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Moderate-to-high intensity inspiratory muscle training improves the effects of combined training on exercise capacity in patients after coronary artery bypass graft surgery: A randomized clinical trial

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ABSTRACT

Background: The effects of adding moderate-to-high intensity inspiratory muscle training (IMT) to short-term aerobic and resistance exercise (combined training [CT]), after coronary artery bypass grafting (CABG) are not established. This study aimed to determine the effects of moderate-to-high intensity IMT + CT on exercise capacity, respiratory muscle strength, inspiratory muscle endurance, quality of life (QoL), and laboratory biomarkers in patients after CABG who were participants of a phase II cardiac rehabilitation program.
Methods: Twenty-four patients were randomly assigned to either the IMT + CT group (n = 12), who performed moderate-to-high intensity IMT with CT or the sham-IMT + CT group (n = 12). Patients completed two sessions per week for 12 weeks. Each patient underwent a cardiopulmonary exercise test, six-minute walk test (6MWT), respiratory muscle strength and endurance evaluation, QoL questionnaire, and serum advanced oxidation protein products, ferric reducing antioxidant power [FRAP], nitrate/nitrate, and high-sensitivity C-reactive protein, before and after the 12-week intervention.
Results: The IMT + CT group showed significantly greater improvements in peak oxygen uptake (1.3 mL·kg^{-1}·min^{-1}; 95% confidence interval [95% CI], 0.5 to 2.2), distance covered during the 6MWT (78.8 m; 95% CI, 28.1 to 129.5), maximal inspiratory pressure (23.0 cmH_2O; 95% CI, 9.3 to 36.7), QoL (−15.1 points; 95% CI, −26.9 to −3.3), and FRAP (83.7 μmol/L; 95% CI, 20.2 to 147.1) compared to the sham-IMT + CT group as a result of the intervention.
Conclusions: Short-term moderate-to-high intensity IMT with CT provided additional benefits in exercise capacity, inspiratory muscle strength, QoL, and antioxidant profile in patients after CABG.
Trial Registration clinicaltrials.gov Identifier: NCT02885077

1. Introduction

Even with major advances in clinical therapy and percutaneous interventions, CABG is the most common cardiac surgery performed worldwide and is an effective treatment in reducing symptoms and mortality in patients with coronary artery disease (CAD) [1,2]. However, CABG is a complex procedure that triggers a series of clinical and functional complications [3].

Inevitably some degree of pulmonary dysfunction is expected in the immediate postoperative period following CABG [4]. These effects may persist and result in reductions in lung volume of 25–30% (3.5 months after CABG) [5], maximum inspiratory and expiratory pressure (MIP and MEP, respectively) compared to predicted values (6 months after CABG) [6], and thoracic mobility (1-year post-CABG) [7].

Currently, the recommendation to include IMT to cardiac rehabilitation (CR) programs has been gaining interest [6,8]. The core strategy of typical CR programs is the exercise-based therapy that combines aerobic and resistance exercise (combined therapy [CT]) [9]. Recent meta-analysis showed that CT is more beneficial than aerobic training (AT) alone for improving physical function in the rehabilitation of CAD

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[10]. Numerous studies have demonstrated that in post-CABG patients participating in phase I CR programs, the benefits of IMT include re-establishing pulmonary function, reducing the length of hospital stay, improvement QoL and exercise capacity [11,12]. Nevertheless, there is a lack of studies in phase II CR, despite the promising results demonstrated in post-CABG patients and those with chronic heart failure (CHF) [8,12,13].

To date, most of the previous studies have used IMT programs characterized by inspiratory efforts against low to moderate intensity workloads, with a daily frequency and slow load progression [11,12]. Based on the assumption that improvements in inspiratory muscle function are dependent on inspiratory pressure load, the magnitude of the training response tends to increase with the imposed load [14]. Thus, even in an incipient way, the applicability of high-intensity IMT has been studied in healthy individuals [15] and several pathologies [16]. However, no studies have assessed the efficacy of moderate-to-high intensity IMT in addition to CT in CABG patients.

Therefore, the aim of this study was to investigate the effects of a 12-week moderate-to-high intensity IMT plus combined aerobic, and resistance training on exercise capacity, respiratory muscle strength, inspiratory muscle endurance, QoL, and laboratory biomarkers in CABG patients enrolled in a phase II CR program.

