

Clinical Research**Cardiac response to exercise in mild-to-moderate chronic obstructive pulmonary disease****Hao-Yan Wang¹, Qiu-Fen Xu¹, Yao Xiao²***1. Department of Respiratory Medicine, Beijing Friendship Hospital, Capital Medical University, Beijing 100050, China;**2. Department of Respiratory Medicine, Beijing Anzhen Hospital, Capital Medical University, Beijing 100050, China*

Objective Chronic obstructive pulmonary disease (COPD) increases the risk of cardiovascular problem. The symptom of dyspnea on exertion may be associated with pulmonary dysfunction or heart failure, or both. The study objective was to determine whether cardiac dysfunction adds to the mechanism of dyspnea caused mainly by impaired lung function in patients with mild-to-moderate COPD. **Methods** Patients with COPD and healthy controls performed incremental and constant work rate exercise testing. Venous blood samples were collected in 19 COPD patients and 10 controls before and during constant work exercise for analysis of N-terminal-pro-BNP (NT-pro-BNP). **Results** Peak oxygen uptake and constant work exercise time (CWET) were significantly lower in COPD group than in control group (15.81 ± 3.65 vs 19.19 ± 6.16 ml/min kg, $P=0.035$ and 7.78 ± 6.53 min vs 14.77 ± 7.33 min, $P=0.015$, respectively). Anaerobic threshold, oxygen pulse and heart rate reserve were not statistically significant between COPD group and control group. The NT-pro-BNP levels both at rest and during constant work exercise were higher in COPD group compared to control group, but without statistical significance. The correlations between CWET and NT-proBNP at rest or during exercise in patients with COPD were not statistically significant. **Conclusions** Heart failure does not contribute to exercise intolerance in mild-to-moderate COPD. (*J Geriatr Cardiol* 2009; 6:147-150).

Key words cardiac response; exercise; COPD; N-terminal-pro-BNP

Introduction

Chronic obstructive pulmonary disease (COPD) is now defined as a preventable and treatable pulmonary disease, characterised by airflow limitation that is not fully reversible and with some significant extrapulmonary effects.¹ Various population-based studies suggest that COPD increases the risk of cardiovascular morbidity and mortality two-fold.²

Brain natriuretic peptide (BNP) and N-terminal-pro-BNP (NT-proBNP) are derived from Pro-B-type natriuretic peptide (proBNP) and synthesized by ventricular myocytes in response to stretching. Levels of BNP and NT-proBNP in plasma have negative correlation with left ventricular systolic function and have been proposed as a diagnostic tool and prognostic marker in patients with heart failure.^{3,4}

Patients with COPD usually suffer from exercise intolerance which is caused by many factors besides airflow limitation.⁵ The aim of this study was to determine whether cardiac factor contributes to the limitation of exercise in patients with mild-to-moderate COPD through examining

cardiac response to peak exercise and the changes of NT-proBNP levels during constant work rate exercise.

Methods**Subjects**

This study included 23 patients with COPD (21 males and 2 females) who met the following criteria: (1) FEV1/FVC ratio <70%, an FEV1 of 30%-80% of predicted value after bronchodilatation; and (2) stable clinical condition for at least 6 weeks. Patients with history of coronary artery disease or clinically overt left or right ventricular failure were excluded. The control group consisted of 21 healthy subjects (17 males and 4 females). The study was approved by the Ethics Committee of Beijing Friendship Hospital. All subjects provided written informed consent.

Pulmonary function tests

Standard forced expiratory spirometry and body plethysmography were performed (Vmax 229, SensorMedics) in all subjects. The pulmonary function included forced expiratory volume in one second (FEV1), forced volume capacity (FVC), residual volume (RV) and total lung capacity (TLC). Procedures were carried out according to ATS standards.⁶

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Incremental exercise tests

Incremental symptom-limited exercise testing was performed on electrically braked cycle ergometer (Ergoline 900, Sensor Medics). The protocol included 3 minutes of rest, 3 minutes of unloaded pedaling, followed by the incremental phase of exercise at a rate of 5 to 20 watts every minute until the subject reached exhaustion or the test was terminated because of safety concern which includes ischemic ECG changes, excessive rise in cuff blood pressure and desaturation to 88% or lower via pulse oximetry. Oxygen uptake (VO_2) and carbon dioxide output (VCO_2) were measured breath-by-breath (Vmax 229, Sensor Medics). Oxygen pulse (O_2 pulse) was calculated by dividing VO_2 by heart rate. Anaerobic threshold (AT) was identified by V-Slope method⁷. The arterial blood gas was obtained at rest and at the peak of the exercise, and measured.

Constant work rate tests

Within one week of incremental exercise test, a constant work rate test was performed at a work rate of 75% of the peak work rate attained on the incremental test. Pulse oximetry was recorded continuously throughout the testing. Blood samples were taken from an antecubital vein at rest and during constant work rate exercise for NT-pro-BNP analysis.

