

Positive end-expiratory pressure attenuates hemodynamic effects induced by an overload of inspiratory muscles in patients with COPD

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Background: Inspiratory muscle training (IMT) using a Threshold[®] device is commonly used to improve the strength and endurance of inspiratory muscles. However, the effect of IMT, alone or with positive end-expiratory pressure (PEEP), on hemodynamic parameters in patients with chronic obstructive pulmonary disease (COPD) remains unknown.

Objective: To assess the effects of an overload of inspiratory muscles using IMT fixed at 30% of the maximal inspiratory pressure (MIP), and IMT associated with 5 cmH₂O of PEEP (IMT + PEEP), on the echocardiographic parameters in healthy subjects and patients with COPD.

Methods: Twenty patients with COPD (forced expiratory volume in 1 second 53.19±24.71 pred%) and 15 age-matched healthy volunteers were evaluated using spirometry, MIP, the COPD assessment test (CAT), and the modified Medical Research Council (mMRC) dyspnea scale. The E- (fast-filling phase) and A- (atrial contraction phase) waves were evaluated at the tricuspid and mitral valves during inspiration and expiration in the following sequence: at basal conditions, using IMT, and using IMT + PEEP.

Results: Patients with COPD had reduced MIPs versus the control group. Ten patients had CAT scores <10 and 12 patients had mMRC scores <2. E-wave values at the mitral valve were significantly decreased with IMT during the inspiratory phase in both groups. These effects were normalized with IMT + PEEP. During the expiratory phase, use of IMT + PEEP normalized the reduction in E-wave values in the COPD group. During inspiration at the tricuspid valve, reduction in E-wave values during IMT was normalized by IMT + PEEP in COPD group. During the expiratory phase, the value of the E-waves was significantly reduced with overload of the inspiratory muscles in both groups, and these effects were normalized with IMT + PEEP. A-waves did not change under any conditions.

Conclusion: Acute hemodynamic effects induced by overloading of the inspiratory muscles were attenuated and/or reversed by the addition of PEEP in COPD patients.

Keywords: echocardiography, mitral valve, tricuspid valve, inspiratory muscle strength, spirometry, Medical Research Council, dyspnea scale

Introduction

Patients with chronic obstructive pulmonary disease (COPD) have lung hyperinflation, which can occur due to the loss of lung elastic recoil, airflow limitations, or insufficient expiratory time to fully exhale the tidal volume. The air that is trapped creates positive end-expiratory pressure (PEEP), known as intrinsic PEEP (PEEPi) or auto-PEEP,^{1,2} which is even greater during periods when the disease is exacerbated.³ PEEPi has been described as an additional load to be overcome by the inspiratory muscles, requiring the generation of a negative pressure equal in magnitude to PEEPi in order to initiate

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inspiratory flow.^{2,4} PEEPi varies in accordance with the severity of the disease and can be directly correlated with the functional residual capacity and inversely correlated with the forced expiratory volume in the first second (FEV₁).⁵ Thus, the increased work demanded by the respiratory muscles, and their subsequent overload, in patients with COPD may induce respiratory fatigue.^{2,3,6,7} Pulmonary hyperinflation also compromises the performance of the respiratory muscles, reducing their ability to generate tension.^{8,9} This respiratory muscle dysfunction is associated with increased risk of hospitalization and premature death.¹⁰

COPD causes permanent changes in the lung parenchyma, and has hemodynamic repercussions, such as pulmonary hypertension, left ventricular dysfunction, and atherosclerosis, leading to significant morbidity and worsening of the prognosis of the disease.¹¹ The increase in intrathoracic pressure caused by PEEPi reduces both the preload of the right and left ventricles and left ventricular compliance, and can increase right ventricular afterload and pulmonary vascular resistance.^{2,12} In addition to hypertrophy, the right ventricle of patients with COPD showed a reduction of the ejection fraction, that is, a decline in the performance of the systolic pumping action of the right ventricle.¹³ Major variations in intrathoracic pressure and lung volume have acute hemodynamic effects, directly influencing venous return.^{14–16} Echocardiography, a simple, cost-effective, noninvasive assessment method,¹⁶ is able to detect cardiac abnormalities and acute hemodynamic effects.¹¹ In a recent study, Houben-Wilke et al¹⁷ evaluated 514 patients referred to pulmonary rehabilitation and demonstrated that more than half of these had echocardiographic abnormalities.

The training of respiratory muscles is an important component of pulmonary rehabilitation^{18,19} and provides significant clinical improvements, such as increased inspiratory muscle strength and endurance, tolerance to physical activity, reduced shortness of breath, and improved quality of life.²⁰ The PEEP valve has been used in pulmonary rehabilitation programs in order to increase the expiratory flow of patients with COPD, and thus reduce lung hyperinflation.^{21,22} The aim of our study was to evaluate whether the association of the PEEP valve and overload of the inspiratory muscles would promote changes in ventricular filling patterns.

Materials and methods

Study design

This observational, cross-sectional, controlled study was conducted at the clinic of the Faculty of Medical Sciences of Minas Gerais and at the Conrad – Diagnóstico por Imagem,

from March to August 2015. Individuals between the ages of 50 and 80 years were included in the study, of which 20 patients diagnosed with COPD were in the case group and 15 healthy subjects were in the control group, following clinical examination and confirmation of normal pulmonary function. The diagnosis of COPD was made in accordance with the 2015 Global Strategy for Diagnosis, Management, and Prevention of COPD (Global initiative for chronic Obstructive Lung Disease [GOLD]) guidelines.²³ Patients with COPD were classified as GOLD I–IV. The modified British Medical Research Council (mMRC) dyspnea scale and the COPD assessment test (CAT) questionnaire were used to assess the shortness of breath and quality of life, respectively. Both methods were previously validated for the Brazilian population.^{24,25} Besides the diagnosis of COPD, the inclusion criteria were clinical stability, absence of infection or exacerbation of disease in the past 4 weeks, and absence of severe heart diseases (ventricular systolic dysfunction, previous cardiac surgery, congenital cardiac malformation, arrhythmia, moderate to severe valvar heart disease, or heart failure) or other comorbidities that could affect the study protocol. The exclusion criteria were pulmonary diseases other than COPD, significant thoracic deformity, neuromuscular diseases, sequelae of neurological diseases, cardiovascular instability (recent myocardial infarction, significant arrhythmias, ventricular systolic dysfunction, previous cardiac surgery, congenital cardiac malformation, moderate to severe heart disease, or heart failure), recent thoracic or abdominal surgeries, diabetes mellitus, chronic kidney disease, and a history of liver failure. Moreover, patients with cognitive impairment that prevented them from performing the tests, women with breast implants, and those with a body mass index (BMI) >35 kg/m² were also excluded from the study.