2. Method

2.1. Study design

The present study protocol was conducted following the Consolidated Standards of Reporting Trials (CONSORT) statement. This randomized, controlled, double-blind, single-center clinical trial conducted at the University Hospital of Santa Maria, Rio Grande do Sul, Brazil. The study was approved by the ethics committee (process no. 1.380.081) and performed in accordance with the Declaration of Helsinki. All subjects provided written informed consent before participation, and the trial was registered at ClinicalTrials.gov (NCT02885077).

2.2. Participant recruitment and group assignment

Recruitment took place between January 2016 and April 2017. All patients were recruited from the waiting list for phase II CR program at the Outpatient Cardiology Clinic of the same hospital. The eligibility criteria included patients undergoing CABG, aged between 45 and 65 years, receiving optimal medical management, and with New York Heart Association functional class I or II. Exclusion criteria were the presence of uncontrolled cardiac arrhythmias, unstable angina, uncontrolled hypertension, peripheral arterial disease, chronic obstructive pulmonary disease, labyrinthitis, and neuromuscular or orthopedic/musculoskeletal limitations.

A computer-generated list of random numbers was used, and a randomization sequence was created by the Random Number Generator Pro v2.00 software (Segobit, Issaquah, WA, USA). Patients were randomized (1:1) by a single investigator blinded to patient identity (I.M.A.) to an IMT + CT or sham-IMT + CT. After randomization, IMT was blinded and study staff who collected data on study outcomes were unaware of study group assignments and all data analyses were also blinded.

2.3. Study endpoints

The primary endpoint of this study was exercise capacity assessed by cardiopulmonary exercise test (CPET) measured as peak oxygen consumption (peak VO_2). The other variables were considered secondary outcomes: submaximal functional capacity, respiratory muscle strength, inspiratory muscle endurance, QoL, and laboratory biomarkers (advanced oxidation protein products [AOPP], FRAP, nitrite/nitrate [NOx] and high-sensitivity C-reactive protein [hsCRP]).

2.4. Measurements

2.4.1. Exercise capacity

The incremental, symptom-limited CPET was used to assess exercise capacity. Patients completed the ramp protocol [17] on a Saturn® 300/100 r treadmill (h/p/Cosmos®, Nussdorf-Traunstein, Germany). The CPET started at a velocity of 3 km/h with no incline. Velocity and inclination were gradually increased until patient exhaustion, with consideration for the patient's physical condition and a predicted test time to completion of 8–12 min. Respiratory exchange ratio (RER), minute ventilation (VE), ventilatory equivalent for carbon dioxide (VE/VCO_2), and partial pressure of end-tidal carbon dioxide ($PETCO_2$), were recorded breath-by-breath through a portable Oxycon Mobile gas analyzer (CareFusion, San Diego, CA, USA). These measurements were obtained at the peak of the CPET. The peak VO_2 ($mL{\cdot}kg^{-1}{\cdot}min^{-1}$) was defined as the highest mean value of VO_2 observed in the last 30 s during the exercise test [18]. Percent-predicted peak VO_2 was calculated according to predicted values [19].

The test was considered to have reached a maximal effort when one or more of the following criteria were observed [18]: failure to increase VO_2 and/or heart rate (HR) even with additional increases in work rate, RER ≥ 1.1, and/or subjective patient-reported rating of perceived exertion (RPE) ≥ 8 (modified Borg scale) [20].

2.4.2. Submaximal functional capacity

The 6MWT was performed according to the ATS guidelines [21]. The longest six-minute walk distance (6MWD) was considered for analysis and compared with predicted values [22].

2.4.3. Respiratory muscle strength

MIP and MEP were evaluated with an MVD 300 digital manometer (MDI®, RS, Brazil). All measurements were done according to ATS/ERS recommendations [23]. The highest pressure was used for analysis and compared to predicted values [24].

2.4.4. Inspiratory muscle endurance

The assessment of inspiratory muscle endurance was performed by using POWERbreathe® Medic Plus (POWERbreathe International Ltd., England, UK), coupled to an analogical pressure transducer (WIKA, Alexander Wiegand SE & Co., Klingenberg, Germany). The assessment consisted of two tests, an incremental and constant test, performed on the same day with an interval of 30 min between them. The incremental test started with 9 cmH_2O (minimum load of the device), held for 2 min, followed by 1 min of rest. The load was then increased by 16 cmH_2O, and so on. The heaviest load that could be sustained for at least 1 min was considered the value of sustained maximal inspiratory pressure (SMIP). The constant test was performed at 80% of SMIP, with the time limit (Tlim) run of 30 min. A similar protocol has been previously reported [25].

2.4.5. Quality of life

The Portuguese version of the Minnesota Living with Heart Failure Questionnaire (MLHFQ) was used to assess patient QoL [26].

