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Effects of bi-level positive airway pressure on ventilatory and perceptual responses to exercise in comorbid heart failure-COPD☆

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ABSTRACT

This study tested the hypothesis that, by increasing the volume available for tidal expansion (inspiratory capacity, IC), bi-level positive airway pressure (BiPAP™) would lead to greater beneficial effects on dyspnea and exercise intolerance in comorbid heart failure (HF)-chronic obstructive pulmonary disease (COPD) than HF alone. Ten patients with HF and 9 with HF − COPD (ejection fraction = 30 ± 6% and 35 ± 7%; FEV_1 = 83 ± 12% and 65 ± 15% predicted, respectively) performed a discontinuous exercise protocol under sham ventilation or BiPAP™. Time to intolerance increased with BiPAP™ only in HF − COPD ($p < 0.05$). BiPAP™ led to higher tidal volume and lower duty cycle with longer expiratory time ($p < 0.05$). Of note, BiPAP™ improved IC (by ~0.5 l) across exercise intensities only in HF − COPD. These beneficial consequences were associated with lower dyspnea scores at higher levels of ventilation ($p < 0.05$). By improving the qualitative" (breathing pattern and operational lung volumes) and sensory (dyspnea) features of exertional ventilation, BiPAP™ might allow higher exercise intensities to be sustained for longer during cardiopulmonary rehabilitation in HF − COPD.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a common and disabling comorbidity of heart failure with reduced left ventricular ejection fraction (HF).(Rutten et al., 2005) Patients with comorbid HF − COPD characteristically present with severe activity-related shortness of breath and poor quality of life (Neder et al., 2018); thus, exercise reconditioning is an important component of the non-pharmacological treatment of these patients.(Evans, 2011) Unfortunately, however, most HF − COPD patients are unable to tolerate moderate-to-high exercise intensities without being precociously limited by dyspnea. (Evans et al., 2010) This patient population, therefore, might derive benefit from adjunct strategies aimed at lessening the unpleasant respiratory sensations associated with physical effort.(Vogiatzis and Zakynthinos, 2013)(Piepoli et al., 2017)(Piepoli et al., 2011).

In this context, non-invasive positive pressure ventilation has long been proposed as a potentially useful adjunct to lessen dyspnea burden and improve exercise tolerance in patients with HF or COPD.(O'Donnell et al., 1999)(Ambrosino and Cigni, 2015)(O'Donnell et al., 1988) (Borghi-Silva et al., 2008) Expiratory positive airway pressure (EPAP) may counterbalance intrinsic positive end-expiratory pressure (PEEPi) (Rossi et al., 1995) (Yan et al., 1997) thereby reducing the inspiratory threshold load in hyperinflated patients with COPD. (Sliwinski et al., 1998) (Petrof et al., 1990) Several authors reported progressive lower limits for tidal volumes expansion (i.e., reduced inspiratory capacity (IC)) in patients with HF ((Laveneziana et al., 2009) (Cross et al., 2012) (Chiari et al., 2013) (Smith and Olson, 2019)). The prevailing view is that this is a consequence of gas trapping secondary to reduced expiratory flow rates due to pulmonary congestion (Agostoni et al., 2002) and/or airway hyperresponsiveness (Cabanes et al., 1989) on the small

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airways caliper. This is likely to worsen under higher respiratory frequency and shorter expiratory time,(Cross et al., 2012) as seen during dynamic exercise. Inspiratory positive airway pressure (IPAP) may reduce the work of breathing and unload the inspiratory muscles in HF and COPD (as reviewed by (Ambrosino and Cigni, 2015)). Lower respiratory frequency and more prolonged expiratory time may also allow better lung emptying thereby decreasing the operational lung volumes. (O'Donnell et al., 2014) The consequent improvement in neuromechanical coupling might be instrumental to decrease dyspnea and increase exercise tolerance. (O'Donnell et al., 1999) (Ambrosino and Cigni, 2015) (O'Donnell et al., 1988) (Borghi-Silva et al., 2008) Thus, combining inspiratory to expiratory (i.e., bi-level) positive airway pressure (BiPAP™) (Renston et al., 1994)(Toledo et al., 2007) (Bittencourt et al., 2017) (Gomes Neto et al., 2017) might be more useful to prolong exercise duration in those with greater restriction to tidal volume expansion (comorbid HF − COPD) than in those with less ventilatory constraints (HF). To the best of the authors knowledge, no previous study has specifically addressed whether HF patients with COPD would derive great physiological (less inspiratory constraints) and sensory (less dyspnea) benefits from BiPAP™ than their counterparts without COPD.

The present prospective study, therefore, was performed with the objective to contrast the physiological and subjective responses to exercise in HF and HF − COPD patients receiving BiPAP™ or sham non-invasive ventilation. We specifically hypothesized that BiPAP™ would increase exertional IC (Guenette et al., 2013) and, assuming stable total lung capacity (TLC),(Stubbing et al., 1980) decrease the operational lung volumes at greater extent in HF − COPD compared to HF alone. Thus, BiPAP™ would avoid (or postpone) the critical inspiratory constraints to tidal expansion leading to less dyspnea and greater tolerance to endurance exercise in this group. Confirmation of the study hypotheses would provide novel evidence in favor of BiPAP™ as an adjunct to exercise training in HF − COPD.

2. Materials and methods

Nineteen men aged 45 or older presenting with an established diagnosis of HF with reduced left ventricular ejection fraction (LVEF ≤ 45% at the time of testing but a previous documented history of LVEF < 40%) were included. Nine patients had a clinical and functional diagnosis of COPD (post-bronchodilator forced expiratory volume in one second (FEV_1)/ forced vital capacity (FVC) ratio < 0.7). Owing to the potential challenges of diagnosing airflow limitation in the presence of HF,(Neder et al., 2018) these patients were also required to present with at least moderate decrements in FEV_1 (≤ 60% predicted) and/or gas trapping (residual volume (RV) ≥ 110% predicted). Exclusion criteria were: exacerbation of COPD and/or decompensation of HF one month prior, significant ventricular arrhythmias, atrial fibrillation, unstable angina, acute myocardial infarction in the previous 12 months, and musculoskeletal and/or neurological alterations that precluded an exercise test. This prospective, cross-sectional study received ethical approval from the Federal University of Sao Paulo Hospital's Research Ethic Board (REB) (#19595/2012) and Dante Pazzanese Institute of Cardiology REB (#68612/2012), Sao Paulo, Brazil.

