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Physiological and sensory consequences of exercise oscillatory ventilation in heart failure-COPD

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ABSTRACT

Background: Exercise oscillatory ventilation (EOV) is associated with poor ventilatory efficiency and higher operating lung volumes in heart failure. These abnormalities may be particularly deleterious to dyspnea and exercise tolerance in mechanically-limited patients, e.g. those with coexistent COPD.
Methods: Ventilatory, gas exchange and sensory responses to incremental exercise were contrasted in 68 heart failure-COPD patients (12 EOV+). EOV was established by standard criteria.
Results: Compared to EOV−, EOV+ had lower exercise capacity, worse ventilatory inefficiency and higher peak dyspnea scores ($p < 0.05$). Peak capillary PCO_2 ($PcCO_2$) was higher and end-tidal CO_2 ($PETCO_2$) was lower in EOV+. Thus, greater (i.e., more positive) P(c-ET)CO_2 and dead space/tidal volume values were found in these patients compared to EOV− ($p < 0.05$). Ventilatory inefficiency was related to increased dead space/tidal volume in EOV+ ($r = 0.74$; $p < 0.01$). Owing to higher operating lung volumes, inspiratory reserve volume (IRV) decreased to a greater extent in EOV+. Tidal volume oscillations consistently ceased when a "critical" IRV was reached (~0.3–0.5 L); thereafter, $PcCO_2$ stabilized or increased and dyspnea scores rose sharply. Exercise capacity was closely related to IRV decrements and peak dyspnea in EOV+ ($r = -0.78$ and 0.84, respectively; $p < 0.01$).
Conclusions: Dyspnea and exercise tolerance are negatively influenced by EOV in heart failure patients presenting with COPD as co-morbidity. Pharmacological and non-pharmacological interventions known to decrease EOV might prove particularly valuable to mitigate symptom burden and exercise intolerance in this specific heart failure group.

1. Introduction

Exercise intolerance is a cardinal symptom of both heart failure [1] and COPD [2]. It has been reported that up to a quarter of elderly patients with a primary diagnosis of systolic heart failure present with COPD as co-morbidity [3,4,5]. Of note, these patients have diminished exercise tolerance, impaired quality-of-life and worse prognosis than their counterparts with each disease in isolation [3,4,5]. Understanding the mechanisms leading to poorer physical capacity in heart failure-COPD is crucial to develop evidence-based strategies to decrease symptom burden and improve tolerance to exertion.

It has been well-established that exercise intolerance in COPD is centrally related to the negative sensory consequences (i.e. dyspnea) of tidal volume (VT) constraints elicited by breathing at higher, poorly-compliant lung volumes [2,6]. Thus, potential ventilatory disturbances brought by coexistent heart failure – particularly if associated with increased "wasted" ventilation and greater operating lung volumes – might be subjectively and functionally deleterious to COPD patients [2,6,7].

Exercise oscillatory ventilation (EOV), a pattern of recurring waxing and waning of ventilation found in 17–51% of heart failure patients [8,9], is characteristically associated with poor ventilatory efficiency [10,11] and increasing operating lung volumes [12]. In fact, EOV+ patients had steeper ventilation to CO_2 output ($\dot{V}CO_2$) slope compared to EOV− [10,11,13]. Moreover, the recurring VT cycles may start from gradually higher end-expiratory lung volumes, particularly when the "wasted" fraction of the breath is increased [12]. Consequently, EOV+ patients with heart failure-COPD could prematurely exhaust their mechanical reserves as they (excessively) ventilate too close to the

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boundaries for chest expansion, i.e., total lung capacity (TLC) [2]. Moreover, considering that heightened neural drive is mechanistically linked to EOV [14,15], greater neuro-mechanical dissociation and worse dyspnea could be anticipated in EOV + patients. Thus, EOV may have a hitherto unexplored role on worsening activity-related dyspnea thereby directly contributing to poorer exercise tolerance in heart failure-COPD.

In this study, we compared standard ventilatory, gas exchange and sensory responses to incremental exercise in EOV + and EOV − patients with heart failure-COPD matched by key clinical and resting cardiopulmonary characteristics. We hypothesized that greater mechanical-ventilatory constraints induced by EOV would negatively impact on dyspnea and exercise tolerance. Confirmation of the study hypothesis would open the perspective to test the effectiveness of pharmacological [15,16] and non-pharmacological interventions [17,18] known to decrease EOV in order to enhance exercise tolerance in these patients.

2. Methods

2.1. Subjects

We reviewed individual incremental cardiopulmonary exercise tests (CPET) which had been prospectively performed in a study involving clinically-stable patients with well-established heart failure and COPD from April 2012 to December 2015 in three laboratories in Brazil and Canada. Patients were required to present with post-bronchodilator forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) ratio <0.70, previous history of cigarette smoking (at least 10 pack-yrs) and echocardiographic left ventricular ejection fraction ≤45% in combination with previous symptoms indicative of heart failure (orthopnea, paroxysmal nocturnal dyspnea, fatigue, peripheral oedema, nocturia more than twice a night, or any combination of these symptoms). As detailed elsewhere [19], disease treatment was optimized and patients underwent CPET only after an agreement had been reached between respirologists and cardiologists regarding disease stability. No patient was under long-term O_2 therapy or had recent (within a year) rehabilitation. All subjects had given written informed consent and the study protocol had been approved by the appropriate Medical Ethics Committees (Sao Paulo Hospital; Hospital de Clinicas of Porto Alegre; and Kingston General Hospital).

2.2. Measurements

2.2.1. Lung function

Spirometry, transfer factor, and static lung volumes were evaluated (1085 ELITE D™, Medical Graphics).

