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Effect of pulmonary hypertension on exercise capacity and gas exchange in patients with chronic obstructive pulmonary disease living at high altitude

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Abstract

Background: Pulmonary hypertension (PH) is associated with decreased exercise tolerance in chronic obstructive pulmonary disease (COPD) patients, but in the altitude the response to exercise in those patients is unknown. Our objective was to compare exercise capacity, gas exchange and ventilatory alterations between COPD patients with PH (COPD-PH) and without PH (COPD-nonPH) residents at high altitude (2640 m). Methods: One hundred thirty-two COPD-nonPH, 82 COPD-PH, and 47 controls were included. Dyspnea by Borg scale, oxygen consumption (VO_2), work rate (WR), ventilatory equivalents (VE/VCO_2), dead space to tidal volume ratio (V_D/V_T), alveolar-arterial oxygen tension gradient ($AaPO_2$), and arterial-end-tidal carbon dioxide pressure gradient ($Pa\text{-}ETCO_2$) were measurement during a cardiopulmonary exercise test. For comparison of variables between groups, Kruskal-Wallis or one-way ANOVA tests were used, and stepwise regression analysis to test the association between PH and exercise capacity. Results: All COPD patients had a lower exercise capacity and higher $PaCO_2$, $A\text{-}aPO_2$ and V_D/V_T than controls. The VO_2 % predicted (61.3 ± 20.6 vs 75.3 ± 17.9; $p < 0.001$) and WR % predicted (65.3 ± 17.9 vs 75.3 ± 17.9; $p < 0.001$) were lower in COPD-PH than in COPD-nonPH. At peak exercise, dyspnea was higher in COPD-PH ($p = 0.011$). During exercise, in COPD-PH, the PaO_2 was lower ($p < 0.001$), and $AaPO_2$ ($p < 0.001$), $Pa\text{-}ETCO_2$ ($p = 0.033$), VE/VCO_2 ($p = 0.019$), and V_D/V_T ($p = 0.007$) were higher than in COPD-nonPH. In the multivariate analysis, PH was significantly associated with lower peak VO_2 and WR ($p < 0.001$). Conclusion: In COPD patients residing at high altitude, the presence of PH was an independent factor related to the exercise capacity. Also, in COPD-PH patients there were more dyspnea and alterations in gas exchange during the exercise than in those without PH.

Keywords

Pulmonary hypertension, chronic obstructive pulmonary disease, altitude, exercise tolerance, cardiopulmonary exercise test

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Introduction

Chronic obstructive pulmonary disease (COPD) is the most prevalent chronic respiratory disease worldwide and is the cause of the highest number of deaths and disability-adjusted life-years attributable to these chronic diseases.[1] Pulmonary hypertension (PH) is a common complication of COPD that is associated with increased morbidity and decreased survival.[2–4] Moreover, a recent meta-analysis

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showed that exercise tolerance is significantly lower in patients with COPD and PH (COPD-PH) than in patients with COPD without PH (COPD-nonPH).[5]

Although there is not a consensus, high altitude is usually defined as an elevation over 2500m (~8200 feet).[6] Although the physiological responses to hypobaric hypoxia start at lower elevations, they are more pronounced above this altitude and the risk of developing altitude illness also increases substantially.[7] In the altitude, the barometric pressure (BP) decreases and therefore the inspired oxygen pressure (PIO_2) and arterial oxygen pressure (PaO_2) also decrease. The increase in ventilation with the decrease of the arterial carbon dioxide pressure ($PaCO_2$) is the main compensating mechanism that attenuates the drop in the PaO_2.[8] In Bogotá, a city located at high altitude (2640 m, BP: 560 mmHg), the $PaCO_2$ at rest in healthy subjects is around 33 mmHg and the PaO_2 65 mmHg, with values lower than 60 mmHg in elderly[9] and even lower in COPD patients.[10,11] In a previous study in COPD patients residing in Bogotá, we demonstrated a high prevalence of PH, particularly in patients with less severe airflow obstruction.[12] Although there are several pathophysiological mechanisms related to the development of PH, probably the alveolar hypoxia at high altitude is a fundamental factor to promote and develop PH in these patients.[13,14]

In patients with COPD living at high altitude, of all GOLD stages, including in those with mild obstruction, we have observed decreased exercise capacity and gas exchange alterations during a cardiopulmonary exercise test (CPET). Unlike similar studies at sea level, the degree of hypoxemia both at rest and during exercise in all degrees of COPD severity was higher, and due to adaptation mechanisms to altitude, there were changes in the ventilatory pattern with lower $PaCO_2$ values and higher ventilatory equivalents (VE/VCO_2).[11] Considering the coexistence of pathophysiological mechanisms related to both pulmonary vascular compromise and COPD, it is expected that the ventilatory and gas exchange alterations during exercise that we have described in patients with COPD residing at high altitude will be more severe in those patients with associated PH.

