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Aerobic exercise capacity in COPD patients with and without pulmonary hypertension

Céline Pynnaert [a], Michel Lamotte [b], Robert Naeije [a,*]

[a] *Department of Pathophysiology, Erasme University Hospital, Brussels, Belgium*
[b] *Department of Cardiology, Erasme University Hospital, Brussels, Belgium*

Summary

Pulmonary hypertension is a common occurrence in advanced COPD, but its effects on exercise capacity remain undetermined. Exercise testing and an echocardiographic examination were performed in 29 patients with advanced stable COPD. Mean pulmonary artery pressure (mPAP) was calculated from the acceleration time of pulmonary flow. Exercise capacity was evaluated by the distance walked in 6 min (6MWD) and by an incremental cardiopulmonary exercise test (CPET). The patients had a forced expiratory volume in 1 s of 1.13 ± 0.49 L, and a 6MWD of 305 ± 66 m (mean $\pm$ SD). The CPET ($n = 24$) showed a: maximum workload of 52 ± 25 W, a peak O_2 uptake of 13.8 ± 4.4 mL/kg/min, a peak heart rate of 127 ± 22 bpm, a peak respiratory exchange ratio 1.06 ± 0.11, a ventilation (V_E)/CO_2 production slope of 37 ± 11, and a peak O_2 pulse 7.5 ± 2.3 mL. The peak V_E was 41 ± 15 L/min, and the calculated maximum voluntary V_E 45 ± 20 L/min. There was no difference in any of the CPET variables and 6MWD between the patients with a mPAP < 30 mm Hg (mPAP 22 ± 6 mm Hg, $n = 15$) and those with a mPAP > 30 mm Hg (mPAP 38 ± 6 mm Hg, $n = 14$). There was no correlation between PAP and any of the exercise measurements. These results suggest that exercise capacity in unselected patients with advanced COPD and mild to moderate pulmonary hypertension is essentially limited by exhaustion of the ventilatory reserve.

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Introduction

Pulmonary hypertension is a common complication of advanced chronic obstructive pulmonary disease (COPD).[1,2]

Increased pulmonary artery pressure (PAP) in these patients is a cause of ''cor pulmonale'' traditionally defined by an alteration in structure and function of the right ventricle secondary to lung disease.[1,2] Pulmonary hypertension in COPD is associated with a decreased survival rate in proportion to increased PAP[3,4] even in patients on long term oxygen therapy.[5]

Exercise capacity is markedly reduced in COPD, in proportion to severity of the disease as assessed by the Global Initiative for Chronic Obstructive Lung Disease

* Corresponding author. Department of Pathophysiology, CP 604, Faculty of Medicine, Université Libre de Bruxelles, 808 Lennik road, B-1070 Brussels, Belgium. Tel.: +322 5553322; fax: +322 555 4124.
E-mail address: rnaeije@ulb.ac.be (R. Naeije).

(GOLD) staging system.[6] Both peak O_2 uptake (VO_2) and the distance walked in 6 min (6MWD) have been reported to be predictors of survival in COPD.[7] Decreased exercise capacity in these patients is multifactorial, due to combined effects of dynamic hyperinflation, decreased ventilatory reserve, and respiratory and peripheral muscle dysfunctions.[8–11] A limitation in the cardiac output and stroke volume responses could also play a role,[12] in relation to right ventricle failure to increase ejection fraction in the face of increased afterload.[13] A combined right heart catheterisation and magnetic resonance imaging study recently confirmed that stroke volume fails to increase in exercising COPD patients, in proportion to severity of resting pulmonary hypertension.[14]

We therefore hypothesized that pulmonary hypertension participates to the limitation of exercise capacity in COPD patients, and that this could be shown non-invasively by a correlation between cardiopulmonary exercise test (CPET) variables and PAP estimated by echocardiography.

