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Physiological insights of exercise hyperventilation in arterial and chronic thromboembolic pulmonary hypertension☆

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ABSTRACT

Background: Pulmonary hypertension (PH) patients show, during exercise, an excessive increase in ventilation (V_E) compared to carbon dioxide output (VCO_2), determining a high V_E/VCO_2 slope. There are several possible causes, including an elevated dead space ventilation (V_D), V_E/perfusion (Q) mismatch and/or an enhanced peripheral or central chemoreceptor activity. We evaluated the causes of exercise hyperventilation in PH patients.
Methods: Eighteen group I and IV PH patients underwent cardiopulmonary exercise test with blood gas analysis at every minute. V_E, alveolar ventilation (V_A) and V_D vs. VCO_2 relationship were calculated. Resting chemoreceptor sensitivity was analyzed through hypoxia/hypercapnia tests.
Results: PeakVO_2 and V_E/VCO_2 slopes were 1.06 ± 0.24 l/min and 39.1 ± 9.0, respectively. Throughout the exercise, 30% of V_E was due to V_D. V_E/VCO_2 slope significantly correlated with V_D/VCO_2 slope ($r = 0.82$, $p < 0.001$) but not with V_A/VCO_2 slope ($r = 0.3$, p = ns). Peak exercise end-tidal CO_2 ($PetCO_2$) correlated with V_D/VCO_2 slope ($r = -0.79$, $p < 0.001$) and V_E/VCO_2 slope ($r = -0.91$, $p < 0.001$). Dead space(DS)/Tidal volume and P(arterial-et)CO_2 were elevated without arterial hypoxemia suggesting a high V_E/Q mismatch. Chemoreceptor peripheral response to hypoxia and central CO_2 response were both enhanced being peripheral responses to hypoxia and hypercapnia 0.416 ± 0.402 (normal ref values = 0.285 ± 0.221) l/min/O_2Sat and 0.076 ± 0.047 (0.066 ± 0.430) l/min/mmHg, respectively; central hypercapnic chemosensitivity was 4.475 ± 3.99 (2.352 ± 0.936) l/min/mmHg.
Conclusions: Increased DS, V_E/Q mismatch and chemorecptor response are among the main mechanisms involved in exercise hyperventilation in PH.
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1. Introduction

Pulmonary hypertension (PH) is still a disease with a deadly prognosis. Therefore, early signs of patients' clinical status deterioration should be looked for carefully to allow, whenever possible, treatment up-titration [1]. In this regard, cardiopulmonary exercise test (CPET) is considered among the most sensitive tools. Specifically, V_E/VCO_2 slope (V_E = total ventilation, VCO_2 = carbon dioxide output) is an important parameter for severity grading and prognosis: the steeper the slope, the worse both disease severity and prognosis. Indeed, patients with PH show, during incremental exercise, a pronounced hyperventilation that leads to an excessive increase in V_E compared to VCO_2, determining a high V_E/VCO_2 slope [2]. Exercise hyperventilation and therefore a high V_E/VCO_2 slope is associated with an elevated ventilation-perfusion (V_E/Q) mismatch and/or an enhanced chemoreceptor activity due to increased sympathetic stimulation [3,4]. Indeed in chronic thromboembolic (CTEPH) and arterial pulmonary hypertension (PAH) physiologic dead space is increased, there is a shift in mean alveolar ventilation/perfusion (V_A/Q) to higher than normal V_A/Q, together with less efficient gas exchange. Mild-to-moderate arterial hypoxemia and hypocapnia are multifactorial being not only related to V_E/Q mismatch and to gas diffusion impairment, but also to the decreasing mixed venous oxygen saturation (PvO_2) and to the development of right-to-left shunt [5,6]. Moreover an increase in circulating catecolamines in PH patients has been previously shown in some reports [7,8] but not in others [9,10]. Velez-Roa et al. [4] demonstrated

Abbreviations: AT, anaerobic threshold; CPET, cardiopulmonary exercise test; DS, dead space; $PaCO_2$, partial pressure of carbon dioxide; PAH, pulmonary arterial hypertension; P(a-et)CO_2, end tidal-to-arterial carbon dioxide pressure gradient; $PetCO_2$, peak exercise end-tidal carbon dioxide; PH, pulmonary hypertension; VCO_2, carbon dioxide output; V_D/V_T ratio, dead space/tidal volume ratio; V_E, pulmonary ventilation; V_D, dead space ventilation; V_A, alveolar ventilation; V_E/Q, ventilation-perfusion.