All studies that have evaluated the effects of PH on exercise capacity, ventilation and arterial blood gases (ABG) in COPD patients have been conducted at sea level.[5] Considering that the response to exercise is unknown in these patients who live at high altitude, our objective was to compare in a CPET, exercise capacity, ABG, and ventilatory alterations among COPD-PH and COPD-nonPH at the altitude of Bogotá.

Methods

Subjects

This was a retrospective study in two hundred and 14 consecutive COPD patients referred between 2000–2018 to the Pulmonary Function Tests Laboratory of the Fundacion Neumologica Colombiana located in Bogotá (2640m) for a CPET. The Institution's Research Ethics Committee approved the study and the use of the anonymous data sets (approval number 201112-17405). Patients with a transthoracic echocardiogram (TTE) available for review and performed in the 3 months before CPET were included. All patients had to have spirometry with forced expiratory volume in the first second (FEV_1)/forced vital capacity (FVC) ratio <0.7, clinical stability for at least 6 weeks, and be residents of Bogotá, to exclude acute changes due to ascent to altitude. To take as a reference the normal response during exercise at high altitude, 47 control subjects, with normal spirometry, of the same age and sex, non-obese, non-smokers, untrained and without a history of cardiopulmonary disease were included.

COPD patients had been referred to CPET for evaluation of exercise capacity, study of dyspnea and exercise limitation, assessment before pulmonary rehabilitation, or preoperative evaluation of benign extrathoracic pathologies. We excluded patients with other pulmonary diseases, chest deformity, pleural disease, or any other cardiac, respiratory, or systemic causes of PH, mainly left ventricular failure, valvular diseases, and thromboembolic pulmonary hypertension. Patients with permanent oxygen treatment were also excluded.

Functional tests at rest

Spirometry, maximal voluntary ventilation (MVV) and inspiratory capacity (IC) at rest were performed on a V-MAX 229d (Sensormedics Inc., Yorba Linda, CA, USA). A certified 3L syringe was used for calibration. Flows and volumes were reported according to BTPS conditions (body temperature, ambient pressure, saturated with water vapor). Spirometry was done according to the standards of the American Thoracic Society and European Respiratory Society and Crapo reference equations were used.[15,16]

Exercise test

Exercise capacity was determined with a symptom-limited incremental test on a cycle ergometer. The test began with a 3-min rest period, followed by 3 min of pedaling without load, with a subsequent increase in workload every minute until the maximum tolerated level was reached.[17] The increment (10–25 W) was individually selected depending on the reported exercise tolerance and resting functional impairment. Continuous recording of the electrocardiogram was performed. The work rate (WR), oxygen uptake (VO_2), CO_2 production (VCO_2), minute ventilation (VE), tidal volume (VT), respiratory frequency (fR), heart rate (HR), oxygen pulse (VO_2/HR), end-tidal carbon dioxide tension ($PETCO_2$), and VE/VCO_2 were recorded as mean values of

Table 1. Variables at rest in healthy controls and patients with chronic obstructive pulmonary disease with and without pulmonary hypertension (N = 261).

	Controls	COPD-nonPH	COPD-PH	p
Subjects	47	132	82	
Age, years	69.1 ± 4.0	69.8 ± 8.2	70.1 ± 9.0	0.802
BMI, kg/m^2	26.6 ± 3.0	26.1 ± 4.1	24.6 ± 4.9[a,b]	0.010
Smoking history, pack-years	—	37.0 (18.0–50.0)	30.0 (17.0–44.5)	0.214
FVC, L	3.13 ± 0.71	2.92 ± 0.85	2.50 ± 0.86[a,b]	<0.001
FVC, % predicted	104.8 ± 16.4	87.4 ± 17.2[a]	80.5 ± 22.0[a,b]	<0.001
FEV_1, L	2.41 ± 0.53	1.53 ± 0.57[a]	1.17 ± 0.50[a,b]	<0.001
FEV_1, % predicted	104.0 ± 16.5	59.3 ± 19.1[a]	50.2 ± 21.6[a,b]	<0.001
FEV_1/FVC, %	77.4 ± 4.8	52.7 ± 12.7[a]	47.3 ± 12.5[a,b]	<0.001
MVV, L/min	104.9 ± 25.6	64.7 ± 25.0[a]	47.2 ± 21.3[a,b]	<0.001
IC, L	2.27 ± 0.55	1.89 ± 0.57[a]	1.67 ± 0.53[a,b]	<0.001
Hemoglobin, g/dL	15.2 ± 1.3	15.7 ± 1.9	15.5 ± 2.4	0.349

Values as mean ± SD or median (P_{25}–P_{75}). P: one-way ANOVA or X^2.
BMI: body mass index; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1s; MVV: maximal voluntary ventilation; IC: inspiratory capacity.
[a]$p < 0.05$ vs. controls.
[b]$p < 0.05$ between COPD-nonPH versus COPD-PH.

