Effects of Expiratory Positive Airway Pressure on Exercise Tolerance, Dynamic Hyperinflation, and Dyspnea in COPD

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INTRODUCTION: The application of expiratory positive airway pressure (EPAP) in patients with COPD during exercise may reduce dynamic hyperinflation, while, on the other hand, it can increase the resistive work of breathing. Therefore, we evaluated the effects of 2 intensities of EPAP during exercise on tolerance, dynamic hyperinflation, and dyspnea in subjects with moderate to very severe COPD. METHODS: We performed a cross-sectional, experimental, 4-visit study. In visit 1, subjects performed symptom-limited cycling incremental cardiopulmonary exercise test (CPET). In visits 2–4, at least 48 h apart, in a randomized order, subjects performed constant CPET without EPAP, EPAP with 5 cm H_2O (EPAP5), or EPAP with 10 cm H_2O (EPAP10). RESULTS: The study included 15 non-hypoxemic subjects ranging from moderate to very severe COPD (mean FEV_1 = 35 ± 11% predicted). Increasing intensities of EPAP during constant CPET tended to cause progressive reduction in exercise tolerance (P = .11). Of note, 10 of 15 subjects demonstrated significantly shorter average exercise duration with EPAP10 compared to the test without EPAP (−151 ± 105 s, P = .03 or −41 ± 26%). Minute ventilation increment was constrained by EPAP, secondary to a limited increase in tidal volume (P = .01). Finally, dyspnea sensation and serial measurements of inspiratory capacity during exercise were similar when comparing the three interventions at isotime and at end-constant CPETs. CONCLUSIONS: The application of EPAP5 or EPAP10 during exercise tended to cause a progressive reduction in exercise tolerance in subjects with COPD without improvement in dyspnea or dynamic hyperinflation at equivalent exercise duration. *Key words: chronic obstructive pulmonary disease; exercise; positive-pressure respiration; inspiratory capacity; dyspnea; respiratory therapy.* [Respir Care 2017;62(10):1298–1306. © 2017 Daedalus Enterprises]

Introduction

Dyspnea and exercise intolerance are among the most common symptoms experienced by patients with COPD, leading to poor quality of life.[1,2] A growing body of evidence suggests that lung hyperinflation is a key factor related to dyspnea and exercise limitation in these patients,[3] and is an important independent risk factor for mortality.[4]

Lung hyperinflation develops as a consequence of increased lung compliance (ie, reduced lung elastance), the

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effects of expiratory flow limitation, or a combination of both.[3] Dynamic hyperinflation during exercise can be defined as the temporary and variable increase of end-expiratory lung volume above the resting value,[5] which may cause functional respiratory muscle weakness, increased work of breathing and impaired cardiocirculatory function, collectively impairing performance.[6,7,8] For these reasons, there is increasing interest in lung-deflating interventions aimed at improving symptoms and physical functioning in this population.

In COPD, dynamic hyperinflation can be reduced during exercise by interventions that either increase expiratory flow (bronchodilators or a mixture of helium and oxygen), increase the time available for expiration (supplemental oxygen or exercise rehabilitation), or both (lung volume reduction surgery).[3,9] In this context, the application of pressure during expiration has long been believed to increase intraluminal airways pressure and shift the equal pressure toward central airways,[10] which potentially can explain the improvement in lung mechanics and hyperinflation by pursed lip breathing.[11,12] However, the clinical benefit of an external expiratory positive airway pressure (EPAP) device during exercise in patients with COPD remains to be determined.[13] It has been effective in reducing dynamic hyperinflation[14,15,16] and post-exercise dyspnea,[17] as well as improving exercise capacity.[14,18,19] On the other hand, EPAP can increase the work of breathing[20] and decrease venous return,[21] which could partially explain the deleterious effect on exercise endurance recently described.[16,22]

Cardiopulmonary exercise testing (CPET) has proven useful in establishing the link between exercise performance and mechanisms of limitation as well as in determining which interventions can improve this relationship. Changes in end-expiratory lung volume during exercise can be reliably estimated from repeated inspiratory capacity measurements.[23,24] The majority of previous studies evaluating the effects of EPAP on clinical outcomes used self-paced tests, inspiratory capacity measurements before and after exercise, and one intensity of EPAP.[14–18] A recent study[19] evaluating 2 levels of EPAP (1 cm H_2O and 10 cm H_2O) on self-paced exercise performance showed that both intensities similarly improved average 6-min walk distance statistically but not clinically.[25] Constant CPET is currently recognized as more responsive than incremental CPET and the 6-min walk test for demonstrating the benefits of a given intervention.[26] To confirm the potential benefits for subjects with moderate to very severe COPD of this intervention during constant CPET on physiologic (inspiratory capacity) and clinical outcomes (dyspnea and exercise tolerance), we investigated the dose response to 2 different intensities of EPAP using an externally paced, high-intensity, constant work-rate (endurance) test.

QUICK LOOK

Current knowledge

Lung hyperinflation is a key mechanism related to dyspnea and exercise limitation in patients with COPD. The application of expiratory positive airway pressure (EPAP) during exercise in these patients seems to reduce dynamic hyperinflation with controversial results on exercise tolerance and dyspnea.

What this paper contributes to our knowledge

Using a high-intensity constant load test with serial measurements of inspiratory capacity during exercise, 2 intensities of expiratory positive airway pressure (5 and 10 cm H_2O) caused a tendency to decrease exercise tolerance without significant benefits on dyspnea and lung hyperinflation. The majority of subjects (67%) showed a reduction in exercise tolerance ($> 5\%$) with expiratory positive airway pressure 10 cm H_2O. Expiratory positive airway pressure induced ventilatory and hemodynamic constraints seem to explain these findings.

