Cardiac Response and N-Terminal-Pro-Brain Natriuretic Peptide Kinetics During Exercise in Patients With COPD

Hao-Yan Wang MD PhD, Qiu-Fen Xu MD, Yao Xiao MD,
Jian Zhang MD, and Al Sperry PhD RRT

BACKGROUND: COPD increases the risk of cardiovascular problems. Dyspnea on exertion can be associated with COPD or heart failure or both. N-terminal-pro-brain natriuretic peptide (NT-pro-BNP) is a marker of cardiac dysfunction, and exercise testing can identify subtle heart abnormalities. OBJECTIVE: To determine whether cardiac dysfunction adds to the mechanism of dyspnea caused primarily by impaired lung function in patients with mild to moderate COPD. METHODS: With 19 COPD patients and 10 healthy control subjects we measured physiologic variables and collected venous blood samples before and during incremental and constant-work-rate exercise, and measured NT-pro-BNP. RESULTS: Peak oxygen uptake and constant-work exercise time were significantly lower in the COPD group than in the control group (16 ± 4 mL/min/kg vs 19 ± 6 mL/min/kg, $P = .04$, and 7.8 ± 6.5 min vs 14.8 ± 7.3 min, $P = .02$). Between the groups there were no significant differences in anaerobic threshold, oxygen pulse (oxygen uptake divided by heart rate), or heart-rate reserve (difference between predicted and measured maximum heart rate). Both at rest and during constant-work exercise, NT-pro-BNP was not significantly higher in the COPD group than in the control group. In the COPD patients there was no significant correlation between constant-work exercise time and NT-pro-BNP at rest or during exercise. CONCLUSIONS: Heart failure did not contribute to exercise intolerance in patients with mild to moderate COPD. *Key words: chronic; obstructive; pulmonary; disease; COPD; dyspnea; exertion; heart failure; Brain natriuretic peptide; N-terminal-pro-BNP; cardiac; exercise; cardiac response.* [Respir Care 2011;56(6):796–799. © 2011 Daedalus Enterprises]

Introduction

COPD has substantial extrapulmonary effects,[1] including cardiovascular morbidity and mortality.[2-4] Brain natriuretic peptide (BNP) and N-terminal-pro-BNP (NT-pro-BNP) are derived from Pro-B-type natriuretic peptide (pro-BNP), which is synthesized by ventricular myocytes in response to stretching.[5,6] Plasma BNP and NT-pro-BNP negatively correlate with left-ventricular systolic function and peak oxygen uptake (peak $\dot{V}_{O_2}$) during exercise, which suggests that NT-pro-BNP may be a useful marker of heart failure.[7,8]

Patients with COPD usually have exercise intolerance, which can be caused by factors other than air-flow limitation.[9] We studied whether cardiac factors contribute to exercise limitation in patients with mild to moderate COPD, by examining cardiac response to peak exercise and changes in NT-pro-BNP during constant-work-rate exercise.

Methods

This study was approved by the ethics committee of Beijing Friendship Hospital. All subjects provided written informed consent.

Drs Wang, Xu, and Zhang are affiliated with the Department of Respiratory Medicine, Beijing Friendship Hospital, Capital Medical University, Beijing, China. Dr Xiao is affiliated with the Department of Respiratory Medicine, Beijing Anzhen Hospital, Capital Medical University, Beijing, China. Dr Sperry is affiliated with Air Liquide, Paris, France.

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Correspondence: Hao-Yan Wang MD PhD, Department of Respiratory Medicine, Beijing Friendship Hospital, Capital Medical University, 95 Yong An Road, Xuan Wu District, Beijing 100050 China. E-mail: haoyanw@126.com.

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Subjects

We recruited 23 patients with COPD (21 males, 2 females) who had participated in and been screened for our COPD study program and satisfied the following criteria: FEV_1/forced vital capacity < 70%, post-bronchodilator FEV_1 30–80% of predicted, and in stable condition for at least 6 weeks. We excluded patients with a history of coronary artery disease, diabetes, high blood pressure, clinically overt left or right ventricular failure (orthopnea, neck-vein distention, peripheral fluid retention), or ischemic ST-segment changes on electrocardiogram at rest or during peak exercise.

The control group included 21 healthy subjects (17 males, 4 females).

Pulmonary Function Tests

We conducted standard forced expiratory spirometry and body plethysmography (Vmax 229, VIASYS Healthcare/SensorMedics, Yorba Linda, California) according to the American Thoracic Society standards[10] in all subjects. We measured FEV_1, forced vital capacity, residual volume, and total lung capacity.