30 s throughout the test. For data analysis, the average of these variables was evaluated during 3 min of rest and in the last minute of peak exercise. VO_2 values were compared with the reference values of Hansen et al.[18,19]

Arterial blood gases sample was taken from a single arterial puncture at rest and at peak exercise. The alveolar-arterial oxygen difference (A-aPO_2) was calculated using the alveolar gas equation: $FIO_2 \times (BP-47) - PaCO_2 \times [FIO_2 + (1 - FIO_2)/RER] - PaO_2$, where FIO_2 (inspired fraction of oxygen) = 0.2093, mean BP ∼ 560 mmHg and RER = measured respiratory exchange ratio. The dead space to tidal volume ratio (V_D/V_T) was calculated with the $PaCO_2$ and $PETCO_2$. The anaerobic threshold (AT) was determined non-invasively using the v-slope method.[17] The sensation of dyspnea and muscle fatigue at rest and at peak exercise were assessed using the Borg scale.[20] Because differences in exercise capacity were expected between the COPD groups, the dyspnea score was corrected for peak VE.[21] IC was measured at rest and at peak exercise and the exercise-rest change in IC was expressed in L and as percentage of IC predicted normal values.[22]

Pulmonary hypertension

The presence of associated PH was evaluated by TTE in all patients. The systolic pulmonary artery pressure (sPAP) was considered abnormally increased when the maximum tricuspid regurgitation peak velocity (TRV) was greater than 3.4 m/s, equivalent to an estimated systolic sPAP >50 mmHg (assuming right atrial pressure of 5 mm Hg),[23,24] which is accepted as a high probability of PH.[25] Seventy two patients with intermediate probability of PH (TRV 2.8–3.4 m/s) were excluded to avoid misclassification into the groups with and without PH. COPD-nonPH was defined when TTE was normal or the PH probability was low due to TRV ≤2.8 m/s (sPAP ≤36 mmHg), and there were no additional echocardiographic variables suggestive of PH.[25]

Data analysis

The normality of variables was tested using the Kolmogorov-Smirnov test. The mean and standard deviation or median and interquartile ranges for the quantitative variables and proportions for the qualitative variables were calculated. For the comparison of variables at rest and peak exercise between the 3 groups (COPD-nonPH, COPD-PH and control subjects), the non-parametric Kruskal-Wallis test or the one-way ANOVA test was used, with the Bonferroni post hoc test for multiple comparisons.

Stepwise regression analysis was used to test the association between PH, demographic and functional variables (age, sex, body mass index (BMI), FEV_1, FVC, ABG at rest) and exercise capacity (VO_2 in ml/min and WR in watts). Two-tailed hypotheses were formulated with a significance level of less than 0.05. The statistical program SPSS version 20.0 was used.

Results

Participant characteristics

Two hundred and 14 patients with COPD were analyzed, 62.1% men, 132 (61.7%) in the COPD-non-PH group and 82 (38.3%) in the COPD-PH one. The median (P_{25}–P_{75}) of sPAP in the COPD-PH group was 58.5 (53.0–67.0). The 47 controls included were the same age as the COPD patients.

Compared with the COPD-nonPH group, the BMI (p = 0.029), FVC (p = 0.028), FEV_1 (p = 0.003), and IC (p = 0.020) were lower in the COPD-PH group. There were no differences between the groups in age, sex, smoking index, or hemoglobin values (Table 1).

Exercise capacity and cardiovascular response

Chronic obstructive pulmonary disease patients had a lower exercise capacity than controls of the same age. In comparison to COPD-nonPH, COPD-PH patients reached lower VO_2 (892.1 ± 304.1 mL/min vs. 1154.9 ± 367.1, $p < 0.001$) and WR (58.7 ± 23.4 W vs. 80.3 ± 30.6; $p < 0.001$) at peak exercise (Figure 1). There was no difference in HR at peak exercise, but the VO_2/HR was significantly lower in the COPD-PH group (7.2 ± 2.5 vs 9.1 ± 3.3; $p < 0.001$) (Table 2).

Ventilatory response and symptoms

COPD-PH patients achieved a lower VE and VT at peak exercise than in COPD-nonPH, without differences in VE/VVM (p = 0.119), delta IC, L (p = 0.058) and VT/IC (p = 0.819). The VE/VCO_2 nadir was higher in COPD-PH (40.6 ± 9.0 vs 37.9 ± 6.2; p = 0.019) (Figure 2). At peak exercise, VE-adjusted dyspnea was higher in the COPD-PH group (p = 0.011). The main symptom to stop the exercise was fatigue of the lower limbs in normal subjects and in COPD-nonPH and dyspnea in the COPD-PH group (p = 0.010) (Table 2).

