Respiratory Training Late After Fontan Intervention: Impact on Cardiorespiratory Performance

Lamia Ait Ali^{1,2} · Alessandro Pingitore¹ · Paolo Piaggi⁵ · Fabio Brucini¹ · Mirko Passera¹ · Marco Marotta² · Alessandra Cadoni³ · Claudio Passino^{2,4} · Giosuè Catapano² · Pierluigi Festa²

Received: 6 July 2017 / Accepted: 4 January 2018 / Published online: 19 January 2018
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Abstract

Fontan palliation allows patients with “single ventricle” circulation to reach adulthood with an acceptable quality of life, although exercise tolerance is significantly reduced. To assess whether controlled respiratory training (CRT) increases cardiorespiratory performance. 16 Adolescent Fontan patients (age 17.5 ± 3.8 years) were enrolled. Patients were divided into CRT group ($n = 10$) and control group (C group, $n = 6$). Maximal cardiopulmonary test (CPT) was repeated at the end of CRT in the CRT group and after an average time of 3 months in the C group. In the CRT group a CPT endurance was also performed before and after CRT. In the CRT group there was a significant improvement in cardiovascular and respiratory response to exercise after CRT. Actually, after accounting for baseline values, the CRT group had decreased breathing respiratory reserve (-15 , 95% CI -22.3 to -8.0 , $p = 0.001$) and increased RR peak ($+4.8$, 95% CI 0.7 – 8.9 , $p = 0.03$), VE peak ($+13.7$, 95% CI 5.6 – 21.7 , $p = 0.004$), VO_2 of predicted ($+8.5$, 95% CI 0.1 – 17.0 , $p = 0.05$), VO_2 peak ($+4.3$, 95% CI 0.3 to 8.2 , $p = 0.04$), and VO_2 workslope ($+1.7$, 95% CI 0.3 – 3.1 , $p = 0.02$) as compared to the control group. Moreover, exercise endurance time increased from 8.45 to 17.7 min ($p = 0.01$). CRT improves cardiorespiratory performance in post-Fontan patients leading to a better aerobic capacity.

Keywords Congenital heart disease · Fontan circulation · Controlled respiratory training · Ergospirometry

Introduction

The outcome of patients with congenital heart disease (CHD), even functionally single ventricle has improved drastically in the last decades due to improvement in diagnostics, cardiac surgery, and intensive care procedures [1]. The surgical staged treatment of patients with single ventricle, based on the “Fontan circulation” that separates the systemic and pulmonary circulations, with the systemic venous

return being connected to the pulmonary arteries without the interposition of the right ventricle pump [2]. This surgical intervention allows these patients to reach adulthood with an acceptable quality of life despite a still a non-negligible mortality and morbidity [3]. However, the consequence of these “unnatural” hemodynamics is a limitation of the normal increases in pulmonary pressures and transpulmonary flow, that, in turn, reduces preload reserve and the increase in cardiac output (CO) [4, 5]. The clinical implication is therefore a reduction in exercise tolerance typical in these patients. Recently a multicentre cohort from the USA Fontan network highlighted the central role of the lungs in post-Fontan palliation in responding to exercise [6].

Controlled breathing is a method of respiratory training that is a fundamental procedure of Pranayama Yoga and is characterized by conscious slow and deep acts of breathing based on diaphragmatic contraction and relaxation without any kind of instrumentation [7]. The controlled breathing practice provides benefits on well-being in healthy subjects [8] and in patients with different diseases, including heart failure [9–11]. Furthermore, in patients with chronic

✉ Alessandro Pingitore
pingi@ifc.cnr.it

¹ Clinical Physiology Institute, CNR, Via Moruzzi 1, 56124 Pisa, Italy

² Fondazione G. Monasterio, Regione Toscana, Pisa, Italy

³ Pediatric Cardiology, Brotzu Hospital, Cagliari, Italy

⁴ Institute of Life Sciences, Scuola Superiore Sant’Anna, Pisa, Italy

⁵ National Institute of Diabetes and Digestive and Kidney Disease, National Institutes of Health, Phoenix, AZ, USA

obstructive pulmonary disease diaphragmatic breathing was associated with a significant increase in tidal volume and reduction in breathing frequency, leading to higher ventilation and oxygen saturation, with a reduction in dead space ventilation and ventilatory equivalent for carbon dioxide [12]. The aim of this pilot study was to assess the effect of controlled respiratory training in adolescents post-Fontan palliation patients on exercise tolerance, metabolic capacity, ventilator, and cardiocirculatory response to exercise. We therefore hypothesized that respiratory training increases cardiorespiratory performance in this population through the improvement in ventilation efficiency.

