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

Sumito Inoue, Yoko Shibata, Hiroyuki Kishi, Joji Nitobe, Tadateru Iwayama, Yoshinori Yashiro, Takako Nemoto, Kento Sato, Masamichi Sato, Tomomi Kimura, Akira Igarashi, Yoshikane Tokairin, Isao Kubota

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 (FEV1) and per cent predicted FEV1 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.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a leading cause of mortality globally. In Japan, there is an 8% prevalence of airflow limitation in participants over 40 years old, 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. The severity of COPD is usually categorised according to respiratory functions such as forced expiratory volume in 1 s (FEV1) and per cent predicted FEV1 (% FEV1). Although patients with COPD and compromised respiratory function have shown lower exercise tolerance, other factors including cardiac function, aerobic capacity, respiratory or skeletal muscle function, and dynamic hyperinflation have been previously associated with exercise tolerance.

Recently, a decreased exercise tolerance has been strongly associated with a poor prognosis, independent of pulmonary function. The BODE Index, determined by the body mass index (BMI), airway obstruction (as measured by FEV1), dyspnoea (as measured by the Modified Medical Research Council (mMRC) Dyspnea Scale), and exercise tolerance (as measured by the 6 min walk test (6MWT)), is one of the best predictors of mortality in patients with COPD. 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.
Patients with COPD frequently experience exacerbations due to respiratory infection, respiratory failure and death. 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. 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 FEV1/forced vital capacity (FVC) ratio of <0.7. The reference values for respiratory function were based on guidelines from the Japanese Respiratory Society. Smoking habits were self-reported.

Patients with COPD underwent 6MWT following guidelines published by the American Thoracic Society (ATS). 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.

**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). 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. This protocol was the same as that used in a previously reported study. An automatic algorithm in the analysis software (ZIO station, ZIO soft, Tokyo, Japan) was used 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. We used the receiver operating characteristic (ROC) curve to determine the cut-off value for LV stroke volume (LVS), 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,
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, %FEV₁, FEV₁/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, 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 %FEV₁, IC and LVSV were significant risk factors for a shorter 6MWT distance.

### Table 1 Profiles of patients (n=57)

<table>
<thead>
<tr>
<th>Gender</th>
<th>Male (%)</th>
<th>54 (94.7%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>71.5±8.0</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.5±3.2</td>
<td></td>
</tr>
<tr>
<td>Brinkman index</td>
<td>1197±602</td>
<td></td>
</tr>
<tr>
<td>mMRC scale</td>
<td>0/1/2/3/4</td>
<td></td>
</tr>
<tr>
<td>10/16/25/6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOLD classification</td>
<td>10/16/25/6</td>
<td></td>
</tr>
<tr>
<td>Distance in 6MWT (m)</td>
<td>418.2±103.9</td>
<td></td>
</tr>
<tr>
<td>Respiratory function</td>
<td>2.82±0.79</td>
<td></td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>98.6±27.2</td>
<td></td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>133±0.57</td>
<td></td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>46.2±10.2</td>
<td></td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>51.9±20.9</td>
<td></td>
</tr>
<tr>
<td>IC (L)</td>
<td>1.99±0.56</td>
<td></td>
</tr>
</tbody>
</table>

**Cardiac parameters measured by MDCT**

| LVEF (%) | 53.5±10.9 |
| LVEDV (mL) | 96.5±34.3 |
| LVEDVI (mL/m²) | 61.6±22.7 |
| LVESV (mL) | 46.3±24.1 |
| LVSV (mL) | 29.5±16.4 |
| LVCO (L/min) | 50.4±16.6 |
| LVCI (L/min/m²) | 3.6±1.2 |
| RVEF (%) | 2.3±0.8 |
| RVEDV (mL) | 34.4±12.5 |
| RVESV (mL) | 121.5±38.4 |
| RVESVI (mL/m²) | 77.2±23.1 |
| RVSV (mL) | 80.2±32.2 |
| RVCI (L/min/m²) | 51.0±19.7 |
| RVCO (L/min) | 41.2±18.7 |
| RVCI (L/min/m²) | 3.0±1.2 |

**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; FEV₁, 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; LVEF, left ventricular ejection fraction; LVSV, left ventricular stroke volume; LVCO, left ventricular cardiac output; MDCT, multidetector CT; mMRC, modified British Medical Research Council; RVCI, right ventricular cardiac index; RVCO, right ventricular cardiac output; RVDD, right ventricular end diastolic diameter; RVESV, right ventricular end systolic volume; RVESVI, right ventricular end systolic volume index; RVSV, right ventricular stroke volume; TR-PG, tricuspid regurgitation-pressure gradient.