Methods

Patients

We reviewed the records of consecutive patients with stable COPD in whom lung function tests, a 6-min walk test, a CPET, and an echocardiography had been performed within the same week. All the patients gave an informed written consent to the study, which was approved by the Institutional Review Board of the Erasme University Hospital. There were 19 men and 10 women, aged 63 ± 10 years (mean $\pm$ SD). The diagnosis of COPD rested on a history of cigarette smoking, cough and sputum production, and demonstration of irreversible airflow obstruction, following the guidelines of the American Thoracic Society (ATS) and the European Respiratory Society (ERS).[15] Exclusion criteria included a recent COPD exacerbation (within 1 month), a myocardial infarction, hypertension, angina, left heart failure or neuromuscular conditions that could interfere with the exercise tests. The patients had optimal bronchodilator therapy, and 10 of them were on continuous low-flow oxygen. The patients were in stages III ($n = 16$) and IV ($n = 13$) of the ATS/ERS Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification.[16]

Six-minute walk test

All the patients underwent a 6MWD test following the ATS guidelines.[17] The patients were instructed to walk back and forth at their own pace in a 35 m corridor to cover as much ground possible in the allotted time. A physiotherapist supervised the test, telling the patient the remaining exercise time every 2 min. The patients were allowed to stop and take a rest during the test, but were instructed to resume walking as soon as possible. To control for the learning effect, each patient needed to have had at least one previous test on a separate day. Dyspnea during the test was evaluated with the modified Borg dyspnea score.[18]

Cardiopulmonary exercise testing

Each patient underwent a physician-supervised standard incremental cycle ergometer CPET until the symptom-limited maximum.[19] The work rate was increased by 5 or 10 W per min, after 1 min pedalling at 0 W, for an average duration of CPET of approximately 10 min. The patients were instructed to stop exercising immediately if they felt dizziness or chest pain. Breath-by-breath ventilation, O_2 and CO_2 concentrations, and derived minute ventilation, VO_2 and VCO_2 were determined using the Cardiopulmonary Exercise System ''CPX/D'' (Medical Graphics, St Paul, MN). Heart rate was measured using a continuously monitored electrocardiogram. Blood pressure was measured at the end of each workload increment using an automatic sphygmomanometer. Pulse oximetric saturation (SpO_2) was measured using a Nonin 8500 M device (Nonin Medical, Minneapolis, MN). Peak VO_2 was defined as the VO_2 measured during the last 30 s of peak exercise. Oxygen pulse was calculated by dividing VO_2 by heart rate. The anaerobic threshold was detected using the V-slope method.[19] Maximum voluntary ventilation (MVV) was estimated from the forced expiratory volume in 1 s (FEV_1) by the equation: $FEV_1 \times 40$ L/min.

Echocardiography

Echocardiography was performed with a Vivid 7 ultrasound system (GE Ultrasound, Norway). Mean PAP (mPAP) was calculated from the pulsed Doppler pulmonary artery flow acceleration time, using the following equation: mPAP = 79−0.45 (AT), where AT mean the acceleration time of pulmonary flow.[20] Systolic PAP (sPAP) was estimated from a trans-tricuspid gradient calculated from the maximum velocity of continuous Doppler tricuspid regurgitation (TR), with 5 mm Hg assigned to right atrial pressure, using the equation: sPAP = $TR^2 \times 4 + 5$ mm Hg.[21] Mean PAP was calculated as $0.6 \times$ sPAP + 2.[22]

Pulmonary function tests

Standard pulmonary function tests were performed according to actualised American Thoracic Society/European Respiratory Society guidelines[23] and previously reported European predictive values.[24]

Statistics

Results are presented as mean $\pm$ SD. The statistical analysis consisted in unpaired Student's t tests and correlation calculations.[25]

Results

The patients had a FEV_1 of 1.13 ± 0.49 L (40% predicted, range 31−50%), corresponding to GOLD stages III and IV. The MVV was estimated at 45 ± 20 L/min (limits of normal: 81−203 L/min). The arterial blood gas analysis showed a pH of 7.42 ± 0.05, an arterial PO_2 (PaO_2) of 71 ± 13 mm Hg and $PaCO_2$ of 39 ± 6 mm Hg. The echocardiography showed an

mPAP estimated from the acceleration time of pulmonary blood flow of 30 ± 10 mm Hg. Fourteen of the 29 patients had a mPAP above this value, at 38 ± 6 mm Hg, while the mPAP was at 22 ± 5 mm Hg in other patients. A sufficient quality TR for the estimation of sPAP could be obtained in 18 patients. It allowed for the calculation of a mPAP of 31 ± 7 mm Hg, not significantly different from a mPAP of 28 ± 8 mm Hg calculated from the acceleration time of pulmonary flow in the same patients.