Arterial blood gases, dead space and $PETCO_2$

During exercise, PaO_2 and saturation were significantly lower and $PaCO_2$, A-aPO_2 and V_D/V_T significantly higher in all patients with COPD than in controls ($p < 0.001$). At rest, the PaO_2 and SaO_2 were lower and A-aPO_2 higher in COPD-PH patients than in the COPD-nonPH ($p <$ 0.001). Similarly, at peak exercise, the PaO_2 and SaO_2 were lower ($p < 0.001$) and A-aPO_2 higher ($p < 0.001$) in COPD-PH patients than in the COPD-nonPH. Also, the VD/VT (p = 0.007) and Pa-$ETCO_2$ (p = 0.033) at peak exercise were higher in the COPD-PH group. There were no differences between COPD groups in the $PaCO_2$ (Table 3) (Figure 2).

Multivariate analysis

The multivariate analysis showed that the presence of PH was significantly associated with lower peak VO_2, adjusted by, age, sex, BMI, FEV_1 % predicted and $AaPO_2$ ($p <$ 0.001). Also, PH was associated with lower peak WR, adjusted by, age, sex, BMI and FEV_1 % predicted ($p <$ 0.001) (Table 4).

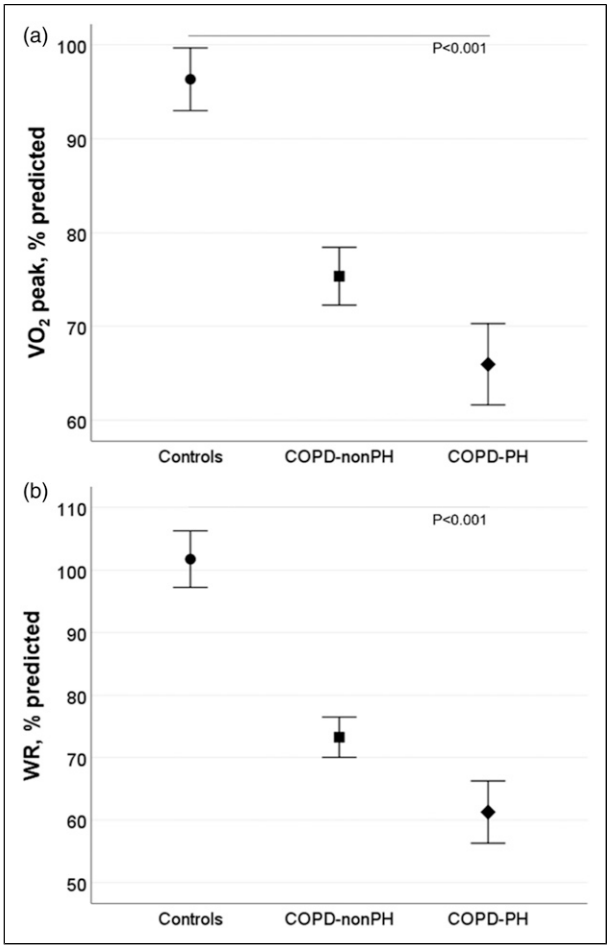

Figure 1. Oxygen consumption (a) and work rate (b) at peak exercise in healthy controls and COPD patients. VO_2: Oxygen consumption; WR: work rate. ●: controls; ■: COPD-nonPH; ♦: COPD-PH; P: one-way ANOVA.

Discussion

The main findings of this study, with a significant number of COPD patients residing at high altitude, were the following: (1) The presence of PH was an independent factor related to decreased exercise capacity in COPD patients. (2) There was more ventilatory inefficiency and gas exchange alterations during exercise, with higher VE/VCO_2, VD/VT, Pa-$ETCO_2$, and $AaPO_2$, and lower PaO_2 and SaO_2, in patients with COPD-PH than in COPD-nonPH. (3) In all COPD patients, there was ventilatory limitation for exercise, although this ventilatory limitation in COPD-PH occurred at a significantly lower peak WR compared to COPD-nonPH.[4] In comparison with studies at sea level, both in control subjects and patients with COPD residing at altitude, due to the lower PIO_2, hypoxemia at rest and during exercise was more severe, and because of the compensatory increase in ventilation, $PaCO_2$ and $PETCO_2$ were lower, and the VE/VCO_2 ratio higher.

Table 2. Peak exercise variables in healthy controls and chronic obstructive pulmonary disease patients with and without pulmonary hypertension (N = 261).

