ORIGINAL RESEARCH

Inspiratory Muscle Training Increases Endurance Time in Patients with Fontan Circulations

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Introduction

Single ventricle (SV) physiology comprises multiple types of cardiac malformations in which there is only a single well-developed ventricle. Contemporary palliation consists of committing the well-formed ventricle to the aorta as the "systemic" ventricle, leaving the patient without a sub-pulmonary ventricle. Currently, a Glenn shunt (superior vena cava to pulmonary artery connection) is usually performed around 6 months of age followed by a Fontan procedure (inferior vena cava to pulmonary artery connection) between 18 months and 4 years. Resting cardiac output is usually reduced and maximal exercise oxygen uptake ($\dot{V}O_2$) averages 60-65% that of healthy subjects of similar age and gender.[1-4] Fontan circulations are particularly dependent upon inspiratory muscle function to drive anterograde pulmonary blood flow (PBF),[5] with the negative intrathoracic pressure of inspiration leading to large increases in PBF.[6-7]

Inspiratory muscle training (IMT) is an intervention which strengthens the respiratory muscles. Subjects perform tidal breathing through a hand-held device with a one-way valve and an adjustable level of resistance to inspiration. IMT has been shown to cause significant improvements in inspiratory pressures, peak $\dot{V}O_2$ and quality of life in a number of clinical populations including chronic obstructive pulmonary disease and congestive heart failure.[8-13]

Given the unique dependence of cardiac output upon inspiratory muscle function in Fontan circulations, we hypothesized that IMT might enhance PBF and thus improve exercise tolerance. To explore this, pulmonary function, exercise parameters and self-reported variables were measured before and after IMT in a sample of adults with Fontan circulations.

Methods

Subjects

Adult subjects of at least 59 inches in height (due to dimensions of the cycle ergometer) were identified from the Adult Congenital Heart Disease Clinic at Harbor-UCLA Medical Center and the Ahmanson/UCLA Adult Congenital Heart Disease Center at Ronald Reagan UCLA Medical Center. Exclusion criteria included the presence of a sub-pulmonary ventricle, pregnancy or any contraindication to stress testing. The study was conducted at Harbor-UCLA Medical Center and was approved by the institutional review board at the Lundquist Institute at Harbor-UCLA Medical Center. Written informed consent was obtained from all subjects.

Study Design

Subjects were characterized at baseline by demographics, cardiac history and pulmonary function tests including maximal inspiratory and expiratory pressures (MIP and MEP). Functional capacity was characterized by NYHA class and by peak $\dot{V}O_2$ measured during incremental exercise testing on a stationary cycle. On a separate testing day, exercise endurance time was measured at a fixed work rate. The RAND SF-36 and symptom rating by Borg scales were used for assessment of patient-centered variables. After baseline assessment, subjects underwent 6-8 weeks of IMT, then returned for repeat measurement of the study variables.

Baseline Testing

Pulmonary function testing was performed in accordance with American Thoracic Society standards[14-15] in a body plethysmograph. MIP and MEP were performed in triplicate from residual volume and total lung capacity, respectively.[16] Exercise testing was performed on an electronically braked cycle ergometer with the patient breathing through a mouthpiece interfaced with a metabolic cart (SensorMedics) for breath-by-breath measurement of ventilatory flow rates, gas tensions and related variables for calculation of $\dot{V}O_2$, minute

ventilation (VE), and carbon dioxide output ($\dot{V}CO_2$). Electrocardiogram and pulse oximetry were monitored continuously. Modified Borg scores for dyspnea and leg fatigue were recorded intermittently. The incremental protocol began with 3 minutes of cycling with no resistance to pedaling followed by a continuous increase in work rate in a "ramp" profile. The rate of increase in work rate ranged from 10-20 watts/minute with the goal of the patient reaching symptom-limitation in 8-10 minutes as previously described.[17] Exercise continued until limited by symptoms or terminated for safety concerns. Constant work rate testing was performed on a separate test day within 2 weeks with the work rate set at 80% of peak work rate attained on incremental testing. Subjects were instructed to continue cycling for as long as possible and exercise duration was measured to the nearest second. MIP and MEP were measured prior to each exercise test and again serially following exercise to detect decrements attributable to respiratory muscle fatigue. NYHA functional class was determined by the principal investigator based on interview and the RAND-36 questionnaire was self-administered.

