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ORIGINAL COMMUNICATION

High-intensity training in patients with spinal and bulbar muscular atrophy

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Abstract

Objective Long duration, moderate-intensity exercise is not well tolerated in patients with spinal and bulbar muscular atrophy (SBMA). This study investigated whether patients with SBMA can benefit from high-intensity training (HIT).

Methods Ten patients with SBMA were randomized to 8 weeks of supervised HIT [$n=5$; age = 50 (25–63) years] followed by 8 weeks of self-training or 8 weeks of no training followed by 8 weeks of non-supervised HIT [$n=5$; age = 50 (26–54) years]. Training consisted of 2×5-min exercise periods with 1-min cyclic blocks of intermittent maximal intensity exercise on an ergometer bike. Maximal oxygen capacity (VO_{2max}) and workload (W_{max}) were measured before and after training by incremental exercise tests. Plasma creatine kinase levels, self-rated muscle pain, muscle fatigue, and activity level were monitored throughout the training period.

Results Eight patients completed training. One patient dropped out after 5 weeks of training for private reasons. Another patient was excluded after 4 weeks due to lack of compliance. Eight weeks of training increased both VO_{2max} (1.9 ± 2.3 ml min^{-1} kg^{-1}; $p=0.04$) and W_{max} (15.6 ± 17.9 W; $p=0.03$) in the 8 patients who completed training. There were no changes in plasma creatine kinase levels, self-reported muscle pain or muscle fatigue activity level after training.

Conclusion This pilot study suggests that high-intensity training is safe and improves fitness in patients with SBMA. Unlike low- and moderate-intensity training, HIT is efficacious and favored over other training forms by the patients.

Keywords HIT · Training · Kennedys disease · Spinal and bulbar muscular atrophy

Introduction

Patients with spinal and bulbar muscular dystrophy (SBMA) suffer from degeneration of the motor neurons leading to progressive atrophy and weakness of bulbar and extremity muscles.

Exercise at low- and moderate-intensity causes fatigue and does not improve oxidative capacity in patients with SBMA [1, 2]. This might be due to a neural fatigue related to the need for remaining motor neurons to fire more frequently during exercise and support enlarged motor units [1, 3, 4].

High-intensity training (HIT) is timesaving and efficient in healthy persons [5–8]. We hypothesized that HIT could be better tolerated in patients with SBMA, because motor neurons would only need to be active in a fraction of the time needed for training at moderate activity. The aims of the study were therefore to investigate if, (1) HIT is safe for patients with SBMA; (2) patients are able to improve fitness by performing HIT; and (3) if this form of training is feasible in this patient group.

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Methods

Study design

In this randomized, controlled, parallel pilot study, we investigated the effect of 8 weeks of HIT. Patients were randomized to either (1) a supervised training group followed by optional self-training or (2) no training (usual care) followed by unsupervised training.

Ten men with genetically verified SBMA (CAG repeat lengths 45 ± 4 (range 40–51) were included. Exclusion criteria were: (1) more than 1 h of aerobic exercise training weekly and (2) other medical condition that could confound interpretation of trial results.

Intervention

HIT: patients trained on an ergometer bike for 10 min, 3 times weekly for 8 weeks at home or in fitness centre. Supervised patients performed one of the three weekly training sessions in our clinic. Supervised patients were offered to continue training for another 8 weeks without supervision. They were tested again at the end of this period. Unsupervised patients started of with 8 weeks of no training (usual care), before starting an 8-week unsupervised training. Interval training was based on the 30–20–10 s concept [8] (Fig. 1).

Before training, patients received an instruction lesson and an audio file with a recorded training guide for home use.

