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Aerobic exercise and inspiratory muscle training increase functional capacity in patients with univentricular physiology after Fontan operation: A randomized controlled trial

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ABSTRACT

Background: The effect of exercise training and its mechanisms on the functional capacity improvement in Fontan patients (FP) are virtually unknown. This trial evaluated four-month aerobic exercise training and inspiratory muscle training on functional capacity, pulmonary function, and autonomic control in patients after Fontan operation.

Methods: A randomized controlled clinical trial with 42 FP aged 12 to 30 years and, at least, five years of Fontan completion. Twenty-seven were referred to a four-months supervised and personalized aerobic exercise training (AET) or an inspiratory muscle training (IMT). A group of non-exercise (NET) was used as control. The effects of the exercise training in peak VO_2; pulmonary volumes and capacities, maximal inspiratory pressure (MIP); muscle sympathetic nerve activity (MSNA); forearm blood flow (FBF); handgrip strength and cross-sectional area of the thigh were analyzed.

Results: The AET decreased MSNA ($p = 0.042$), increased FBF ($p = 0.012$) and handgrip strength ($p = 0.017$). No significant changes in autonomic control were found in IMT and NET groups. Both AET and IMT increased peak VO2, but the increase was higher in the AET group compared to IMT (23% vs. 9%). No difference was found in the NET group. IMT group showed a 58% increase in MIP ($p = 0.008$) in forced vital capacity ($p = 0.011$) and forced expiratory volume in the first second ($p = 0.011$). No difference in pulmonary function was found in the AET group.

Conclusions: Both aerobic exercise and inspiratory muscle training improved functional capacity. The AET group developed autonomic control, and handgrip strength, and the IMT increased inspiratory muscle strength and spirometry.

Clinical Trial Registration: ClinicalTrials.gov Identifier: NCT02283255

1. Introduction

Among a wide range of congenital heart defects (CHD) there is an important subgroup with up to 70,000 patients around the world living with single ventricle physiology [1]. The Fontan operation is the surgical treatment in the majority of these patients with either anatomic or functional single ventricle. In this operation the subpulmonary ventricle is bypassed, connecting the systemic veins directly to the pulmonary arteries [2–5]. The lack of a subpulmonary ventricle associated with a non-pulsatile pulmonary flow triggers a sequence of the adaptive mechanisms along the life of these patients [6].

The most frequent consequence of these adaptative mechanisms is the reduction in functional capacity, which is objectively measured by the decreased in peak oxygen consumption (VO_2) [7–11]. Low functional capacity is not only due to central cardiovascular factors and diminished pulmonary function, but is also associated with alterations in the autonomic control, such as increased sympathetic activity, blunted peripheral blood flow and underdeveloped skeletal muscle after Fontan operation [12–16].

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Exercise training is an effective non-pharmacological treatment that improves functional capacity in different populations (i.e. patients with chronic heart diseases [17–20], including CHD) [21–23]. Although exercise training have demonstrated a positive effect on functional capacity in these population [24–27], no controlled clinical trial evaluated the impact of an exercise training program (aerobic and inspiratory) on functional capacity, pulmonary function, and autonomic control in Fontan patients (FP). Therefore, we sought to investigate the effect of 4-month of aerobic exercise training and inspiratory muscle training on functional capacity, pulmonary function, and autonomic control, in patients with univentricular physiology after Fontan operation.

2. Methods

2.1. Trial design

This is a prospective, randomized, controlled clinical trial, conducted in a single center.

2.2. Population

From January 1984 to November 2018, 396 patients underwent a Fontan operation at the Heart Institute, Medical School, University of Sao Paulo, Brazil. FP were selected through a review of medical records, in-hospital and out-patient notes. Excluding patients who died, underwent heart transplantation, and/or who Fontan was a takedown, 347 patients were assessed for eligibility. Were included in the study FP aged between 12 and 30 years, both genders, clinically stable, without arrhythmias, with preserved ventricular function, and with a minimum of five years of follow-up after Fontan operation.

Patients were excluded if they showed diagnosis of hypoplastic left heart syndrome, musculoskeletal impairment that reduced their ability to walk, neurological sequelae, genetic syndromes, cognitive or psychiatric disorders, history of atrial or ventricular arrhythmias requiring anti-arrhythmic drugs and having pacemaker implantation. Patients with heart failure, pulmonary hypertension, protein-losing enteropathy, severe hypoxemia (oxygen saturation < 80%), paresis, or diaphragmatic paralysis, with or without plication, moderate to severe asthma, as well as patients living outside the city of Sao Paulo were also excluded. Fig. 1 shows of the eligible population. The reasons for the exclusion of the 305 patients were: 164 not met inclusion criteria (17 FP aged >30 years, 75 FP aged <12 years, 30 FP year of follow-up <5 years and, 42 FP with complications); 99 lived outside of Sao Paulo, 24 unable to contact for follow up and 18 declined to participate.

2.3. Study design

Recruitment began in December 2014 and closed in August 2018. All subjects voluntarily signed the informed consent before participation in the study. The institutional ethics committees on human research approved the study under the number CAAE 01998712.7.0000.0068. This trial is registered on ClinicalTrials.gov (number: NCT02283255) with 4 arms (aerobic training, respiratory training, aerobic plus respiratory training, and non-exercise training). However, a non-planned modification occurred due to the difficulty in recruiting patients for the combined training group (aerobic plus respiratory training). Therefore, we decided to keep 3 groups in this randomized clinical trial. Additionally, the CONSORT (Consolidated Standards of Reporting Trials) checklist was used in the present study.

Before baseline evaluation, FP were randomized into three groups: Aerobic Exercise Training (AET) and Inspiratory Muscle Training (IMT). AET and IMT prescription and monitoring were strictly followed as previously determined individually according to protocol. All patients were evaluated before and after the 4-month intervention period. Aet and IMT patients were compared to and Non-exercise Training group (NET, a control group). NET group were also evaluated at baseline and after 4 months and were instructed to continue with their usual physical activities and not to participate in any exercise training programs. (Fig. 1).