Incremental Exercise Tests

Incremental symptom-limited exercise testing was performed with an electronically braked cycle ergometer (Ergoline 900, VIASYS Healthcare/SensorMedics, Yorba Linda, California). The protocol included 3 min of rest and 3 min of unloaded pedaling, followed by the incremental exercise phase, in which the work rate increased by 5–20 watts per minute until the subject reached exhaustion or the test was terminated for safety (eg, ischemic electrocardiogram changes, excessive rise in blood pressure, S_{pO_2} decrease to ≤ 88%). The difference between the predicted maximum heart rate (220 minus age) and the maximum heart rate achieved during exercise is referred to as the heart-rate reserve.

We measured $\dot{V}_{O_2}$ and carbon dioxide output breath by breath (Vmax 229, VIASYS Healthcare/SensorMedics, Yorba Linda, California). Oxygen pulse was calculated by dividing $\dot{V}_{O_2}$ by heart rate. Anaerobic threshold was identified with the V-slope method combined with ventilatory equivalents for oxygen and carbon dioxide.[11] We took arterial blood samples at rest and during peak exercise.

Constant-Work-Rate Tests

Within one week of the incremental exercise test, a constant-work-rate test was performed at 75% of the peak work rate determined in the incremental exercise test. We recorded S_{pO_2} continuously throughout constant-work-rate testing.

Table 1. Baseline Characteristics

	COPD Group	Control Group	*P*
Women/men (no.)	2/21	4/17	NA
Age (y)	60.0 ± 8.2	55.9 ± 11.7	.19
Height (cm)	169 ± 7	165 ± 9	.15
Weight (kg)	71.8 ± 9.5	68.1 ± 11.2	.25
FEV_1 (L)	1.66 ± 0.62	2.46 ± 0.67	.003
FEV_1 (% predicted)	62 ± 20	105 ± 9	< .001
FEV_1/FVC (%)	49 ± 11	78 ± 3	< .001
RV/TLC (%)	52 ± 15	32 ± 6	< .001
P_{aO_2} at rest (mm Hg)	98 ± 22	100 ± 9	.82
P_{aCO_2} at rest (mm Hg)	41 ± 4	40 ± 6	.56

± values are mean ± SD.
NA = not applicable
FVC = forced vital capacity
RV = residual volume
TLC = total lung capacity

NT-Pro-BNP Analysis

To measure NT-pro-BNP we took venous blood samples from an antecubital vein, at rest and during exercise. We transferred each venous blood sample to a tube containing ethylenediaminetetraacetic acid and centrifuged at 3,000 revolutions/min for 15 min. The plasma was stored at −70°C until analysis. NT-pro-BNP was measured via enzyme immunoassay (Biomedical Medizinprodukte, Vienna, Austria).

Statistical Analysis

Analyses were with statistics software (SPSS 11.5, SPSS, Chicago, Illinois). Normal distributed data are expressed as mean ± SD. Differences between the 2 groups were analyzed with independent-sample tests for normally distributed parametric data. We used line-regression analysis to assess the relationship between NT-pro-BNP and exercise endurance time. $P < .05$ was considered significant.

Results

We studied 23 patients with COPD and 21 healthy control subjects. All the subjects completed the incremental symptom-limited exercise testing. Nineteen COPD subjects and 10 control subjects completed the constant-work-rate testing (Table 1).

Table 2. Cardiac Response to Incremental Exercise*

Characteristics	COPD Group	Control Group	*P*
Work (watts)	92.4 ± 24.9	128.7 ± 38.0	.003
Peak heart rate (beats/min)	132 ± 18	140 ± 24	.20
Peak $\dot{V}_{O_2}$ (mL/min/kg)	16 ± 4	19 ± 6	.04
Anaerobic threshold (mL/min/kg)	10 ± 3	10 ± 3	> .99
Heart-rate reserve (beats/min)	28 ± 17	24 ± 22	.45
Peak oxygen pulse (mL/beat)	8.7 ± 2.5	9.5 ± 2.5	.32
P_{aO_2} during exercise (mm Hg)	93 ± 18	111 ± 13	.002
P_{aCO_2} during exercise (mm Hg)	42 ± 4	40 ± 5	.21

* All values are mean ± SD.
$\dot{V}_{O_2}$ = oxygen uptake

Table 3. Exercise Tolerance Relative to NT-Pro-Brain Natriuretic Peptide

	COPD Group	Control Group	*P*
Constant-work exercise time (min)	7.8 ± 6.5	14.8 ± 7.3	.02
N-terminal-pro-brain natriuretic peptide (ng/L)			
At rest	4,572 ± 1,243	4,476 ± 1,026	.84
During exercise	4,804 ± 1,027	4,303 ± 772	.19

All values are mean ± SD.