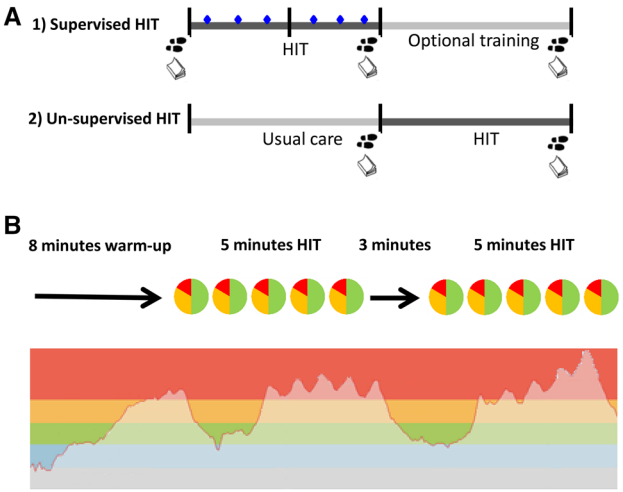

Fig. 1 Study design. (i) Ten male SBMA patients were randomized to either (1) 8 weeks usual care followed by 8 weeks unsupervised high-intensity training (HIT) ($n=4$) or 2) 8 weeks supervised HIT with weekly visit followed by 8 weeks of optional training ($n=5$). Patients were tested before, during and after training. Patients wore pedometers and filled in activity logs, to measure activity level. Following symbols marks | = test days; blue diamond = supervised training session performed in our lab; 👣 = pedometer worn for a week prior to test; 📝 = daily activity log on self-rated activity level, muscle pain, and fatigue. (ii) Patients trained on a bicycle ergometer. They had three training sessions a week. One training session consisted of 8-min warm-up followed by to 5-min HIT blocks separated by a 3-min break. The 5-min blocks were build up by 5 circles, where patients trained 30 s in low intensity, 20 s in moderate intensity, and 10 s all out 5 times repeatedly. Heat rate data from a patient during an HIT session is shown. The colours marks the different pulse zones. In interval peaks, the patient reaches the red zone, which is close to heart rate max

Functional outcomes

Primary outcome

Changes in maximal oxidative capacity (VO_{2max}) and performed workload (W_{max}) were primary outcome measures. VO_{2max} and W_{max} were tested before and after training with an incremental test to exhaustion, with workload increases every minute, on a cycle ergometer (Lode Excalibur Sport, The Netherlands). Pulmonary gas exchanges were measured continuously with breath-by-breath indirect calorimetry (Cosmed Quark CPET, Italy).

Secondary outcomes

Secondary outcomes included the 6-min walk test (6MWT) [9], assessed before and after training, and changes in activity levels assessed by a pedometer (Omron Walking Style Pro Pedometer HJ-720IT-E2) worn on 4–7 consecutive days before, during and after training. Two weeks before training and during training, subjects were instructed to register training daily in a log book. For each training session, they recorded self-rated level of physical activity, fatigue, and muscle pain on a visual analogue scale (VAS).

Safety outcomes

Plasma creatine kinase (CK) was measured during the trial as a marker of muscle damage.

Compliance

Participants wore a pulse-watch (Polar Pro Trainer Software) during training sessions. Heart rate data were downloaded to monitor compliance and register intensity of training.

Table 1 Baseline data demography and clinical characteristics of participants

	Mean	SD	Range
Age	53	12	25–64
BMI (kg m^{-2})	25	4	19–32
Quadriceps strength (kg)	10	7	6–27
VO2max baseline (ml min^{-1} kg^{-1})	23	12	14–51
6MWT (m)	329	213	38–676
Creatine kinase (U/l)	707	498	76–1800
Steps (km/day)*	3.2	3.2	0.1–9.1

Shows demographic baseline data for 10 male SBMA patients collected on the test day before training start. Data are shown as mean age, BMI, quadriceps muscle strength, maximal oxygen capacity (VO_2max), six-min walk test (6MWT), and Creatine Kinase (CK)

*Steps were mean m/day measured by pedometer that patients worn 7 days prior to training start

Statistical analysis

Values are expressed as mean ± standard deviation (SD) or mean (range). Changes within groups were analysed using a student's *t* test for paired data.

Ethics

This study was registered at https://www.clinicalTrial.gov and approved by the Danish National Committee for Health Research Ethics (H-4-2014-035), and Danish Data Protection Agency (30-1333). Subjects gave written consent to participate. The study was conducted in accordance with the principles of the Helsinki Declaration.