2.4.6. Laboratory biomarkers

Blood samples were collected from all patients after a minimum period 8-h overnight fast. Serum was used for the analysis of endothelial function (NOx) and inflammatory profile (hsCRP), and plasma was used to assess the oxidant (AOPP) and antioxidant profile (FRAP). More details of these assessments have been reported previously [27–29].

2.5. Intervention

After baseline evaluations, all patients completed IMT, followed by CT, two times per week for 12 weeks, totaling 24 sessions, under the direct supervision of a physical therapist.

2.5.1. Inspiratory muscle training (IMT)

IMT was performed in all patients using the POWERbreathe® Medic Plus (POWERbreathe International Ltd., England, UK) inspiratory training device for five sets of 10 repetitions each, with a one-minute interval between each set. Rates of perceived inspiratory effort on a modified CR10 Borg Scale (4–6 of 10) [20] also be used to determine the highest tolerable load for each patient. During training, patients were instructed to maintain diaphragmatic breathing. The subjects assigned to the IMT + CT group was submitted to the moderate-to-high intensity IMT, with an initial load set at 50% of MIP during the first two weeks to allow for an adjustment period. After that, load increases occurred as follows: 55% of MIP in week 3, 60% of MIP in week 4, 65% of MIP in week 5, 70% of MIP at week 6, 75% of MIP in week 7, and 80% of MIP in weeks 8. From weeks 9 to 12, the load was adjusted weekly to maintain 80% of MIP. Conversely, in the sham-IMT + CT group, the minimum load of the device (9 cmH_2O) was kept constant during the study period.

2.5.2. Combined aerobic and resistance training (CT)

All patients were enrolled in a phase II CR program, where physical training comprised aerobic and resistance exercises [8]. Each CT session lasting approximately 60 min. The 30-minute period aerobic exercise training was performed on a motorized treadmill (ATL 10200, Inbramed, Porto Alegre, RS, Brazil); with a target training HR corresponding to the HR obtained at the first ventilatory threshold during baseline CPET [9,17] including five-minute warm up and cool down periods. Exercise intensity target was also be based on the RPE, usually between 4 and 6 on the modified Borg scale. The resistance exercises for upper limbs and lower limbs were performed with dumbbells, shin guards or elastic bands with three sets of 10 repetitions per muscle group with an interval of 30 s of rest between sets. The intensity adjusted to 50% of the load one repetition maximal test [8,9,30]. It should be noted that monitoring of vital signs was carried out constantly.

2.6. Sample size calculation

The primary endpoint (peak VO_2) was used to calculate the sample size. Based on the data from a previous study [8] a sample size of 12 patients was required in each group to detect a between-group difference of 3.8 ± 1.7 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$ in peak VO_2 after CR program with a statistical power of 80% and α level of $p < 0.05$.

2.7. Statistical analysis

The data were analyzed using the GraphPad Prism 5 statistical software (GraphPad Software Inc., San Diego, CA, USA). The normality of the variables was assessed by the Shapiro-Wilk test. The Student's *t*-test for paired samples was used to compare the data before and after the intervention. The effect of moderate-to-high intensity IMT plus combined aerobic and resistance training over time was compared between groups via two-way analysis of variance (ANOVA). In addition, we used analysis of covariance (ANCOVA), as a supportive analysis, to compare differences between groups after the intervention, adjusting for values of the respective outcomes at baseline [31]. Effect size was calculated using Cohen's d. The continuous variables are reported as a mean ± standard deviation (SD) and 95% confidence interval (95% CI), and the categorical variables are presented in absolute frequencies and percentages. The significance level was set at 5% for all analyses ($p < 0.05$).

3. Results

Twenty-four patients were randomized into either the IMT + CT group (n = 12) or the sham-IMT + CT group (n = 12). All subjects completed the study (Fig. 1). No adverse events were observed during the study. Patient demographics are described in Table 1.

3.1. Exercise capacity and submaximal functional capacity outcomes

There was a 22.5% increase in peak VO_2 in the IMT + CT group (4.3 mL·kg^{-1}·min^{-1}; 95% CI, 4.2 to 4.5; Cohen's d = 4.7) and a 16.7% increase in the sham-IMT + CT group (3.2 mL·kg^{-1}·min^{-1}; 95% CI, 3.0 to 3.4; Cohen's d = 4.2). However, the IMT + CT group had an improvement in peak VO_2 more than the sham-IMT + CT group (1.3 mL·kg^{-1}·min^{-1}; 95% CI, 0.5 to 2.2; Cohen's d = 5.5) (Fig. 2A). Similarly, ANCOVA showed a higher peak VO_2 in the IMT + CT group (Table 2). The other variables during CPET are presented in Table 2.

