ORIGINAL ARTICLES

Exercise Limitation in Patients With Chronic Obstructive Pulmonary Disease at the Altitude of Bogota (2640 m): Breathing Pattern and Arterial Gases at Rest and Peak Exercise

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OBJECTIVE: To describe the response to exercise of normal subjects and patients with chronic obstructive pulmonary disease (COPD) in Bogota, Colombia (altitude: 2640 m; atmospheric pressure: 560 mm Hg) and compare it with data published on COPD patients at sea level. Healthy people increase their minute ventilation to attenuate hypoxemia ($PaCO_2$: 30 mm Hg; PaO_2: 63 mm Hg).

MATERIAL AND METHOD: A descriptive study was carried out on healthy subjects and COPD patients. Exercise limitation was determined by an incremental test on a cycle ergometer.

RESULTS: The study enrolled 16 healthy subjects and 25 COPD patients (forced expiratory volume in 1 second: 43.3% [SD 13%]). Minute ventilation at rest was greater in COPD patients compared with healthy subjects, it was not adequately sustained during exercise, and there was a reduction in peak oxygen uptake (53.0% [15%]). At peak exercise, inspiratory capacity decreased (–0.62 [0.34] L), the ratio of minute ventilation to maximal voluntary ventilation increased, and severe hypoxemia occurred (PaO_2: 49.9 [9.9] mm Hg). There was significant correlation between hypoxemia and the percentage of predicted peak oxygen uptake (r=0.60), leg fatigue (r=–0.62), percentage of predicted peak inspiratory capacity (r=0.61), and the percentage of predicted peak tidal volume (r=0.49). Minute ventilation at rest was shown to be higher, there was a greater reduction in the inspiratory capacity during exercise, and hypoxemia was more severe at rest and during exercise for patients with COPD in Bogota, compared with those at sea level.

CONCLUSIONS: Patients with COPD living in Bogota were shown to have lower tolerance to exercise evidenced by ventilatory limitation and severe hypoxemia. Increased minute ventilation at rest, greater reduction in inspiratory capacity, and severity of hypoxemia during exercise were the main differences between COPD in Bogota and at sea level.

Key words: *Chronic obstructive pulmonary disease. Exercise. Dynamic hyperinflation. Breathing pattern. Arterial blood gases. Altitude.*

Limitación a la tolerancia al ejercicio en pacientes con EPOC a la altura de Bogotá (2.640 m). Patrón respiratorio y gasometría arterial en reposo y en ejercicio pico

OBJETIVO: Describir la respuesta al ejercicio en sujetos normales y en pacientes con enfermedad pulmonar obstructiva crónica (EPOC) en Bogotá (altura: 2.640 m; presión atmosférica: 560 mmHg) y establecer diferencias con los datos publicados de pacientes con dicha enfermedad a nivel del mar. Las personas sanas a esta altura aumentan la ventilación alveolar para atenuar la hipoxemia (presión arterial de CO_2: 30 mmHg; presión arterial de O_2: 63 mmHg).

MATERIAL Y MÉTODO: Se realizó un estudio descriptivo en pacientes con EPOC y en sujetos sanos. La capacidad de ejercicio se determinó con una prueba incremental en un cicloergómetro.

RESULTADOS: Se incluyó en el estudio a 16 sujetos sanos y 25 pacientes con EPOC (volumen espiratorio forzado en el primer segundo del 43,3 ± 13%). En comparación con los sujetos sanos, en los pacientes con EPOC se observó un aumento de la ventilación minuto en reposo que no se mantuvo adecuadamente en el ejercicio, así como disminución del consumo de oxígeno pico (53,0 ± 15%). En ejercicio pico la capacidad inspiratoria disminuyó (–0,62 ± 0,34 l), la relación ventilación minuto/ventilación voluntaria máxima aumentó y hubo una intensa hipoxemia (presión arterial de O_2 de 49,9 ± 9,9 mmHg). Esta hipoxemia se correlacionó significativamente con el porcentaje del valor predicho del consumo de oxígeno pico (r = 0,60), la fatiga de los miembros inferiores (r = –0,62), el porcentaje predicho de la capacidad inspiratoria pico (r = 0,61) y el porcentaje predicho del volumen corriente pico (r = 0,49). En comparación con los datos publicados a nivel del mar, en los pacientes con EPOC la ventilación minuto en reposo fue mayor, hubo una mayor disminución de la capacidad inspiratoria durante el ejercicio y la hipoxemia fue más grave tanto en reposo como en ejercicio.

CONCLUSIONES: En los pacientes con EPOC residentes en Bogotá demostramos intolerancia al ejercicio determinada por limitación ventilatoria e hipoxemia severa. El aumento de la ventilación minuto en reposo, la mayor disminución de la capacidad inspiratoria y la gravedad de la hipoxemia durante el ejercicio fueron las principales diferencias con la EPOC a nivel del mar.