Methods

Patients

The enrolled population consisted of 16 adolescent patients post-Fontan palliation (14 males, age 17.5 ± 3.8 years) referred to our outpatient clinic for routine follow-up. This is a tertiary referral center at which patients with CHD are evaluated and followed. Inclusion criteria were: (1) clinical stability (NYHA class I); (2) no diuretic therapy at the enrollment and during the training duration. Patients were divided into 2 groups: group 1: controlled respiratory training (CRT group, $n = 10$) and group 2 control group (C, $n = 6$). CRT group and C group had similar demographic, anthropometric, and clinical characteristics as shown in Table 1. Patients enrolled in the CRT group were close to the hospital and this was due to favor their weekly participation to the CRT sessions. Therefore, patients living far from the center entered the C group. Two patients in the CRT group were subsequently excluded from analysis because of reduced compliance to bicycle exercise, due to mild reduced cerebral development. Data on medical and surgical history, clinical status, peripheral oxygen saturation, NYHA functional class, medical therapy, cardiac magnetic resonance, and echocardiogram were collected and are summarized in Table 1. Medication did not change during the training period. Furthermore, all the enrolled subjects had a low exercise regimen and did not change it during CRT program. All patients underwent baseline spirometry, and single-breath diffusing capacity of the lung for carbon monoxide (DLCO), and incremental cardiopulmonary exercise test (CPET). CPET was repeated at the end of CRT in CRT group and after an average time of 3 months in the C group. In the 8 patients in the CRT group an endurance test was performed before and after CRT. The research protocol was approved by the local ethics committee review board (Prot 0015-17 2014 P). All patients or legal guardians gave informed consent, and authorized physicians to use their clinical data in accordance with Italian law. All procedures

performed in the study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Controlled Respiratory Training

CRT consisted of weekly 2 h sessions, lasting 3 months. This was divided into 2 parts: theoretical and practical. In the theoretical session the educational sessions were the anatomy and physiology of the respiratory system, breathing control and breathing awareness, visualization. The practical part was performed indoors and outside, paying attention to personal comfort and environmental quietness. The first step consisted of teaching the optimal position for correct breathing: sitting in a comfortable position with a straight spine or in the “lotus or “diamant” pose if possible. Patients were encouraged to slowly inhale and bring the air into the bottom of their lungs with the diaphragm, then continue inhaling to open and expand the rib cage upward and finishing inhalation with clavicle respiration. The exhalation time is twice as long as the inhalation time: for example, when an inspiration lasts 4 s, expiration will last 8 s. In the first step the inspiration and expiration were repeated without a break, with nasal inhaling and oral exhaling, in order to control air flux. In the second step both air inhalation and exhalation were accomplished nasally with breaks at maximal inspiration and at maximal expiration. These breaks lasted for 2 s at the beginning and up to 8 s at the end of the training. These exercises gave patients a heightened awareness of their breathing thus enabling them to control both frequency and deepness. The control and the awareness of breathing were further enhanced using visualization techniques that are typical in yoga practice with the aim to increase concentration towards breathing. The weekly CRT sessions lasted 2 h each, for a total number of 14 sessions in the 3 months. Participants were invited to perform CRT exercises at home and were regularly encouraged by their parents and our trainers through mobile-phone messages and/or whatsapp communication.

Lung Function Measurement

In all the patients evaluated under stable clinical conditions, we obtained pulmonary function tests at baseline. Lung function studies included the spirometry for static and dynamic lung volume measurements: total lung capacity, TLC; slow vital capacity, SVC; forced vital capacity, FVC; and derived indices as forced expiratory volume in the first second and its percentage of vital capacity (FEV_1/VC ratio). Spirometry was performed by experienced technologists. Three spirometric measurements were obtained and the highest values were chosen in conformity with ATS/ERS standards [13].

