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Inspiratory muscle training did not improve exercise capacity and lung function in adult patients with Fontan circulation: A randomized controlled trial

Celina Fritz [a,*,1], Jan Müller [a,b,1], Renate Oberhoffer [a,b,1], Peter Ewert [a,1], Alfred Hager [a,1]

[a] Department of Congenital Heart Disease and Pediatric Cardiology, Deutsches Herzzentrum München, Technical University of Munich, Germany
[b] Institute of Preventive Pediatrics, Department of Sport and Health Sciences, Technical University of Munich, Germany

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ABSTRACT

Backgrounds: Patients with Fontan circulation have no subpulmonary ventricle and a passive pulmonary perfusion. Considerable percentage of the pulmonary blood flow is driven by pressure shift due to respiration. Impairments in respiratory musculature strength are associated with a reduced exercise capacity. This study investigated the effect of a daily six months inspiratory muscle training (IMT) on exercise and lung capacity in adult Fontan patients.

Methods: After a lung function and cardiopulmonary exercise test (CPET), 42 Fontan patients (50% female; 30.5 ± 8.1 years) were randomized into either an intervention group (IG), or a control group (CG). The IG performed a telephone-supervised, daily IMT of three sets with 10–30 repetitions for six months.

Results: After six months of IMT, the IG did not improve in any exercise and lung capacity parameter compared to CG. VO_2peak (ΔVO_2peak: IG: 0.05 [−1.53; 1.33] ml/kg/min vs. CG: −0.50 [−1.20; 0.78] ml/kg/min; $p = .784$) and FVC (ΔFVC: IG: 0.07 [−0.16; 0.22] l vs. CG: −0.05 [−0.24; 0.18] l; $p = .377$) remained unchanged, while FEV1 trended to improve (ΔFEV_1: IG: 0.05 [−0.07; 0.13] l vs. CG: −0.10 [−0.19; 0.03] l; $p = .082$). Only oxygen saturation at rest improved significantly (ΔSpO_2: IG: 1.50 [−0.25; 3.00] % vs. CG: −0.50 [−1.75; 0.75] %; $p = .017$).

Conclusions: A daily six months IMT did not improve exercise and lung capacity and lung volumes in Fontan patients.

1. Introduction

The Fontan procedure, which was first performed in the 70s, and its modification, the total cavopulmonary connection (TCPC) is nowadays still the most common palliative surgical procedure for patients with single ventricle anatomies, which are not suitable for biventricular repair [1–3]. In the course of surgery the systemic venous return is directly connected to the pulmonary arteries, without passing a sub-pulmonary ventricle [4,5]. Due to these hemodynamic limitations of a missing subpulmonary chamber, pulmonary arterial and systemic venous blood flow are strongly affected by modest intrathoracic pressure shifts, since approximately 30% of flow in the systemic venous pathway is driven by respiration [6,7]. In patients with Fontan circulation, blood flow in the inferior vena cava is increased during inspiration phase, enhancing the systemic venous blood return into the lungs considerably [8,9].

Young adults with severe CHD, and Fontan circulation in particular, show respiratory and skeletal muscle weakness, and higher prevalence of respiratory muscle dysfunction, which are comparable to those of adults with advanced heart failure [10]. So the physiology of patients with Fontan circulation and patients with heart failure is partially coinciding. Both patient groups have impaired exercise capacity, reduced cardiac output, shallow and fast respiration [11,12]. Furthermore, respiratory muscle weakness correlates well with reduced exercise capacity in these patients [10,13]. Results of a meta-analysis and a systematic review show an increase in exercise capacity and an amelioration in dyspnea in patients with heart failure due to a respiratory muscle training which obtained improvements in respiratory muscle strength and endurance [14,15].

Also in a recent study in children with Fontan circulation a daily inspiratory muscle training (IMT) of six weeks improved inspiratory muscle strength and ventilatory efficiency in a cardiopulmonary exercise

* Corresponding author at: Department of Pediatric Cardiology and Congenital Heart Disease, Deutsches Herzzentrum München, Lazarettstr. 36, D-80636 München, Germany.
E-mail address: fritz@dhm.mhn.de (C. Fritz).
[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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test (CPET) [16]. It is therefore reasonable that an individually adjusted IMT in adult patients with Fontan circulation improves parameters of ventilation and exercise capacity.

