Effects of right ventricular dysfunction on exercise capacity and quality of life and associations with serum NT-proBNP levels in COPD: an observational study

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Abstract

Objective: During the course of chronic obstructive pulmonary disease (COPD), pulmonary hypertension (PH) and right ventricular (RV) failure may develop due to elevated afterload of the RV. In those patients, exercise capacity is reduced due to pulmonary and cardiac limitations. We investigated relationships between serum N-terminal of proB-type natriuretic peptide (NT-proBNP) and RV functions with exercise capacity and quality of life in patients COPD.

Methods: An observational case-control study was conducted. We enrolled 31 moderate and severe COPD patients, and 20 subjects without chronic diseases as control group. Parameters reflecting the right ventricular diastolic and systolic functions by echocardiography along with serum NT-proBNP levels were assessed. Cardiopulmonary exercise testing and Short Form-36 (SF-36) were applied.

Results: Serum NT-proBNP levels were higher in COPD patients than control group (p=0.003). Serum NT-proBNP level was found to be related with pulmonary arterial pressure. Serum NT-proBNP levels were negatively correlated with anaerobic threshold oxygen uptake (AT VO_2) and peak oxygen uptake (PVO_2) values. Early ventricular filling velocity (Em) was lower in COPD patients. Em wave was significantly correlated with O_2 pulse. There was a positive relationship between tricuspid E/A ratio and VO_2 value at AT. SF-36 domains of physical functioning, general health and role limitation due to physical disorder were significantly correlated with AT VO_2, PVO_2 and O_2 pulse.

Conclusion: Exercise limitation may be predicted by assessment of right ventricule functions and NT-proBNP levels and exercise limitation impairs quality of life in COPD patients. *(Anadolu Kardiyol Derg 2014; 14: 370-7)*

Key words: COPD, pulmonary hypertension, NT-proBNP, cardiopulmonary exercise testing, right ventricular dysfunction, quality of life.

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity all over the world and characterized by irreversible airway obstruction (1). Impaired exercise capacity can result from ventilatory limitation, respiratory muscle weakness and abnormal gas exchange together with cardiac limitation in COPD patients. Pulmonary hypertension and right heart failure may develop in the course of COPD. Pulmonary hypertension (PH) with increased right ventricle load, failure and elevated pulmonary vascular resistance is a cause of early death. Development of PH is also associated with poor quality of life and exercise limitation. Diastolic dysfunction is defined as inconvenient increase in right ventricle diastolic pressure with insufficient filling of right ventricle. Right ventricular dysfunction can be seen before the development of pulmonary hypertension and cor pulmonale in COPD patients (2-4).

N-terminal of proB-type natriuretic peptide (NT-proBNP) is a precursor of brain natriuretic peptide (BNP). Measurement of NT-proBNP level is more reliable than measurement of BNP due to the short half life of BNP. N-terminal proB-type natriuretic peptide (NT-proBNP) is an important and helpful indicator in differentiating congestive heart failure from lung diseases (5). However, elevated NT-proBNP levels have been found in patients with COPD and in patients with right ventricular dysfunction (6, 7). Moreover, increased NT-proBNP levels can be seen in many diseases such as left ventricular dysfunction, right ventricular dysfunction secondary to pul-

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monary diseases, infectious diseases, endocrinological disorders, and high output status without decreased left ventricular ejection fraction (8). Therefore measurement of NT-pro BNP levels can also be useful in the diagnosis of impaired right ventricular functions in COPD patients.

Dyspnea is a major symptom limiting exercise capacity in COPD patients (1). Cardiopulmonary exercise testing is a noninvasive tool in the diagnosis of pulmonary and cardiovascular diseases and also helps to determine disease severity.

Although significance of serum NT-proBNP in COPD patients has been investigated previously, there has been no study investigating the relationship between serum NT-proBNP and exercise capacity in COPD patients according to our knowledge. We hypothesize that serum NT-proBNP level might indicate impaired right ventricular functions, quality of life and exercise limitation in COPD patients.

