International Journal of Cardiology 168 (2013) 780–788

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Resistance training improves cardiac output, exercise capacity and tolerance to positive airway pressure in Fontan physiology☆

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ARTICLE INFO

Article history:
Received 9 August 2012
Accepted 7 October 2012
Available online 13 November 2012

Keywords:
Congenital heart disease
Single ventricle
Fontan operation
Cardiac rehabilitation
Exercise training
Cardiac function

ABSTRACT

Background: Subjects with Fontan-type circulation have no sub-pulmonary ventricle and thus depend exquisitely on the respiratory bellows and peripheral muscle pump for cardiac filling. We hypothesised that resistance training to augment the peripheral muscle pump might improve cardiac filling, reduce inspiratory-dependence of IVC return to the heart and thus improve exercise capacity and cardiac output on constant positive airway pressure (CPAP).

Methods: Eleven Fontan subjects (32+/−2 years, mean+/−SEM) had cardiac magnetic resonance imaging (MRI) and exercise testing (CPET); six underwent 20 weeks of high-intensity resistance training; others were non-exercising controls. After training, CPET was repeated. Four trainers had MRI with real-time flow measurement at rest, exercise and on CPAP in the trained state and following a 12-month detrain.

Results: In the trained state, muscle strength increased by 43% ($p=0.002$), as did total muscle mass (by 1.94 kg, $p=0.003$) and peak VO_2 (by 183 ml/min, $p=0.02$). After detraining, calf muscle mass and peak workload had fallen significantly ($p<0.03$ for both) as did peak VO_2 (2.72 vs. 2.18 l/min, $p<0.001$) and oxygen pulse, a surrogate for SV (16% lower, $p=0.005$). Furthermore after detraining, SV on MRI decreased at rest (by 11 ml, $p=0.01$) and during moderate-intensity exercise (by 16 ml, $p=0.04$); inspiratory-dependent IVC blood return during exercise was 40% higher ($p=0.02$). On CPAP, cardiac output was lower in the detrained state (101 vs. 77 ml/s, $p=0.03$).

Conclusions: Resistance muscle training improves muscle mass, strength and is associated with improved cardiac filling, stroke volume, exercise capacity and cardiac output on CPAP, in adults with Fontan-type circulation.

1. Introduction

First described in 1971 by Fontan and Kreutzer [1] as a surgical option for patients with tricuspid atresia, the remarkable Fontan procedure is now commonly performed to palliate various forms of essentially single-ventricle congenital heart disease (CHD), with increasing numbers surviving to adulthood. The Fontan circuit, which functions without the sub-pulmonary ventricle as a power source to pump blood through the lungs, relies heavily on the respiratory bellows to draw blood into the pulmonary vascular bed during inspiration [2]. As a consequence, cardiac output in these subjects falls during positive pressure ventilation [3].

Despite surgical advances in the Fontan operation there are important long-term consequences from living without a sub-pulmonary circulatory pump. Whilst subjects with a well-functioning Fontan-type circulation perform quite well during low-level day-to-day activities, they are generally limited during more intense levels of exercise; a major contributor to this limitation is reduced cardiac filling, due to the altered anatomy and physiology [4–7].

Even the normal heart cannot increase cardiac output more than a few percent without the aid of the periphery [8]. During upright exercise the peripheral pumping mechanism must overcome the effects of gravity to enable diastolic filling. At the onset of exercise stroke volume rises, by about the same volume as when a subject goes from supine to sitting [9]. This refilling of the ventricle is from blood mobilised from the

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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http://dx.doi.org/10.1016/j.ijcard.2012.10.012

lower extremities [10]. In addition, venous compliance in the leg has been shown in normal subjects to have a close negative correlation with calf surface area and muscle mass [11] and in the Fontan circulation the effects of gravity have been shown to adversely affect anterograde inferior vena caval (IVC) flow [12]. This suggests that an enhanced peripheral muscle mass and associated skeletal muscle pump could be especially important in those with Fontan physiology.

We hypothesised that muscle resistance training to augment the peripheral muscle pump might improve cardiac filling and stroke volume in the Fontan circulation and reduce the inspiratory dependence of IVC blood return to the heart. For the same reasons, we postulated that resistance training might also improve exercise capacity and cardiac output during constant positive airway pressure (CPAP).

2. Methods

2.1. Subjects

Twenty-six adults were recruited for testing. Sixteen were subjects (3 female, 13 male) with Fontan circulation from our CHD database at Royal Prince Alfred Hospital (RPAH), Sydney, Australia; nine of these subjects able to commit to an intensive 20-week isolated muscle-strengthening programme were assigned to the training arm and the other 7 were enrolled as Fontan controls. All subjects were NYHA Class I to II with resting transcutaneous oxygen saturations above 94%. Exclusion criteria included frequent symptomatic arrhythmias, clinical evidence of heart failure, symptomatic inguinal hernia, severe aortic dilatation and functionally significant physical or intellectual impairment. For the training group, major inclusion criteria were geographical proximity to the study gymnasium and work circumstances that would allow commitment to the training programme. Patient characteristics are shown in Table 1. Ten healthy age–sex matched controls were recruited from the general community for aspects of testing where healthy control data were required. Both Fontan subjects and healthy controls were required to be doing less than 2 regular exercise sessions per week to be eligible for the study. Standard magnetic resonance imaging (MRI) exclusion criteria were applied when appropriate.