NT-proBNP analysis

Samples of venous blood collected before and during exercise were transferred to a tube containing EDTA and centrifuged at 3000r/min for 15 minutes. The plasmas were stored in a -70°C freezer until analysis. Enzyme immunoassay was used for quantitative determination of NT-proBNP (Biomedica Medizinprodukte GmbH & Co KG).

Statistical analysis

Statistical analysis was carried out using SPSS 11.5 package. Normally distributed data are expressed by means \pm SD. Differences between the two groups were performed

using independent-samples *t* test for normally distributed parametric data. Line regression analysis was performed to assess the relationship between NT-proBNP and exercise endurance time. Values of $P < 0.05$ were considered as significant.

Results

Twenty three patients with COPD and 21 healthy controls were involved in this study. All subjects completed incremental symptom-limited exercise testing. The baseline data of these subjects are shown in Table 1. Nineteen subjects of COPD group and 10 subjects of control group completed constant work rate testing with enough venous blood samples obtained for analysis of NT-pro-BNP.

Pulmonary function

As shown in Table 1, our study subjects had mild to moderately impaired lung function with a FEV1 of 61.52 ± 20.25 of the predicted value. The RV/TLC was significantly higher in COPD group than that in control group, suggesting air trapping. There were no significant differences in PaO_2 and PaCO_2 between COPD group and control group at rest.

Cardiac response to peak exercise

The maximal incremental exercise results are shown in Table 2. The COPD group had a significant lower peak VO_2 value compared to control group (15.81 ± 3.65 ml/min \cdot kg vs 19.23 ± 6.12 ml/min \cdot kg, $P = 0.035$). The AT was 9.88 ± 2.69 ml/min \cdot kg in COPD group and 9.83 ± 2.56 ml/min \cdot kg in control group. There was no statistically significant difference in AT between the two groups ($P = 0.951$). The O_2 pulse tended lower in COPD group than that in control group, but without statistic significance (8.74 ± 2.51 vs 9.50 ± 2.54 ml/beat, $P = 0.323$). The heart rate reserve (HRR) was similar in the two groups. The PaO_2 at peak exercise was significantly

Table 1 Baseline characteristics and resting pulmonary function data

Characteristics	COPD (n=21)	Control (n=17)	<i>t</i> value	<i>P</i> value
Women/men	2/19	4/13		
Age (yrs)	60.0 ± 8.2	55.9 ± 11.7	1.342	0.187
Height (cm)	168.6 ± 6.8	165.0 ± 9.2	1.460	0.152
Weight (kg)	71.8 ± 9.5	68.1 ± 11.2	1.164	0.251
FEV1 (L)	1.66 ± 0.62	2.46 ± 0.67	-3.227	0.003
FEV ₁ (% predicted)	61.52 ± 20.25	105.00 ± 8.87	-6.165	<0.0001
FEV ₁ /FVC (%)	49.00 ± 10.55	77.89 ± 3.33	-11.719	<0.0001
RV/TLC (%)	52.20 ± 15.21	31.64 ± 6.37	5.129	<0.0001
PaO_2 at rest (mmHg)	98.28 ± 21.62	99.77 ± 9.44	-0.231	0.819
PaCO_2 at rest (mmHg)	40.59 ± 4.34	39.55 ± 5.59	0.584	0.564

lower in COPD group than that in control group (92.65 ± 17.82 mmHg vs 110.51 ± 13.07 mmHg, $P=0.002$).

Exercise tolerance and NT-pro-BNP levels

The constant work exercise time (CWET) was significantly lower in COPD group than that in control group (7.78 ± 6.53 min vs 14.77 ± 7.33 min, $P=0.015$). The NT-pro-BNP levels both at rest and during exercise were higher in the COPD group compared with the that in control group, but without statistical significance. In the COPD group, mean NT-proBNP level rose from 4572.39 ± 1243.33 ng/L at rest to 4803.86 ± 1027.07 ng/L at the end of exercise, while in the control group, it decreased from 4475.71 ± 1025.50 ng/L to 4303.18 ± 771.74 ng/L at the end of exercise (Table 3). Nine of 19 COPD patients showed an increase in NT-proBNP at exercise compared to rest. Three of 10 controls showed an increase in NT-proBNP at exercise compared to that at rest. The correlations between CWET and NT-proBNP at rest or during exercise were not statistically significant.