Pulmonary Function

Our patients had mildly to moderately impaired lung function (see Table 1). Their mean ± SD FEV_1 was 62 ± 20% of predicted. The ratio of residual volume to total lung capacity was significantly higher in the COPD group, which reflects air trapping. There were no significant at-rest differences in P_{aO_2} or P_{aCO_2} between the groups.

Cardiac Response to Peak Exercise

Table 2 shows the maximum incremental exercise results. The COPD group had a significantly lower peak $\dot{V}_{O_2}$ (16 ± 4 mL/min/kg vs 19 ± 6 mL/min/kg, $P = .04$). The anaerobic threshold was 10 ± 3 mL/min/kg in both groups. The oxygen pulse was nonsignificantly lower in the COPD group (8.7 ± 2.5 mL/beat vs 9.5 ± 2.5 mL/beat, $P = .32$). Heart-rate reserve was also similar. Peak-exercise P_{aO_2} was significantly lower in the COPD group (93 ± 18 mm Hg vs 111 ± 13 mm Hg, $P = .002$).

Exercise Tolerance and NT-Pro-Brain Natriuretic Peptide

The constant-work exercise time was significantly lower in the COPD group (7.8 ± 6.5 min vs 14.8 ± 7.3 min, $P = .02$). Both at rest and during exercise, NT-pro-BNP was nonsignificantly higher in the COPD group (Table 3). Nine of the 19 COPD patients and 3 of the 10 control subjects had increased NT-pro-BNP during exercise. The correlations between constant-work exercise time and NT-pro-BNP were not statistically significant at rest ($r = -0.07$, $P = .71$) or during exercise ($r = -0.11$, $P = .59$).

Discussion

Exercise intolerance—one of the main symptoms of COPD—is associated with functional impairment of the lung, heart, skeletal muscle, and other systems.[12-14] In our cohort, although exercise capacity (measured as peak $\dot{V}_{O_2}$) was lower in the COPD patients than in the control subjects, the oxygen pulse, anaerobic threshold, and heart-rate reserve were not significantly lower. The constant-work exercise time was lower in the COPD group, but NT-pro-BNP was not significantly different at rest or during exercise, and did not significantly change during exercise in either group.

Oga et al[15] found that COPD patients have a reduction tendency in exercise capacity, and that the decline in peak $\dot{V}_{O_2}$ is more rapid than the decline in FEV_1. Stated in another way, exercise capacity in COPD is affected not only by pulmonary function but also by other factors. A recent study by Mannino et al[4] found that patients with stage 3 or 4 COPD had a high prevalence of diabetes, hypertension, and cardiovascular disease. Our study included 3 patients with stage 1 COPD, 14 with stage 2 COPD, and 6 with stage 3 COPD; none had a history of diabetes, hypertension, or cardiovascular disease. Oxygen pulse (the amount of oxygen extracted per heart beat) can be used to estimate stroke volume during exercise.[11] We found no significant difference in peak oxygen pulse between the COPD group and the control group. A lower anaerobic threshold means reduced oxygen delivery to muscle cells. We found no significant difference in anaerobic threshold between our COPD and control groups. These results suggest that the cardiac response to exercise in patients with mild to moderate COPD is relatively normal.

NT-pro-BNP is elevated in congestive heart failure and thus is diagnostic for heart failure.[8,16] One study found that NT-pro-BNP negatively correlated with right-ventricular ejection fraction and that it identifies patients with pulmonary hypertension and right-ventricular systolic dysfunction.[17] Our COPD patients had a slightly and nonsignificantly higher NT-pro-BNP than our healthy subjects, both at rest and during exercise. Therefore, cardiac factors may not contribute to exercise intolerance in patients with mild to moderate COPD. These results concur with those of Stewart and Lewis,[18] who reported that, in the absence of

coronary artery disease and overt cor pulmonale, cardiac output response to exercise was normal in some COPD patients who had less severe air-flow limitation and lung hyperinflation.

Nine of our 18 COPD patients and 3 of our 10 control subjects had higher NT-pro-BNP during exercise, but the mean NT-pro-BNP did significantly increase during exercise in either group. These results agree with those of other studies,[19] in which BNP in patients with chronic heart failure was not significantly altered by exercise.

Funk et al[14] studied 22 patients with COPD (5 with stage 2, 9 with stage 3, and 8 with stage 4 COPD) and found that left-ventricular diastolic dysfunction could be assessed with Doppler echocardiography. That study included patients with more severe COPD than ours, and they did not study change in cardiac function during exercise. We do not know the relationship between left-ventricular diastolic dysfunction and cardiac response to exercise in COPD.