The 6-min walk test

The patients walked 305 ± 110 m, with an increase in heart rate from 96 ± 11 to 119 ± 18 beats/min and a SpO_2 decreased from 93 ± 5 to $90 \pm 5\%$. The Borg dyspnea score reached 6.4 ± 1.2.

The cardiopulmonary exercise test

The CPET variables, which were obtained in only 24 of the patients, are shown in Table 1. The patients presented with marked decreases in peak VO_2, workload, peak V_E and peak heart rate. The V_E/VCO_2 slope was moderately increased. The maximum RER was below 1.1, suggesting sub-maximum test. On the other hand, peak V_E, was close to the estimated MVV, with a mean difference of only 4 L/min, suggesting ventilatory limitation.

Comparisons between COPD with and without a mPAP > 30 mm Hg

The comparison of CPET and 6MWD of the COPD patients with a mPAP below and above 30 mm Hg is shown in Table 2. There was no difference in any of the exercise test variables between the two groups of patients. There was no difference in resting arterial blood gases, resting SpO_2 or peak exercise SpO_2 between the two groups of patients.

There were no correlations between mPAP and respectively peak VO_2 or 6MWD (Figs. 1 and 2).

There were no correlations either between mPAP, peak VO_2 and 6MWD and resting arterial blood gases, resting SpO_2 or peak exercise SpO_2.

Table 1 Cardiopulmonary exercise test variables in 29 COPD patients.

Variables	COPD	Limits of normal
Peak work rate, W	52 ± 29	129—241
Peak VO_2, ml/kg/min	13.8 ± 4.4	23—32
Peak O_2 pulse, ml/beat	7.5 ± 2.3	9.1—16.5
Peak RER	1.06 ± 0.11	1.15—1.25
Peak V_E, L/min	41 ± 15	70—108
V_E/VCO_2 slope	37.1 ± 12.2	33—35
Peak HR, beats/min	127 ± 22	150—178
Peak SpO_2, %	94 ± 3	95—100

RER: respiratory exchange ratio; VO_2: oxygen uptake; V_E: ventilation; VCO_2: carbon dioxide output; HR: heart rate; SpO_2: pulse oximetry oxygen saturation. Limits of normal are from Ref. 19.

Table 2 Comparison of 6-min walk distance (6MWD), cardio-respiratory exercise test (CPET) variables and maximum voluntary ventilation (MVV) between COPD patients with mean pulmonary artery pressure (mPAP) below 30 mm Hg ($n = 15$, 9 men and 6 women) or above 30 mm Hg ($n = 14$, 10 men and 4 women).

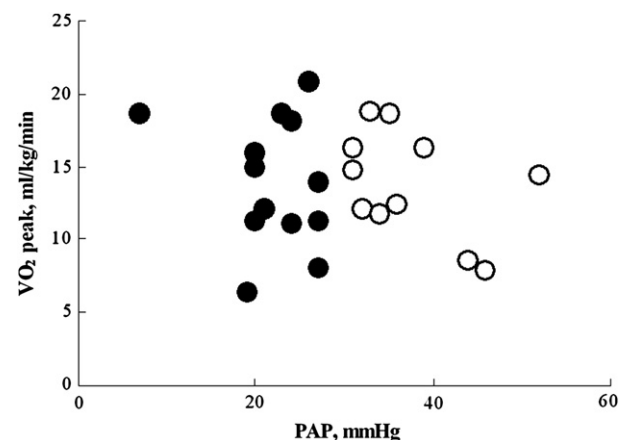| Variables	mPAP < 30 mm Hg	mPAP > 30 mm Hg	P
6MWD, m	318 ± 89	293 ± 110	NS
Peak work rate, W	50 ± 37	54 ± 42	NS
Peak VO_2, ml/kg/min	14.4 ± 4.2	13.7 ± 3.8	NS
Peak O_2 pulse, ml/beat	6.8 ± 1.7	7.9 ± 2.1	NS
Peak RER	1.03 ± 0.16	1.09 ± 0.22	NS
Peak V_E, L/min	40 ± 22	42 ± 17	NS
V_E/VCO_2 slope	38 ± 18	35 ± 17	NS
Peak HR, beats/min	129 ± 33	126 ± 33	NS
MVV, L/min	48 ± 23	42 ± 15	NS
Peak SpO_2, %	93 ± 3	94 ± 3	NS

For abbreviations: see Table 1.
CPET measurements were obtained in 13 patients with a mPAP < 30 mm Hg and 11 patients with a mPAP > 30 mm Hg.

