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RESEARCH ARTICLE

PERIPHERAL MICROCIRCULATION ADAPTATIONS IN RESPONSE TO THE ADDITION OF INSPIRATORY MUSCLE TRAINING IN HEART FAILURE CARDIAC REHABILITATION REGIMEN.

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Abstract

Background: Exercise intolerance, dyspnea on exertion and respiratory muscle fatigue are predominant features of chronic heart failure adding to disease severity. Inspiratory Muscle Training (IMT) has been recently integrated into traditional exercise-based cardiac rehabilitation regimens. We opted to evaluate the effect of IMT on the peripheral muscle microcirculation of patients with stable chronic heart failure participating in cardiac rehabilitation.

Method and Material: Twenty-five stable patients with chronic heart failure underwent cardiac rehabilitation with aerobic exercise and resistance training 3×/week for 12 weeks. Subjects were randomly assigned to the intervention group that performed IMT or the control group that performed Sham-IMT in addition to standard CR regimen. Systemic microcirculation was assessed via near-infrared spectroscopy (NIRS) and the 3-min vascular occlusion technique at the thenar muscle. Cardiorespiratory exercise testing, pulmonary function and muscle strength assessment were also performed, at baseline and following completion of the cardiac rehabilitation program.

Results: Both groups equally improved their cardiorespiratory fitness, left ventricular ejection fraction and muscle strength ($p>0.05$ for between-group comparisons). The intervention group showed higher NIRS-derived reperfusion rate, maximum inspiratory pressure and lung function as compared to the control group ($p<0.05$).

Conclusions: Reperfusion rate is a known surrogate for endothelial function. Therefore, the addition of structured IMT in targeted cardiac rehabilitation marked beneficial effects on systemic microcirculation.

Keywords: Exercise training, inspiratory muscle training, microcirculation, near infra-red spectroscopy, chronic heart failure.

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INTRODUCTION

Chronic heart failure (CHF) is a complex, progressive syndrome with cumulative health cost burden worldwide.[1] Hallmark clinical features such as exercise intolerance, dyspnea on exertion and ominously diminished functional capacity add to disease morbidity, poor health-related quality of life and hospitalization rate.[2-5]

Pathophysiology behind limited exercise capacity is multifactorial including central cardiac mechanisms, pulmonary reserve decline, neurohormonal perturbations, skeletal muscle abnormalities and alterations in peripheral microcirculation.[2] Additionally, respiratory muscle weakness seems to play a pivotal role in experiencing breathlessness and selective termination physical activity.[6-8] Respiratory muscle strength has been recognized as an independent predictor of CHF long-term survival.[9-11]

In response to growing scientific information and public health concerns, experts have developed strong practice guideline recommendations regarding multidisciplinary cardiac rehabilitation (CR) programs for CHF patients.[12] Inspiratory Muscle Training (IMT) has been recently integrated into traditional exercise-based CR programs in patients with stable CHF and respiratory muscle weakness.[13-18] However, the underlying mechanism for such systemic effect to the CHF population remains unclear.

Near-infrared spectroscopy (NIRS) is a non-invasive, indirect method of assessing tissue oxygenation (StO2). The information obtained from StO2 measurements can be further enriched by applying the vascular occlusion technique (VOT). This methodology simulates physiological ischemic stress to uncover microcirculatory vascular impairment in different patient populations. NIRS-VOT has been studied in evaluating peripheral muscle microcirculation as a surrogate for endothelial function.[19-26]

We hypothesized that structured exercise of the respiratory muscles may exert beneficial effects on heart failure-related exercise intolerance through alterations in peripheral microcirculation. The aim of the study was to investigate the systemic impact of IMT to peripheral microcirculation via NIRS-VOT methodology in CHF patients with reduced ejection fraction (HFrEF) undergoing combined AET-RT CR program.

MATERIALS AND METHODS

Study design

We conducted a randomized control trial of CHF patients enrolled in a 12-week cardiac rehabilitation program. Patients were referred to our Exercise and Rehabilitation Laboratory from outpatient heart failure clinics within our academic healthcare system.

Inclusion criteria were (i) stable CHF condition under optimal medical treatment, (II) left ventricular ejection fraction (EF) ≤ 49% and (iii) New York Heart Association (NYHA) classification functional status ≥ II.