Inspiratory Muscle Training

After baseline assessments, subjects began a 6- to 8-week trial of IMT using a commercially available handheld device in which a one-way valve provides resistance to inhalation over a range of inspiratory flow rates (Threshold®, Philips Respironics). Subjects were instructed to perform IMT twice daily for 20 minutes per session with at least 4 hours between sessions. The initial pressure threshold on the device was set at 30% of the measured MIP, consistent with protocols used in prior studies of IMT in heart failure.[11-13] Subjects were instructed to increase the inspiratory load by 1 cm of H_2O/week to a maximum of 41 cm H_2O. Subjects for whom 30% baseline MIP exceeded the maximum inspiratory load setting on the device were instructed to perform IMT at the maximum setting (41 cm H_2O) throughout the study. All subjects were contacted weekly via telephone or email to reinforce training schedules and ensure adjustment of the inspiratory load.

Post IMT Assessments

Testing

After IMT, measurements of MIP and MEP and incremental and constant work rate exercise endurance testing were repeated, utilizing the same protocols and work rates as baseline testing. Exercise tests were performed on different dates within 2 weeks of each other and subjects continued IMT until all testing was completed.

Patient Centered Measures

NYHA functional class and RAND-36 scores were re-assessed. Once all testing was completed, subjects provided feedback on the acceptability of the study intervention in a post-study questionnaire and an exit interview.

Analysis

Values for variables at peak exercise were defined as the average of breath-by-breath data over the final 30 seconds of exercise. Graphical analysis was used for identification of anaerobic threshold. For the constant work rate test, endurance time was defined to the nearest second. Estimates were made of the initial, "phase I" increase in $\dot{V}O_2$ at the start of constant work rate exercise as a marker of the initial exercise-induced increase in PBF.[18] This was calculated by subtracting the average value of $\dot{V}O_2$ during the last 30 seconds of pre-exercise rest from the average measured over the first 30 seconds of exercise.

Statistics

To evaluate effects of the intervention, paired t-tests were used to compare baseline and post-IMT values of MIP, MEP and exercise variables. Variables were treated as independent without correction for multiple comparisons. Paired t-tests were also used to compare end-exercise variables for incremental versus constant work rate tests at the pre and post intervention time points. Patient-centered measures were analyzed descriptively as NYHA functional class and scores for individual domains of the RAND-36 using the provided scoring system. Acceptability of IMT intervention to the subjects was assessed from the questionnaire administered at the end of IMT and an informal exit interview.

Results

Eight subjects were screened and enrolled for the study. One subject was excluded at the first visit due to inability to complete the baseline incremental exercise test because of symptomatic sinus tachycardia early in exercise. The remaining 7 subjects completed the entire protocol. There were no other adverse events during testing or IMT.

Demographics

Baseline characteristics of the subjects are shown in Table 1. Of note, 3 subjects had a history of hemidiaphragm paresis demonstrated on prior imaging, including 1 who had undergone a diaphragm plication procedure.

Baseline pulmonary function testing

Pulmonary function at baseline is shown in Table 2. Mean lung volumes and diffusing capacity were mildly to moderately reduced relative to healthy predicted values. Subjects with hemidiaphragm dysfunction represented the lower end of the observed measures. MIP and MEP are shown in Table 3. Most of the subjects had values within ranges reported for healthy persons of similar age and gender. This contrasts with prior reports of reduced respiratory pressures in patients with Fontan circulations.[19-20]

Exercise Function and Respiratory Muscle Strength

Baseline Testing

At baseline, peak exercise capacity of the subjects was reduced with peak $\dot{V}O_2$ ranging from 14.2 to 23.6 ml/min/kg, or 50-83% of the age, gender and size based predicted values (Table 3). Anaerobic threshold values averaged 40% of the predicted peak $\dot{V}O_2$ value, which approximates the lower limit of normal, with values for 3 of the subjects in the normal range and values for the other 4 below normal. These findings are consistent with prior reports of exercise function in the Fontan population.[2-4] Oxygen saturation by pulse oximeter at peak exercise averaged 92% (range 86-99%). $\dot{V}O_2$ attained at the end of constant work rate endurance testing was not different than the peak values attained on incremental testing (Figure 1).