Discussion

The present results shown that mild to moderate pulmonary hypertension in patients with advanced COPD does not affect exercise capacity, which appears to be essentially determined by an early exhaustion of the ventilatory reserve.

The exercise test profile in the present COPD patients population was characterized by marked decreases in 6MWD, peak VO_2, and maximum workload, with a RER on average below the cut-off of 1.15 required for the diagnosis of a peak or maximum exercise test. The ventilatory reserve was markedly lowered. This is typical of advanced COPD[19] in

Figure 1 Peak oxygen uptake (VO_2) plotted against resting mean pulmonary artery pressure (mPAP) in patients with advanced COPD, 11 with a mPAP > 30 mm Hg, 13 with a mPAP < 30 mm Hg. There was no correlation between peak VO_2 and mPAP. Empty circles: mPAP > 30 mm Hg.
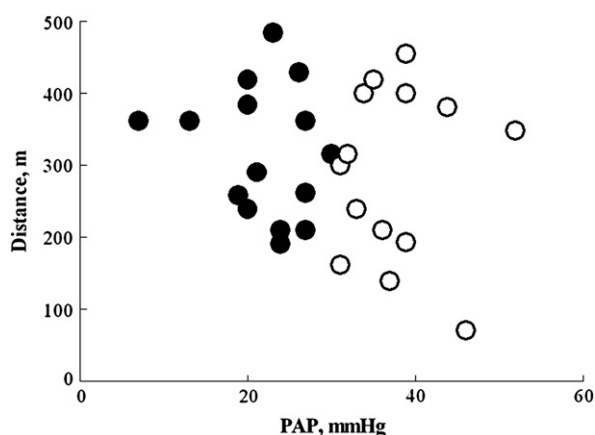
Figure 2 Six-minute walk distance plotted against resting mean pulmonary artery pressure (mPAP) in patients with advanced COPD, 14 with a mPAP > 30 mm Hg, 15 with a mPAP < 30 mm Hg. There was no correlation between peak VO_2 and mPAP. Empty circles: mPAP > 30 mm Hg.

keeping with previously reported studies.[8,9] The ventilatory reserve in normal subjects normally amounts to an average of 38 L/min, whether MVV is directly measured or estimated from a FEV_1.[19] A value of less than 11 L/min is strongly suggestive of a ventilatory limitation to exercise capacity.[19] It is of interest that the ventilatory reserve in the present series of COPD patients appeared to be more decreased in the patients with the higher PAP, suggesting more advanced disease, but the difference did not reach significance.

Decreased exercise capacity in COPD is multifactorial. Increased airway resistance and lung compliance cause a dynamic hyperinflation, which, together with respiratory muscle fatigue, decreases the ventilatory reserve.[8,10] Several studies have also reported a peripheral skeletal muscle dysfunction,[9] but whether this adds to the decrease in ventilatory reserve to limit exercise capacity is not entirely clear.[11]

Isolated pulmonary hypertension, like in pulmonary arterial hypertension, is associated with a decreased 6MWD, and a CPET showing decreased peak VO_2, workload and pulse pressure, early lactic acidosis, increased ventilatory equivalents but preserved ventilatory reserve, and impaired chronotropic response.[26] This is similar to the exercise test profile characteristic in congestive heart failure.[27] We therefore reasoned that some of these characteristics would be identifiable in COPD patients with increased PAP. This was not the case in the present study, except a marked decrease in maximum O_2 pulse suggesting a decrease in maximum stroke volume. A combined invasive hemodynamic and magnetic resonance imaging study in COPD patients exercised to 40% of maximum workload showed a limitation in the increase in stroke volume and no decrease in end-systolic right ventricular volume as compared to controls, and this was related to resting PAP.[14] Another invasive study from the same authors, performed on a small group of 25 COPD patients, of whom 10 presented with increased PAP (to 33 ± 7 mm Hg), showed that the only CPET differences related to the presence of pulmonary hypertension were an increase in ventilatory equivalents for CO_2, and a decreased SpO_2.[28] However,