The aims of the current study were (1) to investigate the effect of a telephone-supervised, daily inspiratory muscle training for six months on exercise capacity and (2) on lung volumes in adult patients with Fontan circulation.

2. Methods

2.1. Study subjects

Through databases of the Deutsches Herzzentrum München overall 656 adult patients with univentricular heart after palliative Fontan operation, were identified fulfilling the inclusion criteria (18 years and older, Fontan physiology), were identified (Fig. 1). Patients who underwent cardiac catheter examination in the last six months or heart surgery in the last twelve months were excluded from the study. Further exclusion criteria were a change in drug administration in the last 3 months, planned intervention in the near future, neuromuscular mental disease, moderate to severe ventricular dysfunction as well as an instable general state of health. During initial medical consultation and examination five patients met the exclusion criteria and could not be included.

Therefore 42 patients (50% female; 30.5 ± 8.1 years; age 18 to 51 years old) out of 209 eligible patients participated in our study over the period from January 2017 until October 2018. 16 of our study patients were born with a tricuspid atresia, five with a double outlet right ventricle (DORV), one with a double inlet right ventricle (DIRV), 13 with a double inlet left ventricle (DILV), two patients with a hypoplastic right ventricle and a transposition of the great arteries (TGA), three with hypoplastic right ventricle and a congenitally corrected transposition of the great arteries (ccTGA) and two patients with a single right ventricle and a complete atrioventricular septal defect (cAVSD). Hence study population consists of nine patients who underwent atriopulmonary anastomosis (APA), eight who underwent atrioventricular anastomosis (AVA) and 25 who underwent TCPC (Table 1).

After baseline assessments (visit 1), consisting of a lung function test (LFT) and a CPET, 42 patients were randomized into either an intervention group (IG, $n = 20$) or control group (CG, $n = 22$). The IG started performing a telephone-supervised, daily IMT until a six months follow-up (visit 2). The daily intervention was performed with an inspiratory resistive training device (POWERbreathe International Ltd., Southam, UK). Within the first six months after baseline evaluation the CG continued their usual activities and did not get any treatment. At the six months follow-up (visit 2) this group started IMT under the same conditions, including weekly telephone supervision till 12 months re-evaluation (visit 3). To assess the sustainability of the training program, the IG was asked to continue performing IMT without weekly telephonic-supervision until 12 months reevaluation (visit 3). This independent six-months IMT period of the CG was performed from 12 months follow-up until 18 months re-evaluation (visit 4). The