Exclusion criteria were (i) valvular disease, (ii) severe peripheral vascular disorders, (iii) pulmonary disease, (iv) uncontrolled arterial hypertension, (v) neuro-muscular diseases and (vi) contraindications to performing a cardiopulmonary exercise testing (CPET) according to the American Thoracic Society-American College of Chest Physicians statement for CPET.[28]

Stratified patient randomization was conducted by a blinded investigator according to predicted inspiratory muscle strength (cut-off point 70%) and predicted VO2peak (cut-off point 65%) prior to enrollment. Patients were allocated to the intervention group (IG) that received IMT/AET/RT or the control group (CG) that received Sham-IMT/AET/RT.

The study was approved by the Ethics Committee of "Evangelismos" Hospital, Athens, Greece. Written informed consent was obtained from all patients prior to enrolment in the study. Peripheral muscle microcirculation via NIRS, echocardiography indices, respiratory muscle strength, pulmonary function, CPET parameters as well as peripheral muscle strength and endurance were assessed before and after the completion of the CR program.

Measurements

Pulmonary function

Spirometry was performed at sitting position in accordance with the American Thoracic Society guidelines.[28] Forced expiratory volume at 1st second (FEV1), forced vital capacity (FVC) and the FEV1/FVC ratio were extracted as the percentages of predicted values.

Respiratory muscle strength

Maximal inspiratory pressure (MIP) was evaluated using the Quark device (Cosmed, Italy). The measurement was obtained through a mouthpiece and expressed in cmH_2O. Patients were in a sitting position and exhaled until reaching residual volume followed by maximum inhalation, according to the method described by Black & Hyatt (1969).[27]

Cardiopulmonary exercise testing (CPET)

Exercise capacity was assessed via CPET on a bicycle ergometer (Ergoline 800; SensorMedics Corporation, CA, USA), with increasing workload and estimated duration of 8-12 minutes.[29] Gas exchange was assessed through a low-resistance valve with Vmax 229 instrument (SensorMedics Corporation, CA, USA).[23] Electronic system with specialized software (Vmax 229, Sensor Medics, CA, USA) was utilized to evaluate oxygen uptake (VO2), carbon dioxide output (VCO2) and ventilatory equivalent (VE) per breath. Heart rate was recorded via 12-lead ECG (Marquette Max, Marquette Hellige GmbH, Freiburg, Germany) before, during and immediately after the test. Blood pressure was assessed every two minutes using a mercury sphygmomanometer. CPET parameters considered were VO2peak, anaerobic threshold (AT), oxygen consumption at anaerobic threshold (VO2AT), ventilation / carbon dioxide output (VE/VCO2) slope, maximal workload, breathing reserve (BR), heart rate recovery at 1 minute (HRR_1 min). VO2peak was calculated as the average of values recorded during the 20-second period prior to termination of exercise and AT was determined by the V-slope technique.

Near-Infrared Spectroscopy (NIRS)

The application and physiological aspects of NIRS in humans have been validated elsewhere.[19-26] This is a non-invasive, easily applicable technique that provides continuous recording of tissue hemoglobin through absorption of infrared radiation. Infrared radiation in muscle tissue is absorbed by chromophore elements such as hemoglobin.[36] Oxygenated and non-oxygenated hemoglobin absorbs different wavelengths of infrared radiation allowing indirect quantification of tissue oxygen saturation and therefore microcirculation and endothelial function. StO2 was evaluated at the thenar muscle of the upper limb at rest and following with the 3-minute vascular occlusion technique (VOT) (InSpectra; Hutchinson Technology, Hutchinson, Minnesota).[24,30] Venous and arterial ischemia was induced with a pneumatic cuff around the upper arm that was inflated to a pressure of 50 mm Hg above the systolic blood pressure for a total duration of 3-minutes under continuous StO2 monitoring. StO2 derived curves were analyzed with the Inspectra software analysis program.