Methods

Subjects

Subjects with a clinical and functional COPD diagnosis according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD)[27] criteria, without any modification in their COPD treatment in the last 6 months, were consecutively recruited from our COPD out-patient tertiary care clinic. Subjects were excluded if they had an acute cardiac or pulmonary disorder during the study period or within the 8 weeks prior to study entry, absence of dynamic hyperinflation during incremental CPET, any other pulmonary, cardiac, orthopedic, or neurological disease that limited exercise tolerance, or if they were unable to comply with the study procedures.

Study Design

The Institutional Ethics Committee approved all aspects of this cross-sectional, experimental, 4-visit, proof-of-concept study (No. 1.094.384). Clinical and resting pulmonary function variables (spirometry, static lung volumes by whole-body plethysmography and diffusing capacity of the lung for carbon monoxide) were performed within, at most, 6 months before the first visit and obtained from medical records. During visit 1, subjects performed symptom-limited cycling incremental CPET. During visits 2–4, at least 48 h apart, they were randomized to perform con-

Fig. 1. Experimental device applied to obtain different EPAP intensities during exercise. A: Without EPAP, B: EPAP 5 cm H_2O, and C: EPAP 10 cm H_2O. EPAP = expiratory positive airway pressure.

stant CPET without EPAP, EPAP with 5 cm H_2O (EPAP5), or EPAP with 10 cm H_2O (EPAP10). Randomization was done by computer-generated random letters (simple method) considering the 6 possible sequences for a block of 18 subjects (http://www.randomization.com) and thereafter shuffled in opaque sealed envelopes.

Procedures

CPETs were performed on an electrically braked cycle ergometer (Corival, Lode, Groningen, the Netherlands) using a computer-based exercise system (Vmax Encore, CareFusion, Yorba Linda, CA). The following data were recorded as a mean of 20 s: oxygen uptake ($\dot{V}_{O_2}$, mL/min), minute ventilation ($\dot{V}_E$, L/min), breathing frequency (f, breaths/min), and tidal volume (V_T, L). Subjects rated their shortness of breath and leg effort using the 0–10 Borg scale[28] immediately after inspiratory capacity measurements every 2 min and at peak exercise. Dynamic hyperinflation was defined as a reduction in inspiratory capacity from rest ≥ 150 mL or 4.5% of predicted.[29] Oxyhemoglobin saturation (S_{pO_2}, %) was continuously measured by pulse oximetry (Takaoka Oxicap, São Paulo, Brazil). In incremental CPET, after a baseline of loadless pedaling for 2 min, the rate of power increment was individually selected (usually 5–10 W/min) to provide an exercise duration of 8–12 min. Constant CPET was performed with loaded pedaling at ~75% of the peak work load achieved during incremental CPET. Symptoms and physiologic variables were compared at rest, maximal tolerable exercise, and at isotime, which is the longest exercise duration common to all constant CPET performed by a given individual. All constant CPET were performed using a nose clip and breathing through a silicone mouthpiece attached to a 2-way non-rebreathing T-shaped valve (2600 Medium, Hans Rudolph, Shawnee, KS), with an additional estimated dead space of 50 mL. During constant CPET without EPAP, all diaphragms of the valve were removed. The intensity of the EPAP offered with this device was verified with an external pressure transducer (MVD-300, Microhard System, Globalmed, Porto Alegre, Brazil) in the first 3 subjects included. Keeping all diaphragms of the T-shaped valve in place resulted in ~5 cm H_2O. The addition of the spring linear pressure resistor (Vital Signs, Totowa, NJ) adjusted at 5 cm H_2O at the expiratory port of the valve resulted in a net expiratory pressure of ~10 cm H_2O. Thereafter, to obtain the EPAP level of 5 cm H_2O, the diaphragms of the Hans Rudolph valve were used in their usual position. To obtain the EPAP of 10 cm H_2O, the spring linear pressure resistor was connected to the outlet port of the Hans Rudolph valve and the resistor was adjusted to deliver a pressure of 5 cm H_2O (Fig. 1). Shorter exercise duration was defined as any reduction in exercise tolerance during constant CPET with EPAP versus without EPAP.

Statistical Analysis

A sample size of 17 subjects was estimated, on the basis of a previous study, to detect an expected difference in inspiratory capacity variation from rest to peak exercise of 0.4 L (SD = 0.3) comparing tests with and without EPAP.[15] In an interim analysis with the first 15 subjects, we decided to interrupt the study due to a clear tendency of exercise tolerance reduction associated with significant reduction in V_T expansion and without difference in exercise dyspnea at isotime using EPAP.