Informed written consent was obtained from all subjects and the study was approved by the Sydney Local Health District Ethics Review Committee (RPAH Zone). The study protocol conformed with the ethical guidelines of the Declaration of Helsinki. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

2.2. Study design

Study design is illustrated in Fig. 1. Initial testing comprised cardiopulmonary exercise testing (CPET), body composition scanning via dual-energy X-ray absorptiometry (DXA) and standard cardiac MRI. In addition, calf muscle phosphorus spectroscopy (MRS) to assess skeletal muscle metabolism and real-time free breathing MR analysis (FBMR) were performed in 6 Fontan subjects, together with age and sex matched normal controls. During FBMR subjects were studied at rest, during low and moderate levels of exercise, whilst on CPAP and during a Valsalva manoeuvre. The 9 training subjects then commenced a progressive 20-week resistance-training programme. Fontan-control subjects were simply asked to continue with their usual lifestyle. At the conclusion of the 20 weeks, subjects were restudied with CPET and DXA. MRS and FBMR were repeated in 4 of the training subjects who completed the study and had initially undergone those investigations.

Early into training, we learnt that, due to a technical issue, the FBMR data at baseline pre-strength training were unable to be analysed adequately. As a result, a 12-month detrain period was added to the project for these 4 FBMR subjects, so that they could be analysed in both trained and detrained states.

2.3. Cardiopulmonary exercise testing

CPET comprised a ramp-protocol cycle test on an electrically braked bicycle ergometer (Lode Corival; Lode BV, Groningen, The Netherlands). CPET method is described in detail elsewhere (see Online Supplement). Oxygen pulse, a surrogate for stroke volume during CPET, was calculated by dividing VO_2 (oxygen uptake) by heart rate. Anaerobic threshold was calculated using the V-slope method, by a blinded observer. Peak VO_2 and peak workload were compared to predicted normal values [13]. Eighty percent of the untrained peak work (0.8 isotime) was calculated and important parameters were then compared at that workload. Delta values were calculated by subtracting the post-training (or in the case of non-trainers, post-control period) result from the baseline result.

One training subject stopped his post-training CPET prematurely due to anxiety. At the point of cessation his physiologic parameters (such as heart rate, respiratory quotient and VO_2) suggested he had not reached exhaustion and thus this subject's data were subsequently removed, from peak exercise data analysis only.

2.4. Body composition assessment

Total body composition and non-dominant calf composition were assessed by total body DXA (Lunar Prodigy: GE Healthcare, Milwaukee, USA) to determine lean mass and fat mass. For the calf, total body scans were analysed offline; a region of interest was placed over the calf area using the tibial plateau and the tip of the lateral malleous as landmarks. All DXA studies and offline assessment were performed by a single observer.

2.5. Phosphorus magnetic resonance spectroscopy

Phosphorus magnetic resonance spectroscopy was used to non-invasively assess skeletal muscle metabolism at rest, during exercise and recovery. The scanning sequence is described in more detail within Online Supplementary Methods.

Spectra were quantified using the Java-based magnetic resonance user interface (jMRUI version 2.0, EU Project) to obtain relative concentrations of inorganic phosphate, phosphocreatine (PCr) and ATP. Kinetics of post exercise PCr recovery was assessed by least-squares fit of PCr relative signal intensity time course to an exponential function. Because pH changes during exercise were minimal, the exponential rate constant of PCr recovery, k, can be taken as a measure of overall muscle mitochondrial capacity, an integrated system property depending on intrinsic mitochondrial numbers and function and on cardiovascular delivery of substrate and oxygen to the muscle.

2.6. Cardiac magnetic resonance imaging

MR imaging was performed using a 1.5 T MR scanner (Philips Medical Systems, Best, The Netherlands) equipped with a 5-ch cardiac receive coil and a dedicated MR workstation (Philips Medical Systems). Detailed methodology for assessment of ventricular volumes and function together with flow quantification is included in the Supplementary Online Material.

2.7. Free breathing real-time magnetic resonance imaging

Prior to entering the magnet subjects were taught to perform a Valsalva manoeuvre through instruction and demonstration and trialled on CPAP (method outlined in Supplementary Material along with detailed explanation of FBMR scanning methodology).

Real-time flow measurements [2] were performed in the sequence of SVC, aorta then IVC at rest, during a Valsalva manoeuvre, after 2 min of CPAP and then during exercise. Each set of data consisted of 200 consecutive, real-time (no ECG-triggering), phase-contrast, 43 ms flow acquisitions. This equated to 8.6 s of flow data. ECG and respiratory waveforms were simultaneously collected and saved for off-line analysis.

Table 1
Patient characteristics.

	Trainers (n = 6)	Non-trainers (n = 5)
Age (years)	31 +/− 4	32 +/− 1
Sex	1 female, 5 male	1 female, 4 male
Type of repair	2 APC, 3 intracardiac TCPC (1 with fenestration), 1 extra-cardiac conduit (converted from APC)	2 APC, 2 intracardiac TCPC, 1 extra-cardiac conduit
NYHA class	3 NYHA I, 3 NYHA II	3 NYHA I, 2 NYHA II
Sats (%)	97 +/− 1	99 +/− 1
Age at first surgery (years)	11 +/− 4	12 +/− 2
Time since last Fontan repair (years)	21 +/− 1	18 +/− 2
Ventricular function at echocardiography	3 normal, 2 mild impairment, 1 mild–moderate impairment	2 normal, 2 mild impairment, 1 mild–moderate impairment
Body mass index (kg/m^2)	27 +/− 1	25 +/− 1

Data are mean +/− SEM.
Abbreviations: APC—atriopulmonary connection and TCPC—total cavopulmonary connection.