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Aerobic training in adults after atrial switch procedure for transposition of the great arteries improves exercise capacity without impairing systemic right ventricular function

Mechthild Westhoff-Bleck [a,*], Bernhard Schieffer [a], Uwe Tegtbur [b], Gerd Peter Meyer [a], Ludwig Hoy [c], Arnd Schaefer [a], Ezequiel Marcello Tallone [a], Oktay Tutarel [a], Ramona Mertins [a], Lena Mara Wilmink [a], Stefan D. Anker [d,e], Johann Bauersachs [a], Philipp Roentgen [a]

[a] *Department of Cardiology and Angiology, Hannover Medical School, Germany*
[b] *Institute of Sports Medicine, Hannover Medical School, Germany*
[c] *Department of Biometrics, Hannover Medical School, Germany*
[d] *Applied Cachexia Research, Department of Cardiology, Campus Virchow Clinic, Charité — Universitätsmedizin, Berlin, Germany*
[e] *Center for Clinical and Basic Research, IRCCS San Raffaele, Rome, Italy*

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ABSTRACT

Background: Exercise training safely and efficiently improves symptoms in patients with heart failure due to left ventricular dysfunction. However, studies in congenital heart disease with systemic right ventricle are scarce and results are controversial. In a randomised controlled study we investigated the effect of aerobic exercise training on exercise capacity and systemic right ventricular function in adults with D-transposition of the great arteries after atrial redirection surgery (28.2 ± 3.0 years after Mustard procedure).

Methods: 48 patients (31 male, age 29.3 ± 3.4 years) were randomly allocated to 24 weeks of structured exercise training or usual care. Primary endpoint was the change in maximum oxygen uptake (peak VO_2). Secondary endpoints were systemic right ventricular diameters determined by cardiac magnetic resonance imaging (CMR). Data were analysed per intention to treat analysis.

Results: At baseline peak VO_2 was 25.5 ± 4.7 ml/kg/min in control and 24.0 ± 5 ml/kg/min in the training group (p = 0.3). Training significantly improved exercise capacity (treatment effect for peak VO_2 3.8 ml/kg/min, 95% CI: 1.8 to 5.7; p = 0.001), work load (p = 0.002), maximum exercise time (p = 0.002), and NYHA class (p = 0.046). Systemic ventricular function and volumes determined by CMR remained unchanged. None of the patients developed signs of cardiac decompensation or arrhythmias while on exercise training.

Conclusions: Aerobic exercise training did not detrimentally affect systemic right ventricular function, but significantly improved exercise capacity and heart failure symptoms. Aerobic exercise training can be recommended for patients following atrial redirection surgery to improve exercise capacity and to lessen or prevent heart failure symptoms. (Clinical Trial Registration: ClinicalTrials.gov #NCT00837603)

1. Introduction

Exercise intolerance represents a clinically common feature of acquired heart failure and adult congenital heart disease. Similarities in pathophysiology suggest that guideline-based heart failure therapies, including exercise training, might also be beneficial in adult congenital heart disease. While in "traditional" acquired left ventricular dysfunction aerobic exercise training represents an established, safe and efficient method to improve heart failure symptoms [1–4], studies in congenital heart disease are scarce and in part contradictory [5–8], which is attributable to both heterogeneous patient population and training programmes including only short intervention times between 6 and 12 weeks.

Particularly challenging is the question of whether congenital abnormalities with a systemic morphological right ventricle (RV) are suitable for training programmes, as exercise training might have detrimental effects on the hypertrophied subaortic RV already burdened to chronic pressure overload. In this regard, Winter and colleagues evaluated a heterogeneous patient population with subaortic right ventricles. They reported that aerobic exercise training improved peak VO_2 despite a lacking effect on exercise time, workload and symptoms of heart failure. In particular the effect of training on subaortic RV function remains unresolved [8].

Since pioneers like Senning and Mustard established correction procedures in patients with D-transposition of the great arteries (D-TGA)

* Corresponding author at: Department of Cardiology and Angiology, Hannover Medical School, Carl-Neuberg-Str. 1, D 30625 Hannover, Germany. Tel.: +49 511 532 2568; fax: +49 511 532 3229.
E-mail address: Westhoff-Bleck.Mechthild@MH-Hannover.de (M. Westhoff-Bleck).