The goal of this study was to investigate relationships between serum NT-proBNP level and right ventricular functions with exercise capacity and quality of life in patients with COPD.

Methods

A case control observational study was designed. The Ethics Committee of our university certified the study protocol and study was conducted within research project as KA09/274.

Study population

Patients with COPD followed in department of pulmonary diseases outpatient clinic between August 2009 and August 2010 were consecutively included. All participants provided informed consent. COPD was diagnosed based on the criteria defined in Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (1).

Thirty-one patients with moderate, severe and very severe COPD patients during stable period and 20 healthy individuals were recruited to the study. Subjects in the control group were older than 40 years of age without any medical disorders.

COPD patients during acute exacerbation period, patients with asthma, hypoxia, pneumonia, left ventricular systolic dysfunction, valvular pathology, arrhythmia, renal failure, diffuse parenchymal lung diseases, lung carcinoma and other malignancies, neuromuscular disorders affecting exercise capacity and subjects younger than 40 years of age were all excluded from the study.

Study protocol

Pulmonary function tests, echocardiography, plasma NT-pro BNP measurement, CPET and short form-36 (SF-36) questionnaire were performed to all subjects.

Pulmonary function tests

Pulmonary function tests (PFTs) were performed with a clinical spirometer (SensorMedics Vmax spectra 229, Bilthoven, The Netherlands). Maximal expiratory flow maneuver was performed by patients and control subjects. Forced expiratory volume at 1 second (FEV_1) and forced vital capacity (FVC) values were obtained and FEV_1/FVC was calculated. Standard PFTs including spirometry and lung volumes were evaluated according to the previously described guidelines (9). Patients with post-bronchodilator FEV_1 <80% of predicted value, FEV_1/FVC <70%, and irreversible airflow obstruction were recruited to the study (10). Post-bronchodilator FEV_1 values were used to define disease stage according to the GOLD severity classification.

Echocardiography

Tissue Doppler and 2-dimensional echocardiographic measurements of 31 patients with moderate, severe and very severe COPD patients during stable period and 20 healthy individuals were carried out in the supine position according to the recommendations of American Society of Echocardiography with Acuson Sequoia C-256 (Acuson Corporation, California, USA) cardiac ultrasound machine and 3.5 MHz probe (11). Apical 4-chamber, and parasternal long-axis views were obtained. The left ventricular ejection fraction (EF%) was calculated using the modified Simpson's rule (12).

Mean pulmonary arterial pressure (PAP) was figured out by the formula of 79- (0.45X pulmonary artery acceleration time) (13, 14).

Right ventricular diastolic velocities were obtained by using pulsed tissue Doppler imaging [early ventricular filling -early diastolic wave (Em) and late diastolic wave during atrial contraction (Am)]. Peak early (E) and late (A) diastolic velocities of tricuspid valve were recorded during apical 4-chamber view. Assessment of right ventricular (RV) diastolic function was carried out by pulsed Doppler of the tricuspid inflow and tissue Doppler of the lateral tricuspid annulus. Grading of RV diastolic dysfunction was performed. Patients with tricuspid E/A ratio <0.8 was determined as grade 1 RV diastolic dysfunction and a tricuspid E/A ratio of 0.8 to 2.1 with an E/e' ratio >6 as grade 2 RV diastolic dysfunction (pseudonormal filling). We had no subject with a tricuspid E/A ratio >2.1 with deceleration time <120 ms. Tricuspid Annular Plane Systolic Excursion (TAPSE) - was measured from the tricuspid lateral annulus (15, 16).

