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Decreased left ventricular stroke volume is associated with low-grade exercise tolerance in patients with chronic obstructive pulmonary disease

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ABSTRACT

Background: Low-grade exercise tolerance is associated with a poor prognosis in patients with chronic obstructive pulmonary disease (COPD). The 6 min walk test (6MWT) is commonly used to evaluate exercise tolerance in patients with COPD. However, little is known regarding the relationship between cardiac function and exercise tolerance in patients with COPD. The aim of this study was to identify predictive factors in cardiac function for low-grade exercise tolerance in patients with stable COPD.

Methods: We recruited 57 patients with stable COPD (men 54, women 3) to perform the 6MWT. Patients with underlying orthopaedic disease or heart failure were excluded. Cardiac function was evaluated by echocardiography and contrast-enhanced cardiac CT. We also measured pulmonary function and the 6MWT distance.

Results: Forced expiratory volume in 1 s (FEV_1) and per cent predicted FEV, along with left ventricular end diastolic volume and left ventricular cardiac output as measured by cardiac CT, were significantly related to the 6MWT distance. On multivariate analysis, left ventricular stroke volume was the factor most closely associated with a decreased walked distance in the 6MWT.

Conclusions: Decreased left ventricular stroke volume was associated with low-grade exercise tolerance in patients with stable COPD without heart failure.

KEY MESSAGES

- What is the most predictive clinical parameter for low-grade exercise tolerance in patients with stable chronic obstructive pulmonary disease (COPD)?
- We show that decreased left ventricular stroke volume obtained from cardiac CT scan was associated with low-grade exercise tolerance in patients with stable COPD.
- The data suggest that cardiac CT scanning may be beneficial for the evaluation of cardiac function and decreased left ventricular stroke volume was associated with low-grade exercise tolerance in patients with stable COPD.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a leading cause of mortality globally.[1 2] In Japan, there is an 8% prevalence of airflow limitation in participants over 40 years old,[3 4] and it is presumed that many patients with COPD remain undiagnosed.

Recently, COPD has come to be considered both a respiratory disease, and a systemic disease.[5–7] The severity of COPD is usually categorised according to respiratory functions such as forced expiratory volume in 1 s (FEV_1) and per cent predicted FEV (% FEV_1).[8] Although patients with COPD and compromised respiratory function have shown lower exercise tolerance,[9] other factors including cardiac function, aerobic capacity, respiratory or skeletal muscle function, and dynamic hyperinflation have been previously associated with exercise tolerance.[10–13] Recently, a decreased exercise tolerance has been strongly associated with a poor prognosis, independent of pulmonary function.[10] The BODE Index, determined by the *b*ody mass index (*B*MI), airway *o*bstruction (as measured by FEV_1), *d*yspnoea (as measured by the Modified Medical Research Council (mMRC) Dyspnea Scale), and *e*xercise tolerance (as measured by the 6 min walk test (6MWT)), is one of the best predictors of mortality in patients with COPD.[14] Owing to this, it is important to accurately assess exercise tolerance to predict the prognosis of patients with COPD. The 6MWT provides a practical and simple test to evaluate exercise tolerance in these patients.[11 15]

Patients with COPD frequently experience exacerbations due to respiratory infection, respiratory failure and death.[16] In addition to respiratory infections or respiratory failure, cardiovascular diseases have shown a significant association with COPD and are reported to be a major cause of death in patients with COPD.[1] Based on these findings, we need to consider exercise tolerance and the presence of cardiovascular disease in the management of patients with COPD.

Echocardiography is commonly used to evaluate cardiac function. However, this method has serious limitations in the evaluation of some patients with COPD with overinflated lungs and persistent expansion of the thoracic wall. Ultrasonic waves are poorly transmitted through air, and do not conduct well in lung tissue. Overinflated lungs degrade the quality of cardiac imaging with echocardiography. However, recent technological developments in multidetector CT (MDCT) now enable the assessment of end-diastole and end-systole cardiac volumes. Therefore, an MDCT evaluation of cardiac function in patients with COPD may be superior to that obtained with echocardiography, because overinflated lungs do not limit the MDCT examination.

In this study, we evaluated cardiac function in patients with stable COPD using 64-slice MDCT, and analysed the correlations between cardiac functions and exercise tolerance. The aim of this study was to identify predictive factors in cardiac function for low-grade exercise tolerance in patients with stable COPD.