Data are reported as mean ± SD or as median (range) according to distribution, unless otherwise stated. Generalized estimating equations were used to test for significant differences between interventions (without EPAP, EPAP5, EPAP10) at different time points (rest, isotime, and end-exercise), which is considered more sensitive than repeated measure analysis of variance to detect a given significant difference between and among groups and interventions.[30] Pearson correlation analysis was performed between baseline cardiorespiratory variables (Tables 1 and 2) with exercise tolerance difference (EPAP10 − EPAP). Thereafter, significant correlations were assessed through multivariate linear regression analysis (stepwise method). A paired *t* test was used to compare exercise duration without EPAP versus EPAP10. All tests were 2-sided, and $P < .05$ was considered statistically significant. Statistical

Table 1. Baseline Characteristics of Subjects

Variables	Values
Male sex, *n* (%)	8 (53.3%)
Age, y	60.9 ± 12.3
Weight, kg	71.6 ± 13.3
Height, cm	167 ± 7
Body mass index, kg/m^2	25.8 ± 5.5
Modified Medical Research Council score	3 (2–3)
Baseline Dyspnea Index score	4 (3–5)
Smoking history, pack-years	55 (25–101)
Current smokers, *n* (%)	2 (13%)
Former smokers, *n* (%)	13 (87%)
Resting lung function	
FEV_1, L (% pred)	1.06 ± 0.36 (35 ± 11)
FVC, L (% pred)	2.25 ± 0.64 (59 ± 16)
FEV_1/FVC, %	0.47 ± 0.09
Total lung capacity, L (% pred)	7.39 ± 1.35 (132 ± 30)
Functional residual capacity, L (% pred)	5.23 ± 1.79 (166 ± 64)
Residual volume, L (% pred)	4.87 ± 1.22 (269 ± 95)
D_{LCO}, mmol/min/kPa (%pred)	2.89 ± 0.99 (33 ± 12)
S_{pO_2}, %	96 ± 2

Data are presented as mean ± SD or median (range), unless otherwise stated.
% pred = % of predicted
D_{LCO} = diffusing capacity of the lung for carbon monoxide
S_{pO_2} = oxyhemoglobin saturation by pulse oximetry

analyses was performed with SPSS statistics software (Version 22.0, Chicago, IL).

Results

The study included 15 non-hypoxemic subjects ranging from moderate to very severe COPD (2 subjects with GOLD stage II, 7 with stage III, and 6 with stage IV),[27] with moderate to severe resting lung hyperinflation and reduction in diffusing capacity of the lung for carbon monoxide. Accordingly, they reported relevant dyspnea for activities of daily life (Table 1) and were receiving symptomatic treatment in accordance with current evidence-based guidelines.[27] All were using a combination of long-acting $ß_2$-agonists plus inhaled steroid and short-acting bronchodilators on an as-needed basis; 6 subjects were additionally being treated with a long-acting muscarinic receptor antagonist. No subjects participated in a pulmonary rehabilitation program or were engaged in regular exercise activities in the last 12 months before inclusion.

During incremental CPET, all subjects presented reduced peak aerobic capacity and dynamic hyperinflation, ranging from −0.97 L to −0.15 L (Table 2). Exercise tests were stopped most frequently due to severe leg discomfort/fatigue ($n = 8$), dyspnea ($n = 5$), or a combination of both ($n = 2$).

The application of different intensities of EPAP during constant CPET tended to cause a progressive reduction in exercise tolerance (Fig. 2). Of note, 10 of 15 subjects (67%) presented shorter exercise duration (ranging from −269 s to −12 s) with EPAP10 compared to the test without EPAP [−151 ± 105 s, $P = .03$ or −41 (−85 to −5%)]. Total lung capacity (TLC) and FVC (both ex-

Table 2. Metabolic, Ventilatory, Cardiac, and Sensory Responses to Cycling Symptom-Limited Incremental Cardiopulmonary Exercise Testing

Variables	Values
Workload, watts	38 ± 17
$\dot{V}_{O_2}$, mL/min (% pred)	874 ± 223 (45 ± 22)
$\dot{V}_{O_2}$, mL/kg/min	12.7 ± 4.3
$\dot{V}_{CO_2}$, mL/min	821 ± 257
$\dot{V}_E$, L/min	32.5 ± 7.9
f, breaths/min	31 ± 5
V_T, L	1.09 ± 0.3
$\dot{V}_E$/maximum voluntary ventilation	0.85 ± 0.17
Slope $\dot{V}_E/\dot{V}_{O_2}$, L/L	33.5 ± 7.3
Inspiratory capacity, L (% pred)	1.52 ± 0.44 (51 ± 15)
ΔInspiratory capacity, L	−0.57 ± 0.28
Heart rate, beats/min (% pred)	120 ± 13 (76 ± 9)
O_2 pulse, mL/beats	8.3 ± 2.0
$\Delta\dot{V}_{O_2}/\Delta$work, mL/min/watts	9.8 ± 2.2
S_{pO_2}, %	92 ± 6
ΔS_{pO_2}, %	−4 ± 5
Borg Dyspnea, units	7 (5–9)
Borg Leg Discomfort, units	8 (5–10)

Data presented as means ± SD or median (range). All responses were recorded at peak exercise.
$\dot{V}_{O_2}$ = oxygen uptake
$\dot{V}_{CO_2}$ = carbon dioxide production
$\dot{V}_E$ = minute ventilation
f = breathing frequency
V_T = tidal volume
ΔInspiratory capacity = change from rest
S_{pO_2} = oxyhemoglobin saturation by pulse oximetry

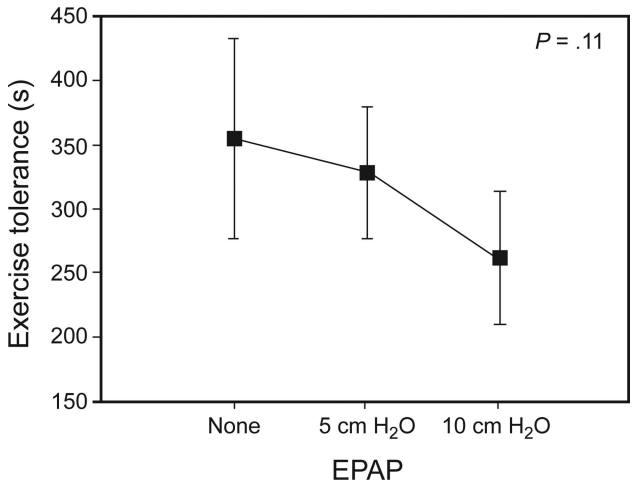

Fig. 2. Exercise tolerance with progressive intensities of EPAP. EPAP = expiratory positive airway pressure.

