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Exertional acidotic responses in idiopathic pulmonary fibrosis: The mechanisms of exertional dyspnea

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ABSTRACT

To understand the mechanism of exertional dyspnea, we postulated that, despite hyperoxia during exercise, patients with idiopathic pulmonary fibrosis (IPF) might not regulate exertional acidosis by ventilatory compensation to stop exercise. The exercise responses during 30% O_2 or compressed air (CA) were examined in 13 patients with IPF. The PaO_2, $PaCO_2$, and HCO_3^- levels were higher during exercise with hyperoxia than with CA. At peak exercise, hyperoxia reduced the plasma lactate level. The dyspnea-ratio (%) of the $\Delta\dot{V}_{O_2}$ (peak minus resting oxygen uptake) curve reached a break point that occurred at a similar exercise point with hyperoxia and CA, preceded by a break point in the breathing frequency-ratio of the $\Delta\dot{V}_{O_2}$. Accordingly, the dyspnea score and pH each reached similar levels with hyperoxia and CA to stop exercise. Regardless of breathing CA or 30% O_2, IPF patients did not regulate exertional acidosis by ventilatory compensation to stop exercise, resulting in reaching a specific pH.

1. Introduction

Exertional dyspnea is a major symptom that often leads to activity limitation in patients with idiopathic pulmonary fibrosis (IPF) (ATS/ERS, 2000; Gross and Hunninghake, 2001). In some IPF patients, the degree of exercise-induced hypoxemia may be very severe, but the intensity of dyspnea might not be so severe. Though the mechanism of the exertional dyspnea is multifactorial (ATS, 1999; O'Donnell et al., 1998; Parshall et al., 2012) and is incompletely understood, we previously showed that, in patients with restrictive and obstructive lung diseases, under normoxia: (i) the changes in exercise-induced acidosis were associated with the intensity of exertional dyspnea and (ii) the dyspnea and sympathetic break points during exercise occurred similarly in these patients at the lactate threshold point (Miki et al., 2009, 2010, 2012). In addition, regardless of the inhaled oxygen concentration, (i) patients with chronic obstructive pulmonary disease (COPD) did not develop ventilatory compensation for exertional acidosis, and stopped exercise to reach a specific pH level and (ii) their hyperoxic conditions did not alter the pattern of exertional dyspnea during a standardized exercise program (Miki et al., 2012). Between obstructive and restrictive lung diseases, there are obvious pathological differences (O'Donnell et al., 2009), but investigating the common mechanism of exertional dyspnea may be interesting and helpful in the management of these patients. We postulated that, despite hyperoxia during exercise, patients with IPF might not regulate exertional acidosis using ventilatory capacity to stop exercise, resulting in reaching a specific pH level.

In a randomized, single-blind study of patients with stable IPF, exercise responses to compressed air (CA) and 30% O_2 were compared in terms of dyspneic pattern, as well as cardiopulmonary, acidotic, and sympathetic parameters. Whether the dyspnea break point, which was identified in patients inhaling CA during exercise, is also affected with inhaling 30% O_2 was also investigated.

2. Methods

2.1. Subjects

This study included 13 clinically stable patients with IPF who developed exertional dyspnea while performing routine tasks. The entry criteria included: (i) clinically stable IPF (no respiratory infection for at least 4 weeks prior to the study); (ii) absence of any other

Abbreviations: BMI, body mass index; CA, compressed air; COPD, chronic obstructive pulmonary disease; CPET, cardiopulmonary exercise testing; *f*, breathing frequency; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; HCO_3^-, bicarbonate ion; HR, heart rate; IPF, idiopathic pulmonary fibrosis; iso-time, standardized endurance time during exercise; LT, plasma lactate level; MVV, maximum voluntary ventilation; NE, plasma norepinephrine level; $PaCO_2$, arterial carbon dioxide tension; PaO_2, arterial oxygen tension; PFT, pulmonary function testing; THR, target heart rate; VC, vital capacity; $\dot{V}_E$, minute ventilation; $\dot{V}_{O_2}$, oxygen uptake; VT, tidal volume.

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Table 1
Patients' baseline characteristics ($n = 13$).

Age, years	68.5 (5.8)
Sex, male/female	11/2
BMI, kg/m^2	22.8 (2.2)
Smoking history	
Never smoker/smoker	5/8
Pulmonary function	
FEV1, L	1.79 (0.39)
%FEV1, % predicted	69.8 (10.1)
FEV1/FVC, %	88.3 (10.4)
VC, L	2.21 (0.55)
%VC, %	71.4 (13.2)
RV/TLC	32.7 (6.7)
FRC	1.88 (0.5)
%DLco, %	49.0 (9.7)

Data are presented as means (SD) unless otherwise stated.
Abbreviations: BMI, body mass index; DLco, diffusing capacity for carbon monoxide; FEV1, forced expiratory volume in 1 s; FRC, functional residual capacity; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; VC, vital capacity.