Palabras clave: *Enfermedad pulmonar obstructiva crónica. Ejercicio. Hiperinflación pulmonar. Patrón respiratorio. Gases arteriales. Altitud.*

Introduction

Exercise limitation in chronic obstructive pulmonary disease (COPD) is due to closely related patho-physiological mechanisms such as *a)* increase in airway resistance, airflow limitation, and dynamic hyperinflation; *b)* increase in respiratory muscle load; *c)* gas exchange abnormalities with hypoxemia and possibly hypercapnia and acidemia; *d)* hypoxic vasoconstriction which, together with inflammatory vascular remodeling, leads to pulmonary hypertension; *e)* peripheral muscle dysfunction; and *f)* systemic circulation of inflammatory mediators and metabolic, nutritional, and body composition disorders.[1-4]

The body undergoes physiological adaptation at the altitude of Bogota (2640 m; atmospheric pressure: 560 mm Hg) to reduce hypoxemia caused by the lower partial oxygen pressure. Healthy subjects adapt to this altitude mainly through an increase in minute ventilation, thus their breathing pattern at altitude is different from the pattern at sea level. $PaCO_2$ in healthy subjects in Bogota is 30 (SD 2) mm Hg because of this ventilatory adaptation.[5] In young people, normal PaO_2 ranges from 65.7 to 67.6 mm Hg and oxygen saturation from 92.2% to 93.5%.[5] Healthy subjects aged over 60 years also hyperventilate ($PaCO_2$: 30 mm Hg), but they show a slight decrease in PaO_2.[6] In patients with COPD, small decreases in PaO_2 can cause a large decrease in arterial oxygen saturation because of the position of PaO_2 on the hemoglobin dissociation curve. Hypoxic vasoconstriction may occur, which in turn may induce cor pulmonale.[7,8]

In addition to the well-documented ventilatory mechanisms, gas exchange abnormalities and pulmonary hypertension may therefore contribute to exercise limitation in patients with severe COPD in Bogota. Given the lack of research on limiting mechanisms, breathing pattern, and gas exchange at rest and at peak exercise at the altitude of Bogota, this study aimed to compare patients with COPD and normal subjects in Bogota. An additional objective was to compare our results with findings for patients with COPD at sea level.

Material and Method

A descriptive study was performed in outpatients of the Fundación Neumológica Colombiana who consented to participate in the exercise study and to undergo other tests and examinations that are common at their age. Patients with COPD (forced expiratory volume in 1 second [FEV_1]/forced vital capacity [FVC]<70%; FEV_1<60%) were enrolled provided they had been clinically stable for at least 4 weeks and were not in a pulmonary rehabilitation program. Patients with asthma, sequelae of tuberculosis, abnormalities in the chest cavity, bronchiectasis, and cardiovascular disorders other than cor pulmonale were excluded. An echocardiogram was taken for all patients. The study was approved by the local Institutional Review Board/Ethics Committee.

Lung Function Tests

Spirometric parameters and maximal voluntary ventilation (MVV) were determined for all subjects. Single-breath carbon monoxide diffusing capacity (DLCO) was measured in COPD patients with the V-MAX 229 system (Sensormedics Inc, Yorba Linda, CA, USA) in accordance with the guidelines of the American Thoracic Society. Carbon monoxide lung diffusion was adjusted to the altitude of Bogota (2640 m; atmospheric pressure: 560 mm Hg) with the Crapo reference equations.[9,10]

Exercise capacity was measured with an incremental test limited by symptoms on a cycle ergometer in conjunction with the V-Max 229 respiration gas analyzer. Oxygen uptake ($\dot{V}O_2$) and CO_2 production were compared with the reference values of Hansen et al.[11,12] The exercise test started with a 2-minute rest period followed by 2 minutes of pedaling with no load. The work load was then increased after every minute (5-10 W in patients with COPD and 10-15 W in healthy subjects) until the maximal tolerated load was reached. The increase in work load lasted for approximately 10 minutes with this procedure, in accordance with recommendations.[13] Electrocardiograms were recorded continuously and oxygen saturation was determined by continuous pulse oximetry. Minute ventilation (V_E), tidal volume (VT), respiratory rate, inspiratory time, expiratory time, total cycle time, inspiratory flow (VT/inspiratory time) and expiratory flow (VT/expiratory time) were averaged over 20-second intervals throughout the test. Averages during the 2-minute rest period and the last minute of peak exercise were used for data analysis. Arterial blood gases were sampled at rest and at peak exercise. The alveolar-arterial oxygen gradient $P(A-a)O_2$ was calculated with the simplified alveolar gas equation. The dead space/VT ratio was determined from expired CO_2 pressure.[13] The lactate threshold was derived noninvasively from the ventilatory parameters.[13,14] Perceived dyspnea and muscle fatigue were assessed using the Borg scale.[15]

Inspiratory capacity (IC) was measured at rest, every 2 minutes during exercise, and at peak exercise for all patients with COPD.[16-18] Reference values for IC were calculated as the difference between predicted values of total lung capacity and functional residual capacity.