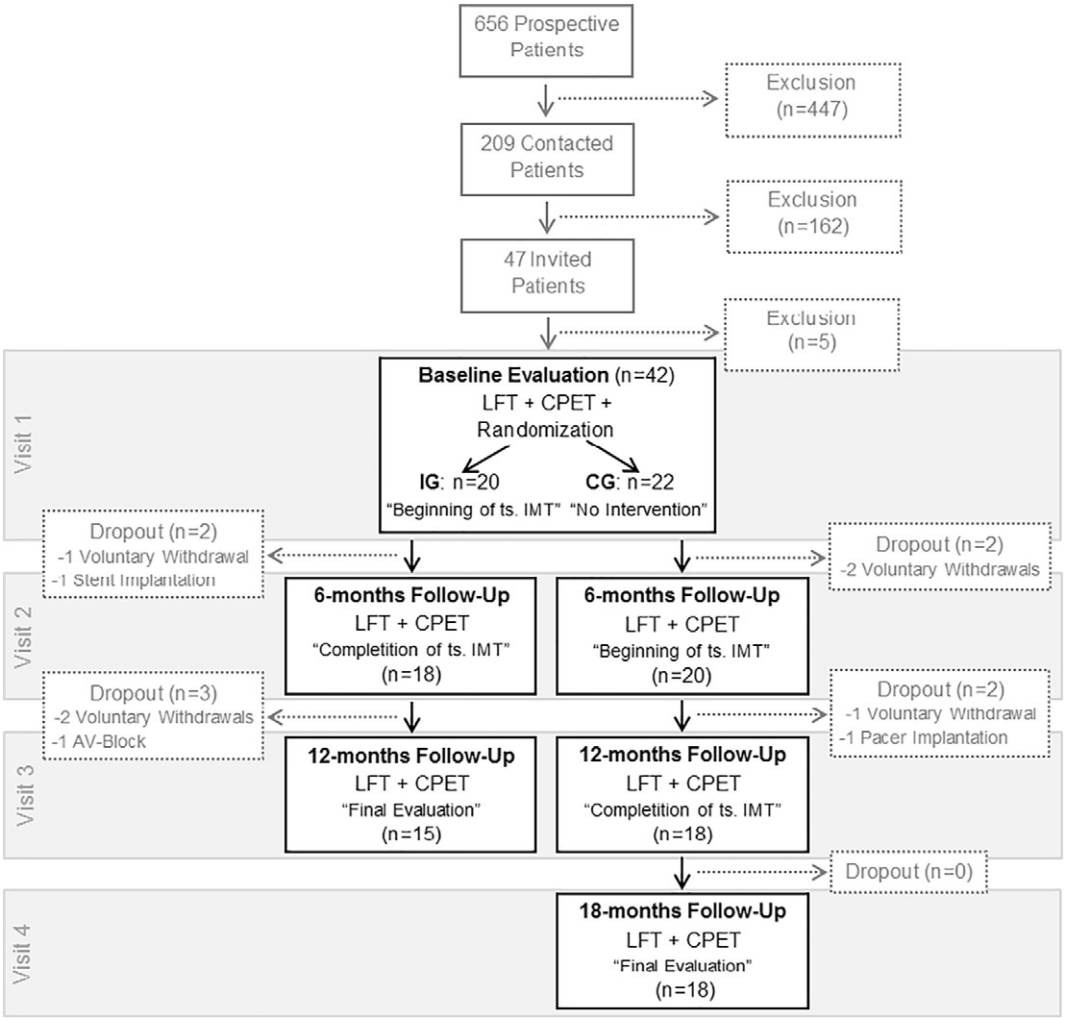

Fig. 1. Course of study. LFT: lung function test; CPET: cardiopulmonary exercise test; IG: intervention group; CG: control group; ts. IMT: telephone-supervised inspiratory muscle training.

Table 1
Patients characteristics of study population.

Patients characteristics	Study population ($n = 42$)	Intervention group ($n = 20$)	Control group ($n = 22$)
Gender, female %	21 (50%)	9 (45%)	12 (55%)
Age, years	28.6 [24.7; 36.5]	28.8 [25.3; 38.3]	27.7 [23.7; 36.0]
Height, cm	170.0 [162.8; 177.5]	170.0 [163.5; 176.0]	170.5 [162.3; 178.5]
Weight, kg	67.0 [56.9; 78.0]	68.2 [58.8; 78.0]	66.3 [54.3; 78.3]
BMI, kg/m^2	22.0 [20.8; 26.2]	22.0 [21.3; 25.8]	22.6 [19.7; 26.5]
Age at Fontan surgery, years	6.3 [4.0; 9.9]	6.2 [3.4; 7.8]	6.5 [4.1; 11.8]
Diagnosis			
Tricuspid atresia	16	9	7
Double outlet right ventricle	5	2	3
Double inlet right ventricle	1	0	1
Double inlet left ventricle	13	7	6
Transposition of the great arteries	2	1	1
Congenitally corrected transposition of the great arteries	3	0	3
Single right ventricle and a complete atrioventricular septal defect	2	1	1
Ventricular morphology			
Left	36	18	18
Right	5	2	3
Indeterminate	1	0	1
Type of palliation			
AVA	8	7	1
APA	9	3	6
TCPC	25	10	15
Medication			
Anticoagulation (oral)	33	16	17
Thrombosis inhibitor	5	1	4
Beta blocker	16	8	8
ACE inhibitor/AT inhibitor	10	7	3
Digitalis	1	0	1
Diuretic	7	2	5
PDE5 inhibitor	2	0	2
Antiarrhythmics	2	0	2
No medication	2	2	0

