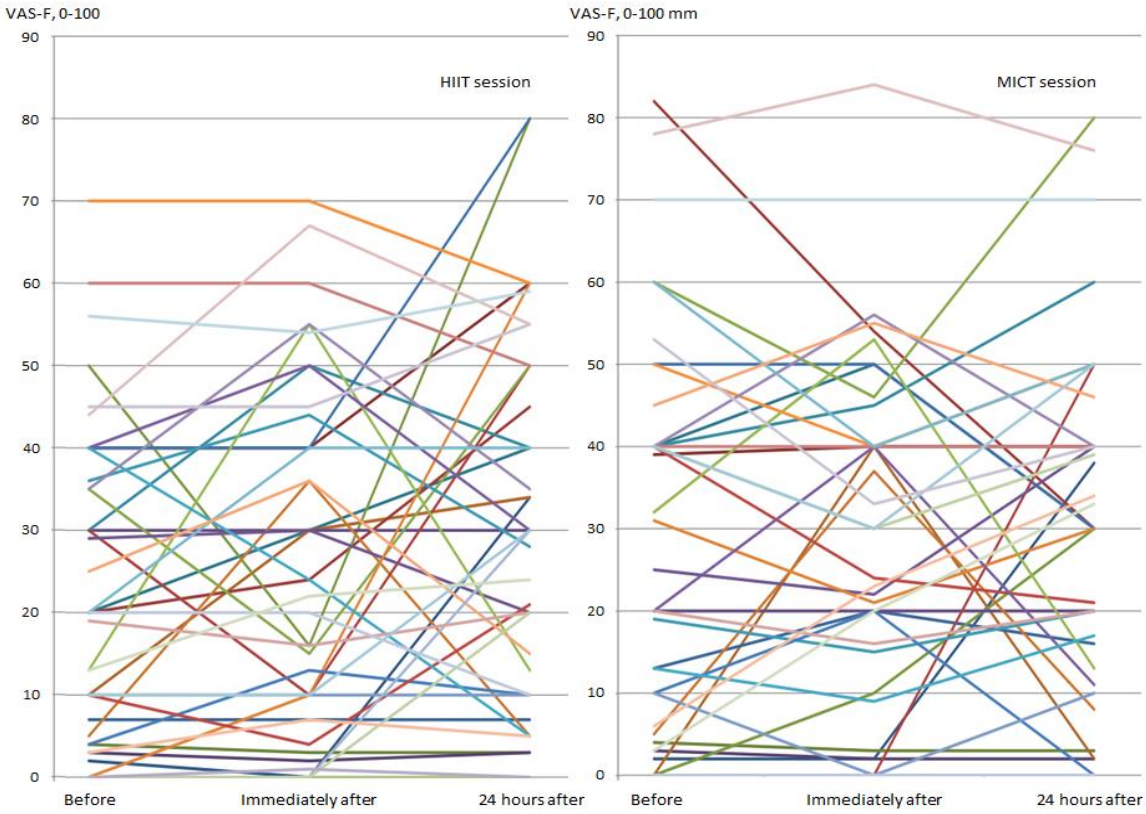


Figure 3. The individual variation in fatigue development scores following the HIIT and the MICT sessions.

Evaluation of the feasibility of the HIIT session showed that all 41 patients were able to complete the session. The mean heart rate was 90% of HR_{max} and mean Borg CR10 score of breathlessness was 5.8. The target intensity of 85% of HR_{max} was reached by 33 of the patients (80%), and 40 out of 41 patients (98%) graded their perceived breathlessness to be ≥ 5 on the Borg CR10 scale. Only one patient did not reach the target intensity of neither heart rate nor Borg CR10 score.

4.2 Paper II

The aim of this study was to investigate whether one single session of high-intensity resistance training with high loads/low number of repetitions (5RM) would affect fatigue differently than one single session of moderate-intensity resistance training with low loads/high number of repetitions (25RM).

One of the participants performing RT on chest press. Private photo with permission.

Assessments of fatigue and calculations of changes in fatigue were made using the same procedure as in Paper I.

The main finding was that one single session with 5RM did not induce more fatigue than one single session with 25RM. Actually, there was statistically significant difference in favor of 5RM immediately after the sessions, showing a decrease in fatigue of 3 ± 18 mm following the 5RM session, compared to an increase in fatigue of 5 ± 15 mm following the 25RM session (p = 0.004). No statistically significant difference in mean change in fatigue between 25RM and 5RM was sees 24 hours after the sessions. The individual variation in fatigue development following the 5RM and the 25RM sessions are presented in Figure 4.

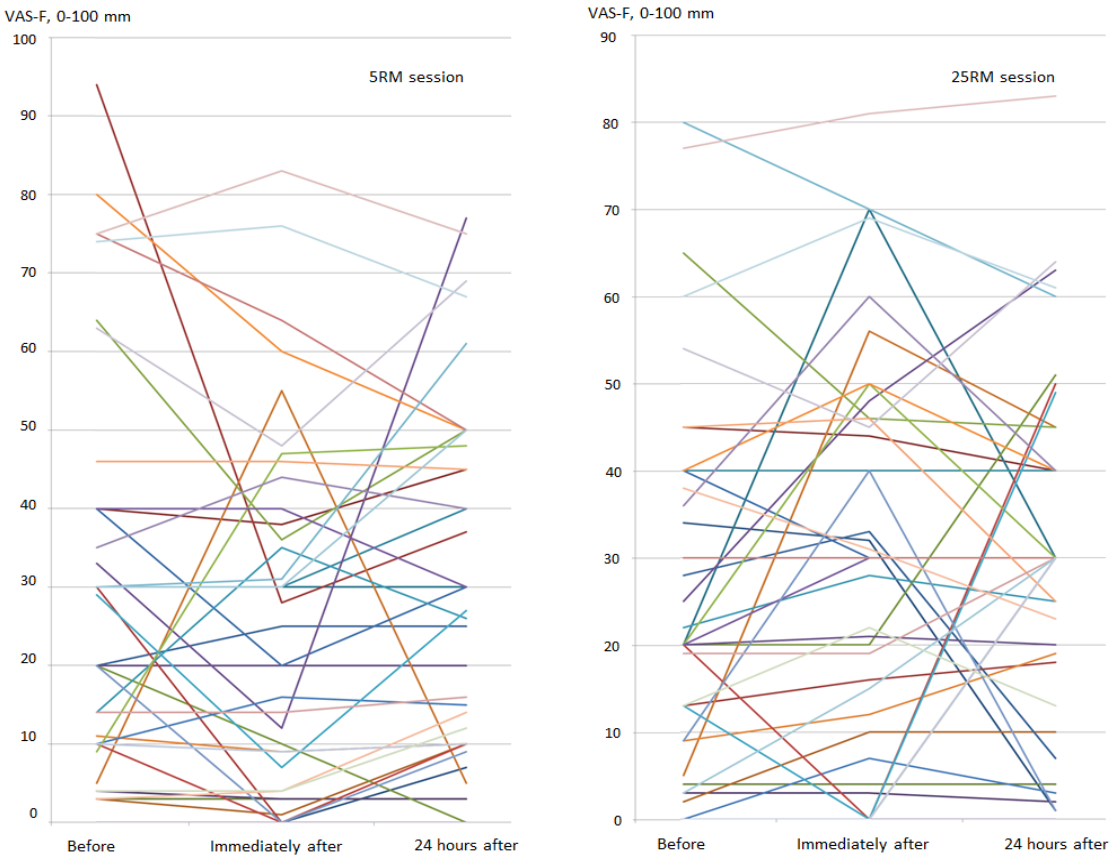


Figure 4. The individual variation in fatigue development scores following the 5RM and the 25RM sessions.

Due to the lack of knowledge, there has been an uncertainty regarding the dosage of exercise intensity and its impact on sarcoidosis-related fatigue. Our findings in Papers I and II are the first to indicate that high-intensity endurance and resistance training do not appear to induce a higher increase in fatigue levels than moderate-intensity endurance and resistance training. Our results are warranted towards defining the most optimal exercise program without worsening of sarcoidosis-related fatigue, and might lead to increased safety for both patients and physiotherapists in relation to the prescription of exercise training.

The repeated assessments of fatigue reported immediately before each of the four exercise sessions in Papers I and II gives a clear picture of the individual variation (Figure 5). The fatigue scores are reported on four different days, whilst the fatigue assessments prior to the HIIT/MICT and the 5RM/25RM were assessed at the same time of the day, either in the morning or in the afternoon, respectively.

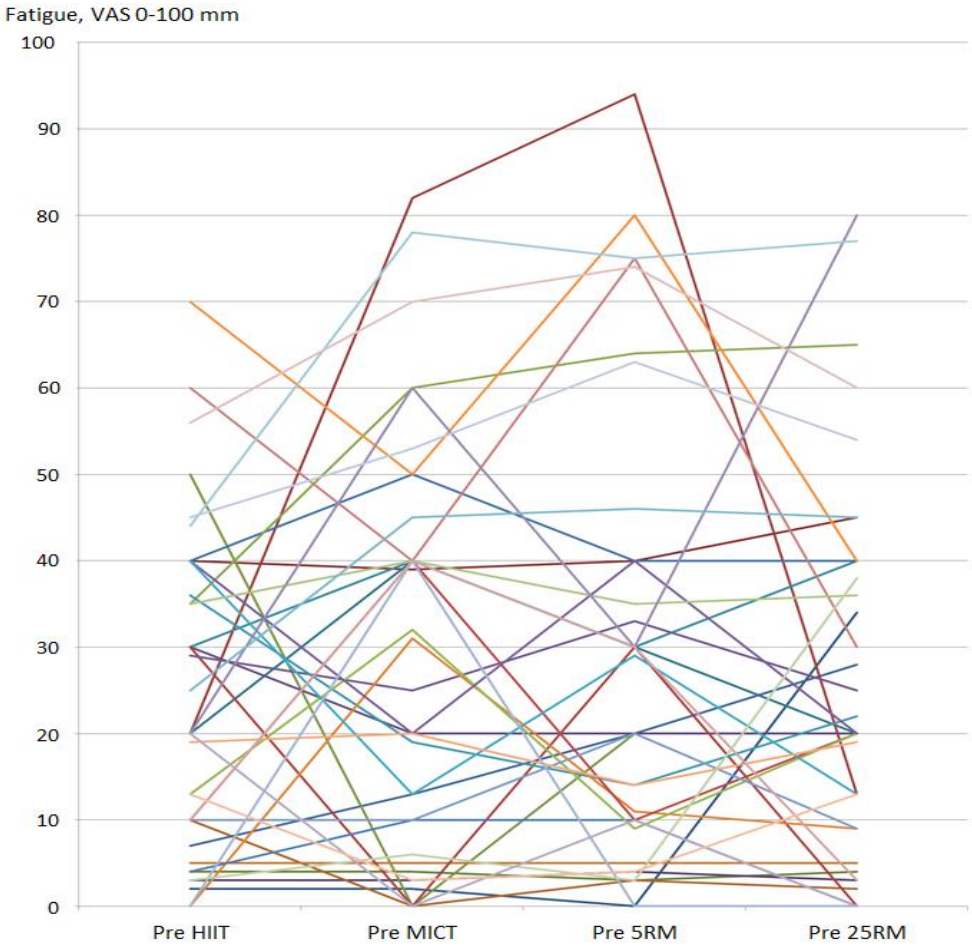


Figure 5. Individual fatigue score assessed immediately before each of the sessions in Papers I and II.

4.3 Paper III

The primary aim of this study was to evaluate the impact of a 4-week inpatient interdisciplinary PR program on exercise capacity ($\dot{V}O_{2peak}$) and fatigue (FAS), where the HIIT protocol in Paper I and the 5RM protocol in Paper II were included as the main components of the patients' individual exercise training program. A secondary aim was to examine whether there was an association between baseline fatigue and changes in $\dot{V}O_{2peak}$ following PR.

There was a statistically significant improvement in exercise capacity with a mean increase in $\dot{V}O_{2peak}$ of 1.2 ± 2.3 $mL \cdot kg^{-1} \cdot min^{-1}$ (p = 0.002), and a mean decrease in fatigue by 1.7 ± 3.9 points (p = 0.009) after 4 weeks of PR. The individual variation in changes of $\dot{V}O_{2peak}$ and fatigue are shown in Figure 6. Our results add promising evidence for the benefit of PR, including high-intensity exercise training, in patients with sarcoidosis.