NIRS measurements were performed prior to the initiation and following the completion of the CR program. Evaluated NIRS parameters were:

- StO2 at baseline
- Oxygen consumption rate (OCR, %/min) represents the 1st-degree slope (downslope) of hemoglobin desaturation during ischemic phase
- Reperfusion rate (RR) represents the 1st-degree slope (upslope) following vascular occlusion release (Figure 1).[30]

Peripheral muscle strength and endurance

All the patients underwent a single-maximal-repetition (1-RM) test of the knee extensors and chest press muscles to evaluate maximum quadriceps strength and determine the targeted intensity of resistance training. The 1-RM test was based on the maximal amount of weight that a person could lift with one repetition applying appropriate technique.[31] Subsequently, the endurance strength test was based on the maximum number of weight-lift repetitions at 65% 1RM.

Echocardiography

Left ventricular ejection fraction (LVEF) was assessed via echocardiography prior to the initiation and following the completion of the CR program.

Exercise training protocols

Aerobic training and muscle training

Both the intervention group (IG) (IMT/AET/RT) and the control group (CG) (Sham-IMT/AET/RT) exercised 3 times per week for 12 weeks, to complete a total of 36 sessions. Aerobic training was performed on an electromagnetically cycle ergometer (Ironman M3 Upright cycle). Patients started their sessions with a warm-up low-resistance phase at intensity corresponding to

45% VO2peak.

Our CR AET regimen was based on a a previously published Norwegian protocol.[32] There was a 3-minute phase at 50% VO2peak followed by sets of 4 minutes at 80% VO2peak alternating with 3 minutes at 50% VO2peak. The number of sets progressively increased, i.e. 2 sets during week#1, 3 sets during week#2 and 4 sets during weeks#3-12. Similarly, exercise intensity and workload increased gradually, reaching 25% by the end of the three-month intervention.

Upon completion of the AET part, both groups performed muscle strengthening exercises, including weightlifting of the quadriceps muscles (knee extension) and anterior chest muscles (chest press). Patients performed 3 sets of 10-12 repetitions at 60% - 75% 1-RM.

Inspiratory muscle training

IMT is a form of resistance exercise designed to strengthen inspiratory muscles by means of providing resistance during inspiration. IMT was performed at the beginning of the program in addition to usual exercise (aerobic training/muscle strengthening) using the Powerbreath kh2 device and the application of a nose clip. The IG subjects exercised from 35% to 60% MIP with a progressive increase of 5% per 6 sessions. Respectively, the CG (Sham-IMT) exercised at 10% MIP throughout the entire 12-week-period[33-34] (Figure 2). Each IMT session included 5 sets (10 breaths/set), with a 1–2-minute break between sets.

Statistical analysis

Continuous variables are presented as mean ± standard deviation. Normality of distribution was evaluated with the Shapiro-Wilk test. Statistical significance was set as P values <0.05. Paired t-test and Wilcoxon signed rank test were used for comparisons within the groups. Factorial analysis of variance with two factors (group x time, ANOVA 2x2) and Mann-Whitney U test were performed for between-group comparisons. Statistical analysis was performed with IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, NY, USA).

RESULTS

Twenty-five out of 34 subjects who met inclusion criteria completed the 12-week CR program. Nine patients dropped out due to inability to follow scheduling requirements (Figure 3). Baseline demographic data and clinical characteristics are presented in Table 1. There was no difference between groups at baseline ($p>0.05$).

Respiratory muscle training displayed a positive effect in microcirculation parameters (Table 2). Reperfusion Rate (RR) increased in the IG ($p<0.05$), while no difference was observed in the CG ($p>0.05$). Such RR increase in the IG was statistically important compared to the CG ($p<0.05$), Figure 4a. In contrast, StO2 and OCR failed to show improvement within either group ($p>0.05$) or between the two groups ($p>0.05$), Figures 4 b & c respectively.

HRR_1, MIP ($p<0.001$), predicted MIP ($p<0.001$) and FEV1/FVC ($p=0.039$) were improved in the IG group compared to the CG ($p>0.05$). Both groups improved similarly their cardiorespiratory fitness, LVEF, peripheral muscle strength and endurance. No between-group differences were observed ($p>0.05$)

DISCUSSION

The present study is a randomized control trial to evaluate peripheral microcirculation adaptations in response to structured IMT in patients with chronic HFrEF within the scheme of a combined cardiac rehabilitation (AET & RT) program. The major observation is that IMT resulted in microcirculatory alterations as evidenced by significant reperfusion rate (RR) improvement in the IG.