Limitations

Our sample size was small and we did not compare different stages of COPD. Also, our control group had more women than our COPD group, which may have influenced our results.

Conclusions

Although patients with mild to moderate COPD have lower exercise capacity, their cardiac response to incremental or constant-work exercise is relatively normal, which suggests that exercise intolerance in patients with mild to moderate COPD may not be related to cardiac factors, if there is no clinically overt left or right ventricular failure. Further studies with more COPD patients are needed to evaluate cardiac response to exercise.

REFERENCES

1. Celli B, MacNee W; ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J 2004;23(6):932-946. Erratum in: Eur Respir J 2006;27(1):242.
2. Mannino DM, Watt G, Hole D, Gillis C, Hart C, McConnachie A, et al. The natural history of chronic obstructive pulmonary disease. Eur Respir J 2006;27(3):627-643.
3. Wang HY, Xu QF, He X, Nie S. Survey of comorbid diseases in patients with COPD in Beijing (abstract). Am J Respir Crit Care Med 2010;181(Suppl):A5936.
4. Mannino DM, Thorn D, Swensen A, Holguin F. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. Eur Respir J 2008;32(4):962-969.
5. Gardner RS, Ozalp F, Murday AJ, Robb SD, McDonagh TA. N-terminal pro-brain natriuretic peptide. A new gold standard in predicting mortality in patients with advanced heart failure. Eur Heart J 2003;24(19):1735-1743.
6. Wu AH, Smith A, Wieczorek S, Mather JF, Duncan B, White CM, et al. Biological variation for N-terminal pro and B-type natriuretic peptides and implications for therapeutic monitoring of patients with congestive heart failure. Am J Cardiol 2003;92(5):628-631.
7. Thaman R, Esteban MT, Barnes S, Gimeno JR, Mist B, Murphy R, et al. Usefulness of N-Terminal Pro-B-type natriuretic peptide levels to predict exercise capacity in hypertrophic cardiomyopathy. Am J Cardiol 2006;98(4):515-519.
8. Lainchbury JG, Campbell E, Frampton CM, Yandle TG, Nicholls MG, Richards AM, et al. Brain natriuretic peptide and n-terminal brain natriuretic peptide in the diagnosis of heart failure in patients with acute shortness of breath. J Am Coll Cardiol 2003;42(4):728-735.
9. Plankeel J, McMullen B, Macintyre NR. Exercise outcomes after pulmonary rehabilitation depend on the initial mechanism of exercise limitation among non-oxygen-dependent COPD patients. Chest 2005;127(1):110-116.
10. American Thoracic Society. Standardization of spirometry: 1994 update. Am J Respir Crit Care Med 1994;152(3):1107-1136.
11. American Thoracic Society; American College of Chest Physicians. ATS/ACCP statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 2003;167(2):211-277. Erratum in: Am J Respir Crit Care Med 2003:1451-1452.
12. O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2001;164(5):770-777.
13. Saey D, Michaud A, Couillard A, Côté CH, Mador MJ, LeBlanc P, et al. Contractile fatigue, muscle morphometry and blood lactate in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2005;171(10):1109-1115.
14. Funk GC, Lang I, Schenk P, Valipour A, Hartl S, Burghuber OC. Left ventricular diastolic dysfunction in patients with COPD in the presence and absence of elevated pulmonary arterial pressure. Chest 2008;133(6):1354-1359.
15. Oga T, Nishimura K, Tsukino M, Sato S, Hajiro T, Mishima M. Exercise capacity deterioration in patients with COPD: longitudinal evaluation over 5 years. Chest 2005;128(1):62-69.
16. Passino C, Poletti R, Bramanti F, Prontera C, Clerico A, Emdin M. Neuro-hormonal activation predicts ventilatory response to exercise and functional capacity in patients with heart failure. Eur J Heart Fail 2006;8(1):46-53.
17. Blyth KG, Groenning BA, Mark PB, Martin TN, Foster JE, Steedman T, et al. NT-proBNP can be used to detect right ventricular systolic dysfunction in pulmonary hypertension. Eur Respir J 2007;29(4):737-744.
18. Stewart RI, Lewis CM. Cardiac output during exercise in patients with COPD. Chest 1986;89(2):199-205.
19. Krüger S, Graf J, Merx MW, Stickel T, Kunz D, Hanrath P, et al. Brain natriuretic peptide kinetics during dynamic exercise in patients with chronic heart failure. Int J Cardiol 2004;95(1):49-54.