There was an increase in the 6MWD from pre- to post-intervention – 30.3% in the IMT + CT group (125.0 m; 95% CI, 104.6 to 145.8; Cohen's d = 2.27) and 13.9% in the sham-IMT + CT group (56.0 m; 95% CI, 45.5 to 66.5; Cohen's d = 1.07). The IMT + CT group had an improvement in 6MWD more than the sham-IMT + CT group (78.8 m; 95% CI, 28.1 to 129.5; Cohen's d = 2.69) (Fig. 2B). Similarly, ANCOVA showed a higher 6MWD in the IMT + CT group (Table 2).

3.2. Respiratory muscle strength, and inspiratory muscle endurance

MIP values significantly increased 33.7% in the IMT + CT group (24.2 cmH_2O; 95% CI, 20.5 to 28.0; Cohen's d = 0.56) and 3.5% in the sham-IMT + CT group (2.5 cmH_2O; 95% CI, 0.6 to 4.3; Cohen's d = 0.19). However, the IMT + CT group had a significantly greater increase in MIP compared to the sham-IMT + CT group (23.0 cmH_2O; 95% CI, 9.3 to 36.7; Cohen's d = 4.75) (Fig. 2C). ANCOVA also showed improved in MIP values in the IMT + CT group (Supplementary material online, Table S1).

The inspiratory muscle endurance, expressed as SMIP and Tlim, showed a significant increase only in the IMT + CT group (Supplementary material online, Table S1).

3.3. Quality of life (QoL)

Changes in QoL after the intervention are presented in Fig. 2D. An improvement in QoL was observed by a 60.5% reduction in MLHFQ scores in the IMT + CT group (95% CI, −37.4 to −21.4; Cohen's d = 2.46) and a 34.5% reduction in the sham-IMT + CT group (95% CI, −25.5 to −10.8; Cohen's d = 1.26). Further, the IMT + CT group exhibited a significantly greater reduction in MLHFQ scores than the sham-IMT + CT group (−15.1 points; 95% CI, −26.9 to −3.3; Cohen's d = 3.6). ANCOVA also showed greater improved in MLHFQ scores in the IMT + CT group (Supplementary material online, Table S1).