Cardiopulmonary exercise test

Cycle ergometer (Ergo-metrics 900; SensorMedics Bilthoven, The Netherlands) was used for cardiopulmonary exercise test (CPET). All subjects underwent symptom-limited exercise with a facemask (Rudolph Face Mask for Exercise Testing; Hans Rudolph Inc., Kansas City, MO, USA) fixed on face. After three-min baseline resting period records, a three-min warm-up period (60 rpm was the maintainance pedaling rate) was started. And then incremental work (10-15 W elevation for each minute) was applied (17). An automated exercise testing system (Desktop Diagnostics/CPX; Medical Graphics Corporation, St. Paul, MI, USA) was used for collecting data. The maximum work rate for half a minute was saved. During CPET, continious monitorization of 12 lead electrocardiography, blood pressure, and pulse oxygen saturation was performed. Peak oxygen uptake (PVO_2 mL/

kg/min), peak CO_2 output, and VE/VCO_2 values were evaluated. The two-slope method was used to determine anaerobic threshold (AT L/min). The equation of Wasserman et al. (17) was used to determine age-predicted values. Symptoms like fatigue, dyspnea, dizziness for ending the test were also noted.

The SF-36 questionnaire

The SF-36 questionnaire was used to evaluate quality of life (QOL) (18, 19). This questionnaire has been validated for COPD patients previously. The subjects's daily routine activities, social life and exercise performance were determined with 36 questions of this item. Main eight domains as physical function, social function, physical and emotional role function, mental health, bodily pain, vitality, and general health perception were found. A computer algorithm was used to score the responses to the SF-36 (20).

NT-proBNP measurement

Blood samples were drawn in tubes containing EDTA. Plasma NT-proBNP was measured with electrochemiluminescence immunoassay on an Elecsys 2010 system (Roche Diagnostics, Mannheim, Germany). NT-proBNP concentrations were measured as pg/mL. Serum NT-proBNP was evalauted as normal when below 84 pg/mL for males and 155 pg/mL for females.

Statistical analysis

Statistical analysis was accomplished using SPSS (SPSS version 20.0; SPSS Inc., Chicago, IL, USA). Data was expressed as mean values±SD and median (range min-max) for continious variables, percentage for categorical variables in descriptive analysis. Distribution of continuous variables were checked with Shapiro-

Table 1. Demographic data of study population

	COPD patients (n=31)	Control subjects (n=20)	*P*
Age, mean±SD, years*	61.2±7.5	59.3±7.0	0.671
Gender F/M n (%)**	3 (9.7) / 28 (90.3)	8 (40) / 12 (60)	0.015
Weight (mean±SD)*, kg	74.4±17.2	75.4±12.8	0.831
Height (mean±SD)*, cm	166.9±8.4	165.9±7.1	0.645
BMI (mean±SD)*, kg/m^2	26.5±4.6	27.3±3.9	0.508
Pack year (mean±SD)*	48.5±16.0	26.4±18.0	0.001
Smoking history n (%)**			
Active smoker	12 (38.7)	6 (30.0)	0.004
Ex-smoker	17 (54.8)	5 (25.0)	
Never smoked	2 (6.5)	9 (45.0)	

Data was expressed as mean values±SD for age, weight, height, BMI and pack year.
Data was expressed as percentage for gender and smoking history.
BMI - body mass index; COPD - chronic obstructive pulmonary disease; F/M - female/male
*Student's t-test.
**Pearson chi-square test and Fisher Exact test.

Table 2. Pulmonary function test, cardiopulmonary exercise testing, serum NT-proBNP. echocardiography and SF-36 results of study population