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an increase in muscle sympathetic activity by microneurography which was partially counteracted by hyperoxia. Regardless the chemoreflex activity and its relation with hyperventilation has never been previously studied. Indeed, both the central and the peripheral chemoreceptor systems regulate the ventilatory response to stimuli such as hypoxia and hypercapnia. For example, patients with heart failure show an increased chemoreceptor sensitivity, which is among the primary causes of the enhanced ventilatory response to exercise frequently reported and considered among the strongest heart failure prognostic markers [11].

In conclusion, there are at present no data concerning peripheral or central chemoreceptor activity in patients with PH and about its influence on the ventilatory response during exercise. Indeed, the intense ventilatory response to exercise in PH subjects is likely due to the increase in dead space ventilation (V_D), which reflects an enhanced V_E/Q mismatch, but a causative/modulating role of chemoreceptor hyperactivity is undefined.

Aim of the present study is to evaluate the role of peripheral (O_2/CO_2) or central (CO_2) chemoreceptor activity and of the V_E/Q mismatch in the genesis of exercise-induced hyperventilation in PH patients of group I and IV. To do so, we tested the chemoreceptor response at rest, both applying hypoxic and hypercapnic stimuli, and the ventilatory response during exercise, analyzing its two components, V_A and V_D.

2. Methods

2.1. Patient selection and study procedures

Sixteen group I PAH patients, including 4 cases with connective tissue disease, and two group IV PH patients in stable hemodynamic status and on optimized medical therapy were evaluated.

Inclusion criteria were: a) age ≥ 18 and ≤80, b) ability to understand the research protocol and willingness to sign the study informed consent, c) diagnosis of class I and IV PH d) stable hemodynamic status and optimized medical treatment for at least 2 months; e) ability to perform maximal CPET and evaluation of pulmonary diffusing capacity for carbon monoxide (D_LCO).

The exclusion criteria were: comorbidities influencing per se exercise performance, usual contraindications for CPET, PH associated with left heart and pulmonary disease, congenital heart diseases with evident cardiac shunts, continuous oxygen therapy.

The protocol was approved by the local ethics committee (CE n. CCM257, ClinicalTrials.gov NCT02892981), and it was performed in accordance with institutional guidelines and with the Declaration of Helsinki. All patients provided written informed consent before entering the study.

All patients enrolled in the study underwent a familiarization CPET in order to customize the exercise protocol so as to get a duration of approximatively 10 min. CPET was performed with a cycle ergometer, in a standard sitting position, and ventilatory gas concentration and flow were measured and analyzed breath by breath (Sensor Medics, VMax Spectra-229, Yorba Linda, CA) using a mask or a mouthpiece to compute ventilatory and gas exchange variables. Exercise was self-terminated by the patients when they felt exhaustion.

Within a week from the familiarization CPET, patients underwent spirometry, alveolar-capillary diffusion for carbon monoxide test and study CPET; after positioning a small arterial cannula in the radial or brachial artery, blood gas analysis was carried out at rest and every minute during loaded exercise. V_E and expiratory gas concentration were measured breath by breath. Anaerobic threshold (AT) was measured using a standard methodology [12].

Oxygen uptake (VO_2) at peak exercise and at AT, partial pressure of end-tidal carbon dioxide ($PetCO_2$) values at rest, at peak and at AT, and peak respiratory gas exchange ratio (RER) are reported as a 20-second average. V_E/VCO_2 slope was measured throughout the exercise considering all breaths. V_D was calculated rearranging the V_E equation: $V_D = V_D/V_T * V_E$ being $V_D/V_T = (PaCO_2\text{-}PECO_2) / PaCO_2$ and $PECO_2 = 863 * VCO_2 / V_E$, where VT = tidal volume, $PaCO_2$ is the arterial partial pressure of CO_2, $PECO_2$ is the average expiratory partial pressure of CO_2 and 863 is a constant. V_A was then calculated as $V_E - V_D$. V_D and V_A vs. VCO_2 relationship were calculated by linear regression analysis using the ventilatory data recorded every minute along with blood gas analysis. When compared with V_D and V_A vs. VCO_2, the V_E vs. VCO_2 relationship was calculated using the data obtained in correspondence of arterial blood samples and not of each breath.