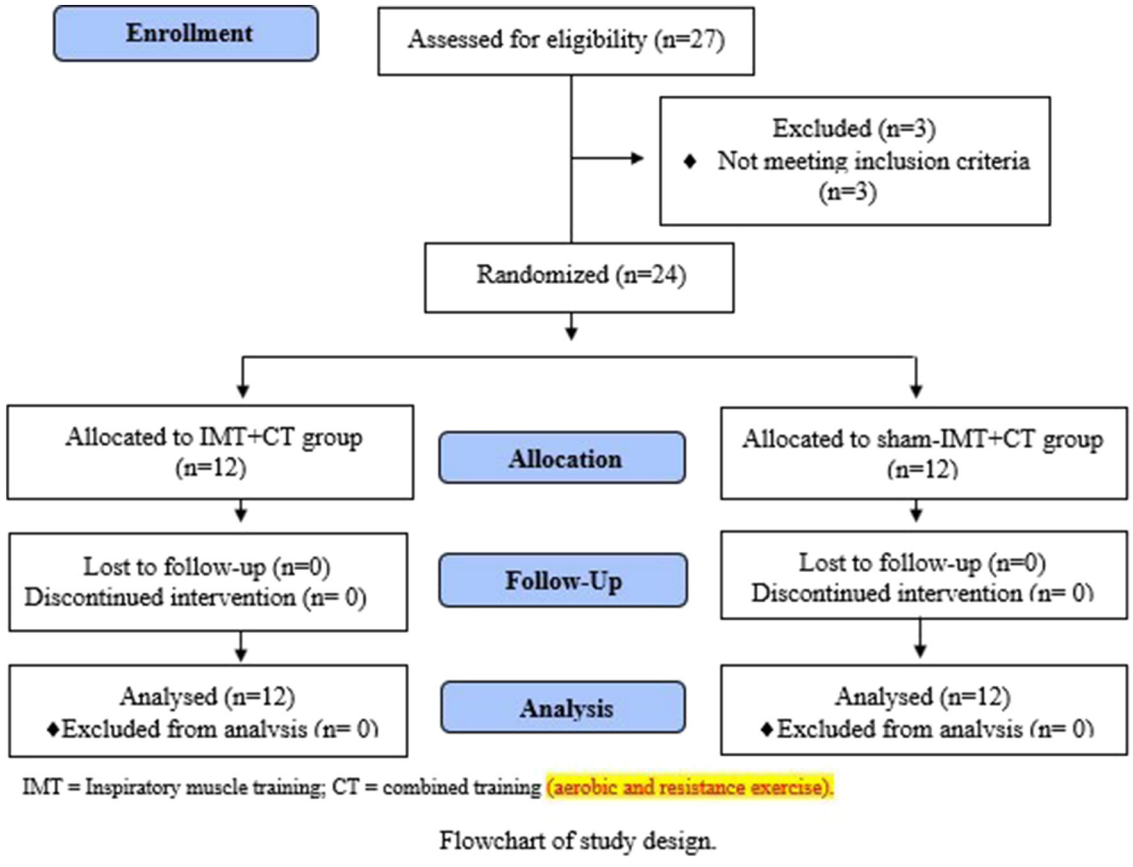

Fig. 1. Flowchart of study design.

Table 1
Baseline characteristics of the two groups.

Variable	IMT + CT (n = 12)	Sham-IMT + CT (n = 12)
Anthropometrics		
Age, years	55.0 ± 7.0	56.6 ± 5.5
Male sex, n (%)	8 (66.7)	9 (75.0)
Body mass index, kg/m^2	26.3 ± 4.4	26.4 ± 4.8
LVEF, (%)	60.5 ± 7.7	59.9 ± 8.6
NYHA class		
I, n (%)	3 (25.0)	3 (25.0)
II, n (%)	9 (75.0)	9 (75.0)
Extent of disease		
1- vessel, n (%)	2 (16.7)	–
2- vessel, n (%)	3 (25.0)	7 (58.3)
3- vessel, n (%)	5 (41.7)	1 (8.3)
4- vessel, n (%)	2 (16.7)	4 (33.3)
Time after CABG (days)	40.8 ± 2.1	42.2 ± 1.6
Risk factors		
Diabetes mellitus, n (%)	4 (33.3)	4 (33.3)
Hypertension, n (%)	9 (75.0)	8 (66.7)
Medications		
ACEI/ARB, n (%)	9 (75.0)	8 (66.7)
Acetylsalicylic acid, n (%)	10 (83.3)	8 (66.7)
Clopidogrel or triclopidine, n (%)	3 (25.0)	4 (33.3)
Diuretics, n (%)	6 (50.0)	5 (41.7)
β-blocker, n (%)	6 (50.0)	7 (58.3)
Statin, n (%)	9 (75.0)	10 (83.3)
Warfarin, n (%)	1 (8.3)	1 (8.3)

Data are expressed as mean (SD) or n (%). IMT = inspiratory muscle training; CT = combined training (aerobic and resistance exercise); LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker.

3.4. Laboratory biomarkers

The levels of AOPP were unchanged in both groups after the intervention. However, there was an increase in FRAP levels of 70.5% in the IMT + CT group (139.9 μmol/L; 95% CI, 88.1 to 191.7; Cohen's d = 2.22) and 65.3% in the sham-IMT + CT group (100.6 μmol/L; 95% CI, 47.2 to 154.0; Cohen's d = 1.39). Further, the IMT + CT group had a greater increase in the antioxidant profile compared to the sham-IMT + CT group (83.7 μmol/L; 95% CI, 20.2 to 147.1; Cohen's d = 0.47). Similarly, ANCOVA showed a higher in FRAP levels for the IMT + CT group.

NOx levels were also increased in both groups; however, no differences were observed between the groups. Regarding the inflammatory status a reduction was observed in both groups; however, no differences were observed between the groups (Supplementary material online, Table S2).

4. Discussion

To the best our knowledge, this is the first randomized clinical trial that evaluated the effects of adding 12-week moderate-to-high intensity IMT plus CT program in CABG patients enrolled in a phase II CR program. The main findings demonstrated that moderate-to high-intensity IMT plus CT promotes additional benefits in exercise capacity, 6MWD, inspiratory muscle strength, QoL, and antioxidant profile. In addition, there were improvements in inspiratory muscle endurance only in the IMT + CT group. Previous studies reported that inspiratory muscle strength is an important determinant of functional capacity after CABG; therefore, IMT can potentially lead to improvements in exercise performance of these patients [12]. Recently, our research group conducted a quasi-experimental study to evaluate the short-term effects of low intensity IMT plus CT in CABG patients enrolled in a phase II CR program. We observed that a significant improvement in peak VO_2 in the IMT plus CT group [8]. Similarly, a small clinical trial which evaluated the effects of 12-week low-intensity IMT plus aerobic exercise training in patients with CHF, demonstrated additional significant improvement in peak VO_2 in the intervention group [13].