Table 1 Demographic, anthropometric, and clinical characteristics of the two study groups

	All patients (n: 14)	CRT group (n: 8)	C group (n: 6)	<i>p</i>
Age (years)	17.5 (10.4: 22.8)	17.8 (12.8: 22.8)	17.5 (10.4: 22.4)	0.51
BMI	19.7 (14.8: 24.5)	18.4 (14.8: 21.2)	19.7 (15.5: 24.5)	0.43
BSA (m ²)	1.56 (1.1: 2.04)	1.56 (1.18: 1.68)	1.53 (1.1: 2.04)	0.79
Diagnosis				0.29
DORV + PS + VSD	1	0	1	
TGA + VSD	1	1	0	
DILV	4	3	1	
HLHS	2	1	1	
Mitral atresia-VSD	2	0	2	
PAIVS	1	0	1	
Tricuspid atresia	2	2	0	
Ventricle type				0.24
Two complex ventricles	2	1	1	
Right ventricle	6	2	3	
Left ventricle	6	5	2	
Age at Fontan (years)	3.96 (0.8: 7.4)	3.6 (0.8: 7.4)	4.2 (3.2: 4.7)	0.69
Follow-up from Fontan	13.7 (6: 19.3)	14.1 (9.5: 19.3)	13.4 (6: 19.2)	0.5
Fontan type				0.69
Extracardiac conduit	10	5	5	
Intracardiac conduit	1	1	0	
Intracardiac tunnel	2	1	1	
Kawashima	1	1	0	
Peripheral O ₂ Sat (%)	95 (88: 99)	95.5 (90: 99)	95 (88: 97)	0.33
Cardiac index (l/min/m ²)	3.1 (2.2: 3.7)	3.1 (2.2: 3.7)	3.1 (2.7: 3.5)	0.99
Ventricle EDVI (ml/m ²)	101 (58: 164)	93 (67: 164)	120 (58: 162)	0.62
Ventricle EF (%)	47 (29: 68)	49 (29: 68)	42 (37: 54)	0.33
Moderate systemic AV valve regurgitation ^a	6 (43%)	4 (50%)	1 (17%)	0.21

AV atrioventricular, BMI Body Mass Index, BSA body surface area, C Group control group, CRT controlled respiratory training, DILV double inlet left ventricle, DORV double outlet right ventricle, EF ejection fraction, EDVI end-diastolic volumes indexed, HLHS hypoplastic left heart syndrome, PAIVS pulmonary atresia intact ventricular septum, PS pulmonary stenosis, TGA transposition of great arteries, VSD ventricular septal defect

^aModerate: more than trivial, no patient have a severe AV valve regurgitation

Airway obstruction was considered for a ratio of FEV₁/SVC below the 5th percentile of predicted value (less than 88% of predicted value), and ventilatory restriction if FEV₁/SVC ratio was normal for a TLC below the 5th percentile of predicted less than 80% of predicted value [14]. DLCO was determined using the single-breath method in conformity with ATS/ERS recommendations [15]. Alveolar volume was measured during the single-breath maneuver using helium as the inert gas. Carbon monoxide transfer coefficient was also evaluated, expressed as the ratio between DLCO and alveolar volume (DLCO/VA) as a percentage of the predicted value. Both DLCO and the DLCO/AV ratio were considered abnormal for values 80% lower than the predicted value. Maximal Voluntary Ventilation (MVV) was estimated multiplying FEV₁ value by a correction factor of 40 [16]. Lung function tests were obtained in the same day of CPET.

