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Research Article

Improvement in Exercise Capacity after Inspiratory Muscle Training is Related to Increased Calf Blood Flow during Inspiratory Load in COPD

Marina Axmann de Castro[1], Luiz Felipe Fröhlich[1], Gaspar R Chiappa[2], Marli M Knorst[1,3], JAlberto Neder[4] and Danilo C Berton[1,3]*

[1]*Graduation Program in Pulmonology, Federal University of Rio Grande do Sul (UFRGS), Brazil*
[2]*Exercise Pathophysiology Research Laboratory, Hospital de Clínicas de Porto Alegre (HCPA), Brazil*
[3]*RespiratoryDivision, Hospital de Clínicas de Porto Alegre (HCPA), Brazil*
[4]*Division of Respirology, Queen's University and Kingston General Hospital, Canada*

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***Corresponding author**

Danilo C Berton, Rua Ramiro Barcelos, 2350, Room 2050. Postal Code: 90035-003, Porto Alegre, RS, Brazil, Email: dcberton@gmail.com

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Abstract

Objective: Inspiratory Muscle Training (IMT) used in isolation confer several clinical and physiologic benefits in patients with Chronic Obstructive Pulmonary Disease (COPD). We investigated if improvement in exercise tolerance in COPD patients after IMT would be related to a possible increase in Calf Blood Flow (CBF) during Inspiratory Resistive Load (IRL).

Methods: Patients performed IMT (30% of maximal inspiratory pressure; MIP) using a pressure threshold device 30 min/day, 7 times/week, during 8 weeks. High intensity constant load cardiopulmonary exercise test and CBF measurements during IRL (60% of MIP until exhaustion) by venous occlusion plethysmography were evaluated before and after training. Patients were classified as "improvers" if presented the minimum clinically important improvement in exercise tolerance (Tlim) of 33% after IMT.

Results: Seven patients completed the full training period (8 wks) and performed all study evaluations (65.3±9.7yr; FEV_1= 41±17%pred; MIP=97±34cm H_2O). Three patients were considered "improvers". There was no difference in baseline characteristics between groups (p>0.05). "Improvers" tended to reduce exercise dyspnea at isotime (p =0.056) and significantly improved their CBF during IRL protocol after IMT compared to "non-improvers" (p=0.015).

Conclusion: Patients who improved Tlim after IMT significantly increased their CBF during IRL compared to "non-improvers".

Introduction

Several patients with Chronic Obstructive Pulmonary Disease (COPD) still remain breathless and presenting exercise intolerance despite medical therapy. In this context, pulmonary rehabilitation has been recognized to improve clinical outcomes (dyspnea, exercise capacity, and health related quality of life) through a comprehensive approach including several strategies [1,2].

At present time, current evidence indicates that Inspiratory Muscle Training (IMT) used in isolation promotes benefits in several outcomes [3], however its routine use as an essential component of pulmonary rehabilitation is still not recommended [1,2].

It was demonstrated in healthy individuals that fatiguing contractions of the inspiratory muscles and the consequent accumulation of metabolic products activate type IV phrenic afferents, resulting in pronounced increase in sympathetic vasoconstrictor activity. This mechanism is thought to be particularly important during sustained heavy intensity exercise in healthy humans, where it modulates the competition for blood flow between the respiratory and working locomotor muscles [4-7]. In COPD patients, the rise in ventilatory work during dynamic exercise can require 25-40% of oxygen consumption (VO_2) [8]. Slower maximal relaxation rate of esophageal (pleural) sniff pressure (reflecting inspiratory muscle fatigue) [9] was observed in COPD patients walking to exhaustion [10] that was attenuated with pressure support ventilation [11]. Therefore, a substantial part of cardiac output would be redirected from peripheral muscles in order to attend to an elevated metabolic demand from inspiratory muscles [12]. In fact, it was previously shown that Non-Invasive Ventilation (NIV) (supposedly reducing the workload imposed on inspiratory muscles) improved exercise tolerance and peripheral oxygen supply in patients with COPD [13]. Similar findings have also been found in patients with heart failure, either by NIV [14] or IMT [15].

In this context, improving the oxidative capacity and the "roof" for maximum pressure generation of inspiratory muscles possibly could increase blood flow to peripheral muscles during

inspiratory loading. Therefore, we aimed investigate if an improved exercise tolerance after IMT would be associated with increased blood flow to lower limbs during Inspiratory Resistive Loading (IRL) in COPD patients.