However, to our knowledge, no studies have been carried out evaluated the effects of moderate to-high-intensity IMT plus CT in patients with CAD. One study showed that addition of high-intensity IMT (60% of SMIP, 3 times/week, 10 weeks) to moderate intensity aerobic exercise (3–5 times/week) in patients with ventricular assist device resulted in additional improvement in peak VO_2 and increased 6MWD [32]. These findings are consistent with our study, even with lower training frequency (2 times/week) over a short intervention period (12 weeks), we showed additional improvement peak VO_2 by 22.5% and 6MWD by

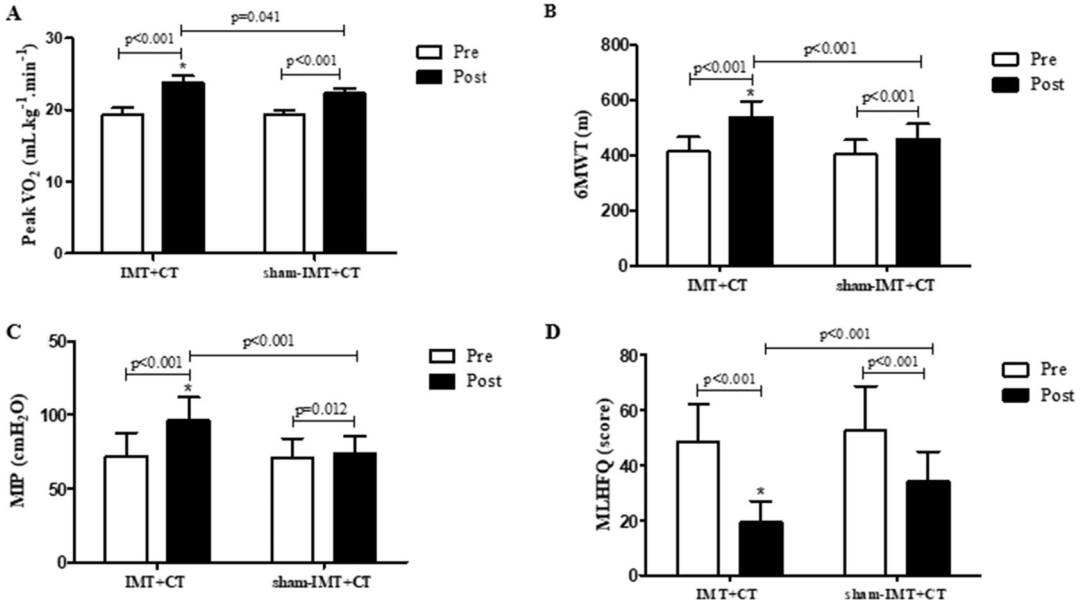

Fig. 2. Within- and between-group comparisons for: A, Exercise capacity (peak-oxygen uptake - peak VO_2); B, Submaximal functional capacity (six-minute walk test - 6MWT); C, Inspiratory muscle strength (maximum inspiratory pressure - MIP and D, QoL (Minnesota Living with Heart Failure Questionnaire - MLHFQ) from pre to post-intervention. Intragroup comparison: Student T test. Comparison between groups: two-way ANOVA. *Significant difference ($p < 0.05$) in IMT+CT group compared to sham-IMT+CT group. Data are expressed as mean (SD). IMT = inspiratory muscle training; CT = combined training (aerobic and resistance exercise).

Table 2
Changes in cardiopulmonary exercise test and submaximal functional capacity.

