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Inspiratory muscle training improves autonomic modulation and exercise tolerance in chronic obstructive pulmonary disease subjects: A randomized-controlled trial

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ABSTRACT

Objectives: We aimed to evaluate the effect a regular inspiratory muscle training program on autonomic modulation measured by heart rate variability, exercise capacity and respiratory function in chronic obstructive pulmonary disease subjects (COPD).
Design: Single-center controlled study, with balanced randomization (1:1 for two arms).
Setting: A COPD reference hospital localized in Sao Luís, Brazil.
Participants: 22 COPD subjects joined the study.
Interventions: Three times a week for four weeks inspiratory muscle training (IMT) at 30% of PI_{max}.
Main outcome measures: Pulmonary capacities and inspiratory pressure, total six-minute walk test and, cardiac autonomic modulation.
Results: The intervention group showed improvements in the cardiac autonomic modulation, with increased vagal modulation (total variability and HF [ms^2; adjusted $p < 0.05$]); increased expiratory and inspiratory capacities and, increased distance in the 6-min walk test.
Conclusion: 12 weeks of IMT at 30% of the maximal inspiratory pressure increased cardiac autonomic modulation, expiratory and inspiratory and exercise capacity in COPD subjects.

1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is one of the leading causes of death worldwide (Halbert et al., 2006; Prince et al., 2015). Recent estimates point out that in 2020, COPD will be the third largest cause of death in the world (Ford et al., 2015). In addition, COPD is directly related to the development of autonomic imbalance, atherosclerosis and other cardiovascular complications (Mazzuco et al., 2015; van Gestel and Steier, 2010). Recent data have shown that cardiovascular diseases can be responsible for the greater number of hospitalizations, as well as 25% mortality in COPD subjects (Choudhury et al., 2014).

Among the variables affected, COPD causes autonomic dysfunction, as well as, reduced forced expiratory volume, decreases in oxygen consumption (VO_2), low exercise tolerance and decreased respiratory muscle strength (Lacasse et al., 2005; Leidy et al., 2014). This fact contributes to a marked respiratory muscle desynchrony, accompanied by a fast and superficial respiratory pattern in certain activities such as tying a shoe, teeth brushing, etc (Stjepanovic et al., 2016). Also, the simple sustained elevation of the upper limbs in these subjects may lead to a significant increase in dyspnea sensation (Janaudis-Ferreira et al., 2014; Stjepanovic et al., 2016).

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COPD subjects present a increased vagal autonomic modulation, as shown by other studies, mainly during the acute exacerbations (Kabbach et al., 2017). This increased vagal modulation might be one of the mechanisms responsible for the bronchoconstriction, so markedly present in COPD subjects (Audrit et al., 2017; Chong et al., 2017).

Other studies have already demonstrated the beneficial impacts of exercise training, such as running or strength exercises on autonomic modulation and exercise tolerance of COPD subjects (Borghi-Silva et al., 2009; Mohammed et al., 2016). Other exercises, such as inspiratory muscle training (IMT) in COPD subjects have been extensively described for its benefits in respiratory capacity and exercise tolerance (Dellweg et al., 2017; Montemezzo et al., 2014).

In addition, IMT has been shown as an effective strategy to improve cardiac autonomic control in hypertensive subjects and peripheral sympathetic activity in subjects with heart failure, increasing their functional capacity, the overall quality of life and cardiorespiratory fitness (Sin and Paul Man, 2003).

The heart rate variability (HRV) is a clinical tool used to measure the balance between sympathetic and parasympathetic (vagal) modulation through the data collection of the RR intervals. The reduction in the HRV has been associated with increased risk for cardiovascular disease and acute cardiac events, such as myocardial infarction (La Rovere et al., 1998; Thayer et al., 2010).

Since COPD subjects are at a higher risk of developing cardiovascular diseases (Chen et al., 2015; Sin and Paul Man, 2003) and have a marked vagal modulation (Janaudis-Ferreira et al., 2014), efficient strategies for reducing vagal-mediated bronchoconstriction, increasing respiratory capacities and, increasing exercise tolerance in this population are urgent. However, to this date, no study has ever investigated the effect of IMT on autonomic modulation of COPD subjects.