Methods

Subjects

Patients with spirometric evidence of chronic air-flow limitation (post-bronchodilator Forced Expiratory Volume in one second (FEV_1) <70% predicted, FEV_1/Forced Vital Capacity (FVC) <0.7) [16] and presenting with a long history of smoking (>20pack-years) were recruited consecutively from a specialized tertiary clinic care center in the management of COPD. They were receiving continuously formoterol/budesonide (12/400μg) twice day (dry powder inhaler), short-acting bronchodilators as rescue medications, and did not participate in pulmonary rehabilitation in the last 24 months. Main exclusion criteria were: exacerbation of COPD in the previous 3 months or during the study, cardiac disease (acute coronary syndrome in previous 3 months or cardiac ejection fraction <50%), long term oxygen therapy or arterial oxygen saturation <90% at rest, neuromuscular disease, peripheral arterial disease, cancer, and patients who were physically unable to move.

Study design

This prospective cohort, single-blind study (blinded outcome assessors) is a post hoc subanalysis of a research project approved by Independent Ethic Committee (HCPA Nº 194.217) and results previously reported in abstract form [17]. All subjects signed written informed consent.

Patients' prescribed treatment was maintained at stable doses throughout the study. Resting lung function tests and incremental cardiopulmonary exercise test (Inc CPET) were performed only at baseline. All other evaluations were performed before and after the training period. Maximum Static Inspiratory Pressure (MIP) were measured weekly during the study to adjust IMT load.

Study Procedures

Intervention: Inspiratory muscle trainer device (Power-breath Light or Medium Resistance™, Southam, UK) set at 30% of MIP was used for a 8-week IMT, 7 times/week, once day during 30 min. Each week, six training sessions were performed at home and one training session was supervised at study center, adjusting the load at 30% of MIP. During training, subjects were instructed to maintain diaphragmatic breathing, with a breathing rate at 15 to 20 breaths/min.

Maximum static inspiratory pressure: The MIP was obtained with a pressure transducer (MVD-500 V.1.1™, Micro hard System, Global med, Porto Alegre, Brazil) and was determined with a deep inspiration from residual volume against an occluded airway having a minor air leak (2mm). The highest pressure (peak) of five measurements was used for analysis (at least three reproducible, i.e. <10% variation, otherwise more maneuvers were performed) [18].

Resting lung function tests: Spirometry was performed using a calibrated pneumotachograph (Eric Jaeger™, GmbH, Wüerzburg, Germany). FVC (L), FEV_1 (L) and FEV_1/FVC ratio were measured before and 15 min after inhalation of salbutamol 400 μg via metered-dose inhaler. Constant volume whole body plethysmography and single breathe Lung Diffusion Capacity for Carbon Monoxide (D_LCO) were performed using an automated testing equipment (Eric Jaeger™, GmbH). Lung volumes measurements include Total Lung Capacity (TLC), Functional Residual Capacity (FRC) and Residual Volume (RV). Recommended standards and reference values were based on previous publications [19-21].

Cardiopulmonary exercise testing: Maximal Inc CPET was performed on an electrically braked cycle ergometer (ER-900™, Ergoline, Jaeger, Würzburg, Germany) with load increments of 5-10 W/min. Subjects were instructed to maintain a pedaling frequency of 60 rpm. During the test, gas exchange variables were measured breath-by-breath (OxyconPro™, Jaeger). Heart Rate (HR) was determined from a 12-lead electrocardiogram. Perception of dyspnea was measured by Borg scores at regular intervals.

In high intensity constant-load exercise testing (ctCPET), patients exercised at a work rate of 75% of the individual peak work rate obtained from Inc CPET. The test was terminated when patients indicated that they were exhausted and/or were unable to maintain a pedaling frequency >40 revolutions per minute for 20 s. This total time was recorded as cycle exercise tolerance (Tlim). Dyspnea Borg scores were evaluated before and during exercise at 2 min intervals. Isotime was defined as the longest exercise duration common to both ctCPET performed before and after intervention.

Inspiratory resistive load (IRL) protocol: Patients used a nose clip and breathed continuously into a 2-way Lloyd valve (Warren E. Collins, Inc., Braintree, Massachusetts, USA) with low resistance connected to a POWER breathe™ Inspiratory Muscle Trainer (Southam, UK) with inspiratory pressure set at 60% of MIP. During the protocol, subjects maintained a Breathing Frequency (fb) of 15 breaths/min and duty cycle (inspiratory time/total respiratory cycle) of 0.3, oriented by a researcher using a metronome. After a resting phase of 3 minutes, individuals started breathing against the pre-defined inspiratory resistance until exhaustion [15]. The objective of this protocol is increase the inspiratory muscle work until fatigue to induce a sympathetically mediated reflex. Therefore, systemic Blood Pressure (BP), Heart Rate (HR) and CBF (see below) were measured at the end of resting phase, in the first 2 minutes of breathing against inspiratory pressure and at interruption of the protocol. Mean BP was calculated as diastolic + 1/3(systolic-diastolic). End-tidal partial pressure of carbon dioxide ($PETCO_2$) and oxyhemoglobin saturation by pulse oximetry (SpO_2) were also measured at baseline and end of the protocol to control for potential confounder of the response.