MATERIALS AND METHODS

Participants

We recruited 57 patients with stable COPD (54 men, 3 women) who were free of any exacerbations in the 3 months prior to this study. None of the 57 patients had any disability affecting their ability to perform the 6MWT, such as orthopaedic disease or heart failure. None of the patients with COPD had been diagnosed with heart failure by their physicians. All participants gave written informed consent. The diagnosis of COPD was based on spirometry demonstrating a postbronchodilator FEV_1/forced vital capacity (FVC) ratio of <0.7.[17] The reference values for respiratory function were based on guidelines from the Japanese Respiratory Society.[18] Smoking habits were self-reported.

Patients with COPD underwent 6MWT following guidelines published by the American Thoracic Society (ATS).[19] The patients walked on a flat, hard-surfaced corridor, and were encouraged every 60 s during the test. Patients were allowed to stop walking and rest during the test if they felt fatigue or dyspnoea; however, they were instructed to restart walking as soon as they were able to.[19]

Evaluation of cardiac function

Cardiac function was evaluated by echocardiography and contrast-enhanced cardiac CT. Transthoracic echocardiography was performed (Hewlett-Packard/Philips Sonos 7500 ultrasound instrument, Philips Healthcare, Amsterdam, The Netherlands) and left ventricular (LV) and left atrial diameters were measured in the two-dimensional parasternal long-axis view. LV ejection fraction was calculated using the biplanar method of disks (modified Simpson rule).[20] Cardiac MDCT was performed using a 64-slice MDCT scanner (Aquilion 64, Toshiba, Tokyo, Japan). A total of 51–100 mL of contrast media (Iopamidol, Bayer Co, Leverkusen, Germany) was injected at a flow rate of 3.0–4.6 mL/s, depending on the patient's body weight. The region of interest was placed between the ascending aorta and descending aorta, and scanning was started when the CT density reached 250 Hounsfield units (HU) at the ascending aorta or 180 HU at the descending aorta. The area between the diaphragm and the tracheal bifurcation (collimation width 0.5 mm, rotation speed 0.4 s/rotation, tube voltage 120 kV and effective tube current 400–450 mA) was scanned. Cardiac images were evaluated during most of the motionless phase of the cardiac cycle, which was most frequently the mid-diastolic phase, with retrospective cardiac gating at 75% of the inter-beat (R-R) interval.[21–23] This protocol was the same as that used in a previously reported study.[23] An automatic algorithm in the analysis software (ZIO station, ZIO soft, Tokyo, Japan) was used[20 22] to evaluate cardiac volumes and output. The patients' profiles, respiratory function and cardiac parameters measured by MDCT or echocardiography are summarised in table 1.

Statistical analyses

All data are expressed as means±SD. The relationships between continuous variables were evaluated using Spearman's rank correlations. Univariate and multivariate analyses were used to identify risk factors for low-grade exercise tolerance with the 6MWT. We used a distance of 350 m in the 6MWT as the cut-off value in the univariate and multivariate analysis, because this distance was used as the cut-off value in previous studies to determine low-grade exercise tolerance in patients with COPD.[11 14 15] We used the receiver operating characteristic (ROC) curve to determine the cut-off value for LV stroke volume (LVSV), for detecting the risk for <350 m distance in the 6MWT. All statistical analyses were performed using JMP V.11.0.0 software (SAS Institute, Cary, North Carolina, USA). A p<0.05 was defined as statistically significant.

RESULTS

We compared the cardiac parameters obtained from echocardiography and MDCT. In 3/57 patients, we were unable to measure cardiac parameters with echocardiography because of their overinflated lungs. There was a significant correlation between the LV diastolic diameter, obtained from echocardiography, and the LV end diastolic volume (LVEDV), obtained from MDCT (R=0.339,

Table 1 Profiles of patients (n=57)