Median and interquartile [IQR 25; 75].
cm: centimeter; kg: kilogram; BMI: body mass index; m^2: square meter; AVA: atrioventricular anastomosis; APA: atriopulmonary anastomosis; TCPC: total cavopulmonary connection; ACE: angiotensin converting enzyme; AT: angiotensin; PDE: phosphodiesterase.

study consisted of three visits for the IG and four visits for the CG, where a CPET and a LFT were performed, respectively. All tests were implemented by the same experienced sports scientist (C.F.).

A total of nine dropouts had to be registered during the whole study. In the CG two dropouts were recorded before the beginning of telephone-supervised intervention period. During intervention period four patients dropped out in both groups (IG: $n = 2$; CG: n = 2). Solely in the IG three further dropouts were registered after completion of supervised training period. Summarizing data from overall 38 study patients (IG: $n = 18$; CG: $n = 20$) were considered for randomized evaluation of IMT (Fig. 1).

This study was a prospective, single-centre, randomized controlled trial. It was conducted in accordance with the Declaration of Helsinki (revision 2008) and the Good Clinical Practice guidelines. The study protocol was approved by the local ethical board (project number 52/14S) of the Technical University of Munich and registered in the DRKS.de website (registration ID: DRKS00010477). All participants gave a written informed consent and agreed to an anonymous publication of their data.

2.2. Inspiratory muscle training (IMT)

After baseline evaluation patients were instructed by an experienced sports scientist (C.F.) in term of the IMT. Physiology of the respiratory system and device's handling were explained, and different breathing techniques were illustrated and conducted with the patient. Patients were instructed to begin the inhalation phase with diaphragmatic breathing and to continue inhaling by expanding the rib cage. Incorrect breathing and malposition were corrected immediately.

Patients used an inspiratory resistive training device (POWERbreathe International Ltd., Southam, UK) for three sets with 10–30 repetitions once daily. The device's inspiratory load was adjusted individually until maximum for every training session to maintain an optimal training effect. During inhalation phase patients breathed towards an individually adjustable resistance, generated by varying the compression of a spring-loaded valve. An adjustment from 10 cm H_2O to 90 cm H_2O was possible. Accordingly, sufficient vacuum pressure needed to be generated during inspiration. Exhalation phase was unloaded.

To be able to support the patients, clarifying questions and assess compliance, the first six months training period was telephone-supervised weekly, since the training sessions were performed at home. During the second six months training period, patients were instructed to continue the IMT independently, since no telephone-supervision was implemented. Both groups performed IMT under the same conditions. While the IG started with the telephone-supervised training session subsequent to baseline evaluation, no training was undertaken by the CG. Latter started with the first training period under telephone supervision subsequent to six months follow-up and continued with the second training period after 12 months re-evaluation (Fig. 1).

2.3. Measurement of exercise capacity

Incremental symptom-limited CPET until exhaustion on an electronically braked bicycle ergometer was performed in upright position according to recent guidelines [17]. To define the baseline, a 3-min rest period was observed. Following a 3-min warm-up period without load, a ramp wise increase of load with 10, 15, 20 or 30 watts per minute was set. To determine each subject's limit of tolerance within 8 to 12 min after warm-up, the load increase was adjusted individually, based on the expected exercise capacity estimated by the investigator. Subsequent to exhaustion, a 5-min recovery period proceeded, consisting of an initial cycling phase with minimal load for 2 min and an adjacent resting phase lasting for 3 min. Throughout testing patients complied with pedaling at a cadence between 60 and 80 rpm and were encouraged verbally to achieve maximal exhaustion.