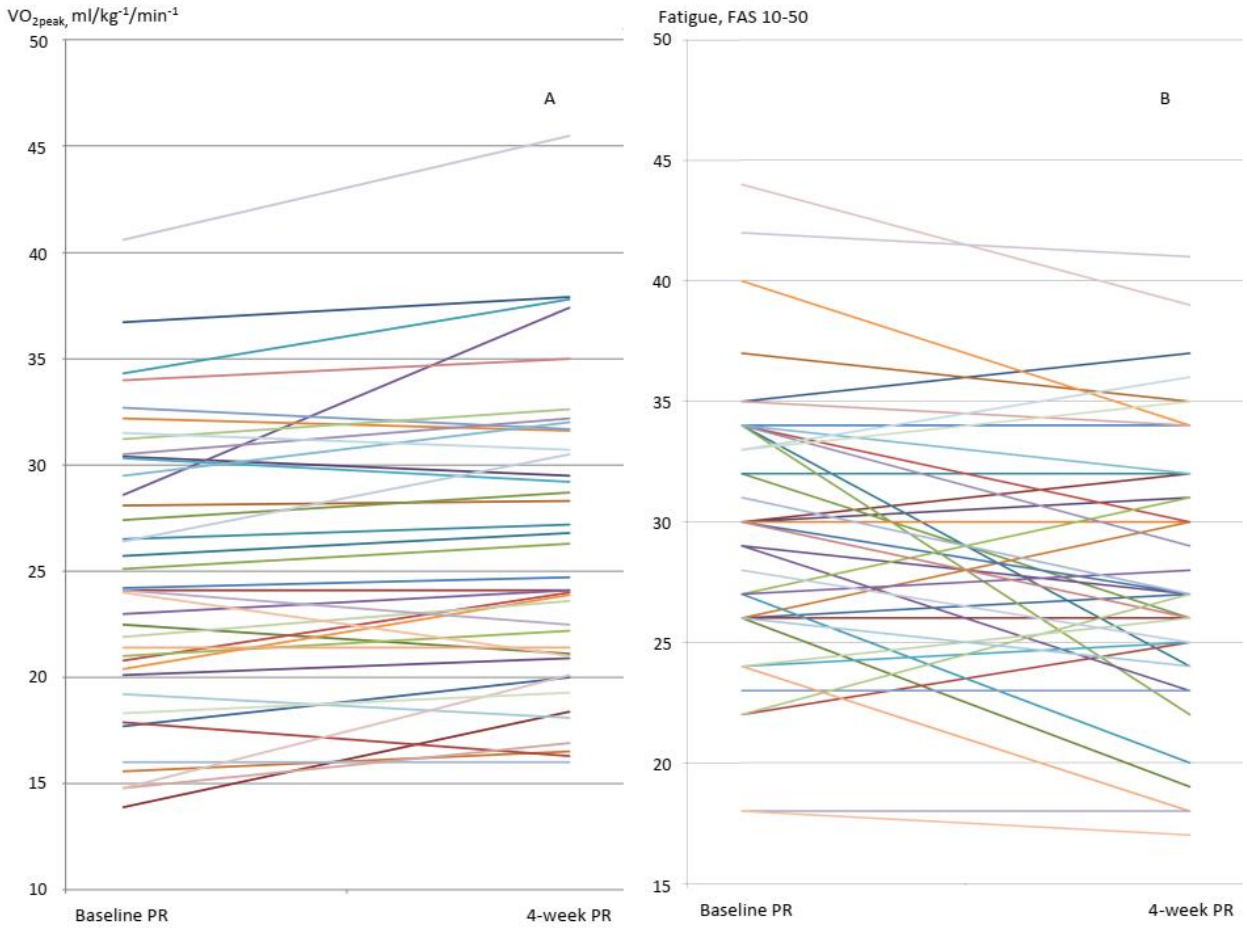


Figure 6. Individual changes in exercise capacity (A) and fatigue (B) after four weeks of PR. V̇O2peak: peak oxygen uptake; FAS: fatigue assessment scale; PR: pulmonary rehabilitation.

Surprisingly, we found a statistically significant positive correlation between baseline fatigue and change in $\dot{V}O_{2peak}$ after PR ($r = 0.49$, $p = 0.001$), where a higher fatigue score at baseline was associated with a larger improvement in exercise capacity. Nevertheless, baseline fatigue only partly predicted changes in exercise capacity after PR.

Our finding is encouraging for patients suffering from fatigue, revealing that PR improves exercise capacity even in very fatigued patients. The results might also contribute to less fear of aggravating fatigue in relation to exercise training for both patients and health-care professionals.

5. Discussion

The discussion will be structured in three main parts. In the first section, methodological considerations will be discussed and thereafter the main results in section two, whilst clinical consequences and future perspectives will be discussed in the third section.

5.1 Methodological considerations

5.1.1 Study design

Papers I and II: Due to the small sample of patients with sarcoidosis in general and especially patients attending PR, a crossover design was considered to be the most suitable study design. In a crossover trial, all participants receive sequences of treatment with the object of studying differences between individual treatments (81). Thereby they act as their own controls reducing the sample size required to achieve statistical power. Another aspect we considered to be in favour of a crossover design was the outcome measure of perceived fatigue. Fatigue is a symptom with a wide individual variation, where some patients report only a mild fatigue, others intermittent fatigue that varies during the day, and a third group describe all day fatigue (39). By being their own controls, we eliminated the between-subject variability in fatigue in addition to the random variation that might occur between two groups (82, 83).

A weakness with a crossover design is the possibility of a carry-over effect, where the intervention given in the first sequence might affect the effect of the intervention given in the next sequence (81). In our two studies, it was not only the interventions that could give a carry-over effect, but also affection on fatigue from other exercise sessions the patients participated in as part of the normal PR program. To avoid carry-over effects, we imposed restrictions on exercise training 48 hours before the interventions in the two studies, as a washout period of fatigue from previous exercise sessions.

Paper III: A pre-experimental, one-group pre-post design was used to explore the impact on exercise capacity and fatigue from the 4-week PR program. A pre-post design is useful in order to assess whether any changes have occurred, and is frequently used in physical exercise studies (84).

Therefore, a weakness with the one-group pre-post design is the lack of a control group and thereby we cannot draw any causal conclusions about the possible changes. At an early stage of the planning process, we discussed including a control group. And again, due to the small sample of eligible patients with sarcoidosis and the limited time, the decision was made to use a study design where the included participants acted as their own controls. This could be done by adding a third measure point of exercise capacity and fatigue four weeks prior they attended PR. Thereby, the changes from four weeks prior to PR until attending PR would have worked as the control period, while changes from attending PR until the end of the PR program would have been the intervention period. However, our patients travel from all over Norway and we therefore concluded that the extra load of travelling and taking days off from family and work by being their own control, was neither practical or economically feasible. However, we considered our pre-experimental one-group design to be a useful contribution to demonstrate feasibility for whether the PR program should be recommended for further efficacy testing.

Another weakness with a pre-post design is the response shift bias. This occurs if the participants have changed the metric for answering the fatigue questionnaire (FAS) from pre till post PR, because they had gained a new understanding about the concept of fatigue during the PR program (85). We tried to prevent this bias by sending information about sarcoidosis-related fatigue by e-mail/letter before they arrived for PR. In addition, I explained the term fatigue again verbally to each of the participants the day they arrived at our clinic to be sure they had understood the concept of sarcoidosis-related fatigue.

5.1.2 Internal validity

Internal validity is defined as the ability of a study to measure what it was intended to measure in the studied population (86). When designing a study, internal validity is mainly threatened by systematic errors, such as selection bias, information bias, confounding factors, and random errors.

Selection bias

Selection bias occurs if the recruited participants' representativeness differ from the entire population of patients with pulmonary sarcoidosis (86). Selection bias may occur if the

investigators or the process of invitation systematically avoids offering inclusion to patients who fulfil the inclusion criteria, or if certain patients are more likely to deny participation in the study. Both were possible biases in our project. As the referral system for attending PR was based on referral from the patients` general practitioner or pulmonary physician, patients with asymptomatic or less severe pulmonary sarcoidosis who did not seek medical attention were not invited. We were also aware of that patients at a certain age/life situation with small children or work commitments were more likely to refuse participation in our study due to the setting of a 4-week inpatient PR. To compensate for this well known selection biases, we collaborated with the Norwegian Sarcoidosis Association, where they informed their members about our project in newsletters and meetings before the study started. This might have been a reason for the increase of approximately 30% of the annual number of patients with sarcoidosis referred to the LHL Hospital, from 30 patients before 2016 to 40 patients between 2016–2017. The LHL Hospital is the only clinic offering PR to patients with pulmonary sarcoidosis in Norway, and 70% of all patients with sarcoidosis attended the hospital during the inclusion period were included in the study and should be representative for patients with pulmonary sarcoidosis in Norway. However, it is likely that less severe/asymptomatic patients and patients at a certain age were not represented in our sample.

Information bias

Information bias can be a result of misclassification or systematic measurement errors (86). Sarcoidosis is a diagnose of elimination, where pulmonary sarcoidosis is the manifestation that usually takes the longest to diagnose. Therefore, we carefully examined the medical journal before inclusion to ensure that the diagnosis of pulmonary sarcoidosis was verified. Since the mean time since diagnosis in our sample was approximately 8 years, we assumed no misclassification of the diagnosis pulmonary sarcoidosis had occurred.

Misclassification of fatigue was a possible information bias as none of the patients in our sample were familiar with grading their fatigue. Fatigue assessed by FAS, which is a categorical scale varying from "Never" to "Always", could have led to misclassification if the patients placed their scores in an incorrect category. As the results in Paper III were based on the changes in FAS score, independently of the categorization of fatigue, misclassification regarding FAS did not influence the results.

Confounding factors

A confounding factor is defined as a third variable that is associated to both the exposure and the outcome, and might lead to wrong conclusions or to too strong/weak associations if not taken into account (86).

Physiologic exercise-induced fatigue was one possible confounding factor when assessing fatigue in relation to the exercise sessions in Papers I and II. We tried to prevent this confounding factor by differentiating sarcoidosis-related fatigue and exercised-induced fatigue using different scales. In our ordinary PR program, all patients are trained to use the Borg CR10 scale to grade their perceived exhaustion in relation to exercise intensity. By combining the use of the Borg CR10 scale during the exercise sessions and VAS-F to grade fatigue before and after the exercise sessions, the patients became very aware of the difference of sarcoidosis-related fatigue and exercise-induced fatigue. The results in Paper I imply that they managed to differentiate between those two aspects of fatigue, shown as no difference in fatigue scores between the HIIT and the MICT sessions as assessed immediately after exercising, while there was a significant difference in exercise-induced fatigue graded as breathlessness at the same measure point between the two sessions. Also, our clinical experience is that patients with sarcoidosis-related fatigue are easily able to describe sarcoidosis-related fatigue as something completely different than exercise-induced fatigue.

Randomization and matching are methods to prevent confounding factors, which were not relevant in our crossover and one-group pre-post design studies. A third method taken to prevent confounding factors is by multivariate analyses. In Paper III, we used a multivariate regression analysis to avoid the effects of known confounders, however, we are aware that there is always a risk of unknown confounding factors.

Random error

Random errors are unpredictable errors and shown as the variability in the data that we cannot easily explain (86). In small sample sizes, random errors may influence the result by obscuring the real differences, and including a larger sample size improve the precision of estimation (86). Random errors can also occur when entering data in the database. In our study with 41 patients, it was manageable to thoroughly check for plotting errors and all

outcome variables were controlled several times. When plotting the $\dot{V}O_{2peak}$ data, we were two investigators who checked that the plotted peak values were in keeping with the protocol.

5.1.3 External validity

Internal validity is a prerequisite for external validity, and external validity means that we can generalize the results from the study population to apply to patients outside of the study population (86). Because our sample was recruited from patients refereed to the LHL Hospital for PR by their physician, the general population of patients with pulmonary sarcoidosis in Norway was not invited to participate. However, since the LHL Hospital is a nation wide clinic, the geographical distribution of the participants was taken account for. In addition, our sample was more or less comparable in age, gender distribution, lung function, body mass index, functional capacity and fatigue score to samples in comparable studies of patients with sarcoidosis (14, 15, 51). Nevertheless, based on the inclusion process and the normal to mild lung functions, our sample of patients with pulmonary sarcoidosis is representative for symptomatic patients with less severe lung function impairments.

5.1.4 Reliability

Reliability basically applies how exactly the research work operations have been carried out (83). In our three studies, reliability was dependent on the degree of consistency in which the instruments and questionnaires measured what they were supposed to measure. If repeated measures give small variations only, it suggests that the reliability is high (83).

In Papers I and II, VAS-F was used to assess changes in fatigue in relation to one single exercise session. The VAS-F has shown good reliability in a test-retest over 1-2 days with a intraclass correlation coefficient (ICC) of 0.74 (45), where a ICC > 0.7 or higher is considered as "acceptable" (87). In relation to reliability, it is important to consider factors which can influence variation when planning an experiment (83). As individual daily variation in fatigue is well known amongst patients with sarcoidosis (39), we tried to prevent the influence of daily variation in two ways. First, by organizing the two different sessions in Paper I and Paper II to be performed approximately at the same time of the day, either before lunchtime or after lunchtime. This was to prevent the daily variation of fatigue from influencing the assessment of fatigue following the two sessions we wanted to compare. Secondly, by

randomizing the endurance training (Paper I) and the resistance training (Paper II) to be performed before or after lunchtime. If the endurance sessions (Paper I) were performed before lunchtime, the resistance sessions (Paper II) were performed after lunchtime, and vice versa. This was to prevent that all four sessions (Paper I and Paper II) were performed at the same time of the day and thereby were influenced by morning or afternoon fatigue.
An advantage regarding reliability is that VAS-F is a simple scale which is easy to understand and requires minimal time for completion (< 1 minute), which was important to be able to capture the "here and now" perception of fatigue (45). A limitation, which is common in all self-reported scales anchored by two extreme statements (no fatigue – extreme fatigue), is the avoidance responders have for choosing the extreme ends (45). This was also seen in our sample regarding extreme fatigue, where scores ≥ 90 mm were only rated by one patient immediately before the 5RM session in Paper II. Since the mean scores of VAS-F for all measure points ranged between 22 ± 19 mm and 31 ± 22 mm, we assume avoidance of the extreme upper end did not influence our results.