Statistical Analysis

Means and standard deviations were calculated for quantitative parameters. The differences in mean spirometry parameters, peak exercise values, and arterial blood gases were compared with the Student *t* test for independent samples. The difference between IC at peak exercise and at rest in patients with COPD was compared using the Student *t* test for paired samples. The Pearson correlation coefficient was used to determine the degree of association between continuous variables. Two-sided hypotheses were tested at a significance level of .05. All analyses were performed with the SPSS program, version 10.0.

Results

Characteristics of Patients at Rest

Seven of the 25 patients with COPD were women. All patients had moderate obstruction (FEV_1: 43.3% [13%] of the predicted value) with decreased MVV (63.1% [22%] of the predicted value), normal or decreased IC at rest (80.2% [15%] of the predicted

value), and moderate to severe decrease in carbon monoxide lung diffusion (DLCO: 53.1% [26%] of the predicted value). Twenty-one of these patients (84%) had echocardiographic evidence of pulmonary hypertension. The spirometric parameters of the 16 healthy nonsmokers (7 women and 9 men) were normal, and their mean age and body mass index were similar to those of patients with COPD (Table 1).

Parameters During Exercise

Exercise was stopped in patients with COPD when symptoms of dyspnea (score on Borg scale: 6.4 [2.8]; range: 1-9) or leg fatigue (score on Borg scale: 5.1 [2.1];

range: 1-9) developed. No patient had to stop the test due to desaturation, arrhythmia, precordial pain, or other symptoms. At peak exercise, patients with COPD reached a lower work load than healthy subjects (52.0% [18%] compared with 100.3% [18%] of the predicted value; $P<.001$) and had a lower $\dot{V}O_2$ (53.0% [15%] compared with 92.5% [14%] of predicted; $P<.001$). In the patients who reached lactate threshold (14 out of 25), $\dot{V}O_2$ was lower than in healthy subjects (38.1% [8%] compared with 55.3% [13%] of predicted; $P<.001$). Patients with COPD had a lower heart rate (82.6 [11.3] bpm compared with 92.3 [6.4] bpm) and oxygen pulse (peak $\dot{V}O_2$/heart rate) (63.3% [14%] compared with 99.8% [13%]; $P<.001$). The V_E/MVV ratio was higher in patients with COPD (80.6 [16] compared with 56.2 [9]; $P<.001$). Peak VT (expressed as percentage of predicted FVC) and peak V_E (expressed as percentage of predicted MVV) were lower for patients with COPD. A significant decrease in IC from baseline to peak exercise was observed in patients with COPD for both the absolute value (-0.62 [0.34] L; 95% confidence interval, 0.43-0.79 L; $P<.001$) and percentage of predicted (21.9% [0.4%]; 95% confidence interval, 16.3-27.5%; $P<.001$) (Table 2).

Breathing Pattern

At rest, patients with COPD had significantly greater V_E and inspiratory flow than healthy subjects. During exercise, the increase in V_E was significantly lower in patients with COPD. Patients also had lower inspiratory and expiratory flows and lower VT. Healthy subjects had a lower decrease in inspiratory time than in expiratory time during exercise, therefore the inspiratory time/total cycle time ratio increased from 0.41 (0.005) at rest to 0.48 (0.03) at peak exercise

TABLE 1
Characteristics of Subjects Included in the Study

	Without COPD (n=16)	With COPD (n=25)
Age, years	58.2 (4.7)	60.7 (9.1)
BMI, kg/m²	26.6 (3.6)	23.9 (4.4)
FVC, L	3.61 (1.0)	2.95 (0.81)‡
FVC, % predicted	104.8 (11.6)	77.4 (13.6)†
FEV₁, L	2.79 (0.77)	1.29 (0.41)†
FEV₁, % predicted	100.5 (13.5)	43.3 (13.4)†
FEV₁/FVC, %	77.5 (5.6)	44.7 (11.5)†
MVV, L/min	122.2 (36.1)	53.8 (18.7)†
MVV, % predicted	127.5 (18.7)	63.1 (22.5)†
IC, L	–	2.19 (0.6)
IC, % predicted	–	80.2 (15.8)
DLCO, mL/mm Hg/min	–	14.68 (6.7)
DLCO, % predicted	–	53.10 (26.3)
DLCO/V$_A$, mL/mm Hg/min/L	–	3.20 (1.3)
DLCO/V$_A$, % predicted	–	65.7 (26.9)

*COPD indicates chronic obstructive pulmonary disease; BMI, body mass index; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second; MVV, maximal voluntary ventilation; IC, inspiratory capacity; DLCO, diffusing capacity of the lung for carbon monoxide; V$_A$, alveolar volume.
†$P<.001$; ‡$P<.05$.

