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Effect of exercise training in patients with cardiac sarcoidosis after induction of oral corticosteroid therapy

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Abstract. *Background and aim:* To our knowledge, no study has investigated altered muscle strength in patients with cardiac sarcoidosis (CS). This retrospective observational study investigated the relationship between quadriceps isometric strength (QIS) and exercise training (ET) in patients with CS. *Methods:* Eighteen patients who participated in a 4-month ET programme immediately after initiating oral corticosteroids were studied. They underwent 3–5 ET sessions per week during hospitalisation and 1–2 sessions per week after discharge. We measured their QIS at the beginning of the ET programme and at 1 and 4 months after programme enrolment. The patients received 29±4 mg/day prednisolone during the corticosteroid induction period and 15±4 mg/day prednisolone during the corticosteroid tapering period. *Results:* They continued ET and showed significant QIS weakness in the early corticosteroid induction period (0.52±0.12 to 0.48±0.11 kgf/kg, *P*=.048) and no significant improvement during the corticosteroid tapering period (0.53±0.08 to 0.58±0.06 kgf/kg, *P*=.099). Patients who received ≤12.5 mg/day prednisolone reported an improved QIS-to-body weight ratio. *Conclusions:* Patients with CS treated with 30 mg/day prednisolone showed poor QIS early in the corticosteroid induction period, even with ET. Patients with CS who receive corticosteroids may be more susceptible to developing corticosteroid myopathy.

Key words: rehabilitation, corticosteroid, exercise, muscle strength, sarcoidosis

Introduction

Patients with sarcoidosis experience organ- and non-organ-specific symptoms, including exercise intolerance and muscle weakness (1,2); cardiac involvement can also cause exercise intolerance. Patients with cardiac sarcoidosis (CS) may develop life-threatening arrhythmias and severe heart failure, causing poor prognosis (3). Oral corticosteroid therapy is often used to delay progression, with an initial dose of 30 mg of prednisolone for the first 4 weeks, but it can cause steroid myopathy (3,4). Exercise training (ET) improves exercise tolerance and muscle strength in patients with sarcoidosis (5,6). Although these studies typically excluded patients with heart disease, ET may be implemented for patients with CS because there is evidence showing the benefits of ET for chronic heart failure (7). To the best of our knowledge, no study has investigated the effects of ET or changes in muscle strength when introducing oral corticosteroid therapy in patients with CS.

This study investigated the relationship between muscle strength and ET in patients with CS after introducing oral corticosteroid therapy.

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Methods

Ethical considerations

This study complied with the Declaration of Helsinki and was approved by the Ethics Committee of our institution (M26-015-14). Due to the study's retrospective nature, the ethics committee waived the requirement for informed consent with an opt-out procedure.

Study population and medication therapy

We retrospectively investigated 87 patients with CS who participated in an ET programme at our institution between November 2002 and January 2022. We included patients who commenced oral corticosteroids during hospitalisation. CS was diagnosed based on guidelines using histological or clinical diagnosis (3). Patients were eligible for ET participation if they met the following criteria: left ventricular ejection fraction ≤40%, percent predicted peak oxygen uptake ≤80%, and B-type natriuretic peptide level ≥80 pg/mL. The patients' quadriceps isometric strength (QIS) was measured at three time points: baseline (prior to ET), 1 month (after corticosteroid induction), and 4 months (after corticosteroid tapering). The 1-month measurement was used in both analyses, serving as the endpoint of the induction period and the baseline of the tapering period. The following patients were excluded from the analysis: those with missing QIS data, those with history of stroke, and those already participating in rehabilitation programmes. Typically, oral prednisolone was administered during hospitalisation at an initial dose of 30 mg/day for the first 4 weeks and tapered by 5 mg/day at 2–4-week intervals, according to the CS guidelines (3). After the prednisolone dose was decreased to 20 mg/day, the patient was discharged from the hospital.