CardioPulmonary Exercise Test (CPET) Before and After Respiratory Training

CPET was performed on an electrically braked cycle ergometer (Ergostik, Geratherm, Germany) in accordance with ATS/ACCP recommendations [17]. The protocol included three stages: resting, unloaded pedaling, and exercise. The external work rate was incremented continuously using the ramp protocol and the patients were encouraged to cycle until exhaustion (maximal exercise symptom-limited). The patients were asked to specify the reason(s) why they stopped exercising. During the test, the electrocardiogram was monitored by telemetry, and the arterial oxygen saturation measured by pulse oximetry (SpO₂). The test was interrupted if any of the following events occurred: signs of ischemia on the

electrocardiogram, hypertension (systolic blood pressure 220 mmHg or diastolic blood pressure 120 mmHg), second or third degree heart block, or severe desaturation (SpO₂ B 80%). Ergospirometry test was used for assessing the physical performance outcomes of ventilatory, cardiovascular, and metabolic response to maximal exercise.

The following variables were measured at peak exercise through breath by breath analysis of inhaled and exhaled gases: Oxygen uptake (VO₂), and its relationship with heart rate and external work (pulse oxygen or VO₂/HR and VO₂/Work slope); CO₂ production (VCO₂) and gas ventilatory equivalents (VEVO₂, VEVCO₂); the physiological dead space to the tidal volume ratio (V_d/V_t), and tidal volume to slow vital capacity ratio (V_T/SVC); minute ventilation expressed as the highest value recorded either during exercise or at the first time recovery phase (VE_{peak}); breathing respiratory reserve (BRR, expressed as the difference in liters between MVV and VE_{peak}). The anaerobic threshold (AT) was estimated by V slope method and ventilatory equivalent method [17]. Maximal exercise capacity was expressed as external work rate achieved (W), and peak oxygen uptake normalized for the body surface area (VO_{2peak} ml/min/kg) on the modified Weber and Janicki scale. The endurance test was performed before and after training only for CRT group. The test was performed based on the 80% workload reached in maximal CPET, and aerobic endurance derived from the effective measure of the exercise time in minutes and the anaerobic threshold achieved.

Statistical Analysis

Continuous variables normally distributed by the Shapiro–Wilk normality test were presented as means $\pm$ SD or mean with its 95% confidence interval (CI), as indicated. Continuous variables with skewed distribution were presented as median and as median and range. Categorical variables were presented as counts and percentages. The Student's unpaired *t* test was used to compare values of normally distributed variables between the CRT group and the control group at baseline. The Mann–Whitney U test was used for variables with skewed distributions. Within-group changes were evaluated by the Wilcoxon test. As the assumption of Gaussian distribution may not be valid in our relatively small sample size, non-parametric analyses were always performed to confirm results obtained by parametric tests. Changes in each spirometry and maximal cardiopulmonary test parameter between the two groups were evaluated by analysis of covariance (ANCOVA) accounting for baseline values. A *p* value < 0.05 was considered statistically significant. All analyses were performed using SPSS (version 21.0).

Results

Baseline Results

The population study consisted in 14 patients (2 females), age: 17.5 (10.4; 22.8) years. The most frequent diagnosis was double inlet ventricle and single ventricle morphology was more likely left. The Fontan operation, was performed at median age of 3.96 (0.8; 7.4) years, most frequently with an extracardiac conduit. Six patients underwent a fenestrated Fontan but the fenestration was yet patent at the time of the study in only 3 patients. The parameters of spirometry at rest and ergospirometry performed before training were similar between the two groups, although C group had a slightly better, but not significant, lung function and metabolic capacity to exercise (Table 2). A restrictive pattern was found in 6/14 patients (43%); there were no differences in the prevalence of restrictive pattern between the CRT group and the C group (Table 2). VO_{2peak} was low in both groups indicating a deconditioned level to exercise. There were no significant differences in weight-normalized and percent-predicted VO_{2peak} between the two groups as well as global ventricular function.

Exercise Program Adherence

During all the CRT period, patients were clinically stable and did not need of any kind of therapeutic or medical intervention. The number of the training sessions over 3 months were 14. Median adherence to CRT was 11, range 6–14. All subjects performed training at home with a frequency of 4 ± 1.5 h a week.