With this insight, the aim of this study was to evaluate the effect of IMT in respiratory function, exercise capacity, and, autonomic function in COPD subjects.

2. Materials and methods

2.1. Trial design and study place

This was a single-center, randomized-controlled study, with balanced randomization (1:1 for two groups). The sample was composed of subjects with diagnosed with COPD recruited at the Pulmonary Rehabilitation Program between 2016 and 2017 at the *Hospital Universitario Presidente Dutra*, a reference center in Sao Luis, Brazil, the capital of Maranhão'state (Fig. 1). The control group received no intervention and was evaluated before and 12 weeks after. The IMT group received an intervention with inspiratory muscle training (IMT) during 12 weeks (described further in the text). All methods in this study were approved by the Institutional Ethics Review Board and followed the Helsinki guidelines. Also, the study was registered in the Brazilian Registry of Clinical Trials, with the number RBR-4mz6w9.

2.2. Eligibility criteria

Our sample consisted of subjects with COPD without heart failure or pulmonary hypertension, with inspiratory muscle weakness (PI_{max} < 70% of predicted) and with stable pharmacological treatment, i.e., no drug change at least one month before the start of IMT. Also, subjects with comorbidities (i.e. diabetes and/or hypertension) were not enrolled.

Were excluded of this study subjects with functional limiting factors that would interfere with the performance of IMT and/or the exercise capacity test, such as: acute myocardial infarction three months before inclusion in the study, unstable angina or unstable ventricular arrhythmia or in the last three months prior to initiation, acute respiratory disease, rheumatic diseases, degenerative diseases, neurological sequelae, cognitive deficit etc.

2.3. Primary outcomes

2.3.1. Respiratory muscle strength

All participants underwent an IMT familiarization before the training protocol for two weeks, and then the Maximal inspiratory pressure (PI_{max}) and Maximal expiratory pressure (PE_{max}) tests took place.

The PI_{max} and PE_{max} were determined in deep inspiration and expiration from residual volume against an occluded airway with a minor air leak (2 mm), following a previously described procedure (Ferreira et al., 2013). The highest pressure of the six measurements was defined as PI_{max} and PE_{max}.

During the experimental sessions, the subjects remained in the sitting position in a comfortable chair. The session of IMT consisted of a 30 min (in a clinical setting) three times a week, using the Threshold Inspiratory Muscle Training device (POWERbreathe Medic + Plus, NCS, Barueri, SP, Brazil). The inspiratory load was set at 30% of PI_{max},

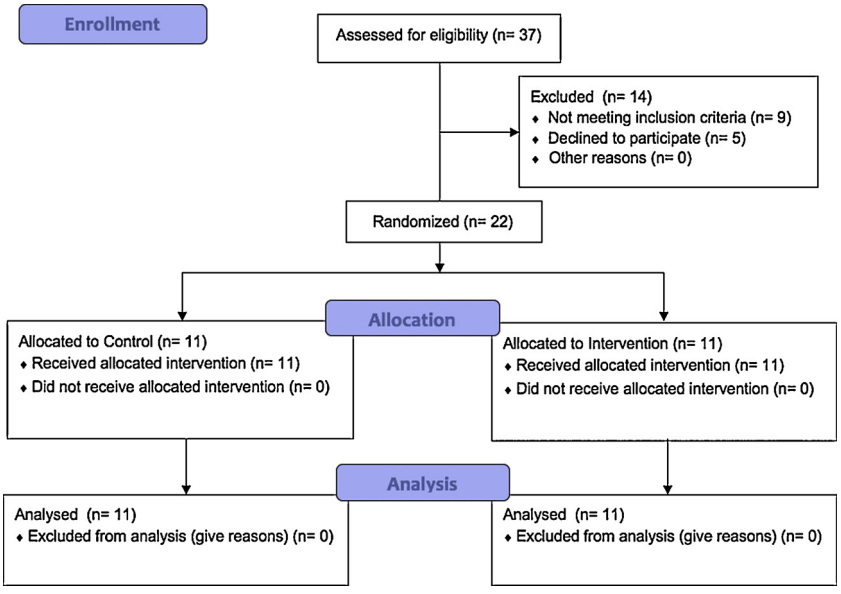

Fig. 1. CONSORT flux diagram of subject recruitment.