sildenafil treatment during 3 months in 15 COPD patients with moderate pulmonary hypertension (mPAP 22 ± 9 mm Hg at rest and 32 ± 11 mm Hg at exercise) did not restore stroke volume or exercise capacity.[29] The present results are in keep with the notion that mild to moderate pulmonary hypertension does not add to ventilatory limitation (or peripheral skeletal muscle dysfunction) to limit aerobic exercise capacity.

The present data confirm that COPD patients at exercise present with a markedly decreased O_2 pulse, indicating a limitation in the increased in stroke volume.[30] This could be explained by a decreased right ventricular output because of increased PVR.[14] However, as already mentioned, the CPET profile in COPD is not suggestive of a cardiac limitation. The slope of the VO_2—Q relationship in COPD is not different from controls, but interrupted at a lower maximum VO_2.[31] Furthermore, decreasing PVR with sildenafil therapy does not increase stroke volume in exercising COPD.[29] A recent study reported that O_2 pulse was decreased in exercising COPD patients in proportion to increased inspiratory to total lung capacity ratio, suggesting cardiac depression caused by direct mechanical compression by hyperinflated lungs.[32] Still, it remains difficult to understand why this cardiopulmonary interaction would not be cause of earlier anaerobic threshold and higher respiratory exchange ratio at peak levels of exercise. The predominant limiting effect of dynamic hyperinflation on exercise capacity in COPD is more probably decreased maximum ventilation.

Pulmonary artery pressure in the present study was estimated from Doppler measurements of the acceleration time of pulmonary flow[20] and the velocity of tricuspid regurgitation.[21] Both methods have been shown to be reasonably well correlated to invasively measured mean and systolic PAP respectively.[33] However, sufficient quality tricuspid regurgitant jets for the estimation of sPAP are recovered in less than half of COPD patients, and their predictive value is poor.[34,35] Good quality pulmonary flow waves can be recovered in most COPD patients, with a satisfactory correlation to invasively measured PAP ($r = 0.7$) and an acceptable 84% positive predictive value for pulmonary hypertension.[35] Mean PAP measured from the acceleration time of pulmonary flow has been shown to be tightly correlated to the invasive measurement of PAP in chronically hypoxic high altitude inhabitants.[36] We therefore believe that the accelerations' times of pulmonary flow in the present study allowed for a satisfactory assessment of the presence and severity of pulmonary hypertension.

Most recently, Sims et al. reported an inverse correlation between mPAP and the 6MWD demonstrated by multivariate analysis in 362 patients with COPD who underwent a right heart catheterisation at evaluation for lung transplantation, with − 11 m for every 5 mm Hg increase in mPAP, $P = 0.04$.[37] A similar but non-significant tendency was noted in the present study. Borderline significance on a much larger patient population would argue against a strong impact of PAP on exercise capacity in any individual patient.

Lack of invasive hemodynamic measurements and small sample sizes are important limitations to this study. However, right heart catheterisations are not anymore recommended

in the evaluation of COPD patients, and few patients with advanced forms of the disease have both interpretable echocardiographic and CPET measurements. It is therefore unlikely that larger patients' populations will easily be investigated for a more accurate quantification of the effects of pulmonary hypertension on aerobic exercise capacity.

In conclusion, exercise capacity in COPD is essentially limited by a decreased ventilatory reserve. Whether pulmonary hypertension might limit exercise capacity in particular and uncommon subgroups of patients with more severe pulmonary hypertension (mPAP > 40 mm Hg) and more moderate impairment of lung mechanics, so-called ''out of proportion'' pulmonary hypertension,[4] remains to be investigated.

Conflict of interest

The authors have no conflict of interest about the reported study.

Acknowledgments

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