Gender male (%)	54 (94.7%)
Age (years)	71.5±8.0
BMI (kg/m^2)	21.5±3.2
Brinkman index	1197±602
mMRC scale	
(0/1/2/3/4)	14/30/9/2/2
GOLD classification	
(I/II/III/IV	10/16/25/6
Distance in 6MWT (m)	418.2±103.9
Respiratory function	
FVC (L)	2.82±0.79
%FVC (%)	98.6±27.2
$FEV_{1.0}$ (L)	1.33±0.57
$FEV_{1.0}$/FVC (%)	46.2±10.2
$FEV_{1.0}$/$FEV_{1.0}$ p (%)	51.9±20.9
IC (L)	1.99±0.56
Cardiac parameters measured by MDCT	
LVEF (%)	53.5±10.9
LVEDV (mL)	96.5±34.3
LVEDVI (mL/m^2)	61.6±22.7
LVESV (mL)	46.3±24.1
LVESVI (mL/m^2)	29.5±16.4
LVSV (mL)	50.4±16.6
LVCO (L/min)	3.6±1.2
LVCI ($L/min/m^2$)	2.3±0.8
RVEF (%)	34.4±12.5
RVEDV (mL)	121.5±38.4
RVEDVI (mL/m^2)	77.2±23.1
RVESV (mL)	80.2±32.2
RVESVI (mL/m^2)	51.0±19.7
RVSV (mL)	41.2±18.7
RVCO (L/min)	3.0±1.2
RVCI ($L/min/m^2$)	1.9±0.8
Cardiac parameters measured by echocardiography	
LVDd (mm)	45.0±7.4
LVDs (mm)	28.1±5.8
LVEF (%)	68.5±9.7
TR-PG (mm Hg)	15.5±13.8

6MWT, 6 min walk test; BMI, body mass index; FEV_1, forced expiratory volume in 1 s; %FVC, per cent predicted FVC; FVC, forced vital capacity; IC, inspiratory capacity; LVCI, left ventricular cardiac index; LVCO, left ventricular cardiac output; LVDd, left ventricular diastolic diameter; LVDs, left ventricular systolic diameter; LVEDV, left ventricular end diastolic volume; LVEDVI, left ventricular end diastolic volume index; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; LVESVI, left ventricular end systolic volume index; LVSV, left ventricular stroke volume; MDCT, multidetector CT; mMRC, modified British Medical Research Council; RVCI, right ventricular cardiac index; RVCO, right ventricular cardiac output; RVEDV, right ventricular end diastolic volume; RVEDVI, right ventricular end diastolic volume index; RVEF, right ventricular ejection fraction; RVESV, right ventricular end systolic volume; RVESVI, right ventricular end systolic volume index; RVSV, right ventricular stroke volume; TR-PG, tricuspid regurgitation-pressure gradient.

p=0.0107; figure 1A). There was also a significant correlation in the ejection fraction obtained with both methods (R=0.549, p<0.001; figure 1B). We also analysed the correlation between clinical background and data and the 6MWT distance in patients with COPD (table 2).

There was no correlation between age and BMI with the 6MWT distance. Per cent predicted FVC, $\%FEV_1$,