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a notable number of patients reached adulthood [9,10]. However, for several reasons the total number of patients with atrial redirection surgery can only roughly be estimated: First, at the time of operation patients had not been centrally registered. Second in Germany later efforts of national registries to evaluate adults living with congenital heart disease could not enrol all adults. Thus assessment can only be based on birth rates and on the assumption of disease prevalence and operative availabilities. We assume that in Germany there might be 1500–2000 patients living with atrial redirection surgery. They represent a unique group of young adults with subaortic morphological right ventricles at risk of both progressive deterioration of ventricular function and declining functional capacity which is presumably based on structural changes as well as physical deconditioning caused by sedentary life style [11–13]. Compared to healthy individuals, young adults with previous atrial redirection surgery present with lower maximum exercise capacity as well as a fivefold higher decline of peak VO_2 over an observation period of 3·5 years [14]. In this setting exercise training seems to be a required therapeutic approach to maintain or even improve functional capacity, however the impact on RV function needs to be clarified.

Currently, data evaluating the impact of exercise training on subaortic morphological RV function as well as on functional capacity are lacking. The present study only included patients with subaortic morphological RV after atrial redirection surgery for these patients are characterized by a distinct hemodynamic feature which might be particularly hazardous in exercise training. Rigid baffles promote a lacking increase in stroke volume during exercise which together with hypertrophy might enforce exercise dependent ischemia already reported in these patients [19–22].Thus we investigated the effect of 6-month aerobic exercise training on cardiorespiratory and subaortic RV function in a prospective randomised trial.

Table 1
Patients characteristics.

	All patients	Control	Training	P-value
Age (years)	29.3 ± 3.4	28.6 ± 3.1	29.9 ± 3.1	0.24
Age at operation (months)	11.0 ± 8.7	9.7 ± 5.8	12.8 ± 11.7	0.23
Years since operation	28.2 ± 3.0	27.3 ± 3.1	29.0 ± 2.7	0.07
Gender (male)	31	18	13	0.23
Body mass index	25.4 ± 4.4	25.3 ± 3.9	25.7 ± 4.9	0.68
Simple Transposition (n)	30	15	15	1.00
Re-operation (n)	8	6	2	0.12
NYHA class (I/II)	3 1/17	18/6	13/11	0.23
ACE-inhibition (n) *	16	8	8	1.00
Beta-blocker (n)	7	3	4	1.00
History of SVT †	17	6	11	0.22
Sinus node dysfunction (n)	27	13	14	0.77
TI (I/II) °	45/3	22/2	23/1	0.83
Baffle leak	11	5	6	1.0
QRS duration (ms)	109 ± 19	108 ± 23	110 ± 16	0.64
NT-proBNP (ng/l) ‡	196 ± 147	169 ± 109	222 ± 175	0.22
ALT (U/l) §	34 ± 17	32 ± 18	35 ± 18	0.65
Creatinine (μmol/l)	78 ± 13	74 ± 12	81 ± 14	0.04
Urea (μmol/l)	5.4 ± 1.3	5.1 ± 1.4	5.7 ± 1.0	0.10
Haemoglobin (g/dl)	15.4 ± 1.3	15.3 ± 1.4	15.6 ± 1.1	0.19

* Angiotensin converting enzyme inhibitors, † supra-ventricular tachycardia,° Subaortic AV-Valve regurgitation with mild (I) and moderate (II) incompetence ‡ brain natriuretic peptide, § alanine aminotransferase.

2. Methods

2.1. Patients

Adult patients with previous atrial redirection surgery for D-TGA were eligible for the study. At our institution all patients underwent the Mustard procedure. Additional inclusion criteria were: stable heart failure according classification of New York Heart association (NYHA) class I/II, unchanged medication (angiotensin converting enzyme inhibitors, beta-blockers) for the last 6 months, no physical training programme at inclusion, and the physical and mental ability to follow a controlled training programme. Exclusion criteria were: clinical diagnosis of NYHA functional class III–IV, known pulmonary vascular disease, significant baffle-obstruction, recent onset or change of heart failure medication within the last 6 months, pregnancy, pacemaker or defibrillator implantation, history of ventricular arrhythmias, renal/liver insufficiency, claustrophobia, and mental retardation. The study was approved by the Hannover Medical School ethics committee. All patients provided written informed consent. This study is registered at ClinicalTrials.gov number NCT00837603.