After signing written informed consent, participants were invited to attend the research setting on five different days at least 48 h apart. On the first visit, patients were medically assessed in a clinical specialized in patients with comorbid HF − COPD to ensure clinical stability of both diseases; moreover, they performed transthoracic echocardiogram and full pulmonary function tests with arterial blood gas analyses. After a second visit in which the patients underwent a ramp-incremental cardiopulmonary exercise test (CPET) on a stationary cycle ergometer, they attended the laboratory for individual titration of the most comfortable IPAP (cmH_2O) and EPAP (cmH_2O) levels. In the last two visits, the patients underwent a progressive, discontinuous CPET under sham ventilation or BIPAP™ in a random fashion. Randomization was performed by drawing: a non-member of the research team chose a folded paper containing the name of the intervention.

Pulmonary function tests (spirometry, static lung volumes, lung diffusing capacity and maximal inspiratory pressures) performance and interpretation followed current guidelines (ELITE D™, Medical Graphics Corporation, St. Paul, MN, USA).(Pellegrino et al., 2005) The transthoracic echocardiogram was performed by a single echocardiographer (IE33 xMatrix™, Philips Medical System, Andover, MA, USA) using an S5-1 transducer (1–5 MHz), with the patient in his left lateral decubitus.

The ramp-incremental CPET (American Thoracic Society and American College of Chest Physicians, 2003) to symptom-limited peak work rate (WR) was conducted on an electronically-braked cycle ergometer (Ergoline 800 s, SensorMedics, Yorba Linda, CA) using the SensorMedics Vmax229d™ system. The discontinuous CPETs were performed in an electronically-braked cycle ergometer (Corival™ 400 Medical Graphics Corporation (MGC), St. Paul, MN, USA) using the CPX™ system (MGC). In addition to standard CPET variables, O_2 saturation was measured by pulse oximetry (SpO_2, %) and heart rate (HR, bpm) was determined by the R-R interval of a 12-lead ECG. Dyspnea and leg discomfort intensity were measured with the modified 10-point Borg scale. Arterialized capillary (Pc, mmHg) blood samples were drawn from the earlobes. Maximal voluntary ventilation (MVV, L.min) was estimated as FEV_1 x 40.(American Thoracic Society and American College of Chest Physicians, 2003) Reported values of all variables are mean of the last 30 s of each exercise bout.

With the purpose of assessing the physiological and sensory responses at quasi-steady state conditions, the discontinuous CPETs were performed at progressively higher exercise intensities: 20% peak WR (very mild), 40% peak WR (mild), 60% peak WR (moderate) and 80% peak WR (heavy). The exercise bouts from very mild to moderate intensities lasted 4 min each with 4 min resting in-between bouts. The heavy intensity bout was sustained to symptom limitation (Tlim, s). In order to obtain non-invasive indexes of exertional lung mechanics (O'Donnell et al., 2017), patients performed at least 3 IC (L) maneuvers which were individually reviewed for acceptability and reproducibility according to established recommendations (Guenette et al., 2013). The end-expiratory lung volume (EELV, L) was estimated as total lung capacity (TLC, L) minus IC and the end-inspiratory lung volume (EILV, L) as EELV plus tidal volume (VT, L).(O'Donnell et al., 2017). We a priori defined the presence of critical inspiratory constraints by an EILV/TLC ratio > 0.8 and/or VT /IC ratio > 0.7 (Guenette et al., 2013)(O'Donnell et al., 2017).

The mechanical ventilator EVITA™ 4 (Dräguer Medical AG & Co, KgaA, Lübeck, Germany) delivered BiPAP™or sham ventilation (1 cmH_2O EPAP) with a FIO_2 of 0.21. Technical and operational issues concerning BiPAP™ application followed standard practices.(Alviar et al., 2018) A tight-fitting full-face mask (Performax™, Koninklijke, Philips N.V) was used. To minimize air leak, this mask was attached to the patient with a four-point upper strap fastener and pressure clips. The interventions were applied at rest (10 min before exercise), throughout exercise and recovery. Patients were not told whether they would receive sham ventilation or BiPAP™ at a given visit.

2.1. Statistical analysis

The statistical software package used was IBM™ SPSS™ Statistics version 19. No formal sample size calculation was performed due to the lack of previous studies addressing the effects of BiPAP™ on IC in the population of interest (HF − COPD). The unpaired *t*-test (or Mann-Whitney test when appropriated) were used to compare between-subject differences. The χ^2 test was used to compare frequencies. Linear mixed models with post-hoc of Bonferroni were used to compare dyspnea intensity and cardiorespiratory, metabolic, gas exchange and operating lung volumes at rest and during iso-work rates. A $P < 0.05$ level of significance was used for all analyses.

Table 1
General characteristics and resting functional data in heart failure (HF) patients presenting or not with chronic obstructive pulmonary disease (COPD) as co-morbidity.