according to a study conducted previously (Dall'Ago et al., 2006), during 12 weeks, 3x/week in intercalated days (exception for Saturday and Sunday) for the IMT group, and no load was set for the control group. During exercise, subjects were instructed to maintain diaphragmatic breathing at a rate of 15–20 breaths/min. All sessions were performed at the same time of the day (i.e., 0800–1100). Subjects that did not complete the minimum of five sessions per week had their data not analyzed at the end of the study but, remained at the intervention until the end.

2.3.2. Respiratory function

In the morning of the day reserved to baseline measurements, a Spirometry test (MicroLoop Spirometer, CareFusion, Yorba Linda, CA, USA) was performed by a qualified technician. The subjects underwent the spirometry test in the sitting position, wearing a nose clip. Each individual underwent a forced spirometry to obtain the following parameters: forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), as well as the ratio of FEV1 to FVC (FEV1/FVC, expressed as a percentage). In addition to the automatic evaluation performed by the software device, the quality of spirometric tests was assessed according some criteria, including: the number of acceptable maneuvers according to American Thoracic Society (ATS) (Miller et al., 2005), ranging from 0 to 3, the highest kept by the spirometry software; the reproducibility (FEV1 and FVC were considered reproducible according to ATS criteria when the best two trials differed by not more than 200 mL). Measurements of maximal respiratory pressures were performed by a blinded investigator. A pressure transducer (MVD-300, Globalmed, Porto Alegre, Brazil) connected to a system with two unidirectional valves (DHD Inspiratory Muscle Trainer, Chicago, IL, USA) was used. The Global Initiative for Obstructive Lung Disease Criteria (GOLD) was also used for disease severity classification (Antonelli-Incalzi et al., 2003).

2.3.3. Heart rate variability

RR interval was continuously recorded during 10 min in individuals sitting, using an electrocardiogram device (Micromed Wincardio 600hz, Brasilia, DF, Brazil) to power spectral analyses of HRV. The spectrum resulting from the Fast Fourier Transforms modeling is derived from all the data present in a minimum five-minute window from the recorded signal; it includes the entire signal variance, regardless of whether its frequency components appear as specific spectral peaks or as nonpeak broadband powers. The RR interval variability was evaluated in the time and frequency domains. Spectral power for low (LF: 0.03–0.15 Hz) and high (HF: 0.15–0.4 Hz) frequency bands was calculated by means of power spectrum density integration within each frequency bandwidth, using a customized routine (MATLAB 6.0, Natick, MA, USA) (Rodrigues et al., 2013).

2.4. Secondary outcomes

2.4.1. Blood pressure

The procedures for the measurement of blood pressure (BP) were according to the guidelines of the "The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7)" (Chobanian et al., 2003). In summary, subjects remained in the sitting position in a comfortable chair for 20 min. With an automatic and noninvasive BP monitor (BP710, Omron, Tokyo, Japan), three measurements of BP were performed on the right arm, with at least a 2-min interval between each one.

2.4.2. The six-minute walk test (6MWT)

The 6MWT was conducted in accordance with established guidelines from the American Thoracic Society (Enrichi and Sherrill, 1998; Enright, 2003). Considering a possible learning effect, the test was performed at screening and habituation visit (Enrichi and Sherrill, 1998; Enright, 2003).