Parameters	COPD patients	Control subjects	*P*
FEV_1/FVC	47.19±10.76	78.20±5.73	**0.000**
FEV_1, L	1.60±0.47	3.73±0.74	**0.000**
FEV_1, %	56.77±13.10	120.1±14.47	**0.000**
FVC L	3.59±0.90	4.86±0.94	**0.000**
FVC, %	98.32±13.77	130.7±16.19	**0.000**
FEF_{25-75}, %	17.16±8.27	92.55±28.58	**0.000**
TLC L	6.55±1.62	6.55±1.17	0.998
TLC, %	106.42±21.27	120.85±12.88	**0.004**
VC L	3.60±0.90	4.86±0.94	**0.000**
VC, %	96.48±14.99	125.30±17.50	**0.000**
RV L	2.96±1.04	1.90±0.36	**0.000**
RV, %	133.42±48.45	104.40±17.29	**0.050**
IC L	2.18±0.68	3.14±0.65	**0.000**
MVV	69.03±31.73	129.80±34.66	**0.000**
AT VO_2 mL/kg/min	13.32±4.04	19.57±5.12	**0.000**
AT VO_2 L/min	1.01±0.35	1.46±0.41	**0.000**
AT VCO_2	1.05±0.36	1.51±0.43	**0.000**
AT VEO_2	38.14±7.48	31.55±4.59	**0.000**
AT $VECO_2$	36.76±7.21	31.05±4.33	**0.000**
PVO_2 L/min	1.26±0.38	1.87±0.46	**0.000**
PVO_2 mL/kg/min	16.93±3.86	24.69±4.86	**0.000**
$PVCO_2$ L/min*	1.46 (0.56-11.2)	2.24 (1.25-3.32)	0.000
$PVEO_2$	1.74±1.83	2.26±0.60	**0.000**
VE/VCO_2	33.19±8.38	30.89±4.10	0.148
PET CO_2	4.66±0.72	4.66±0.55	0.981
Breathing reserve	20.69±22.17	60.79±27.68	**0.000**
Pulse reserve	38.48±15.79	50.65±30.30	0.288
O2 pulse	11.13±4.00	18.71±8.57	**0.001**
Exercise duration, sec	257.42±108.93	400.0±154.10	**0.000**
Serum NT-proBNP (pg/mL)	100.03±82.40	48.25±34.87	**0.003**
RV EF, %	47.52±5.16	51.15±3.96	0.206
RV diastolic diameter	33.34±8.15	33.55±5.30	0.189
RV systolic diameter	17.03±4.86	17.06±3.04	0.282
Em	9.88±2.60	14.90±4.87	0.360
Am	13.85±3.68	15.74±5.25	0.081
Em/Am ratio	0.71±0.18	0.95±0.20	0.471
TAPSE	2.26±0.46	2.64±0.38	**0.040**
Tricuspit E	50.55±12.51	55.45±8.63	0.176
Tricuspit A	51.77±10.57	47.95±8.57	0.131
E/A	0.99±0.25	1.16±0.18	0.907
RA diameter	3.35±0.41	3.19±0.25	0.658

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RV diameter	2.98±0.29	2.74±0.30	0.973
mean PAP*, mm Hg	35 (30-55)		
Physical functioning*	75 (15-100)	97.5 (50-100)	0.000
Mental health	61.62±17.88	68.18±15.30	0.474
General health	49.94±18.24	71.95±10.51	0.518
Vitality*	66.5 (20.5-90)	74.7 (30.5-100)	0.037
Role limitation due to an emotional disorder *	100 (0-100)	100 (50-100)	0.018
Pain*	100 (12-100)	100 (41-100)	0.036
Social functioning*	100 (25-100)	100 (50-100)	0.092
Role limitation due to a physical disorder*	66.6 (0-100)	88.8 (0-100)	0.04

Data was expressed as mean±SD for parameters with normal distribution and *median for parameters with skewed distribution (range min-max).

*Comparisons of these parameters between two groups were made by Mann-Whitney U test.

Other parameters of two groups were compared with Student's t-test.

Am - late diastolic wave during atrial contraction; AT - anaerobic threshold; CPET - cardiopulmonary exercise test; COPD - chronic obstructive pulmonary disease; Em - early diastolic wave; FEF_{25-75}% - forced expiratory flow at 25-75%; FEV1 - forced expiratory volume at 1 second; FVC - forced vital capacity; IC - inspiratory capacity; MVV - maximum voluntary ventilation; NT-pro BNP - N-terminal of pro B-type natriuretic peptide; PAP - pulmonary arterial pressure; PET CO_2 - partial pressure of end-tidal carbon dioxide; $PVCO_2$ - peak CO2 output, PVO_2-peak oxygen uptake; RA diameter - right atrium diameter; RV diameter - right ventricle diameter; RV EF - right ventricle ejection fraction; RV - residuel volume; SF-36 - short form-36; TAPSE - tricuspid annular plane systolic excursion; TLC - total lung capacity; VC - vital capacity; $VECO_2$ - ventilatory equivalent for CO_2; VEO_2 - ventilatory equivalent for O_2.