TABLE 2
Parameters at Peak Exercise

	Witout COPD (n=16)	With COPD (n=25)	*P*
Work load, W	123.4 (42.1)	68.8 (30.1)	<.001
Work load, % predicted value	100.3 (18.7)	52.0 (18.6)	<.001
$\dot{V}O_2$, L/min	1597.3 (477.3)	904.0 (299.6)	<.001
$\dot{V}O_2$, % predicted value	92.56 (14.5)	53.04 (15.8)	<.001
$\dot{V}O_2$, mL/kg/min	23.1 (4.8)	13.8 (4.3)	<.001
$\dot{V}O_2$ at LT, L/min	965.7 (285.9)	634.7 (132.7)	.001
$\dot{V}O_2$ at LT, % predicted value	55.3 (13.0)	38.1 (8.4)	<.001
Heart rate, beats/min	148.6 (11.8)	132.7 (16.4)	.002
Heart rate, % predicted value	92.3 (6.4)	82.6 (11.3)	.001
Oxygen pulse, mL/beat	10.7 (2.9)	6.9 (2.2)	<.001
Oxygen pulse, %	99.8 (13.6)	63.3 (14.7)	<.001
V_E/VCO₂ at LT	37.2 (3.3)	47.1 (8.4)	<.001
V_E/MVV, %	56.2 (9.1)	80.6 (16.2)	<.001
MVV-V_E, L	55.1 (23.8)	12.1 (11.8)	<.001
Peak VT, % predicted FVC	53.4 (8.2)	31.8 (7.7)	<.001
Peak V_E, % predicted MVV	70.7 (9.9)	49.3 (15.1)	<.001
Peak IC, L	–	1.58 (.38)	–
Peak IC, % predicted value	–	58.3 (12.0)	–
ΔIC, L	–	–0.62 (.34)	–
ΔIC, % predicted value	–	–21.9 (0.4)	–

*COPD indicates chronic obstructive pulmonary disease; $\dot{V}O_2$, oxygen uptake; VCO₂, carbon dioxide production; LT; lactate threshold; V_E, minute ventilation; MVV, maximal voluntary ventilation; VT, tidal volume; FVC, forced vital capacity; IC, inspiratory capacity; ΔIC, peak IC–basal IC.

TABLE 3
Breathing Pattern and Arterial Blood Gases at Rest and at Peak Exercise

	Rest		Exercise	
	Witout COPD	With COPD	Witout COPD	With COPD
V_E, L	11.5 (1.96)[†]	13.6 (3.2)	67.1 (16.9)[‡]	41.7 (12)
VT, L	767 (389)	719 (157)	1851 (610)[†]	1191 (299)
RR, breaths/min	17 (5)	20 (4)	36 (7)	36 (8)
Ti, s	1.59 (0.5)[†]	1.22 (0.2)	0.82 (0.15)[‡]	0.70 (0.1)
Te, s	2.32 (0.9)	2.01 (0.5)	0.93 (0.31)	1.06 (0.3)
VT/Ti, L/s	0.493 (0.11)[†]	0.608 (0.1)	2.34 (0.57)[‡]	1.77 (0.4)
VT/Te, L/s	0.328 (0.06)	0.389 (0.1)	2.01 (0.42)[‡]	1.17 (0.4)
Ti/Ttot	0.41 (0.05)	0.38 (0.04)	0.48 (0.03)[‡]	0.40 (0.04)
$PaCO_2$, mm Hg	30.3 (2.4)	31.5 (3.9)	26.8 (2.9)[‡]	34.5 (4.8)
PaO_2, mm Hg	63.1 (3.6)[†]	52.9 (7.4)	73.3 (6.7)[‡]	49.9 (9.9)
SaO_2, %	92.4 (1.4)[†]	86.8 (4.3)	93.7 (1.5)[‡]	80.1 (10.2)
pH	7.42 (0.02)	7.41 (0.04)	7.32 (0.04)	7.32 (0.05)
HCO_3^-, mEq/L	20.2 (1.7)	20.1 (2.0)	14.6 (2.7)[‡]	17.7 (1.9)
$P(A-a)O_2$, mm Hg	8.7 (4.4)[†]	18.6 (8.4)	10.9 (6.2)[‡]	25.2 (10.3)
V_D/VT	0.33 (0.13)[†]	0.44 (0.11)	0.10 (0.08)[†]	0.33 (0.10)

*COPD indicates chronic obstructive pulmonary disease; V_E, minute ventilation; VT, tidal volume; RR, respiratory rate; Ti, inspiratory time; Te, expiratory time; VT/Ti, inspiratory flow; VT/Te, expiratory flow; Ti/Ttot; Ti/total time ratio; $PaCO_2$, arterial blood pressure of carbon dioxide; PaO_2, arterial blood pressure of oxygen; SaO_2, saturation of arterial blood oxygen; HCO_3^- bicarbonate; $P(A-a)O_2$, alveolar-arterial oxygen gradient; V_D/VT, dead space/tidal volume ratio.
Differences between healthy subjects and patients with COPD.
[†]$P<.05$ at rest; [‡]$P<.05$ during exercise

(P<.001). In contrast, patients with COPD showed a smaller decrease in expiratory time, leading to a slight increase in the inspiratory time/total cycle time ratio from 0.38 (0.04) at rest to 0.40 (0.04) at peak exercise (P=.48) (Table 3 and Figure 1).