Results

Intervention

Five patients were randomized to the supervised group and 5 patients to the unsupervised group. One patient in the supervised group dropped out after 4 weeks training for private reasons. One patient in the unsupervised group was excluded after 4 weeks training due to lack of compliance. Dropout rate and training compliance was almost identical in supervised and unsupervised groups, and therefore, training data for the two groups were pooled. Baseline data are showed in Table 1.

Eight patients completed 8 weeks of training with 22.9 ± 2.9 training sessions (target 24 sessions).

Pulse data showed that patients trained with a high heart rate in the interval passes. Average training heart rate was 85 ± 10% compared to the patient's maximal heart rate defined in the incremental test.

Maximal heart rate reached in 5-min training peaks was 95 ± 11% compared to tested values.

Primary outcomes

HIT

Training improved both fitness and workload performance in the 8 patients after 8 weeks of HIT. VO_{2max} increased by 8% [1.9 ± 2.3 ml min^{-1} kg^{-1} ($p = 0.04$)] and W_{max} by 16% [15.6 ± 17.9 W ($p = 0.03$)] (Fig. 2).

Usual care

There was no change in fitness during the non-training period in patients following their usual care.

Optional training

Three of the four patients who completed supervised training, continued with 8 weeks of unsupervised training. They trained 35–50 min per week during the 8 extra weeks. The increase in VO_{2max} and W_{max}, obtained after supervised training, was maintained after the optional training period.

The patient who chose not to continue training was the youngest and least affected patient.

Secondary outcomes

Training did not significantly increase 6-min walking distance in patients [15 ± 37 m ($p = 0.26$)] (Fig. 2).

Pedometer data from two patients were unavailable, because the patients forgot to wear the pedometer. Training tended to reduce daily walking distance from 3.1 ± 3.2 to 2.4 ± 2.4 km/day ($p = 0.09$).

Safety outcomes and training preference

No rise in CK levels occurred after 8 and 16 weeks of training. Self-rated muscle fatigue, muscle pain, and activity level remained the same throughout the training period. After completing 8 weeks of HIT, patients were asked about