Gas exchange and ventilation were measured via a breath-by-breath gas exchange analysis (Encore, SensorMedics, Viasys Healthcare, Yorba Linda, California, USA). During the entire examination saturation of peripheral oxygen and a 12-lead ECG were recorded. Furthermore, blood pressure measurements were taken every 2 min. Peak oxygen uptake (VO_2peak) was calculated as the highest mean oxygen consumption obtained during any 30-second time interval. Reference values for gender, age, body height, and body mass, expressed in "% predicted" were calculated as previously described. Reference values for peak heart rate were calculated 208–0.7 x age according to Tanaka and colleagues [18,19]. Compliance criteria for a valid CPET were achieved when either respiratory exchange ratio (RER) was ≥1.05, or peak heart rate was ≥85%. Cyanotic patients (oxygen saturation < 90% at rest or at peak exercise) were rarely able to reach the above mentioned thresholds, however they were included in the study, independent of those criteria [20,21].

2.4. Measurement of lung function

Prior CPET forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1) and the FEV_1/FVC ratio were performed in a computerized spirometer test (Encore, SensorMedics, Viasys Healthcare, Yorba Linda, California, USA) in a seated upright position according to recent standardization of spirometry [22]. During the measurement patients utilized a nose clip and mouthpiece. Every patient performed at

least three technically acceptable trials, while the best value was recorded to determine the degree of airflow. To ensure the reproducibility of the test, the two best values should not differ >5% [22]. Lung function measurements are expressed in liters and as percentage of the predicted values, corrected for gender, height, age and weight according to Pellegrino and colleagues. [23]

2.5. Data analysis

The Kolmogorov-Smirnov test failed to show normality in the primary outcome parameter peak oxygen uptake and other variables. Therefore, all descriptive data were shown in median and interquartile [IQR 25; 75] range. Pre-treatment and post-treatment data from the IG were compared to the data from the CG with a Wilcoxon rank sum test (Δ). Mann-Whitney *U* Test was used to compare the differences between IG and CG. Sample size calculation was performed with the assumption to increase peak oxygen uptake by 3 ml/kg/min due to the intervention. With an 80% power, $\alpha = 5\%$ and a dropout rate of 20% the minimum number of 40 patients was estimated.

All analyzes were performed using SPSS (version 23.0, IBM Corporation, Armonk, NY, USA) and a two-tailed probability value <.05 was considered statistically significant for all tests.

3. Results

Study characteristics of the patients with Fontan circulation of both groups are displayed in detail in Table 1.

3.1. Exercise capacity

At six months re-evaluation both groups had not improved their VO_2peak and Vo_2peak predicted (ΔVO_2peak: IG: 0.05 [−1.53; 1.33] ml/kg/min vs. CG: −0.50 [−1.20; 0.78] ml/kg/min; $p = .784$; ΔVO_2peak predicted: IG: 0.65 [−5.02; 5.95] % vs. CG: 0.08 [−3.84; 7.63] %; $p = 919$), without any significant difference between IG and CG. Additionally no significant difference was found between the IG and the CG concerning ventilatory efficiency ($\Delta VEVCO_2$slope: IG: 0.90 [−1.33; 3.33] vs. CG: 0.50 [−0.78; 2.00]; $p = .740$).

The only significant result was an increase of oxygen saturation at rest in the IG in comparison to the CG (ΔSpO_2: IG: 1.50 [−0.25; 3.00] % vs. CG: −0.50 [−1.75; 0.75] %; $p = .017$) after six months IMT. Detailed overview of the parameters of exercise capacity after the randomized phase is demonstrated in Table 2.

3.2. Lung function

After six months of IMT, no significant changes could be observed between the IG and the CG concerning FVC and FVC predicted (ΔFVC: IG: 0.07 [−0.16; 0.22] l vs. CG:-0.05 [−0.24; 0.18] l; $p = .377$; ΔFVC predicted: IG: 2.56 [−4.08; 5.74] % vs. −1.27 [−6.22; 3.69] %; $p = .217$). Further, FEV_1 and FEV_1 predicted did not change significantly after IMT between the IG and CG (ΔFEV_1: IG: 0.05 [−0.07; 0.13] l vs. CG: −0.10 [−0.19; 0.03] l; $p = .082$; ΔFEV_1: IG: 2.43 [−1.50; 3.88] % vs. CG: −2.38 [−5.16; 1.94] %; $p = .072$). Detailed overview of the lung values is demonstrated in Table 2.