The Research Ethics Committee of the Faculty of Medical Sciences of Minas Gerais (CEPCM-MG) approved the study (reference number 758.360). All patients provided written informed consent.

Selection of participants

Participants were selected on the basis of the medical records of the Clinical Medicine and Pneumology departments of the Faculty of Medical Sciences of Minas Gerais (Figure 1). Out of the 71 medical records from the Clinical Medicine Department analyzed, only 15 subjects met the inclusion criteria and they were allocated to the control group. For the experimental group, 340 medical records from the Pneumology Department were analyzed, including 116 patients diagnosed with COPD. Eighty-four patients were excluded owing to severity of the disease,

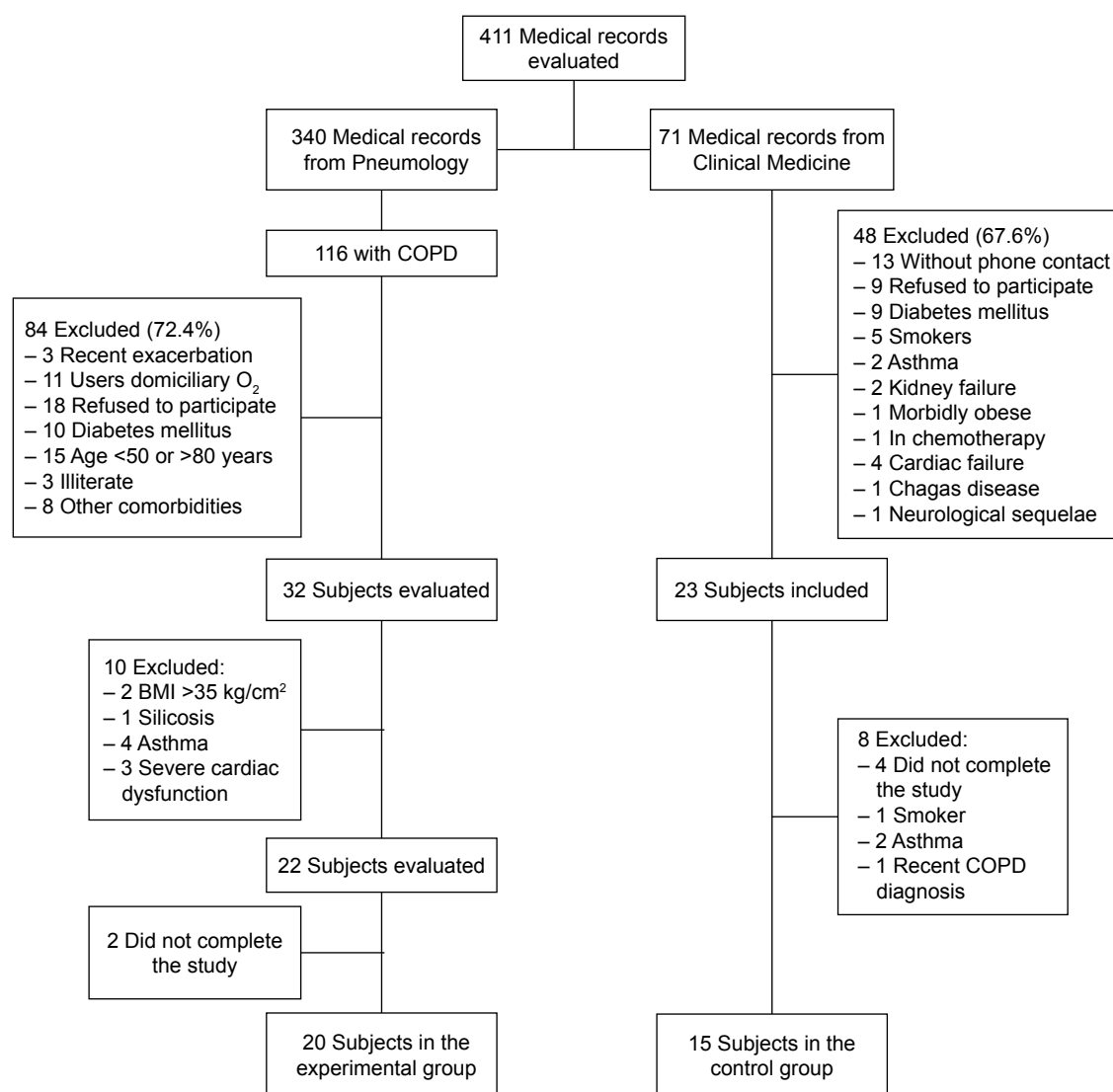


Figure 1 Selection of participants for the control and COPD groups.

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease.

illiteracy, and/or other associated comorbidities. Thirty-two patients were evaluated and 10 were excluded from the study for the following reasons: five with other pulmonary diseases, two morbidly obese, and three with heart disease. Twenty-two patients fulfilled all the inclusion criteria of the study, and only two among them did not complete the study. Therefore, the experimental group consisted of 20 participants with COPD.