After 12 weeks of training, RR was a significantly important differentiator between the two treatment arms. Considering that participant groups were comparable at baseline, RR change and consequently, endothelial adaptations can be attributed to the cumulative IMT effect. To our knowledge this is the first intervention study to justify the benefits of long-term IMT in addition to the standard AET/RT exercise regimen through endothelial functionality assessed by NIRS.

While StO2 represents tissue oxygenation at baseline, the occlusion of venous and arterial perfusion facilitates real-time evaluation of tissue O2 restoration and micro-vascular responsiveness. Therefore, the rate that peripheral tissue can recover its capacity for oxygen extraction depends on endothelial integrity

and functionality. Previous studies have validated the application of NIRS occlusion technique in assessing physiological muscle adaptations in exercise clinical trials, as well as microvasculature impairment in CHF populations.[23-26,31,35-38] In addition, several exercise regimens targeted at CHF patients of different severity, have shown beneficial effects on RR and vascular reactivity.[24,26,31,37]

Notably, the NIRS measurement at the thenar muscle occurred at a distant location from the target of IMT intervention, the inspiratory muscles. Such observation implies a potentially systemic effect of IMT to remote areas that do not actively participate in the mechanical work. This finding is aligned with previous work of our group by Tzanis et al.[31] A cohort of CHF patients underwent CPET on a bicycle ergometer with increasing intensity of lower extremity exercise. This regimen resulted in significant alterations of microcirculation parameters assessed by NIRS indicating that exercise of individual muscles may elicit systemic effect to non-exercising skeletal muscles too.

Such systemic effect may be facilitated by local endothelial production of paracrine factors in response to exercise-induced stimuli.[37,38] Laoutaris et al published that high intensity inspiratory muscle training can suppress systemic CHD-induced inflammation by modulating apoptosis mediators, reducing the expression of myocardial biomarkers and downregulating pro-inflammatory cytokines.[39] Similarly, the VentHeFT trial displayed lower levels of systemic inflammation and myocardial stress, named C-reactive protein (CRP) and N-terminal pro B-type natriuretic peptide (NTproBNP), respectively, in patients who performed combined AT/IMT versus AT alone.[41]

Likewise, the link between peripheral microcirculation and macro-vascular reactivity has been previously suggested by the correlation between NIRS-VOT derived RR and flow-mediated dilation of the branchial artery (FMDBA) in healthy individuals.[41] Craighead et al., took a step further and showed a 45% mean increase in FMDBA in adults with systemic hypertension who followed inspiratory muscle strength versus Sham. Ex-vivo assessment revealed greater Nitric Oxide (NO) bioavailability and reduced oxidative stress in the IMT group further supporting such systemic endothelial impact.[42]

Selective IMT has been shown to decrease sympathetic nerve activity resulting in reduction in peripheral vascular resistance, reduced systemic afterload and better macro- and micro-circulation.[14,15,23,42,43] A few studies have shown that fatiguing contractions of the inspiratory muscles lead to increased sympathetic vasoconstrictor activity that triggers the so called "inspiratory muscle metaboreflex". Metaboreflex augments blood flow to resting and exercising muscles to attenuate respiratory muscle oxygen demand-delivery mismatch during respiratory fatigue in CHF patients.[45] Moreno et al. reported data on the intercostal and forearm muscle oxygenation with NIRS in CHF patients.[45] This potential mechanism is further supported by preceding observations that respiratory muscle resistance training led to decreased blood lactate concentrations46 and improved oxygen consumption in athletes.[48]

Despite the above scientific evidence, our study found no significant change in oxygen consumption rate (OCR) in both the IMT and Sham-IMT groups. This observation was previously encountered when our team compared CHF patients of two different exercise protocols: high intensity interval training (HIIT) combined with RT versus only HIIT. Patients who completed the combined HIIT/RT program demonstrated an increase in RR, whereas patients who performed HIIT showed improved OCR.[31] On the other hand, once our team interrogated the acute effects of IMT, we observed a meaningful increase in the OCR of CHF patients following just a single bout of IMT prior to participation in any CR protocol.[48] A potential explanation for this could be that sustainable training may provoke selective optimization of anaerobic mechanisms, i.e. glycolysis, creatine kinase and improved mechanical performance of muscle work, leading to reduced oxygen cost for certain workload, as a corollary of the addition of muscle strength.[37]