Effect of Respiratory Training on CardioRespiratory Response to Exercise

After accounting for baseline values, on average the CRT group had decreased breathing respiratory reserve (-15 , 95% CI -22.3 to -8.0 , $p=0.001$) and increased RR peak ($+4.8$, 95% CI 0.7 – 8.9 , $p=0.03$), VE peak ($+13.7$, 95% CI 5.6 – 21.7 , $p=0.004$), VO₂ of predicted ($+8.5$, 95% CI 0.1 – 17.0 , $p=0.05$), VO₂ peak ($+4.3$, 95% CI 0.3 – 8.2 , $p=0.04$), and VO₂ workslope ($+1.7$, 95% CI 0.3 – 3.1 , $p=0.02$) as compared to the control group.

All the CPT parameters are reported in Table 3. Significant changes occurring after CRT are reassumed in the following points:

Table 2 Spirometry and maximal cardiopulmonary test characteristics of the two groups

	CRT group	Control group	<i>p</i>
TLC (% of predicted)	75.5 (53; 125)	100 (65; 111)	0.5
FEV1 (% of predicted)	72 (46; 114)	96.5 (58; 121)	0.2
FEV1/VC (% of predicted)	103 (82; 115)	99.6 (77; 108)	0.3
MVV	110.8 (60.8; 154.8)	141 (53; 175)	0.4
TLCO (% of predicted)	59 (36; 101)	60 (45; 83)	0.6
Obstructive pattern <i>N</i> (%)	1 (12%)	0 (0%)	0.4
Restrictive pattern <i>N</i> (%)	4 (50%)	2 (33%)	0.72
Max workload (W)	89.5 (54; 135)	103 (56; 138)	0.4
VO _{2peak} (ml/kg/min)	21.3 (18.6; 32.9)	28 (14.1; 32.6)	0.34
VO ₂ (% of predicted)	45.5 (37; 70)	57.5 (29; 86)	0.33
HR rest (BPM)	96 (77; 116)	76 (60; 111)	0.15
HR peak (BPM)	141.5 (103; 170)	145 (132; 172)	0.5
HR peak (% of predicted)	71.5 (51; 85)	72 (67; 82)	0.47
RR (rest)	19.5 (14; 26)	18.5 (14; 22)	0.13
RR (peak)	36 (33; 49)	33.5 (29; 38)	0.15
Oxygen pulse (VO ₂ /HR) (peak)	8 (5.8; 14.5)	9.4 (5.5; 13.9)	0.7
VO ₂ /Work slope	9.25 (4.5; 13.6)	10.6 (8.7; 12.2)	0.33
VE _{peak} (l/min)	36 (30; 72)	56.5 (33; 76)	0.13
VE/CO ₂ slope	34.3 (24.8; 38)	32 (29; 44)	0.79
VT rest (l/min)	0.5 (0.3; 0.69)	0.54 (0.33; 0.78)	0.3
VT peak (l/min)	1 (0.78; 1.56)	1.68 (0.86; 2.3)	0.06
V _d /V _t peak	0.12 (0.1; 0.15)	0.12 (0.09; 0.15)	0.8
Breathing respiratory reserve (l/min)	66.5 (21.8; 101)	79.7 (20.2; 112)	0.79

CRT controlled respiratory training, HR heart rate, FEV1 forced expiratory volume in 1 s, MVV maximal voluntary ventilation, TLC total lung capacity, TLCO alveolar-capillary lung transfer of monoxide carbon-ique, RR respiratory rate, VE minute ventilation, VO₂ peak O₂ consumption, VT tidal volume

- (1) Improvement in metabolic capacity as shown by a significant increase in both weight-normalized and percent-predicted peak VO₂ (Table 3).
- (2) Improvement in ventilatory response to exercise, as demonstrated by a significant increase in peak VE and lower BRR, and also the tendency of VT to increase, although it was not statistically significant.
- (3) Improvement in cardiocirculatory response, as shown by the lower resting heart rate, and the increase in VO₂/work slope (Table 3).

Moreover, these improvements occurred in absence of ventilation/perfusion mismatching, as shown by similar values of VE/VCO₂ slope and physiological dead space–tidal volume ratio (V_d/V_t) before and after CRT (Table 3).

