Original Article

Acute Inspiratory Muscle Training Modifies Hemodynamic Indices in Patients with Heart Failure with Preserved Ejection Fraction

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Abstract

Background: **Heart failure with preserved ejection fraction (HFpEF), a syndrome associated to decrease functional capacity, is quite difficult to manage. Inspiratory muscle training (IMT) has been used to treat symptoms and to improve functional capacity of patients with HFpEF. Thus, we aimed to evaluate the immediate effects and after 1 h of IMT on arterial pulsatile hemodynamics and on hemodynamic indices of left ventricular filling derived from Doppler echocardiography in patients with HFpEF.**

Methods: **Eighteen patients with HFpEF who underwent IMT at an intensity of 80% of maximum inspiratory pressure were evaluated by Doppler echocardiogram in the pre, post-immediate and post-late periods; furthermore, pulsatile hemodynamic variables were collected. Functional capacity was assessed using the 6-minute walk test.**

Results: **The population was composed predominantly of women (66.7%), mean age of 61.3 (7.2) years. Modifications were observed in the non-invasive LV filling pressure index (E/e’) (pre: 10.33 (SD, 3.15) vs post: 8.73 (SD, 2.24); p < 0.001) and in the pulse wave velocity (pre: 8.33 (SD, 1.67) vs post: 7.63 (SD, 1.66) m/s; p < 0.001), as well as pulse pressure (pre: 54.81 (SD, 18.73) vs post: 48.52 (SD, 15.74) mm Hg; p = 0.023).**

Conclusion: **Our results demonstrated that a unique session of high-intensity IMT improved hemodynamic indices of LV filling and arterial stiffness in patients with HFpEF.**

Keywords: **Heart Failure/physiopathology; Stroke Volume; Inspiratory Reserve Volume; Hemodynamic; Echocardiography/methods; Rehabilitation; Pulmonary Medicine; Respiratory System; Dyspnea.**

Introduction

Heart failure with preserved ejection fraction (HFpEF) is a clinical syndrome of greater prevalence in women, older adults, and patients with hypertension and diabetes.[1,2] Its main mechanism of action is pathophysiological dysfunction in left ventricle (LV) filling. Such dysfunction can result in increased LV filling pressure, left atrial pressure, and pulmonary artery pressure, which can be altered at baseline or during exercise.[3] Dyspnea and fatigue are common symptoms in patients with HFpEF, being one of the main causes of exercise intolerance.[4,5]

Central and peripheral arterial stiffness represents another important mechanism for HFpEF development. Altered pulsatile hemodynamic indices are associated with intolerance to effort, as they indicate worsening of ventriculo-arterial coupling, basically due to excessively increased LV afterload, hindering LV ejection performance.[6-8]

In addition to cardiovascular factors, respiratory muscles strength (RMS) has an additional role in global hemodynamic performance, influencing cardiac output, pulmonary pressure, and pulmonary arterial resistance, which contributes to activation of cardiovascular reflexes, limiting exercise tolerance in patients with HFpEF.[9-12]

Inspiratory muscle training (IMT) at moderate intensity (30% of maximal inspiratory pressure [MIP]) has already shown benefits in functional capacity and quality of life in patients with HFpEF.[13] However, data about the effects of IMT on LV filling function and on behavior of arterial pulsatile hemodynamics have not been properly investigated, especially at intensities greater than 30% of MIP. Therefore, this study aimed to evaluate the immediate effect and after 1 h of IMT at 80% of MIP on LV diastolic function and arterial stiffness in patients with HFpEF.

Methods

Study design and population

This is a quasi-experimental cross-sectional study. Patients from a tertiary hospital in southern Brazil, aged over 45 years,

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who met the European Society of Cardiology criteria for HFpEF at the time the study was designed[14,15] and who were clinically stable without previous hospitalization of 30 days were included. Patients with angina pectoris, atrial fibrillation, or atrial flutter during examination, pericardiopathies and musculoskeletal problems that prevented performance of functional capacity test were excluded.

After initial invitation, patients were informed about the echocardiogram to assess cardiac indexes and confirm the diagnosis; RMS assessment by MIP and maximal expiratory pressure (MEP); 6-minute walk test (6MWT); and assessment of arterial pulsatile hemodynamics. Patients who agreed to participate in the present study signed a free and informed consent form, according to the project approved by the ethics committee of the corresponding institution (39338614.0000.53.49).