Wilk test. Homogenity of variances was analysed with Levene test. Mean of two groups with normally distributed variances were compared with Student's t test. Comparisons of parameters without normal distribution between two groups were made by Mann-Whitney U test. Pearson chi-square test and Fisher exact test were used for the analysis of categorical variables. Spearman rho correlation coefficient was used to determine correlations between parameters without normal distribution and Pearson correlation coefficient was used to determine correlations between parameters with normal distribution. P<0.05 was accepted as significant.

Results

Baseline characteristics

Demographic data of study population is demonstrated at Table 1. There was significant difference between patient and control groups in terms of smoking status (p=0.004). No significant statistical difference was found in terms of body mass index of patient and control group (p=0.508).

Pulmonary function tests and CPET results

FEV_1 (liter and %), FVC (liter and %), FEV_1/FVC ratio, TLC (%), VC (liter and %), FEF_{25-75} (%) and MVV values were decreased in patient group significantly (p=0.000) (Table 2).

We found significant differences between patient and control groups in terms of AT VO_2, AT VCO_2, AT VEO_2, AT $VECO_2$ values, PVO_2,VE, breathing reserve, O_2 pulse and exercise duration (p=0.000) (Table 2). Serum NT-proBNP values were significantly higher in COPD patients than control group (mean serum NT-proBNP: 100.03±82.40; 48.25±34.87 respectively, p=0.000) (Table 2).

Table 3. Relationships between NT-proBNP level with smoking, age, pulmonary function test, echocardiography, and cardiopulmonary exercise testing results in COPD patients

	NT-Pro BNP	
Parameters	**rho**	***P***
mean PAP*	0.651	0.016
Tricuspit E	-0.126	0.377
Tricuspit A	0.090	0.530
E/A	-0.186	0.190
TAPSE	0.005	0.974
Em	-0.154	0.281
Am	0.068	0.635
Em/Am rate	-0.182	0.202
RV EF%	-0.093	0.514
RA diameter	0.079	0.584
RV diameter	0.185	0.194
RV diastolic diameter	0.140	0.329
RV systolic diameter	0.111	0.438
Cigarette pack year	0.354	0.025
Age	0.422	0.002
FEV_1 L	-0.439	0.001
FEV_1, %	-0.269	0.049
FVC, %	-0.295	0.035
IC L	-0.407	0.003
VC L	-0.544	0.000
AT VO_2 mL/kg/min	-0.462	0.001
AT VO_2 L/min	-0.372	0.008
AT VCO_2	-0.372	0.008
PVO_2 L/min	-0.441	0.001
PVO_2 mL/kg/min	-0.527	0.000
O2 pulse	-0.388	0.005
VE/VCO_2	-0.041	0.776
PET CO_2	0.071	0.621

*Spearman Correlation analysis was performed.

Other correlations were performed with Pearson Correlation Analysis

Am - late diastolic wave during atrial contraction; AT - anaerobic threshold; CPET - cardiopulmonary exercise test; COPD - chronic obstructive pulmonary disease; Em - early diastolic wave; FEV_1 - forced expiratory volume at 1 second; FVC - forced vital capacity; IC - inspiratory capacity; MVV - maximum voluntary ventilation; NT-pro BNP - N-terminal of pro B-type natriuretic peptide; PAP - pulmonary arterial pressure; PET CO_2 - partial pressure of end-tidal carbon dioxide; $PVCO_2$ - peak CO_2 output, PVO_2 - peak oxygen uptake; RA diameter - right atrium diameter; RV diameter - right ventricle diameter; RV EF - right ventricle ejection fraction; TAPSE - tricuspid annular plane systolic excursion; VC - vital capacity; $VECO_2$ - ventilatory equivalent for CO_2, VEO_2 - ventilatory equivalent for O_2.