3.3. Side effects

In three study patients atrial flutter was already diagnosed and appeared during the study. In two of these patients atrial flatter could be terminated by electrical cardioversion. In one patient a cardiovascular ablation was performed resulting in a sinus arrest and an uneventful pacemaker implantation. The above-mentioned serious adverse events occurred during the patient's training phase. Nevertheless, due to the patient's previous medical history implicating up to four cardioversions a year, these events were unlikely attributable to the IMT.

Another patient was diagnosed with a diaphragmatic axial hernia during post-intervention period. According to the patient's own statements no IMT was performed after the completion of the telephone-supervised training period. An association between the IMT and the appearance of the diaphragmatic axial hernia could be conceivable, since its onset could be provoked by the increased inspiratory pressure during the training phase.

4. Discussion

This study did not show an improvement in exercise capacity or lung function after a weekly telephone-supervised, daily IMT for six months.

There is sufficient evidence that exercise limitations in patients with Fontan circulation are due to reduced stroke volume that originates from insufficient preloading conditions. Apart from these cardiac conditions, pulmonary issues have to be considered [4,24,25]. Patients with Fontan circulation show restrictive ventilatory function in terms of reduced FVC and FEV_1 [2,26]. In young patients with Fontan circulation reduced FVC is common and associated with impaired exercise capacity, since a low breathing reserve limits their exercise performance [2]. In terms of a restricted compensation of ventilatory inefficiency, a low FVC was shown to be a stronger predictor for reduced exercise capacity than markers for ventricular dysfunction or ventricular morphology [2]. Therefore, exercise limitation may be traced not only to cardiovascular, but also to pulmonary factors, such as a low breathing reserve and an increased pulmonary vascular resistance [2,24].

Up to now two studies of IMT in patients with Fontan circulation were conducted. A significant improvement in maximal inspiratory pressure was observed in young patients with nonfenestrated extracardiac conduit by Laohachai due to daily six week IMT [16]. In contrast to the results in young patients with Fontan surgery, an increase in maximal inspiratory pressure after 12 weeks of IMT could not be observed in a small cohort of eleven adult patients with Fontan circulation by Wu et al. [27]. In the current study we did not measure maximal inspiratory pressure. In the same cohort by Wu et al., no change in peak tidal volume was found [27]. Though, a significant higher peak work rate as well as a tendency to ameliorated ventilatory efficiency and increased exercise capacity could be identified in these patients [27]. A significant enhancement of ventilatory efficiency during exercise was shown in young patients with Fontan circulation, maybe representing an improvement in ventilation/perfusion matching, whereas an increase in oxygen saturation or O_2 pulse could not be observed [16].

There are two main differences in the current study and the study by Laohachai et al. concerning the training structure and duration of the IMT. The current cohort performed an IMT, consisting of 3 sets with 10–30 repetitions once a day, and started the training without inspiratory load on the device and increased it at their discretion until maximum. This procedure represents strength training, whereas the patients in the other study performed endurance training. These patients trained for 30 min a day and the load on the device was set to 30% of particular maximal inspiratory pressure being reached at baseline evaluation. At first re-evaluation after three weeks, the load was adjusted to potential changes in maximal inspiratory pressure [16]. Total duration was six weeks, whereas patients of the current cohort trained for six months. Taking these facts into account it can be concluded that endurance training is superior to strength training, also in case of shorter duration.

Yet, three months of controlled respiratory training without any training device, improved VO_2peak and endurance time during CPET in a small cohort of adolescent patients with Fontan circulation [28]. This respiratory training form is based on diaphragmatic respiration and increases negative intrathoracic pressure, due to higher depth of inspiration, and optimizes systemic venous return [28]. Hence the load does

Table 2
Mean differences between intervention group and control group after six months inspiratory muscle training.