Experimental protocol

At the first session, all participants underwent a pulmonary function test, and patients with COPD also underwent a bronchodilator test. After 15 minutes of rest, the maximal inspiratory pressure (MIP) was measured. Then, the participants were familiarized with the Threshold[®] inspiratory muscle training (IMT) set at 30% MIP, both with and without

PEEP, in order to become acquainted with the instrument and the procedure that would be used during echocardiography. In addition, the participants in the experimental group answered two questionnaires: CAT to evaluate the impact of the disease on their daily life, and mMRC to assess the level of dyspnea. At the second session, the echocardiographic examination was performed over three different procedures: basal respiration without inspiratory overload and without the PEEP valve (sham device), respiration with inspiratory overload of 30% MIP, and respiration with overload associated with the PEEP valve (IMT + PEEP), in that order.

Pulmonary function test

The pulmonary function test was performed in both the control and experimental groups, according to the guidelines

of the American Thoracic Society/European Respiratory Society,²⁶ using the Spirolab[®] spirometer (Medical International Research, Rome, Italy). The bronchodilator test was performed only in the experimental group. Medication was discontinued 8–12 hours before spirometry was performed. The same examiner performed all pulmonary function tests. The equations proposed by Pereira et al²⁷ were used to calculate the predicted values.

Assessment of strength of the inspiratory muscles

MIP was evaluated in both groups from the residual volume using a MVD300 digital manometer (Globalmed[®], Porto Alegre – RS, Brazil). The participants were evaluated in a sitting position at 90°, with their feet on the floor. At least five measurements were performed for each participant, with an interval of 1 minute rest between each maneuver. The MIP value used was the highest from the five maneuvers, providing that the difference between the two highest measurements did not exceed 5%. The equations proposed by Pereira²⁸ were used to calculate the predicted values.

Following the evaluation of MIP, participants were familiarized with the Threshold[®] IMT (Respironics HealthScan, Inc, Parsippany, NJ, USA) using 30% of the aforementioned MIP, with or without 5 cmH₂O PEEP, in a randomized order, with 5 minutes between measurements (Figure 2).

Dyspnea assessment and CAT

The CAT questionnaire was used to evaluate symptoms in subjects with COPD.^{25,29} It is composed of eight items: cough, sputum production, chest tightness, shortness of breath, limitations in household activities, confidence in leaving the house, sleep, and energy.

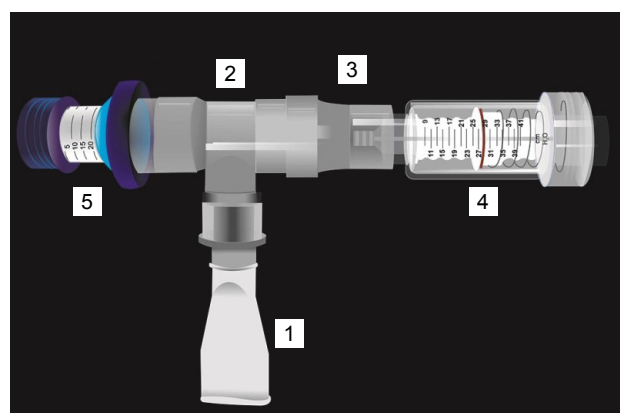


Figure 2 Threshold[®] IMT device, associated with the PEEP valve used in the study.
Notes: 1: Mouthpiece; 2: T-piece adapter; 3: unidirectional valve; 4: Threshold[®] IMT, set at 30% of MIP; 5: PEEP valve, set at 5 cmH₂O.

Abbreviations: IMT, inspiratory muscle training; MIP, maximum inspiratory pressure; PEEP, positive end-expiratory pressure.

The mMRC dyspnea scale was used to evaluate how dyspnea affects the activities of daily living in patients. This scale consists of five items corresponding to the level of dyspnea that limits their activities in daily life.^{24,30}

Echocardiography

The Doppler echocardiographic study included three methods: M-mode, two-dimensional, and Doppler (pulsed, continuous, and color flow mapping). Acuson Cypress Siemens 5.0 echocardiographic equipment (Siemens Medical Solutions, Malvern, PA, USA) with waves ranging from 2.0 to 4.0 MHz, was used to perform the tests. Echocardiographic measurements in the M-mode and color flow mapping were obtained according to the criteria established by the American Society of Echocardiography and the European Association of Cardiovascular Imaging.³¹ An expert sonographer evaluated the studies, and all images were recorded and analyzed later.

This was a double-blind examination, since neither the echocardiographer nor the participants were aware of the procedures. During the tests, patients were positioned in the supine and left semi-lateral position and instructed to breathe normally. The E- (fast-filling phase) and A-waves (atrial contraction phase) were evaluated at the tricuspid and mitral valves at three different times in the following sequence: during basal respiration (sham device), during inspiratory overload at 30% of MIP, and during inspiratory overload in combination with the PEEP valve with 5 cmH₂O (IMT + PEEP).

Statistical analysis

The sample size was obtained to test the difference between the two means of overload of the inspiratory muscles, with or without the PEEP valve, in healthy volunteers and patients with COPD. We used a significance level of 5%, a power of 90%, and assumed that the variance of the measures of overload of the inspiratory muscles in patients with COPD was two times higher than that of healthy volunteers. Therefore, we obtained the values of 15 healthy subjects and 20 patients with COPD.³²

The variables are presented as mean \pm standard deviation. The Kolmogorov–Smirnov test was used to assess normality of the data. The paired *t*-test was used to compare the intragroup data of baseline breathing, with overload of the inspiratory muscles and overload of the inspiratory muscles associated with the PEEP valve. The unpaired *t*-test was used to compare the intergroup data. Data analysis was performed using GraphPad Prism version 5.0 (GraphPad Software Inc, La Jolla, CA, USA). The significance level was set at $p < 0.05$.

Results

Table 1 shows the patients' anthropometric data, pulmonary function, CAT, and mMRC scores, and inspiratory muscle strength. There was no significant difference regarding the sex, age, and height of the subjects included in the study. The values for weight and BMI were significantly lower in the COPD group. Similar results were found for the pulmonary function test, with significantly lower forced vital capacity, FEV₁, and Tiffeneau index in participants with COPD. Regarding the severity of COPD, 70% of the participants were classified as GOLD II or III, 50% had CAT score <10, and 60% had mMRC score <2. The MIP values found in the COPD group were significantly lower than those of the control group.