All subjects had evidence of chronotropic impairment with peak exercise heart rates (HR) less than 80% of the predicted maximal age-predicted HR (range 46-75% of predicted). One subject was in chronic atrial fibrillation and 2 subjects had paced rhythms. Peak $\dot{V}O_2$/HR values ranged widely from 60-141% of predicted values, likely reflecting heterogeneity in ventricular morphology, Fontan type and chronotropic responsiveness. Peak ventilation on the incremental test averaged 57% of the subjects' maximum voluntary ventilation (range 36-77%). There was no consistent change in MIP or MEP measured in the 10 minutes following maximal exercise compared to that measured before (data not shown).

Post IMT Testing

IMT was associated with a mean increase in MIP of 19.1 cm/H_2O +/- 15.6 ($p=0.001$). Peak $\dot{V}O_2$ and anaerobic threshold (AT) were both numerically higher on the post IMT testing than prior, but this did not reach statistical significance. There were also no significant changes in peak values of work rate, HR or respiratory exchange ratio (RER) during incremental exercise testing following IMT. There was, however, a significant increase in endurance time of 98 seconds on the constant work rate test (from 324 +/- 107 seconds before IMT to 422 +/- 92 seconds after IMT, $p<0.001$). Pre- and post-training profiles of pulmonary gas exchange are shown for 1 subject in Figure 1.

Findings in Subjects with Hemidiaphragm Paresis

Because the presence of hemidiaphragm paralysis might significantly affect measures made in this study, results for the 3 patients with this finding were reviewed separately and appeared to be qualitatively similar to those of the group as a whole. Both MIP and endurance time increased from pre- to post-IMT testing.

Phase I $\dot{V}O_2$

There were no significant differences in the estimated phase I $\dot{V}O_2$ amplitude (as reflected in first 30 seconds of constant work rate test) after IMT when compared with baseline (Table 3). There were also no significant differences in HR, $\dot{V}O_2$/HR or VE during the phase I period after IMT (data not shown).

Patient-centered Outcomes

Domain scores from RAND-36 scores were tabulated but statistical formal testing was not performed due to the small sample size and multiple comparisons. However, average scores in the domains of role limitations due to physical health problems, social functioning, pain and general health were all numerically higher following IMT. NYHA functional class and the highest Borg scores did not significantly change.

Acceptability of IMT

An exit questionnaire was used to assess the acceptability of this intervention to the subjects. Six out of the 7 subjects reported performing IMT exercises daily twice a day as directed. Many subjects described the exercises as being difficult but becoming easier over time. In response to open ended questions, all subjects noted subjective improvements in their exercise tolerance and reported less dyspnea and/or "easier" breathing during spontaneous activities.

Discussion

Major Findings

IMT was associated with improved exercise tolerance, reflected by exercise endurance time, as well as subjective improvement in breathing. Our findings are similar to Laohachai et al, which also found that 6 weeks of IMT improved MIP but not peak $\dot{V}O_2$.[21] They reported improvements in resting ejection fraction on cardiac MRI after 6 weeks of IMT, suggesting that augmentation of inspiratory muscle strength may in turn augment cardiac output. Lack of improvement in peak $\dot{V}O_2$ could be due to insufficient statistical power to identify small changes in this parameter, or from exercise limitation being due to factors other than circulatory capacity. Our findings are also concordant with those reported by Wu et al,[22] who found that IMT improved peak work rate and demonstrated a trend toward higher peak $\dot{V}O_2$ and improved ventilatory efficiency. However, the finding of improved endurance time is unique to the present study.

Endurance Time

Exercise endurance time was chosen as the endpoint for this study because it can be more responsive to interventions than other exercise parameters and is increasingly used as a clinically meaningful outcome in interventional studies.[23] Endurance time is related in a curvilinear fashion to work rate

for exercise above a threshold work rate, referred to as termed critical power, which is above an individual's AT and defines the upper limit of sustainable exercise (Figure 2). Exercise in the range above critical power predictably leads to fatigue and exercise ends as subjects reach their maximal $\dot{V}O_2$. This is evidenced in the present study by subjects reaching similar $\dot{V}O_2$ values at the end of both constant work rate and incremental tests (Figure 1). Critical power increases after interventions that increase maximum $\dot{V}O_2$ and anaerobic threshold, and shifts in critical power can result in substantial increments in endurance times, especially for work rates in the asymptotic region of the relationship (Figure 2). This provides a basis for understanding how relatively trivial enhancements in conventional parameters of exercise function can confer significant benefit in tolerance for daily activities.[24]