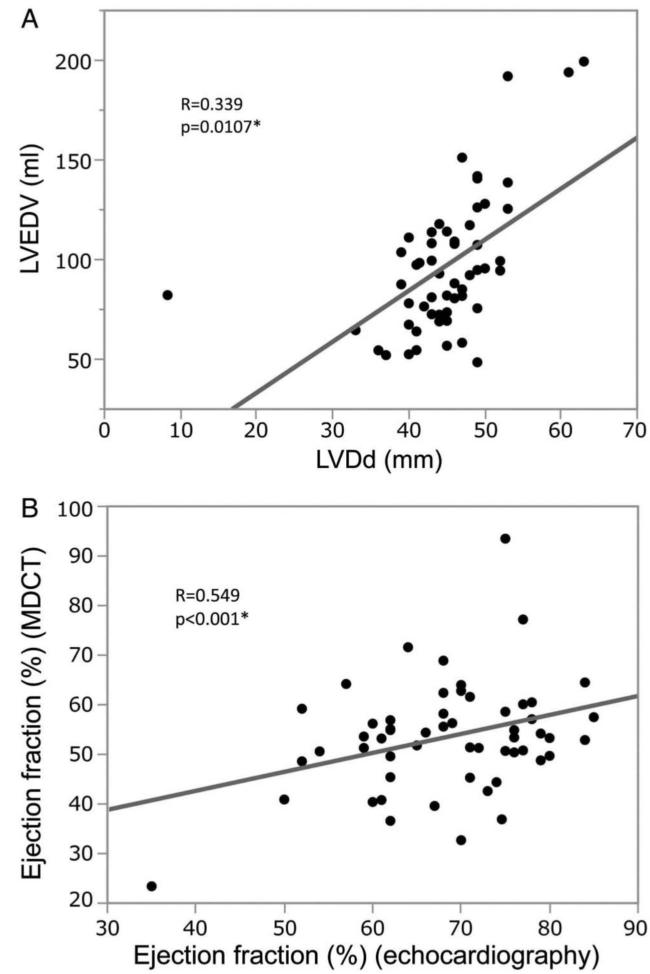

Figure 1 Correlations between LVEDd obtained from echocardiography and LVEDV obtained from MDCT (A), and between EF obtained from echocardiography and MDCT (B). EF, ejection fraction; LVEDd, left ventricular end diastolic diameter; LVEDV, left ventricular end diastolic volume; MDCT, multidetector CT.

FEV_1/FVC and inspiratory capacity (IC) showed a significantly positive correlation with the 6MWT distance. In addition, cardiac parameters derived from MDCT imaging, including LVEDV, LVEDV index (LVEDV/body surface area), LVSV, LV cardiac output (LVCO) and LV cardiac index (LVCO/body surface area) demonstrated a significantly positive correlation with the 6MWT distance. In contrast with the cardiac parameters measured by MDCT, there were no significant correlations between cardiac parameters measured by echocardiography and the 6MWT distance.

Since a <350 m 6MWT distance was used in a previous study as the cut-off value for low-grade exercise tolerance in patients with COPD,[15] we used this cut-off value in the univariate and multivariate analysis (table 3). In this study, 11 patients did not reach a distance of 350 m in the 6MWT.

In the univariate analysis, a decreased $\%FEV_1$, IC and LVSV were significant risk factors for a shorter 6MWT distance.

Table 2 Correlation between distance in 6MWT and parameters

	R	p Value
Age	0.241	0.0702
BMI	0.221	0.0988
Respiratory function		
%FVC	0.341	0.0094
$\%FEV_1$	0.366	0.0051
FEV_1/FVC	0.329	0.0124
IC	0.453	0.0004
Cardiac parameters measured by MDCT		
LVEF	0.234	0.0800
LVEDV	0.332	0.0116
LVEDVI	0.273	0.0402
LVESV	0.156	0.2451
LVESVI	0.123	0.3601
LVSV	0.458	0.0003
LVCO	0.390	0.0027
LVCI	0.333	0.0114
RVEF	0.226	0.0910
RVEDV	0.193	0.1499
RVEDVI	0.149	0.2689
RVESV	0.071	0.6001
RVESVI	0.026	0.8499
RVSV	0.275	0.0385
RVCO	0.195	0.1455
RVCI	0.167	0.2138
Cardiac parameters measured by echocardiography		
LVDd	0.055	0.6891
LVDs	0.026	0.8529
LVEF	0.122	0.3715
TR-PG	0.144	0.3001

Clinical data for each parameters are described in table 1.
6MWT, 6 min walk test; BMI, body mass index; $\%FEV_1$, per cent predicted FEV_1; FEV_1, forced expiratory volume in 1 s; %FVC, per cent predicted FVC; FVC, forced vital capacity; IC, inspiratory capacity; LVCI, left ventricular cardiac index; LVCO, left ventricular cardiac output; LVDd, left ventricular diastolic diameter; LVDs, left ventricular systolic diameter; LVEDV, left ventricular end diastolic volume; LVEDVI, left ventricular end diastolic volume index; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; LVESVI, left ventricular end systolic volume index; LVSV, left ventricular stroke volume; MDCT, multidetector CT; RVCI, right ventricular cardiac index; RVCO, right ventricular cardiac output; RVEDV, right ventricular end diastolic volume; RVEDVI, right ventricular end diastolic volume index; RVEF, right ventricular ejection fraction; RVESV, right ventricular end systolic volume; RVESVI, right ventricular end systolic volume index; RVSV, right ventricular stroke volume; TR-PG, tricuspid regurgitation-pressure gradient.

Table 3 Univariate analysis to detect the risk of shorter distance of 6MWT

	OR	95% CI	p Value
Age, per 1SD increase	1.76	0.86 to 4.03	0.1237
BMI, per 1SD increase	0.70	0.33 to 1.38	0.3156
$\%FEV_1$, per 1SD increase	0.31	0.10 to 0.75	0.0064
IC, per 1SD increase	0.46	0.20 to 0.94	0.0317
LVSV, per 1SD increase	0.15	0.03 to 0.45	0.0002

6MWT, 6 min walk test; BMI, body mass index; $\%FEV_1$, per cent predicted FEV_1; FEV_1, forced expiratory volume in 1 s; IC, inspiratory capacity; LVSV, left ventricular stroke volume.