Table 3. Physiologic and Perceptual Responses at Isotime With Different Intensities of EPAP During Constant Load Cardiopulmonary Exercise Tests

Variable	Without EPAP	EPAP 5 cm H_2O	EPAP 10 cm H_2O	*P*
$\dot{V}_{O_2}$, mL/min	913 ± 213	766 ± 507	564 ± 182†‡	<.001†‡
$\dot{V}_{CO_2}$, mL/min	808 ± 325	720 ± 240	598 ± 247	.20
$\dot{V}_E$, L/min	34.3 ± 8.5	28.3 ± 8.9	22.0 ± 8.1†	<.001†
f, breaths/min	31 ± 6.5	29 ± 5.4	30 ± 9.2	.47
V_T, L	1.11 ± 0.30	1.02 ± 0.34	0.76 ± 0.23†	<.001†
V_T/Inspiratory capacity, %	0.72 ± 0.07	0.65 ± 0.07	0.47 ± 0.11†‡	<.001†; .001‡
V_T/T_I, L/s	1.6 ± 0.2	1.2 ± 0.3*	0.9 ± 0.3†‡	.002*†; <.001‡
V_T/T_E, L/s	0.86 ± 0.23	0.83 ± 0.30	0.63 ± 0.23†‡	.001†; .02‡
Inspiratory capacity, L	1.57 ± 0.46	1.57 ± 0.50	1.65 ± 0.54	.90
ΔInspiratory capacity from rest, L	–0.31 ± 0.38	−0.32 ± 0.19	−0.14 ± 0.38	.18
Inspiratory reserve volume, L	0.45 ± 0.23	0.55 ± 0.23	0.89 ± 0.42†‡	<.001†; .004‡
End-expiratory lung volume, L	5.6 ± 1.1	5.8 ± 1.1	5.6 ± 1.1	.94
End-inspiratory lung volume, L	6.8 ± 1.1	6.8 ± 1.1	6.4 ± 1.1	.56
End-inspiratory lung volume/Total lung capacity	0.95 ± 0.03	0.92 ± 0.03*	0.87 ± 0.03†‡	.002*; .001‡‡
Heart rate, beats/min	120 ± 15	113 ± 11	115 ± 15	.36
O_2 pulse, mL/beat	7.6 ± 1.5	6.7 ± 1.9	4.9 ± 1.5†‡	.001†‡
$\dot{V}_E/\dot{V}_{CO_2}$, L/L	38.4 ± 5.4	39.7 ± 5.8	38.3 ± 6.1	.76
Slope $\dot{V}_E/\dot{V}_{CO_2}$, L/L	31.3 ± 7.7	34.5 ± 8.9	36.4 ± 15.1	.10
$P_{ET}CO_2$, mm Hg	36 ± 3	36 ± 3	33 ± 3	.10
S_{pO_2}, %	92 ± 3	91 ± 3	92 ± 3	.93
Borg Dyspnea, units	7 (5–8)	6 (3–9)	7 (5–9)	.94
Borg Leg Discomfort, units	7 (5–9)	7 (5–8)	7 (7–9)	>.99

Values are means ± SD or median (range).
* Without EPAP vs EPAP 5 cm H_2O.
† Without EPAP vs EPAP 10 cm H_2O.
‡ EPAP 5 cm H_2O vs EPAP 10 cm H_2O.
EPAP = expiratory positive airway pressure
$\dot{V}_{O_2}$ = oxygen uptake
$\dot{V}_{CO_2}$ = carbon dioxide production
$\dot{V}_E$ = minute ventilation
f = breathing frequency
V_T = tidal volume
T_I = inspiratory time
T_E = expiratory time
ΔInspiratory capacity = change from rest
$\dot{V}_E/\dot{V}_{CO_2}$ = ventilatory equivalent for carbon dioxide
P_{ETCO_2} = end-tidal carbon dioxide pressure
S_{pO_2} = oxygen saturation by pulse oximetry

pressed as percentage predicted) were the only baseline cardiorespiratory parameters significantly correlated with exercise tolerance change with EPAP, but only TLC remained as an independent variable in multivariate regression analyses (R^2 = 0.34; unstandardized coefficient B = −2.91, *P* = .02).

Minute ventilation increment during exercise was constrained by EPAP, secondary to a limited increase in V_T (Table 3 and Table 4) (Fig. 3). Even without a significant impact on inspiratory capacity, the blunted V_T response allowed the maintenance of a higher inspiratory reserve volume and lower end-inspiratory lung volume/TLC ratio at a standardized exercise time (isotime). Nevertheless, dyspnea sensations were similar along the exercise tests comparing the three interventions (Tables 3 and 4, Fig. 3). Interestingly, a significant reduction in inspiratory (V_T/T_I) and expiratory (V_T/T_E) flows were observed at isotime with crescent intensities of EPAP (Table 3), which was observed only regarding inspiratory flows at maximal tolerable exercise (Table 4).

Finally, the application of EPAP during constant high-intensity exercise tests caused a significant dose-response reduction in oxygen pulse at submaximal exercise (Table 3).