Table 2 shows the hemodynamic parameters for the mitral valve in both groups during the inspiratory and expiratory phases, at baseline conditions, and with overload of the inspiratory muscles, associated with or without the PEEP valve. The value of the E-waves decreased significantly

during the inspiratory phase with the overload of the inspiratory muscles in both groups. These effects were normalized with the addition of the PEEP valve.

Regarding mitral valve flow, during the expiratory phase, the value of the E-waves was significantly reduced with overload of the inspiratory muscles in the COPD group, and the addition of the PEEP valve normalized those measures. In the control group, during the expiratory phase, there was no difference in E-wave values between basal respiration and IMT; however, an increase in E-wave values with IMT + PEEP was observed as compared to IMT alone.

Table 3 shows the same hemodynamic parameters for the tricuspid valve during inspiration and expiration for both groups at baseline conditions, IMT, and IMT + PEEP. In the inspiratory phase, values of the E-waves decreased significantly with the overload of the inspiratory muscles in both groups. These effects were normalized with the addition of the PEEP valve only in COPD group. Regarding tricuspid valve flow, during the expiratory phase, it was observed that the values for the E-waves were significantly reduced with the overload of the inspiratory muscles in both groups. The addition of the PEEP valve normalized these measures.

The intergroup evaluation is depicted in Figure 3. A significant reduction in the E-wave values was observed in the COPD group compared to the control group only at the mitral valve during basal respiration, IMT, and IMT + PEEP procedures, both for inspiration and expiration. At the tricuspid valve, E-wave values were similar in both groups. A-wave values were similar between groups in all situations.

The heart rate (HR) increased significantly in both groups during IMT and IMT + PEEP, during both the inspiratory and expiratory phases. PEEP was found to attenuate the increase in HR imposed by IMT (Table 4).

In the inspiratory phase, HR was significantly higher in the COPD group during IMT compared to the control group. In the expiratory phase, there was a significant increase in HR in the COPD group compared to the control for all three procedures (Figure 4).

When we compared the values of E-waves at the mitral valve during inspiration and expiration, we observed that these were lower in both groups during expiration for basal respiration, IMT, and IMT + PEEP. The A-waves were lower only during basal expiration of the control group compared to inspiration. There was no significant difference in A-wave values between the inspiratory and expiratory phases in the COPD group (Figure 5). With the exception of A-wave during IMT + PEEP in the control group, at the tricuspid valve, both E- and A-wave values were significantly lower during

Table 1 Anthropometric data, pulmonary function, CAT, and mMRC scores, and respiratory muscle strength

Parameter	Control (n=15)	COPD (n=20)	p-value
	Mean ± SD	Mean ± SD	
Age (years)	59.33±6.11	64.45±7.48	0.054
Sex (F/M)	9/6	9/11	1.54
Weight (kg)	74.87±12.18	61.27±15.84	0.031
Height (cm)	161.7±9.23	157.3±7.55	0.28
BMI (kg/cm ²)	28.58±3.55	24.52±5.027	0.031
FVC (L)	3.18±0.67	2.20±0.91	0.001
FVC (% of predicted)	96.56±15.35	73.54±29.91	0.01
FEV ₁ (L)	2.603±0.59	1.25±0.66	<0.001
FEV ₁ (% of predicted)	106.7±18.99	53.19±24.71	<0.001
FEV ₁ /FVC (%)	0.81±0.44	0.55±0.12	<0.001
GOLD, n (%)			
I	–	3 (15)	–
II	–	7 (35)	–
III	–	7 (35)	–
IV	–	3 (15)	–
CAT, n (%)			
<10	–	10 (50)	–
≥10	–	10 (50)	–
mMRC, n (%)			
<2	–	12 (60)	–
≥2	–	8 (40)	–
MIP (cmH ₂ O)	93.4±29.34	71.2±20.91	0.02
MIP (% of predicted)	114.1±34.04	80.05±23.85	0.001

Note: Bold represents statistically significant values.

Abbreviations: BMI, body mass index; CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; F, female; FEV₁, forced expiratory volume in 1 second; FEV₁/FVC, Tiffeneau index; FVC, forced vital capacity; GOLD, Global initiative for Chronic Obstructive Lung Disease; M, male; MIP, maximum inspiratory pressure; mMRC, modified Medical Research Council; SD, standard deviation.

Table 2 Echocardiographic parameters evaluated at the mitral valve at baseline conditions, with an overload of the IMT and an overload + PEEP (IMT + PEEP)

Variable	Group	Baseline, cm/s	IMT, cm/s	IMT + PEEP, cm/s	p-value baseline × IMT	p-value baseline × IMT + PEEP	p-value IMT × IMT + PEEP
Inspiratory phase							
E	Control	85.7±12.5	78.5±9.0	86.2±10.1	0.0216*	0.8426	0.0168#
	COPD	73.9±15.3	64.5±12.0	70.5±13.4	0.0043*	0.1512	0.0038#
A	Control	82.6±13.2	80.3±15.2	80.1±7.9	0.2168	0.4963	0.9444
	COPD	76.5±18.1	72.6±13.8	76.1±12.8	0.2581	0.9064	0.1262
Expiratory phase							
E	Control	78.3±10.4	75.0±10.9	81.9±12.3	0.1976	0.1753	0.0087#
	COPD	64.3±13.0	57.6±11.2	63.8±12.5	0.0043*	0.7109	0.0019#
A	Control	78.1±13.5	79.1±16.6	78.7±9.4	0.5925	0.8305	0.9274
	COPD	75.9±18.6	73.0±16.3	75.5±15.0	0.3588	0.8985	0.1418

Notes: Data are expressed as mean ± SD. E: fast-filling phase; A: atrial contraction phase. *IMT compared to basal respiration; #IMT compared to IMT + PEEP.

Abbreviations: COPD, chronic obstructive pulmonary disease; IMT, inspiratory muscles training; PEEP, positive end-expiratory pressure; SD, standard deviation.

expiration compared to inspiration in both groups and for all three procedures (Figure 6).