2.4.3. Random allocation sequence and blinding

Participants were randomly assigned from a sequence list generated by a computer (randomizer.org) by an individual who was not part of the investigators involved in the study, in two groups: Control and Intervention with IMT (Fig. 1), in a 1:1 allocation ratio. The allocation was concealed, using the opaque envelopes method. The researchers responsible for the day-to-day protocol implementation had no contact with those involved in the control group, and the workloads of the controls were assigned by the chief medical doctor at the center.

2.4.4. Statistical analysis

Data are presented as mean ± standard deviation and differences between control versus treated (95% confidence interval). Normality of data was tested using the Shapiro-Wilk test. Statistical differences between the groups were obtained by an Analysis of Covariance (ANCOVA). Statistical differences between groups were obtained by repeated measures ANOVA. The level of significance was set at $p < 0.05$. The effect size (ES) was calculated to evaluate the effect size of the intervention versus control procedure (Morris, 2008). In the present study, significant clinical effect was considered when ES > 0.80. The software R (version 3.4.3 "Kite-Eating tree") was used for statistical analysis.

Table 1
Metabolic and hemodynamic effects of IMT in control and intervention groups.

	Control (n = 11)		IMT (n = 11)			
	Baseline	After	Baseline	After	Adjusted differences[a] (IC95%)	ES
Male/Female	9/2	9/2	8/3	8/3	–	–
Height (cm)	171 ± 3	171 ± 3	169 ± 2	169 ± 2	–	–
Age (years)	70 ± 8.0	70 ± 8.0	66 ± 8.5	66 ± 8.5	–	–
Weight (kg)	66 ± 9	66 ± 9	62 ± 9	59 ± 8	–	–
SAP (mm/Hg)	140.69 ± 14.23	138 ± 17.23	135.59 ± 19.06	130.45 ± 16.01	−6.04 (−16.44, 4.36)	−0.15
DAP (mm/Hg)	81.15 ± 13.26	81.00 ± 9.60	77.82 ± 12.94	74.36 ± 15.55	−7.85 (−15.53, -0.16)	−0.25
6MWT (meters)	386 ± 120	391 ± 75.25	368 ± 73.11	486 ± 74.56	12.85 (−40.69, 65.06)[b]	1.09[c]
Body Mass Index (kg/m^2)	25 ± 4	26 ± 5	25 ± 4	23 ± 3	−0.42 (−2.61, 1.77)	−0.54

Values are presented as absolute number, mean ± standard deviation or adjusted mean difference (95% confidence interval). IMT: inspiratory muscle training; ES: Effect size; SAP: systolic arterial pressure; DAP: diastolic arterial pressure; BMI: body mass index.

[a] ANCOVA adjusted for age, weight and baseline.

[b] Significant difference ($p < 0.05$).

[c] Clinically relevant (ES > 0.80).

Table 2
Respiratory effects of IMT in control and intervention groups.

	Control (n = 11)		IMT (n = 13)		Adjusted differences[a] (IC95%)	ES
	Baseline	**After**	**Baseline**	**After**		
PI_{max} (cm/H_2O)	58 ± 16	59 ± 16	62 ± 20	84 ± 26	13.83 (1.28, 26.37)[b]	1.15[c]
PE_{max} (cm/H_2O)	76 ± 32	70 ± 23	85 ± 30	109 ± 77	25.16 (8.86, 41.45)[b]	0.95[c]
FVC (liters)	2.00 ± 0.7	1.92 ± 0.7	2.28 ± 0.7	2.08 ± 0.8	0.23 (−0.19, 0.64)	0.17
FVC (% of predicted)	51 ± 4	48 ± 4	57 ± 5	55 ± 2	−2.40 (−5.14, 5.49)	−0.21
FEV1 (liters)	1.04 ± 0.4	1.16 ± 0.6	1.34 ± 0.6	1.08 ± 0.8	0.16 (−0.16, 0.48)	0.72
FEF 25-75%	0.64 ± 0.3	0.65 ± 0.3	0.75 ± 0.8	0.65 ± 0.4	−0.01 (−0.23, 0.21)	0.17

Values are presented as mean ± standard deviation or adjusted mean difference (95% confidence interval). IMT: inspiratory muscle training; ES: Effect size.
[a] ANCOVA adjusted for age, weight and baseline.
[b] significant difference ($p < 0.05$).
[c] clinically relevant (ES > 0.80).