ET programme

ET comprised 3–5 sessions per week during the hospitalisation period. After discharge, home-based exercise training was combined with 1–2 in-hospital-supervised ET sessions per week, as described previously (8). The ET comprised moderate-intensity walking, cycling on a bicycle ergometer, and performing low-intensity resistance training in 20–60-minute sessions (8).

Physical performance

QIS was measured using the μ-Tas MF-1 assembly (8, 9). In summary, the measurement was carried out twice on the left and right sides. The highest strength values on the right and left sides were averaged and expressed relative to the body weight (BW) at the beginning of the ET (kgf/kg). The participants were asked to walk continuously for 6 min with maximum effort, and their distances were recorded at the beginning of the ET (10, 11).

Statistical analyses

Data are presented as mean and standard deviation, median and interquartile range, or number and percentage. Categorical variables were compared using Fisher's exact test. Comparisons between groups were performed using the unpaired Student's *t* test or the Wilcoxon rank-sum test, depending on the normality of the distribution. Comparisons within groups were performed using the paired t-test or the Wilcoxon signed-rank test. Receiver operating characteristic curves were constructed by plotting true positive rates (sensitivity) against false-positive rates (1-specificity) to determine the best cut-off value for differences between the QIS recovery and non-recovery groups. In this study, almost all patients were treated with cardiac implantable electronic devices. Therefore, recovery was defined as 11.9% based on a study that reported an 11.9% increase in QIS in patients with heart failure treated with cardiac resynchronisation therapy (12). All statistical analyses were performed using JMP version 14.3.0 (SAS Institute, Cary, NC, USA). For all statistical tests, statistical significance was set at $P<.05$.

Results

Eighteen patients met the inclusion criteria (Figure 1).

Of these, five patients were excluded from the QIS change analysis during the corticosteroid induction period due to a loss of baseline data. Six patients were excluded from the analysis of QIS changes during the corticosteroid tapering period due to loss to follow-up (n=5) and death (n=1). After hospitalisation, patients started their initial dose of prednisolone, 30±2 mg. Patients started ET 17±12 days

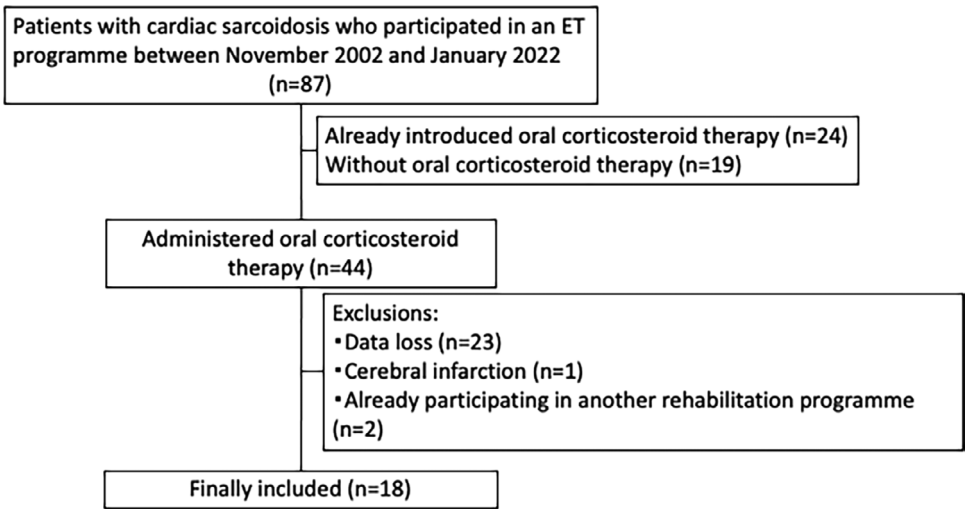

Figure 1. Participant selection flowchart. *Abbreviation:* ET: Exercise training.

after the initiation of oral corticosteroid therapy (prednisolone dose at initial ET, 29±4 mg). The baseline characteristics of the 18 patients with CS are shown in Table 1. The mean age of the patients was 62±10 years; 50% were male, and none received methotrexate.