Discussion

This study indicates, for the first time, that combination of the PEEP valve with the Threshold IMT® device, with an overload of 30% of MIP, normalizes the mitral and tricuspid filling velocities as evaluated during the inspiratory and expiratory phases in patients with COPD.

COPD is one of the major causes of morbidity and mortality worldwide, and has very heterogeneous clinical outcomes according to the severity and progression of the disease.³³ Lee et al evaluated 428 patients with COPD and observed discrepancies between mMRC and CAT criteria in identifying patients with multiple symptoms.³⁴ They concluded that a CAT score ≥15 is a better indicator for the “multiple

symptoms group” in the management of patients with COPD. According to the results of the present study, 53% of patients with COPD had a CAT score ≥15.

Similar to other results from the literature,⁸ patients with COPD in the present study showed a 23% reduction in MIP compared to the control group, showing a reduction in inspiratory muscle strength in patients with COPD. A systematic review by Geddes et al³⁵ suggests that respiratory muscle training significantly increases the strength and endurance of the inspiratory muscles, improves tolerance to physical activity, and reduces dyspnea in patients with COPD. The optimal intensity for IMT is not known, and different studies suggest the use of an overload of 15%–80% of MIP.³⁶ In this study, we used an inspiratory overload of 30% of MIP, which was the recommended initial resistance in a previous study.³⁶ The device used in this study was the

Table 3 Echocardiographic parameters evaluated at the tricuspid valve at baseline conditions, with an overload of the IMT and an overload + PEEP (IMT + PEEP)

Variable	Group	Baseline, cm/s	IMT, cm/s	IMT + PEEP, cm/s	p-value baseline × IMT	p-value baseline × IMT + PEEP	p-value IMT × IMT + PEEP
Inspiratory phase							
E	Control	60.1±6.0	56.2±7.0	60.1±7.3	0.040*	0.9779	0.1742
	COPD	60.6±7.1	54.0±7.3	62.1±8.5	<0.0001*	0.4829	<0.0001#
A	Control	54.5±5.4	53.7±7.0	52.5±6.7	0.5908	0.2527	0.5090
	COPD	50.1±6.6	50.3±8.6	51.9±9.4	0.9332	0.1522	0.4288
Expiratory phase							
E	Control	55.5±6.4	48.9±4.4	55.6±7.6	0.0006*	0.9773	0.0130#
	COPD	52.8±6.5	48.1±7.5	54.8±8.1	0.0004*	0.3091	0.0006#
A	Control	50.9±5.6	49.5±8.1	51.5±6.5	0.3875	0.6511	0.2632
	COPD	46.1±6.8	46.9±8.4	48.6±7.1	0.6038	0.0449^	0.2587

Notes: Data are expressed as mean ± SD. E: fast-filling phase; A: atrial contraction phase. *IMT compared to basal respiration, ^IMT + PEEP compared to basal respiration, #IMT compared to IMT + PEEP.

Abbreviations: COPD, chronic obstructive pulmonary disease; IMT, inspiratory muscles training; PEEP, positive end-expiratory pressure; COPD, chronic obstructive pulmonary disease; SD, standard deviation.