2.2. Protocol

A total of 115 patients with previous Mustard procedure were identified from the database of the grown-up congenital heart diseases outpatient clinic. Eighty-one patients were found to be eligible for the study. We approached these patients and 48 of them agreed to participate in the study. At our institution cardiorespiratory exercise testing is routinely performed, all participants were familiar with this technique. Characteristics are presented in Table 1. After given written consent, patients were randomised 1:1 to either training or control group (Fig. 1). At baseline and after 24 weeks, all patients received physical examination, 12-lead electrocardiogram, blood sample taking, and a questionnaire to assess quality of life (Kansas City Cardiomyopathy Questionnaire) [15]. After cardiac magnetic resonance imaging (CMR) and echocardiography, all patients performed symptom limited cardiorespiratory exercise testing.

2.3. Assessments

CMR scans were acquired with a 1·5 Tesla Siemens Avanto scanner (Siemens AG, Erlangen, Germany). Routine assessment of cardiac anatomy was performed. Then a contiguous short axis stack was acquired for analysis of mass (mass), enddiastolic (EDVI) as well endsystolic (ESVI) volume, ejection fraction (EF), and stroke volume (SV) subaortic morphological right ventricle (RV), as described previously [16]. All parameters were indexed to body surface area.

Echocardiography assessments included measurements of ventricular diameters and diastolic function. Testing of diastolic subaortic ventricular dysfunction included measurements of peak early mitral valve filling velocity (E wave), peak atrial filling velocity (A wave), E/A ratio, deceleration time, ratio of peak atrial velocity and peak velocity of the mitral annulus early wave during diastole (E/e′) as well as isovolumetric relaxation time (IVRT). All scans were evaluated by two observers blinded to all clinical data. All patients received 24-hour Holter electrocardiogram to exclude arrhythmias. Patients randomised to training participated in a structured exercise programme with a goal of improved exercise capacity over a period of 24 weeks. As home equipment, patients received a bicycle ergometer and heart rate monitors (Polar USA Inc. New York, New York).

Patients in the training group were advised to document heart rate and number and duration of training units. In order to optimise adherence to the training protocol, training group patients received weekly phone calls (Fig. 1). Patients in the control group were encouraged to remain at the usual level of physical activity.

Since the impact of training on subaortic RV function is unknown, we chose low intensity exercise training for safety reasons. In addition we wanted to avoid over-training associated adverse impact on physical capacity. During the study training was recommended at a heart rate corresponding to 50% of oxygen uptake calculated as the mean of the last 6 breathing circles at maximum exercise capacity. Adherence of training was calculated as percentage of desired training units as derived from the patients training protocol.

Exercise intensity increased gradually over time. Training started with 3 times exercise training lasting 10 minutes for the first 3 weeks followed by 15 minutes over

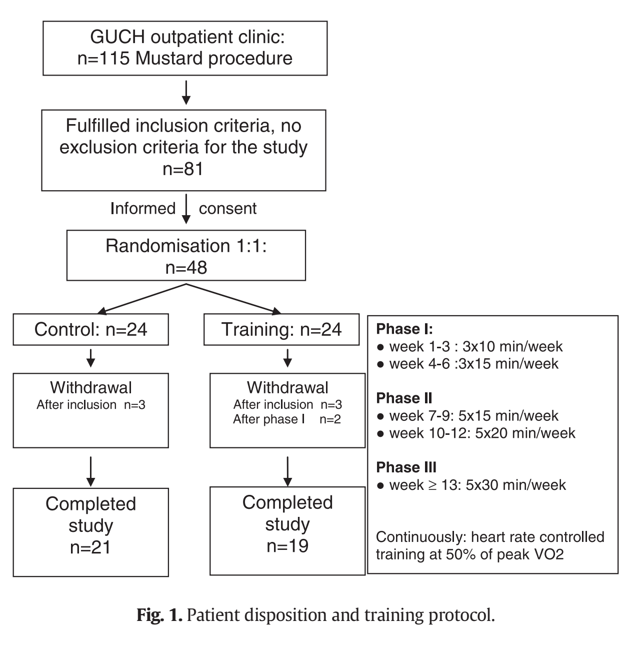

Fig. 1. Patient disposition and training protocol.