Variables evaluation

Echocardiography

The evaluation of LV hemodynamic was performed by a 2-dimensional (2D) M-mode 10 standard Doppler echocardiogram (Siemens Acuson X 300, Siemens Medical Solutions USA Malvern, PA, USA) according to the recommendations of the American Society of Echocardiography.[16] The echocardiograms were performed by the same operator. All echocardiographic recordings were obtained in digital format and recorded with an average of 3 cardiac cycles for analysis. The spectral Doppler recordings of mitral flow were obtained from the apical 4-chamber view to assess LV filling dynamics. The following variables were measured: peak early (E wave) and late (A wave) transmittal filling velocities in centimeters per second; E/A ratio; deceleration time of the E velocity in milliseconds (from the peak of E velocity to baseline). Spectral tissue Doppler was performed in the apical portion of the 4 chambers, the sample volume was set at 5 x 5 mm and placed at the junction of the LV septal and lateral wall with the mitral ring and 3 consecutive cardiac cycles, which were transferred to a workstation and analyzed. Peak velocities during systole, onset of diastole (E') and late diastole (a') were measured and the mean of both sites was analyzed. The non-invasive LV filling pressure index was assessed by early diastolic mitral inflow velocity and mitral annular tissue velocity ratio (E/e'). The test was performed before RMS assessment, immediately after IMT (post-immediate), and 1 hour after IMT (post-late).

Arterial stiffness measured by pulse wave velocity

The assessment of arterial stiffness was performed by analyzing pulse wave velocity (PWV) and pulse pressure (PP) based on the oscillometric method, using data from the brachial artery pressure. The recordings were made at a diastolic pressure level for about 10 s using a conventional adult blood pressure cuff available in 2 sizes (24-34 and 32-42 cm) and a high accuracy pressure sensor (Mobil-O-Graph NG, IEM GmbH, Stolberg, Germany).[17]

Respiratory muscle strength test

RMS was always assessed by the same evaluator measuring MIP and MEP. Measurements were obtained using a pressure analyzer (Globalmed MVD300, Porto Alegre, Brazil). The procedures were repeated 6 times and the 3 greatest measures were considered valid, as long as the variation between them was not greater than 10%, following the guideline for pulmonary function tests.[18] The patients were positioned seated, elbows supported, and a nasal clip was applied. The air passed through a nozzle transmitted the pressure level to the pressure transducer. MIP and MEP were considered to be the highest value of 3 measures selected.[19] IMT intensity was determined by the highest value MIP (80%) for training protocol. The test was conducted after echocardiography and pulsatile hemodynamics.

Six-minute walk test

The 6MWT was always performed by the same evaluator according to recommendations by the American Thoracic Society.[20] The test was conducted in an adapted corridor with markings of 30 meters. Patients were instructed to walk the longest distance possible over 6 minutes, always with encouragement. Pre-effort and post-effort blood pressures were checked, and heart rate was monitored during test.

Intervention protocol

Inspiratory muscle training

Individuals were submitted to an IMT session with an intensity of 80% of MIP. The PowerBreathe Classic light resistance model was used with intensity adjusted from 10 to 90 cm H_20. Three sets of 10 minutes were performed with recovery of 1 minute between each set. After IMT end, patients underwent echocardiogram and pulsatile hemodynamics evaluations again to assess immediate effects. In addition, they waited for 1 hour at rest to repeat the assessments.

Statistical analysis

The variables were described in simple and relative frequency for categorical variables, and mean and standard deviation for continuous variables. To analyze the differences between continuous and categorical variables in the pre-, post-immediate, and post-late periods, the Generalized Estimation Equations method and Bonferroni correlation were used for multiple comparisons. For the sample calculation, expecting to reach a difference of 3.3 in the E/e' index between pre- and post-protocol and considering a power of 80% and an alpha error of 5%, we estimated a sample of 18 participants. The data were analyzed using the SPSS version 18.0 statistical program.

Results

The study population consisted of 18 individuals with predominance of the female gender. The main associated comorbidities were systemic arterial hypertension, diabetes mellitus and obesity. In addition, drug therapy beta-blockers were the most used.