In Paper III, an incremental treadmill CPET was used to measure exercise capacity. The advantage of using the CPET is the standardized procedures and protocols, which are important factors that reduce the risk of variability in measures. The equipment was calibrated every morning and immediately before each test. Specialised and experienced bioengineers were responsible for that the performances of the tests were in accordance to the standardised protocol, and they were experienced in taking care of the patients as well as pushing them to their peak exercise tolerance. The patients performed the pre PR and the post PR CPET using the same equipment and protocol, and performed the tests at the same time of the day, either before lunchtime or after. A last factor was that both the CPET, which was used to evaluate the changes in exercise capacity, and the endurance exercise sessions, which aimed at improving exercise capacity, were performed on a treadmill. All these factors contributed to increasing the reliability of the measures of exercise capacity.

5.1.5 Statistical perspectives

Several statistical methods were discussed and tested in relation to the analysis of the crossover design data in Papers I and II; paired sample t-test, mixed between ANOVA and mixed models. A the use of the different methods gave similar results (p-values), and our papers were planned to be published in journals were t-tests are more common than mixed

models, we were advised to use the paired sample t-test in our analyses by a statistician at the University of Oslo.

In Paper III, we discussed whether to use intention to treat (ITT) or per protocol (PP) when analysing the data. We had four missing CPET data and three missing FAS data post PR due to seasonal influenza. Analyses of the baseline characteristic between ITT (n = 41) and PP (n = 37) showed no statistically significant difference; age (p = 0.574), BMI (p = 0.356), lung function (p = 0.563), 6MWD (p = 0.350), FAS (p = 0.430) and $\dot{V}O2_{peak}$ (p = 0.491). Neither analyses between the two methods of the changes of outcome measures after PR differed statistically significantly; FAS (p = 0.443) and $\dot{V}$O2peak (p = 0.402). We chose the ITT analyses with the same sample size, n = 41, presented in the text, all tables and figures. Regarding the missing values, we used the "last observation" at baseline PR to replace the missing values after PR in the ITT analyses.

5.2 Discussion of the main results

The three papers in this thesis all explored sarcoidosis-related fatigue in relation to exercise training. Firstly, it was important to investigate whether high-intensity exercise training would affect fatigue development differently than moderate-intensity exercise training. Then to evaluate the impact of 4-week PR, including the high-intensity protocols in patients with sarcoidosis.

5.2.1 Exercise intensities and the impact on fatigue.

In Papers I and II, we investigated whether the development of fatigue would differ between one single session of high-intensity versus moderate-intensity, both for endurance and resistance exercise training. Fatigue assessed by the VAS-F was the main outcome. Fatigue baseline scores, assessed immediately before each exercise session, did not differ, neither between the two endurance sessions or the two resistance sessions. The stable baseline fatigue was a prerequisite for a further comparison of fatigue development, as the changes in fatigue both immediately after exercising and 24 hours later were calculated from the baseline scores.

Endurance training was the focus in Paper I, where the findings indicated a small trend towards an increase in fatigue within both the HIIT and the MICT. However, the difference in

fatigue between the HIIT and the MICT was not significant, with only 2 ± 14 mm difference in fatigue scores immediately after, and 6 ± 24 mm difference 24 hours after the sessions. Paper II investigated the difference in fatigue development between one single session of resistance training with high-intensity (5RM) and one single session of moderate-intensity (25RM). There was no significant difference between the two sessions as measured immediately after exercising, where a decrease in fatigue of 3 ± 18 mm was seen following the 5RM session and an increase in fatigue of 5 ± 15 mm was seen following the 25RM session. However, this difference of 8 mm was below the 10 mm which is considered as the minimal clinically important change of VAS-F (66). The difference in fatigue of 6 ± 25 mm between the two sessions 24 hours later was not significant. Our findings from Papers I and II indicated that high-intensity exercise training did not increase fatigue more than moderate-intensity exercise training, which was our main aim of the investigation and is of clinical relevance.

To our knowledge, there exist no other studies in patients with sarcoidosis comparing fatigue development between high-intensity and moderate-intensity exercise training. Therefore, it was promising to observe that our findings in Paper I were consistent with an nearly identical crossover study by Sandler et al. (65), comparing fatigue development between one session of HIIT and MICT in patients with chronic fatigue syndrome. Even if the 14 patients with chronic fatigue syndrome reported a statistically significant increase in fatigue following both the HIIT and the MICT session, the main results revealed no significantly difference in fatigue development between the two sessions of endurance training. Since the results from both our study and those from Sandler et al. (65) were based on the fatigue response after one single session only, we do not know whether the fatigue development will remain similar, or hopefully decrease, in a program of longer duration. Exercise studies of 12 weeks duration in patients with sarcoidosis have shown promising, although not conclusive, results regarding fatigue. However, those studies have predominantly used moderate-intensity exercise programs (14, 15, 54). Therefore a randomized control study by Kampshoff et al. (88) of 277 cancer survivors, where fatigue is also a prominent symptom, was supportive of our findings. They evaluated the effectiveness of a 12-week exercise program including both endurance and resistance training on symptoms of fatigue. The cancer survivors were randomized to exercise with either high-intensity, low-to-moderate-intensity or to a non-exercise control group. Both the high-intensity and moderate-intensity group showed a significant and clinically meaningful reduction in fatigue compared to the control group. Whether the

disease-related fatigue in patients with sarcoidosis, chronic fatigue syndrome and cancer is comparable, is to our knowledge unknown. Nevertheless, rationale amongst others has traditionally been to advise patients with both sarcoidosis and chronic fatigue syndrome to perform moderate-intensity exercise training whilst avoiding the worsening of fatigue (10, 89). We assume that the lack of studies evaluating high-intensity exercise training, in combination with the mystery of fatigue, where both causes and treatments are unknown and the prognostic course is unpredictable, might be explanatory factors to why moderate-intensity is commonly used in patients with sarcoidosis. Therefore, the results from Papers I and II add a useful insight into the impact of different exercise intensities on fatigue in patients with sarcoidosis. This supports the work by Sandler et al. (65) and Kampshoff et al. (88), as high-intensity did not increase fatigue more than moderate-intensity exercise training in patients with cancer and chronic fatigue syndrome either. Our findings are also valuable towards defining the most optimal exercise program, especially as high-intensity exercise training has shown to be more effective to improve both exercise capacity and maximal muscle strength compared to moderate-intensity exercise training (13, 56, 57, 60).

The heterogeneity and individual variation in fatigue, which has been described in patients with sarcoidosis (39, 40), are clearly confirmed in Papers I and II with standard deviations nearly equal to the mean scores of fatigue. The individual variations in fatigue development in relation to the exercise sessions are presented in Figure 3 and Figure 4 with both increases, decreases and more or less unchanged fatigue development after exercising. It was also interesting to observe that this individual variation was present regardless of exercise modality, shown in Figure 5. This figure shows the measurements of fatigue performed immediately before each exercise session and with at least 48 hours since performing other strenuous exercise training, as assessed on four different days. The adding of a third measure point of fatigue 24 hours after the exercise sessions was also of clinical interest. This measure point was primarily based on feedback from patients reporting onset of fatigue the day after a physical activity, which they considered to be more frustrating than an acute onset, as the latter is more expected. Significant increase in fatigue from baseline were observed 24 hours after both the HIIT and the 25RM session. However, the increase of 8 ± 17 mm (HIIT) and 6 ± 18 mm (25RM) did not reach the minimal clinically important difference of 10 mm. Nevertheless, it is important for both patients and health professionals to be aware of the individual pattern of fatigue onset. Unfortunately, this individual development of fatigue is difficult to predict, both based on the pre-exercise fatigue scores and in relation to different

exercise intensities. Therefore, it was also of clinical interest to observe that, despite some patients having high pre-exercise fatigue scores, all 41 patients managed to conduct all four exercise sessions in Papers I and II.

Since the impact of high-intensity interval training has not been explored in patients with sarcoidosis, it was of clinical interest to study the feasibility of the HIIT protocol in Paper I. Our findings revealed good compliance as all the 41 patients completed the entire HIIT session and no adverse events occurred whatsoever. In addition, 40 of 41 patients achieved the intended intensity of 85% of HR_{max} and/or Borg CR10 score ≥ 5, which demonstrate the feasibility of our HIIT protocol. Other exercise studies of patients with sarcoidosis have only described the intended intensity protocol, but have not reported whether the participants actually achieved the intended intensity (14, 15, 53, 54). The HIIT protocol with 4 intervals of 4 minutes work (4x4), is a protocol that is well established and even recommended for cardiovascular diseases as an optimal protocol (90). However, we chose a modified version with 4 intervals of 3 minutes work (4x3) as this protocol has shown to be feasible for most patients with pulmonary diseases attending our hospital and was well established in our PR program. The 4x3 protocol demonstrated to be feasible for our sample of patients with sarcoidosis as well, as all 41 patients managed to complete the HIIT session. A low-intensity interval protocol was used by Strookappe et al. (14) in an exercise study in patients with sarcoidosis, comprising of 10 intervals alternating 40 seconds of 50-60% of peak work rate and 60 seconds with lower intensity. Our clinical experience with short-duration intervals of < 1 minute is that patients find it difficult administering the rapid shifts between high and low intensity, especially on a treadmill. Another advantage with the 4 x3 min protocol, which has been used in our PR-clinic over the last decade, is the good transferability to other equipment and activities both indoors and outside. Secondly, several studies have demonstrated that patients find high-intensity interval training more motivating than moderate-intensity, providing a positive influence on their general health (88, 91), which supports the implementation of our HIIT protocol in relation to long-term adherence to exercise training.

The results in Papers I and II are based on fatigue development following one single session only. However, this was a first step towards defining the optimal exercise program in terms of intensity to improve exercise capacity and peripheral muscle strength. The most important and positive finding from our studies was that high-intensity exercise training did not increase/worsen fatigue. Still, it is important to point out that our aims were not to explore

whether high-intensity exercise training should be recommended instead of moderate-intensity in patients with sarcoidosis, but to compare fatigue development between different exercise intensities. To summarise, our results indicated that the fatigue development following one exercise session was regardless of the choice of intensity. These are the first studies that have demonstrated that exercise training with high-intensity in patients with sarcoidosis seems to be well tolerated and safe, and did not increase fatigue more than moderate-intensity exercise training. Therefore, our preliminary findings are promising for both patients, who do not need to be afraid of worsening their fatigue, and for health-care professionals who are prescribing exercise training programs for patients with sarcoidosis. This is particularly relevant as poor exercise intolerance and reduced muscle strength are common clinical features in patients with sarcoidosis. Fatigue is still a mystery, but based on our results we suggest that exercise training should be prescribed based on the patient's aims and limitations, rather than the fear of worsening fatigue.

5.2.2 Pulmonary rehabilitation and the impact on exercise capacity and fatigue

In Paper III we demonstrated that a 4-week inpatient PR program significantly improved exercise capacity and decreased fatigue amongst patients with sarcoidosis. To measure exercise capacity, a CPET was performed at baseline and following PR, where $\dot{V}O_{2peak}$ was the outcome measure for exercise capacity. Reduced exercise capacity is defined as $\dot{V}O_{2peak}$ < 84% of predicted values (92), and has been reported in 50-88% in patients with sarcoidosis (6). As 76 % of the patients demonstrated reduced $\dot{V}O_{2peak}$ at baseline, our sample seems representative of patients with sarcoidosis.

$\dot{V}O_{2peak}$ gives an objective picture of exercise capacity, and the use of a CPET provides a precise measure of the effects of exercise training following PR (92). To our knowledge, this was the first study using $\dot{V}O_{2peak}$ as an outcome measure to evaluate the impact of PR or exercise training program in sarcoidosis. Paper III revealed that $\dot{V}O_{2peak}$ improved significantly from 24.6 ± 6.8 $mL \cdot kg^{-1} \cdot min^{-1}$ at baseline to 25.8 ± 7.2 $mL \cdot kg^{-1} \cdot min^{-1}$ following PR. The ability to improve exercise capacity with 1.2 ± 2.3 $mL \cdot kg^{-1} \cdot min^{-1}$ in 4 weeks is promising for several reasons. Firstly, one of the early physiological parameters seen in sarcoidosis is impaired $\dot{V}O_{2peak}$ (93), whilst a substantial number of patients have reported exercise intolerance as a "strong" or "very strong" impediment (51). Therefore, counteracting deconditioning and improving exercise capacity seems to be an important target for treatment

and is clinically relevant in the management of patients with sarcoidosis. Secondly, $\dot{V}O_{2peak}$ is a precise measure of cardiorespiratory fitness and is strongly and inversely related to the risk of cardiovascular diseases (94). An increase of 3.5 $mL \cdot kg^{-1} \cdot min^{-1}$ has shown to lower the risk of cardiovascular events by 17 % in men and 12 % in women (94). As diseases of the circulatory system are among the most common comorbidities in sarcoidosis (95), exercise training to increase $\dot{V}O_{2peak}$ is clinically relevant to prevent comorbidities which can provide a further adverse impact on health and quality of life in these patients. Thirdly, it is also important to remember that in two-thirds of patients with sarcoidosis, the disease "burns-out" with a spontaneous remission within two years from initial presentation (17). Despite this, a substantial number of patients in clinical remission present with symptoms of fatigue where physical activity level and muscle strength are still reduced (41). Based on the results in Paper III, exercise-based PR might be an important tool in the prevention of reduced exercise capacity and the subsequent side-effects this can result in for both patients with sarcoidosis and for those in clinical remission.