Variable	IMT + CT (n = 12)				Sham-IMT + CT (n = 12)				Interaction effect (group vs time)		Group differences	
	Pre Mean ± SD	Post Mean ± SD	Mean difference (CI 95%)	*p*-Value[a]	Pre Mean ± SD	Post Mean ± SD	Mean difference (CI 95%)	*p*-Value[a]	Mean difference (CI 95%)	*p*-value[b]	Mean difference (CI 95%)	*p*-Value[c]
Clinical outcome												
Peak VO_2 ($mL{\cdot}kg^{-1}{\cdot}min^{-1}$)	19.3 ± 0.9	23.6 ± 1.1	4.3 (4.2 to 4.5)	<0.001	19.1 ± 0.8	22.3 ± 0.4	3.2 (3.0 to 3.4)	<0.001	1.3 (0.5 to 2.2)	0.041	1.2 (0.4 to 2.3)	0.042
6MWT (m)	412.9 ± 53.1	537.9 ± 56.8	125.0 (104.6 to 145.8)	<0.001	403.1 ± 50.9	459.1 ± 53.0	56.0 (45.5 to 66.5)	<0.001	78.8 (28.1 to 129.5)	<0.001	76.7 (28.3 to 129.6)	<0.001
CPET variables												
RER	1.1 ± 0.1	1.3 ± 0.1	0.2 (0.1 to 0.2)	<0.001	1.1 ± 0.1	1.2 ± 0.1	0.1 (0.0 to 0.2)	0.048	0.1 (−0.1 to 0.2)	0.548	0.1 (−0.2 to 0.1)	0.545
VE (L/min^{-1})	52.2 ± 20.2	62.5 ± 18.9	10.3 (4.9 to 15.8)	<0.001	50.1 ± 13.4	56.9 ± 14.3	6.8 (−4.5 to 18.1)	0.210	5.6 (−10.5 to 21.7)	0.550	5.5 (−9.8 to 20.3)	0.550
VE/VCO_2	32.9 ± 1.3	31.6 ± 3.7	−1.3 (−3.5 to 0.9)	0.224	31.3 ± 5.1	30.3 ± 4.1	−1.0 (−4.0 to −2.0)	0.479	1.3 (−2.3 to 5.0)	0.268	1.5 (−2.1 to 4.9)	0.265
PET CO_2 (mm Hg)	36.2 ± 2.9	38.3 ± 2.2	2.1 (0.7 to 3.4)	0.005	37.4 ± 4.5	39.0 ± 4.9	1.6 (0.1 to 3.0)	0.034	0.7 (−2.9 to 4.2)	0.535	0.7 (−2.5 to 4.0)	0.538
Exercise capacity (% pred.)												
Peak VO_2	72.4 ± 14.4	88.7 ± 17.7	16.3 (14.2 to 18.4)	<0.001	71.0 ± 13.3	83.0 ± 16.5	12.0 (9.8 to 14.2)	<0.001	5.7 (−9.1 to 20.4)	0.581	5.8 (−9.2 to 18.1)	<0.001
Submaximal functional capacity (% pred.)												
6MWT	74.5 ± 8.6	97.1 ± 7.5	22.6 (19.4 to 25.9)	<0.001	73.6 ± 9.6	84.6 ± 9.6	11.1 (8.9 to 13.3)	<0.001	12.5 (3.9 to 21.1)	0.010	12.6 (3.7 to 22.3)	0.010

Data are expressed as mean (SD). [a]Intragroup comparison: Student *t*-test. [b]Comparison between groups: two-way: ANCOVA. IMT = inspiratory muscle training; CT = combined training (aerobic and resistance exercise); Peak VO_2 = peak oxygen uptake; 6MWT = six-minute walk test; CPET = cardiopulmonary exercise test; RER = respiratory exchange ratio; VE = minute ventilation; VE/VCO_2 = ventilatory equivalent for carbon dioxide; PET CO_2 = partial pressure of end-tidal carbon dioxide. Significant difference ($p < 0.05$).

30.3% in the IMT + CT group. It is suggested that additional benefit in exercise capacity can be achieved with a lower training frequency when moderate-to-high intensity IMT is associated with the addition of resistance training to traditional moderate intensity aerobic training.

Although peak VO_2 improved significantly in both groups, the addition of moderate-to high-intensity IMT associated with CT resulted in a small but significant benefit in IMT + CT over the sham-IMT + CT group. Even with patients who did not have inspiratory muscle weakness, this finding may have been speculatively explained by the fact that IMT attenuated activity of the inspiratory muscle metaboreflex which would improve blood to peripheral muscles, and possibly inducing improvement in exercise capacity, as previously demonstrated in patients with CHF [33]. Nevertheless, inspiratory muscle metaboreflex was not assessed in the present study and should be considered as an endpoint in future investigations.

Patients who undergo CABG surgery usually showed a persistent reduction in respiratory muscle strength, observed as lower MIP and MEP values [6], which is in line with values for respiratory muscle strength showed at baseline in our study. In the present study, MIP and MEP increased significantly in both groups post-intervention. This increase is consistent with previously study, which reported that low-intensity IMT induced improvements in inspiratory muscle strength [34]. We also observed a significant additional improvement in MIP in the IMT + CT group. This result is clinically relevant because almost previous studies have reported similar additional improvement in MIP after a long-term follow-up [32,35].