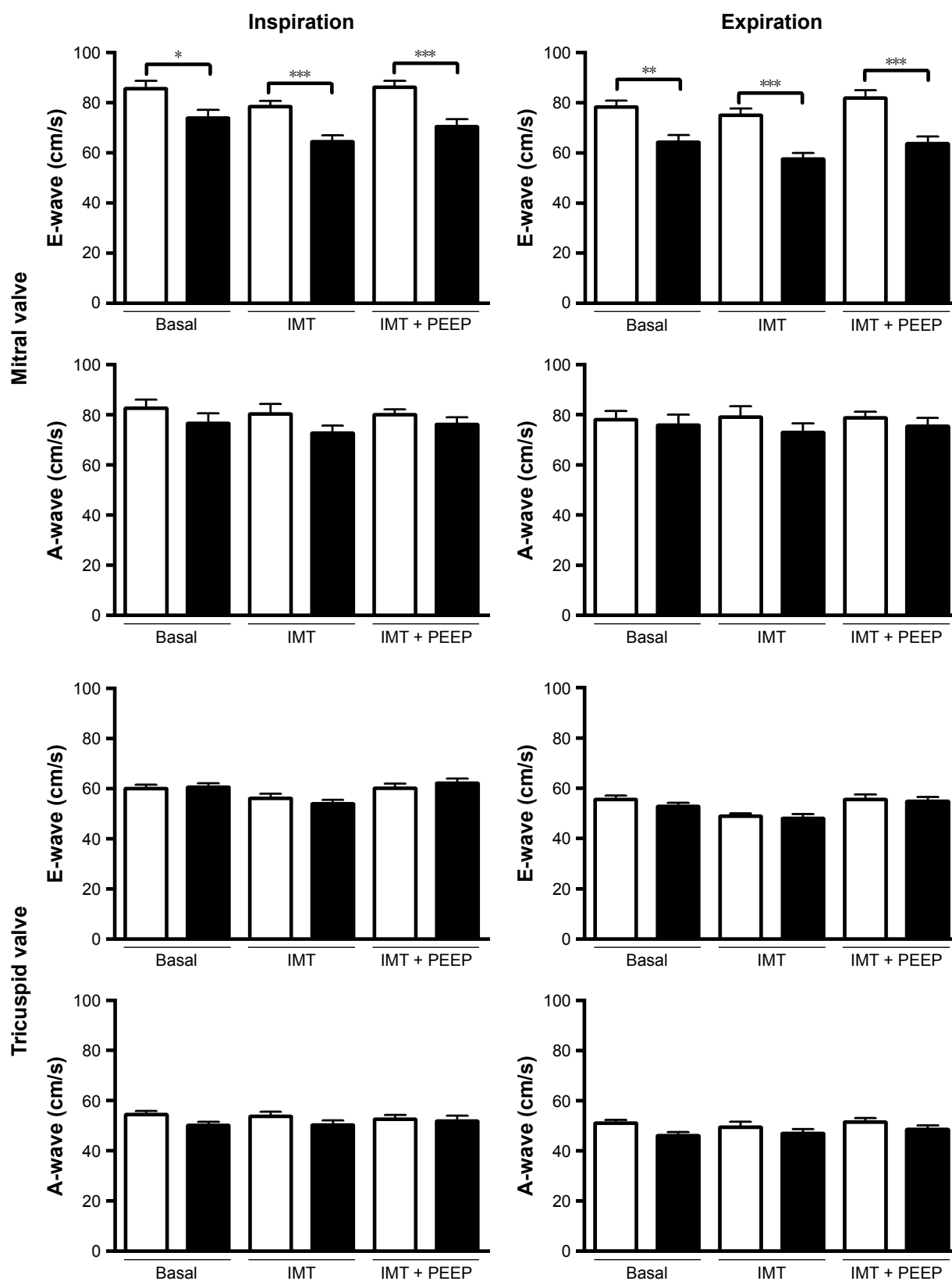


Figure 3 Echocardiographic parameters of the control (white bars) and COPD (black bars) groups during basal respiration with IMT overload and inspiratory overload associated with the PEEP valve (IMT + PEEP).

Notes: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Abbreviations: COPD, chronic obstructive pulmonary disease; IMT, inspiratory muscle training; PEEP, positive end-expiratory pressure.

Table 4 Changes in participants' heart rate during the inspiratory and expiratory phases in the experimental and control groups during basal respiration, with an overload of the IMT, and an overload of the inspiratory muscles associated with the PEEP valve (IMT + PEEP)

Group	Basal, bpm	IMT, bpm	IMT + PEEP, bpm	p-value basal × IMT	p-value basal × IMT + PEEP	p-value IMT × IMT + PEEP
Inspiratory phase						
Control	66±2	69±2	68±2	<0.0001*	0.0046^	0.0002#
COPD	68±3	73±5	70±5	<0.0001*	0.0005^	0.0009#
Expiratory phase						
Control	69±3	73±3	71±3	<0.0001*	0.0013^	<0.0001#
COPD	77±6	81±6	79±6	<0.0001*	0.0049^	0.0006#

Notes: Data are expressed as mean ± SD. *IMT compared to basal respiration, ^IMT + PEEP compared to basal respiration, #IMT compared to IMT + PEEP.

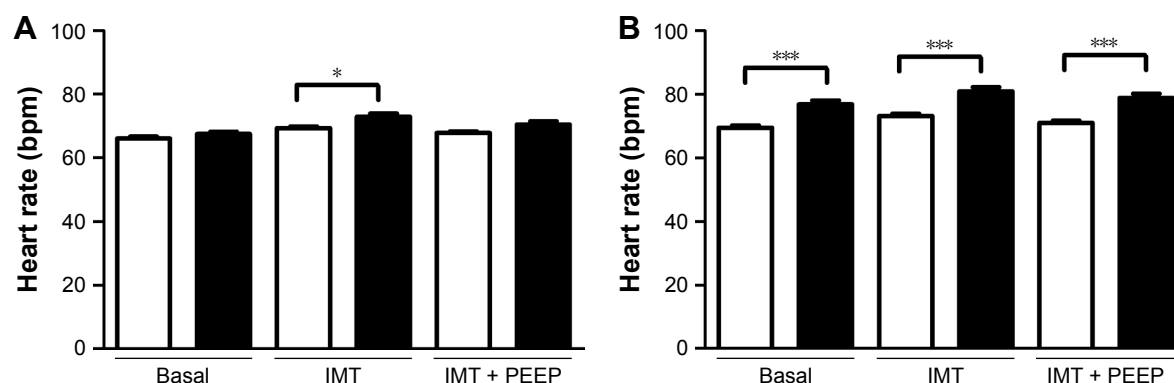
Abbreviations: COPD, chronic obstructive pulmonary disease; IMT, inspiratory muscles training; PEEP, positive end-expiratory pressure; SD, standard deviation.

Threshold IMT®, widely recommended for strengthening of the inspiratory muscles.^{20,35,37}

Chronic pulmonary diseases can alter left and right ventricular function owing to pulmonary hyperinflation, increased pulmonary vascular resistance, and increased negative intrathoracic pressure generation.³⁸ In the present study, we postulated that overloading of the inspiratory muscles would promote changes in the ventricular filling patterns due to increased intrapleural negativity, and that the PEEP valve could modulate this effect. In patients with COPD, the main effect of the PEEP valve is an increase in expiratory flow and reduction in pulmonary hyperinflation.^{21,22} The external PEEP extends the expiratory time and reduces respiratory frequency, reducing airway collapse and therefore dynamic hyperinflation.²¹ The reduction of PEEPi reduces the inspiratory threshold and consequently reduces the workload of inspiratory muscles.

The echocardiographic parameters evaluated were the E- and A-waves, which respectively correspond to the rapid ventricular filling phase and atrial contraction. In the present study, we observed a significant reduction in mitral inflow during IMT, as measured via the E-waves, in both groups.

Our data are in accordance with Cheyne et al who reported that an increase of −20 cmH₂O in intrapleural pressure resulted in a reduction of left ventricle systolic volume at the expense of a reduction of left ventricular diastolic volume, probably due to interventricular interaction.³⁸ The increased negative intrathoracic pressure imposed by the overload of inspiratory muscles increases the left ventricular afterload, since it increases left ventricle transmural pressure, thus, reducing the cardiac output.³⁹ Yuan et al¹⁵ also reported that the pressure on the right side of the heart is greater than that on the left during inspiration with overload, which moves the interventricular septum to the left and thus impairs left ventricular filling. The addition of the PEEP valve normalized these measurements, probably by attenuating the increase in negativity of pleural pressure imposed by inspiratory muscle overload and simultaneously by reducing afterload of the left ventricle. Similar results were observed for the tricuspid valve in patients with COPD. IMT reduced the E-waves in patients with COPD during both the inspiratory and expiratory phase. Association of the PEEP valve with overload of the inspiratory muscles also normalized the E-wave values.