	HF (N = 10)	HF-COPD (N = 9)
Demographic		
Age, years	61.1 ± 6.7	66.2 ± 5.9
Body mass index, kg/m^2	26.4 ± 3.4	25.0 ± 2.9
Clinical		
NYHA class (I/II:III/IV)	7:3	8:1
Ischemic heart failure, N	9	6
Smoking, pack/yrs	40 ± 26	54 ± 36
Comorbidities		
Diabetes, N	6	2
Chronic kidney disease, N	0	3
Heart failure treatment		
β-blockers, N	10	9
ACE-I or ARBs, N	10	8
Furosemide, N	10	9
Digoxin, N	4	4
Others	10	9
Lung function		
FVC, L (% pred)	3.29 ± 0.55 (83 ± 11)	3.08 ± 0.50 (81 ± 13)
FEV_1, L (% pred)	2.56 ± 0.42 (83 ± 12)	1.91 ± 0.46* (65 ± 15 *)
FEV_1/FVC	0.77 ± 0.04	0.62 ± 0.09*
IC, L (% pred)	2.66 ± 0.73 (85 ± 21)	2.33 ± 0.62 (76 ± 20)
TLC, L (% pred)	5.79 ± 0.77 (88 ± 12)	6.04 ± 1.21 (92 ± 21)
RV, L (% pred)	2.49 ± 0.27 (119 ± 15)	2.82 ± 0.97 (130 ± 49)
IC/TLC	0.45 ± 0.07	0.39 ± 0.06*
D_{LCO}, mL/min/mmHg (% pred)	20.9 ± 5.0 (63 ± 16)	16.3 ± 4.7 (50 ± 16)
MIP, cmH_2O (% pred)	−86 ± 28 (81 ± 26)	−73 ± 33 (72 ± 31)
Arterial blood		
pH	7.42 ± 0.04	7.39 ± 0.03
HCO_3^-, mEq/L	23 ± 2	22 ± 2
$PaCO_2$, mmHg	33 ± 4	35 ± 2
PaO_2, mmHg	85 ± 11	76 ± 8
SaO_2, %	96 ± 3	95 ± 2
Echocardiogram		
LVEF, %	30 ± 6	35 ± 7
LVEDV, mm	67 ± 9	68 ± 6
LVMI, g/m^2	146 ± 35	175 ± 39
LA, mm	45 ± 5	48 ± 7
PSAP, mmHg	45 ± 12	51 ± 16
TAPSE, mm	18 ± 5	18 ± 4

* $P < 0.05$. Values are mean ± SD or median [range]. *Abbreviations*: NYHA = New York Heart Association; mMRC = modified Medical Research Council scale; ACE-I = angiotensin-converting-enzyme inhibitor; ARB = angiotensin receptor blockers; FVC = forced vital capacity; FEV_1 = forced expiratory volume in one second; IC = inspiratory capacity; TLC = total lung capacity; RV = residual volume; D_{LCO} = lung diffusing capacity for carbon monoxide; pH = hydrogen-ionic potential; HCO_3^- = bicarbonate; Pa = arterial partial pressure; Sa = arterial saturation; LVEF = left ventricular ejection fraction; LVEDV = left ventricular end-diastolic volume; LVMI = left ventricular mass index; LA = left atrium; RV = right ventricle; PASP = pulmonary artery systolic pressure; TAPSE = tricuspid annular plane systolic excursion.

3. Results

3.1. Clinical and resting functional characteristics

Most patients were men in the mid 60 s, New York Heart Association functional class I or II, mildly overweight with HF secondary to ischemic heart disease (Table 1). There were no significant between group differences in HF treatment ($p > 0.05$). As expected by the co-existence of an obstructive airway disease, the HF−COPD group had evidences of airflow limitation with lower FEV_1, higher static lung volumes and a trend to lower lung diffusing capacity. Albeit not statistically significant, maximum inspiratory pressure (MIP) also tended to be lower in this group. The groups were well-paired concerning to arterial blood gas tensions and echocardiographic variables (Table 1).

3.2. Incremental CPET

Patients from both groups showed moderately impaired peak exercise capacity (as based on % predicted peak O_2 uptake ($\dot{V}O_2$) and WR) (American Thoracic Society and American College of Chest Physicians, 2003) (Table 2). Despite similar peak minute ventilation ($\dot{V}E$), the lower estimated maximal voluntary ventilation (MVV) in HF−COPD led to a lower peak ventilatory reserve (i.e., high $\dot{V}E$/MVV ratio) in this group ($p < 0.05$). Patients from the HF−COPD group typically showed lower $\dot{V}E$-carbon dioxide output ($\dot{V}CO_2$) slopes and higher intercepts than their counterparts with HF. Both groups reported similarly-high dyspnea and leg effort scores at exercise cessation (Table 2).

3.3. Breathing pattern and timing of breathing

All patients tolerated well the active intervention and sham ventilation: IPAP and EPAP values did not differ in HF versus HF−COPD (14 ± 2 cmH_2O vs. 15 2 cmH_2O and 6 ± 2 cmH_2O vs. 5 ± 1 cmH_2O, respectively; $p > 0.05$). As shown in Fig. 1, similar $\dot{V}E$ at a given exercise intensity with BiPAP™ compared to sham ventilation (*panels A*) was obtained with a slower and deeper breathing pattern (panels in both groups (*panels B-D*)($p < 0.05$). The timing of breathing was also modified by BiPAP™: lower duty cycles (lower inspiratory time (TI)/total respiratory time (TTOT) ratio) and more prolonged expiratory times (TE) were observed, particularly at lower exercise intensities

Table 2
Physiological and sensory responses to incremental CPET in heart failure (HF) patients presenting or not with chronic obstructive pulmonary disease (COPD) as co-morbidity.