As expected, IG achieved significantly better MIP, predicted MIP, and FEV1/FVC ratio than the respective CG at the end of the CR program, in accordance with available literature on respiratory muscle strength and lung function.[15,17] It is likely that IG subjects started off CR with lower average PIM values than controls. However, there was no statistically significant difference between the two cohorts at baseline, potentially due to the small sample size.

Despite this general agreement regarding respiratory muscle

performance, IMT effectiveness on hemodynamic parameters, peak VO2, VE/VCO2 and biomarkers remain debatable.[6,7,13,16,17] Careful appraisal of existing literature reveals conflicting evidence. In a systematic review and meta-analysis, Fernandez-Rubio et al, concluded that variability in disease severity, exercise protocols and heterogeneity of analyses preclude deriving conclusions regarding the additional effect of IMT into cardiac rehabilitation.[49] Our study results are aligned with Laoutaris et al that reported no significant additional benefits to AT/RT in VO2peak compared to AT/RT alone.[18] Apart from a small improvement in HRR_1 and LVEF in the IG, the rest of cardiorespiratory indices, peripheral muscle strength and endurance improved similarly in both groups.

Similar to the IG, CG subjects increased their muscle strength, endurance and exercise capacity by achieving greater work and oxygen consumption at anaerobic threshold. Unexpectedly, such improvement was not adequately reflected in their peripheral microcirculation indices. It is plausible that despite stratified randomization, patients enrolled in the CG may have CHF of higher severity failed to meet cardiac rehabilitation goals.

Limitations

Our study results should be interpreted in the context of some potential limitations. Although the randomization process was blinded, the research personnel in charge of exercise execution and evaluation were not. In addition, the limited exercise effect in CG participants may have occurred due to sampling bias related to CHF severity. Finally, the small sample size may account for underpowered results of "between-group" comparisons. A larger patient population is needed for result generalizability.

CONCLUSION

To conclude, this study suggests an alternative rationale to justify the favorable effect that IMT exerts when it complements AT/RT CR regimens. In addition to aerobic capacity, muscle strength and overall cardiorespiratory functional status, the improved RR reflects beneficial adaptations in peripheral microcirculation of HFrEF patients. NIRS-derived RR could serve as a non-invasive biomarker of endothelial functionality and monitoring of IMT rehabilitation success in patients with CHF.

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ANNEX

FIGURE 1. Vascular occlusion technique-StO2 derived into four phases: baseline, ischemia, reperfusion and hyperemia.

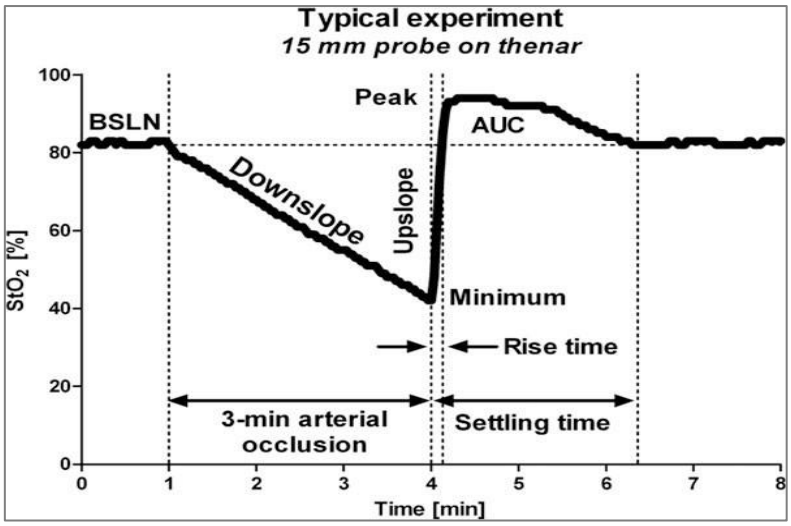


FIGURE 2. Inspiratory muscle training program.