Paper III is the first study evaluating the impact of PR in patients with sarcoidosis where a $\dot{V}O_{2peak}$ was the outcome measure for exercise capacity. The $\dot{V}O_{2peak}$ increased significantly with 1.2 ± 2.3 $mL \cdot kg^{-1} \cdot min^{-1}$ after 4 weeks PR, which was an improvement of 5% from baseline values. A clinically relevant improvement in $\dot{V}O_{2peak}$ is hard to define. This because the training response in relation to improvement of $\dot{V}O_{2peak}$ is highly individual, where the most important factors are the persons' initial fitness level, exercise intensity, training frequency and duration of the program (55). A general guideline for expected improvement in exercise capacity after 3 months of aerobic exercise training range between 5-25% (55), while the ATS/ERS statement in PR have reported improvements in $\dot{V}O_{2peak}$ between 10-20% after 8 weeks of PR (50).

The individual variations in change of $\dot{V}O_{2peak}$ was clearly demonstrated in our results and visualized in Figure 6A. The changes ranged from a reduction of - 3.0 $mL \cdot kg^{-1} \cdot min^{-1}$ (-13%) to an improvement of 9.8 $mL \cdot kg^{-1} \cdot min^{-1}$ (35%). According to exercise physiology, people with a low $\dot{V}O_{2peak}$ at baseline have an increased possibility of improving exercise capacity compared to those with a high $\dot{V}O_{2peak}$ at baseline (55). However, this was not seen in our sample as patients both in the upper and lower range of baseline $\dot{V}O2peak$ increased exercise capacity significantly. The results in Paper III suggest that we cannot predict improvement in $\dot{V}O_{2peak}$ following PR based on the baseline $\dot{V}O_{2peak}$ in patients with sarcoidosis.

The significant improvement of 1.2 $mL \cdot kg^{-1} \cdot min^{-1}$ following 4 weeks of PR in Paper III was consistent with the significant improvement of 1.24 $mL \cdot kg^{-1} \cdot min^{-1}$ reported in a review comparing PR versus no PR in ILD (9), but less than the improvements in a study of patients with sarcoidosis by Strookappe et al. where they achieved an improvement of 2.3 $mL \cdot kg^{-1} \cdot min^{-1}$ (14). There are several differences between our study and the two other references that might have influenced the results. The improvement in our study was based on a 4-week interdisciplinary PR program, while the two latter were based on 8-12 weeks of exercise training only. As the duration of the exercise program is essential for improvement, the significant improvement in our study was promising in relation to the short duration of intervention. We also assume that the content of our PR program, where the individual exercise sessions were based on the high-intensity protocols from Papers I and II, could be a contributor factor to the significant improvement in exercise capacity despite the short duration. We therefore believe that our PR program, in relation to exercise intensity and duration, might be relevant for defining the optimal training program in patients with sarcoidosis. In addition, the results from the studies mentioned above were based on studies where exercise training was the only intervention. Therefore, Paper III adds useful knowledge about the impact of an interdisciplinary The PR program on exercise capacity amongst patients with sarcoidosis. Since sarcoidosis is one of the rare ILDs, further studies in this patient group are therefore warranted (8).

To secondary outcome in Paper III was to evaluate the impact of PR on fatigue, where the FAS was used to assess subjective symptoms of fatigue. Based on the findings from Papers I and II, that one single session of high-intensity exercise training did not increase fatigue, the high-intensity exercise protocols were thereby safely included in to the 4-week PR program. The statistically significant decrease of FAS of 1.7 ± 3.9 points following the PR program was therefore promising. However, this was below the MCID of 4 points, and less than the mean 4.09 points decrease in fatigue reported by Lingner et al following PR in a sample of patients with sarcoidosis (51). The smaller decrease in fatigue in our study compared to that of Linger et al is difficult to explain, as the two studies were comparable in content and duration. Both samples included patients with sarcoidosis only, and with similar setting of an inpatient interdisciplinary PR program of short duration (3 weeks compared to our 4 weeks). Supportive evidence for our findings have also been reported in studies exploring the effects of 12-13 weeks of exercise training in sarcoidosis, with a mean decrease of 2.7 points (15)

and 4.2 points (14). It must be noted that in the study by Strookappe et al (14), a clinical relevant decrease in fatigue was also achieved by 48.5 % of the patients in the non-exercising control group. Even if the existing studies display a variation in changes of fatigue, it seems reasonable to conclude that exercise-based PR does not worsen fatigue which should lead to increased safety for health-care professionals prescribing exercise programs, and mastery for patients suffering from fatigue.

Despite the positive impact on fatigue observed after exercise-based PR, the variation in fatigue development has to be highlighted. The individual variation following one single exercise session which was demonstrated in Papers I and II was also seen in Paper III and visualized in Figure 6B. Even though the mean decrease in fatigue was statistically significant in Paper III, only 32% of the patients achieved a clinical relevant decrease of 4 points. This was coincidental with 39% of the patients with a 4 point decrease reported after 3 weeks of PR by Lingner et al. (51), and 33% reported after 13 weeks of exercise training by Marcellis et al (15). In addition, 61% of our sample reported an unchanged fatigue score. This reveals that a substantial number of patients with sarcoidosis do not change fatigue levels following exercise training and PR. Nevertheless, it is important to note that only 7% of the sample in Paper III reported a clinically relevant worsening of fatigue after PR. We could speculate whether participating in an interdisciplinary PR program might raise the patients' awareness of fatigue and thereby result in them reporting an increased fatigue compared to baseline. The MCID of 4 points is a useful tool for evaluating the response in fatigue following an intervention. However, due to the wide individual variation in both severity of fatigue and response to interventions, it is important to be aware of that a change of one point on the FAS might be perceived differently for a patient with severe fatigue at baseline compared to a patient with normal to mild fatigue at baseline, as described by De Kleijn and colleagues (47). For patients suffering from fatigue, it may be just as important to gain a knowledge of the low risk of worsening fatigue following PR.

As fatigue is described as a burdensome symptom and reduced exercise capacity is a common clinical feature in sarcoidosis, it was of clinical interest to evaluate whether the baseline fatigue score would influence the ability to improve exercise capacity following PR. Surprisingly, we found a positive, thus moderate, correlation between baseline fatigue and changes in $\dot{V}O_{2peak}$, where a high fatigue score at baseline was related to a larger improvement in $\dot{V}O_{2peak}$ after PR. However, results from the multivariate linear regression analysis revealed

that only 11% of the changes in $\dot{V}O_{2peak}$ were explained by the baseline fatigue score. Interestingly, our results were in line with a recent published prospective responder analysis of 446 COPD patients with fatigue following a 12 week interdisciplinary PR program (96). The COPD patients who were responders on fatigue following PR were characterized with more severe fatigue at baseline, in addition to being better responders to other outcomes such as exercise tolerance and health status, than COPD patients with less severe fatigue at baseline (96).

The findings in Paper III suggest that a 4-week inpatient interdisciplinary PR program improves exercise capacity and reduces fatigue in patients with sarcoidosis, and provides support that PR should be offered to this group of patients. This study also provides support for introducing individual exercise training programs of high-intensity into a PR program, which seems beneficial even for even patients with severe fatigue. Paper III highlights the importance of measuring fatigue and targeting treatment with an individual approach due to the individual variation and response to PR shown in this paper. Patients with sarcoidosis are at a rather young age, and are characterized by debilitating fatigue and impaired exercise tolerance, with symptoms persisting even following remission of the disease (41). Therefore, further investigations on fatigue and which components of PR could be important contributors in reducing fatigue in sarcoidosis is warranted.

5.3 Strengths and limitations

Strength

We believe that the strength of the inpatient PR setting was reflected in the adherence of 100% in relation to the exercise sessions and the measures of VAS-F in Papers I and II. All exercise sessions and ratings of VAS-F were supervised by the same person (me), which increased the likelihood of all the different exercise protocols and ratings of fatigue were consistent with the protocols. All participants were admitted to PR at our clinic and were personally informed and invited to participate in the current study by telephone and a letter/email. By addressing everyone with a personal invitation, they were all very motivated. This was also demonstrated by the flowchart of inclusion where the four who declined to participate, had reasons that were not related to lack of motivation for exercise training. By using a crossover design and paired data we eliminated the individual variations in fatigue.

Limitations

The rationale for including two patients who reported FAS scores of 18 points at baseline, which was below the established cut-off for fatigue of > 21, can be debated. In hindsight, a fatigue score ≥ 22 might have been added as inclusion criteria. Also, the choice to investigate the differences in fatigue development following only one single session in Papers I and II was a limitation in relation to predicting the long-term impact on fatigue, especially the impact of the high-intensity sessions (HIIT and 5RM).

The lack of a control group in Paper III is a limitation regarding the changes in exercise capacity and fatigue. Therefore, we do not know whether the improvement in fatigue was caused by the PR program or if it would have also occurred if the patients had stayed at home. In hindsight, an assessment of health related quality of life would have been a relevant additional outcome measure in Paper III, especially as sarcoidosis-related fatigue has a substantial impact on the patients' quality of life (63).

5.4 Clinical consequences and future perspectives

5.4.1 Implications for clinical practice

For me as a clinician, one of the most important implications of this thesis has been gaining a new and broader understanding about patients with sarcoidosis. Prior to this ph.d.-project, patients with sarcoidosis attending our clinic were seen as a group of challenging patients. They were more demanding compared to patients with COPD, in the sense that they sought information, objective tests and examinations that could give them any concrete answers about the disease and it's symptoms. Now I clearly understand their frustration, given the nature of the diagnosis of sarcoidosis; of unknown cause and with an unpredictable prognosis, in addition with the symptom of fatigue that also has an unknown cause, with no treatment options and which might persist even if the disease burns out. Therefore, the inclusion of FAS as a routine baseline assessment seems to be very useful in the management of sarcoidosis. Many patients have had this extreme feeling of exhaustion for years, without knowing about fatigue as a phenomena or that fatigue is the most common symptom of sarcoidosis. When we started to assess and explain the symptom of fatigue in this project, we experienced the

patients became relieved and were able to accept and cope with the burden of fatigue in a better way.

One other implication which may be valuable for clinical practice was the experience of the repeated assessments of fatigue in relation to the exercise session (VAS-F in Papers I and II). By guiding the patients in being able to differentiate between grading sarcoidosis-related fatigue and exercise-induce exhaustion using VAS-F and Borg CR10 scale, respectively, they became more conscious and thus felt safer as to what was a natural exhaustion from exercise training and what was disease-related fatigue. And as the results showed, fatigue did not increase following exercise training, even if they perceived the session as exhausting on the Borg CR10 scale or that the loads were very heavy. Therefore, I consider supervised sessions with guidance in grading the patients' fatigue as a beneficial strategy at the start of an exercise program. This may increase self-efficacy in coping with their fatigue. My experience was that even those who graded VAS-F high before the sessions did not hesitate to perform the high-intensity sessions, suggesting that this increased sense of safety may contribute to a higher adherence to exercise training at home. Of course, the factor of being supervised may also explain the high adherence to the high-intensity exercise sessions.

The origin for this doctoral thesis was the uncertainty I had as a physiotherapist considering how to improve exercise capacity without worsening fatigue. This uncertainty was also reported in previous studies where "high-frequency, low-impact" exercise was recommended to avoid the aggravation of fatigue (10, 15). The feasibility of our HIIT protocol, and the non-aggravation of fatigue following both the HIIT and the 5RM protocol, is therefore of clinical relevance for several reasons. First and foremost in relation to the patients who experienced a great deal of mastery by being able to exercise at high-intensity, and thus getting the feeling of being "normal" again. This, in combination with less or unchanged fatigue, can improve self-efficacy. Thereafter, the precise description of our high-intensity protocols of HIIT and 5RM, which make them easily transferable both to clinical practice and to home-based exercise, as they are regardless of available exercise equipment. However, to increase adherence to maintaining exercise training after PR, I think it would be valuable to give the patients experience about both the high- and moderate intensity training protocols. Our exercise advice should be based on initial tests combined with the patient's individual goals. To include the patients in decision making about which exercise protocol they prefer, gives them more responsibility for making "exercise as their medication".