	HF (N = 10)	HF-COPD (N = 9)
Peak WR, W (% pred)	72 ± 30 (57 ± 19)	62 ± 17 (56 ± 13)
Peak $\dot{V}O_2$, mL/min (% pred)	1124 ± 393 (62 ± 18)	1079 ± 254 (67 ± 13)
Peak HR, bpm (% pred)	119 ± 22 (82 ± 24)	107 ± 26 (69 ± 16)
Peak SpO_2, %	97 ± 1	94 ± 4*
Peak *f*, rpm	34 ± 7	31 ± 7
Peak $\dot{V}E$, L/min	51 ± 13	50 ± 15
Peak $\dot{V}E/MVV$, %	57 ± 12	76 ± 22*
Peak $PETCO_2$, mmHg	30 ± 5	32 ± 5
Peak VD/VT	0.28 ± 0.11	0.27 ± 0.08
$\dot{V}E/\dot{V}CO_2$ nadir	36 ± 6	36 ± 3
$PETCO_2$ at $\dot{V}E/\dot{V}CO_2$ nadir, mmHg	34 ± 4	36 ± 5
$\dot{V}CO_2$ at $\dot{V}E/\dot{V}CO_2$ nadir, mL/min	805 ± 254	714 ± 292
$\Delta\dot{V}E$-$\Delta\dot{V}CO_2$ slope	40 ± 10	35 ± 6
$\Delta\dot{V}E$-$\Delta\dot{V}CO_2$ intercept, L/min	0.1 ± 3.0	2.2 ± 3.1
Peak dyspnea score	7 [6 – 9]	9 [6 – 10]
Peak leg effort score	7 [6 – 9]	9 [5 – 10]

* $P < 0.05$. Values are mean ± SD or median [range]. *Abbreviations*: WR = work rate; $\dot{V}O_2$ = oxygen uptake; HR = heart rate; SpO_2 = oxygen saturation by pulse oximetry; *f* = respiratory rate; $\dot{V}E$ = ventilation; MVV = maximal voluntary ventilation; PET = end-tidal partial pressure; VD/VT = dead space / tidal volume ratio; $\dot{V}CO_2$ = carbon dioxide output.

(Fig. 2, *panels A and B*) Table 3. Owing to large VT (Fig. 1, *panels B*) and shorter TI, mean inspiratory flow (VT/TI ratio) improved in both groups (*panels C*).

3.4. Operational lung volumes and dyspnea

The most noticeable between-group differences were observed on the behavior of the operational lung volumes: as shown in Fig. 3, BiPAP™ was associated with a more consistent improvement in IC throughout exercise intensities in HF − COPD than HF (*panels A*). Thus, there was a significant downward displacement of the operational lung volumes with BiPAP™ only in the HF − COPD group (i.e., lower EELV/TLC ratio) leading to greater inspiratory reserves across exercise intensities (*panels C*). Those beneficial effects of BiPAP™ in the operational lung volumes were associated with a marked improvement in dyspnea scores at 80% peak WR (*panels D*) (Table 3). In fact, Tlim increased significantly only in this group (sham versus BiPAP™ (median [range]) = 4.08 [3.21–7.46] min versus 4.48 [3.21–4.50] min and 4.35 [3.25–4.50] min versus 4.66 [3.48–7.85] min for HF and HF − COPD, respectively; $p < 0.05$ for the latter group). Despite longer exercise duration, the HF − COPD group still reported lower dyspnea scores with BiPAP™ at Tlim (9 [6–10] vs. 9 [5–9] and 10 [6–10] s vs. 7 [6–10], respectively; $p < 0.05$ for the HF − COPD group).

4. Discussion

The present study seems to constitute the first investigation to explore the hypothesis that non-invasive ventilation (BiPAP™) on exercise would be associated with greater physiological and sensory benefits to HF patients with coexistent COPD than their counterparts without COPD. In line with our premises, we did find that BiPAP™ set to individual patients' comfort increased IC and decreased the operational lung volumes throughout progressive exercise only in HF − COPD (Fig. 3). Those beneficial effects were likely instrumental to improve dyspnea at higher ventilatory demands and increase endurance time in HF − COPD but not in HF. Our results therefore suggest a role for BiPAP™ as an ergogenic aid in clinical scenarios in which more prolonged exercise is particularly desirable, such as during rehabilitation sessions for patients with comorbid HF − COPD.(Vogiatzis and Zakynthinos, 2013)

Our sample of never-trained patients was representative of the population of HF patients who are commonly referred to exercise reconditioning. The HF − COPD population, in particular, closely resembled that involved in previous clinical physiology investigations. (Arbex et al., 2016)(Rocha et al., 2016)(Rocha et al., 2017) As expected, these patients tended to present with more impaired lung function with a combined obstructive and restrictive pattern of dysfunction (Neder et al., 2018) rather than the typical mild restrictive pattern seen in HF alone (Apostolo et al., 2012) (Agostoni et al., 2007). Of note, peak WR was similar between the groups (Table 2) thereby allowing us to match them regarding to submaximal exercise intensities (% peak WR).

There has been growing interested in the HF − COPD population as the prevalence of this association is higher than expected by the occurrence rate of each disease in isolation (as recently reviewed in (Neder et al., 2018)). It follows that our target population will be progressively more frequent in rehabilitation programs worldwide. (Evans et al., 2010) (Vogiatzis and Zakynthinos, 2013) Nevertheless, there is a remarkable paucity of evidence to guide the practitioner on the specific needs of these patients. In this context, our key results indicate that non-invasive ventilation, an adjunct to increase exercise tolerance which has been successfully tested in both diseases in isolation (6–9)(15–18) does present with a greater potential to help HF patients suffering concomitantly from COPD.

Although dyspnea is an important contributor to exercise intolerance in HF and COPD, the relative influence of increased respiratory neural drive and disturbed lung mechanics to symptom genesis differs: a high drive is the dominant feature in the former (Piepoli et al., 2010) (Guazzi et al., 2010) (Dubé et al., 2016) whereas impaired neuromechanical coupling is paramount in moderate to severe COPD. (O'Donnell et al., 1999) (Faisal et al., 2016) (Laveneziana et al., 2009) Owing to the abundant evidence that reducing the operational lung volumes is crucial to allow a given drive to be translated into larger lung-chest wall displacement, greater improvement in neuromechanical coupling in the HFaPD group was likely the main mechanism behind dyspnea improvement in our study (Fig. 3, *panels D*)(O'Donnell et al., 2017).