	Controls	COPD-nonPH	COPD-PH	p
Subjects	47	132	82	
WR, W	103.6 ± 34.8	80.3 ± 30.6[a]	58.7 ± 23.4[a,b]	<0.001
WR, % predicted	101.7 ± 14.9	73.3 ± 17.8[a]	61.3 ± 20.6[a,b]	<0.001
VO_2, ml/min	1412.3 ± 415.5	1154.9 ± 367.1	892.1 ± 304.1	<0.001
VO_2, % predicted	96.3 ± 11.4	75.3 ± 17.9	66.0 ± 19.7	<0.001
VO_2 AT, % predicted	63.5 ± 14.5	53.9 ± 14.0[a]	57.0 ± 18.7[a]	0.004
VO_2/kg, ml/kg/min	20.7 ± 4.0	16.9 ± 4.8[a]	14.2 ± 4.0[a,b]	<0.001
$\Delta VO_2/\Delta WR$, ml/min/W	11.1 ± 1.8	10.3 ± 2.6	9.5 ± 2.7[a]	0.003
RER	1.17 ± 0.10	1.09 ± 0.12	1.04 ± 0.11[a,b]	<0.001
HR, beats/min	143.2 ± 12.3	129.5 ± 18.7[a]	126.7 ± 21.9[a]	<0.001
HR, % predicted	86.8 ± 7.1	78.7 ± 11.2[a]	77.0 ± 13.1[a]	<0.001
Oxygen pulse, ml/beat	10.0 ± 3.1	9.1 ± 3.3	7.2 ± 2.5[a,b]	<0.001
Oxygen pulse, % predicted	111.7 ± 15.0	97.1 ± 25.2[a]	87.3 ± 29.5[a,b]	<0.001
VE, L/min	60.9 ± 18.9	47.7 ± 16.2[a]	36.9 ± 13.2[a,b]	<0.001
VT, ml/min	1654.2 ± 456.7	1295.8 ± 392.7[a,b]	1065.3 ± 356.5[a,b]	<0.001
f_R, rpm	37.1 ± 6.6	37.1 ± 6.8	34.4 ± 6.7[b]	0.011
VE/MVV, %	58.3 ± 11.0	77.5 ± 17.5[a]	82.6 ± 20.6[a]	<0.001
VE/VCO_2 nadir	35.4 ± 3.4	37.9 ± 6.2	40.6 ± 9.0[a,b]	<0.001
Delta IC, L	—	-0.533 ± 0.336	-0.401 ± 0.341	0.058
Delta IC, % IC predicted	—	17.2 (11.7–28.2)	14.6 (8.9–19.9)	0.101
VT/IC	—	0.80 ± 0.13	0.81 ± 0.13	0.819
Dyspnea, Borg units	4.0 (3.0–6.0)	4.0 (3.0–5.0)	4.0 (3.0–6.0)	0.661
Dyspnea/VE peak	0.08 ± 0.05	0.11 ± 0.07	0.14 ± 0.10[a,b]	<0.001
Reason for stopping				
Breathing discomfort	13 (27.7)	51 (38.6)	46 (56.1)[a,b]	0.010
Leg discomfort	27 (57.4)	55 (41.7)	24 (29.3)[a]	
Both	7 (14.9)	26 (19.7)	12 (14.6)	

Values as mean ± SD, median (P_{25} - P_{75}) or N (%). P: one-way ANOVA or X^2.
WR: work rate; VO_2: oxygen uptake; AT: anaerobic threshold; RER: respiratory exchange ratio; HR: heart rate; VE: minute ventilation; VT: tidal volume; fR: respiratory frequency; MVV: maximal voluntary ventilation; VE/VCO_2: ventilatory equivalent for carbon dioxide; IC: inspiratory capacity. Delta IC: exercise-rest change in IC.
[a]$p < 0.05$ vs. controls.
[b]$p < 0.05$ between COPD-nonPH versus COPD-PH.

In this study in COPD patients living at high altitude, the presence of PH was a factor associated with decreased exercise capacity. This association was maintained after adjusting for FEV_1, BMI, sex, and age. Previous studies conducted at sea level have also shown lower VO_2[26–29] and WR[26,27,29–31] during exercise in patients with COPD-PH compared to those with COPD-without PH, data that have been confirmed in a recent meta-analysis.[5] In this meta-analysis, in addition to the differences in VO_2 and WR, a lower VO_2/HR was demonstrated in those patients with PH.[5] In contrast, other publications did not demonstrate the association between decreased exercise capacity and PH in patients with COPD,[32,33] which could be explained mainly by limited sample sizes.[5]

As expected, all patients with COPD had ventilatory limitation for exercise, dynamic hyperinflation (DH), and limitation in VT expansion, demonstrated by the decrease of the IC and the increase of the VE/MVV and VT/IC ratios,[34–36] without differences between groups, although the ventilatory limitation in COPD-PH occurred at a significantly lower peak WR compared to COPD-nonPH. Consistent with our findings, in a previous metanalysis, COPD-PH patients had lower peak VO_2 and WR than COPD-nonPH, with no differences in VE/MVV ratio between groups.[5] In addition to the ventilatory limitation, COPD-PH patients had lower VO_2/HR, and higher VE/VCO_2, VD/VT, Pa-$ETCO_2$, hypoxemia and A-aPO_2, than COPD-nonPH patients, probably related to the pulmonary vascular compromise.[37–39] The lower VO_2/HR is a manifestation of the alteration of the stroke volume that can be seen in the presence of PH. The ventilatory inefficiency (high VE/VCO_2 ratio) is a hallmark abnormality in patients with pulmonary vascular disease that primarily results from high VD/VT and the higher values of Pa-$ETCO_2$ and