2.2.2. Cardiopulmonary exercise testing

Patients performed a symptom-limited incremental CPET on a cycle ergometer using the Vmax229d System (SensorMedics). After 2 min of unloaded cycling, the work rate (WR, W) was incremented according to reported exercise tolerance (typically 5–10 W). Oxygen uptake ($\dot{V}O_2$, L/min), carbon dioxide output ($\dot{V}CO_2$, L/min), minute ventilation ($\dot{V}E$, L/min), end-tidal partial pressure for CO_2 ($PETCO_2$, mm Hg), VT (L) and breathing frequency (*f*, cycles/min) were averaged at 10 s intervals. Heart rate (HR, bpm) was obtained from a 12-lead ECG. Arterial oxygen saturation was measured by pulse oximetry (SpO_2, %). Breathlessness and leg effort scores were rated according to the 10-point Borg category-ratio scale. Slope and intercept of the linear $\dot{V}E$–$\dot{V}CO_2$ relationship were determined by linear regression from unloaded to peak exercise. Peak ventilation was expressed relative to the estimated maximal voluntary ventilation (MVV (L/min) = $FEV_1 \times 35$). Serial inspiratory capacity (IC, L) maneuvers tracked the operating lung volumes, i.e. end-inspiratory and end-expiratory lung volumes (EILV and EELV, respectively) and inspiratory reserve volume (IRV). In EOV + patients, care was taken to have patients

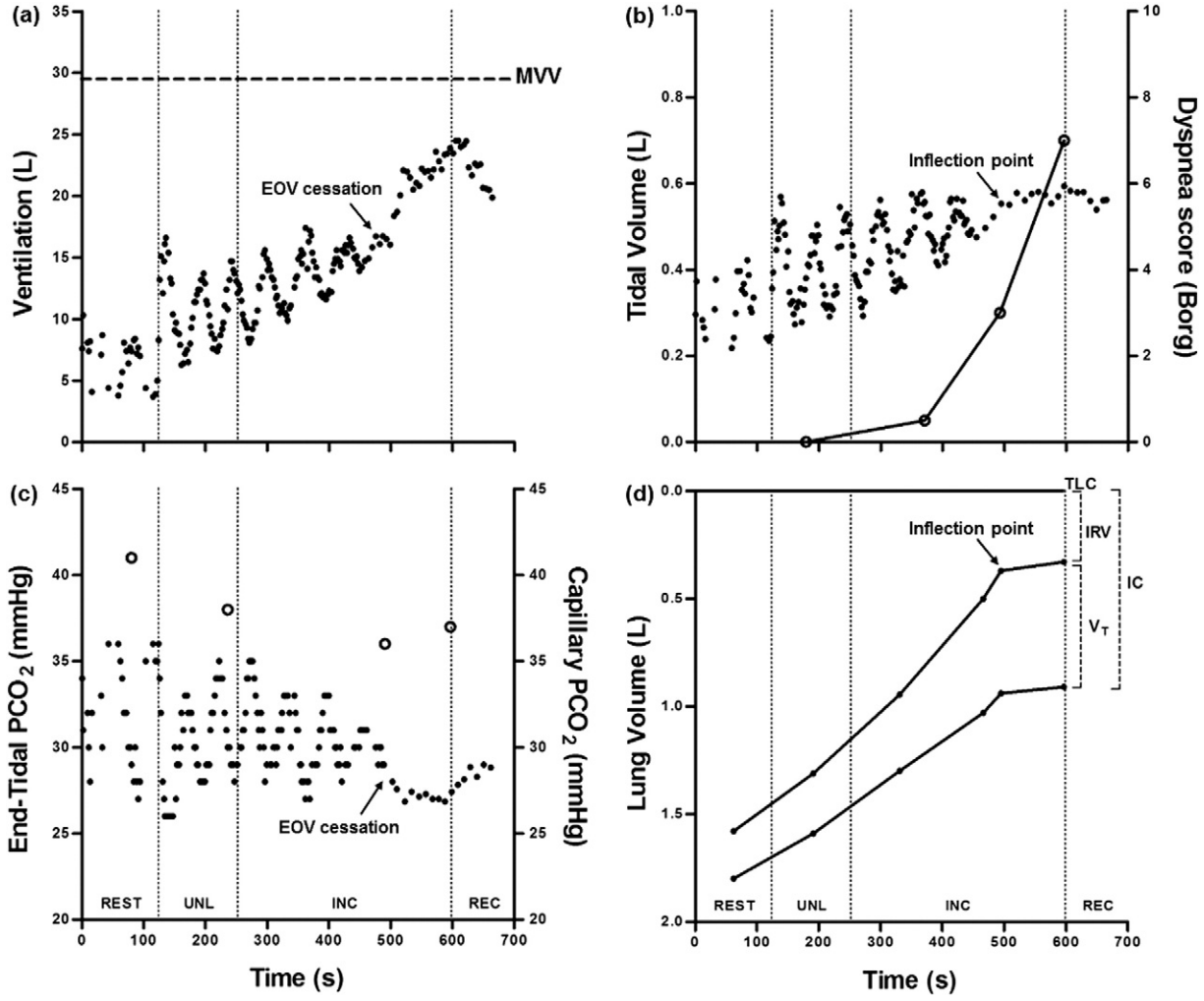

Fig. 1. Physiological and perceptual responses to incremental exercise in a representative patient with heart failure-COPD (female, age = 63 yrs., height = 146 cm) presenting with exercise oscillatory ventilation (EOV). *Abbreviations*: MVV = maximal voluntary ventilation; TLC = total lung capacity; IRV = inspiratory reserve volume; VT = tidal volume; IC = inspiratory capacity.