Arterial Blood Gases and Gas Exchange

At rest, $PaCO_2$ was similar for patients with COPD and healthy subjects, but patients had significantly lower PaO_2 (52.9 [7.4] mm Hg) and oxygen saturation and higher $P(A-a)O_2$ and calculated dead space. During exercise, $PaCO_2$ increased, and PaO_2 (49.9 [9] mm Hg) and oxygen saturation (80.1% [10.2%]) decreased for patients with COPD whereas the opposite occurred for healthy subjects. For patients with COPD, there was a greater increase in $P(A-a)O_2$ and the dead space/VT ratio

did not decrease sufficiently. Metabolic acidemia was more severe in healthy subjects but patients with COPD showed a significant decrease in blood bicarbonate levels compared with values at rest (mean decrease: 2.34 [1.34] mEq/L; P<.001) (Table 3).

The parameters at rest that best correlated with peak $\dot{V}O_2$ were FEV_1 as a percentage of the predicted value (r=0.66) (Figure 2), MVV as a percentage of predicted and the FEV_1/FVC ratio (Table 4). The parameters at peak exercise that best correlated with peak $\dot{V}O_2$ were IC as a percentage of predicted (r=0.77) (Figure 3A), V_E as a percentage of predicted MVV (r=0.74) (Figure 3B), VT as a percentage of predicted FVC (r=0.61) (Figure 3C), and maximal inspiratory and expiratory flows. The arterial blood gas parameter that best correlated with peak $\dot{V}O_2$ during exercise was PaO_2 (r=0.60) (Figure 3D and
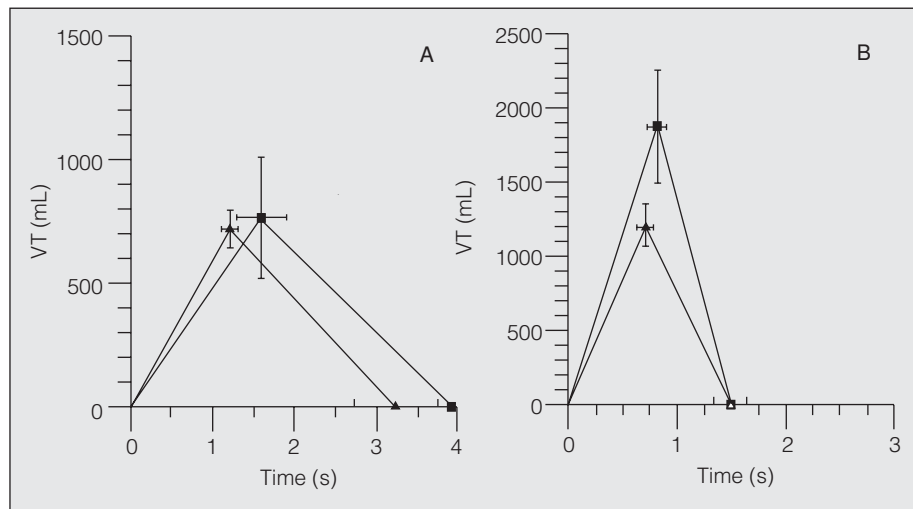

Figure. 1. Mean spirograms at rest (A) and at peak exercise (B) in healthy subjects (■) and patients with chronic obstructive pulmonary disease (▲). Inspiratory flows were significantly greater in patients than in healthy subjects, and at peak exercise the increase in inspiratory and expiratory flows was significantly lower, likewise for tidal volume (VT).
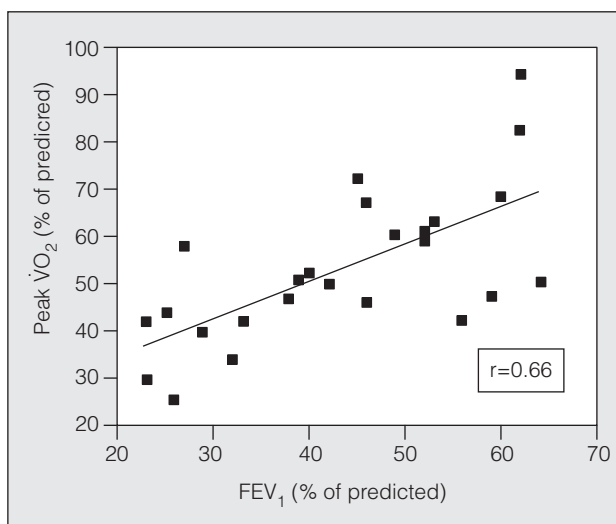
Figure 2. Correlation between peak oxygen uptake ($\dot{V}O_2$) and forced expiratory volume in 1 second (FEV_1) in patients with chronic obstructive pulmonary disease.

Table 4). Moreover, V_E at peak exercise (percentage of predicted MVV) correlated significantly with maximal inspiratory times (r=0.45) and maximal expiratory times (r=0.59), maximal flows (VT/inspiratory time [r=0.52] and VT/expiratory time [r=0.53]), VT (percentage of predicted FVC) (r=0.56), and decrease in the absolute IC value (r=–0.61) and IC as a percentage of predicted (r=–0.57).