Additionally, we also observed an improvement in inspiratory muscle endurance only in the IMT + CT group. A previous study demonstrated similar increases in MIP and SMIP after high-intensity IMT combined with aerobic exercise [32]. In contrast, a study conducted in patients with CHF only showed the increase in SMIP after high intensity IMT compared with sham-IMT combined with aerobic exercise [34]. These conflicting findings are likely due to variations in the type of training applied to the inspiratory muscles (strength or endurance), the mode of training, and the intensity, duration, and frequency used. Strength or endurance gains can be achieved at 60% to 80% of MIP [36].

We observed that the addition of moderate-to high-intensity IMT associated with CT resulted in additional improvement in QoL of IMT + CT group. Consistent with this finding, high-intensity IMT combined with exercise training has been reported to provide additive benefits in QoL in patients with CHF [32,34]. Our results are supported by a recent meta-analysis that showed combined exercise and IMT may improve QoL in patients with CHF [37].

Our study is the first to report the effects of moderate-to-high intensity IMT + CT on endothelial function, inflammatory biomarker, antioxidant activity, and oxidative profile in CABG patients in a phase II CR program. Surprisingly, we observed that only antioxidant activity increased considerably in the IMT + CT group. This result is novel, as no previous studies have reported improvement in antioxidant capacity after moderate-to high-intensity IMT associated with CT. Our results also show that the improvement in antioxidant capacity in IMT + CT group occurred despite no decrease in oxidative profile. A recent meta-analysis indicated that regardless of intensity, volume, type of exercise and studied population, antioxidant parameters seem to increase after exercise training [38]. Further studies are warranted to investigate of mechanism behind by which the addition of IMT plus CT can be beneficial to improved antioxidant capacity in CABG patients enrolled in a phase II CR program. In addition, future research should be carried out using the strategy presented in this study, composed of CT and IMT, through the telehealth interventions, that offer an alternative deliver model of typical CR programs for individuals less able to access center-based cardiac rehabilitation [39], to investigate whether similar benefits to those found in our study can be obtained using electronic health approaches.

4.1. Strengths and limitations

A strength of this study is that adherence to the intervention was 100%. All subjects completed 24 exercise sessions over the 12-week training period. We performed both the IMT and exercise training program fully supervised by the investigators. We also used a lower frequency training protocol over a short-term intervention and included serum and plasma biomarkers of endothelial function and oxidant-antioxidant profile that had not been reported in previous studies comparing moderate-to-high intensity IMT and sham-IMT.

Although all patients followed a nutritional education or individual counseling sessions to improve lifestyle behaviors, a limitation of this study is the lack of tracking of dietary intake control during the intervention. We did not have a sedentary control group. Although the patients were instructed to not perform any other form of exercise during the intervention, we did not measure daily physical activity, which could have affected our primary outcome. Future research should be directed toward addressing these limitations. Finally, the training period was maintained for 12 weeks, which does not allow us to conclude that the beneficial effects is long-term.

5. Conclusions

The present study showed that a short-term moderate-to-high intensity IMT provided additional benefits in exercise capacity, inspiratory muscle strength, QoL, and antioxidant profile in patients after CABG.

The potential clinical practice implications of this study support the importance for the addition of moderate-to-high intensity IMT on CR programs to enhance performance and becoming an effective, simple and inexpensive strategy. Large trials are needed to investigate the long-term beneficial effectiveness of this protocol in CABG patients enrolled in a phase II CR program.

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Author contributions

TDS, SNP, LCP, MBP and IMA were involved in developing the trial concept and design. TDS, SNP, LCP, NSG, RNM, IMA acquired data. DMC performed statistical analysis. TDS, DMC, PDL and IMA performed analysis and interpretation of data. TDS, DMC, PDL, MBP and IMA drafted the manuscript. All authors read and approved the final manuscript. IMA is the guarantor of this study.

CRediT authorship contribution statement

Tamires Daros dos Santos: Methodology, Data curation, Formal analysis, Writing - original draft. **Sergio Nunes Pereira:** Methodology, Data curation. **Luiz Osório Cruz Portela:** Methodology, Data curation. **Dannuey Machado Cardoso:** Formal analysis, Data curation, Writing - original draft. **Pedro Dal Lago:** Formal analysis, Data curation, Writing - original draft. **Naiara dos Santos Guarda:** Data curation. **Rafael Noal Moresco:** Data curation. **Marisa Bastos Pereira:** Methodology, Writing - original draft. **Isabella Martins de Albuquerque:** Methodology, Data curation, Formal analysis, Writing - original draft.

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