3. Results

3.1. Overall characteristics

Table 1 shows the hemodynamic parameters, submaximal exercise capacity, peak oxygen consumption and body mass index (BMI) variables. All subjects were classified GOLD A class with grade I-II airflow obstruction. The subjects had a mean of 1.3 ± 0.4 exacerbations, but all with no hospital admissions in the last month before the protocol.

3.2. Respiratory function and Inspiratory muscle strength

No differences were found between control and IMT groups for FVC (liters and % of predicted), FEV1 (liters), FEV1/FVC, and FEF25/75 both in baseline period as after 12 weeks. Additionally, improvements in the PI_{max} and PE_{max} in IMT group after 12 weeks were found when compared to the control group (adjusted $p < 0.05$, effect size > 0.80; Table 2).

3.3. Blood pressure

No differences were found between control and IMT groups for age, BMI, systolic and diastolic arterial pressure both in baseline period as after 12 weeks ($p > 0.05$; Table 1).

3.4. Cardiac autonomic modulation

Table 3 shows the autonomic modulation by heart rate variability in time and frequency domains of the control and IMT groups. No statistical differences were found between control and IMT groups for time (except for total variability) and frequency domains (except for HF [ms^2]). Nevertheless, RMSSD (ES = 1.46), SDNN (ES = 0.92), SD1 (ES = 1.14) and SD2 (ES = 1.31) showed a strong clinical significance indicating higher values in the IMT group (ES > 0.80), but with no statistical difference (adjusted $p > 0.05$). In addition, the total variability and HF (ms^2) showed a clinically significant increase and a statistical significance in IMT group after 12 weeks when compared to the control group (ES 0.88 and 0.91, adjusted $p < 0.05$, respectively; Table 3).

3.5. MWT

No significant statistical difference was found in the 6MWT between groups (adjusted $p > 0.05$). However, a clinically significant effect size was found in the comparison between groups indicating higher values of 6MWT distance in the IMT group (ES = 1.09).

4. Discussion

This study aimed to evaluate the effect of 12 weeks of IMT at 30% of the maximum inspiratory pressure (PI_{max}) on respiratory function, exercise capacity, and autonomic function in COPD subjects. The main finding of our study shows that a regular protocol of IMT was effective to improve maximal inspiratory and expiratory muscle strength, cardiac autonomic modulation and, functional capacity measured by the 6MWT in COPD subjects. However, the IMT protocol failed in show any

Table 3
Heart rate variability in time and frequency domain in control and IMT groups.

	Control (n = 11)		IMT (n = 11)		Adjusted differences[a] (IC95%)	ES
	Baseline	After	Baseline	After		
Time domain						
SDNN (ms)	13.87 ± 6.25	12.76 ± 4.6	13.99 ± 5.0	18.12 ± 5.2	7.05 (−17.78, 31.88)	0.92[c]
RMSSD (ms)	17.11 ± 7.92	14.66 ± 5.86	16.04 ± 6.17	24.18 ± 5.88	2.78 (−0.76, 6.32)	1.46[c]
Total variability (ms^2)	228 ± 242	182 ± 116	218 ± 146	352 ± 212	201 (7.88, 396)[b]	0.88[c]
Frequency domain						
LF (ms^2)	66.21 ± 37.34	72.92 ± 48.45	91.82 ± 92.31	141 ± 177	20.17 (−124, 84.44)	0.59
HF (ms^2)	95.77 ± 75.11	110 ± 86.99	126 ± 77.52	211 ± 74.38	58.86 (6.72, 111)[b]	0.91[c]
LF (nu)	40.00 ± 11.75	44.23 ± 19.46	39.85 ± 17.89	32.70 ± 21.12	−2.98 (−14.29, 8.34)	−0.73
HF (nu)	58.15 ± 10.92	55.42 ± 19.56	60.15 ± 17.89	67.30 ± 21.12	4.38 (−6.89, 15.64)	0.64
LF/HF	0.76 ± 0.4	0.80 ± 0.5	0.80 ± 0.5	0.95 ± 0.7	0.17 (−0.18, 0.51)	0.23
Nonlinear domain						
SD1 (ms)	13.71 ± 7.90	12.53 ± 5.87	12.31 ± 3.84	18.10 ± 6.04	1.00 (−2.82, 4.81)	1.14[c]
SD2 (ms)	28.19 ± 14.46	26.99 ± 12.35	25.92 ± 10.01	40.96 ± 13.43	5.62 (−2.61, 13.85)	1.31[c]