5.4.2 Implications for future research

In Papers I, II and III we used measures of blood lactate as an objective measure of exhaustion, taken both at rest and after each exercise session/CPET. Our sample had a mean resting blood lactate level of 2.1 ± 0.9 mmol/L, which was slightly high, although within the normal reference values at rest of < 2.5 mmol/L (97). In light of a recent study of patients with chronic fatigue syndrome, where they demonstrated an abnormal blood lactate accumulation for any absolute output during a repeated CPET compared to healthy subjects, it would have been interesting to explored if the same mechanism was present in patients with sarcoidosis-related fatigue. Lien et al. (98) discussed the possibility of a disturbed energy metabolism, proposing a disturbed pyruvate dehydrogenase kinase which could limit the pyruvate flux disturb and thereby affect the clearance of blood lactate through oxidation in fatigued patients (98). Due to the unexplained mechanisms behind sarcoidosis-related fatigue, we assume future research exploring blood lactate accumulation in sarcoidosis during exercise would be valuable.

Simultaneously with this project, data regarding activity levels and daily variation in fatigue was collected 10 days prior to PR, 29 days during PR, and 10 days after PR. A sub-group of the participants in our study wore an activity monitor (ActiGraph). Additionally, daily variation of fatigue was collected by a SMS-track system (sms-track.com), where the patients received SMS three times daily, at 8.00am, 15.00pm and 20.00pm. For each SMS they replied with a number between 0-10 (0 = no fatigue and 10 = extreme fatigue) to grade their fatigue level at that moment. This data has not yet been analyzed, but may give useful information whether there is an association between activity levels and changes in fatigue in a daily home setting. In addition, the data might also give knowledge about whether an inpatient PR program affects activity levels and daily variation of fatigue differently than daily life at home, both before and after PR.

Finally, to optimize the effects of PR in patients with sarcoidosis, we think it will be necessary to explore more in detail which elements of an interdisciplinary PR program have the greatest impact on fatigue. To date, a combination of group sessions and individual approaches is given to patients undergoing PR, both for exercise training and education sessions. Due to the complexity of fatigue, we assume a combination of quantitative and

qualitative outcome measures is needed to gain more insight about which components of PR might improve fatigue.

6. Conclusion

The studies of this thesis have provided more insight about fatigue as the most common and burdensome symptom in patients with sarcoidosis and its relation to exercise training and PR. We have shown that one exercise training session with high-intensity did not worsen fatigue when compared to moderate-intensity exercise training and that patients with sarcoidosis benefit from PR in relation to improvements in fatigue and exercise capacity.

To answer our main research question of the three papers we concluded:

Paper I: One endurance session of HIIT did not affect acute fatigue in patients with sarcoidosis more than one session of MICT. The HIIT protocol of 85 % of HR_{max} and/or Borg CR10 score ≥ 5 was feasible as all participants managed to complete the entire session with the target intensity.

Paper II: One single session of resistance training with high-intensity, defined as 5RM with high loads/few repetitions, did not affect fatigue more than one session moderate-intensity resistance training, defined as 25RM with low loads/high number of repetitions.

Paper III: A 4-week inpatients PR program improved exercise capacity and decreased fatigue in patients with sarcoidosis. Baseline fatigue was partly related to change in $\dot{V}O_{2peak}$ following PR, where patients with higher level of baseline fatigue were associated with a larger improvement in $\dot{V}O_{2peak}$.

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Appendices

Appendix I

The content of the 4-week PR program

AKTIVITETSPLAN FOR TEAM 5

LHL-klinikkene Glittre

Aktivitetsplanuke 1				Kalenderuke: 8	
	Mandag	**Tirsdag**	**Onsdag 22/2**	**Torsdag 23/2**	**Fredag 24/2**
09.00			Inntak av nye pasienter	Inntak av nye pasienter	
09.30					
10.00					
10.30					
11.00				Kl: 11:00 – 11:30 Trim nivå I Gymsalen	
11.30					
12.00	Lunsj	Lunsj	Lunsj	Lunsj	Lunsj
13.00			Inntak av nye pasienter	Inntak av nye pasienter	Kl 13:00 – 13:30 Velkomstmøte Rom 441
13.30					
14.00					Fysioterapeut er tilgjengelig i styrkerommet
14.30					
15.00					
			18.00: Informasjonsmøte	17.00–18.30: Åpent basseng / 17.00 – 17.30 Informasjon om prosjektet rom 441	
				18.00: Informasjonsmøte	

For ytterligere informasjon om aktiviteter på ettermiddag / kveld og i helgene - se i pasientpermen og oppslag på tavlene på teamene.

Aktivitetsplanuke 2				Kalenderuke: 9	
	Mandag 27/2	**Tirsdag 28/2**	**Onsdag 1/3**	**Torsdag 2/3**	**Fredag3/3**
09.00		**08.30 – 12.00** **Legevisitt** *(Se tavle eller eget oppslag for rekkefølge og tidspunkt)* *(Si ifra på vaktrom om du har kolliderende avtaler)*	**Trim nivå II** Gymsalen	**Fysisk aktivitet og helse!** **Ta et aktivt valg!** v/ fysioterapeut Auditoriet 1. etg.	**Om å leve med sarkoidose m/psykolog** **Rom 441**
09.30		**Fysioterapeut er tilgjengelig i styrkerommet.** *(Tilpass oppmøte før/etter din legevisitt)* □			
10.00	**Psykomotorisk bevegelsesgruppe** Gymsalen Ta med pledd eller ekstra genser		**Informasjon om sarkoidose m/ lege** **Kursrom 1**		
10.30					
11.00		**Trim nivå I** Gymsalen □	**Turgruppe med fysioterapeut** Oppmøte 1 etg ved hovedinngang	**Trim nivå I** Gymsalen	
11.30					
12.00	**Lunsj**	**Lunsj**	**Lunsj**	**Lunsj**	**Lunsj**
13.00	Kl: 13:00 – 14:15 Undervisning ved sosionom: **Kommunale tjenester og deler av folketrygdloven** Auditoriet 1. etg.	Undervisning ved ernæringsfysiolog: **Sunt, helsefremmende kosthold** Auditoriet 1. etg.		**Kl 13:00 – 15:00** **Undervisning med sosionom** Arbeidsrettet lungerehabilitering Kursrom 1	
13.30					
14.00		**Trening i basseng** Bassenget	**Medisinsk Yoga** Gymsalen Ta på en ekstra genser		
14.30					
15.00					
	Kl. 17.30 – 18.30: Temakveld i aud 1 etg. "å leve med kronisk sykdom" Til dere i sarkoidosegruppa. Personen er tilgjenglig for spørsmål etterpå!	Kl 17.30 – 18.30 **"Hjemover"** Undervisning ved Lærings- og mestringssenteret Auditoriet 1. etg		17.00 – 18.30: **Åpent basseng**	

For ytterligere informasjon om aktiviteter på ettermiddag / kveld og i helgene - se i pasientpermen og oppslag på tavlene på teamene.

Aktivitetsplanuke 3				Kalenderuke: 10	
	Mandag 6/3	**Tirsdag 7/3**	**Onsdag 8/3**	**Torsdag 9/3**	**Fredag 10/3**
09.00	Undervisning ved ergoterapeut: **Mestring av dagliglivets gjøremål** Auditoriet 1. etg.	**08.30 – 12.00** **Legevisitt** *(Se tavle eller eget oppslag for rekkefølge og tidspunkt)* *(Si ifra på vaktrom om du har kolliderende avtaler)*	**Trim nivå II** Gymsalen		
09.30		**Fysioterapeut er tilgjengelig i styrkerommet.** *(Tilpass oppmøte før/etter din legevisitt)* □		**09.30 – 10.45** **Samtalegruppe og ukeslutt med sykepleiertjenesten** Rom 441	
10.00	Kl 10.30 – 11.45 **Samtalegruppe med sykepleiertjenesten** Rom 441				9.30 – 10.15 **Kosthold ved sarkoidose** Undervisning m/ klinisk ernæringsfysiolog
10.30					
11.00		**Trim nivå I** Gymsalen	**Turgruppe med fysioterapeut** Oppmøte 1. etg ved hovedinngangen	**11:00 – 11:30** **Trim nivå I** Gymsalen	10.30 – 11.15 Undervisning ved LMS: **Mestring** Auditoriet 5. etg.
11.30					
12.00	**Lunsj**	**Lunsj**	**Lunsj**	**Lunsj**	**Lunsj**
13.00	**Kl 13.00 – 13.45** **"Hva med trening?"** m/ fysioterapeut Rom 441		Undervisning ved psykolog: **Å leve med lungesykdom** Auditoriet 1. etg.		Gruppe ved ergoterapeut: **Praktiske tips for daglige gjøremål utendørs** Ergoterapikjøkkenet, u.etg.
14.00		**Trening i basseng** Bassenget	**Medisinsk Yoga** Gymsalen Ta på en ekstra genser		
15.00		**Informasjon med Norsk Sarkoidoseforening** Tone Nilsen, Rom 441			
				17.00 – 18.30: **Åpent basseng**	

Aktivitetsplanuke 4	Kalenderuke: 11

	Mandag 13/3	Tirsdag 14/3		Onsdag 15/3	Torsdag 16/3	Fredag 17/3
09.00		**08.30 – 12.00 Legevisitt** *(Se tavle eller eget oppslag for rekkefølge og tidspunkt)* *(Si ifra på vaktrom om du har kolliderende avtaler)*		**Trim nivå II** Gymsalen		
09.30			**Fysioterapeut er tilgjengelig i styrkerommet.** *(Tilpass oppmøte før/etter din legevisitt)*			
10.00	**Psykomotorisk bevegelsesgruppe** Gymsalen Ta med pledd eller ekstra genser					**Samtalegruppe og oppsummering med sykepleiertjenesten** Rom 441
10.30						
11.00	**Spørsmål og svar om sarkoidose m/lege** Rom 448		**Trim nivå I** Gymsalen	**Turgruppe med fysioterapeut** Oppmøte 1 etg. ved hovedinngangen	**Trim nivå I** Gymsalen	
11.30						
12.00	**Lunsj**	**Lunsj**		**Lunsj**	**Lunsj**	**Lunsj**
13.00	**Undervisning ved sosionom** Sykepengeordningen og arbeidsavklaringspenger Auditoriet 1. etg.	Kl13:00 – 15:00 Kurs ved ernæringsfysiolog: **Endring av kostvaner for deg som vil ned i vekt – del 1** Treningskjøkken 2. etasje *(Påmelding til sykepleietjenesten)*			Kl13:00 – 15:30 Kurs ved ernæringsfysiolog: **Endring av kostvaner for deg som vil ned i vekt – del 2** Treningskjøkken 2. etasje *(Påmelding til sykepleietjenesten)*	
13.30						
14.00			**Trening i basseng** Bassenget	Kl 14:00 **Medisinsk Yoga** Gymsalen. Ta på en ekstra genser		
14.30						
15.00						
					17.00 – 18.30: **Åpent basseng**	

Aktivitetsplanuke 1	Kalenderuke: 12

	Mandag 20/3 Pårørendedag	Tirsdag 21/3	Onsdag 22/3	Torsdag	Fredag
09.00			**Utreise – ute av rommet innen kl. 09.00**		
09.30					
10.00		**Brukerevaluering** Datarom u. etg.			
10.30					
11.00		Kl: 11:00 – 11:30 **Trim nivå I** Gymsalen			
11.30					
12.00	**Lunsj**	**Lunsj**	**Lunsj**		
13.00					
13.30					
14.00		**Trening i basseng** Bassenget			
14.30					
15.00					

Appendix II

Fatigue Assessment Scale (FAS), the Norwegian version

Spørreskjema for måling av utmattelse: Fatigue Assessment Scale (FAS)

I følgende skjema står 10 utsagn som gjelder hvordan du normalt føler deg.
Vennligst sett ring rundt det svaralternativet som passer best. Vennligst gi et svar til hvert spørsmål, selv om du ikke har plager for øyeblikket.
Til hvert utsagn kan du velge mellom 5 svaralternativ rangert fra aldri til alltid,

1. **aldri**
2. **sjelden** (én gang i måneden eller sjeldnere)
3. **regelmessig** (noen ganger i måneden)
4. **ofte** (ukentlig)
5. **alltid** (daglig)

	aldri	sjelden	regelmessig	ofte	alltid
1. Jeg har problemer med utmattelse.	○	○	○	○	○
2. Jeg blir lett trøtt.	○	○	○	○	○
3. Jeg gjør for lite hver dag.	○	○	○	○	○
4. Jeg har nok energi	○	○	○	○	○
5. Fysisk føler jeg meg utslitt.	○	○	○	○	○
6. Jeg har problemer med å komme i gang med aktivitet.	○	○	○	○	○
7. Jeg har problemer med å tenke klart.	○	○	○	○	○
8. Jeg liker ikke å forsøke noe nytt.	○	○	○	○	○
9. Mentalt føler jeg meg utslitt.	○	○	○	○	○
10. Når jeg er opptatt med noe klarer jeg lett å holde hodet klart.	○	○	○	○	○