Despite the absence of invasive measurements of lung mechanics, several results allow us to elaborate further on the mechanisms behind the physiological effects of BiPAP™ in the HF − COPD group. The beneficial consequences on inspiration can by appreciated by the fact that the same ventilation under BiPAP™ compared to sham (Fig. 1, *panels A*) was reached with higher mean inspiratory flows (Fig. 2, *panels C*) under lower duty cycle (Fig. 2, *panels A*). Owing to the latter, the longer

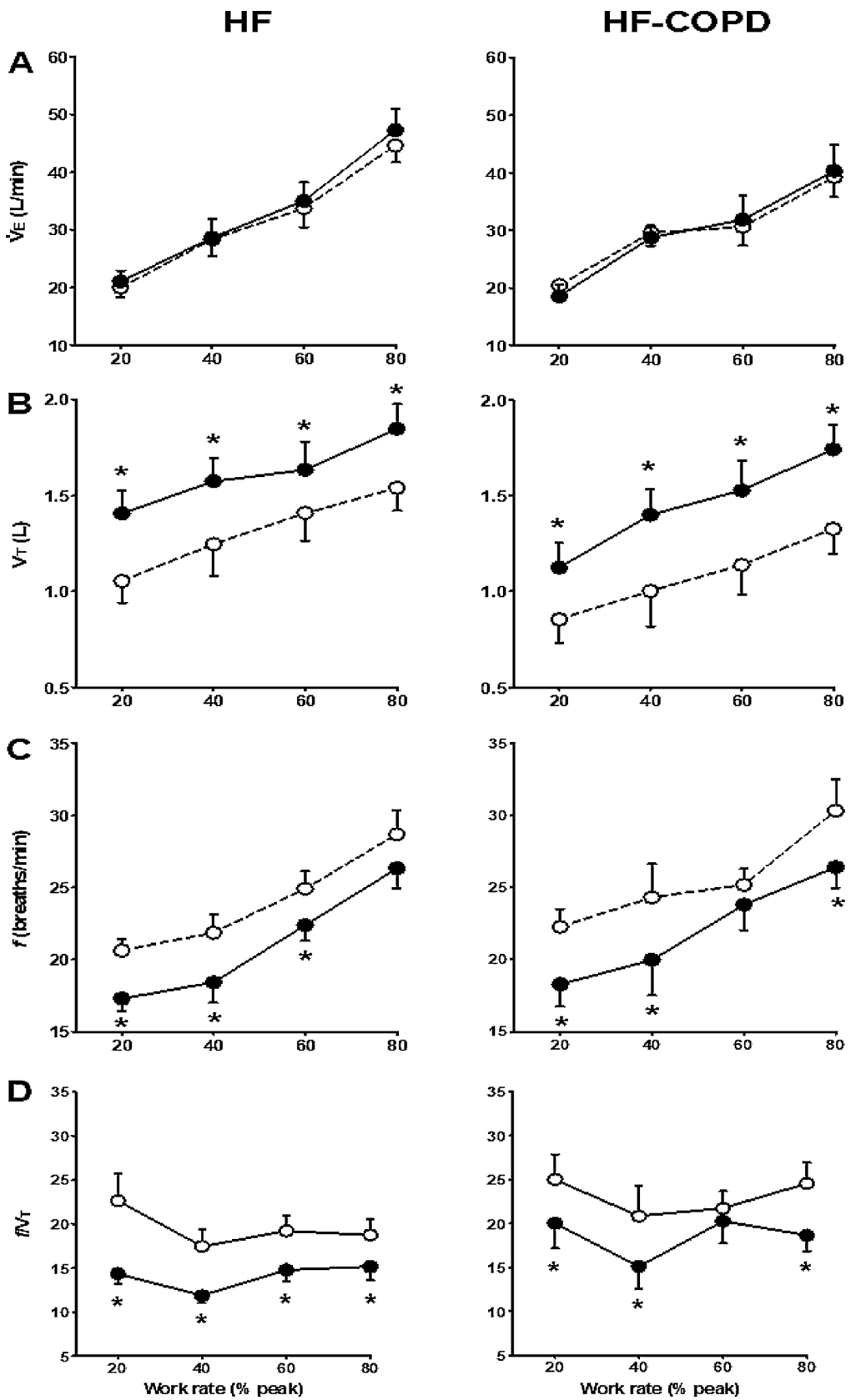

Fig. 1. Minute ventilation (V̇E) and breathing pattern in response to BiPAP™ (*closed symbols*) and sham non-invasive ventilation (*open symbols*) across exercise intensities in HF patients presenting or not with comorbid COPD. Note that the same V̇E (*panels A*) was obtained with higher tidal volume (VT, *panels B*) and lower respiratory frequency (*f*, *panels C*) during active intervention, i.e., BiPAP™ decreased the *f*/VT ratio.
* $p < 0.05$ for between-intervention comparisons at iso-work rate. Values are means ± SEM