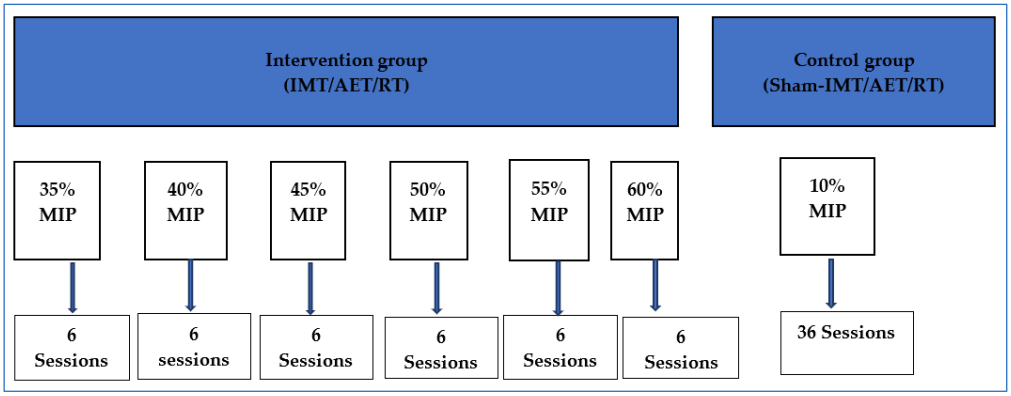


FIGURE 3. Study population flowchart.

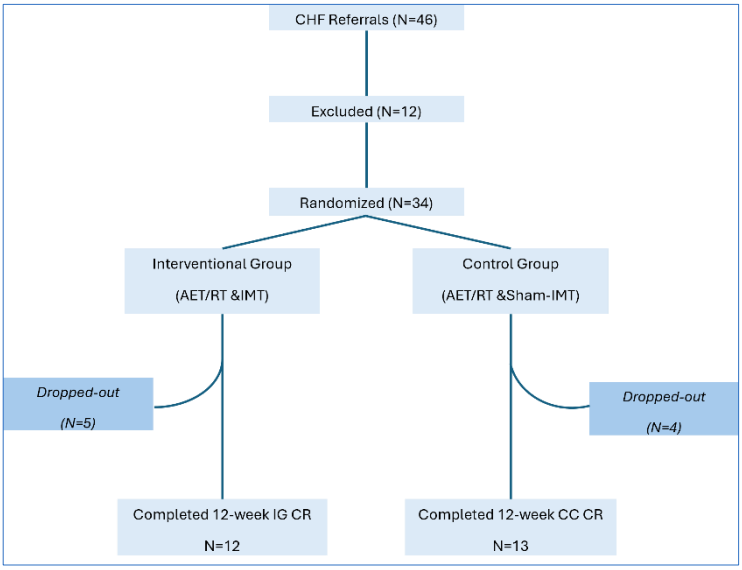
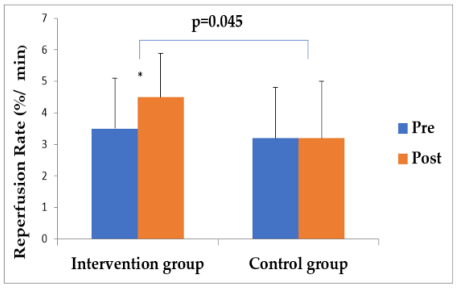
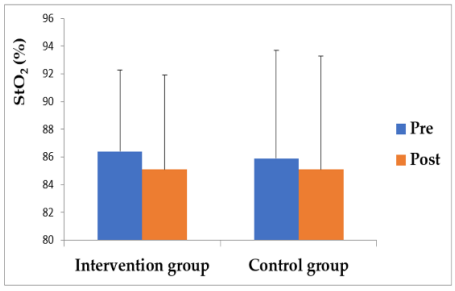


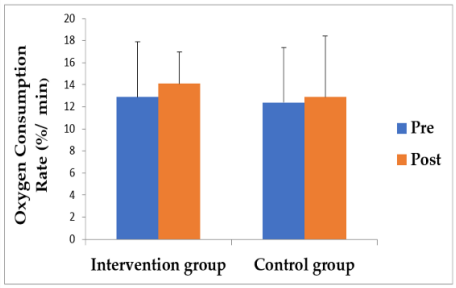
FIGURE 4. IMT effects on NIRS indices of peripheral microcirculation



4A. Effect of IMT on reperfusion rate (RR %/min). (*) within-IG group difference (p=0.037) and between groups (p=0.045). No difference with the CG.