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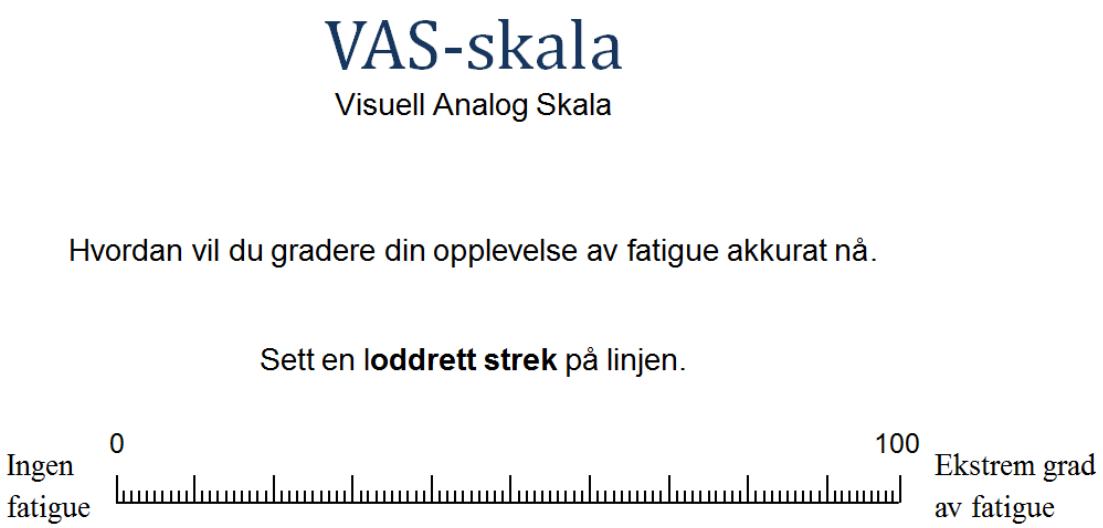
Appendix III

Visual Analogue Scale - Fatigue (VAS-F)



Papers I-III

I

Journal of
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Article

The effects of High- versus Moderate-Intensity Exercise on Fatigue in Sarcoidosis

Anita Grongstad [1,2,*], Nina K. Vøllestad [2], Line M. Oldervoll [3,4], Martijn A. Spruit [5,6,7] and Anne Edvardsen [1]

1 LHL Hospital Gardermoen, 2067 NO Jessheim, Norway; Anne.Edvardsen@lhl.no
2 Department of Interdisciplinary Health Sciences, University of Oslo, 0318 NO Oslo, Norway; n.k.vollestad@medisin.uio.no
3 LHL, Clinics Trondheim, 7041 NO Trondheim, Norway; Line.Merethe.Oldervoll@lhl.no
4 Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, Norwegian University of Technology and Science (NTNU), 7491 NO Trondheim, Norway
5 Department of Research & Education, CIRO, Center of Expertise for Chronic Organ Failure, 6085 NM Horn, The Netherlands; martijnspruit@ciro-horn.nl
6 Department of Respiratory Medicine, Maastricht University Medical Centre, NUTRIM School of Nutrition and Translational Research in Metabolism, 6229 HX Maastricht, The Netherlands
7 REVAL—Rehabilitation Research Center, BIOMED—Biomedical Research Institute, Faculty of Rehabilitation Sciences, Hasselt University, 3590 BE Diepenbeek, Belgium
* Correspondence: anita.grongstad@lhl.no; Tel.: +47-470-35-247

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Abstract: Background: Fatigue is a common symptom in patients with sarcoidosis. Despite lacking evidence on whether high-intensity interval training (HIIT) will aggravate fatigue, moderate-intensity exercise is often recommended. This study aimed to investigate whether a single session of HIIT would affect fatigue differently from a single session of moderate-intensity continuous training (MICT). Methods: Forty-one patients with pulmonary sarcoidosis were recruited to a cross-over study. All patients completed one treadmill session of HIIT (85% of peak heart rate (HRpeak)) and one of MICT (70% of HRpeak). Fatigue was assessed with the Visual Analogue Scale 0–100 mm, before (T0), after (T1), and 24 hours after (T2) each exercise session. Paired sample t-test was used to compare changes in fatigue from T0 to T1 and from T0 to T2 between HIIT and MICT. Results: No statistically significant difference in fatigue levels was found between HIIT and MICT, either at T1 (3.6 (13.5) and 1.4 (13.5)) or at T2 (8.2 (17.0) and 2.1 (17.1)). Conclusions: A single session of HIIT did not affect fatigue differently than a single session of MICT. These preliminary findings support the need for further research on the long-term effect of HIIT on fatigue in patients with sarcoidosis.

Keywords: pulmonary sarcoidosis; endurance training; high-intensity interval training; feasibility

1. Introduction

Sarcoidosis is a multisystem granulomatous disorder affecting any organ. The lung is involved in more than 90% of the patients [1]. Up to 80% of the patients with sarcoidosis report moderate to severe fatigue as one of the most disabling symptoms [2]. Sarcoidosis-related fatigue is a complex symptom reported by patients, and objective measurements such as lung function tests and chest radiography correlate poorly with patients' perceptions of fatigue [3]. Patients with sarcoidosis have a reduced exercise capacity compared to healthy individuals [4]. Because of the complexity of fatigue, both patients and healthcare professionals express reservations in relation to exercise intensities and, in turn, the potential aggravation of fatigue. To our knowledge, only four studies have explored the effects of an exercise program on sarcoidosis-related fatigue in patients with pulmonary sarcoidosis [5–8].

They showed promising improvements in exercise capacity after three months, but the effects on fatigue are still inconclusive [9]. One of the studies reporting less improvement than expected in exercise capacity and fatigue thought this was due to the low intensity of the exercise programs considered [7], while the only study using high-intensity exercise showed a statistically significant improvement in fatigue and believed it was related to the increased exercise capacity [8]. There is good evidence that high-intensity interval training (HIIT) is more effective to improve cardiorespiratory fitness than moderate-intensity continuous training (MICT) in both healthy individuals and patients with cardiovascular diseases [10–13]. Exercise studies have shown positive effects on fatigue in cancer patients [14] and patients suffering from chronic fatigue syndrome (CFS) [15]. One reason for not including high-intensity exercise has been the risk of worsening fatigue, which may lead to high drop-out rates [7], but a study of patients with CFS showed that one session of HIIT did not aggravate fatigue more than one session of MICT [16]. To date, it remains unknown whether high-intensity exercise will affect fatigue differently compared to moderate-intensity exercise in patients with pulmonary sarcoidosis. Therefore, the main aim of this study was to investigate whether a single session of HIIT would affect sarcoidosis-related fatigue differently from a single session of MICT. The second aim was to evaluate the feasibility of an HIIT session in patients with sarcoidosis with the following outcomes: (1) completion of the entire session with four repetitions of 3 min; (2) adherence to the target heart rate (HR) and perceived exertion; (3) events during the session.

2. Material and Methods

2.1. Study Design and Subjects

The study had a crossover design with a convenience sample of patients with pulmonary sarcoidosis recruited from LHL Hospital Gardermoen, a national pulmonary rehabilitation (PR) clinic in Norway. Patients (>18 years) with pulmonary sarcoidosis diagnosed in accordance with accepted guidelines [1], who attended a four-week exercise-based PR between April 2016 and June 2017 were eligible for this study. Patients were excluded if they (1) had a concurrent and predominant diagnosis of another significant respiratory disorder (asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, or lung carcinoma); (2) had unstable cardiovascular disease; (3) were not able to perform the required physical tests and exercise training sessions because of co-morbidities. All patients were in a stable phase of the disease, and those on medication continued using their standard medication (steroids and methotrexate). The Regional Committee for Medical and Health Research Ethics approved the study (2014/2020), and written informed consent was obtained from each study participant. The study was registered at the ClinicalTrials.gov (NCT02735161) before the first patient was included.

2.2. Background Variables

Information about medical history was collected from the pulmonary physician's medical report. Body composition and lung function tests were performed according to international guidelines [17] and reference values [18]. Maximal exercise capacity (peak oxygen uptake, VO_2peak) was assessed by a cardiopulmonary exercise test (CPET) (Ganshorn Schiller CS-200/ Vyntus CPX) on a treadmill, using a modified Bruce Protocol with reference values from a Norwegian population [19]. Submaximal exercise capacity was assessed by the 6 min walk test (6MWT) in accordance with standard criteria [20]. Fatigue was assessed using the Fatigue Assessment Scale (FAS). FAS is validated in patients with sarcoidosis [21,22] and consists of 10 items: five questions reflecting physical fatigue and five questions reflecting mental fatigue on a categorical response from 1 to 5. The total score range is from 10 to 50 points, where the cut-off for fatigue is >22 points [21]. All background data were collected at the first or second day of the PR program, and all patients responded to the questionnaires before the exercise tests.

2.3. Exercise Sessions

All 41 patients in this crossover study performed two supervised exercise sessions on a treadmill (Technogym Jog 500, Technogym S.p.A, Cesena, Emilia Romagna, Italy) manufacturer, city, state, country), i.e., one HIIT session and one MICT session. As the patients primarily were participants in a four-week PR program, the choice of two sessions separated by a week was due to practical considerations. The HIIT session was performed the first week, and the MICT session was performed the second week. The two exercise sessions were conducted at the same time of the day to avoid the influence of individually daily variations of fatigue. The HIIT session consisted of a 6 min warm-up, four intervals of 3 min (4 × 3 min), active pauses of 2 min between each interval, and a 2 min cooldown with a total duration of 26 min. The target intensity of the 3 min intervals was >85% of peak heart rate (HRpeak) based on the obtained HRpeak from the CPET and/or perceived exertion of breathlessness $\geq$5 (severe) on the Borg CR10 scale [23]. During exercise, breathlessness was assessed, and HR was monitored using a sport watch (Polar V800, Polar Electro, Kempele, Finland) manufacturer, city, state, country). Speed and/or elevation were adjusted during the 3 min intervals to achieve 85% of HRpeak or Borg CR10 $\geq$ 5. The 2 min active pauses and the cooldown period consisted of either walking or jogging at an intensity corresponding to 3 (moderate) on the Borg CR10 scale.

The target intensity of the MICT session was 70% of HRpeak; HR was monitored and controlled during the entire session by a Polar sport watch. To keep the intensity constant, the treadmill function "Constant Pulse Rate" was used. The treadmill then automatically adjusted speed and/or elevation during the session to maintain the target intensity of 70% of HRpeak. Equal energy expenditure (kcal) was used to equate the HIIT and MICT sessions, and warm-up was included in both sessions, estimated by the Polar V800 watch. The MICT session lasted until the patient had consumed the same amount of individual kcal as in the HIIT session. The Polar V800 "Smart calories" function is based on the following individual parameters: gender, date of birth, bodyweight, height, HRpeak, resting HR, VO2peak, and a grading of how hard/often they usually exercise (hours per week). The Polar V800 has shown to be the most accurate sport watch for estimating kcal during aerobic activities in healthy individuals [24]. The wash-out time for fatigue as a response to a single exercise session is, to our knowledge, not known. To avoid carry-over effects of fatigue from other exercise sessions and physical activities in the PR program, the patients were not allowed to perform strenuous exercise 48 h before and 24 h after both sessions. The two sessions were supervised by a physiotherapist/project coordinator.

2.4. Outcome Variables

2.4.1. Fatigue

Several studies have failed to identify physiological biomarkers which correlate with sarcoidosis-related fatigue as a response to exercise in sarcoidosis [25–27], so the unidimensional Visual Analogue Fatigue scale (VAS-F) was found to be the most appropriate measure of fatigue in this study. The scale ranges from 0 to 100 mm, 0 indicates no fatigue, and 100 extreme fatigue. Fatigue was measured one minute before the exercise sessions (T0), one minute after the exercise sessions were completed (T1), and 24 hours after the sessions were completed (T2). The patients were each time asked to immediately report their perceived sarcoidosis-related fatigue. This scale has shown good reliability over 1–2 days [28] and sensitivity to changes in patients with interstitial lung disease (ILD) [29] and rheumatoid arthrosis (RA) [30]. The minimal clinically important difference (MCID) of change in VAS-F of 10 mm was established in patients with RA [31].

2.4.2. Other Variables

To monitor the intensity of the two exercise sessions, HR and perceived breathlessness were used. HR was monitored continuously using the sport watch Polar V800. Breathlessness was assessed with the Borg CR10 scale [23]. This is a nonlinear category-ratio scale anchored between 0 (no exertion) to

10 (extreme), where 3 correspond to "moderate", and 5 to "severe". HR and breathlessness from the HIIT session correspond to the mean values in the second and third min during the 4 × 3 min intervals, and the mean values in every third min during the entire MICT session. Blood lactate was assessed by capillary puncture on a fingertip and was taken before, immediately after, and 24 h post-exercise, and immediately analyzed with a blood gas analyzer (ABL 800 Flex, Radiometer).

2.5. Statistical Analyses

Power calculation was based on a change in MCID of 10 mm for VAS-F [31], an alpha value of 0.05, and a power value of 0.8. This led to a need for inclusion of 40 participants; p values of <0.05 were considered as statistically significant. All relevant variables were tested for normal distribution by visual inspection of the histograms, Q-Q plots, and test of normality. Because of 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 within and between the HIIT and the MICT sessions. All statistical analysis was performed with SPSS version 22 (SPSS Inc, Chicago, IL, USA).

