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

Mauricio Gonzalez-Garcia¹,²,⁴ ●, Carlos Eduardo Aguirre-Franco¹,² ●, Leslie Vargas-Ramirez¹,³ ●, Margarita Barrero¹ ● and Carlos A Torres-Duque¹,² ●

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 (VO₂), work rate (WR), ventilatory equivalents (VE/VCO₂), dead space to tidal volume ratio (VD/VT), alveolar-arterial oxygen tension gradient (AaPO₂), and arterial-end-tidal carbon dioxide pressure gradient (Pa-ETCO₂) 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 PaCO₂, A-aPO₂ and VD/VT than controls. The VO₂ % 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 PaO₂ was lower (\( p < 0.001 \)), and AaPO₂ (\( p < 0.001 \)), Pa-ETCO₂ (\( p = 0.033 \)), VE/VCO₂ (\( p = 0.019 \)), and VD/VT (\( p = 0.007 \)) were higher than in COPD-nonPH. In the multivariate analysis, PH was significantly associated with lower peak VO₂ and WR (\( p < 0.001 \)). Conclusion: In COPD-PH 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

¹Pulmonary Function Testing Laboratory, Fundación Neumológica Colombiana, Bogotá, Colombia
²Faculty of Medicine, Universidad de la Sabana, Chía, Colombia
³Instituto Neumológico del Oriente, Bucaramanga, Colombia
⁴Faculty of Medicine, Sports Medicine Group, Universidad El Bosque, Bogotá, Colombia

Corresponding author:
Mauricio Gonzalez-Garcia, Fundación Neumológica Colombiana, CR 12B 161-85, Bogotá, Colombia.
Email: mgonzalez@neumologica.org
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 (PIO2) and arterial oxygen pressure (PaO2) also decrease. The increase in ventilation with the decrease of the arterial carbon dioxide pressure (PaCO2) is the main compensating mechanism that attenuates the drop in the PaO2.8 In Bogotá, a city located at high altitude (2640 m, BP: 560 mmHg), the PaCO2 at rest in healthy subjects is around 33 mmHg and the PaO2 65 mmHg, with values lower than 60 mmHg in elderly9 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 PaCO2 values and higher ventilatory equivalents (VE/VCO2).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 trans-thoracic 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 (FEV1)/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 cardio-pulmonary 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 (VO2), CO2 production (VCO2), minute ventilation (VE), tidal volume (VT), respiratory frequency (fR), heart rate (HR), oxygen pulse (VO2/HR), end-tidal carbon dioxide tension (PETCO2), and VE/VCO2 were recorded as mean values of
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. VO2 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-aPO2) was calculated using the alveolar gas equation: FIO2 × (BP-47) - PaCO2 × [FIO2 + (1 - FIO2)/RER] - PaO2, where FIO2 (inspired fraction of oxygen) = 0.2093, mean BP ∼ 560 mmHg and RER = measured respiratory exchange ratio. The dead space to tidal volume ratio (VD/VT) was calculated with the PaCO2 and PETCO2. 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), FEV1, FVC, ABG at rest) and exercise capacity (VO2 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 (P25–P75) 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.

### 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/m²           | 26.6 ± 3.0 | 26.1 ± 4.1 | 24.6 ± 4.9<sup>a,b</sup> | 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<sup>a,b</sup> | <0.001 |
| FVC, % predicted     | 104.8 ± 16.4 | 87.4 ± 17.2<sup>a</sup> | 80.5 ± 22.0<sup>a,b</sup> | <0.001 |
| FEV<sub>1</sub>, L    | 2.41 ± 0.53 | 1.53 ± 0.57<sup>a</sup> | 1.75 ± 0.50<sup>a,b</sup> | <0.001 |
| FEV<sub>1</sub>, % predicted | 104.0 ± 16.5 | 59.3 ± 19.1<sup>a</sup> | 50.2 ± 21.6<sup>a,b</sup> | <0.001 |
| FEV<sub>1</sub>/FVC, % | 77.4 ± 4.8 | 52.7 ± 12.7<sup>a</sup> | 47.3 ± 12.5<sup>a,b</sup> | <0.001 |
| MVV, L/min           | 104.9 ± 25.6 | 64.7 ± 25.0<sup>a</sup> | 47.2 ± 21.3<sup>a,b</sup> | <0.001 |
| IC, L                | 2.27 ± 0.55 | 1.89 ± 0.57<sup>a</sup> | 1.67 ± 0.53<sup>a,b</sup> | <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 (P25–P75). P: one-way ANOVA or X<sup>2</sup>. BMI: body mass index; FVC: forced vital capacity; FEV<sub>1</sub>: forced expiratory volume in 1 s; MVV: maximal voluntary ventilation; IC: inspiratory capacity. <sup>a</sup>p < 0.05 vs. controls. <sup>b</sup>p < 0.05 between COPD-nonPH versus COPD-PH.
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$_2$ ($892.1 \pm 304.1$ mL/min vs. $1154.9 \pm 367.1$, $p < 0.001$) and WR ($58.7 \pm 23.4$ W vs. $80.3 \pm 30.6$; $p < 0.001$) 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 ($7.2 \pm 2.5$ vs $9.1 \pm 3.3$; $p < 0.001$) (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 ($40.6 \pm 9.0$ vs $37.9 \pm 6.2$; $p = 0.019$) (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 VD/VT 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 ($p < 0.001$) 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 A-aPO$_2$ ($p < 0.001$). Also, PH was associated with lower peak WR, adjusted by, age, sex, BMI and FEV$_1$ % predicted ($p < 0.001$) (Table 4).