Table 4 Multivariate analysis to detect the risk of shorter distance of 6MWT

	OR	95% CI	p Value
Model A			
$\%FEV_1$, per 1SD increase	0.36	0.04 to 1.55	0.1909
LVSV, per 1SD increase	0.05	0.003 to 0.36	0.0005
Model B			
IC, per 1SD increase	0.74	0.27 to 1.84	0.5138
LVSV, per 1SD increase	0.04	0.003 to 0.27	<0.0001

Data were adjusted for age and BMI.
6MWT, 6 min walk test; BMI, body mass index; $\%FEV_1$, per cent predicted FEV_1; FEV_1, forced expiratory volume in 1 s; IC, inspiratory capacity; LVSV, left ventricular stroke volume.

The results of the multivariate analyses are shown in table 4. Parameters obtained from cardiac CT were strongly associated with each other (data not shown). LVSV was thought to be the best predictor of low-grade exercise capacity because it showed the lowest p value among all cardiac parameters (table 2). Therefore, LVSV was applied in the multivariate analyses. Furthermore, there was a strong association between low-grade exercise capacity and $\%FEV_1$ and IC (R=0.658, p<0.0001), and these were separately included in the multivariate analyses (table 4, models A and B).

LVSV was a significant predictive factor for low-grade exercise tolerance, independent of age, BMI and pulmonary functions including $\%FEV_1$ (model A) and IC (model B). We used a ROC curve analysis to determine the LVSV cut-off value for discriminating between patients with COPD who could or could not walk 350 m in the 6MWT. The area under the curve was 0.844, and the cut-off value was 42.2 mL, with a sensitivity of 0.8261 and a specificity of 0.8182 (p=0.004; figure 2).

DISCUSSION

In this study, we showed that a decreased LVSV is associated with a reduced exercise tolerance in patients with stable COPD. In these patients, the 6MWT distance was significantly correlated with pulmonary functions indicating the degree of airflow limitation ($\%FEV_1$) and air trapping (IC). The 6MWT distance was also significantly correlated with cardiac function, such as LVSV, measured by cardiac CT scanning. However, there was no correlation between exercise tolerance and age, BMI or cardiac parameters measured by echocardiography. In the univariate and multivariate analyses, decreased LVSV was the most significant predictive factor for low-grade exercise tolerance.

Cardiovascular diseases are reported to be a major cause of death in patients with COPD; ~27% of these patients die of cardiovascular diseases including atherosclerosis and heart failure.[1] Echocardiography is a simple, non-invasive and commonly used method for the evaluation of cardiac function. However, echocardiography is sometimes difficult in patients with COPD

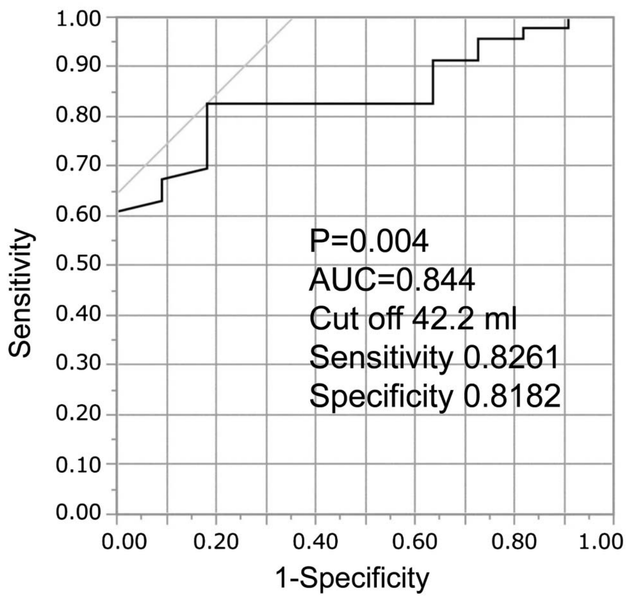

Figure 2 Determination of the LVSV cut-off value for the discrimination of reaching a walking distance >350 m in the 6MWT in patients with COPD. ROC curve analysis was performed to determine the LVSV cut-off value for the discrimination of reaching a walking distance of >350 m in 6MWT in patients with COPD. The AUC was 0.844, and the cut-off value was 42.2 mL, with a sensitivity of 0.8261 and a specificity of 0.8182 (p=0.004). 6MWT, 6 min walk test; AUC, area under the curve; COPD, chronic obstructive pulmonary disease; LVSV, left ventricular systolic volume; ROC, receiver operating characteristic.