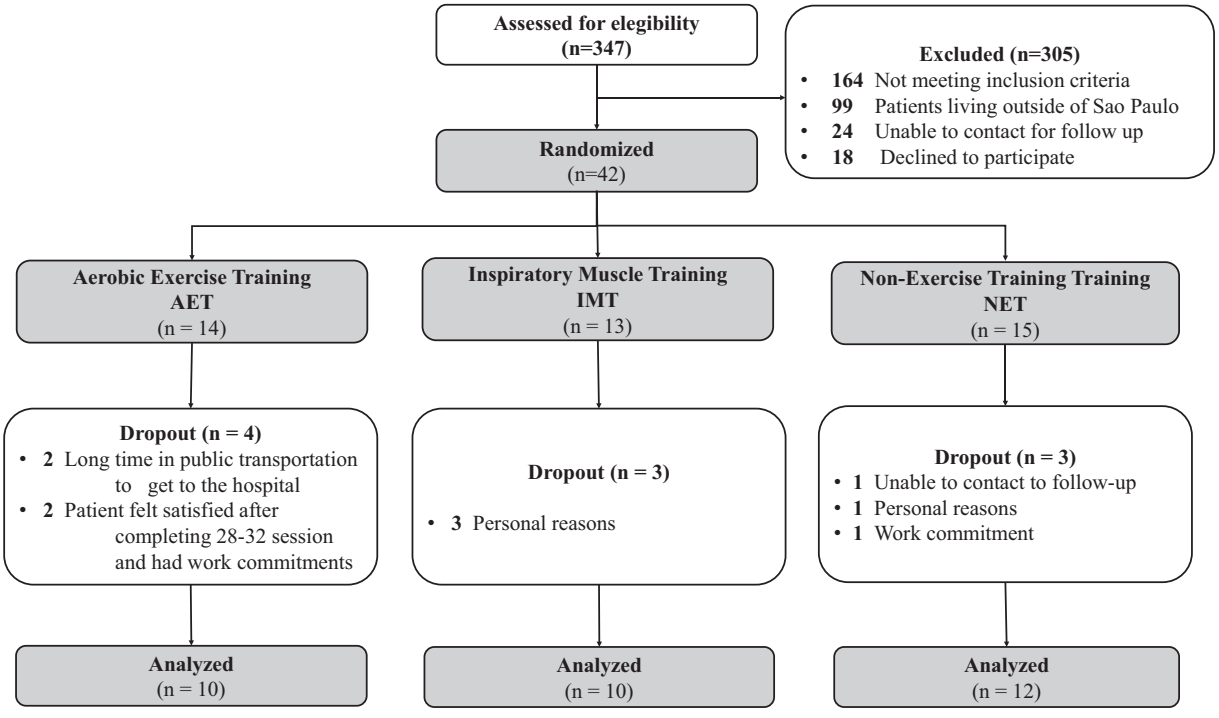

Fig. 1. Study enrollment and randomization in three groups: Aerobic Exercise Training, Inspiratory Muscle Training, and Non-exercise Training; dropout reasons and analysis. **Legend:** Flowchart of Eligibility and Randomization. AET: Aerobic Exercise Training; IMT: Inspiratory Muscle Training; NET: Non-exercise Training.

2.4. Randomization

The randomization scheme was generated by using the Web site Randomization.com (randomization.com). The patients were randomized in blocks.

2.5. Aerobic exercise training protocol

Four-month supervised exercise training was performed in hospital three times a week, 60-min exercise sessions (48 sessions in total). Each session consisted of 40 min on a treadmill, 15 min of subjective light resistance training (including chest press, squat, pull down, leg extension, shoulder press, calf raises, leg curl, and sit-ups), and 5 min of cool down and stretching. The AET was individually prescribed according to their heart rate (HR) from maximal cardiopulmonary exercise testing (CPT), and patients exercised between ventilatory threshold (VT) and respiratory compensation point (RCP). During the sessions HR, systolic blood pressure, oxygen saturation, and exhaustion (i.e. Borg scale from 7 to 20) were monitored. An exercise physiologist supervised all sessions. In the first 12 weeks, HR was maintained at T frequency. Between the 12th to 24th week, there was a progressive increase in the effort and HR was maintained between AT and RCP. In the last 12 sessions of the program HR was maintained close to RCP frequency.

2.6. Inspiratory muscle training protocol

Four-month exercise training were carried out daily, three sets of 30 repetitions using the POWERbreathe® device (POWERbreathe International Limited, Southam, UK), three sets of 30 repetitions. Maximal inspiratory pressure (MIP) measures were performed in all patients before the intervention, and patients exercised at 60% of individual MIP. Patients were instructed to inhale using diaphragm musculature, trying to expand the rib cage, to avoid the use of accessory muscles, and breathing at a rate of 12 to 16 breaths/min.

A nose clip was worn to ensure that patients were breathing exclusively through the training device. All patients had a supervised session of IMT with a physiotherapist once a week for the first two months and once every two weeks for the last two months. The load was adjusted during the supervised sessions. Patients were encouraged to maintain their habitual activities during the protocol.

2.7. Compliance

The minimum required compliance in the study was 75% of completed sessions. Patients of the AET group needed to complete at least 36 out of 48 training sessions, and patients of the IMT group required to complete at least five sessions/week for four months.