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**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.
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 FEV1, BMI, sex, and age. Previous studies conducted at sea level have also shown lower VO2 and WR during exercise in patients with COPD-PH compared to those with COPD-without PH, data that have been confirmed in a recent meta-analysis. In this meta-analysis, in addition to the differences in VO2 and WR, a lower VO2/HR was demonstrated in those patients with PH. In contrast, other publications did not demonstrate the association between decreased exercise capacity and PH in patients with COPD, which could be explained mainly by limited sample sizes.

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, 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 metaanalysis, COPD-PH patients had lower peak VO2 and WR than COPD-nonPH, with no differences in VE/MVV ratio between groups. In addition to the ventilatory limitation, COPD-PH patients had lower VO2/HR, and higher VE/VCO2, VD/VT, Pa-ETCO2, hypoxemia and A-aPO2, than COPD-nonPH patients, probably related to the pulmonary vascular compromise. The lower VO2/HR is a manifestation of the alteration of the stroke volume that can be seen in the presence of PH. The ventilatory inefficiency is a hallmark abnormality in patients with pulmonary vascular disease that primarily results from high VD/VT and the higher values of Pa-ETCO2 and

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

| Subjects | Controls | COPD-nonPH | COPD-PH | p |
|----------|----------|------------|---------|---|
| Subjects | 47 | 132 | 82 | | |
| WR, W | 103.6 ± 34.8 | 80.3 ± 30.6a | 58.7 ± 23.4ab | <0.001 |
| WR, % predicted | 101.7 ± 14.9 | 73.3 ± 17.8a | 63.1 ± 20.6ab | <0.001 |
| VO2, ml/min | 1412.3 ± 415.5 | 1154.9 ± 367.1 | 892.1 ± 304.1 | <0.001 |
| VO2, % predicted | 96.3 ± 11.4 | 75.3 ± 17.9 | 66.0 ± 19.7 | <0.001 |
| VO2 AT, % predicted | 63.5 ± 14.5 | 53.9 ± 14.0a | 57.0 ± 18.7a | 0.004 |
| VO2/kg, ml/kg/min | 20.7 ± 4.0 | 16.9 ± 4.8b | 14.2 ± 4.0ab | <0.001 |
| ∆VO2/∆WR, ml/min/W | 11.1 ± 1.8 | 10.3 ± 2.6 | 9.5 ± 2.7a | 0.003 |
| RER | 1.17 ± 0.10 | 1.09 ± 0.12 | 1.04 ± 0.11ab | <0.001 |
| HR, beats/min | 143.2 ± 12.3 | 129.5 ± 18.7a | 126.7 ± 21.9a | <0.001 |
| HR, % predicted | 86.8 ± 7.1 | 78.7 ± 11.2a | 77.0 ± 13.1a | <0.001 |
| Oxygen pulse, ml/beat | 10.0 ± 3.1 | 9.1 ± 3.3 | 7.2 ± 2.5ab | <0.001 |
| Oxygen pulse, % predicted | 111.7 ± 15.0 | 97.1 ± 25.2a | 87.3 ± 29.5ab | <0.001 |
| VE, L/min | 60.9 ± 18.9 | 47.7 ± 16.2a | 36.9 ± 13.2b | <0.001 |
| VT, ml/min | 1654.2 ± 456.7 | 1295.8 ± 392.7ab | 1065.3 ± 356.5ab | <0.001 |
| fn, rpm | 37.1 ± 6.6 | 37.1 ± 6.8 | 34.4 ± 6.7b | 0.011 |
| VE/MVV, % | 58.3 ± 11.0 | 77.5 ± 17.5a | 82.6 ± 20.6a | <0.001 |
| VE/VCO2 nadir | 35.4 ± 3.4 | 37.9 ± 6.2 | 40.6 ± 9.0ab | <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 ± 0.10ab | <0.001 |
| Reason for stopping | | | | |
| Breathing discomfort | 13 (27.7) | 51 (38.6) | 46 (56.1)ab | 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 (P25 - P75) or N (%). P: one-way ANOVA or X^2. WR: work rate; VO2: 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/VCO2: ventilatory equivalent for carbon dioxide; IC: inspiratory capacity. Delta IC: exercise-rest change in IC.