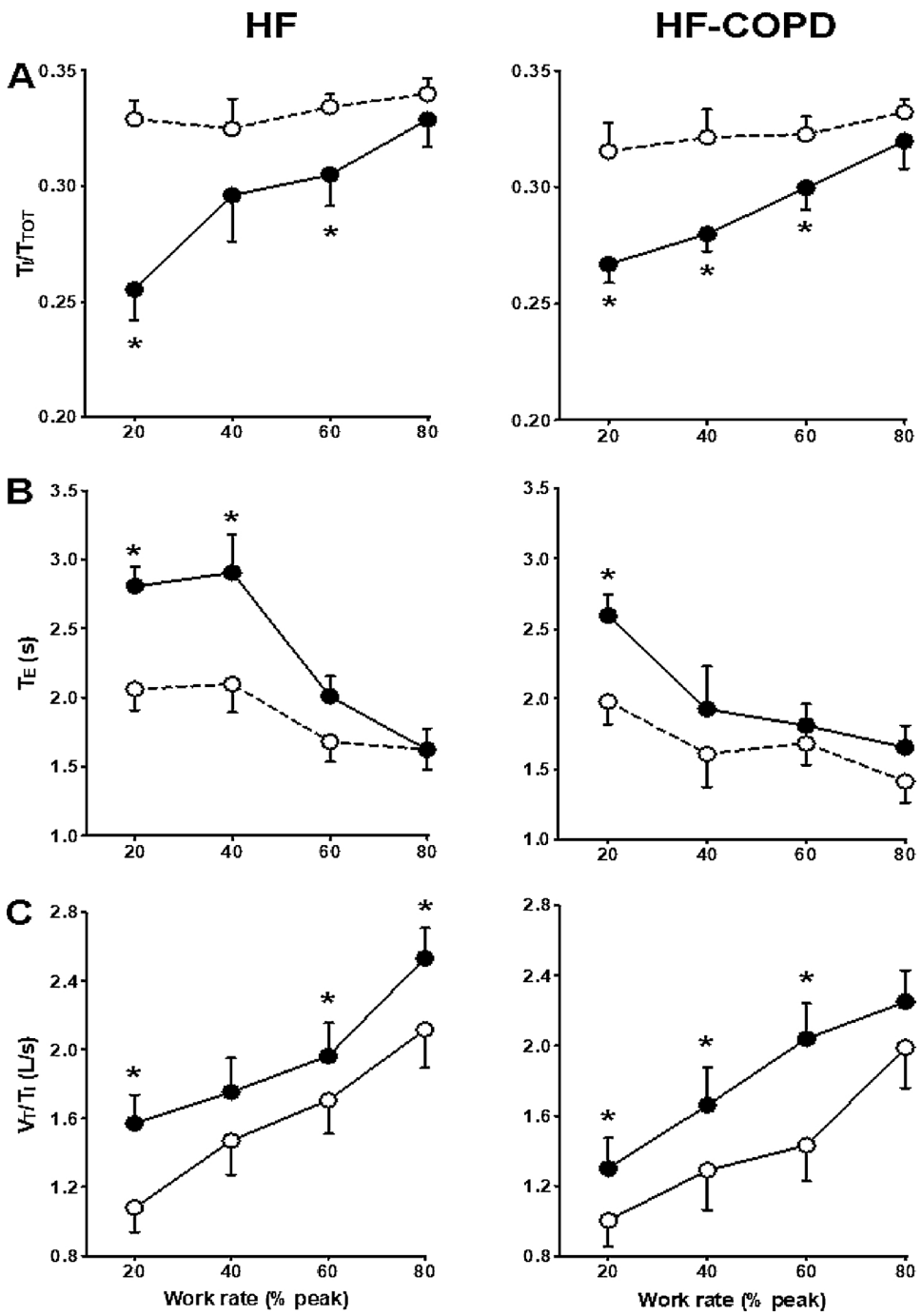

Fig. 2. The timing of breathing in response to BiPAP™ (*closed symbols*) and sham non-invasive ventilation (*open symbols*) across exercise intensities in HF patients presenting or not with comorbid COPD. Note that at milder exercise intensities active intervention led to lower duty cycle (inspiratory time (TI)/total respiratory time (TTOT) ratio) (*panels A*) and longer expiratory time (TE) (*panels B*). Owing to higher tidal volume (VT, Fig. 1B) and shorter TI, mean inspiratory flow (VT/TI ratio) significantly increased with BiPAP™ (*panels C*).
* $p < 0.05$ for between-intervention comparisons at iso-work rate. Values are means ± SEM

respiratory time (lower respiratory frequency) (Fig. 1, *panels C*) was disproportionately spent on expiration (Fig. 1, *panels B*); thus, there was a longer time for a more complete emptying of the lungs under BiPAP™. Counterbalancing PEEPi with EPAP may have also helped to decrease the inspiratory work at a given lung volume. (Rossi et al., 1995) (Yan et al., 1997) Although those beneficial findings were qualitatively similar in the HF group, they were conceivably more relevant to dyspnea alleviation in patients who were already breathing at higher lung volumes (Table 1). It seems therefore logical to suggest that BiPAP™ would be particularly useful in the subset of patients with even greater hyperinflation at rest and more severe dyspnea than those assessed in the present study.

Our results also highlight the key importance of increasing the "room to breathe" (IC) in patients with HF − COPD.(Faisal et al., 2016) IC is particularly relevant to determine the limits for tidal expansion in patients with expiratory flow limitation, i.e. those in whom EELV is dynamically determined.(O'Donnell et al., 2014) The downward displacement of the EILV further away from the critical inspiratory constraints (shaded area in Fig. 3, *panels B and C*) has been consistently associated with better lung mechanics and lower dyspnea.(O'Donnell

Table 3
Physiological and sensory responses to progressive, discontinuous exercise test under SHAM and non-invasive ventilatory (NIV) in heart failure (HF) patients presenting or not with chronic obstructive pulmonary disease (COPD) as co-morbidity.