Despite the sample showed characteristic values for moderate diastolic dysfunction (E/e'), the distance covered in 6MWT demonstrates a good functional capacity, representing absolute average by Weber's class A individuals. In addition, PWV values appear to be within normal range for arterial stiffness, as well as cardiac output (3.94 (SD, 0.17) L/min) and cardiac index (2.05 (SD, 0.09) L/min/m^2). However, PP values are high, identifying possible aortic stiffness with valve regurgitation. The baseline sample characteristics are described in Table 1.

After 1 h of IMT, a significant change in E/e' was observed compared to the initial values (10.33 (SD, 3.15) vs 8.73 (SD, 2.24); $p < 0.001$) and also a reduction between the post-immediate and the post-late periods (10.38 (SD, 3.23) m/s vs 8.73 (SD, 2.24) m/s; $p < 0.011$) (Figure 1).

In relation to arterial stiffness, there were significant changes in PWV between pre- and post-late periods (8.33 (SD, 1.67) vs 7.63 (SD, 1.66) m/s; $p < 0.001$) and between post-immediate and post-late periods (8.24 (SD, 1.78) vs 7.63 (SD, 1.66) m/s; $p < 0.001$) (Figure 2). Similarly, PP showed significant changes between pre- and post-late periods (54.81 (SD, 18.73) mm Hg vs 48.52 (SD, 15.74) mm Hg; $p < 0.001$) and between post-immediate and post-late periods (57.92 (SD, 16.21) mm Hg vs 48.52 (SD, 15.68) mm Hg; $p < 0.001$) (Figure 3).

Discussion

The present study evaluated the immediate effect and 1 hour after IMT on hemodynamic indexes of LV filling, as well as on pulsatile arterial hemodynamic indexes in patients with HFpEF. The main finding of the present study was that IMT modified hemodynamic indexes of LV filling and pulsatile hemodynamics, demonstrating the positive effects of high-intensity training.

Table 1 – Anthropometric, respiratory, echocardiographic, and hemodynamic characteristics

Variables (N = 18)	Values (mean (SD) or %)
Anthropometric data	
Age (years)	61.3 (7.2)
Height (cm)	160 (0.9)
Body mass (kg)	84.1 (16.4)
BMI (kg/m^2)	32 (4.6)
Female (%)	66.7
Drug therapy (%)	
Beta-blocker	76.5
ACEi	47.1
ARB	35.3
CCB	41.2
Furosemide	41.2
Continuation	
Thiazide	52.9
ARA	29.4
Nitrate	23.5
Hydralazine	11,8
Antiplatelet	52.9
Comorbidities (%)	
Systemic hypertension	94.1
Diabetes	41.2
Obesity	47.1
Smoking	5.9
Coronary artery disease	35.3
Chronic obstructive pulmonary disease	5.9
Renal failure	7.3
Stroke	4.7
Rheumatic disease	6.8
Functional capacity	
NYHA I – II (%)	94.4
NYHA III (%)	5.6
6MWT (meters)	431.4 (117.2)
Respiratory variables	
MIP (cm H_2O)	73.6 (17.8)
Predicted MIP (cm H_2O)	115.8 (6.9)
70% of predicted MIP (cm H_2O)	80.8 (4.9)
MEP (cm H_2O)	124 (28.9)
Predicted MEP (cm H_2O)	90.8 (19)
70% of predicted MEP (cm H_2O)	65.6 (14.8)
Inspiratory weakness (%)	61.1
Echocardiographic variables	
Simpson EF (%)	64.2 (11.7)
E/e'	9.8 (3.6)
E/A	1 (0.7)
IRT	103.8 (87)
LAV	73.7 (25.7)
iLAV	39.4 (10.2)
Teicholz iLVM (g/m²)	119.4 (47.3)
Pulsatile hemodynamics variables	
PWV (m/s)	8.3 (1.7)
CPP	54.8 (4.3)
Aix	32.2 (12.8)

BMI: body mass index; ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; CCB: calcium channel blocker; ARA: angiotensin receptor antagonists; NYHA: New York Heart Association; 6MWT: 6-minute walk test; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure; EF: ejection fraction; IRT: isovolumetric relaxation time; E: peak E-wave velocity; e': peak early diastolic velocity on tissue Doppler; LAV: left atrial volume; iLAV: indexed left atrial volume; iLVM: indexed left ventricular mass; PWV: pulse wave velocity; CPP: central pulse pressure; Aix: augmentation index.