After a month of ET, the patients were administered 22±3 mg/day prednisolone. The patients had significantly worse QIS/BW ratios during the corticosteroid induction period (0.52±0.12 to 0.48±0.11 kgf/kg, *P*=.048) (Figure 2A). Overall, 80% of patients experienced muscle weakness during the corticosteroid induction period. The patients had no significant improvement in QIS/BW ratios during the corticosteroid tapering period (0.53±0.08 to 0.58±0.06 kgf/kg, *P*=.099) (Figure 2B). We performed a receiver operating characteristic curve analysis to determine whether daily oral corticosteroid administration at 4 months could predict improved corticosteroid myopathy in patients with CS. The optimal prednisolone dose for predicting QIS improvement was 12.5 mg/day (sensitivity: 1.00; specificity: 0.67). Patients were categorized into two groups based on their prednisolone dose at 4 months (≤12.5 mg/day or >12.5 mg/day). Patients who received ≤12.5 mg/day prednisolone had significant improvement in the QIS/BW ratios during the corticosteroid tapering period (0.49±0.07 to 0.59±0.03 kgf/kg, *P*=.043) (Figure 2C). On the contrary, patients who received >12.5 mg/day prednisolone exhibited no significant improvement in the QIS/BW ratios during the corticosteroid tapering period (0.58±0.06 to 0.57±0.09 kgf/kg, *P*=.917) (Figure 2D). The ΔQIS (change in QIS between one month and 4 months)/BW ratio showed more improvement in the ≤12.5 mg dose group than in the >12.5 mg dose group (0.098±0.090 vs. −0.003±0.065, *P*=.049).

At baseline, patients taking a dose ≤12.5 mg/day had lower body mass indices and higher statin prescription rates than those taking different doses (Table 2).

As shown in Table 3 patients who received ≤12.5 mg/day prednisolone at 4 months had a significantly lower mean corticosteroid dose during the corticosteroid tapering period than the other patients. Attendance of ET during the corticosteroid induction period (*P*=.531), corticosteroid tapering period (*P*=.365), and total number of sessions (*P*=.576) were similar in the ≤12.5 mg and >12.5 mg dose groups.

No serious arrhythmic events such as sustained ventricular tachycardia or implantable cardioverter-defibrillator (ICD) discharges were observed during any of the in-hospital exercise training sessions. During the follow-up period, two patients with either an ICD or a cardiac resynchronization therapy defibrillator experienced anti-tachycardia pacing therapy delivered by their devices—one while at home and the other during hospitalization but outside of exercise sessions. These episodes were not temporally associated with exercise sessions.

Table 1. Patient characteristics

	All (n=18)
Age, years	62±10
Male sex	9 (50)
Body mass index, kg/m^2	23.4±3.0
Comorbidity	
Isolated CS	12 (67)
Dyslipidaemia	9 (50)
Diabetes	3 (17)
Obesity	6 (33)
Device	
Cardiac resynchronization therapy	8 (44)
Implantable cardioverter defibrillator	7 (39)
Pacemaker	2 (11)
None	1 (6)
Left ventricular ejection fraction, %	37±9
Left ventricular end-diastolic diameter, mm	61±12
Left ventricular end-systolic diameter, mm	51±12
B-type natriuretic peptide, pg/mL	131 [55, 253]
Estimated glomerular filtration rate, mL/min/1.73 m^2	58±16
Medication	
Diuretic	9 (50)
β-Blocker	16 (89)
Statin	10 (56)
Antiarrhythmic agent	5 (28)
Initial dose of prednisolone	30±2
Dose of prednisolone on beginning exercise-based cardiac rehabilitation, mg	29±5
Dose of prednisolone after a month, mg	22±3
6-min walk distance, m	537±64

Abbreviation: CS, cardiac sarcoidosis. Data are presented as mean±standard deviation or n, %