**Figure 4** HR in the control (white bars) and COPD groups (black bars) during basal respiration, overload of IMT, and overload of inspiratory muscle associated with the PEEP valve (IMT + PEEP), in the inspiratory (A) and expiratory (B) phases.

Notes: * $p < 0.05$; *** $p < 0.001$.

Abbreviations: COPD, chronic obstructive pulmonary disease; IMT, inspiratory muscle training; PEEP, positive end-expiratory pressure; HR, heart rate.

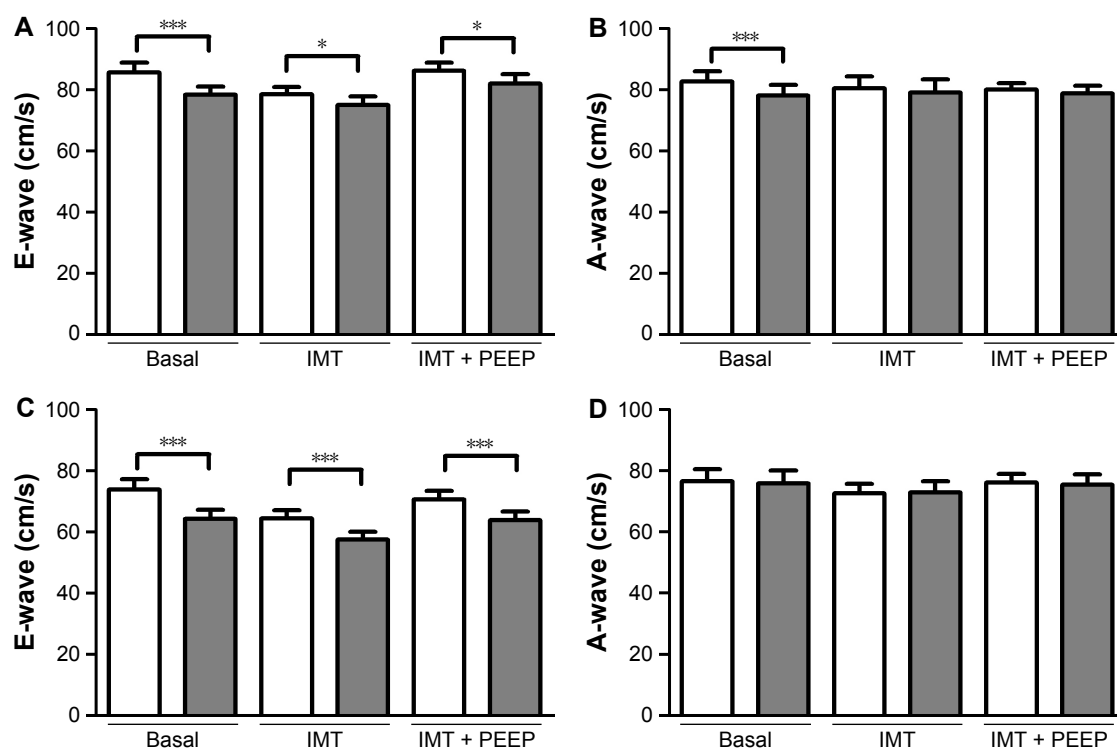


Figure 5 Analysis of E- and A-waves during inspiratory phase (white bars) and expiratory phase (gray bars) at the mitral valve in the control group (**A** and **B**) and COPD group (**C** and **D**) during basal respiration, overload of IMT, and overload of inspiratory muscles associated with the PEEP valve (IMT + PEEP).

Notes: * $p < 0.05$; *** $p < 0.001$.

Abbreviations: COPD, chronic obstructive pulmonary disease; IMT, inspiratory muscle training; PEEP, positive end-expiratory pressure.

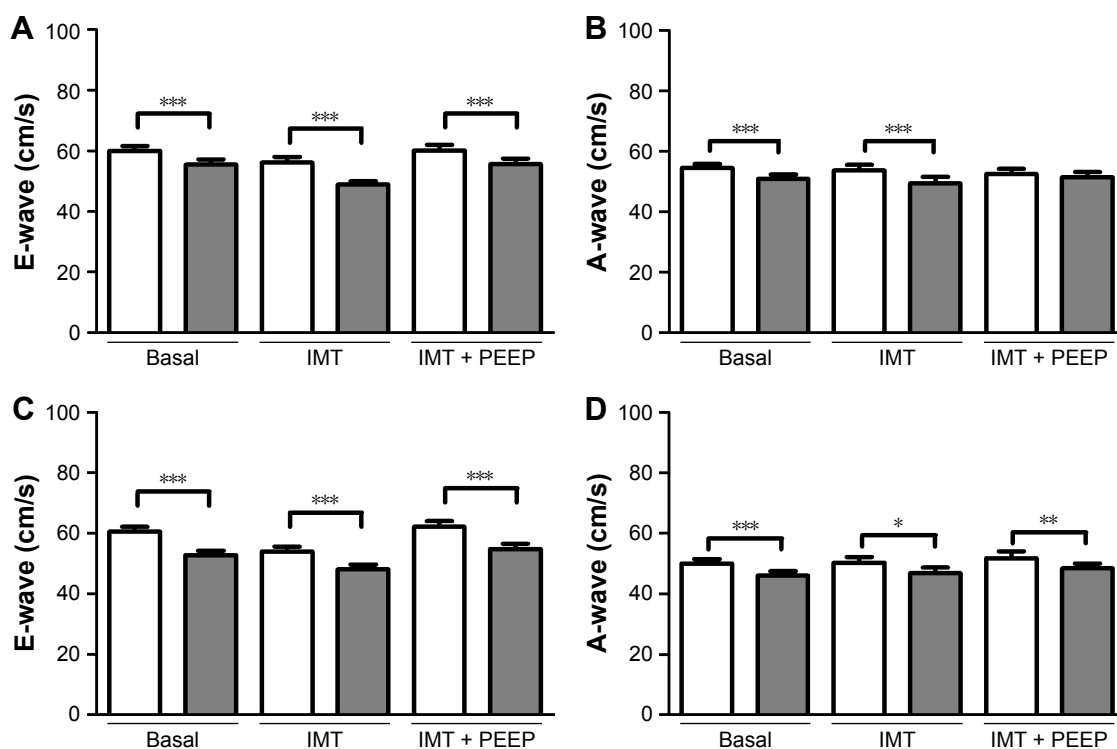


Figure 6 Analysis of E- and A-waves during inspiratory phase (white bars) and expiratory phase (gray bars) at the tricuspid valve in the control group (**A** and **B**) and COPD group (**C** and **D**) during basal respiration, overload of IMT, and overload of inspiratory muscles associated with the PEEP valve (IMT + PEEP).