2.8. Outcomes

Endpoints: changes from baseline to four months after intervention in:

- Functional capacity (peak VO_2)
- Pulmonary function (pulmonary volumes and capacities, maximal inspiratory pressure)
- Autonomic control (muscle sympathetic nerve activity and forearm blood flow)

2.9. Cardiovascular magnetic resonance

All subjects performed cardiovascular magnetic resonance (CMR) on a 1.5 T MRI system (Achieva Intera, Philips, Netherlands). Volumes and ventricular function were measured by Simpson's method on short-axis images and were indexed for body surface area (BSA). Stroke volume (SV) was calculated by deducting the end-systolic volume (ESV) from the end diastolic volume (EDV). Because of the differences in body size, EDV and ESV were indexed to BSA.

2.10. Plasma measurements of B-type natriuretic peptide and norepinephrine

Blood samples were collected from a peripheral vein in the morning, after 30 min of rest for the analysis of plasmatic level of B-type natriuretic peptide (BNP) and norepinephrine [28–30]. In our institution, the limit detection for norepinephrine is 12.5 pg/mL, with reference values set to 40 to 268 pg/mL. Reference value to BNP set to less than 100 pg/mL.

2.11. Cardiopulmonary exercise test

The functional capacity was performed by a stress test on a treadmill, with a Sensor Medics equipment - Vmax Analyzer Assembly and Encore 29S. A 12-lead electrocardiogram was recorded throughout the exercise test (Micromed - Cardio PC 13). All patients were submitted to individualized ramp protocols (Modified Balke protocol) with increments of 1 MET (metabolic equivalent) per minute.

The evaluation of ventilation was measured by breath-by-breath method. Blood pressure was measured at rest, every 2 min during exercise and every minute throughout recovery. All measurements were performed by the same observer using auscultatory method. The maximal functional capacity was determined by absolute peak VO_2 (L/min) and relative peak VO_2 (mL/kg/min) and expressed as a percentage of the predicted values for healthy age- and gender-matched subjects as reported by Drinkwater et al. [31] and Morris et al. [32] The completion of the test occurred when, despite verbal encouragement, the patient could no longer maintain the exercise intensity, heart rate peak >85% of predicted and/or respiratory exchange ratio (RER) peak >1.0. [33]

2.12. Six-minute Walking Test

The submaximal capacity and walking ability were assessed by six-minute walking test (6MWT), which was performed according to the standard walk test protocol [34].

2.13. Lung function test

All measurements were obtained by Elite DL Medgraphics, Minneapolis, MN, as recommended by the American Thoracic Society guidelines. The predicted values were calculated according to the reference equations for the Brazilian population. Forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and FEV_1/FVC ratio was studied, and the predicted values calculated from the equations reported by Pereira et al. [35] and Mallozi et al. [36] Total lung capacity was measured by whole-body plethysmography, and the predicted values were calculated following the equations reported by Neder et al. [37] The diffusion capacity of carbon monoxide (DLCO) was measured with a single breath methodology using equipment with a neon chromatography column, and it was considered the predicted values according to the equations proposed by Crapo et al. [38]

2.14. Respiratory muscle strength

The respiratory muscle strength was measured by maximal inspiratory pressure (MIP) during the lung function test using Elite DL Medgraphics, Minneapolis, MN equipment. The maximum value of the three maneuvers that varied less than 20% was considered, and the predicted values were according to Neder et al. [39] and Hulzebos et al. [40]

2.15. Microneurography

Muscle sympathetic nerve activity (MSNA) was evaluated by the direct technique of recording the multiunit of the efferent postganglionic pathway in the fibular nerve located immediately below the fibular head in the right leg as previously described [15]. The sympathetic nerve activity was analyzed by continuous recording of muscle sympathetic activity during resting condition for 10 min using the Windaq program. The neurogram was analyzed manually by counting the number of bursts that occurred during each minute (bursts/min).

2.16. Venous occlusion plethysmography

The forearm blood flow (FBF) was evaluated using a mercury-filled silastic placed around the forearm, five centimeters away from the humeral-radial joint, connected to a low-pressure transducer and a plethysmograph (Hokanson AI6, United States) also as previously described [15].

2.17. Magnetic resonance imaging of the thigh musculature

The thigh musculature was assessed with a whole-body 3.0 T MRI system (Achieva Intera, Philips, Netherlands) using Spectro surface coil 14 Phosphorus. Through DICOM file viewer and medical imaging software (OsiriX medical imaging Software, Altlanta, USA) was analyzed and quantified the cross-sectional area (CSA) of the thigh of young Fontan patients and healthy subjects and the percentage of intramuscular fat (IMF) as previously described [15].

2.18. Handgrip strength

Handgrip strength was assessed in the upper limb on the side of the non-dominant by a dynamometer (Stoelting®, United States) and was used to represent the peripheral skeletal muscle strength. Three replicates measures were performed, maintaining maximum contraction for a period of 5 s for each trial, with the non-dominant limb in a neutral position (elbow flexed at 90°). The time interval between one trial and another was 1 min to avoid muscle fatigue during the test. The maneuver was repeated three times, considering the highest value reached.

2.19. Quality of life assessment

We used the Short Form-36 questionnaire to evaluate the quality of life through eight components: 1. Functional capacity (10 items), 2. Physical aspects (4 items), 3. Pain (2 items), 4. General health (5 items), 5. Vitality (4 items), 6. Social aspects (2 items), 7. Emotional aspects (3 items), 8. Mental health (5 items), and one question of comparative evaluation between current and one year ago health conditions. The transformation of responses into scores (0 to 100 scale) of each component results in a better or worse general health state. The questionnaire was validated for Portuguese and can be applied for people aged 12 to 80 [41].

2.20. International Physical Activity Questionnaire (IPAQ) - Short form

This questionnaire evaluates the level of physical activity based on 3 types of activities, weak, moderate, and vigorous. From the sum of these activities, the subjects were classified into 4 categories: “Sedentary”, “Insufficient active”, “Active”, and “Very active”. The measure of the volume of physical activity performed weekly was computed by the weight of each type of activity by the energy required in METS (metabolic equivalents). The total physical activity in MET-min/week was computed by the sum of Walking + Moderate + Vigorous MET-min/week scores, as described by IPAQ processing and analysis guidelines [42,43].

