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Aerobic exercise capacity in COPD patients with and without pulmonary hypertension

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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.

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

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(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