Discussion

Exercise intolerance, one of the main symptoms in COPD, is associated with function impairment of lung, heart, skeletal muscle and so on.^{8,9,10} Cardiopulmonary exercise testing provides an objective evaluation of function of heart and lung through observing cardiac and pulmonary response to exercise. In this study, we demonstrated that although the exercise capacity indicated as peak VO_2 is decreased in patients with COPD, the O_2 pulse, AT and HRR were not significantly lower than that in the controls. In constant work rate testing, although CWET in the COPD group was lower than that in the control group, NT-proBNP levels in the two groups were not significantly different

both at rest and at the end of exercise testing. NT-proBNP levels did not change significantly during exercise both in control group and COPD group.

Oga¹¹ showed that patients with COPD had a reduction tendency in exercise capacity and the decline in peak VO_2 was more rapid than the decline in FEV1. That means exercise capacity in COPD is affected not only by pulmonary function but also by other factors. A recent study by Mannino et al¹² showed stage 3 or 4 COPD had a high prevalence of diabetes, hypertension and cardiovascular disease. Our study included 3 patients with stage 1, 14 patients with stage 2 and 6 patients with stage 3. They had no history of diabetes, hypertension and cardiovascular disease. O_2 pulse reflects the amount of O_2 extracted per heart beat and is used as estimator of stroke volume during exercise. Our results showed that there was no significant difference in peak O_2 pulse between the COPD group and the control group. A lower AT means reduced oxygen delivery to muscle cells for aerobic metabolism. We found no reduced AT in COPD compared to that in the controls. These results suggest that the cardiac response to exercise in mild-to-moderate COPD is relatively normal.

NT-proBNP is elevated in congestive heart failure and can be used as a diagnostic tool for heart failure.⁴ One study showed NT-proBNP correlated negatively with right ventricular ejection fraction and can be used as a means of identifying patients with pulmonary hypertension who have right ventricular systolic dysfunction.¹³ We found that COPD patients had a little higher NT-proBNP than the healthy subjects both at rest and during exercise, but without significance. Therefore, the cardiac factor may not contribute to exercise intolerance in patients with mild-to-moderate COPD. These results are in agreement with some of results of study by Stewart, who reported that in the absence

Table 2 Cardiac response to incremental exercise

Characteristics	COPD group(n=19)	Control group (n=10)	t value	P value
Peak VO_2 (ml/min • kg)	15.81 ± 3.65	19.19 ± 6.16	-2.186	0.035
AT(ml/min • kg)	9.88 ± 2.69	9.83 ± 2.56	0.062	0.951
HRR(beats/min)	28.22 ± 16.68	23.70 ± 22.39	0.756	0.454
Peak O_2 pulse(ml/beat)	8.74 ± 2.51	9.50 ± 2.54	-1.000	0.323
Pa O_2 during exercise(mmHg)	92.65 ± 17.82	110.51 ± 13.07	-3.356	0.002
PaCO $_2$ during exercise(mmHg)	42.33 ± 3.66	40.27 ± 5.46	1.274	0.212

Data are presented as mean \pm SD.

Table 3 Exercise tolerance and NT-pro-BNP levels

Characteristics	COPD group(n=19)	Control group(n=10)	t value	P value
CWET (min)	7.78 ± 6.53	14.77 ± 7.33	2.598	0.015
NT-proBNP at rest(ng/L)	4572.39 ± 1243.33	4475.71 ± 1025.50	-0.211	0.835
NT-proBNP during exercise (ng/L)	4803.86 ± 1027.07	4303.18 ± 771.74	-1.341	0.191

Data are presented as mean \pm SD. CWET=Constant work exercise time

of coronary artery disease and overt cor pulmonale, cardiac output response to exercise was normal in some COPD patients who had less severe airflow limitation and lung hyperinflation¹⁴.

In our study, 9 of 18 COPD patients showed an increase in NT-proBNP at exercise compared to that at rest, whereas 3 of 10 controls showed an increase in NT-proBNP, but the mean NT-proBNP levels did not show significant increase during exercise both in COPD group and control group. These results are in agreement with those of other studies¹⁵, which demonstrated that BNP levels in patients with chronic heart failure were not significantly altered by exercise.

Funk et al¹⁰ studied 22 patients with COPD (five stage 2, nine stage 3, and eight stage 4) and found left ventricular diastolic dysfunction assessed by Doppler echocardiographic methods in COPD. His study included more severe COPD patients than ours and he did not study the change of cardiac function during exercise. We do not know the relationship between left ventricular diastolic dysfunction and cardiac response to exercise in COPD. Further studies including more patients are needed to evaluate cardiac response to exercise in different stages of COPD.

In summary, we found that although patients with mild-to-moderate COPD had a decreased exercise capacity, their cardiac response to both incremental and constant work exercise was not abnormal. This study suggests that the cardiac factor may be not one of the factors causing exercise intolerance in mild-to-moderate COPD, if there are no clinically overt left or right ventricular failure.

Acknowledgement

This work was supported by the Beijing Municipal Science & Technology Commission (grant No. z080507030808025).

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