2.21. Sample size

The sample size was calculated according to previous studies [24,25]. Based on a 20% increase in relative peak VO_2 (mL/kg/min) after the intervention compared to baseline, 15 patients per group (AET, IMT, and NET) was calculated to have 80% power to detect the difference at a 2-sided significance level of 0.05.

2.22. Statistical analysis

The Shapiro-Wilk test was performed to assess the normality of continuous variables. The data are presented as median and interquartile range. Baseline comparisons among groups were tested using Kruskal–Wallis test for continuous variables. The dichotomous data are presented as counts and percentages, and the differences between groups were evaluated using the Chi-square test or Likelihood test. The effect of exercise training was tested with Wilcoxon Signed Ranks test. Comparisons of the variables among groups before and after the intervention were performed using Kruskal–Wallis test. The same was performed to test the delta between the measures before and after training among the three groups. Spearman correlation were performed between variables. Tests were considered of statistical significance if p-values were < 0.05. Statistical analyses were performed using the computer program SPSS version 23.0 (Chicago, IL, USA).

3. Results

3.1. Baseline characteristics and exercise training analysis

Among the forty-two FP evaluated at baseline and randomized to the AET ($n = 14$), IMT ($n = 13$) and, NET ($n = 15$) groups. Ten patients (23,8%) dropped out before the end the protocol (Fig. 1). The AET group had more dropouts compared to IMT and NET [4 (28%) vs. 3 (23%) vs. 3 (20%)], respectively. After 4-month period of protocol group AET had 10 FP, group IMT had 10 FP and group NET had 12 FP. All patients in our study did not practice sports activities at baseline period. When we assessed the physical activity level by IPAQ, we found 10 (31%) patients classified as sedentary; 11 (35%) as insufficiency active, 10 (31%) active, and 1 (3%) very active ($p = 0.429$). There was no difference in MET/weeks among groups at baseline ($p = 0.790$).

Baseline characteristics from FP is showed in Table 1. No significant difference was found between AET, IMT and NET for age, gender, body mass index (BMI) and New York Heart Association functional class. We found difference before intervention between AET and IMT group in FVC ($p = 0.019$) and handgrip strength ($p = 0.008$).

Although there was an improvement in ejection fraction and stroke volume after training, these values were not statistically significant; the same occurred with EDVi (mL/m2) and ESVi (mL/m2). These findings could be explained due to the small sample size and all the subjects presenting with normal ventricular function before training. Perhaps these changes could be visualized by doing the exam during the effort (cycle ergometer) than at rest.

3.2. Functional capacity

Comparing the functional capacity before and after the intervention, we identified a 23% increase (27.0 (23.2–32.7) to 33.3 (26.8–39.1) mL/kg/min 0.012) in peak VO_2 and 20% in age predicted peak VO_2 in the AET group. Absolute peak VO_2 also increased after intervention (34%) mainly in AET group [1.42 (1.29–2.23) vs 1.91 (1.43–2.72) L/min $p = 0.011$]. IMT group presented a 9% [26.6 (21.3–31.1) to 29.1 (22.6–32.9) mL/kg/min $p = 0.008$] increase in peak VO_2 and 6% in age predicted peak VO_2 after the intervention. Contrary, NET group did not show any changes in functional capacity after four months of follow-up. Fig. 2A and B show peak VO_2 delta variation among groups studied.

Table 1
Baseline characteristics of the Fontan patients.

	All	Randomization			
Variables	**(32)**	**AET (10)**	**IMT (10)**	**NET (12)**	**p**
Age at test *(years)*	20 (15–25)	21 (16–29)	15 (13−22)	21 (15–25)	0.122
Gender *(M/F)*	10/22	5/5	1/9	4/8	0.128
BMI *(kg/m²)*	21.3 (18.9–24.1)	20.9 (19.5–26.2)	20.1 (17.5–22.6)	22.4 (19.6–27.8)	0.338
MET-min/week	382 (58–1181)	488 (99–708)	363 (0–1652)	510 (58–1986)	0.790
O_2 saturation at rest *(%)*	95 (93–97)	95 (93–97)	96 (95–97)	94 (92–96)	0.284
BNP *(pg/mL)*	20 (9–40)	12 (9–41)	31 (12–40)	18 (11–42)	0.676
EDVi (mL/m²) by CMRI	79 (62–96)	83 (55–111)	68 (55–97)	80 (73–89)	0.795
ESDi (mL/m²) by CMRI	35(28–42)	36 (33–49)	30 (20–48)	34 (29–39)	0.682
EF *(%)* by CMRI	58 (54–64)	58 (53–66)	58 (53–65)	58 (54–64)	0.961
Stroke volume *(mL)* by CMRI	57 (41–70)	58 (48–83)	46 (40–61)	62 (38–81)	0.084
NYHA-functional class I/II, *n*	25:7	7:3	7:3	11:1	0.316
Age at Fontan *(years)*	8 (7–11)	7 (7–12)	8(7–9)	8 (6–11)	0.946
Follow-up at Fontan *(years)*	11 (8–15)	12 (10–19)	8 (7–13)	11 (8–16)	0.147
Diagnosis, n					0.771
Tricuspid valve atresia	13	5	4	4	
Pulmonary valve atresia	6	2	1	3	
Mitral valve atresia	2	1	0	1	
Heterotaxy syndrome	2	0	1	1	
Others	9	2	4	3	
Ventricular morphology, n					0.941
Left	25	8	7	10	
Right	4	1	2	1	
Both	3	1	1	1	
Type of Fontan, n					0.426
Extracardiac conduit	24	6	8	10	
Lateral tunnel	8	4	2	2	
Staged at Glenn procedure, *n*	23	6	7	10	0.465
Fenestrated, *n*	12	4	5	3	0.467
Medications, n					
ACE inhibitor	12	3	3	6	0.530
Antiplatelet	4	0	2	2	0.193
Anticoagulant	28	10	8	10	0.193
Beta-blocker	2	0	2	0	0.084
Diuretics	2	1	1	0	0.375

ACE: angiotensin-converting enzyme; AET: Aerobic Exercise Training; BMI: Body mass index; BNP: B-type natriuretic peptide; CMRI: cardiovascular magnetic resonance imaging; EDVi: indexed end-diastolic volume; EF: ejection Fraction; ESVi: indexed end-systolic; IMT: Inspiratory Muscle Training; MET: metabolic equivalent; volume; NET: Non-Exercise Training; NYHA: New York Heart Association.