Values are presented as mean ± standard deviation or adjusted mean difference (95% confidence interval). IMT: inspiratory muscle training; ES: Effect size.
[a] ANCOVA adjusted for age, weight, baseline, 6-min walk test and forced vital capacity.
[b] Significant difference ($p < 0.05$).
[c] Clinically relevant (ES > 0.80).

improvements in respiratory function. Although some studies have associated decreased inspiratory muscle strength and decreased heart rate variability (Ferreira et al., 2013; Laoutaris et al., 2008; Montemezzo et al., 2014; Rodrigues et al., 2018), no studies exist to this date demonstrating that chronic respiratory muscle training could improve autonomic modulation.

Similarly, other studies have shown that IMT improves inspiratory muscle strength, with a protocol setting ranging between 8 and 12 weeks long, not only in COPD subjects, but also in other clinical conditions such as type II diabetes (Corrêa et al., 2011), heart failure (Mello et al., 2012) and hypertension (Ferreira et al., 2013). In COPD, the IMT can promote improvements in inspiratory endurance and strength, dyspnea sensation, functional exercise capacity and, consequently, quality of life (HS et al., 2001; Weiner et al., 2000).

Weiner and colleagues in 2003, showed that 60% of PI_{max} and PE_{max} during three months promoted significant improvements both in inspiratory and expiratory muscle strength (Weiner et al., 2000). Additionally, these changes were associated with increases in the 6MWT distance. Furthermore, Riera et al. 2001, showed that IMT at 60% and 70% of PI_{max} promoted increases in walking capacity, sleep quality, but no changes in peak VO_2 were found (HS et al., 2001).

However, Berry et al. in 1996, showed that IMT at 80% of the PI_{max} during six weeks in combination with general exercise training is not more effective than exercise training alone (Berry et al., 1996). This absence of significance in the IMT and common exercise combination group can be partially explained by the fewer number of participants, the exercise protocol duration and, the fact that all subjects enrolled in his work were already familiarized with the IMT protocol previously. Also, Goldstein and colleagues in 1989, did not observe differences in pulmonary function, exercise tolerance, inspiratory muscle strength or inspiratory muscle endurance (Goldstein et al., 1989). However, his study had a small number of subjects and a short time of intervention. In addition, a recent meta-analysis showed that IMT is not capable of improving walking distance in the 6MWT (Neves et al., 2014).

It's important to notice that we used a lower workload and weekly training frequency compared to other studies, using from 60 to 80% of PI_{max} 7-times a week (de Abreu et al., 2017), and we yet achieved significant improvements in exercise tolerance and autonomic modulation, indicating that lower inspiratory pressure loads can also be beneficial to COPD subjects. In addition, higher loads can lead to low adherence, which is already low in the known IMT interventions, due to lack of perceived benefit and exacerbation of symptoms (Sørensen and Christensen, 2018).

In our study, we demonstrate that IMT improves the PI_{max}, PE_{max} and exercise capacity; hence the quality of life was not evaluated. Although other studies have demonstrated the impact of IMT on quality of life (HS et al., 2001), inspiratory muscle strength and endurance (Berry et al., 1996), improvements in sensation of dyspnea (HS et al., 2001; Weiner et al., 2000) and increases in functional exercise capacity (HS et al., 2001; Lacasse et al., 2005).