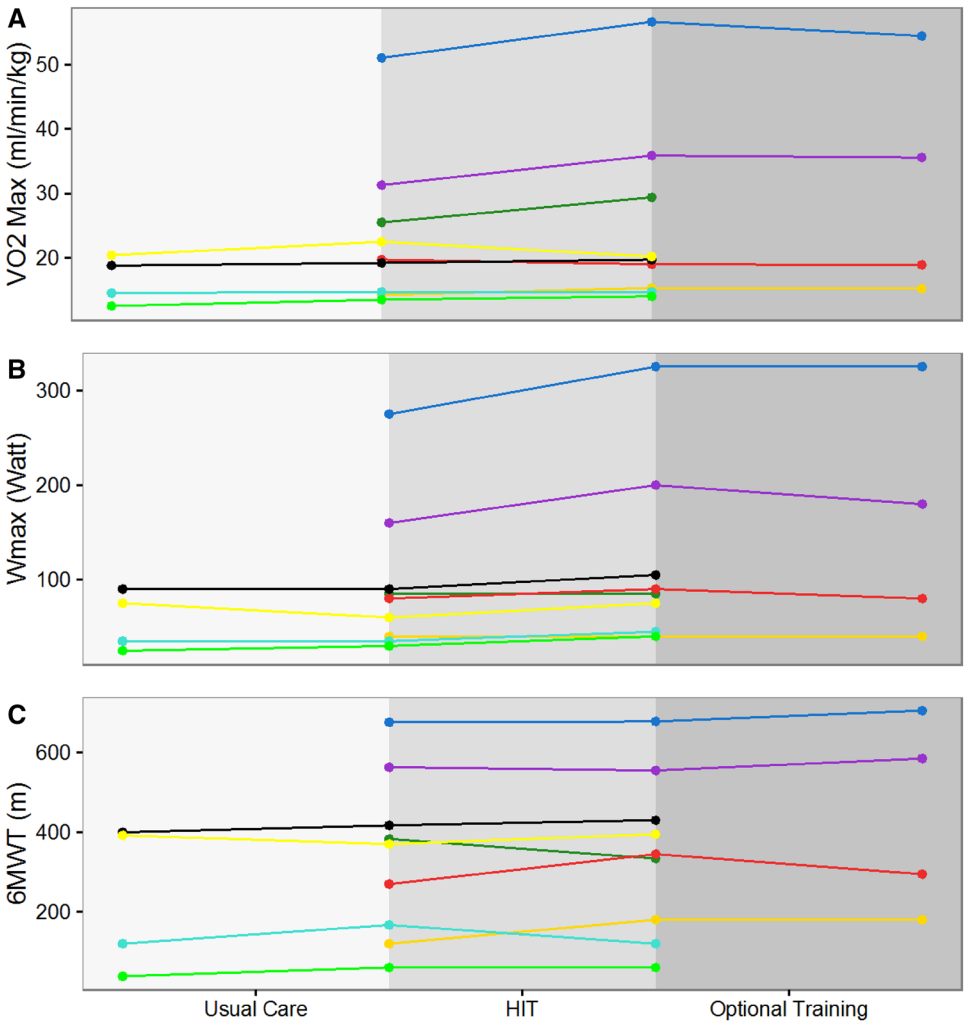

Fig. 2 Patients were tested before usual care, before high-intensity training (HIT) and after training ($n=4$), or before HIT, after HIT and after optional training. **a** Maximal oxygen capacity (VO_2max) was measured on a bicycle ergometer to exhaustion. VO_2max values are shown as ml oxygen per minute per kg. **b** Data show maximal workload containing during the VO_2max test. **c** Patients did a 6-min walk test (6MWT) where patients walks as long as possible in 6 min

their training preference, and all patients answered that they preferred HIT over other training forms.

Discussion

The main findings of this study are that in patients with SBMA: (1) HIT is well tolerated and associated with a high compliance; (2) HIT significantly increases fitness; (3) HIT is safe as judged by stable CK levels, no reported adverse event, and no changes in reported muscle fatigue and pain; and (4) patients liked the training and wished to continue after completing the first 8 weeks of training. In SBMA, these findings are new, as the only two other training studies performed in patients with SBMA found that fitness was not improved and that patients disliked regular training at low- and moderate intensity and did not want to continue training [1, 2]. Similar findings of exercise-induced fatigue and unwillingness to continue the training program were found in two studies of low-to-moderate-intensity training in patients with spinal muscular atrophy type III [3, 10], which suggests that training of longer duration is not suitable for patients with motor neuron diseases [1, 3, 4, 10]).

A likely explanation for the efficacy of HIT and inefficacy of lower intensity training in SBMA could relate to the longer period of restitution between training bouts, and the shorter period that the large motor units in SBMA need to be active vs. longer duration low-to-moderate-intensity training. Long-term effects and compliance of HIT should be studied in SBMA.

In conclusion, HIT is well tolerated and safe for patients with SBMA. It increases fitness and training does not decrease patient's daily activity level, and should be considered as a rehabilitation strategy for patients affected by SBMA.

Author contributions KH: design of study, analysis, acquisition, and interpretation of data and drafting the manuscript. GA: design of study, analysis, acquisition, and interpretation of data and critical revision of manuscript. AB: analysis, acquisition of data, and critical revision of

manuscript. HA: acquisition of data and critical revision of manuscript. JV: design of study, interpretation of data, and critical revision of the manuscript.

Compliance with ethical standards

Conflicts of interest Dr. Andersen, Dr. Heje, and Dr. Buch reports no disclosure. Dr. Vissing reports having received research and travel support, and/or speaker honoraria from Sanofi/Genzyme, Ultragenyx Pharmaceuticals, Santhera Pharmaceuticals and aTyr Pharma, and served as consultant on advisory boards for Sanofi/Genzyme, aTyr pharma, Ultragenyx Pharmaceuticals, Santhera Pharmaceuticals, Sarepta Therapeutics, NOVO Nordisk, Alexion Pharmaceuticals and Stealth Biotherapeutics within the last 3 years.

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