There was no change in VE / CO_2 slope after training. This normal VE / CO_2 slope response suggests that our Fontan patients do not have abnormal chemoreflex sensitivity. Therefore, an improvement in the VE/ CO_2 slope was not expected after the interventions.

AET and IMT groups improved the walked distance in 6MWT after the intervention, but there was no difference among groups after intervention as demonstrated in Table 2.

3.3. Pulmonary function

The IMT promoted 58% increase in MIP ($p = 0.008$), 14% increase in FVC (0.011), and 10% increase in FEV1 ($p = 0.011$). Maximal voluntary ventilation also increased significantly in the IMT group after the intervention ($p = 0.012$). IMT did not contribute to improving DLCO. When compared the values after intervention among groups, we found significant difference in MIP between IMT and NET group [−103 (−134- -90) vs. -58 (−75- -49) $p < 0.001$]. The AET no modified any pulmonary function parameter. All results are in Table 2. Fig. 2C and D show the pulmonary function delta variation among groups studied.

3.4. Autonomic control

After 4-month period of intervention, there was an improvement in autonomic control in the AET group represented by a reduction in MSNA [27 (25–32) vs. 22 (18–25) burst/min $p = 0.042$] and an increase in FBF [1.63 (1.06–1.87) vs. 1.99 (1.65–2.30) mL/min/100 mL p = 0.012]. Comparisons among groups after intervention demonstrated that MSNA in AET group was significant lower compared to both IMT and NET groups ($p = 0.043$ and $p = 0.035$) respectively, and the FBL was significantly higher compared to NET group ($p = 0.021$). There was no change in MSNA and FBF in the IMT and NET groups (Table 2). Fig. 2E and F show the delta variation in autonomic control among all groups.

The plasmatic level of norepinephrine did not change after interventions, and there was no correlation between MSNA and FBL. This finding could be explained by the higher confidence interval observed in norepinephrine measures. We found negative correlation between norepinephrine and the peak VO2 ($r = -0.742$ $p = 0.014$); peak heart rate ($r = -0.0738$ $p = 0.015$) and handgrip strength ($r = -0.652$ $p = 0.041$) after training in AET group.

There was no change in resting heart rate after the AET. However, there was significant heart rate decrement in the first and the second minute in recovery after exercise cessation. The median chronotropic index in the AET group was at the lower limit of normality before training, this value was normalized after the intervention (> 0.80 according to Wilkoff et al.) [44]. The Δ heart rate 1_{min} was >12 beats/min, this cut-off has been used as a protective factor of morbimortality for cardiovascular events. These data is Table 2.

3.5. Cross-sectional area of the thigh and muscle strength

CSA of the thigh did not change within and between groups studied. On the other hand, there was an increase in handgrip strength only in the AET group. This value after the intervention was significantly higher in the AET group than IMT ($p = 0.016$). (Table 2).