Calf blood flow measurement: Calf Blood Flow (CBF) was measured by venous occlusion plethysmography (Hokanson™, TL-400, Bellevue, WA, USA) as previously described [22]. Briefly, the limb was positioned above heart level and was supported in the thigh and ankle to ensure proper venous drainage. A strain gauge was positioned on the right calf at the point of maximum circumference. During the entire protocol, a BP cuff on the thigh was alternately inflated to 60 mmHg and deflated in 10s cycles. Additionally, another cuff was placed on the ankle and inflated to suprasystolic levels (240 mmHg) to occlude foot circulation. CBF (mL/100 mL/min) was determined manually on the basis of a minimum of three separate readings.

Statistical analysis: Subjects were classified according obtainment of the Minimum Clinically Important Difference (MCID) in Tlim of +33% from baseline after IMT ("improvers" *vs* "non-improvers")

Table 1: Baseline characteristics of studied patients (n=7).

Variables	Values
Demographics/ Anthropometrics	
Female sex, nº (%)	4 (57%)
Age, years	65.3 ± 9.7
Weight, Kg	66.1 ± 11.9
Height, cm	159.6 ± 9.2
BMI, Kg/m^2	25.8 ± 2.6
BDI	6.7 ± 1.6
Resting Lung Function	
FEV_1, L (%pred)	0.80 ± 0.15 (37 ± 16)
FEV_1 post BD, L (%pred)	0.87 ± 0.18 (41 ± 17)
FVC, L (%pred)	1.86 ± 0.37 (58 ± 9)
FVC post BD, L (% pred)	2.01 ± 0.30 (61 ± 12)
FEV_1/ FVC, %	43 ± 1
FEV_1/ FVC post BD, %	43 ± 1
TLC, L (%pred)	7.67 ± 1.71 (144± 9)
RV, L (% pred)	5.53 ± 1.40 (295 ± 41)
IC rest, L (%pred)	1.88 ± 0.64 (77 ± 21)
IC rest/TLC, %	27 ± 1
D_LCO, mL/min/mmHg (% pred)	6.94 ± 2.74 (28 ± 10)
MIP, cm H_2O (%pred)	97 ± 34 (109 ± 31)
Peak incremental exercise	
VO_2, mL/min (%pred)	971 ± 184 (77 ± 20)
VE, L/min	29 ± 8
VE/MVV	0.81 ± 0.13
fb breaths/min	27 ± 4
VT, L	1.09 ± 0.21
HR, %pred	78 ± 6
Dyspnea Borg score	9.0 (0.0 - 9.0)
Leg effort Borg score	9.0 (4.0 - 9.0)
IC, L	1.45 ± 0.31

Data are presented as mean ±SD or median (range), unless otherwise stated.
Definition of abbreviations: BMI: Body Mass Index; **BDI:** Baseline Dyspnea Index; **mMRC:** Modified Medical Research Council Dyspnea Scale; **FEV_1:** Forced Expiratory Volume in one second; **% pred:** % of predicted; **BD:** Bronchodilator; **FVC:** Forced Vital Capacity; **TLC:** Total Lung Capacity; **RV:** Residual Volume; **IC:** Inspiratory Capacity; **D_LCO:** diffusing capacity of the lung for carbon monoxide; **MIP:** Maximal Inspiratory Pressure; **VO_2**: oxygen uptake; **VE:** minute ventilation; **MVV:** Maximal Voluntary Ventilation; **fb:** Breathing Frequency; **VT:** Tidal Volume; **HR:** Heart Rate.

[23]. Student t Test or corresponding nonparametric tests were used to compare continuous variables, as appropriate. CBF responses at different time (pre and post intervention) and moments during IRL protocol (baseline and final) were evaluated with Generalized Estimating Equation (GEE).

A probability value of ≤ 0.05 was considered to be significant. Statistical analysis was completed with a commercial software package (SPSS; PASW Statistics for Windows, Version 18.0. Chicago, USA).

Table 2: Inspiratory muscle strength, exercise tolerance (Tlim) and exercise dyspnea at isotime in patients with ("Improvers") and without ("non-improvers") clinically significant increments in Tlim after inspiratory muscle training.