* p < 0.05 vs. controls.

** p < 0.05 between COPD-nonPH versus COPD-PH.
A-aPO2 reflects ventilation/perfusion imbalance.\textsuperscript{37-40} Increased VE/VCO\textsubscript{2} ratio is related to different mechanisms, generally coexisting, including mechanical ventilatory restrictions, gas exchange abnormalities, high VD/VT, enhanced chemosensitivity, and abnormal PaCO\textsubscript{2} set point.\textsuperscript{40} In these COPD patients, there was a similar degree of DH, restrictive mechanical constriction, and PaCO\textsubscript{2}, but in those with PH, there was greater VD/VT, hypoxemia, desaturation, elevated Pa-ETCO\textsubscript{2} and A-aPO\textsubscript{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\textsubscript{2} ratio, which has been related to greater dyspnea on exercise in patients with COPD.\textsuperscript{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.\textsuperscript{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.\textsuperscript{41}

In this study, in both controls and COPD patients, PaCO\textsubscript{2} and PETCO\textsubscript{2} were lower and VE/VCO\textsubscript{2} higher, compared to descriptions at sea level, which is explained by higher ventilation, a well-recognized compensatory mechanism for adapting to altitude.\textsuperscript{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\textsubscript{2} at rest and during exercise, which was higher than what we describe in the present study in both COPD-nonPH and COPD-PH.\textsuperscript{26,27,30,32,33} Similarly, in a study of COPD patients residing in Bogota, but without evaluation of PH, we demonstrated that PaO\textsubscript{2} at rest and during exercise was lower than that reported at sea level, in patients of similar age and severity of the obstruction.\textsuperscript{43} This low PaO\textsubscript{2} can be explained, in addition to V/Q alterations and hypercapnia, by the low PIO\textsubscript{2} secondary to the decrease in BP.\textsuperscript{44}

![Figure 2. PaO\textsubscript{2} (a), VE/VCO\textsubscript{2} (b), Vd/Vt (c) and Pa-ETCO\textsubscript{2} (d) in healthy controls and COPD patients. PaO\textsubscript{2}: partial pressure of arterial oxygen; VE/VCO\textsubscript{2}: ventilatory equivalent for carbon dioxide; VD/VT: dead space to tidal volume ratio; Pa-ETCO\textsubscript{2}: arterial-end-tidal carbon dioxide pressure gradient. ○: controls; ■: COPD-nonPH; ●: COPD-PH; P: one-way ANOVA.](image-url)
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. 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. 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. 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.