Compelling evidence suggests that subjects with COPD have increased values of heart rate at rest, higher levels of blood norepinephrine, increased sympathetic nervous activity, decrease in baroreflex sensitivity and reduced heart rate variability (HRV) (Bernardi et al., 2008). These studies reported that COPD subjects show decreased values in several indexes of heart rate variability such as NN50, pNN50, SDNN, RMSSD, RR intervals, SD1, SD2, all compared to control groups (Mohammed et al., 2015). Additionally, studies had shown that frequency domain indexes HF and LF are correlated with FEVC1 and inspiratory capacity/total lung capacity ratio, and residual volume/total lung capacity ratio (Mazzuco et al., 2015).

In our study, we demonstrated that IMT increases autonomic function in COPD subjects by increases in linear indexes SD1, SD2, vagal modulation in frequency domain by increase in HF (ms^2) and in the time domain by improving RMSSD, total power, and SDNN, indicating an increased overall variability in the subjects submitted to the IMT protocol. Among all the mechanisms responsible for the decreased HRV in COPD, the hypoxia plays an important role. In COPD subjects, is possible that autonomic dysfunction can be caused by a present intermittent hypoxia (Engström et al., 2009). Additionally, findings suggest that autonomic dysfunction is characterized by a predominance of sympathetic activity that significantly modulates inflammatory reactions (Bédard et al., 2010; Heindl et al., 2001). Also, a measure of the parasympathetic modulation, the pNN50, had a significant negative correlation with serum IL-6 levels in COPD in other studies (Chhabra and Dash, 2014).

Cardiac autonomic dysfunction encompasses various and multiple disorders and might be associated with increased incidence of cardiovascular diseases in subjects with COPD (van Gestel and Steier, 2010). Several studies have shown relevant clinical data about the role of the autonomic function as an important physiological marker for prognostic and stratification in subjects with COPD (Gunduz et al., 2009; van Gestel and Steier, 2010). Also, decreased HRV is associated with cardiovascular mortality in several conditions (Thayer et al., 2010).

Furthermore, cardiovascular diseases contribute to independent factors of greater morbidity and mortality in subjects with COPD (Curkendall et al., 2006). Studies have shown that cardiovascular diseases can be responsible for the greater number of hospitalizations, as well as 25% mortality in these subjects (Choudhury et al., 2014). Data from other studies presented that IMT can be an important therapeutic strategy to improve cardiac autonomic control in other populations, such as hypertensive subjects and, peripheral sympathetic activity in subjects with heart failure, increasing their functional capacity and overall quality of life (Sin and Paul Man, 2003). Our group have demonstrate that IMT promote increases in HRV in several conditions like heart failure (Mello et al., 2012), metabolic syndrome (Feriani et al., 2017), young smokers (Rodrigues et al., 2013) and, subjects with insulin resistance (Silva et al., 2013). These findings may be explained by the fact that IMT activates pulmonary vagal afferents, inhibiting the sympathetic activity (Goso et al., 2001; Malik, 1996). Moreover, IMT may reduce chemoreflex activity, decreasing sympathetic activity by improving oxygen supply due to augmentation of tidal volume (Bernardi et al., 2008; Rodrigues et al., 2013).

Despite the positive results, the sample size calculation was not performed, probably causing a sample underestimation. In addition, we stress the importance of the ES calculation, since it is less influenced by the sample size than the inferences centered on the p value. Despite the statistical approach used in this study, we suggest further studies with larger sample sizes, since a recent systematic review conducted included studies with sample sizes varying between six and 11 subjects per group (Neves et al., 2014).

5. Conclusion

In conclusion, our study demonstrated that IMT at 30% of PI_{max} for 12 weeks positively affected exercise capacity, PI_{max}, PE_{max} and, autonomic function in a group of GOLD II COPD subjects.

Conflicts of interest

All authors declare no conflicts of interest.

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