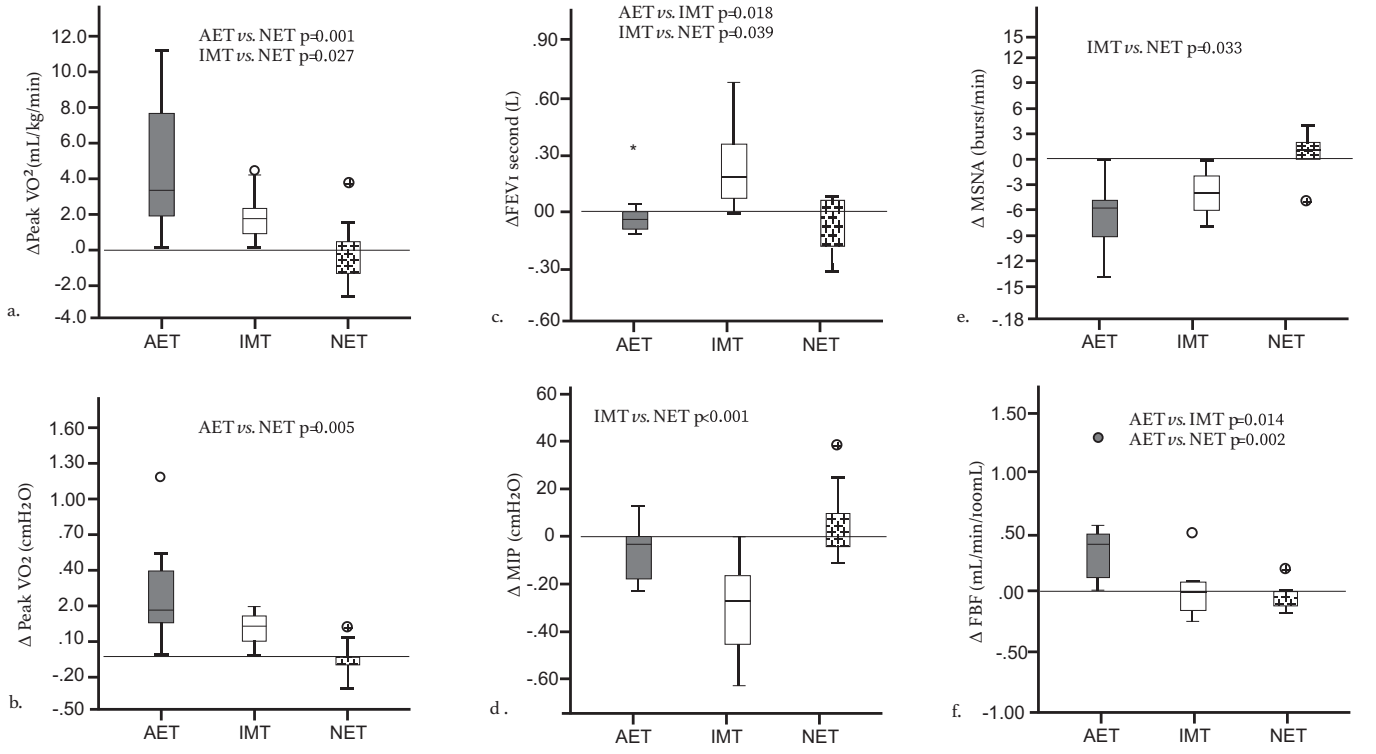

Fig. 2. Shows the comparison among groups Aerobic Exercise Training, Inspiratory Muscle Training, and Non-exercise Training regarding the delta changes in six variables from baseline to post intervention. **Legend:** Delta variations in a. Peak VO_2 (mL/kg/min); b. Peak VO2 (L/min); c. FEV1 (forced expiratory volume one second); d. MIP (maximal inspiratory pressure); e. MSNA (muscle sympathetic nerve activity); f. FBF (forearm blood flow) from baseline to post-intervention are on y-axis, and the x-axis is the three groups Aerobic Exercise Training (AET), Inspiratory Muscle Training (IMT), and Non-exercise Training (NET). Each graph exhibits the difference among groups regarding the variation delta of each of the variables analyzed.

3.6. Quality of life

Regarding the quality of life, the patients from AET group reported an improvement of physical functioning [65 (54–95) vs. 90 (80–95) $p = 0.018$] and emotional role functioning [33 (0−100) vs. 100 (83–100) $p = 0.026$] domains after 4 months; and the patients from IMT group also had higher scores in emotional role functioning [65 (25–100) vs. 100 (92–100) $p = 0.039$] and in vitality domain [70 (54–78) vs. 83 (60–86) $p = 0.043$] domain.

No adverse events occurred throughout the study. Exercise training in FP patients was safe and there were no complaints from patients.

4. Discussion

To our knowledge, this is the first randomized controlled trial that evaluated the effect of supervised exercise training and inspiratory muscle training on functional capacity, lung function, and autonomic control in adolescent and adult patients in the late postoperative period of Fontan. Our main finding was that aerobic exercise and inspiratory muscle training improved peak VO_2, but AET showed higher improved compared to IMT and an important improvement in autonomic control. On the other hand, we only observed an increase in pulmonary function in IMT group, with no change in autonomic control.

At baseline, the functional capacity expressed by peak VO_2 and the age predicted peak VO_2 in our patients was similar to those related in previous studies [11,45,46]. Among 42 FP 26% had peak VO_2 above 80% of age predicted. Cordina and d'Udeken [47] reported in a recent review of data from the Australia and New Zealand Fontan Registry, that approximately 10% of adults with Fontan circulation showed with normal exercise capacity. They called them as "Super-Fontans" and commented that these patients participate in moderate-to-vigorous sporting activities (at least three times per week). This was expressed differently in our sample. In our study, patients did not practice sports activities and when we assessed the physical activity level by IPAQ, we found no differences among them. Hedlund et al. [48] measured the physical activity using accelerometer recordings over a consecutive seven days and self-reported exercise. They did not find a difference in the total activity measure between Fontan and healthy controls, even though Fontan patients reported less time engaged in regular physical exercise.

Recently, we demonstrated that suboptimal peripheral blood supply and diminished exercise capacity in Fontan patients are associated with an underdeveloped skeletal muscle and reduced muscle strength [15]. Our data corroborates with Cordina et al. [13], which demonstrated abnormalities skeletal muscle represented for wasting in the sarcopenic range and impaired post exercise phosphocreatine resynthesis in a group of children and adults with Fontan in NYHA class I/II, and the lean mass correlated with peak VO_2. It is well known that peak VO_2 depends on peripheral and central components, which are blunted in FP, and exercise training may have a role in improving oxygen extraction from skeletal muscle. For instance, while we did not observe any difference in CSA of the thigh, it is possible that after the exercise training program, Fontan patients could have an improvement in mitochondrial function and better arteriovenous oxygen extraction.

The increase in peak VO_2 after AET in our study was higher than demonstrated in previous studies [24–27,49–52]. We speculated that the variation in peak VO_2 showed after the training programs reported in these studies could be explained by characteristics of the programs, as the setting (home or supervised), exercise type (aerobic, resistance), duration (months), frequency (sessions/week) and intensity. The rigor in the prescription of the exercise (HR at AT up to PCR) and the monitoring during the training were probably responsible to an important increase in the functional capacity in the AET group.

Table 2
Results: aerobic exercise and inspiratory muscle training compared with no exercise training in fontan patients.