significant diseases, including neuromuscular diseases, malignancies, cardiac diseases, anemia, peripheral vascular diseases, and/or any disorders of the pleura or chest wall, including respiratory muscle weakness; (iii) no sympatholytic, sympathomimetic, corticosteroid, or immunosuppressive treatment before and at the time of the study; (iv) able to tolerate cardiopulmonary exercise testing (CPET) for at least 4 min (i.e., ≥4 measurement points) to ensure adequate evaluation; and (v) exercise limitation caused primarily by exertional dyspnea on CPET (i.e., breathing discomfort either alone or in conjunction with leg discomfort was the primary reason for stopping exercise). The 13 patients with IPF satisfied the clinical criteria for IPF of the ATS/ERS (ATS/ERS, 2000). The presence of all of the major diagnostic criteria, as well as at least three of the four minor criteria, was required for diagnosis (ATS/ERS, 2000). High-resolution computed tomography scans were assessed independently by three experienced readers; all three readers had to agree in order that the chest radiographic diagnosis be confirmed. In one patient who did not meet the clinical criteria due to a slightly reduced VC (%VC, 90.1%), the results of surgical lung biopsy, which demonstrated the histological findings of usual interstitial pneumonia, were accepted for making the diagnosis of IPF. In addition, high-resolution computed tomography findings did not show obvious findings of combined pulmonary fibrosis and emphysema (CPFE) in any patient. None of the patients had previously qualified for long-term oxygen therapy before the time of CPET. Table 1 shows the participants' characteristics.

2.2. Study design

The study was conducted from 2004 through 2011 according to the Declaration of Helsinki and Good Clinical Practice guidelines. Our institutional review board approved the randomized, single-blinded protocol. After providing their written, informed consent, the patients were familiarized with all procedures, which comprised two CPETs in random order. That is, the patients breathed either Fio_2 30% O_2 or CA (Fio_2 21%), recovered for 30 min (washout), and then breathed the other mixture. The participants breathed through a mask attached to a low resistance, two-way, non-rebreathing valve (total dead space, 150 mL) that was injected with 30% O_2 and CA from gas cylinders into a 200-L Douglas bag for inspiration during CPET. The participants were blinded to which oxygen concentration they breathed. CPETs were performed in the afternoon, and the patients avoided caffeine, heavy meals, alcohol, and major physical exertion before CPET.

2.3. Cardiopulmonary exercise testing (CPET)

Symptom-limited exercise tests were conducted using a treadmill with the Sheffield (Sheffield, 1972) or one of two modified Sheffield protocols and a CPET system (Vmaxs-29C, CareFusion 207, Palm Springs, CA, USA) (Miki et al., 2009). The exercise protocol was selected after considering the intensity of the subject' s daily activities and the pulmonary function test results. CPET was performed until patient exhaustion or the presence of signs indicating that exercise should stop. Expired gas data were measured breath-by-breath and collected as 30-s averages at rest, during exercise at 2-min intervals, and at end-exercise. In addition, dyspnea (Borg scale), leg fatigue intensity, and arterial blood were analyzed at rest and during the last 15 s of each exercise stage and at end-exercise. Blood gases were analyzed, and plasma norepinephrine and lactate values were measured in blood samples as described earlier (Miki et al., 2009).

2.4. Pulmonary function testing (PFT)

The patients underwent PFT using an Autospirometer System 9 (Minato Medical Science; Osaka, Japan) within two weeks before CPET, as described previously (Miki et al., 2009).

2.5. Data and statistical analysis

Break point. A break point was determined for each patient using the intersection of two lines on plots of individual dyspnea-$\dot{V}_{O_2}$, lactate (LT)-$\dot{V}_{O_2}$, norepinephrine (NE)-$\dot{V}_{O_2}$, and breathing frequency-$\dot{V}_{O_2}$ curves during exercise (Miki et al., 2009). To illustrate the relationship between the cardiorespiratory parameters and each standardized oxygen uptake, namely the ratio (%) of Δoxygen uptake ($\dot{V}_{O_2}$) (=peak $\dot{V}_{O_2}$ – resting $\dot{V}_{O_2}$) that occurs during exercise, the values of the parameters at each ratio of $\dot{V}_{O_2}$ were calculated for each patient by linear interpolation between adjacent measurement points, as previously described (Miki et al., 2009).

Iso-time was defined as the highest equivalent exercise time for each subject. The values of the cardio-respiratory parameters at Iso-time were calculated by linear interpolation between adjacent measurement points for each subject.

Sample size calculation. It was estimated that at least 11 patients were needed to detect a change in the Borg dyspnea scale of 1 point induced by supplemental 30% oxygen, which was calculated using an estimated SD of 1.1, as found at our laboratory, for a one-sample two-tailed test, $\alpha = 0.05$, and a power of 0.80 (Machin et al., 2008).

The data are expressed as means ± SD or SE unless otherwise indicated. The exercise changes between CA and 30% O_2 were analyzed using paired *t*-tests. The statistical significance of differences due to interaction between the exercise phase and oxygen mixture was determined using repeated-measures ANOVA. All data were analyzed using Statview 5.0 (Abacus Concepts, Berkeley, CA). *P* values of 0.05 were regarded as significant.

3. Results

3.1. Peak exercise responses to oxygen

The distribution of reasons for stopping exercise did not differ after either 30% O_2 or CA. Most participants stopped primarily because of dyspnea (30% O_2, 92% versus CA, 92%), and fewer stopped because of a combination of dyspnea and leg discomfort (30% O_2, 8% versus CA, 8%) regardless of what they inhaled. Endurance time was significantly increased by 30% ± 44% (mean ± SD) while breathing 30% O_2. The breathing frequency (f), minute ventilation ($\dot{V}_E$), and