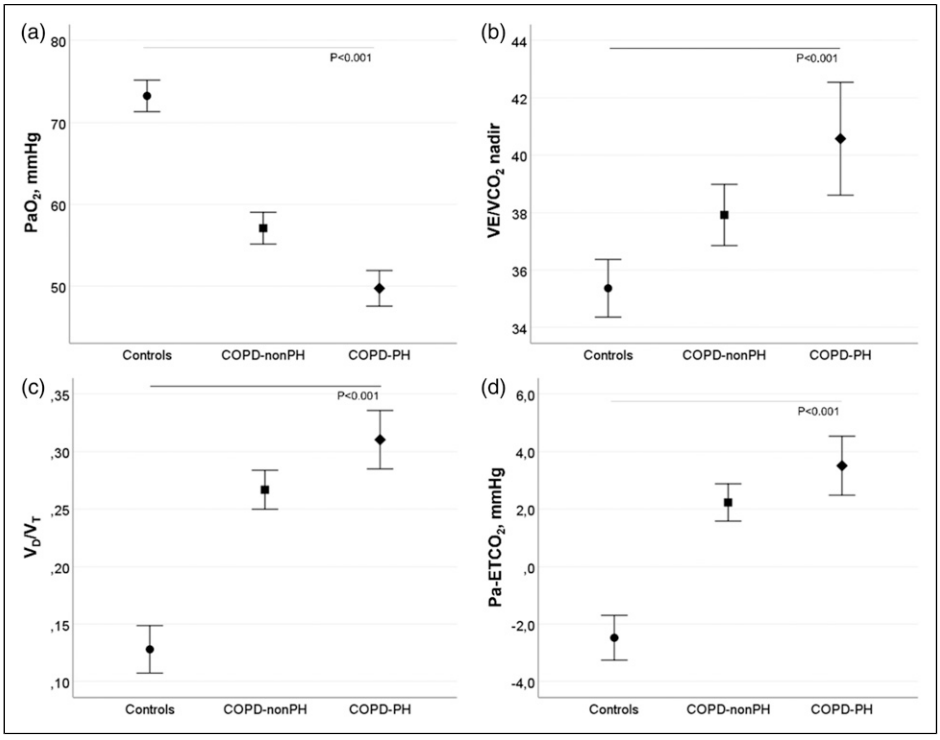

Figure 2. PaO_2 (a), VE/VCO_2 (b), V_D/V_T (c) and $Pa\text{-}ETCO_2$ (d) in healthy controls and COPD patients. PaO_2: partial pressure of arterial oxygen; VE/VCO_2: ventilatory equivalent for carbon dioxide; VD/VT: dead space to tidal volume ratio; $Pa\text{-}ETCO_2$: arterial-end-tidal carbon dioxide pressure gradient. ●: controls; ■: COPD-nonPH; ♦: COPD-PH; P: one-way ANOVA.

$A\text{-}aPO_2$ reflects ventilation/perfusion imbalance.[37–40] Increased VE/VCO_2 ratio is related to different mechanisms, generally coexisting, including mechanical ventilatory restrictions, gas exchange abnormalities, high VD/VT, enhanced chemosensitivity, and abnormal $PaCO_2$ set point.[40] In these COPD patients, there was a similar degree of DH, restrictive mechanical constriction, and $PaCO_2$, but in those with PH, there was greater VD/VT, hypoxemia, desaturation, elevated $Pa\text{-}ETCO_2$ and $A\text{-}aPO_2$, related probably to the pulmonary vascular disease, as already mentioned.

In addition to the lower exercise capacity, the COPD-PH patients presented more dyspnea at peak exercise than the COPD-nonPH group. This could be related to the greater compromise of gas exchange and probably to the greater ventilatory inefficiency, demonstrated by higher VE/VCO_2 ratio, which has been related to greater dyspnea on exercise in patients with COPD.[21,41] Although COPD-PH and COPD-non-PH patients had a similar decrease in IC during exercise, as already mentioned, this occurred at a lower WR. This would mean that the rate of development of DH was higher in COPD-PH, which could also explain the greater dyspnea during exercise in these patients. Unfortunately, we did not have IC and dyspnea measurements throughout the exercise to assess these dynamic changes.[35,36] All these greater ventilatory alterations in COPD-nonPH could lead to an earlier cessation of exercise with less fatigue of the lower limbs in this group. Although the dyspnea/VE ratio at peak exercise was higher in COPD-PH than in COPD-nonPH, we did not assess dyspnea as a function of VE and WR throughout the exercise, parameters for a better evaluation of the perceptual response during exercise in these patients.[41]