The evaluation of peripheral and central chemoreceptor sensitivity was performed through hypoxia and hypercapnia tests. The hypoxia test was based on the transient hypoxia; V_E and arterial oxygen saturation (O_2Sat) by peripheral pulse oximetry were measured. The patient inhaled nitrogen for 2–8 breaths repeating the maneuver 10–15 times, in order to obtain a spectrum of O_2Sat ranging between 100% and 70%. The chemoreceptor sensitivity value was calculated as the slope of the trend line between maximum V_E (average of two consecutive breaths) and minimum O_2Sat values in response to any hypoxic stimulus (Fig. S1). The peripheral response to hypercapnia [13] was evaluated through the single-breath technique (the patient inhaled a mixture of 13% CO_2 in air for a single breath); V_E and end-expiratory CO_2 fraction ($FetCO_2$) were measured. The sensitivity of the chemoreceptor was calculated using the following formula: $V_Es\text{-}V_Ec$ / ($FetCO_2s\text{-}FetCO_2c$) * (PB-47), where s and c indicate the data collected after hypercapnic stimulus and those collected during control air breathing, respectively; PB is the atmospheric pressure in mmHg (Fig. S2). Finally, the evaluation of the central response to hypercapnia was made through a re-breathing technique (the patient breathed through a reservoir containing 7% CO_2 and 93% O_2 for 4 min); V_E and $PetCO_2$ were evaluated. The slope of the curve describing the relationship between V_E and $PetCO_2$ identified the central chemoreceptor sensitivity (Fig. S3) [14,15].

2.2. Statistical analysis

Continuous variables are presented as mean ± standard deviation. Categorical variables are presented as frequencies and percentages. The correlation between variables was assessed using linear regression analysis. A best-fit straight line was used to analyze linear data sets. Statistical significance was accepted at $p < 0.05$.

3. Results

Patients' clinical characteristics are reported in Table 1. All patients performed the entire research protocol. The standard spirometry and diffusing capacity for carbon monoxide (D_LCO) showed a forced vital capacity (FVC) of 87 ± 22%, a forced expiratory volume in 1 s (FEV1) of 82 ± 20% (predicted value), a FVC/FEV1 of 77.2 ± 8.52%, a D_LCO of 60 ± 16% (predicted value). CPET parameters are reported in Table 2. The peak respiratory gas exchange ratio (RER) was 1.08 ± 0.08, indicating that some subjects may not have performed a real maximal effort. The V_E/VCO_2 relationship was linear throughout the exercise test in 14 out of 18 patients, while in 4 patients the respiratory compensation point, defined by an increase in V_E/VCO_2 slope with a reduction in $PetCO_2$, was identified near the end of the exercise. These latter 4 patients showed a better exercise performance as evidenced by a greater peak VO_2 and workload (peak VO_2 = 1.27 ± 0.2 l/min in the 4 patients with two distinct V_E/VCO_2 slopes vs. 1.00 ± 0.2 in the remaining 14 patients, p = 0.02; peak workload 87.3 ± 16.5 watts and 59.3 ± 22.4, respectively, p = 0.03). Table 3 shows

Table 1
Baseline characteristics of PH patients.

Demographics	
N	18
Sex male (%)	7 (39)
Age (years)	56 ± 15
BMI (kg/m^2)	24.9 ± 3.39
LVEF (%)	61.5 ± 4.4
Systolic blood pressure (mmHg)	117 ± 14
Diastolic blood pressure (mmHg)	70 ± 8
Heart rate (beats/min)	70 ± 10
NYHA class II (%)	17 (94%)
NYHA class III (%)	1 (6%)
Atrial fibrillation (%)	2 (11%)
PH group 1 (%)	16 (89%)
PH group 4 (%)	2 (11%)
Hemodynamic parameters	
PAPm (mmHg)	39 ± 11
PAWP (mmHg)	10 ± 3
CO (l/min)	4.76 ± 0.97
PVR (WU)	5.99 ± 3.60
Therapy	
Ambrisentan 5 mg/die (%)	4 (22)
Bosentan 250 mg/die (%)	4 (22)
Macitentan 10 mg/die (%)	8 (44)
Tadalafil 40 mg/die (%)	4 (22)
Sildenafil 60 mg/die (%)	9 (50)
Inhaled Iloprost 30 mcg/die (%)	1 (6)
Riociguat 7.5 mg/die (%)	1 (6)

BMI = body mass index, LVEF = left ventricular ejection fraction as assessed by echocardiography, NYHA = New York Heart Association, PH = pulmonary hypertension, PAPm = mean pulmonary artery pressure, PAWP = pulmonary capillary wedge pressure, CO = cardiac output, PVR = pulmonary vascular resistance.