4B. Effect of IMT on basal tissue oxygenation (StO_2%). No difference within- or between-groups (p>0.05).



4C. Effect of IMT on oxygenation consumption rate (OCR %/min). No difference within- or between-groups (p>0.05).

TABLE 1. Demographic and clinical characteristics.

	Total Patients	Intervention group (IG)	Control group (CG)
Number of patients (N)	25	12	13
Gender (males/females)	22/3	10/2	12/1
Age (years)	60.3±8.9	59.5±9.2	61.1±8.9
Height (cm)	174.5±9.2	173.4±10.2	175.5±8.6
Weight (kg)	88.4±20.9	86.7±18.9	89.9±23.3
EF (%)	32.3±7.7	31.2±6.4	33.1±8.9
MIP (cmH_2O)	81.9±23.8	73.5±28.4	89.8±15.9
predicted MIP (%)	89.1±25.6	80.5±29.5	97.1±19.3
NYHA stage (class II/III)	10/15	4/8	6/7
Type of CHF			
Dilated cardiomyopathy [n (%)]	7 (28%)	5 (42%)	2 (15%)
Ischemic cardiomyopathy [n (%)]	17 (68%)	7 (58%)	10 (77%)
Other etiology [n(%)]	1 (4%)	0	1 (8%)
Pharmacological treatment			
ACEI+ARBs [n (%)]	4 (16%)	3 (25%)	1 (8%)
Sacubitril/Valsartan [n (%)]	19 (76%)	9 (75%)	10 (77%)
Diuretics [n (%)]	14 (56%)	8 (67%)	6 (46%)
Aldosterone antagonists [n (%)]	22 (88%)	11 (92%)	11 (85%)
Beta-blockers [n (%)]	22 (88%)	10 (83%)	12 (92%)
Dapagliflozin/Empagliflozin [n (%)]	10 (40%)	5 (42%)	5 (38%)
CPET pre rehabilitation			
VO_2 rest (ml/kg/min)	4.6±0.7	4.6±0.8	4.4±0.8
VO_2 peak (ml/kg/min)	17.9±3.9	18.1±3.7	17.6±4.1
predicted VO_2 peak (%)	72.6±16.7	74.2±17.9	71.1±16.1
VO_2AT (%)	53.4±12.5	56.4±12.6	51.0±12.0
VE/VCO_2 slope	33.4±6.7	34.4±8.3	32.4±5.1
BR (%)	37.8±13.6	35.1±11.5	40.4±15.3
VE (L/min)	67.9±20.5	66.6±21.9	69.2±19.9
Indices of respiratory function			
FVC (%)	92.3±14.1	89.3±14.4	95.1±13.8
FEV_1 (%)	84.5±17.0	79.5±20.8	89.1±11.6
FEV_1/FVC	94.4±12.5	91.0±15.4	97.5±8.5

CHF: Congestive Heart Failure, CPET: Cardiopulmonary exercise test, VO_2: Oxygen consumption, VO_2 peak: Maximal oxygen consumption rate, VE/VCO_2: Minute ventilation/Carbon dioxide production, BR: breathing reserve, VE: Ventilation, AT: Anaerobic threshold, WR: Work rate, HRR_1 min: Heart rate recovery in 1st minute, EF: Ejection fraction, MIP: Maximal inspiratory pressure, FEV_1: Forced expiratory volume at the end of the first second, FVC: Forced vital capacity

TABLE 2. Effect of CR program [IG (AET/RT +IMT) versus CG (AET/RT+ Sham- IMT)] on microcirculation, CPET, respiratory-pulmonary function and peripheral Muscle strength and endurance.