FEV₁/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, 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 %FEV₁, IC and LVSV were significant risk factors for a shorter 6MWT distance.
Cardiac parameters measured by echocardiography:

- LVEF
- LVEDVD
- LVEDVI
- LVESV
- LVESVI
- LVCO
- LVCI
- RVEF
- RVEDV
- RVEDVI
- RVESV
- RVESVI
- RVS
- RVCO
- RVCI

Cardiac parameters measured by MDCT:

- LVEDD
- LVEDVs
- LVESV
- LVEDVI
- LVESVI
- LVCI
- LVSV
- LVCI
- LVSV
- LVCI

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 %FEV1 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 %FEV1 (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).

### Table 2: Correlation between distance in 6MWT and parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>R</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.241</td>
<td>0.0702</td>
</tr>
<tr>
<td>BMI</td>
<td>0.221</td>
<td>0.0988</td>
</tr>
</tbody>
</table>

#### Respiratory function

- %FVC
- %FEV1
- FEV1/FVC
- IC

#### Cardiac parameters measured by MDCT

- LVEF
- LVEDVD
- LVEDVI
- LVESV
- LVESVI
- LVCO
- LVCI
- RVEF
- RVEDV
- RVEDVI
- RVESV
- RVESVI
- RVS
- RVCO
- RVCI

#### Cardiac parameters measured by echocardiography

- LVEDD
- LVEDVs
- LVESV
- LVEDVI
- LVESVI
- LVCI
- LVSV
- LVCI
- LVSV
- LVCI

Clinical data for each parameter are described in Table 1. 6MWT, 6 min walk test; BMI, body mass index; %FEV1, per cent predicted FEV1; FEV1, 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; LVDVs, left ventricular end diastolic volume; LVEDVD, left ventricular end diastolic diameter; LVEDVI, left ventricular end diastolic volume; 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; RVDD, right ventricular end diastolic diameter; RVDDvi, right ventricular end diastolic volume; RVEF, right ventricular ejection fraction; RVESV, right ventricular end systolic volume; RVESVi, right ventricular end systolic volume index; RVS, right ventricular stroke volume; TR-PG, tricuspid regurgitation-pressure gradient.

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per 1SD increase</td>
<td>1.76</td>
<td>0.86 to 3.03</td>
<td>0.1237</td>
</tr>
<tr>
<td>BMI, per 1SD increase</td>
<td>0.70</td>
<td>0.33 to 1.38</td>
<td>0.3156</td>
</tr>
<tr>
<td>%FEV1, per 1SD increase</td>
<td>0.31</td>
<td>0.10 to 0.75</td>
<td>0.0067</td>
</tr>
<tr>
<td>IC, per 1SD increase</td>
<td>0.46</td>
<td>0.20 to 0.94</td>
<td>0.0317</td>
</tr>
<tr>
<td>LVSV, per 1SD increase</td>
<td>0.15</td>
<td>0.03 to 0.45</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

6MWT, 6 min walk test; BMI, body mass index; %FEV1, per cent predicted FEV1; FEV1, 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

<table>
<thead>
<tr>
<th>Model</th>
<th>OR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model A</td>
<td>%FEV1, per 1SD increase</td>
<td>0.36</td>
<td>0.04 to 1.55</td>
</tr>
<tr>
<td></td>
<td>LVSV, per 1SD increase</td>
<td>0.05</td>
<td>0.003 to 0.36</td>
</tr>
<tr>
<td>Model B</td>
<td>IC, per 1SD increase</td>
<td>0.74</td>
<td>0.27 to 1.84</td>
</tr>
<tr>
<td></td>
<td>LVSV, per 1SD increase</td>
<td>0.04</td>
<td>0.003 to 0.27</td>
</tr>
</tbody>
</table>

Data were adjusted for age and BMI. 6MWT, 6 min walk test; BMI, body mass index; %FEV1, per cent predicted FEV1; FEV1, forced expiratory volume in 1 s; IC, inspiratory capacity; LVSV, left ventricular stroke volume.

#### 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 (%FEV1) 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.
In conclusion, decreased LVSV was associated with low-grade exercise tolerance in patients with 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.

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 >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. 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. 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 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. 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.

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, 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, 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.
REFERENCES

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