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 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). |
|---------------------------------------------------------------|
| Subjects | Controls | COPD-nonPH | COPD-PH | p       |
|---------------------------------------------------------------|
|                  | 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   |
| PaCO₂, mmHg       |          |            |         |
| Rest              | 31.0 ± 2.5 | 33.5 ± 4.5<sup>a</sup> | 34.4 ± 5.3<sup>a</sup> | <0.001 |
| Peak exercise     | 28.9 ± 2.8 | 35.1 ± 5.5<sup>a</sup> | 36.4 ± 6.7<sup>a</sup> | <0.001 |
| PaO₂, mmHg        |          |            |         |
| Rest              | 64.7 ± 5.6 | 56.8 ± 7.0<sup>a</sup> | 52.8 ± 7.5<sup>a</sup> | <0.001 |
| Peak exercise     | 73.2 ± 6.5 | 57.1 ± 11.2<sup>a</sup> | 49.8 ± 9.5<sup>a</sup> | <0.001 |
| HCO₃⁻, meq/L      |          |            |         |
| Rest              | 20.8 ± 1.7 | 22.1 ± 2.5<sup>a</sup> | 22.7 ± 3.1<sup>a</sup> | <0.001 |
| Peak exercise     | 16.2 ± 2.2 | 19.4 ± 2.9<sup>a</sup> | 20.6 ± 3.6<sup>a</sup> | <0.001 |
| SaO₂, %           |          |            |         |
| Rest              | 92.9 ± 1.9 | 88.8 ± 4.1<sup>a</sup> | 85.6 ± 6.5<sup>a</sup> | <0.001 |
| Peak exercise     | 93.9 ± 1.7 | 85.0 ± 8.5<sup>a</sup> | 80.5 ± 9.7<sup>a</sup> | <0.001 |
| A-aPO₂, mmHg      |          |            |         |
| Rest              | 7.8 ± 4.1  | 14.7 ± 6.0<sup>a</sup> | 18.0 ± 6.0<sup>a</sup> | <0.001 |
| Peak exercise     | 9.9 ± 5.7  | 19.3 ± 9.0<sup>a</sup> | 24.3 ± 8.7<sup>a</sup> | <0.001 |
| V̅D/V̅T           |          |            |         |
| Rest              | 0.31 ± 0.08 | 0.41 ± 0.09<sup>a</sup> | 0.42 ± 0.09<sup>a</sup> | <0.001 |
| Peak exercise     | 0.13 ± 0.07 | 0.27 ± 0.10<sup>a</sup> | 0.31 ± 0.11<sup>a</sup> | <0.001 |
| Pa-ETCO₂, mm Hg   |          |            |         |
| Rest              | 0.9 ± 3.1  | 4.0 ± 3.2<sup>a</sup> | 4.8 ± 3.5<sup>a</sup> | <0.001 |
| Peak exercise     | −2.5 ± 2.7 | 2.2 ± 3.8<sup>a</sup> | 3.7 ± 4.3<sup>a</sup> | <0.001 |

Values as mean ± SD. P: one-way ANOVA or χ².
PaCO₂: partial pressure of arterial carbon dioxide; PaO₂: partial pressure of arterial oxygen; HCO₃⁻: bicarbonate; SaO₂: oxygen arterial saturation; A-aPO₂: alveolar–arterial oxygen tension gradient; V̅D/V̅T: dead space to tidal volume ratio; PETCO₂: end-tidal carbon dioxide pressure; Pa-ETCO₂: arterial-end-tidal carbon dioxide pressure gradient.

<sup>a</sup>p < 0.05 vs. controls.
<sup>b</sup>p < 0.05 between COPD-nonPH versus COPD-PH.
instead of performing a direct arterial puncture is based on Another limitation was the non-use of an arterial line for 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 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 PaO₂ compared to the peak exercise value, so the degree of hypoxemia could be underestimated. 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 PaCO₂ 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 purposes, 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.

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 VO₂ and VE/VCO₂, 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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ORCID iDs
Mauricio Gonzalez-Garcia https://orcid.org/0000-0003-0768-1972
Carlos Eduardo Aguirre-Franco https://orcid.org/0000-0001-9001-0613

Table 4. Multivariate analysis for peak VO₂ 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 VO₂, ml/min (F=41.45, p<0.001, R²=0.549) |     |            |      |     |      |             |             |
| 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 |
| FEV₁, %                | 4.225 | 0.973 | 0.237 | 4.341 | <0.001 | 2.306 | 6.145 |
| A-aPO₂                 | -8.671 | 3.043 | -0.146 | -2.849 | 0.005 | -14.671 | -2.671 |
| PH /C₀                 | 92.473 | 37.979 | -0.123 | -2.435 | 0.016 | -167.353 | -17.592 |
| Sex /C₀               | 401.076 | 37.689 | 0.533 | 10.642 | <0.001 | 326.767 | 475.385 |
| Age /C₀               | -13.091 | 2.102 | -0.305 | -6.227 | <0.001 | -17.236 | -8.946 |
| BMI /C₀               | 27.733 | 4.156 | 0.340 | 6.673 | <0.001 | 19.539 | 35.927 |
| FEV₁, % /C₀           | 4.225 | 0.973 | 0.237 | 4.341 | <0.001 | 2.306 | 6.145 |
| A-aPO₂ /C₀            | -8.671 | 3.043 | -0.146 | -2.849 | 0.005 | -14.671 | -2.671 |

PH: pulmonary hypertension; BMI: body mass index; FEV₁: forced expiratory volume in 1s; A-aPO₂: alveolar-arterial oxygen tension gradient.

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ORCID iDs
Mauricio Gonzalez-Garcia https://orcid.org/0000-0003-0768-1972
Carlos Eduardo Aguirre-Franco https://orcid.org/0000-0001-9001-0613

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Mauricio Gonzalez-Garcia https://orcid.org/0000-0003-0768-1972
Carlos Eduardo Aguirre-Franco https://orcid.org/0000-0001-9001-0613
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