Effects of IMT on Exercise Capacity and Purported Mechanisms

Effects on Exercise Ventilation

IMT has been reported to enhance exercise function in a number of populations. The mechanisms may differ between populations depending on cause of exercise limitation. By increasing respiratory muscle strength, IMT reduces respiratory muscle effort required for a given ventilatory requirement, which may directly enhance function in patients whose exercise tolerance is limited by lung mechanics such as those with chronic obstructive pulmonary disease (COPD) or neuromuscular weakness. In COPD, IMT improves symptoms of dyspnea and performance on functional tests like the 6-minute walk, but not measures of peak exercise capacity.[8]

Effects on Hemodynamics

IMT may affect exercise hemodynamics both directly and indirectly. Indirectly, reducing the relative work of breathing during high levels of exercise may reduce metabolic requirements and demand for blood flow by the respiratory muscles, therefore allowing more cardiac output to go to locomotor muscles. This mechanism has been invoked to explain the findings of improved endurance time in healthy fit subjects following IMT in whom endurance time increased and $\dot{V}O_2$ kinetics modified without an increase in peak $\dot{V}O_2$.[25]

IMT could also directly affect exercise hemodynamics via augmentation of central venous return and pulmonary perfusion. In healthy subjects with biventricular hearts, inspiration decreases intrathoracic pressure, leading to lower right atrial pressure and a suction effect from the systemic veins. PBF and thus cardiac output are increased due to enhanced right heart filling.[26-27] Fontan patients lack a sub-pulmonic ventricle and respiratory mechanics have even greater hemodynamic importance. It has been estimated that in this population, 1/3 of systemic venous return is dependent upon respiration[5] and inspiration increases PBF and consequently cardiac output by up to 64%.[6-7] The pronounced effects of inspiration upon PBF may be blunted or lost entirely in patients with reduced inspiratory muscle function due to diaphragmatic paralysis.[7] In the present study, even subjects with paralyzed hemidiaphragms demonstrated significant improvements in endurance time despite no change in peak $\dot{V}O_2$.

Potential Effects of IMT in Fontan Patients

Because of the dependence of the Fontan circulation on intrathoracic pressure changes, we hypothesized favorable effects from IMT in this population. Evidence for this was sought in peak exercise $\dot{V}O_2$ which is dependent on cardiac output. In addition, the early exercise (phase I) increase in $\dot{V}O_2$ was estimated as a reflection of the initial exercise-induced increase in PBF and volume.[28] The lack of any change in the phase I $\dot{V}O_2$ amplitude after IMT may reflect a lack of change in the intrathoracic pressures generated during spontaneous tidal breathing, despite increases in the subjects' maximal pressures, or could be due to poor resolution of the response related to noise in the breath-by-breath data measured over a single exercise transition.

Evidence for changes in breathing mechanics or respiratory muscle fatigue were sought in exercise ventilation and post exercise MIP. There was no systematic decrease in maximal respiratory pressures measured following exercise, suggesting that overt respiratory muscle fatigue was not a limiting factor to exercise in these subjects. Similarly, there was no significant change in the peak VE attained during either incremental or constant work rate exercise. Given similar ventilatory volumes and higher MIPs, the subjects were accomplishing the breathing task of exercise utilizing a lower proportion of maximal respiratory muscle function, which may be important in reducing the sense of dyspnea.

Limitations

This study was not blinded or controlled, and the exercise outcomes effort-dependent, so that non-physiological factors could have affected the results. The lack of measurable increases in peak exercise responses to either test protocol argues against the improved endurance times resulting merely from better motivation and effort on post-IMT testing. The small number of subjects limited power to detect modest changes in standard exercise parameters. This was the rationale for selecting endurance exercise time as a more sensitive endpoint. Although low respiratory muscle strength was not an inclusion criterion for the study, most subjects unexpectedly had baseline MIP values within the normal range, likely limiting the potential effect size of the intervention. Finally, this study included relatively healthy subjects as reflected in the average NYHA functional class of 1.3. Subjects with a greater degree of functional impairment or respiratory muscle weakness may benefit more from IMT.

Conclusion

In conclusion, IMT was well tolerated and effective in improving respiratory muscle strength in adults with Fontan circulations. IMT was associated with improvements in exercise endurance time, and improved subjective scores of physical function despite no change in peak $\dot{V}O_2$. These findings support the potential for use of IMT in the Fontan population.