Echocardiographic assessment results

Echocardiographic assessment results are demonstrated at Table 2. TAPSE values were significantly different between

Table 4. Relationships between right ventricular findings with FEV1 and cardiopulmonary exercise testing results in COPD patients.

Echocardiographic	FEV_1 liter		O_2 pulse		PVO_2 mL/kg/min		AT VO_2 L/min	
parameters	rho	*P*	rho	*P*	rho	*P*	rho	*P*
PAP*	-0.138	0.653	-0.244	0.423	-0.436	0.136	-0.290	0.361
RV % EF	0.349	**0.012**	**0.382**	0.034	0.106	0.572	0.190	0.324
RV diastolic diameter	0.133	0.353	0.103	0.582	-0.144	0.440	0.162	0.401
RV systolic diameter	0.144	0.313	0.080	0.670	-0.155	0.405	0.173	0.369
Em	0.610	**0.000**	**0.357**	0.049	0.007	0.969	0.261	0.172
Am	0.393	**0.004**	0.266	0.148	0.043	0.818	-0.008	0.965
Em/Am ratio	0.421	**0.002**	0.171	0.359	-0.017	0.928	0.291	0.125
TAPSE	0.466	**0.001**	0.287	0.118	0.002	0.993	0.233	0.224
Tricuspit E	0.344	**0.013**	0.231	0.212	-0.092	0.623	0.381	**0.042**
Tricuspit A	-0.078	0.587	0.031	0.867	-0.069	0.711	-0.200	0.299
E/A	0.348	**0.012**	0.227	0.219	0.001	0.994	0.569	**0.000**
RA diameter	-0.130	0.363	0.187	0.315	0.046	0.805	0.221	0.249
RV diameter	-0.333	**0.017**	-0.003	0.989	-0.149	0.425	0.202	0.294

*Spearman correlation analysis was performed.
Other correlations were performed by using Pearson correlation analysis
Am - late diastolic wave during atrial contraction; AT - anaerobic threshold; COPD - chronic obstructive pulmonary disease; Em - early diastolic wave; FEV_1 - forced expiratory volume at 1 second; NT-pro BNP-N-terminal of pro B-type natriuretic peptide; PAP - pulmonary arterial pressure; PVO_2 - peak oxygen uptake; RA diameter - right atrium diameter; RV diameter - right ventricle diameter; RV EF - right ventricle ejection fraction; TAPSE - tricuspid annular plane systolic excursion

Table 5. Relationship between SF-36 questionnaire with pulmonary function tests, cardiopulmonary exercise tests and serum NTpro-BNP in COPD patients

	FEV_1 lt		IC		AT VO_2 L/min		PVO_2 L/dk		O_2 pulse		NT- pro BNP	
SF-36	rho	*P*	Rho	*P*	rho	*P*	rho	*P*	rho	*P*	rho	*P*
Physical functioning*	0.688	0.000	0.538	0.000	0.522	0.000	0.520	0.000	0.445	0.001	-0.196	0.168
Mental health**	0.230	0.105	0.157	0.271	0.128	0.382	0.204	0.150	0.169	0.236	-0.083	0.562
General health**	0.614	0.000	0.338	0.015	0.450	0.001	0.487	0.000	0.374	0.007	-0.101	0.24
Vitality*	0.368	0.008	0.355	0.010	0.185	0.202	0.255	0.070	0.304	0.030	-0.219	0.12
RL due to ED*	0.403	0.003	0.376	0.007	0.212	0.145	0.372	0.007	0.404	0.003	-0.225	0.113
Pain*	0.305	0.030	0.257	0.049	0.125	0.392	0.258	0.068	0.234	0.098	-0.190	0.181
Social functioning*	0.218	0.124	0.135	0.345	0.190	0.192	0.199	0.162	0.064	0.653	-0.01	0.94
RL due to PD*	0.403	0.003	0.327	0.019	0.271	0.060	0.412	0.003	0.354	0.011	-0.324	0.02