Discussion

This study revealed that the QIS/BW ratio significantly worsened during the corticosteroid induction period despite continued ET, and the improvement during the corticosteroid tapering period depended on the corticosteroid dose at 4 months. Patients whose prednisolone dosage was reduced to ≤12.5 mg/day at 4 months showed significant improvement in the QIS/BW ratio during the corticosteroid tapering period. In this study, patients' muscle strength weakened after corticosteroid administration and improved with corticosteroid dose reduction, consistent with the characteristics of corticosteroid myopathy. Generally, high-dose, long-term corticosteroid use is a risk factor for the development of corticosteroid myopathy, especially oral prednisolone doses ≥40 mg/day (13). In this study, 80% of the patients experienced muscle weakness during the corticosteroid induction period. Considering that the typical starting dose of prednisolone in this study was 30 mg/day, more patients experienced corticosteroid myopathy than expected. Furthermore, even during the Exercise in Cardiac

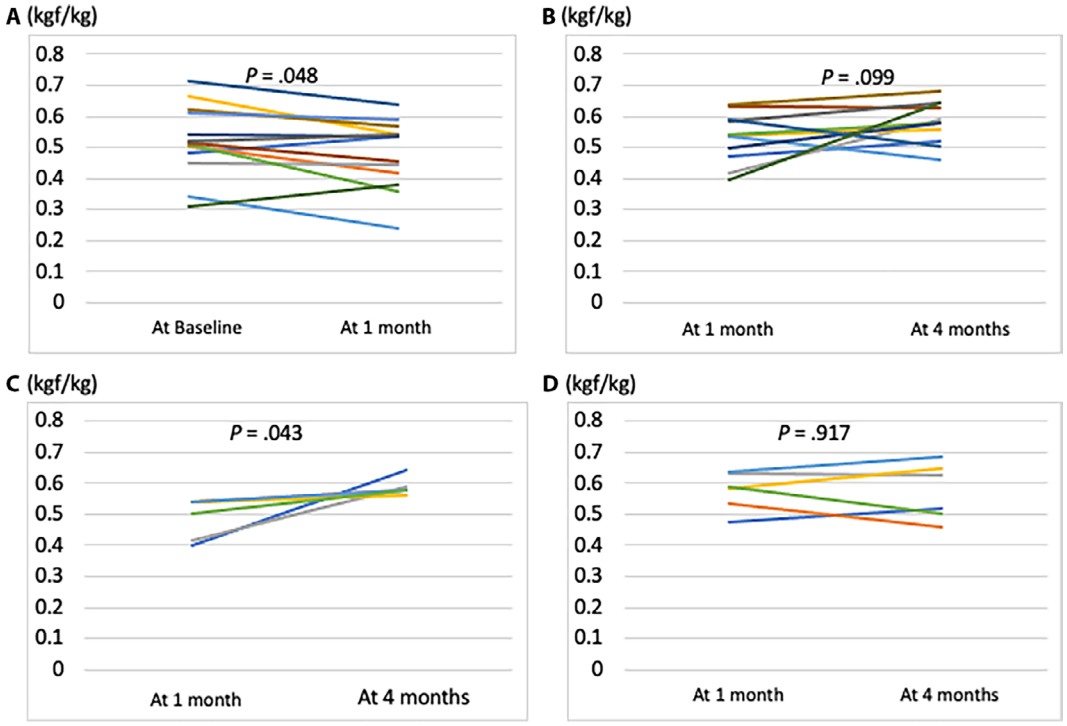

Figure 2. Changes in quadriceps isometric strength (QIS) over the period of the exercise training (ET) program. *Abbreviation:* BW: body weight. **A.** Changes in QIS from baseline to 1 month after ET initiation (corticosteroid induction period). **B.** Changes in QIS from 1 month to 4 months after ET initiation (corticosteroid tapering period). **C.** Changes in QIS from 1 month to 4 months after ET commencement (corticosteroid tapering period) in patients taking ≤12.5 mg daily prednisolone. **D.** Changes in QIS from 1 to 4 months after ET commencement (corticosteroid tapering period) in patients receiving >12.5 mg daily prednisolone.