with overinflated lungs.[24] In addition, determining cardiac stroke volume is very difficult during routine echocardiography. In contrast, cardiac CT scanning overcomes these limitations of echocardiography for the evaluation of cardiac parameters, and cardiac CT data are reproducible.

With this in mind, we evaluated cardiac parameters and function with cardiac CT scanning. In our study, all patients underwent echocardiography and cardiac CT scanning, but in three patients, we were unable to determine the measurements with echocardiography because of overinflated lungs. Although echocardiography-derived cardiac function data failed to show any significant association with exercise tolerance, contrast-enhanced cardiac CT scanning did. Contrast-enhanced cardiac CT scanning is a useful and reliable method for the evaluation of cardiac function, even in patients with COPD with overinflated lungs.

Our data show that a shorter 6MWT distance was associated with a decreased LVSV as measured by cardiac CT. A shorter 6MWT distance was also associated with advanced airflow obstruction. LVSV was the most important predictive factor for decreased exercise tolerance. A shorter 6MWT distance was previously reported to be predictive of a poor prognosis in patients with COPD.[25] Previous studies have considered the relationship between lower cardiac function measured by cardiac CT and a poor prognosis in patients with COPD. Graham and colleagues showed that cardiac diameters measured by MRI have a significantly negative relationship with pulmonary emphysema,[26] and they speculated that the severity of COPD, such as emphysematous changes in the lungs, influences cardiac function. Their findings are consistent with the results of the present study, which showed that a decreased cardiac volume in patients with COPD was strongly associated with low-grade exercise tolerance.

There are some drawbacks to contrast-enhanced cardiac CT scanning. First, participants who undergo contrast-enhanced cardiac CT scanning are exposed to radiation. Participants receive about 10–20 mSv of radiation during the examination, a level thought to be insignificant.[27] Second, cardiac CT scanning is more expensive than echocardiography. In Japan, a cardiac CT scan is about 40 000 yen, while the cost of echocardiography is about 10 000 yen. Third, the injection of contrast media may cause severe adverse events such as renal failure, bronchial constriction and shock; although no severe adverse events were observed in the present study. However, there are additional benefits of contrast-enhanced cardiac CT scanning compared with echocardiography. Cardiac CT scanning allows the evaluation of atherosclerotic regions of the coronary arteries, and we previously reported that calcification in the coronary arteries is associated with low-grade oxygenation in patients with stable COPD.[23]

There are several limitations of our study. First, this study was performed at a single centre, and did not include a large number of participants. Second, although it was previously reported that a short 6MWT distance was associated with a poor prognosis in patients with COPD,[25] we did not investigate patient prognosis in the present study. Third, although some previous reports have investigated the correlations between residual volume (RV) or total lung capacity (TLC) and exercise tolerance,[28] we could not present or analyse data regarding correlations between RV or TLC and exercise tolerance in this study because we could not measure RV and TLC in some patients with COPD due to decreased respiratory function or dyspnoea.

In conclusion, decreased LVSV was associated with low-grade exercise tolerance in patients with stable COPD not diagnosed with heart failure. Cardiac CT scanning may be beneficial for the evaluation of cardiac function and atherosclerosis of the coronary arteries in patients with COPD. Further investigation is needed to determine the relationship between disease progression and prognosis in patients with COPD and the cardiac parameters obtained from cardiac CT scanning.

Contributors SI planned the study and wrote the manuscript. YS advised the plan of the study and proofread the manuscript. HK and TN performed entry of the data. JN and YY analysed data of CT scan. TI performed echocardiography. KS performed statistical analysis. MS and YT performed pulmonary function test. TK and AI performed 6MWT. IK conducted the study.

Competing interests None declared.

Patient consent Obtained.

Ethics approval The study was approved by the Institutional Ethics Committee of the Yamagata University School of Medicine (approval number, 21; approval date, 21 October 2009).

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