With regard to the exercise limiting symptoms, dyspnea (change from resting to peak exercise) correlated with the degree of hyperinflation expressed as change in IC as a percentage of the predicted value (P=.045; r=0.61). Leg fatigue (change from resting to

TABLE 4
Parameters Related to Peak Oxygen Uptake

Parameter	r	r2	P
Resting			
FEV_1, %	0.66	0.44	<.001
MVV, %	0.67	0.45	<.001
FEV_1/FVC	0.52	0.27	.008
VT/Ti	–0.47	0.22	.018
VT/Te	–0.49	0.21	.013
DLCO, %	0.45	0.20	.038
Exercise			
PaO_2, mm Hg	0.60	0.36	.002
SaO_2, mm Hg	0.47	0.22	.020
$P(A-a)O_2$, mm Hg	0.50	0.25	.010
V_E, % predicted MVV	0.74	0.55	<.001
VT, % predicted FVC	0.61	0.37	.013
IC, %	0.77	0.59	<.001
ΔIC, L	–0.54	0.29	.030
Te, s	–0.51	0.26	.009
VT/Ti	0.41	0.17	.044
VT/Te	0.49	0.24	.013

FEV_1 indicates forced expiratory volume in 1 second; MVV, maximal voluntary ventilation; FVC, forced vital capacity; VT/Ti, inspiratory flow; VT/Te, expiratory flow; DLCO, diffusing capacity of the lung for CO; PaO_2, arterial blood pressure of oxygen; SaO_2, saturation of arterial blood oxygen; $P(A-a)O_2$, alveolar-arterial oxygen gradient; V_E, minute ventilation; VT, tidal volume; IC, inspiratory capacity; Te, expiratory time.

peak exercise) correlated with PaO_2 at peak exercise (P=.041; r=-0.62). PaO_2 at peak exercise correlated with peak work load in watts as a percentage of the predicted value (P<.001; r=0.69), peak IC as a percentage of the predicted value (P=.027; r=0.55), peak VT as a percentage of FVC (P=.015; r=0.49), and peak V_E as a percentage of MVV (P=.049; r=0.40), in addition to correlation with peak $\dot{V}O_2$ and muscle fatigue.

Discussion

This group of patients with COPD (FEV_1 of 43.3% [13%]) living in Bogota (altitude: 2640 m) showed exercise limitation due mainly to ventilatory limitation. The main differences between our population of patients with COPD and patients with COPD at lower altitudes were increased V_E at rest, a larger decrease in IC, and severe hypoxemia at peak exercise (49.9 [9.9] mm Hg). Although the PaO_2 of healthy subjects in this study (73 [6.7] mm Hg) would be considered hypoxemic at sea level, these subjects showed normal exercise capacity (peak $\dot{V}O_2$ of 92.5% [14%] and work load of 100.3% [18.7%]).

Exercise Capacity and Symptoms

The exercise capacity of patients with COPD was limited by significant dyspnea and leg fatigue, and low work load (52.0% [18%]) and $\dot{V}O_2$ (53.0% [15%]) compared with healthy subjects. Similar findings have been reported for patients with COPD at sea level.[1] We found a correlation between the increase in dyspnea according to the Borg scale and the decrease in IC, in agreement with other studies that attribute part of this exercise dyspnea to dynamic hyperinflation.[19] Leg fatigue was correlated with a decrease in PaO_2 at peak exercise, perhaps because of a decrease in oxygen supply to functionally impaired peripheral muscles.[3] Studies have shown that muscle fatigue during exercise improves with oxygen administration.[20,21]