Variables	AET ($N = 10$) Before	AET ($N = 10$) After	p	IMT (N = 10) Before	IMT (N = 10) After	p	NET ($N = 12$) Before	NET ($N = 12$) After	p	P-values Among Groups
Cardiopulmonary exercise test										
Peak VO_2 (L/min)	1.42 (1.29–2.23)	1.91 (1.43–2.72)[b]	0.011	1.15 (0.99–1.49)[a]	1.28 (1.13–1.53)[b]	0.008	1.67 (1.40–1.86)[a]	1.61 (1.41–1.87)	ns	0.020
Peak VO_2 (mL/kg/min)	27.0 (23.2–32.7)	33.3 (26.8–39.1)	0.012	26.6 (21.3–31.1)	29.1 (22.6–32.9)	0.008	29.7 (24.9–34.3)	27.6 (23.9–34.6)	ns	ns
Age-predicted peak VO_2 (%)	66 (56–78)	79 (67–90)	0.012	64 (56–80)	68 (60–84)	0.007	77 (61–87)	70 (61–86)	ns	ns
Resting heart rate (beats/min)	90 (88–91)	94 (84–101)	ns	96 (82–106)	91 (80–107)	ns	95 (84–112)	98 (90–105)	ns	ns
Peak heart rate (beats/min)	168 (156–176)	176 (169–181)	0.021	175 (161–188)	176 (164–184)	ns	173 (168–176)	174 (167–180)	ns	ns
Age-predicted peak heart rate (%)	86 (79–91)	91 (84–94)	0.035	87 (78–92)	89 (81–93)	ns	87 (83–91)	87 (83–91)	ns	ns
Δ heart rate $_{1min}$ (beats/min)	17 (12−21)	27 (19–28)	0.021	19 (15–26)	20 (13–36)	ns	16 (12–28)	19 (13–28)	ns	ns
Δ heart rate $_{2min}$ (beats/min)	31 (24–38)	42 (29–45)	0.033	37(23–44)	34 (24–60)	ns	34 (27–45)	34 (27–48)	ns	ns
Chronotropic index	0.79 (0.71–0.96)	0.89 (0.81–1.01)	0.033	0.88 (0.76–0.96)	0.88 (0.68–0.99)	ns	0.84 (0.77–0.92)	0.82 (0.75–0.95)	ns	ns
Slope (VE/VCO2)	31 (27–34)	32 (29–38)	ns	36 (33–43)	36 (33–40)	ns	31 (28–35)	31 (28–34)	ns	ns
RER	1.07 (1.00–1.14)	1.14 (1.10–1.20)	0.021	1.08 (1.05–1.12)	1.10 (1.04–1.13)	ns	1.10 (1.02–1.14)	1.11 (1.01–1.14)	ns	ns
Exercise duration (minutes)	9 (8–9)	10 (8–11)	ns	9 (8–13)	10 (9–12)	ns	9 (8–12)	11 (8–12)	ns	ns
Six-minute walk testing										
Distance (meters)	615 (567–661)	654 (628–686)	0.012	580 (528–616)	617 (537–647)	0.008	593 (578–626)	587 (544–649)	ns	ns
Resting oxygen saturation (%)	95 (93–97)	93 (87–95)	ns	96 (95–97)	93 (90–94)	ns	94 (92–96)	93 (87–95)	ns	ns
Oxygen saturation exercise peak (%)	95 (92–95)	91 (81–94)	0.005	95 (94–97)	90 (85–93)	0.005	94 (90–96)	93 (87–94)	0.005	ns
Lung function test										
FVC (L)	3.1 (2.8–3.9)[a]	3.3 (2.7–3.8)	ns	2.2 (1.9–2.8)[a]	2.5 (2.3–2.9)	0.011	2.7 (2.4–3.3)	2.7 (2.2–3.3)	ns	0.024
Predicted FVC (%)	80 (75–93)	80 (70–94)	ns	83 (65–94)	86 (77–102)	ns	79 (69–88)	80 (56–100)	ns	ns
FEV_1 (L)	2.7(2.2–3.4)	2.9 (2.2–3.3)	ns	2.0 (1.7–2.5)	2.2 (2.1–2.6)	0.011	2.3 (2.0–2.9)	2.3 (1.9–2.8)	ns	ns
Predicted FEV_1 (L)	74 (70–89)	73 (69–88)	ns	76 (67–89)	87 (79–97)	0.015	78 (64–88)	80 (55–93)	ns	ns
MVV (L/min)	108(90–135)	116 (86–135)	ns	80 (69–101)	90 (83–103)	0.012	92 (79–115)	106 (80–119)	ns	ns
TLC (L)	4.7(3.6–5.3)	4.9 (4.0–5.4)	ns	3.4 (3.2–4.0)	3.7 (3.2–4.7)	ns	4.3 (3.3–6.3)	4.0 (3.2–4.9)	ns	ns
Predicted TLC (%)	79 (69–98)	84 (75–103)	ns	76 (74–94)	81 (75–91)	ns	85 (78–89)	87 (66–90)	ns	ns
DLCO (mL/min/mmHg)	20.0 (15.6–25.2)	20.0 (15.0–24.9)	ns	16.2 (12.2–18.1)	18.0 (14.1–18.4)	ns	20.3 (16.0–25.8)	16.0 (14.4–21.7)	ns	ns
Predicted DLCO (%)	61 (49–66)	60 (45–62)	ns	57 (44–64)	61 (51–66)	ns	64 (53–74)	53 (47–77)	ns	ns
MIP (cmH_20)	−70 (−79 - -61)	−76 (−87 - -60)	ns	−66 (−95- -54)	−103 (−134- -90)[b]	0.008	−58 (−77- -50)	−58 (−75- -49)[b]	ns	<0.001
Predicted MIP (%)	66 (58–76)	75 (60–78)	ns	65 (53–91)	102 (90–124)[b]	0.008	57 (48–76)	51 (47–66)[b]	ns	<0.001
Neurovascular control of FBF and MSNA										
FBF (mL/min/100 mL)	1.63 (1.06–1.87)	1.99 (1.65–2.30)[b]	0.012	1.54 (1.42–1.71)	1.57 (1.25–1.73)	ns	1.57 (1.40–1.84)	1.46 (1.22–1.78)[b]	ns	0.018
MSNA (burst/min)	27 (25–32)	22 (18–25)[b]	0.042	30 (25–31)	28(25–29)[bc]	ns	29 (22−32)	26 (25–34)[bc]	ns	0.013
Norepinephrine (pg/mL)	315 (248–382)	294 (157–447)	ns	274 (186–332)	209 (166–387)	ns	272 (202–471)	293 (205–395)	ns	ns
Muscle evaluation										
CSA of the thigh /BMI ($cm^2/kg/m^2$)	3.75 (3.40–4.63)	4.80 (3.93–5.38)	ns	3.80 (3.10–3.90)	3.90 (3.80–4.10)	ns	3.10 (2.75–4.40)	3.25 (2.65–5.05)	ns	ns
Percentage of IMF (%)	7.6 (5.8–9.0)	6.0 (5.7–10.5)	ns	8.5 (7.0–9.5)	9.9 (6.7–10.7)	ns	7.6 (7.4–9.1)	7.5 (6.1–8.6)	ns	ns
Handgrip strength (kgf)	22 (21−31)[a]	24 (24–31)[b]	0.017	18 (13–19)[a]	19 (16–24)[b]	ns	19 (16–24)	21 (19–24)	ns	0.019