**Pearson correlation analysis was performed.
*Spearman Correlation analysis was performed.
AT - anaerobic threshold; COPD - chronic obstructive pulmonary disease; ED - emotional disorder; FEV_1 - forced expiratory volume at 1 second; IC - inspiratory capacity; NT-pro BNP-N - terminal of pro B-type natriuretic peptide; PD - physical disorder; PVO_2 - peak oxygen uptake; RL - role limitation; SF-36 - short form-36

patient and control groups (2.26±0.46 cm; 2.64±0.38 cm respectively, p=0.040). Moreover COPD patients had reduced right ventricular Em wave, Em/Am ratio and tricuspit E wave (Table 2). When we graded right ventricle diastolic dysfunction in study population, 6 (19.3%) COPD patients had grade 1 right ventricle diastolic dysfunction, 8 (54.8%) COPD patients had grade 2 diastolic dysfunction and the rest of COPD patients and control subjects had normal right ventricle diastolic functions.

SF-36 results

Domains of role limitation due to an emotional disorder, pain and role limitation due to a physical disorder were significantly different between patient and control groups (Table 2).

Correlation analyses

When we correlated serum NT-proBNP level of COPD patients with cigarette consumption, pulmonary arterial pressure, pulmonary function test, cardiopulmonary exercise testing, echocardiographic assessments, we found negative correlations between serum NT-proBNP level with pulmonary function test results, AT VO_2, AT VCO_2, PVO_2, and O_2 pulse; positive correlations between serum NT-proBNP level with pulmonary arterial pressure and cigarette consumption (Table 3).

There were significant correlations between FEV_1 (liter) with Em, Am, Em/Am ratio, TAPSE, tricuspit E, E/A ratio and right ventricle diameter; IC and VC (liter) with Em, Am waves, Em/Am ratio and TAPSE values in COPD patients (Table 4). We also found significant relationships between O_2 pulse with right ventricle EF and Em wave; AT VO_2 (L/min) with tricuspit E wave and E/A ratio; AT VEO_2 with right ventricle diameter (Table 4).

There were significant relationships between FEV_1 and IC with SF-36 domains (Table 5). SF-36 domains of physical functioning, general health and role limitation due to physical disorder were significantly correlated with AT VO_2, PVO_2 and O_2 pulse. Moreover we found significant relationship between role limitation due to emotional disorder with PVO_2 and O_2 pulse. Mental health, pain and social functioning domains with cardiopulmonary exercise testing results were not significantly correlated (Table 5). A negative correlation between serum NT-proBNP level with role limitation due to physical disorder was found (p=0.02; r=-0.324) (Table 5).

Discussion

The present study demonstrated significant correlations between serum NT-proBNP level with role limitation due to physical disorder and CPET parameters in COPD patients supporting our hypothesis.

In the present study, early diastolic filling (E wave), right ventricle myocardial early filling (Em), and ratio of Em/Am were decreased in COPD patients and TAPSE values were significantly lower in COPD patients than control subjects suggesting the impaired systolic and diastolic functions of COPD patients. Karabulut et al. (21) found deterioration of right ventricular diastolic functions with progressed disease stage of COPD patients and highlighted the importance of echocardiographic assessments in COPD patients. In parallel with these findings we found significant correlations between FEV_1 with Em wave, Em/Am ratio, TAPSE, tricuspit E wave and E/A ratio in COPD patients. According to these results, we consider that right ventricle systolic and diastolic functions were adversely affected with disease progression.