At rest, four patients in the CRT group and two patients in the C group reached the anaerobic threshold, whereas none reached anaerobic threshold after CRT in the CRT group. Due to the small number of cases, statistical analysis was not performed. At endurance test the time duration of exercise increased significantly at the same aerobic capacity reached expressed as ratio time endurance/VO₂/kg/min (Fig. 1a, b).

In the C group there were no significant differences on respiratory, cardiovascular and metabolic response parameters between the 2 maximal CPT performed within the 3 months' time interval (Table 4). Peripheral baseline arterial oxygen saturation didn't change significantly after CRT training in CRT groups: 95.5 (90; 99) pre- training versus 98 (85; 100), $p = 1$). Furthermore, there was no association between the number of the training sessions with the percentage of improvement of cardiorespiratory, metabolic and respiratory parameters, in part due to the limited statistical power to detect a significant correlation in this sample.

Discussion

The main results of this pilot study showed that adolescents patients who underwent Fontan surgical interventions had a significantly improved VO₂ peak and, more importantly, endurance time after dedicated CRT. This is the first time that CRT has been used in this population, in which there is a compromised pulmonary function, mainly due to a restrictive pattern, as we confirmed, and a low functional capacity as indicated by baseline low peak VO₂. In addition

Table 3 Maximal cardiopulmonary exercise test data before and after CRT in the CRT group

	Before CRT	After CRT	<i>p</i>
Max workload (W)	89.5 (54; 135)	93 (70; 150)	0.06
VO _{2peak} (ml/kg/min)	21.3 (18.6; 32.9)	27.8 (20.5; 32.2)	0.02
VO ₂ (% of predicted)	45.5 (37; 70)	61 (45; 68)	0.03
HR rest (B/min)	96 (77; 116)	87 (73; 103)	0.01
HR peak (B/min)	141.5 (103; 170)	139 (114; 160)	0.73
HR peak (% of predicted)	71.5 (51; 85)	70 (56; 80)	0.46
HR reserve (peak-rest HR)	38 (15; 68)	51 (32; 66)	0.3
RR at rest (Br/min)	19.5 (14; 26)	17 (16; 27)	0.44
RR at peak (Br/min)	36 (33; 49)	43 (36; 46)	0.01
Oxygen pulse (VO ₂ /HR) (peak)	8.1 (5.9; 14.5)	9.3 (7; 16.6)	0.1
VO ₂ /work slope	9.25 (4.5; 13.6)	11.2 (9.3; 13.5)	0.02
VE _{peak} (l/min)	36 (30; 72)	52 (42; 88)	0.01
VE/VCO ₂ slope	34.3 (24.8; 38)	33.9 (25; 40.9)	0.6
VE/VO ₂ (rest)	30.6 (25; 42.8)	28.8 (24.3; 38.8)	0.2
VE/VO ₂ (peak)	30.9 (27.5; 38.8)	38.1 (28.6; 38)	0.01
VT rest (l/min)	0.5 (0.3; 0.69)	0.49 (0.26; 0.67)	0.5
VT peak (l/min)	1 (0.78; 1.56)	1.32 (0.97; 1.93)	0.07
V _d /V _t peak	0.12 (0.1; 0.15)	0.13 (0.11; 0.17)	0.25
Breathing respiratory reserve (l/min)	66.5 (21.8; 101)	62 (28.4; 92.8)	0.06

Significant results are indicated in bold

B/min beat/min, Br/min breath/min, CRT controlled respiratory training, HR heart rate, FEV1 forced expiratory volume in 1 s, MVV maximal voluntary ventilation, TLC total lung capacity, RR respiratory rate, VE minute ventilation, VO₂ peak O₂ consumption, VT tidal volume

Fig. 1 Box-plot diagram illustrated an increasing of exercise time after respiratory training at endurance cardiopulmonary test. Values are expressed in median and range. CRT controlled respiratory training

to the respiratory training proposed in this study, respiratory muscle training, in particular the inspiratory one, has been applied in patients with several pulmonary diseases, like COPD and asthma. This provided benefits in improving pulmonary function, endurance, exercise capacity, alleviating symptoms, and thus improving quality of life [18–20]. Respiratory muscle training was also beneficial in patients

with cardiac diseases as in those with heart failure and atrial fibrillation [21, 22]. Particularly in patients with heart failure, respiratory muscle training improved peak VO₂, walking distance, quality of life and reduced perceived dyspnea and resting heart rate [19]. Respiratory muscle training is usually performed with an instrument that provokes a resistance against which patients have to breath, inducing increase