		Intervention Group (n = 18)			Control Group (n = 20)				
		Baseline Evaluation	6-Months Follow-Up	Difference	Baseline Evaluation	6-Months Follow-Up	Difference	Difference between IG and CG	***p*-value**
Lung Function	FVC, l	3.8 [2.6; 4.9]	3.8 [2.8; 4.6]	0.07 [−0.16; 0.22]	3.6 [3.0; 4.3]	3.6 [2.9; 4.4]	−0.05 [−0.24; 0.18]	0.01 [−0.20; 0.20]	.377
	FVC predicted, %	85.4 [80.1; 96.8]	88.8 [80.4; 95.2]	2.56 [−4.08; 5.74]	87.8 [80.6; 97.6]	88.7 [76.5; 93.5]	−-1.27 [−6.22; 3.69]	0.65 [−5.15; 4.72]	.217
	FEV1, l	3.1 [2.2; 3.9]	3.0 [2.3; 3.7]	0.05 [−0.07; 0.13]	3.0 [2.5; 3.5]	3.0 [2.5; 3.4]	−0.10 [−0.19; 0.03]	−0.03 [−0.13; 0.08]	.082
	FEV1 predicted, %	80.6 [74.3; 90.6]	81.4 [72.8; 88.5]	2.43 [−1.50; 3.88]	84.1 [78.9; 94.5]	83.4 [75.9; 91.6]	−2.38 [−5.16; 1.94]	0.03 [−3.33; 2.90]	.072
Exercise Capacity	FEV1/FVC ratio, %	80.6 [77.8; 84.6]	77.7 [75.2; 84.0]	0.48 [−4.35; 2.40]	82.8 [80.6; 87.4]	81.5 [79.3; 84.9]	−0.88 [−3.71; 1.66]	−0.20 [−4.03; 2.03]	.460
	VO_2 peak, ml/kg/min	23.4 [19.5; 28.5]	23.3 [19.1; 29.5]	0.05 [−1.53; 1.33]	24.1 [18.3; 27.7]	22.5 [18.0; 29.4]	−0.50 [−1.20; 0.78]	−0.23 [−1.36; 1.05]	.784
	VO_2 peak predicted, %	68.7 [64.3; 76.0]	70.1 [62.6; 80.0]	0.65 [−5.02; 5.95]	69.7 [55.6; 81.9]	67.3 [58.4; 80.1]	0.08 [−3.84; 7.63]	0.37 [−4.43; 6.79]	.919
	VE/VCO2 slope	31.3 [27.5; 34.4]	31.4 [28.2; 35.2]	0.90 [−1.33; 3.33]	33.4 [30.0; 36.8]	33.5 [30.5; 36.7]	0.50 [−0.78; 2.00]	0.7 [−1.05; 2.66]	.740
	RER at peak exercise	1.24 [1.17; 1.3]	1.23 [1.15; 1.28]	0.01 [−0.08; 0.05]	1.24 [1.17; 1.28]	1.21 [1.18; 1.26]	0.00 [−0.05; 0.04]	0.00 [−0.07; 0.05]	.942
	Heart Rate max, bpm	148.5 [127.5; 173.0]	142.0 [136.8; 168.0]	−1.00 [−6.00; 3.00]	152.5 [148.0; 169.8]	158.5 [139.0; 167.3]	−2.50 [−6.75; 4.00]	−1.75 [−6.38; 3.50]	.718
	Blood Pressure max, mmHg	170.5 [155.3; 186.3]	174.0 [156.5; 191.0]	6.00 [−3.25; 17.25]	160.0 [150.5; 192.8]	172.5 [143.3; 200.3]	6.00 [−16.75; 23.75]	6.00 [−10.00; 20.50]	.740
	SpO_2 at rest, %	92.0 [89.0; 94.3]	93.5 [91.8; 96.0]	1.50 [−0.25; 3.00]	94.0 [88.5; 95.0]	93.5 [89.0; 95.0]	−0.50 [−1.75; 0.75]	0.50 [−1.00; 1.88]	.017
	SpO_2 at peak exercise, %	89.5 [84.0; 92.5]	90.0 [84.5; 93.5]	1.00 [−2.00; 3.00]	89.5 [84.5; 93.0]	90.5 [83.5; 93.0]	−0.50 [−2.00; 2.00]	0.48 [0.00; 2.50]	.517
	Watts max	158.0 [118.0; 201.3]	156.5 [116.8; 206.5]	0.00 [−10.50; 5.25]	133.0 [115.0; 201.50]	132.5 [108.5; 191.5]	−1.00 [−5.75; 2.00]	−0.50 [−8.13; 3.63]	.633