In COPD patients, right ventricular wall tension causes the release of BNP. Therefore increased serum BNP level has been defined as a powerful marker in diagnosis and severity of PH (22). Increased serum BNP levels have also been reported in patients with PH secondary to acute and/or chronic respiratory diseases (23) In the present study, serum NT-proBNP levels were significantly higher in COPD patients than control subjects. In previous studies, Lang et al. (24) and Chi et al. (25) reported higher BNP levels in COPD patients than control subjects. Bozkanat et al. (26) and Chi et al. (25) showed the significant relationships between serum NT-proBNP with FEV_1 in COPD patients. In the present study we determined significant negative correlations between serum NT-proBNP with FEV_1, FVC, IC and VC as well. Chi et al. (25) determined positive correlation between PAP with NT-proBNP in COPD patients and Bando et al. (27) found higher serum BNP levels in COPD patients with PH than COPD patients without PH. Leuchte et al. (23) showed significant correlation between serum BNP levels with PAP in COPD patients with PAP>35 mm Hg at right heart catheterization. Similar to previous studies we also found significant correlation between PAP with NT-proBNP. Based on this significant correlation, we suggest that NT-proBNP levels might be a prognostic and noninvasive marker in advance disease stages of COPD. However no significant correlations between NT-proBNP with right ventricular diastolic parameters were found in the present study. These results could be attributed to the small sample size and limitations of echocardiography (air trapping, changes of chest wall, etc) in COPD patients. In the literature NT-proBNP level has been associated with age as ventricular compliance decreases with age (28, 29). Similar to the previous reports relationship between NT-proBNP level with age was also determined in the present study.

Quality of life and exercise capacity of COPD patients are impaired (30). Patients generally descibe exercise intolerance as declined response of ventilation to exercise related with airflow limitation (31, 32). Besides, depression and sedentary life style due to dyspnea are contributing factors to exercise intolerance (19). In our study patients with COPD had significant exercise limitation when compared with control subjects. These results can be explained as the importance of inspiratory capacity and vital capacity in response to increased ventilatory demand in COPD patients during exercise.

Several studies have shown exercise limitation in left ventricular dysfunction (22, 33, 34). Kruger et al. (34) have also found negative correlation between serum BNP level with PVO_2 and AT values in 70 patients with congestive heart failure. Eroğlu et al. (35) evaluated the relationship between BNP levels and CPET parameters in patients with dyspnea and isolated left ventricle diastolic dysfunction and found negative correlation between BNP levels and duration of exercise, AT VO_2, and MET on CPET. To the best of our knowledge, this is the first study using CPET, and BNP levels in COPD patients. In the present study, NT-proBNP was negatively correlated with AT VO_2, AT VCO_2 and PVO_2 values. Thus serum NT-proBNP levels can be regarded as a useful biomarker in exercise limitation of moderate-severe COPD patients.

Limited number of studies investigating the effects of diastolic dysfunctions on exercise capacity in COPD patients was found. Cuttica et al. (36) determined significant association between right sided cardiac structural changes with exercise capacity in COPD patients. In the present study, exercise capacity was also affected by diastolic dysfunctions and PH. Although serum NT-proBNP level was not correlated with right ventricle parameters, serum NT-proBNP level was significantly higher in COPD patients than control subjects and right ventricle diastolic and systolic dysfunction was seen in COPD patients and significant relationships between serum NT-proBNP and CPET parameters were found.

We also demonstrated the correlations between SF-36 domains with pulmonary function test results and positive correlations between SF-36 domains with PVO_2 and AT values consistent with the literature (19, 37, 38). However we did not find relationship between PH and quality of life. These results might be due to characteristics of our study population as COPD patients had mild PH. Improvement of quality of life will help to increase exercise capacity in COPD patients. Moreover significant correlation between serum NT-proBNP and role limitation due to physical disorder may indicate the utility of serum NT-proBNP to demonstrate quality of life in COPD patients. These preliminary results should be validated and explored in further studies.

Study limitations

We used echocardiographic assessments however technical difficulties due to hyperinflation can be seen in COPD patients. Right heart catheterization- gold standart diagnostic tool for right ventricular dysfunction and PH- could not be performed to our study population. Small sample size is another limitation of the present study.

Conclusion

Right ventricular dysfunction contribute exercise limitation together with airflow obstruction in moderate and severe COPD patients. Serum NT-proBNP levels can be used to demonstrate exercise capacity and quality of life in COPD patients. Further studies are needed to validate and explore these preliminary results in larger number of moderate and severe COPD patients with right ventricular dysfunction confirmed diagnosis with right heart catheterization.

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