Discussion

The main findings of our study were that, in stable subjects with moderate to very severe COPD, the application of our experimental device during exercise showed a clear tendency to impair exercise tolerance, without clear benefits in terms of dynamic hyperinflation and exercise dyspnea. These are probably be related to the induction of

Table 4. Physiologic and Perceptual Responses From Rest to Maximal Tolerable Exercise With Different Intensities of EPAP During Constant Load Cardiopulmonary Exercise Tests

Variable	Without EPAP		EPAP 5 cm H_2O		EPAP 10 cm H_2O		*P*
	Rest	End-exercise	Rest	End-exercise	Rest	End-exercise	
Time, s	NA	355 ± 1057	NA	329 ± 786	NA	263 ± 813	.36
$\dot{V}_{O_2}$, mL/min	362 ± 69	936 ± 240	285 ± 95	790 ± 240	257 ± 65	661 ± 220†	.002†
$\dot{V}_{CO_2}$, mL/min	316 ± 58	896 ± 243	251 ± 104	733 ± 232*	228 ± 61	612 ± 205†	.02*; .001†
$\dot{V}_E$, L/min	15.9 ± 1.9	34.8 ± 9.6	11.4 ± 3.8	28.8 ± 9.6	12.0 ± 2.7	21.3 ± 6.9†	<.001†
f, breaths/min	20 ± 3	34 ± 7	18 ± 3	32 ± 7	17 ± 3	32 ± 7	.12
V_T, L	0.82 ± 0.23	1.05 ± 0.27	0.64 ± 0.23	0.95 ± 0.34	0.75 ± 0.23	0.71 ± 0.69†	.01†
V_T/Inspiratory capacity, %	0.60 ± 0.11	0.70 ± 0.19	0.43 ± 0.11	0.60 ± 0.11	0.41 ± 0.11	0.46 ± 0.11†	.02†
V_T/T_I, L/s	0.7 ± 0.1	1.6 ± 0.5	0.5 ± 0.1	1.2 ± 0.4	0.5 ± 0.1	1.0 ± 0.3†	.001†
V_T/T_E, L/s	0.2 ± 0.07	0.7 ± 0.15	0.3 ± 0.07	0.8 ± 0.27	0.3 ± 0.07	0.6 ± 0.19	>.99
Inspiratory capacity, L	2.0 ± 0.5	1.5 ± 0.5	1.9 ± 0.5	1.6 ± 0.5	1.8 ± 0.3	1.6 ± 0.5	.19
ΔInspiratory capacity from rest, L	NA	−0.41 ± 1.16	NA	−0.39 ± 0.77	NA	−0.21 ± 1.93	.18
Inspiratory reserve volume, L	1.2 ± 0.3	0.5 ± 0.3	1.3 ± 0.3	0.6 ± 0.2	1.1 ± 0.03	0.9 ± 0.3	.23
End-expiratory lung volume, L	5.2 ± 1.1	5.8 ± 1.5	5.6 ± 1.1	5.9 ± 1.1	5.5 ± 1.1	5.7 ± 1.1	>.99
End-inspiratory lung volume, L	6.0 ± 1.1	6.3 ± 2.3	6.2 ± 1.1	6.5 ± 1.9	6.3 ± 1.1	6.4 ± 1.1	.71
End-inspiratory lung volume/Total lung capacity	0.8 ± 0.7	0.8 ± 2.7	0.8 ± 0.1	0.9 ± 0.01	0.8 ± 0.03	0.9 ± 0.03	.74
Heart rate, beats/min	87 ± 19	124 ± 11	83 ± 11	119 ± 11	85 ± 15	116 ± 11	.11
O_2 pulse, mL/beat	4.2 ± 0.9	7.5 ± 1.8	3.2 ± 1.2	6.7 ± 2.0	3.1 ± 1.0	5.7 ± 1.8	.13
$\dot{V}_E/\dot{V}_{CO_2}$	51.1 ± 8.9	39.0 ± 5.0	51.5 ± 11.6	39.5 ± 6.1	57.0 ± 20.9	35.9 ± 7.7	.063
$\Delta\dot{V}_E/\dot{V}_{CO_2}$, L/L	NA	31.7 ± 6.5	NA	34.9 ± 10.4	NA	29.0 ± 15.8	.59
P_{ETCO_2}, mm Hg	31 ± 3	37 ± 3	29 ± 3	35 ± 3	27 ± 3	34 ± 3	.27
S_{pO_2}, %	97 ± 3	92 ± 3	97 ± 3	91 ± 3	96 ± 3	91 ± 3	.17
Borg Dyspnea, units	0 (0–0.5)	7.5 (6.5–9.25)	0 (0–0.5)	8 (6–10)	0 (0–0.5)	8 (7–9)	.61
Borg Leg Discomfort, units	0 (0–0.5)	7.5 (4.75–9)	0 (0–0.5)	7 (5–9)	0 (0–0.5)	7 (7–10)	.97

Values are means ± SD or median (range).
* Without EPAP vs EPAP 5 cm H_2O.
† Without EPAP vs EPAP 10 cm H_2O.
EPAP = expiratory positive airway pressure
$\dot{V}_{O_2}$ = oxygen uptake
$\dot{V}_{CO_2}$ = carbon dioxide production
$\dot{V}_E$ = minute ventilation
f = breathing frequency
V_T = tidal volume
T_I = inspiratory time
T_E = expiratory time
ΔInspiratory capacity = change from rest
$\dot{V}_E/\dot{V}_{CO_2}$ = ventilatory equivalent for carbon dioxide
P_{ETCO_2} = end-tidal carbon dioxide pressure
S_{pO_2} = oxygen saturation by pulse oximetry

ventilatory (decreased $\dot{V}_E$, decreased V_T, and decreased expiratory and, more markedly, inspiratory flows) and hemodynamic (decreased $\dot{V}_{O_2}$ and O_2 pulse) constraints.