Sarcoidosis with Corticosteroids corticosteroid tapering period, no apparent muscle strength recovery was observed when the daily prednisolone dose was >12.5 mg at 4 months. Patients with chronic heart failure have fewer type I muscle fibres (slow-twitch fibres) and a relatively higher proportion of type IIb muscle fibres (fast-twitch fibres) (14); corticosteroids cause muscle weakness, followed by atrophy of type IIb muscle fibres (4,15). As most patients with CS in this study had heart failure, patients with heart failure with a relatively high percentage of type IIb muscle fibres may be more susceptible to developing corticosteroid myopathy. Of note, it is not always possible to sufficiently reduce corticosteroid use until the end of the ET programme, as this depends on the patient's medical conditions. Therefore, we should evaluate the patient's corticosteroid dosage and consider extending the ET period as appropriate. These findings may be relevant for patients with collagen diseases receiving steroid therapy.

This study has some limitations. First, it was a single-centre study with a small sample size, and we could not adjust for confounding factors such as sex. Second, only patients for whom exercise therapy was requested by the treating cardiologist were included, which may have introduced a selection bias toward clinically stable patients. Although patients with significant arrhythmias were not formally excluded, no serious arrhythmic events were observed during in-hospital exercise sessions. Two patients experienced anti-tachycardia pacing at home during the follow-up period, but these were not temporally associated with exercise sessions.

Conclusions

Patients with CS treated with 30 mg/day prednisolone often experience corticosteroid myopathy, which is difficult to prevent with ET. Improvement in muscle strength depends on the corticosteroid dose

Table 2. Characteristics of the 12 patients in the corticosteroid tapering period

	Prednisolone ≤ 12.5 mg/day (n=6)	**Prednisolone > 12.5 mg/day (n=6)**	***P* value**
Age, years	62±8	59±12	.566
Male sex	2 (33)	2 (33)	1.000
Body mass index, kg/m^2	20.5±1.6	25.9±1.4	<.001
Comorbidity			
Isolated	2 (33)	5 (83)	.242
Dyslipidaemia	5 (83)	2 (33)	.242
Diabetes	2 (33)	0 (0)	.455
Obesity	0 (0)	4 (67)	.061
Device			.530
Cardiac resynchronisation therapy	1 (17)	4 (67)	
Implantable cardioverter defibrillator	3 (50)	2 (33)	
Pacemaker	1 (17)	0	
None	1 (17)	0	
Left ventricular ejection fraction, %	37±9	39±4	.638
Left ventricular end-diastolic diameter, mm	57±9	61±9	.496
Left ventricular end-systolic diameter, mm	47±9	52±10	.385
B-type natriuretic peptide, pg/mL	163 [48, 274]	131 [70, 187]	.631
Estimated glomerular filtration rate, mL/min/1.73 m^2	63±16	59±14	.719
Medication			
Diuretic	4 (67)	3 (50)	1.000
β-Blocker	5 (83)	6 (100)	1.000
Statin	5 (83)	1 (17)	.021
Antiarrhythmic agent	1 (17)	3 (50)	.546
6-min walk distance, m	552±58	570±42	.546

Data are presented as mean±standard deviation or n (%).

Table 3. Change in QIS and follow-up data

	Prednisolone ≤ 12.5 mg/day (n=6)		**Prednisolone > 12.5 mg/day (n=6)**	
	1 month	**4 months**	**1 month**	**4 months**
QIS/BW, kgf/kg	0.49±0.07	0.59±0.03*	0.58±0.06	0.57±0.09
Dose of prednisolone, mg/day	20.8±3.8	9.6±2.9*	23.3±2.6	15.0±0*,†
Mean dose of prednisolone at the corticosteroid tapering period, mg/day	13±4		17±1†	
Attendance of ET at the corticosteroid induction period, session	14±11		18±5	
Attendance of ET at the corticosteroid tapering period, session	20±18		13±9	
Total number of attended ET sessions, session	32±20		28±5	

Abbreviations: ET, exercise training; QIS, quadriceps isometric strength; BW, body weight. Data are presented as mean±standard deviation. *P<.05 vs a month, †P<.05 vs prednisolone ≤ 12.5

during the corticosteroid tapering period. However, further studies are required to confirm this hypothesis.

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Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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