3. Results

3.1. Flowchart and Baseline Characteristics

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

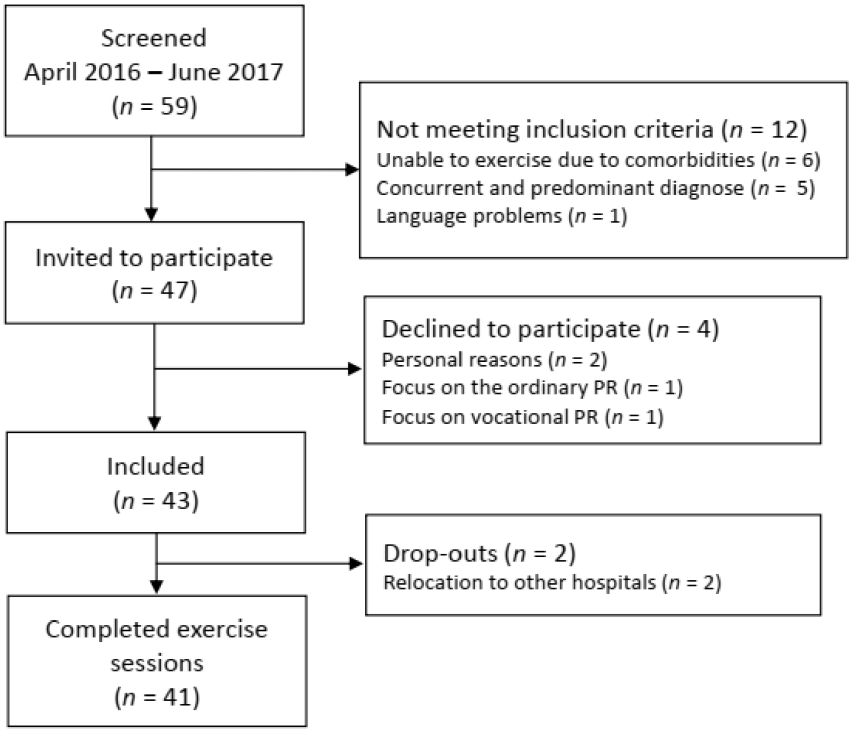

Figure 1. Flowchart of recruitment, inclusion, and drop-outs. PR: pulmonary rehabilitation.

The sample was evenly divided in females and males with normal lung function and slightly reduced exercise capacity. Thirty-nine of the 41 patients (95%) had fatigue FAS score > 22 points (Table 1).

Table 1. Baseline characteristics.

Characteristics	*n* = 41
Gender (M/F)	20/21
Age (years)	53 (11)
BMI (kg/m^2)	30 (6)
FVC (% predicted)	93 (21)
FEV_1 (% predicted)	82 (22)
TLC (% predicted)	93 (17)
DLCO (% predicted)	96 (17)
VO_{2peak} (mL· kg^{-1}·min^{-1})	24.6 (6.8)
VO_{2peak} (% predicted)	72 (19)
6MWD (meter)	580 (81)
Fatigue, FAS (points)	30 (6)
Medication	
Prednisolon (n (%))	11 (27)
Methotrexate (n (%))	6 (15)

Data are presented as mean (SD) or *n* (%). BMI: body mass index, FVC: forced vital capacity, FEV_1: forced expiratory volume in 1 s, TLC: total lung capacity, DLCO: diffusion capacity of the lung for carbon monoxide, VO2peak: peak oxygen uptake, 6MWD: 6-min walking distance, FAS: fatigue assessment scale (10–50 points).

3.2. Fatigue

No statistically significant differences in VAS-F scores were found between HIIT and MICT, neither at T1 (3.6 (13.5) mm vs 1.4 (13.5) mm, $p = 0.326$) nor at T2 (8.2 (17.0) vs 2.1 (17.1), $p = 0.106$). VAS-F increased slightly following both the HIIT and the MICT exercise session, with a statistically significant increase in VAS-F from 22.6 (18.8) mm to 30.9 (21.9) mm, $p = 0.003$ only at T2 after the HIIT session (Table 2).

Table 2. Change in fatigue (VAS-F) within and between HIIT and MICT sessions.

	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)	*p*-Value	Mean Change Mean (SD)	Δ Group Diff. Mean (SD)	*p*-Value
HIIT	22.6 (18.8)	26.2 (20.7)	30.9 (21.9)	3.6 (13.5)			8.2 (17.0) *		
MICT	26.9 (23.7)	28.3 (21.4)	29.0 (21.6)	1.4 (13.5)	2.2 (14.3)	0.326	2.1 (17.1)	6.1 (23.8)	0.106

All data presented as mean (SD). VAS-F: visual analogue fatigue scale, 0–100 mm, T0: before the training session, T1: immediately after the training session, T2: 24 h after the training session, Group Diff.: group difference, HIIT: high-intensity interval training, MICT: moderate-intensity continuous training, * $p = 0.003$.

3.3. Feasibility of HIIT

All 41 patients were able to complete the 26 min HIIT session. The target intensity of 85% of HRpeak was obtained by 33 of 41 patients (80%), and the perceived exertion of breathlessness Borg CR10 > 5 was obtained by 40 of 41 patients (98%) (Figure 2). One patient was not able to reach either 85% of HRpeak or Borg CR10 score of breathlessness of 5. A sub-group analysis showed that there was no statistically significant difference in fatigue, measured with the FAS, between the 33 patients who achieved the target intensity of >85% of HRpeak (FAS 30 (6) points) and the eight who did not achieve 85% of HRpeak (FAS 31(7) points), $p = 0.550$.

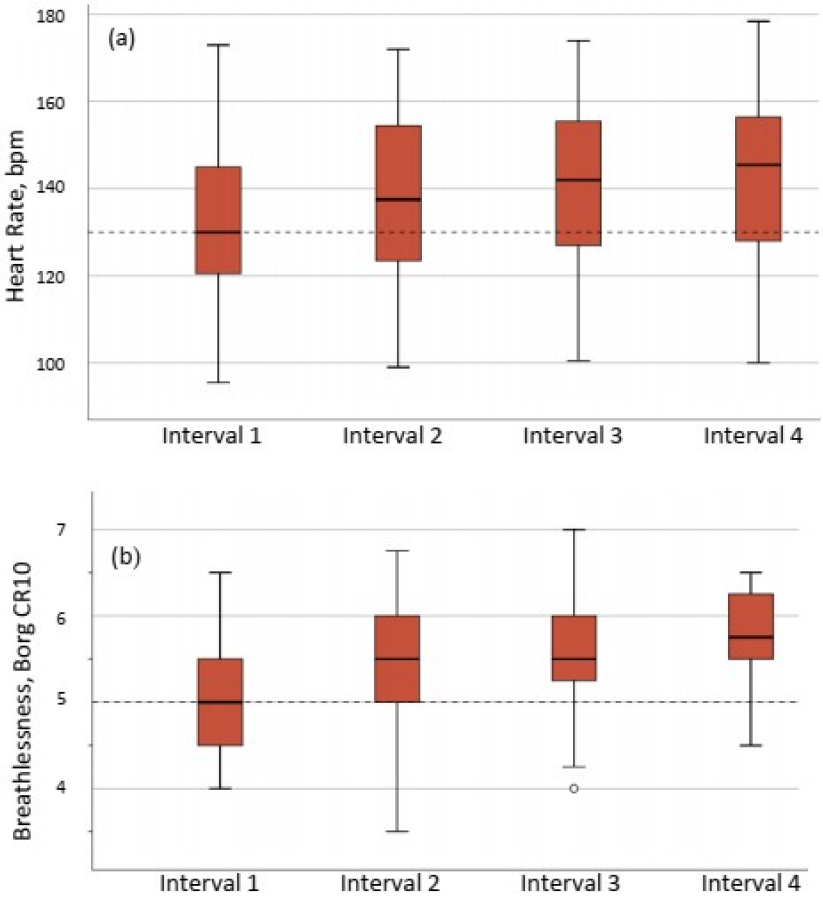

Figure 2. Exercise intensity during the four intervals of the HIIT session expressed as (**a**) percentage of peak heart rate, and (**b**) perceived breathlessness assessed by Borg CR10 scale (range 0–10). The horizontal dotted lines show target intensity, (2b) ○ = outlier, (**a**) 85% of HRpeak and (**b**) Borg CR10 = 5.

The intentional equal energy expenditure between HIIT (185 (65) kcal) and MICT (187 (65) kcal) was met, (p = 0.280) (Table 3). The mean Borg CR10 score and HR and lactate levels measured immediately after the sessions were significantly higher for the HIIT compared to the MICT ($p < 0.0001$) (Table 3). No adverse events occurred either during the HIIT or the MICT session.

Table 3. Exercise responses and duration for HIIT and MICT sessions.

	HIIT n = 41	**MICT n = 41**	**p-Value**
Energy expenditure, kcal	185 (65)	187 (65)	0.28
Breathlessness, Borg CR10	5.8 (0.6)	3.1 (0.8)	0.0001
Heart rate, $\%HR_{peak}$	90 (8)	73 (6)	0.0001
Blood lactate, mmol·L	5.8 (2.7)	2.2 (0.8)	0.0001
Time, min:s	26.00	37:43	0.0001

Data are presented as mean (SD). HIIT: high intensity interval training, MICT: moderate intensity continuous training.

4. Discussion

To our knowledge, this is the first study that has examined the development of sarcoidosis-related fatigue after two exercise sessions with different intensities but with the same total amount of energy expended in patients with pulmonary sarcoidosis. There was no statistically significant difference in fatigue levels between one session of HIIT and one session of MICT, either immediately after (T1), or 24 h after exercise (T2). Our findings are in line with a comparable study by Sandler et al. [16] who compared one session of HIIT and one of MICT in 14 patients with CFS. They also found no statistically significant difference in fatigue between the two sessions. One of the previous arguments against HIIT in patients with sarcoidosis has been the development of fatigue [7]. Both these studies contradict these findings, however, by showing that a single session of HIIT does not aggravate fatigue more than a single session of MICT in patients suffering from fatigue.

When exploring the effects on sarcoidosis-related fatigue in the context of exercise, we have to be aware of the influence of acute exercise-induced fatigue due to physiological stress which increases with increasing exercise intensity [32]. The patients were carefully informed that the focus of self-reported fatigue was sarcoidosis-related fatigue, and not exercise-induced fatigue or peripheral muscle fatigue. In our clinic, we have experienced that patients with fatigue are able to distinguish between sarcoidosis-induced fatigue and exercise-induced fatigue. This is, as expected, confirmed by the statistically significant higher rating of perceived exhaustion of breathlessness (Borg CR10), HR, and blood lactate levels during the HIIT session compared to the MICT session. However, the perception of fatigue did not show any statistically significant difference between the two sessions either immediately after or 24 h after. This is also confirmed by the lack of association between perceived fatigue and exercise intensity, in relation to breathlessness, HR, and blood lactate (data not presented) and suggests that breathlessness, HR, or blood lactate per se may not be the best measures to use as indicators of post-exercise fatigue. The post-exercise measure points in this study were based on a former study and feedback from our patients reporting the onset of acute fatigue on the following day [25]. In this study, a trend toward an increase in fatigue was seen after both the HIIT and the MICT session, with a statistically significant increase 24 h after the HIIT session only. Our observations are in keeping with the study of Sandler et al. [16], showing an increase in fatigue following both the HIIT and the MICT session, even up to 96 hours post-exercise in CFS patients. Both studies show the clinical importance of having several measure points to capture the development of fatigue as a response to exercise. Patients report the onset of fatigue after several hours to be more frustrating than the acute onset, as might be expected after an exercise session. Therefore, the clinical implications of our findings might give the patients better self-efficacy in managing post-exercise fatigue. However, it is important to note that the changes in fatigue shown by this study, including the statistically significant increase of 8.2 mm after HIIT, are not considered to be clinically significant as they are below the MCID of 10 mm [31]. In light of the non-statistically or clinically significant changes of fatigue obtained in our study, it is relevant to discuss the sensitivity of the VAS-F. The VAS-F has been used in another study to measure fatigue as an acute response to exercise in sarcoidosis [25] and has shown good reliability and sensitivity to changes in fatigue [28,29]. Thus, we considered VAS-F to be the most appropriate scale to use per se.