ACE: angiotensin-converting enzyme; AET: Aerobic Exercise Training; BMI: Body mass index; BNP: B-type natriuretic peptide; CMRI: cardiovascular magnetic resonance imaging; CSA: cross sectional area; DLCO: diffusion capacity carbon monoxide; FBF: forearm blood flow; FEV_1: forced expiratory volume one second; FVC: forced vital capacity; IMF: intra-muscular fat; IMT: Inspiratory Muscle Training; MIP: maximal inspiratory pressure; MSNA: muscle sympathetic nerve activity; NET: No Exercise Training; NYHA: New York Heart Association; RER: respiratory exchange ratio; VE: minute ventilation; MVV: maximal voluntary ventilation; TLC: total lung capacity; VE/VCO2: ventilatory equivalent for carbon dioxide. a = baseline difference between groups; b = difference between groups at 4 months (after intervention); c = no difference between IMT and NET groups.

Additionally, autonomic imbalance is a hallmark in many cardiovascular diseases and is associated with lower functional capacity [17,53,54]. Previously, we demonstrated that FP also have an increased sympathetic outflow measured directly by microneurography technique. [15,55] In the present study, after aerobic exercise training, we observed a decreased in MSNA when compared with IMT and NET. Moreover, FBF increased significantly in the AET group. Altogether, this improvement in neurovascular control can contribute to the improvement of functional capacity in FP.

In this study, we revealed a significant improvement in maximal inspiratory pressure, FVC, and FEV_1 after four months of IMT. Additionally, there was an increase in functional capacity, differently from what was demonstrated by some studies, [56,[57] especially by Fritz et al. [58] We speculate that this difference could be explained for variation in the

methodology used. For example: type of device, the difference in % of the load used in training, and total program time.

Both training programs improved the quality of life in FP. Besides the improvement in the physical functioning domain due to AET, an exceptional increase in emotional role functioning was observed in this group of patients. These findings corroborate with Hedlund et al. [51]

In terms of this study, we selected only the "good Fontan" - a patient in his best clinical and surgical condition - and we followed a long list of exclusion criteria for the patients. Although asymptomatic and clinically stable, we demonstrated that these patients had significant lung function impairment, autonomic control changes, blunted peripheral blood supply, and underdeveloped skeletal muscle [14,15]. Subsequently, this clinical trial came with the proposal to improve the functional capacity through the AET and IMT assessing the patient by different system, cardiovascular, pulmonary, and skeletal muscle.

Despite all the limitations of this study, the results were positive for both aerobic and respiratory interventions, and we believe that the combination of both interventions could bring an even higher impact.

We know that Fontan patients are part of a unique and heterogeneous population. Despite the promising initial results of the Fontan operation, some complications inherent to the lack of the subpulmonary ventricle and circulatory adaptation will develop in the long-term follow-up.

Theoretically, there is no contraindication for those developing impaired ventricular function, non-complex arrhythmias, or residual lesions to participate in a structured and supervised exercise program. On the other hand, for patients with a correctable residual lesion compromises functional capacity, we understand they should be treated adequately before referred to an exercise program. Unfortunately, the lack of evidence in the literature on this subgroup of patients demands further studies, including "Bad Fontan" patients, to prove we could use exercise in improving their functional capacity.

From our perspective, physical, recreational, and sports activity should be stimulated as soon as possible after Fontan completion. The patients must be educated and aware that physical exercise need to become a habit in their lives. We understand that it will play a fundamental role in improving/maintaining functional capacity and quality of life throughout their lives. A training program's success depends on an adequate initial assessment, individualized prescription, and patient follow-up (training load adjustment) for training progression when allowed, ensuring functional improvement. Monitoring and type of supervision should be appropriate for every patient and clinical condition.

5. Limitations

We acknowledge the limitations from our study. Sample size is one of them. In the original design, our initial hypothesis was that aerobic training associated with inspiratory training could increase the benefits to the patient. However, we were unable to get enough patients to randomize 4 groups as initially planned. We had many patients that refused to participate in the study due to living far from the hospital, worked full time, and they would not be available for training and/or exams.

6. Conclusion

Both aerobic exercise and inspiratory muscle training improved functional capacity in FP, as demonstrated by an increase in peak VO_2. The mechanisms involved in each training were different. AET developed autonomic control and handgrip strength; the IMT increased inspiratory muscle strength and spirometry. However, the peak VO_2 was higher in patients after intervention in the AET group. Our findings reinforce that aerobic exercise and inspiratory muscle training are an important non-pharmacological treatment for the clinical development of FP.

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The authors declare that they have no conflict of interest.

Author contributions statement

Zafar Said: Graphical abstract; highlights; Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing - original draft; Writing - review & editing.

Hegazy Rezk: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Validation; Opitimization; Writing - original draft; Writing - review & editing.

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