Ventilatory Response and Breathing Pattern

The patients with COPD showed better ventilation at rest than healthy subjects, so $PaCO_2$ of patients was almost normal. The increase in V_E in comparison with healthy subjects is a mechanism to adapt to changes in the ventilation/perfusion ratio and the increase in dead space (dead space/V_T ratio).[4] However, V_E at rest in our patients with COPD was larger than that reported in other studies at sea level,[22] a finding that may be due to the greater ventilatory demand of hypoxemia at high altitude. This increase in V_E at rest was related to a significant increase in inspiratory flow compared with healthy subjects. Increased inspiratory flow, which is measured as a reflection of central respiratory drive,[23-25] would indicate increased drive in the presence of mechanical impedance, as described at altitudes lower
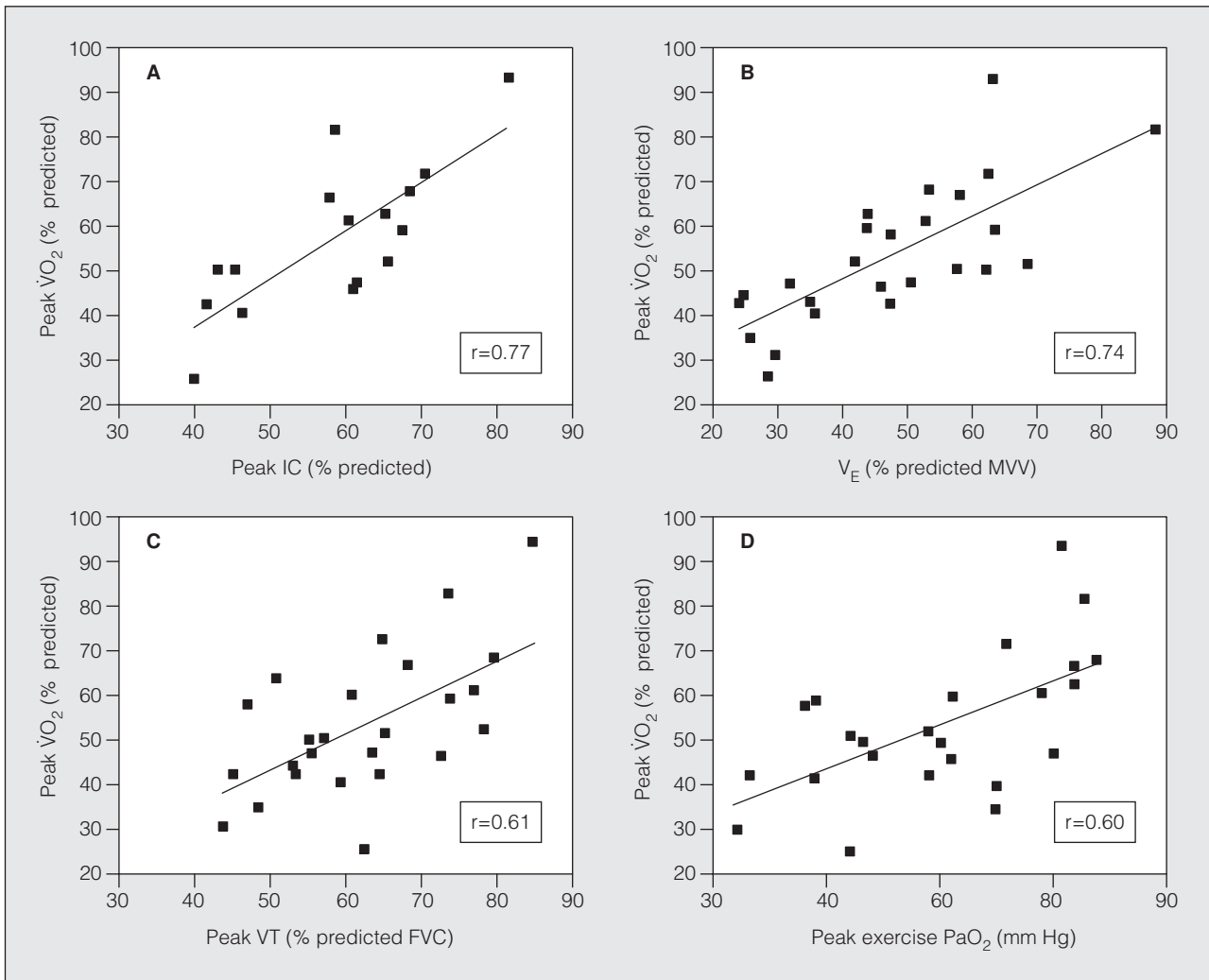
Figure 3. Correlation between peak oxygen uptake ($\dot{V}O_2$) and selected exercise parameters in patients with chronic obstructive pulmonary disease. A, inspiratory capacity (IC); B, minute ventilation (V_E); C, tidal volume (VT) and D, arterial blood pressure of oxygen (PaO$_2$). MVV indicates maximal voluntary ventilation; FVC, forced vital capacity.

than that of Bogota.[26-28]

Patients with COPD showed a decrease in peak V_E during exercise, an increase in the V_E/MVV ratio (80.6% [16%]), and dynamic hyperinflation evidenced by a decrease in IC at peak exercise (ΔIC: –0.62 [34] L). Unlike healthy subjects, the patients could not increase inspiratory and expiratory flows. This led to dynamic hyperinflation and ventilatory limitation which, according to several articles, is due to the unfavorable mechanical conditions of the respiratory muscles in COPD.[1,28,29] Patients with COPD tended to decrease the expiratory time less than healthy subjects during exercise, a strategy that caused a slight increase in inspiratory time/total cycle time. However, this was not enough to counteract the adverse functional consequences of dynamic hyperinflation in contrast to what happens at sea level.[3]

The decrease in IC at peak exercise in our patients (–0.62 [0.34] L) was greater than that found in other studies at lower altitude.[19,29,30] This could be due to a substantial emphysematous component (DLCO: 53.1% [26.3%]). Thus, dynamic hyperinflation increases because of a decrease in elastic recoil,[30] which is associated with an increase in ventilatory demand due partly to an increase in dead space but mainly to severe hypoxemia in our patients at peak exercise (PaO$_2$: 49.9 [9.9] mm Hg). Indeed, hypoxemia correlated with the size of peak IC as a percentage of the predicted value.