The supposed advantage of applying pressure support only during expiration, ie, to attenuate dynamic airway compression and reduce lung hyperinflation (and elastic work of breathing),[10–12] seemed to be counterbalanced by increases in expiratory muscle effort (and resistive working of breathing) during exercise.[20,31] Moreover, because we continuously monitored ventilatory and metabolic parameters during exercise, we used a device (Fig. 1) that allowed measurements of those parameters by a computer-based system while simultaneously applying the pressure in the expiratory outlet. With increased flows during exercise, the Hans Rudolph T valve may offer differential pressure through the inspiratory diaphragm as described in the manufacturer data sheet (http://www.rudolphkc.com/pdf/691151%200713%20K.pdf, *accessed March 27, 2017*). This can be particularly relevant to our results, especially considering how the whole experimental device (pneumotachograph + T valve + spring pressure resistor; Fig. 1) was assembled for the different interventions.

During tests without EPAP, the expiratory diaphragm of the T valve was removed to allow a free pathway for expiration and inspiration. Accordingly, both EPAP interventions (5 cm H_2O and 10 cm H_2O), beyond the increment in expiratory resistance, probably applied some level of inspiratory resistance, which could substantially increase

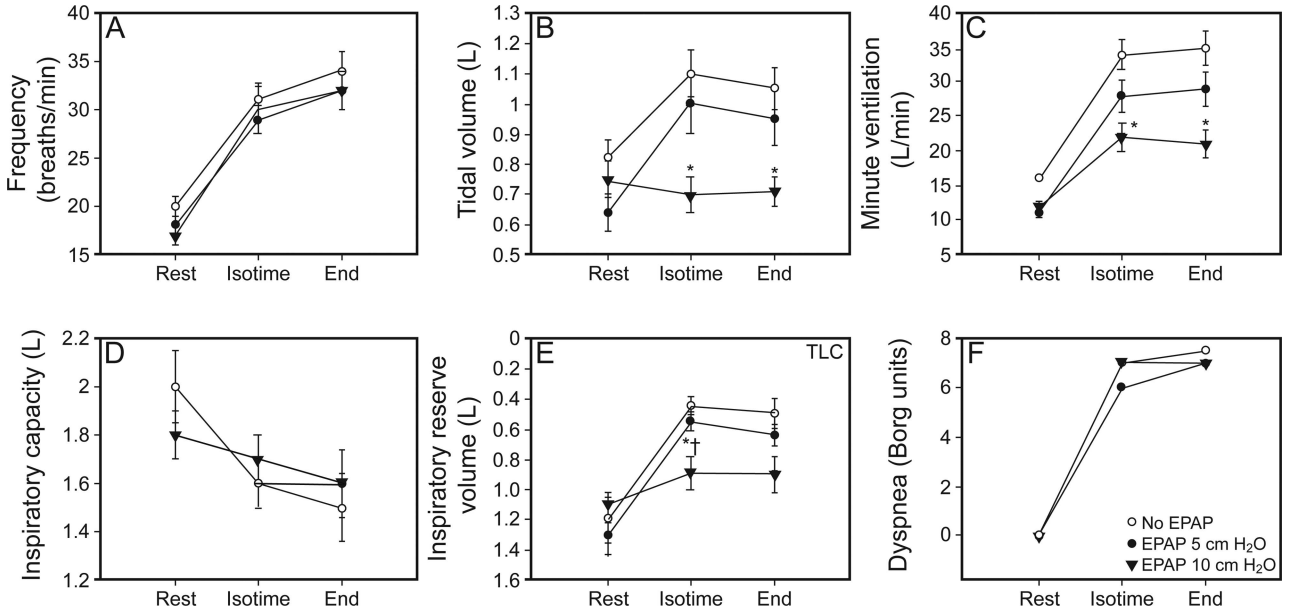

Fig. 3. Breathing pattern, operational lung volumes, and dyspnea sensation without and with different EPAP intensities during exercise. *$P < .05$ vs without EPAP. † $P < .05$ vs EPAP 5 cm H_2O. EPAP = expiratory positive airway pressure.

the work of breathing (especially considering the high exercise f)[8] and contribute to limit V_T increase. The dramatic reduction in inspiratory flow (even higher than the expiratory flow) and the absence of increase in breathing frequency with EPAP5 and EPAP10, which would occur if V_T limitation were secondary to respiratory muscle weakness or fatigue, support this concept. This may also contribute to the contradictory effects of EPAP application on exercise tolerance found in the literature. Studies that used devices with an inspiratory diaphragm[16,22] (like our study) impaired exercise performance, in contrast to those where no inspiratory resistance was applied (control intervention with normal breathing).[14,18] Finally, higher TLC was associated with lower exercise duration with EPAP. Any increased inspiratory resistance would be particularly detrimental to those with more hyperinflation. In contrast to healthy subjects, the combined recoil pressure of the lungs and chest wall is inwardly directed in hyperinflation, resulting in an inspiratory threshold load.[32]

The application of the 2 intensities of EPAP, considering that the inspiratory loads were the same for both interventions, allowed us to observe, that EPAP per se contributed significantly to constrain ventilation (Fig. 3) with a clear tendency to impair exercise tolerance (Fig. 2). While a dose-response reduction in operational lung volumes during exercise was observed with EPAP (ie, increased inspiratory reserve volume and decreased end-inspiratory lung volume/TLC; Table 3), the effect on inspiratory capacity (the true room for V_T expansion) was modest and non-statistically significant. The reduction in exercise lung volumes appear, in fact, to be secondary to a significant constraint to V_T and, without a compensatory increase in breathing frequency, lead to VE remaining lower than expected during exercise as previously described.[20] This can explain a similar dyspnea observed in the present and previous study[17] or even worse dyspnea[22] during exercise, regardless of a significant improvement in important indexes of lung hyperinflation.[33] It means that constraints to V_T increases continued to happen with exercise progression.