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Figures

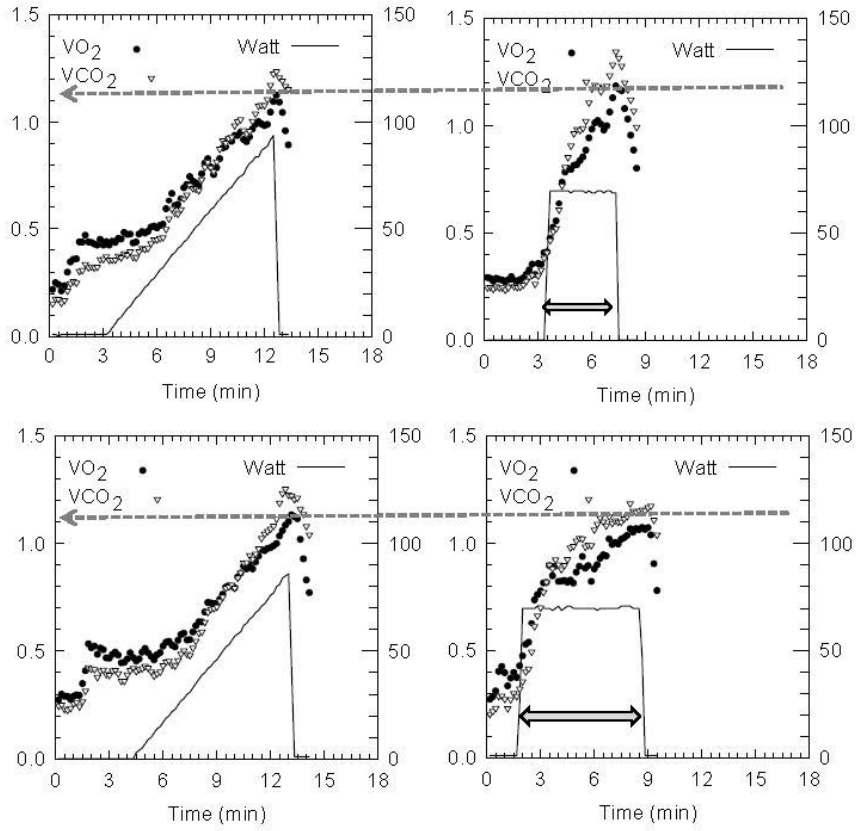

Figure 1. Oxygen uptake ($\dot{V}O_2$; closed symbols) and carbon dioxide output ($\dot{V}CO_2$, open symbols) for incremental (left) and high intensity constant work rate (right) exercise tests before (top) and after (bottom) inspiratory muscle training for 1 representative subject. Work rate profile is shown by solid lines. Peak $\dot{V}O_2$ was similar for both profiles of exercise and at both testing times (dotted lines), but endurance time for the constant work rate test was longer after the intervention (double headed arrows).

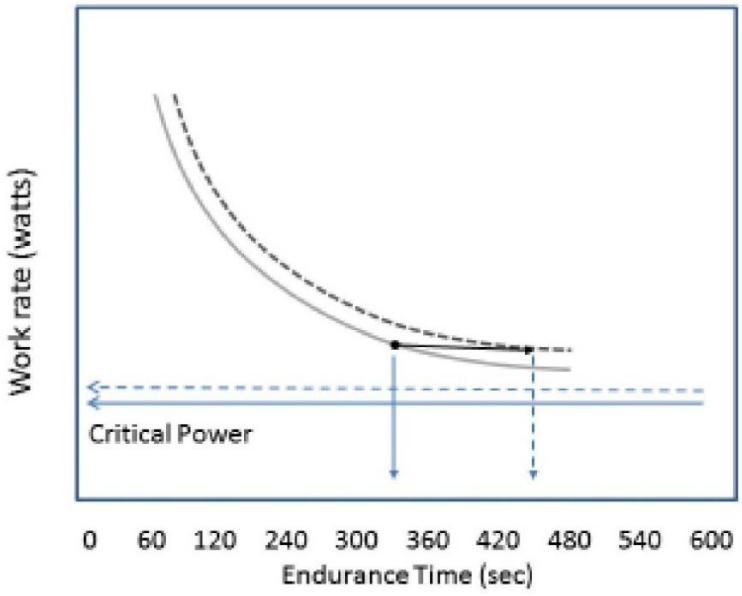

Figure 2. Example of the power-duration curve. Solid curve and horizontal line show the hyperbolic relationship of work rate and endurance time and the horizontal asymptote of the hyperbola which is termed critical power. Dashed curve and line show the shift in positions in response to interventions such as exercise endurance training. Vertical arrows illustrate how a small shift in the curve imparts substantial changes in endurance time for work rates in the lower range of the curve.