The significant relationship between exercise capacity and the ventilatory parameters—peak V_E (percentage of predicted MVV), peak VT (percentage of predicted FVC), and peak IC (percentage of predicted)—indicated that ventilatory limitation is clearly dependent on peak $\dot{V}O_2$ and the degree of dynamic hyperinflation, as expected. Given that peak V_E (percentage of MVV) had the strongest correlation with peak $\dot{V}O_2$, we analyzed its dependence on other variables, finding that the best predictors of V_E were,

once again, peak VT (percentage of FVC), maximal flows (VT/inspiratory time and VT/expiratory time), maximal inspiratory and expiratory times, and decrease in IC.

Hemodynamic Response

Peak heart rate of patients with COPD was lower than healthy subjects, and submaximal in some patients. Ventilatory limitation may have caused some patients to finish the exercise early so cardiovascular stress would be lower.[31] The oxygen pulse (mL/beat) was significantly smaller in these patients with COPD. The exact reason for this is hard to determine, but ventilatory limitation, poor physical condition, or severe hypoxemia may be important. A decrease in oxygen pulse as a hemodynamic consequence of dynamic hyperinflation has also been described, but in patients with more severe disease ($FEV_1 < 35\%$ of predicted) than those in this study.[32] The decrease in oxygen pulse might also indicate pulmonary vascular limitation, particularly because most of these patients had pulmonary hypertension at rest and patients with other types of heart disease were excluded from the study. Several studies have shown increased pulmonary vascular resistance and right ventricular overload during exercise in patients with COPD,[33-36] which could be worsened in our patients by vasoconstriction due to severe hypoxemia. No hemodynamic data during exercise are available from our study at the altitude of Bogota, but an increase in pulmonary vascular resistance was found (5.15 mm Hg/L^{-1}/min) in severely hypoxemic patients (PaO_2: 42 [7] mm Hg) with stable COPD (FEV_1: 45% [25%]). This increase in pulmonary vascular resistance decreased after administration of oxygen (4.77 mm Hg/L^{-1}/min), which suggests that pulmonary hypertension and hypoxemia are related at this altitude.[37] The lactate threshold could not be determined in 44% of our patients with the indirect methods used in this study, but all patients presented metabolic acidosis. When lactate threshold was determined, its value was low, possibly because of pulmonary hypertension and the poor physical condition of patients.

Arterial Blood Gases

At rest, arterial blood gases were normal or showed a slight increase in $PaCO_2$ in patients with COPD because of the compensating increase in V_E, as demonstrated by the study of breathing pattern. Despite the increase in V_E, our patients had mild or moderate hypoxemia compared with healthy subjects without COPD (PaO_2: 52.9 [7.4] mm Hg) and severe hypoxemia in comparison with patients with COPD at sea level, with an increase in $P(A-a)O_2$. At peak exercise, $PaCO_2$ increased, severe hypoxemia (PaO_2: 49.9 [9.9] mm Hg) and desaturation were observed, and $P(A-a)O_2$ increased in patients with severe COPD, in agreement with observations in similar patients at sea level.[1,3,38] The most important difference

in comparison with sea level was the more severe hypoxemia at rest and at peak exercise due mainly to the decrease in inspired oxygen pressure at this altitude. Dead space at rest increased compared with healthy subjects and remained high during exercise, a situation which, in combination with hypoxemia, increased the ventilatory demand of these patients.

The correlation of PaO_2 during exercise with peak $\dot{V}O_2$, peak work load, dynamic hyperinflation, and leg fatigue is of note because it suggests that severe hypoxemia in patients with COPD at the altitude of Bogota contributes to exercise limitation.

This study is important because there are no previous studies on exercise response in healthy subjects and patients with COPD living at this altitude (2640 m). We described some of the factors involved in exercise limitation in this group of patients and performed a detailed analysis of the breathing pattern and gas exchange alterations at rest and during exercise. Respiratory muscle function and peripheral muscle function are known to be impaired in patients with COPD, which may be one of the factors that limits exercise capacity.[39-42] Our study is therefore limited because we did not determine these muscle functions. The study was further limited by the lack of a more detailed evaluation of hemodynamic response and the role of pulmonary hypertension during exercise. In addition to an evaluation of muscle function and hemodynamic response during exercise, future research should include study of adaptive, presumably peripheral, mechanisms that explain the capacity of patients with COPD in Bogota to perform medium intensity physical exercise despite severe hypoxemia. We are also investigating the effect on exercise capacity of administration of different inspired oxygen fractions to patients with COPD and hypoxemia.

Conclusions

Patients with moderate to severe COPD living in Bogota (2640 m) showed a decrease in exercise capacity due mainly to ventilatory limitation. The main differences with sea level are the increase in V_E at rest, the larger decrease in IC during exercise and severe hypoxemia at rest and, above all, at peak exercise (49.9 [9.9] mm Hg). The correlation of peak PaO_2 with exercise capacity (VO_2 and peak work load), the ventilatory parameters (VT and peak IC) and symptoms (leg fatigue) suggest that severe hypoxemia contributes to exercise limitation in these patients.

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