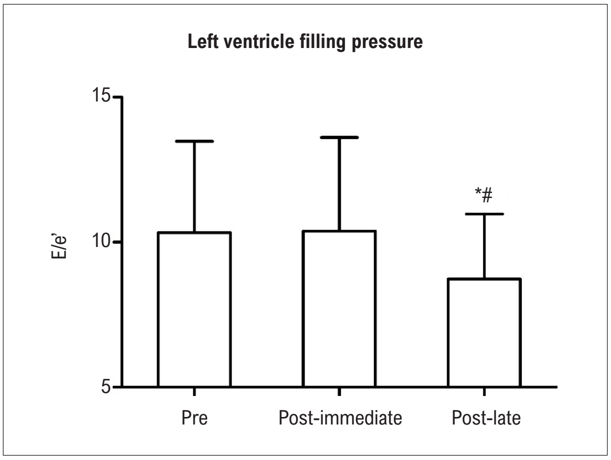

Figure 1 – *Estimation of left ventricle filling pressure pre, post-immediate and post-late. * p < 0.05 between pre- and post-immediate; # p < 0.05 between post-immediate and post-late. E/e': non-invasive index of LV filling.*

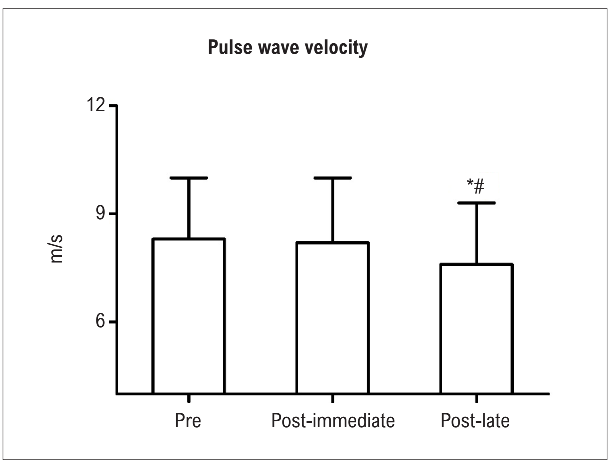

Figure 2 – *Pulse wave velocity pre, post-immediate and post-late. * p < 0.05 between pre- and post-immediate; # p < 0.05 between post-immediate and post-late.*

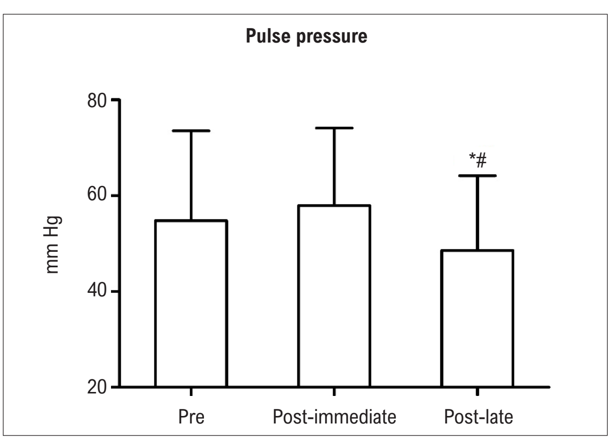

Figure 3 – *Pulse pressure pre, post-immediate and post-late. * p < 0.05 between pre- and post-immediate; # p < 0.05 between post-immediate and post-late.*

There was a significant effect immediately after IMT for E/e′ ratio. We also found a significant effect from the post-immediate to the post-late. These results confirm our hypothesis that IMT would promote positive effects on hemodynamic indexes of LV filling. Some evidences suggest that IMT is effective in modifying E/e′ ratio; however, when performed at an intensity of 30%.[13] Contrary to the literature, we demonstrated that high-intensity IMT (80% of MIP) is able to modify hemodynamic indexes of LV filling. In addition, it is noteworthy that we conducted only 1 supervised IMT session. We believe that maintaining high-intensity IMT for weeks can promote adequate mechanical action in the respiratory muscles, facilitating the redirection of peripheral blood flow, which can generate a stimulus in the bioavailability of nitric oxide and consequently in vasodilation.[21]

With regard to PWV, we found significant differences in comparison between post-immediate and post-late periods. PWV is an important predictor of cardiovascular disease and mortality.[22] In addition, studies show that PWV is directly related to amendment to ventriculo-arterial coupling leading to exercise intolerance and causing hemodynamic changes in the afterload, with consequent increase in dyspnea to small and moderate efforts.[10,12] Although PWV values are within normal range in our sample, PP is high, identifying possible aortic stiffness and valve regurgitation for these patients. Evidence indicates that a value of 50 mm Hg for PP is related to ventricular hypertrophy and mortality from cardiovascular diseases.[23,24] In the present study, we were able to demonstrate that there was a significant reduction in PP immediately after a high-intensity IMT session ($p = 0.023$).