In addition, a significant reduction in $\dot{V}_{O_2}$ was observed accompanied by a significant reduction in oxygen pulse, a surrogate for systolic volume,[6] indicating hemodynamic response impairment. This is possibly related to decreased venous return caused by excessive expiratory muscle recruitment,[21] leading to reduced lung perfusion to ventilation ratio and cardiac output.[1] Furthermore, augmented sympathetic vasomotor outflow during exercise was observed with increasing expiratory resistance.[34] Added to the central hemodynamic and ventilatory constraint, all these mechanisms may contribute to impair exercise capacity.

Although the exercise tolerance reduction with EPAP was not statistically significant in the present sample ($n = 15$), we decided to interrupt the study since there was a clear tendency to exercise performance impairment (the opposite of what was expected) associated with similar exercise dyspnea at isotime (our two main clinical outcomes). Furthermore, two-thirds of the current sample demonstrated a reduction in exercise performance, presenting a statistically and clinically important[35] average reduction in exercise tolerance. Moreover, there was a clear dose-response effect of higher EPAP associated with lower exercise tolerance. Finally, external dead space (V_D) loading

has the potential to stress the ventilatory control system such that a greater $\dot{V}_E$ is required to keep the same arterial carbon dioxide pressure at any given metabolic rate.[36]

This issue is particularly crucial to patients primarily limited by ventilation,[37] with aggravating conditions such as high V_D/V_T even in mild disease compared to healthy controls,[38] which worsens in tandem with COPD severity.[1] Although our experimental device caused a small but potentially clinically relevant increase in V_D, we consider its influence on the main results to be hardly significant because the amount of V_D increase was similar during all interventions.

Conclusions

The delivery of EPAP5 or EPAP10 during exercise tended to cause a progressive reduction in exercise tolerance in subjects with COPD, without significant improvement in exercise dyspnea and dynamic hyperinflation at isotime. Ventilatory and hemodynamic constraints seem to underlie these findings.