	HF (N = 10)		HF-COPD (N = 9)	
	SHAM	NIV	SHAM	NIV
20peak				
$\dot{V}O_2$, L/min	0.54 ± 0.19	0.50 ± 0.14	0.53 ± 0.10	0.43 ± 0.15
HR, bpm	89 ± 21	81 ± 8	81 ± 13	83 ± 19
SpO_2, %	98 ± 1	98 ± 1	96 ± 3	97 ± 1
$PETCO_2$, mmHg	28 ± 3	26 ± 4	27 ± 4	26 ± 7
VT, L	1.01 ± 0.12	1.41 ± 0.12*	0.85 ± 0.12	1.13 ± 0.13*
f, rpm	21 ± 3	17 ± 3*	22 ± 4	18 ± 5*
IC, L	2.77 ± 0.53	2.73 ± 0.68	2.42 ± 0.65	2.85 ± 0.76
Dyspnea score	1 [0 – 2]	1 [1 – 2]	1 [1 – 3]	1 [0 – 3]
40peak				
$\dot{V}O_2$, L/min	0.80 ± 0.26	0.73 ± 0.19	0.72 ± 0.01	0.66 ± 0.05
HR, bpm	92 ± 10	89 ± 10	95 ± 12	93 ± 14
SpO_2, %	98 ± 1	98 ± 1	97 ± 2	97 ± 2
$PETCO_2$, mmHg	29 ± 3	28 ± 3	28 ± 1	28 ± 3
VT, L	1.24 ± 0.17	1.57 ± 0.12*	1.00 ± 0.18	1.40 ± 0.14*
f, rpm	22 ± 3	18 ± 4*	24 ± 5	20 ± 6*
IC, L	2.95 ± 0.33	3.01 ± 0.50	2.62 ± 0.83	2.99 ± 0.58*
Dyspnea score	2 [1 – 3]	2 [1 – 5]	0 [0 – 3]	1 [0 – 5]
60peak				
$\dot{V}O_2$, L/min	0.85 ± 0.33	0.81 ± 0.28	0.74 ± 0.15	0.69 ± 0.25
HR, bpm	107 ± 20	96 ± 12*	86 ± 14	91 ± 17
SpO_2, %	98 ± 1	97 ± 1	96 ± 3	97 ± 1*
$PETCO_2$, mmHg	28 ± 4	27 ± 3	27 ± 5	26 ± 6
VT, L	1.41 ± 0.15	1.64 ± 0.15*	1.14 ± 0.16	1.53 ± 0.15*
f, rpm	25 ± 4	22 ± 4*	25 ± 3	24 ± 5
IC, L	2.59 ± 0.49	2.92 ± 0.49	2.46 ± 0.65	2.89 ± 0.53*
Dyspnea score	3 [2 – 4]	3 [2 – 5]	2 [0 – 5]	2 [0 – 5]
80peak				
$\dot{V}O_2$, L/min	0.97 ± 0.31	0.98 ± 0.35	0.86 ± 0.19	0.83 ± 0.24
HR, bpm	113 ± 23	108 ± 20	95 ± 17	97 ± 15
SpO_2, %	97 ± 3	98 ± 2	95 ± 2	96 ± 3†
$PETCO_2$, mmHg	26 ± 4	25 ± 3	25 ± 5	25 ± 5
VT, L	1.54 ± 0.12	1.85 ± 0.13*	1.33 ± 0.13	1.74 ± 0.13*
f, rpm	29 ± 5	26 ± 4	30 ± 7	26 ± 4*
IC, L	2.49 ± 0.61	2.75 ± 0.72	2.29 ± 0.55	2.67 ± 0.63*
Dyspnea score	9 [6 – 10]	7 [4 – 9]	10 [6 – 10]	4 [3 – 5]*,†

* $P < 0.05$ for between intervention differences in a given group and.

† $P < 0.05$ for between-group differences. Values are mean ± SD or median [range]. *Abbreviations*: $\dot{V}O_2$= oxygen uptake; $\dot{V}CO_2$= carbon dioxide output; HR = heart rate; $\dot{V}E$ = ventilation; MVV = maximal voluntary ventilation; VT = tidal volume; *f*= respiratory rate; IC = inspiratory capacity; EILV = end-inspiratory lung volume; TLC = total lung capacity; EELV = end-expiratory lung volume; PET = end-tidal partial pressure; Pc = capillary pressure; VD/VT = dead space / tidal volume ratio; SpO_2= oxygen saturation by pulse oximetry.

et al., 2017) An alternative explanation for a higher IC in HF − COPD than HF involves a significant increase in TLC (higher "ceiling") rather than a lower EELV (lower "floor") in the former group. Although to date this has never been demonstrated, we cannot be ruled out that a more effective assistance to the inspiratory muscles upwardly shifted TLC in those patients under greater mechanical disadvantage, i.e., HF − COPD.

Regardless of the exact mechanism, the beneficial effects on lung mechanics in HF − COPD were translated to lower dyspnea only at high levels of ventilation, i.e. when the respiratory neural drive was conceivably greater.(Mahler and O'Donnell, 2015) Owing to lower ventilatory 'ceiling" in the HF − COPD group (estimated MVV), BiPAP™ allowed longer exercise duration even if those patients exercised at relatively lower breathing reserves. This suggests that BiPAP™ has a greater role in enhancing tolerance to exercise training (as it is usually performed at the moderate-to-high intensities) than to face the milder demands of daily living.(Piepoli et al., 2011) This is particularly desirable as key physiological and sensory adaptations to training such as improved muscle bioenergetics, lower activation of peripheral ergoreceptors (Piepoli et al., 1996) and dyspnea desensitization are more likely to be reached in response to higher metabolic demands.(Vogiatzis and Zakynthinos, 2013) (Piepoli et al., 2011) Owing to the fact that, by study design, patients were not allowed to exercise for prolonged periods of time at lower exercise intensities, we cannot rule out that BiPAP™ would also improve dyspnea elicited by prolonged exercise (20–30 min) at lower ventilatory stress.