Notes: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Abbreviations: COPD, chronic obstructive pulmonary disease; IMT, inspiratory muscle training; PEEP, positive end-expiratory pressure.

Comparing the two groups, we observed that the COPD group had lower E-wave values in both inspiration and expiration during the three procedures, but only at the mitral valve. Hyperinflation is related to an impaired left ventricular diastolic filling pattern, and this dysfunction seems to be related to a reduced preload.⁴⁰ Another possible reason for the reduction in E-waves in patients with COPD is increased afterload of the right ventricle induced by pulmonary hyperinflation and PEEPi, reducing right ventricular stroke volume and inducing left ventricular hypo-filling.⁴¹ Increased negative intrapleural pressure also increases left ventricular afterload by increasing aortic transmural pressure. We also observed that the HR of the COPD group, in the inspiratory phase, was significantly higher during IMT compared to the control group. In contrast, in the expiratory phase, HR in the COPD group was higher than that in the control group during basal respiration, IMT, and IMT + PEEP. This increase in HR can be attributed to the autonomic dysfunction of HR in this population. Patients with COPD have impaired sympathetic–vagal balance, and changes in the autonomic control of HR are associated with loss of strength in the inspiratory muscles.^{42,43}

In the present study, there were no changes in the atrial contraction phase (A-wave) in the control group during basal respiration, IMT, and IMT + PEEP, in both the inspiratory and expiratory phases of mitral and tricuspid valve flow. Similar results were observed in patients with COPD. With the exception of the IMT + PEEP treatment that significantly increased the A-wave in relation to basal respiration, as evaluated at the tricuspid valve during the expiratory phase, the other parameters did not change. These results suggest that overload of the respiratory muscles did not affect the late filling of the right and left ventricles.

According to Verhoeff and Mitchell,⁴⁴ under normal conditions, the right ventricle receives slightly more volume during inspiration due to the decreased thoracic pressure. In the current study, we demonstrate that the E-wave values were significantly lower during expiration at the tricuspid and mitral valves in both groups and for all three procedures. Our findings are consistent with those of Verhoeff and Mitchell in showing that the passive phase of fast filling is decreased during the expiratory phase in both the control and COPD groups during both normal conditions and when inspiratory load is added, with and without PEEP. These results suggest that the attenuated negative intrathoracic pressure in the expiratory phase, compared to the inspiratory phase, affected the E-wave in the mitral and tricuspid valves similarly in both the control and COPD groups. In contrast, in the mitral

valve of the control group, the A-wave was lower only during basal expiration when compared to inspiration. In the tricuspid valve, the A-wave was lower during the expiratory phase under baseline conditions and with added inspiratory load. These results suggest that the attenuated negative intrathoracic pressure in the expiratory phase, compared to the inspiratory phase, has a greater impact on patients with COPD, especially at the tricuspid valve.

The present study has a number of strengths. This was a controlled study and the sample size was sufficient to detect hemodynamic changes induced by overloading of the inspiratory muscles associated or not with external PEEP. In addition, the mitral and tricuspid inflows were evaluated during both inspiratory and expiratory phases using echocardiography, which can help in the accurate estimation of cardiac hemodynamics. However, the study also has some limitations that should be considered. We did not measure static hyperinflation (inspiratory capacity/total lung capacity) that shows associations with cardiac chamber size, impaired left ventricular diastolic filling pattern, and myocardial performance.⁴⁰ PEEP was set at 5 cmH₂O for all patients instead of being dictated by individual PEEPi. PEEPi is routinely evaluated under static conditions by occluding the airway at end-expiration. However, this measurement is difficult during spontaneous breathing due to expiratory muscle activity and increased respiratory frequency. In this case, PEEPi can be measured by the difference between the maximum airway opening and maximum esophageal pressure, obtained with a Muller maneuver from the end-expiratory volume.⁴⁵ However, the need for placement of an esophageal balloon makes PEEPi difficult to measure in clinical practice. MIP was measured in the sitting position to determine overload of the inspiratory muscles, but during echocardiography the participants were in the left semi-lateral position. Studies show that body position influences inspiratory muscle strength in both young healthy subjects⁴⁶ and patients with COPD.⁴⁷ Thus, the 30% loading of the MIP used during the echocardiographic examination may have been overestimated relative to that which would be assessed in the sitting position. Subjects positioned in left lateral recumbency would be at a respiratory disadvantage because of decreased compliance of the thoracic cage. Another limitation is the overload of the inspiratory muscles established using 30% of MIP. Literature suggests the use of an overload of 15%–80% of MIP. Future combinations of additional loads, along with additional PEEP levels, will help us make more definitive conclusions.

In conclusion, we demonstrated that the acute hemodynamic effects induced by overload of the inspiratory muscles were attenuated and/or reversed by the inclusion of an external PEEP valve. The reduction of E-wave, used to measure preload of the ventricles, can affect systemic oxygen delivery (DO_2), which is calculated as a product of cardiac output, and arterial oxygen content (CaO_2). Cardiac output is calculated as the product of HR and systolic volume, which depends on preload, afterload, and myocardial contractility. The results of the current study might indicate that E-wave reduction affects DO_2 , by adding inspiratory load, and can be normalized by adding PEEP.

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Disclosure

The authors report no conflicts of interest in this work.

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