Median and interquartile [IQR 25; 75], significance value was set to ≤.05, highlighted in bold.
IG: Intervention Group; CG: Control Group; FVC: forced vital capacity; l: liter, FEV_1: forced expiratory volume in the first second; VO_2peak: oxygen uptake at peak exercise; ml/kg/min: milliliter per kilogram per minute; VE/VCO_2slope: slope of the minute ventilation and carbon dioxide production; RER: respiratory exchange ratio; bpm: beats per minute; mmHg: millimeter of mercury; SpO2: peripheral capillary oxygen saturation.

not play a predominant role in the improvement of exercise capacity by inspiratory muscle training. Comparing study patients of the cohorts mentioned above, VO_2peak solely increased in young and adolescent patients with Fontan circulation, but not in adult patients. It can be assumed that an improvement in lung function resulting in increased exercise capacity in adult patients with Fontan circulation cannot be achieved by inspiratory muscle training [16,27,28]. The age of the patients, as well as the differences in surgery and its modifications, considering the fact of improvement in palliation and medical aftercare over the last years, need to be considered when comparing study results.

The association of lung function and exercise capacity was recently confirmed by Callegari et al., who reported a high impact of ventilatory function on exercise limitation and consequently on exercise capacity [26]. In patients with Fontan circulation higher FEV_1 values result in a better VE/VCO_2 slope, indicating improvement in ventilatory function which may result in ameliorating systemic oxygen delivery [26]. Furthermore an increase in FEV_1 is not solely associated with a lower VE/VCO_2 slope, but also with an improvement in oxygen saturation [26].

In the current study oxygen saturation improved significantly after six months of IMT, without an increase in lung function or ventilatory efficiency. These results indicate an enhancement of hypoxic pulmonary vasoconstriction resulting in an improvement in ventilation/perfusion matching, which favors systemic oxygen delivery by the constriction of intrapulmonary arteries reacting to alveolar hypoxia [29]. Patients with Fontan circulation often suffer from reduced oxygen saturation, due to increased pulmonary vascular resistance, restraining hypoxic pulmonary vasoconstriction. Another plausible mechanism could be a reduction in chronic atelectasis following IMT. Hence IMT may improve blood flow of the lungs [29]. Further research focussing primary on oxygen saturation are needed to make those claims.

5. Limitations

Maximal inspiratory pressure was not measured which could have been significantly improved by IMT, as other training studies in patients with Fontan circulation have shown. For a more accurate measurement and a more precise comparison with other studies, the maximal inspiratory pressure should be gathered additionally.

The study patients performed a telephone-supervised, daily IMT at home. This training had been carried out by children and adolescent patients with Fontan circulation in a previous study of the German Heart Centre. In both study groups no problems occurred concerning the handling of the device. Nevertheless, IMT was telephone-supervised and questions could not be answered face-to-face. Furthermore, there was no standardized training in terms of the inspiratory load, since the patients adjusted it individually. Hence, there was no monitoring of the movement execution and no possibility to verify the inspiratory load during six months training period by the experienced sports scientist (C.F.). It might therefore be possible that some patients trained just under submaximal load with a minor impact on muscle development and muscle strength.

6. Conclusion

Six months of weekly telephone-supervised, daily IMT could not improve exercise and lung capacity in adult patients with Fontan circulation. According to current evidence, beneficial effects of IMT in adult patients with Fontan circulation cannot be verified. Therefore, larger studies are warranted in order to gain more insight into the mechanisms of exercise training and the Fontan physiology.

Declaration of competing interest

There are no conflicts of interest.

Acknowledgements

All authors made substantial contributions to conception and the design of the trial. CF sampled and analysed the data and drafted the first version of the manuscript. AH was responsible for conception and design of the study, data monitoring and integrity. RO and PE contributed to design and conception of the study. All authors gave important input for revising and improving the quality of the manuscript and approved the final version of the manuscript. Anja Delanoff and Angela Jung provided language help.

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