In this study, in both controls and COPD patients, $PaCO_2$ and $PETCO_2$ were lower and VE/VCO_2 higher, compared to descriptions at sea level, which is explained by higher ventilation, a well-recognized compensatory mechanism for adapting to altitude.[8,42] In studies conducted at sea level that have compared exercise capacity between COPD-nonPH and COPD-PH patients, there is great variability in the severity of the obstruction and information on alterations in gas exchange is limited. Although this makes comparison with our findings difficult, several of these studies report SpO_2 at rest and during exercise, which was higher than what we describe in the present study in both COPD-nonPH and COPD-PH.[26,27,30,32,33] Similarly, in a study of COPD patients residing in Bogota, but without evaluation of PH, we demonstrated that PaO_2 at rest and during exercise was lower than that reported at sea level, in patients of similar age and severity of the obstruction.[43] This low PaO_2 can be explained, in addition to V/Q alterations and hypercapnia, by the low PIO_2 secondary to the decrease in BP.[44]

Table 3. Gas exchange parameters at rest and peak exercise in healthy controls and chronic obstructive pulmonary disease patients with and without pulmonary hypertension (N = 261).

	Controls	COPD-nonPH	COPD-PH	p
Subjects	**47**	**132**	**82**	
pH				
Rest	7.44 ± 0.03	7.43 ± 0.03	7.43 ± 0.03	0.365
Peak exercise	7.36 ± 0.04	7.36 ± 0.04	7.37 ± 0.05	0.164
$PaCO_2$, mmHg				
Rest	31.0 ± 2.5	33.5 ± 4.5[a]	34.4 ± 5.3[a]	<0.001
Peak exercise	28.9 ± 2.8	35.1 ± 5.5[a]	36.4 ± 6.7[a]	<0.001
PaO_2, mmHg				
Rest	64.7 ± 5.6	56.8 ± 7.0[a]	52.8 ± 7.5[a,b]	<0.001
Peak exercise	73.2 ± 6.5	57.1 ± 11.2[a]	49.8 ± 9.5[a,b]	<0.001
HCO_3^-, me/L				
Rest	20.8 ± 1.7	22.1 ± 2.5[a]	22.7 ± 3.1[a]	<0.001
Peak exercise	16.2 ± 2.2	19.4 ± 2.9[a]	20.6 ± 3.6[a,b]	<0.001
SaO_2, %				
Rest	92.9 ± 1.9	88.8 ± 4.1[a]	85.6 ± 6.5[a,b]	<0.001
Peak exercise	93.9 ± 1.7	85.0 ± 8.2[a]	80.5 ± 9.0[a,b]	<0.001
A-aPO_2, mmHg				
Rest	7.8 ± 4.1	14.7 ± 6.0[a]	18.0 ± 6.0[a,b]	<0.001
Peak exercise	9.9 ± 5.7	19.3 ± 9.0[a]	24.3 ± 8.7[a,b]	<0.001
V_D/V_T				
Rest	0.31 ± 0.08	0.41 ± 0.09[a]	0.42 ± 0.09[a]	<0.001
Peak exercise	0.13 ± 0.07	0.27 ± 0.10[a]	0.31 ± 0.11[a,b]	<0.001
Pa-$ETCO_2$, mm Hg				
Rest	0.9 ± 3.1	4.0 ± 3.2[a]	4.8 ± 3.5[a]	<0.001
Peak exercise	−2.5 ± 2.7	2.2 ± 3.8[a]	3.7 ± 4.3[a,b]	<0.001

Values as mean ± SD. P: one-way ANOVA or X^2.
$PaCO_2$: partial pressure of arterial carbon dioxide; PaO_2: partial pressure of arterial oxygen; HCO_3^-: bicarbonate; SaO_2: oxygen arterial saturation; A-aPO_2: alveolar–arterial oxygen tension gradient; V_D/V_T: dead space to tidal volume ratio; $PETCO_2$: end-tidal carbon dioxide pressure; Pa-$ETCO_2$: arterial-end-tidal carbon dioxide pressure gradient.
[a]$p < 0.05$ vs. controls.
[b]$p < 0.05$ between COPD-nonPH versus COPD-PH.

We highlight the significant number of patients with PH in this study, which is correlated with a previous study at the same altitude in which we showed a high prevalence of PH in patients with COPD, even in GOLD stages 1 and 2, which is probably related with the exposure to chronic hypoxemia at high altitude.[12] On the other hand, the high sPAP values could be explained by the fact that the patients included in the COPD-PH group had to have a TTE with a high probability of PH.

This is the first study conducted at high altitude, which assesses exercise capacity and gas exchange alterations in COPD patients with PH. We resalt the significant number of COPD patients and the inclusion of control subjects that allowed comparisons between groups, and the measurement of ABG and the ventilatory variables that allowed us to comprehensively evaluate the limiting mechanisms of exercise in these patients with PH.