Table 4 Maximal cardiopulmonary exercise test data in control group

	1° CPT	2° CPT	<i>p</i>
Max workload	103 (56; 138)	115 (63; 132)	0.22
VO _{2peak} (ml/kg/min)	28 (14.1; 32.6)	27.3 (14; 30)	0.13
VO ₂ (% of predicted)	57.5 (29; 86)	56.5 (30; 81)	0.23
O ₂ sat (%) at rest	91.5 (86; 97)	92 (86; 97)	1
HR rest	76 (60; 111)	78 (73; 106)	0.89
HR peak	145 (132; 172)	140 (118; 180)	0.28
HR peak (% of predicted)	72 (67; 82)	71(59; 86)	0.34
HR reserve (peak-rest HR)	68 (39; 95)	58.5 (39; 107)	0.46
RR at rest	18.5 (14; 22)	17.5 (10; 29)	0.5
RR at peak	33.5 (29; 38)	35 (32; 38)	0.46
Oxygen pulse (VO ₂ /HR) (peak)	9.4 (5.5; 13.9)	9.95 (5.7; 12.8)	0.89
VO ₂ /Work slope	10.6 (8.7; 12.2)	10.45 (8.3; 12)	0.68
VE _{peak} (l/min)	56.5 (33; 76)	61 (32; 64)	0.89
VE/CO ₂ slope	32 (29; 44)	33 (29; 52.7)	0.08
VT rest (l/min)	0.54 (0.33; 0.78)	0.54 (0.36; 0.87)	0.89
VT peak (l/min)	1.68 (0.86; 2.3)	1.69 (0.88; 1.9)	0.22
V _d /V _t peak	0.12 (0.09; 0.15)	0.1 (0.09; 0.12)	0.46
Breathing respiratory reserve (l/min)	79.7 (20.2; 112)	77.9 (21.2; 112)	0.89

HR heart rate; FEV1 forced expiratory volume in 1 s, MVV maximal voluntary ventilation, TLC total lung capacity, RR respiratory rate, RT respiratory training, VE minute ventilation, VO₂ peak O₂ consumption, VT tidal volume

in inspiratory, and also expiratory, pressure, and thus favoring respiratory muscle contraction. However, the efficacy of respiratory muscle training depends on different factors including the level of inspiratory pressure load, rhythm, muscle shortening speed that may account for the discrepancies in the true effectiveness in clinics [23, 24]. Furthermore, fragile patients could not support forced breathing with the consequence that the effectiveness of breathing exercise may lower. In experimental settings, moreover, resistive breathing was associated to muscle membrane and sarcomere injury of the diaphragm very likely induced by overproduction of free radicals [25, 26].

We, instead, adopted a method of respiratory training based on diaphragmatic respiration, that is natural, unforced, and without instruments. Diaphragmatic respiration increases inspiratory act deepness that augments negative intrathoracic pressure favoring systemic venous return through a suction mechanism. Previous studies showed that spontaneous inspiration as well as negative pressure ventilation increased pulmonary blood flow in early postoperative Fontan patients [27–29]. Penny et al. showed that normal inspiration was associated to 35% higher pulmonary forward flow during inspiration in respect to expiration in Fontan patients [27–29]. Similarly, in the same category of patients, a significant increase of 42% in pulmonary blood flow induced by negative pressure ventilation has been shown in the early postoperative period [29]. Importantly, in another study the increase in pulmonary blood flow has

been associated to improvement in mixed venous saturation, and improvement in stroke volume and CO without changes in heart rate [28]. Accordingly, in our study, there was an improvement in respiratory performance as documented in the improvement in ventilatory capacity, as documented by increase in VE peak and larger use of BRR, and also in cardiac performance, as documented by reduction in resting HR and increase in VO₂/work slope ratio. Thus, in turn, the improvement in cardiorespiratory performance led to significant increase in VO₂ max.