Variables	"Improvers" (n=3)			"Non-improvers" (n=4)		
	Pre IMT	Post IMT	Δ	Pre IMT	Post IMT	Δ
MIP, cm H_2O	107±32	128±29	22±15	89±38	95±26	6±16
MIP, % pred	114±25	140±33	26±18	105±38	113±29	7±19
Tlim, s	544±261	979±407	435±163	221±53†	230±80*	9±29*
Dyspnea at isotime	7 (4-8)	4 (3-7)	-1.7±1.1	7 (5-9)	7 (5-10)	0.3±0.6†
Leg effort at isotime	4 (0-7)	4 (2-8)	1.0±3.0	9 (3-9)	9 (0-10)	-0.6±2.1

Values presented as mean ±SD or median (range).
Definition of abbreviations: MIP: Maximal Inspiratory Pressure; **Tlim:** exercise tolerance during constant load exercise testing.
*p<0.05 between group comparison
†p =0.056 between groups comparison

Results

Seven patients completed the full training period (8 weeks) and performed all study evaluations. They had moderate to very severe COPD, with moderate hyperinflation, severe air trapping and preserved inspiratory muscle strength at baseline (Table 1). Only 2 patients presented a reduced MIP (< 70cm H_2O), one with 62 and other with 69 cm H_2O. All but one patient reported chronic dyspnea (modified Medical Research Council score ≥ 2).

On average, they tended to increase MIP (97±34 to 110±31cm H_2O; p=0.09) and exercise tolerance (360±232 to 551±467s; p=0.09) after IMT. However, only 3 patients reached the MCID for exercise tolerance ("Improvers" Group).There was no difference between groups regarding age, gender, smoking history, anthropometry, lung function and inspiratory muscle strength at baseline (p>0.05). On the other hand, "improvers" tended to reduce exercise dyspnea at isotime (p =0.056) (Table 2) and significantly improved their CBF during IRL protocol after IMT compared to "non-improvers" (interaction p=0.015) (Figure 1).

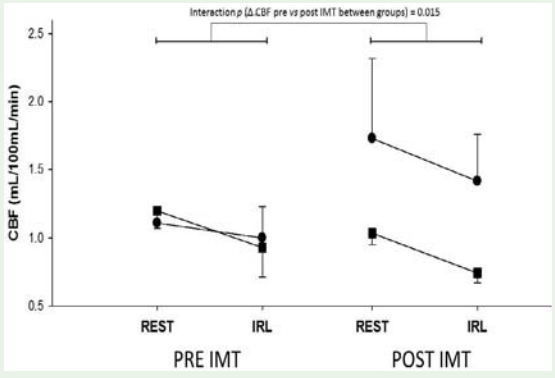

Figure 1: Calf Blood Flow (CBF) at rest and at the end of Inspiratory Resistive Loading (IRL) before and after inspiratory muscle training contrasting patients with (circles) and without (squares) improvement in exercise tolerance.

Discussion

The present study shows that patients obtaining the minimum clinical improvement in exercise tolerance after IMT showed a concomitant increment in their CBF during loading of inspiratory muscles. Therefore, higher blood availability to locomotor muscles during activities that stress inspiratory muscles could partially contribute to better exercise tolerance after an intervention that increases inspiratory muscle strength and possibly, oxidative capacity [24].

Patients with heart failure [25] and COPD [12] may present abnormalities of peripheral circulatory regulation that might contribute to their limited functional capacity. Improvement in peripheral muscle blood delivery during inspiratory loading was reported after IMT in healthy subjects [26] and patients with heart failure [15]. In a similar way, this phenomenon is suggested in the present study with COPD patients. IMT probably increased the load required to elicit the inspiratory muscle reflex inducing peripheral vasoconstriction. This support the concept that IMT might be associated with reduced accumulation of muscle metabolites during fatiguing trial. We must acknowledge, however, that we did not evaluate CBF during exercise and/or whether the inspiratory muscle effort during our ctCPET would be sufficient to cause repercussion on peripheral blood flow. Therefore, future studies should address these issues.

Current evidence from meta-analysis of randomized controlled trials [3] indicates that IMT used in isolation confer benefits in several areas, including inspiratory muscle strength (mean improvement of +13cm H_2O; p=0.01) and a tendency to increase endurance exercise capacity (mean improvement of 198s; p=0.09).Our study was probably not powered enough to detect differences in MIP increments after IMT between groups (22 *vs* 6 cm H_2O in "improvers" *vs* "non-improvers", respectively). The first group probably did IMT more effectively, resulting in greater increment in respiratory muscle force and, consequently, obtaining greater physiological benefits. Accordingly, reduction in exercise dyspnea at isotime tended to be greater in this group, possible reflecting reduced respiratory neural drive [27].

The small sample size could probably underpowered some of our analysis, but this is frequent in IMT trials. For example, in a previous systematic review [3] the sample size of included studies ranged from 11 to 67 patients, and more than half of these works studied less than 30 patients.

Conclusion

The present study showed that patients who clinically improved exercise tolerance after IMT significantly increased their CBF during inspiratory loading compared to "non-improvers".

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