Our study has, naturally, some limitations. As a clinical physiology study involving a frail population which is characteristically difficult to recruit for exercise-based studies, our sample size was necessarily small. Thus, the lack of statistical significance at specific time points in the Figures should be interpreted with caution. Nevertheless, the study was sufficiently powered to show a positive effect of the active intervention (BiPAP™) on the main outcome (IC) in the subpopulation that we were specifically interested (HF − COPD). We recognize that our study was not performed in a clinical setting (e.g. during rehabilitation sessions), i.e. issues such as feasibility, long-term compliance and cost-effectiveness were not addressed. Nevertheless, our main objective was to determine whether there would be a greater physiological rationale for considering BiPAP™ in this specific subset of HF patients. As mentioned, our main results did provide a positive answer to this original question. Of note, additional studies are warranted to investigate whether BiPAP™ would be even more advantageous to prolong exercise duration when used in conjunction with other strategies to enhance exercise tolerance, such as interval exercise.(Meyer et al., 1997) We did not find any signal suggesting a deleterious effect of BiPAP™ on the cardiocirculatory responses to exercise in both groups. Nevertheless, caution should be taken in more severe patients in whom higher mean intra-thoracic pressures may decrease venous return thereby impairing cardiac output on exertion.(Neder et al., 2018)

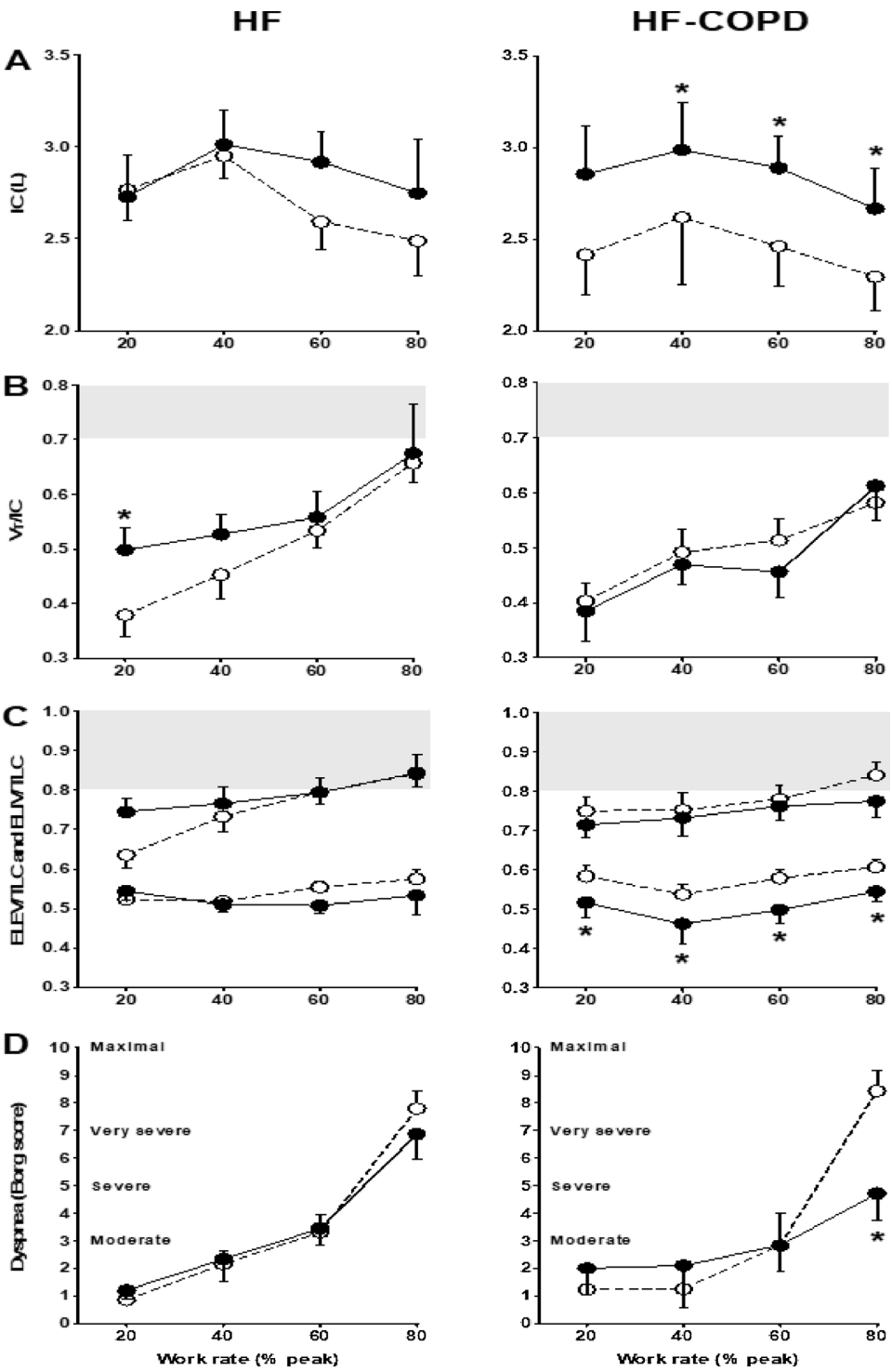

Fig. 3. Operational lung volumes and dyspnea in response to BiPAP™ (*closed symbols*) and sham non-invasive ventilation (*open symbols*) across exercise intensities in HF patients presenting or not with comorbid COPD. Note the more consistent increase in inspiratory capacity (IC) with BiPAP™ (*panels A*) under similar tidal volume (VT)/IC ratio (*panels B*) across exercise intensities in HF − COPD. The downward displacement of the operational lung volumes (*panels C*) was associated with significantly lower dyspnea scores at the highest exercise intensity only in the HF − COPD group (*panels D*).
* $p < 0.05$ for between-intervention comparisons at iso-work rate. Values are means ± SEM. Shaded areas in *panels B and C* represent values associated with critical inspiratory constraints. *Abbreviations*: EILV = end-inspiratory lung volume; EELV = end-expiratory lung volume; TLC = total lung capacity.

In conclusion, BiPAP™ led to lower operational lung volumes and dyspnea which allowed greater tolerance to dynamic exercise performed under high ventilatory stress in patients with comorbid HF − COPD. Our results open the perspective to use this strategy of non-invasive ventilation in selected patients who are particularly dyspneic and hyperinflated in order to enhance their tolerance to more prolonged exercise during cardiopulmonary rehabilitation.

Authors' contributions

Please note attached document.

Conflict of interest

The Author declare that there is no conflict of interest.

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