The increase in pulmonary blood flow and also the improvement in ventilatory performance have important physiological and clinical impact in Fontan patients considering the abnormal hemodynamics of the systemic venous blood return to the pulmonary circulation. In fact, systemic venous blood flows passively through the lungs without being pumped by the right ventricle and its return is possible by the existence of an elevated central venous pressure which is the driving force in the Fontan circulation [30]. Therefore, patients with Fontan circulation typically have a reduction in CO at rest and low ability to boost CO during exercise [30–32]. Cardiac output is the result of the combination of several left ventricle factors including cardiac preload and afterload, contractility, heart rate, as well as right ventricular function and pulmonary circulation [30]. In Fontan patients the increased systemic venous pressure, the absence of the RV pump, and the increased pulmonary vascular resistance, limits or fully abolish preload reserve [4,

33]. In these patients the increase in CO was related only to augmentation of heart rate in the presence of decreased LV diastolic volume whereas preload reserve was low at low dose dobutamine stress test [34]. Dobutamine also showed abnormal pulmonary artery distensibility and wall shear stress suggesting endothelial dysfunction [35]. Interestingly the administration of a single oral dose of sildenafil, a pulmonary vasodilator, increased cardiac index, and exercise capacity in association with the increase in pulmonary blood flow [36]. The key role of the pulmonary system in the hemodynamics of Fontan patients derives from recent evidence showing that a low FVC is predictive of a low peak VO_2 and that this association is stronger than that seen for ventricular morphology or markers of ventricular dysfunction [6]. Moreover, Shafer et al. demonstrate that the skeletal muscle and ventilatory pumps account entirely for the increase in SV during submaximal exercise in patients with Fontan circulation [37]. The increase in endurance time furthermore, occurred at the same aerobic capacity as expressed by the time endurance/ $\text{VO}_2/\text{kg}/\text{min}$ ratio in respect to pre-training, thus indicating an improved cardiorespiratory efficiency. The observed improvement in functional capacity indicates the presence of a functional cardiorespiratory reserve that can be pulled out in order to improve exercise capacity. This is in line with recent evidence showing the efficiency of exercise aerobic training in Fontan patients and the results of a recent published meta-analysis of Sutherland et al. who concluded that exercise training is safe and beneficial in patients with a Fontan circulation and should become standard care within this population [5, 38–43]. Moreover, the increase in exercise performance is also effective to improve quality of life helping to reduce the rate of depression and anxiety, that are frequent in the Fontan population [44].

In addition, CRT may induce directly benefit by favoring relaxation, reduction in perceived exertion, physical and mental wellness and mental applications, as documented in healthy subjects, and provided clinical benefit in the treatment of depression, anxiety, and post-traumatic disorders [9, 10, 45].

Limitation

The small sample of the population study reduces the robustness of the results. However, the sample was homogeneous for age and Fontan type and, although the number was small, there was a significant difference before and after CRT. We did not measure pulmonary blood flow before, during and after training and thus we were unable to ascertain if CRT induced an increase in pulmonary blood flow. Furthermore, we did not assess diastolic function that plays a critical role in maintaining CO during exercise in Fontan patients.

Conclusion

The results of this pilot study show that a simple method of CRT based on diaphragmatic respiration is effective to improve cardiorespiratory performance, in particular significantly increasing exercise endurance time. CRT is safe, natural, easy, feasible and effective. However, larger studies are needed to confirm the results of this pilot study, also taking into account different conditions of CRT in order to optimize it. Furthermore, more studies are needed to assess the psychological benefits in terms of quality of life and self-perception.

Acknowledgements We gratefully thank Ms Elaine Laws for her precious help in the English editing of this manuscript.

Compliance with Ethical Standards

Conflict of interest All the authors have not to declare conflict of interest.

Research involving Human Participants and/or Animals The research protocol was approved by the local ethics-committee review board (Prot 0015-17 2014 P).

Informed Consent All patients or legal guardians gave informed consent, and authorized physicians to use their clinical data in accordance with Italian law.

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