REFERENCES

1. O'Donnell DE, Laveneziana P, Webb K, Neder JA. Chronic obstructive pulmonary disease: clinical integrative physiology. Clinics in Chest Medicine 2014;35(1):51-69.
2. O'Donnell DE, Elbehairy AF, Berton DC, Domnik ND, Neder JA. Advances in the evaluation of respiratory pathophysiology during exercise in chronic lung diseases. Front Physiol 2017;8:82.
3. Langer D, Ciavaglia CE, Neder JA, Webb KA, O'Donnell DE. Lung hyperinflation in chronic obstructive pulmonary disease: mechanisms, clinical implications and treatment. Expert Rev Respir Med 2014; 8(6):731-749.
4. Casanova C, Cote C, de Torres JP, Aguirre-Jaime A, Marin JM, Pinto-Plata V, Celli BR. Inspiratory-to-total lung capacity ratio predicts mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2005;171(6):591-597.
5. O'Donnell DE. Hyperinflation, dyspnea, and exercise intolerance in chronic obstructive pulmonary disease. Proc Am Thorac Soc 2006; 3(2):180-184.
6. Tzani P, Aiello M, Elia D, Boracchia L, Marangio E, Olivieri D, et al. Dynamic hyperinflation is associated with a poor cardiovascular response to exercise in COPD patients. Respir Res 2011;12:150.
7. Watz H, Waschki B, Meyer T, Kretschmar G, Kirsten A, Claussen M, Magnussen H. Decreasing cardiac chamber sizes and associated heart dysfunction in COPD: role of hyperinflation. Chest 2010;138(1):32-38.
8. Loring SH, Garcia-Jacques M, Malhotra A. Pulmonary characteristics in COPD and mechanisms of increased work of breathing. J Appl Physiol 2009;107(1):309-314.
9. Casaburi R, Porszasz J. Reduction of hyperinflation by pharmacologic and other interventions. Proc Am Thorac Soc 2006;3(2):185-189.
10. Mueller RE, Petty TL, Filley GF. Ventilation and arterial blood gas changes induced by pursed lips breathing. J Appl Physiol 1970; 28(6):784-789.
11. Spahija J, de Marchie M, Grassino A. Effects of imposed pursed-lips breathing on respiratory mechanics and dyspnea at rest and during exercise in COPD. Chest 2005;128(2):640-650.
12. de Araujo CL, Karloh M, Dos Reis CM, Palú M, Mayer AF. Pursed-lips breathing reduces dynamic hyperinflation induced by activities of daily living test in patients with chronic obstructive pulmonary disease: A randomized cross-over study. J Rehabil Med 2015;47(10): 957-962.
13. Hernandes NA, Pitta F. Use of expiratory positive airway pressure delivered by a spring load resistor during exercise: a new tool to optimize exercise training in patients with COPD? Respir Care 2012; 57(9):1530-1531.
14. Padkao T, Boonsawat W, Jones CU. Conical-PEP is safe, reduces lung hyperinflation and contributes to improved exercise endurance in patients with COPD: a randomised cross-over trial. J Physiother 2010;56(1):33-39.
15. Monteiro MB, Berton DC, Moreira MA, Menna-Barreto SS, Teixeira PJ. Effects of expiratory positive airway pressure on dynamic hyperinflation during exercise in patients with COPD. Respir Care 2012;57(9):1405-1412.
16. Wibmer T, Rüdiger S, Heitner C, Kropf-Sanchen C, Blanta I, Stoiber KM, et al. Effects of nasal positive expiratory pressure on dynamic hyperinflation and 6-minute walk test in patients with COPD. Respir Care 2014;59(5):699-708.
17. Martin AD, Davenport PW. Extrinsic threshold PEEP reduces post-exercise dyspnea in COPD patients: a placebo-controlled, double-blind cross-over study. Cardiopulm Phys Ther J 2011;22(3):5-10.
18. Nicolini A, Merliak F, Barlascini C. Use of positive expiratory pressure during six minute walk test: results in patients with moderate to severe chronic obstructive pulmonary disease. Multidiscip Respir Med 2013;8(1):19.
19. Russo D, Simonelli C, Paneroni M, Saleri M, Piroddi IM, Cardinale F, et al. Is there an optimal level of positive expiratory pressure (PEP) to improve walking tolerance in patients with severe COPD? Arch Bronconeumol 2016;52(7):354-360.
20. van der Schans CP, de Jong W, de Vries G, Kaan WA, Postma DS, Koëter GH, van der Mark TW. Effects of positive expiratory pressure breathing during exercise in patients with COPD. Chest 1994; 105(3):782-789.
21. Stark-Leyva KN, Beck KC, Johnson BD. Influence of expiratory loading and hyperinflation on cardiac output during exercise. J Appl Physiol (1985) 2004;96(5):1920-1927.
22. Goelzer LS, Medeiros SG, Giacomini AC, Mustafa RC, Müller P de T. Effects of EPAP on exercise tolerance in COPD patients with dynamic hyperinflation and suspected abnormal left ventricular filling pressure by echocardiography. Int J Cardiol 2016;203:888-890.
23. O'Donnell DE, Travers J, Webb KA, He Z, Lam YM, Hamilton A, et al. Reliability of ventilatory parameters during cycle ergometry in multicentre trials in COPD. Eur Respir J 2009;34(4):866-874.
24. Guenette JA, Chin RC, Cory JM, Webb KA, O'Donnell DE. Inspiratory capacity during exercise: measurement, analysis, and interpretation. Pulm Med 2013;2013:e956081.
25. Holland AE, Hill CJ, Rasekaba T, Lee A, Naughton MT, McDonald CF. Updating the minimal important difference for six-minute walk distance in patients with chronic obstructive pulmonary disease. Arch Phys Med Rehabil 2010;91(2):221-225.
26. Puente-Maestu L, Palange P, Casaburi R, Laveneziana P, Maltais F, Neder JA, et al. Use of exercise testing in the evaluation of interventional efficacy: an official ERS statement. Eur Respir J 2016; 47(2):429-460.
27. Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2013;187(4):347-365.
28. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982;14(5):377-81.
29. Guenette JA, Webb KA, O'Donnell DE. Does dynamic hyperinflation contribute to dyspnoea during exercise in patients with COPD? Eur Respir J 2012;40(2):322-329.

30. Ma Y, Mazumdar M, Memtsoudis SG. Beyond repeated-measures analysis of variance: advanced statistical methods for the analysis of longitudinal data in anesthesia research. Reg Anesth Pain Med 2012;37(1): 99-105.
31. Petrof BJ, Calderini E, Gottfried SB. Effect of CPAP on respiratory effort and dyspnea during exercise in severe COPD. J Appl Physiol 1990;69(1):179-188.
32. Papandrinopoulou D, Tzouda V, Tsoukalas G. Lung compliance and chronic obstructive pulmonary disease. Pulm Med 2012;542769, 2012.
33. Casaburi R, Rennard SI. Exercise limitation in chronic obstructive pulmonary disease. The O'Donnell threshold. Am J Respir Crit Care Med 2015;191(8):873-875.
34. Katayama K, Itoh Y, Saito M, Koike T, Ishida K. Sympathetic vasomotor outflow and blood pressure increase during exercise with expiratory resistance. Physiol Rep 2015;3(5).pii:e12421.
35. Puente-Maestu L, Villar F, de Miguel J, Stringer WW, Sanz P, Sanz ML, et al. Clinical relevance of constant power exercise duration changes in COPD. Eur Respir J 2009;34(2):340-345.
36. Whipp BJ, Ward SA, Wasserman K. Ventilatory responses to exercise and their control in man. Am Rev Respir Dis 1984;129:S17-S20.
37. Neder JA, Jones PW, Nery LE, Whipp BJ. Determinants of the exercise endurance capacity in patients with chronic obstructive pulmonary disease. The power duration relationship. Am J Respir Crit Care Med 2000;162:497-504.
38. Elbehairy AF, Ciavaglia CE, Webb KA, Guenette JA, Jensen D, Mourad SM, et al; on behalf of the Canadian Respiratory Research Network. Pulmonary gas exchange abnormalities in mild chronic obstructive pulmonary disease. Implications for dyspnea and exercise intolerance Am J Respir Crit Care Med 2015;191(12): 1384-94.