Because of the need for establishing an optimal training program (mode of exercise, duration, and intensity) for patients with pulmonary sarcoidosis [33], the second aim of this study was to evaluate the feasibility of HIIT as an alternative to traditionally moderate-intensity programs [5–7]. The target intensity of HIIT in the present study was defined as >85% of HRpeak, in keeping with recommendations for high-intensity training [34]. Previous exercise studies of patients with sarcoidosis identified the planned target intensity of heart rate or perceived exertion on Borg scales but did not report if the patients actually achieved it during exercise interventions [5–8]. To our knowledge, this is the first study that demonstrates that patients with sarcoidosis actually manage to achieve and maintain the target intensity during an HIIT session. The adherence to the intended intensity in this study was good. In fact, 80% of the patients achieved $\geq$85% of HRpeak, and 40 out of 41 reported

a Borg CR10 score of ≥5. In addition, all 41 patients managed to complete the entire HIIT session without any events. This indicates that HIIT might be feasible in an exercise program for patients with sarcoidosis. Three of the existing exercise studies in patients with sarcoidosis followed protocols of moderate-intensity training (50–60% of peak work) [5–7]. Although the patients seemed to improve in both exercise capacity and fatigue, the changes were small. In a pilot study by Strookappe et al. [6], only 6/12 patients with sarcoidosis had an improvement of 10% in 6MWD, and only 4/12 showed an improvement in fatigue. In the study by Marcellis et al. [7], 9/18 patient achieved 5–10% improvement in 6MWD, while fatigue was improved by 4 points in 6/18 and 10% in 9/18 patients. As exercise intensity is one of the key factors to improve exercise capacity [34], the moderate-intensity protocols in the above-mentioned studies may be the reason for the small improvements in exercise capacity and potentially small improvements in fatigue. Deconditioning has been proposed to be a contributing factor leading to fatigue [35], and exercise capacity has shown to be significantly associated with fatigue [36]. A goal when treating patients with sarcoidosis could therefore be to improve exercise capacity. As reduced exercise capacity is present in patients with sarcoidosis [4], it is possible that the implementation of HIIT, which is considered most effective in order to improve exercise capacity, could lead to a more significant reduction of fatigue. In addition, HIIT has shown to be more time-efficient and enjoyable compared to MICT [37,38]. This might have certain important clinical implications in terms of exercise adherence.

A review recommends the exercise intensity for patients with sarcoidosis to be personalized and adjusted for daily fluctuations of fatigue [33]. The sample in this study had a mean fatigue score of 30 (6) points (FAS), which is similar to scores determined by other exercise studies of patients with sarcoidosis of FAS ± 30 points [5–7]. Our sub-analysis showed no statistically significant difference in FAS scores between patients who achieved 85% of HRpeak and those who did not during the HIIT. Our findings indicate that the initial level of fatigue does not affect the patient's ability to perform high-intensity exercise training. We agree that exercise intensities in sarcoidosis should be personalized, but on the basis of individual preferences and other considerations, rather than on the basis of the level of fatigue in particular. The burden of comorbidities in sarcoidosis might be relevant when prescribing exercise programs. Cardiovascular comorbidity is reported to be the most prevalent comorbidity in patients with sarcoidosis [39]. In addition, patients with one or more comorbidities show a forceful reduction in physical activity compared to patients without comorbidities [40]. This highlights the importance of initiating physical exercise in this population, both to prevent comorbidities and to improve fatigue.

The HIIT protocol of 4 × 3 min in this study is a modified version of a 4 × 4 min protocol which has shown to be feasible for patients with several other diseases, such as coronary heart diseases, metabolic syndrome, and heart failure [41–43]. Over the past several years, we have gained a great deal of experience with the use of both the 4 × 4 min and the modified 4 × 3 min protocols in patients with different lung diseases. The patients have shown good compliance, and the transferability of the HIIT protocol to other modes of exercises is good. Patients have used the protocol when walking outdoor, both uphill and with increased walking speed on level ground, and on treadmill, stationary cycle, rowing machine, and elliptical cross trainer. This flexibility makes these protocols easy to transfer to available equipment at home-based settings as well, which may increase the long-term adherence to regular exercise for patients with pulmonary sarcoidosis.

One method used when comparing two exercise sessions with different intensity is to equate the total work performed by energy expenditure (kcal) [41–43]. To pre-define the time of each session, the calculation is depended of the average VO2peak [41]. The sample in the current study was heterogeneous in regard to VO2peak (highest: 3.26 L/min and lowest: 0.94 L/min), leading to the same wide range of energy expenditure after the exercise sessions (280 kcal and 69 kcal, respectively). Taking into account the crossover design, the individual kcal consumption measured by a sport watch, not the pre-defined time, was considered as the most appropriate method to equate the two sessions.

Strength and Limitations

Because of the small numbers of patients with sarcoidosis attending PR in Norway with an annual number of 30, a cross-over study was considered as the most appropriate and feasible design. Both sessions were supervised, and regular monitoring of heart rate and perceived exertion ensured the target intensity was reached and contributed to quality assurance of the results. The location of an in-patient PR clinic made it possible to customize the project schedule in relation to the PR schedule, to avoid inflicting additional stress on the participants. However, there are some limitations to this study. Firstly, the absence of a random allocation. Randomization was considered but found difficult to implement, as the two sessions were matched by energy expenditure. If randomized, the MICT protocol must have had a defined duration as well. The caloric consumption after a fixed duration of the MICT session could have resulted in an interruption of the HIIT before completing the 26 min, due to the challenges described in the section above. As feasibility of HIIT was a secondary aim, we considered a random allocation not to be suitable. Secondly, as daily variation of fatigue is reported in patients with sarcoidosis, this could potentially have influenced our results. Measures of VAS fatigue on days without exercise could have been added to control for this bias. Thirdly, the design with only one session of HIIT is a limitation to predict the long-term effects of high-intensity exercise training on fatigue. Finally, since we do not know how exercise of any modalities affects the immunological, muscular, or respiratory functions in sarcoidosis, we cannot preclude that there are differential effects of MICT and HIIT on these systems.

5. Conclusions

The results from this study show that patients with pulmonary sarcoidosis are able to safely perform a single session of HIIT without worsening of sarcoidosis-related fatigue. The change in fatigue was comparable to those seen following an MICT session. These preliminary findings support the need for further research on the long-term effects of HIIT on fatigue in patients with sarcoidosis.

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II

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

Anita Grongstad[1, 2], Nina K. Vøllestad[2], Line M. Oldervoll[3, 4], Martijn A. Spruit[5, 6, 7], Anne Edvardsen[1].

[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

Tel: 0047 470 35 247, E-mail: anita.grongstad@lhl.no

Key Words: Sarcoidosis; Muscle strength training; Resistance training; Sarcoidosis-related fatigue; Exercise training

Abstract

Background: 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. **Objective**: 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. Method: 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 x 5 repetitions maximum (5RM), and one single session of moderate-intensity RT, 2 sets x 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. **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**: 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 program of longer duration

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, whilst 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 in the upper limbs, where studies have reported no significant improvement [9] 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]. 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 sarcoidosis [12] and chronic fatigue syndrome [13], 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 [14]. Studies with high-intensity RT over a longer duration have also reported a reduction in fatigue amongst other patient groups suffering from fatigue, such as people with breast cancer and multiple sclerosis (MS) [15, 16]. The impact of high-intensity RT on fatigue in patients with sarcoidosis has not been studied, and recommendations regarding RT intensity for patients with sarcoidosis are in demand [17]. Increased knowledge regarding whether high-intensity RT aggravates fatigue needs to be explored before introducing high-intensity RT in a program of longer duration. Therefore, the main aim of this study was to investigate whether one single session of high-intensity RT would induce a significant acute increase in fatigue than one single session of moderate-intensity RT.

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) program 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 strength training sessions were performed during the first week of the PR program to avoid, as far as possible, the patients being prevented from participating in the regular PR program due to restrictions from the study (described in detail in the section "Resistance training protocols"). 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 program, 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 guidelines [18] and reference values [19]. Submaximal exercise capacity was assessed by the 6-minute walk test (6MWT) in accordance with standard criteria [20]. 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 [21, 22] and consists of 10-items: five questions reflecting physical fatigue and five 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, whilst scores > 34 indicate severe fatigue [21, 23]. All background data and questionnaires were collected 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 two days later to avoid carry-over effects. In addition, to avoid carry-over effects of fatigue from other exercise sessions in the ordinary PR-program, 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 5RM and 25RM test two days before the first session was performed. The 5RM and 25RM protocols were designed to be approximately equal in volume (repetitions x sets x load). Both sessions included a six minute warm-up on a treadmill and patients had the same rest time of two minutes between sets in both protocols. Self-perceived exertion was regularly graded by the patients during both sessions using the Borg CR10 scale [24]. 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 [14], 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 days [25] and good sensitivity to change in patients with interstitial lung disease [26]. 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 [27]. Fatigue was recorded immediately before the RT sessions (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 fatigue by putting a line on a blank VAS-F scale directly at all 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 mm [27] with an alfa-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. Due to the crossover 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 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 two were excluded due to relocation to other hospitals for further medical investigations, leaving 41 patients being included in the final analysis.

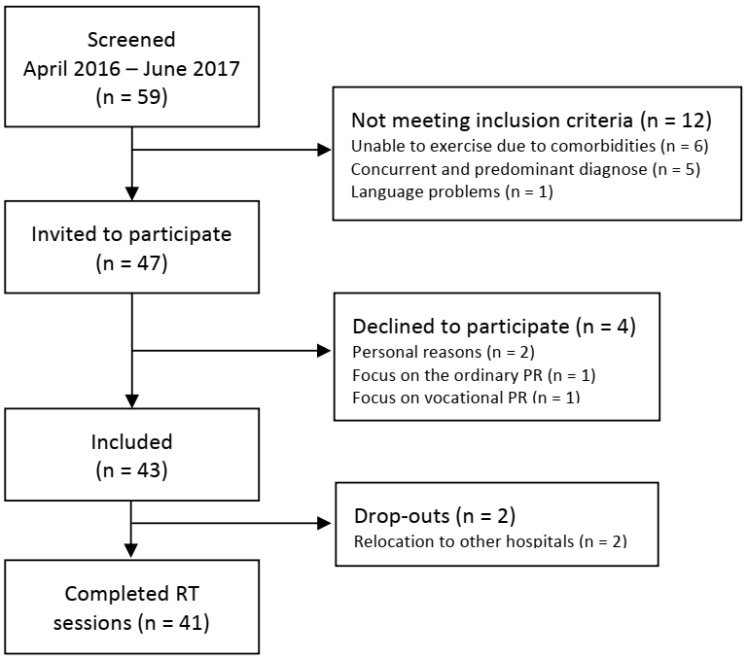

Figure 1. Flowchart of recruitment, inclusion and drop-outs. PR, pulmonary rehabilitation; RT, resistance training.

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, six (15%) with severe fatigue, and two (5%) had FAS score of 18 points.

Table 1. Baseline Characteristics of the Patients with Pulmonary Sarcoidosis. *n* = 41

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)

Data are presented as mean (SD) or n (%). BMI, Body Mass Index; FVC % pred, Forced Vital capacity in percent of predicted; FEV_1 % 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, six minute walking distance; 1RM, One repetition maximum (of leg muscle strength); FAS, Fatigue Assessment Scale.

All patients completed both RT sessions without any adverse events. The acute development of fatigue as measured with VAS-F from T0 to T1, decreased following the 5RM session whilst fatigue increased following the 25RM session, with a statistically significant difference, $p = 0.004$ (Table 2). No statistically significant difference in fatigue development was seen between the two sessions from T0 to T2, $p = 0.147$ (Table 2). There was no statistically significant change in fatigue following the 5RM session, while a statistically significant increase in fatigue was observed following the 25RM session, both at T1, $p = 0.038$, and at T2, $p = 0.047$ (Table 2).

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). 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 x 5 repetitions maximum; 25RM, 2 sets x 25 repetition maximum; *$p < 0.05$.

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).

Table 3. Exercise volume 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
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		.297
T1	6.0 ± 2.2#		9.5 ± 3.5#		< .0001

All data presented as mean (SD). T0: Before training session, T1: Immediately after training session, T2: 24 h after training session. *Between volume 5RM and 25RM, #From T0-T1 within each session, $p < 0.001$.

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. Contrary to previous assumptions of high-intensity aggravating fatigue [9], a statistically significant increase in fatigue was only seen following the moderate-intensity 25RM session with a worsening in fatigue both immediately after the session and 24 hours later. The increase in fatigue immediately after the 25RM sessions was significantly higher than the 5RM session. However, the difference of 8 mm immediately after the 5RM and 25RM sessions did not reach the MCID of 10 mm [27]. 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 programs for patients with sarcoidosis and the patients themselves.

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. However, 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 [16]. A randomised controlled study of breast cancer survivors [15], showed significant improvement in fatigue after 16 weeks of high-intensity RT compared to the control group [15]. It is possible that the mechanisms behind fatigue in cancer 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 [28], and it has been suggested that fatigue in MS and sarcoidosis is at least partially mediated through elevated levels of pro-inflammatory cytokines [29, 30]. As it is well known that endurance training of long enough duration and exercise training of sufficient intensity have a general anti-inflammatory effect [31], this supports exercise training as a core treatment component in patients suffering from fatigue [31].

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 [12]. 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, whilst reporting a low sarcoidosis-related fatigue by the VAS-F scale during a high-intensity interval session [12]. 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 [32], 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 test [9] 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 [14], 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 [33]. 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 program for sarcoidosis patients [17].

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. It is worth noting that our sample of patients with a minor impaired lung function and functional capacity might be a limitation regarding generalising of our results. However, the 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 program of longer duration.

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Declaration of conflicting interests

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