Another important result that we found in the present study was that 61.1% of the sample presented respiratory muscle weakness, with a cutoff point of < 80 cm H_20 for MIP.[19] We know that BMI > 30 kg/m^2 found for the present individuals is directly related to reductions in MIP, due to distension of diaphragm muscle fibers caused by the mechanical action of abdominal fat.[25] A lower BMI is also associated with greater resistance of the respiratory muscles, demonstrating that the reduction of body mass is fundamental for these patients.[26,27]

It is important to reduce the hemodynamic indexes values of LV filling, arterial stiffness and PP, as well as to increase MIP in patients with HFpEF, since all these factors are integrated for the onset of dyspnea and fatigue during efforts.[9] The reduced performance of this integrative system related to dyspnea and fatigue can be explained by abnormal chemoreflex activity, thus resulting in greater ventilation and greater sympathetic activity, hindering arterial baroreflex adjustments and increasing the time of adrenergic vasoconstriction, which results in increased right ventricular afterload.[11,28] This inadequate hyperventilation during exercise modulates the chemoreflex activity due to a higher production of CO_2, making peripheral O_2 extraction difficult and causing inefficiency of metabolic buffer, thus being able to increase neurohumoral activity.[29] Finally, we can affirm that the metaboreflex activity of the respiratory muscles also influences ventilatory response and exercise intolerance in patients with HFpEF. This metaboreflex overload leads to increased phrenic nerve, ventilation, and sympathetic activity, consequently increasing vasoconstriction and fatigue of peripheral muscles.[30,31]

Therefore, the integration processes related to dyspnea and fatigue can directly influence myocardial work and blood flow redistribution.[29] IMT has the potential to rehabilitate patients with HFpEF, and the rationale is related to improving venous return, increasing cardiac output, reducing ventricular afterload regardless of training mode.[11,28,32,33] In addition, IMT can improve functional capacity and consequently promote a better quality of life for patients with HFpEF, since dyspnea and fatigue are associated with a worse prognosis.

The results of the present study are important to promote new questions about the intensity of IMT, since only 1 session with 80% of MIP promoted significant improvements in hemodynamic indices of LV filling and arterial stiffness, without complications during the protocol. Therefore, our results demonstrate that a high-intensity IMT session is effective for improving the parameters evaluated in patients with HFpEF. Nevertheless, it is worth mentioning that high-intensity IMT seems to be a promising strategy in the rehabilitation scenario.

Limitations

The present study has some limitations, among which we can mention the absence of a control group, which would add important information about the effects of IMT. Another limitation is that only 1 IMT session was conducted, causing a gap in the literature on the chronic effects of high-intensity IMT. Finally, we emphasize the importance of research in the area of IMT for patients with HFpEF. Here, we suggest that future studies assess the effects of different intensities of IMT with comparisons to a control group.

Conclusion

Our results demonstrated that a unique session of high-intensity IMT improved hemodynamic indices of LV filling and arterial stiffness in patients with HFpEF. Future studies should test high-intensity IMT consecutive sessions as a rehabilitation method for patients with HFpEF.

Author Contributions

Conception and design of the research and Acquisition of data: Menezes MG, Garcia EL, Grings V, Danzmann LC; Analysis and interpretation of the data: Menezes MG, Grings V, Danzmann LC; Statistical analysis: Menezes MG, Franzoni LT, Danzmann LC; Obtaining financing: Menezes MG, Danzmann LC; Writing of the manuscript and Critical revision of the manuscript for intellectual content: Menezes MG, Garcia EL, Franzoni LT, Grings V, Danzmann LC.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade Luterana do Brasil under the protocol number 393386.14.1.0000.5349. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

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