Table 1: Baseline Demographics

	Age (y)	**Sex**	**Anatomy**	**Fontan type**	**Revision**	**EF**	**Paced**
1	26	F	TA/PA	LT	-	55%	N
2	29	F	TA/PA	LT	-	50%	N
3	25	M	Unbalanced AV canal, DORV	Kawashima	EC (hepatic veins to PA)	35%	N
4	56	M	Double-inlet LV, PS	RA-PA	Modified LT	50%	Y
***5**	28	F	TA, VSD	RA-PA	EC	55%	N
****6**	37	F	DORV	Modified RA-PA	EC	50%	Y
***7**	32	F	DORV, PS	Modified RA-PA	EC	50%	Y

Abbreviations: TA – tricuspid atresia; PA – pulmonary atresia; VSD – ventricular septal defect; DORV – double outlet right ventricle; LT – Lateral tunnel Fontan; EC – Extracardiac Fontan; LV – left ventricle; RV – right ventricle; CoA – coarctation of the aorta; PS – pulmonary stenosis; RA – right atrium; PA – pulmonary artery; EF = ejection fraction.

* indicates subjects with hemidiaphragm paralysis
** indicates subjects with hemidiaphragm paralysis s/p plication

Table 2: Pulmonary Function at Baseline.

	All subjects (n = 7)		**HD paralysis subjects (n = 3)**	
	Mean (SD)	Percent predicted	Mean (SD)	Percent predicted
FVC (L)	2.8 (0.9)	73 (13)	2.4 (0.2)	69.7 (12.5)
FEV 1 (L)	2.2 (0.7)	69 (16)	2 (0.4)	67.3 (20.4)
FEV1/FVC (%)	81 (12)	98 (12)	82.7 (11)	99.3 (13)
VC (L)	2.9 (0.8)	74 (10)	2.4 (0.2)	70.3 (12.5)
TLC (L)	4.1 (0.9)	77 (6.5)	3.5 (0.1)	72.7 (9)
DLCO (%)	10 (3.2)	36 (8.8)	10 (1.8)	38 (8)
MVV (L/min)	89.5 (28.3)	-	78.3 (18)	-
MIP (cm H_20)	109 (39)	-	112 (31.5)	-
MEP (cm H_20)	109 (48)	-	89.3 (34.8)	-

Abbreviations: HD – hemidiaphragm; FVC – forced vital capacity; FEV1- forced expiratory volume at 1 second; VC – vital capacity; TLC – total lung capacity; DLCO – diffusing capacity for carbon monoxide; MVV – maximum voluntary ventilation; MIP – maximum inspiratory pressure; MEP – maximum expiratory pressure

Table 3: Exercise Function Before and After IMT

	Pre-IMT (SD)	**Post-IMT (SD)**	**Mean change (SD)**	**p-value**
Incremental CPET				
Peak WR (W)	91 (29)	98 (26)	7 (7)	0.3
Peak HR (bpm)	120 (24)	124 (21)	6 (15)	0.4
Peak VO2 (L/min)	1.3 (0.5)	1.4 (0.4)	0.10 (0.17)	0.18
Peak VO2 (ml/min/kg)	18.8 (5.6)	20.0 (4.8)	1.2 (2.3)	
Peak VO2 (% predicted)	62 (14)	67 (12)	3.7 (9.5)	
Peak VO2/HR (ml/min/beat)	10.8 (3.0)	11.3 (2.4)	0.42 (1.7)	
AT VO2 (L/min)	0.85 (0.3)	0.98 (0.38)	0.13 (0.21)	0.15
Peak RER	1.11 (0.10)	1.13 (0.11)	0.01 (0.08)	0.99
Peak Borg dyspnea score (n=4)	3 (0.8)	2.5 (1)	0.5 (1.3)	0.8
Peak Borg leg fatigue score (n=4)	2.8 (1.3)	3.3 (1)	-0.5 (1)	0.7
CWR CPET				
80% peak WR (W)	71.9 (23)	n/a (WR stable)	-	-
Peak HR (bpm)	113 (25)	120 (20)	7.4 (20)	0.4
End-exercise VO2 (L/min)	1.3 (0.4)	1.4 (0.4)	0.06 (0.24)	0.96
Endurance time (seconds)	324 (107)	422 (92)	98 (131)	<0.001

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