A limitation of the study was having used TTE to determine the presence of PH. Although TTE is not the gold standard to confirm PH, due to its low cost, availability, and safety, it is a widely used tool in clinical practice to assess the presence of PH in COPD patients.[45] The choice of two cut-off points, for high probability of PH (TRV> 3.4 m/s, equivalent to an estimated sPAP >50 mmHg) and low probability of PH (TRV <2.6 m/s, equivalent to an estimated sPAP <36 mmHg or normal TTE), excluding patients with estimated sPAP between 36 and 50, allowed us to reduce the misclassification bias of patients in the groups with and without PH.[25] Additionally, the usefulness of TTE has been demonstrated in a similar previous study, in which the presence of PH was correlated with exercise capacity in COPD patients, which gives our results more consistency.[29]

Considering that this is a retrospective study with a long period of patients inclusion, there are several possible methodological limitations that should be discussed. First, although the inclusion of patients was carried out for several years, the same protocol and equipment's from the same manufacturer were used. To standardize the predicted

Table 4. Multivariate analysis for peak VO_2 and WR in chronic obstructive pulmonary disease patients.

		Unstandardized coefficients		Standardized coefficients			95% Confidence interval for B	
		B	Std. error	Beta	t	*P*	Lower bound	Upper Bound
Peak VO_2, ml/min (*F=41.45, p<0.001, R^2=0.549*)	(Constant)	950.277	198.238		4.794	<0.001	559.419	1341.135
	PH	−92.473	37.979	-0.123	−2.435	0.016	−167.353	−17.592
	Sex	401.076	37.689	0.533	10.642	<0.001	326.767	475.385
	Age	−13.091	2.102	-0.305	−6.227	<0.001	−17.236	−8.946
	BMI	27.733	4.156	0.340	6.673	<0.001	19.539	35.927
	FEV_1, %	4.225	0.973	0.237	4.341	<0.001	2.306	6.145
	A-aPO_2	−8.671	3.043	−0.146	−2.849	0.005	−14.671	−2.671
Peak WR, W (*F = 46.63, p < 0.001, R^2 = 0.563*)	(Constant)	81.952	15.688		5.224	<0.001	50.997	112.907
	PH	−9.045	3.263	−0.145	−2.772	0.006	−15.484	−2.606
	Sex	34.883	3.278	0.555	10.642	<0.001	28.415	41.351
	Age	−1.379	0.179	−0.388	−7.703	<0.001	−1.732	−1.026
	BMI	1.656	0.354	0.248	4.673	<0.001	.957	2.355
	FEV_1, %	0.440	0.079	0.302	5.568	<0.001	.284	.596

PH: pulmonary hypertension; BMI: body mass index, FEV_1: forced expiratory volume in 1s; A-aPO_2: alveolar-arterial oxygen tension gradient.

values, the same reference values were used in all subjects. Another limitation was the non-use of an arterial line for taking ABG. The recommendation to use an arterial line instead of performing a direct arterial puncture[17] is based on the fact that if there is a delay in taking the sample at the end of the exercise, there may be an increase in PaO_2 compared to the peak exercise value, so the degree of hypoxemia could be underestimated.[46] Although this could indicate that the gas exchange alterations in our patients there could be even greater, we emphasize that the same protocol was performed in all patients and that the results show consistent differences between COPD-PH and COPD-nonPH. On the other hand, it has been described that there are no significant changes in $PaCO_2$ up to 2 minutes after exercise, which would not significantly alter our results. Despite being a study based on patients referred to CPET for different reasons, we excluded patients with other pulmonary and cardiovascular diseases or with other causes of PH that could affect the results. In addition, the sample was made up of patients with various degrees of severity and the classification of the study groups with and without PH was carried out using the same TTE criteria. Although COPD patients were on regular treatment and were free of exacerbations, we did not have a complete registry of medications that could modify exercise capacity in these patients. Finally, we do not have chest CT scans to establish the presence of emphysema or carbon monoxide diffusion tests to evaluate the relationship of these results with PH, gas exchange, and exercise capacity.[47–49]

The impact of PH on exercise capacity and the greater compromise in the ventilatory and gas exchange variables highlights the importance of evaluating the presence of PH in patients with COPD at altitude. Although there are studies that establish a relationship between mortality in COPD and PH, peak VO_2 and VE/VCO_2,[2,4,50] future studies should be carried out to evaluate the prognostic value of these variables, as well as the role of gas exchange alterations in COPD patients with and without PH living at high altitude.

Conclusions

In this study with a significant number of COPD patients and normal subjects residing at high altitude, we were able to establish that the presence of PH was an independent factor related to exercise capacity. In these patients with PH besides lower exercise capacity, dyspnea, ventilatory inefficiency, and gas exchange disturbances during exercise were greater than in COPD-nonPH. Unlike similar studies at sea level, the degree of hypoxemia both at rest and during exercise in these COPD patients was higher at the altitude of Bogotá.

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