Parameters	Control group			Intervention group			P between
	Before CR	After CR	P within	Before CR	After CR	P within	
Peripheral microcirculation							
StO_2 baseline (%)	85.9±7.8	85.1±8.2	0.719	86.4±5.9	85.1±6.8	0.423	0.803
OCR (%/min)	12.4±4.8	12.9±5.5	0.462	12.9±3.6	14.1±2.9	0.263	0.534
RR (%/ min)	3.2±1.6	3.2±1.8	0.480	3.5±1.6	4.5±1.4	0.037	**0.045**
CPET							
VO_2 rest (ml/kg/min)	4.5±0.8	4.6±0.7	0.737	4.6±0.8	4.8±0.9	0.338	0.667
VO_2 peak (ml/kg/min)	17.6±4.1	18.5±4.7	0.139	18.2±3.7	19.2±4.3	0.017	0.721
predicted VO_2 peak (%)	71.1±16.1	73.6±18.3	0.191	74.2±17.9	76.0±17.1	0.266	0.794
VE/VCO_2 slope	32.4±5.1	32.3±5.2	0.345	34.4±8.3	31.7±6.1	0.062	0.110
BR (%)	40.4±15.2	36.2±16.6	0.196	35.1±11.5	33.4±11.5	0.410	0.564
VE (L/min)	69.2±19.9	72.3±23.2	0.525	66.6±21.9	64.3±27.5	0.374	0.650
AT (mL/min)	1103.5±362.1	1238.1±409.9	0.010	1165.8±335.3	1287.7±376.2	0.002	0.817
VO_2AT (%)	50.7±12.3	56.1±11.4	0.001	56.4±12.6	63.0±12.3	0.003	0.606
WR at AT (watts)	63.7±26.5	80.7±33.4	0.006	69.4±30.8	81.0±28.8	<0.001	0.453
Peak WR (watts)	119.1±43.2	128.9±45.5	0.050	120.2±52.0	132.0±49.0	0.033	0.868
HRR_1 min (bpm)	20.6±7.8	18.5±9.2	0.185	28.1±13.8	31.6±15.9	0.048	**0.017**
Echocardiography							
EF (%)	33.3±8.9	34.2±9.5	0.063	31.2±6.4	33.3±7.5	0.059	0.376
Respiratory/pulmonary function							
MIP (cmH_2O)	89.8±15.9	91.0±16.1	0.108	73.5±28.5	98.0±21.4	<0.001	**<0.001**
MIP predicted (%)	97.1±19.3	98.5±19.6	0.123	80.5±29.5	107.2±219.9	<0.001	**<0.001**

FEV_1 (%)	89.1±11.5	87.4±11.6	0.361	79.5±20.8	81.7±20.7	0.129	0.103
FVC (%)	95.1±13.8	92.7±15.7	0.215	89.3±14.4	88.7±15.6	0.688	0.448
FEV_1/FVC	97.5±8.5	97.5±7.0	0.928	91.0±15.4	94.0±15.1	0.040	**0.039**
Peripheral muscle strength and endurance							
1 RM press chest (kg)	66.3±25.1	71.2±27.7	<0.001	63.7±17.3	69.5±19.0	0.002	0.642
1RM knee extension (kg)	41.8±15.6	47.1±17.8	0.002	41.5±14.2	47.5±13.7	<0.001	0.736
Endurance chest press (repetitions)	12.1±2.7	17.9±4.9	<0.001	13.9±3.1	18.8±3.6	0.001	0.554
Endurance knee extension (repetitions)	11.0±3.1	14.9±3.9	0.002	12.6±4.9	16.2±2.5	0.008	0.740

StO2: Tissue oxygen saturation, OCR: Oxygen consumption rate, RR: Reperfusion rate, CPET: Cardiopulmonary exercise test, VO2: Oxygen consumption, VO2 peak: Maximal oxygen consumption rate, VE/VCO2: Minute ventilation/Carbon dioxide production, BR: breathing reserve, VE: Ventilation, AT: Anaerobic threshold, WR: Work rate, HRR_1 min: Heart rate recovery in 1st minute, EF: Ejection fraction, MIP: Maximal inspiratory pressure, FEV1: Forced expiratory volume at the end of the first second, FVC: Forced vital capacity 1RM: 1 Repetition max