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Original article

Cardiovascular function and prognosis of patients with heart failure coexistent with chronic obstructive pulmonary disease

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) often coexists with heart failure (HF), and is considered to be associated with adverse outcomes in HF patients. However, the features of cardiovascular function and the detailed all-cause mortality of HF with COPD remain unclear.
Methods and results: Consecutive 378 patients admitted for HF who underwent spirometry were divided into three groups: HF without COPD (non-COPD group, $n=272$), HF with mild COPD (GOLD I group, $n=82$), and HF with moderate COPD (GOLD II group, $n=24$). The GOLD II group, as compared to non-COPD group, had (1) higher troponin T ($p=0.009$); (2) greater cardio-ankle vascular index ($p=0.032$); and (3) similar cardiac systolic and diastolic function of the right and left ventricle. In addition, rates of cardiac ($p=0.049$), non-cardiac ($p=0.001$), and all-cause mortality ($p=0.002$) were higher in GOLD II group than in non-COPD and GOLD I groups. Importantly, in the Cox proportional hazard analyses, the GOLD stage II was an independent predictor of cardiac ($p=0.038$), non-cardiac ($p=0.036$), and all-cause mortality ($p=0.015$) in HF patients.
Conclusions: HF patients with coexistent moderate COPD (GOLD stage II) have greater myocardial damage, greater arterial stiffness, and higher cardiac and non-cardiac mortality.

Introduction

Chronic obstructive pulmonary disease (COPD) causes systemic inflammation and is frequently associated with cardiovascular diseases [1]. COPD and heart failure (HF) often mutually coexist in clinical practice [2–4]. It has been reported that COPD is associated with adverse clinical outcomes in HF patients [5–8], but COPD is not an independent predictor of HF [9,10]. In HF patients, right ventricular systolic function [11,12], pulmonary atrial pressure [12,13], myocardial damage [14], signal averaged electrocardiogram (ECG) as arrhythmia substrate [15], endothelial function [16], and arterial stiffness [17] are the reported predictors of cardiac events.

However, the features of HF coexistent with COPD from the viewpoint of comprehensive cardiovascular function and the impact of COPD on detailed all-cause mortality in HF remain unclear. The aims of the present study were to investigate (1) clinical features; (2) cardiac function, including right heart function, myocardial damage, and arrhythmia substrate; (3) vascular function including endothelial function and arterial stiffness; and (4) prognosis, including not only cardiac events but also non-cardiac events in HF patients with or without COPD.

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Methods

Subjects and study protocol

This was a prospective observational study which enrolled 388 consecutive symptomatic HF patients who were hospitalized and underwent respiratory function test (spirometry) at Fukushima Medical University between 2009 and 2012. The diagnosis of symptomatic HF was defined based on the Framingham criteria [18]. Patients with acute coronary syndrome, pulmonary thromboembolism, primary pulmonary hypertension, and past history of asthma were excluded. The presence of COPD was defined as forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) < 70% by spirometry according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and the American Thoracic Society/European Respiratory Society guidelines [19,20]. We performed several examinations such as general laboratory tests, flow-mediated dilatation, cardio-ankle vascular index, signal averaged ECG, and echocardiography in patients who were in a relatively stable phase (before discharge), and compared parameters among three groups based on spirometric findings (non-COPD group, GOLD I group, and GOLD II group). Hypertension was defined as the recent use of antihypertensive drugs, or systolic blood pressure ≥140 mmHg and/or a diastolic pressure ≥90 mmHg. Diabetes was defined as the recent use of insulin or antidiabetic drugs, a fasting blood glucose value of ≥126 mg/dl, and/or a hemoglobin A_1c value of ≥6.5%. Dyslipidemia was defined as the recent use of cholesterol-lowering drugs, a triglyceride value of ≥150 mg/dl, a low-density lipoprotein cholesterol value of ≥140 mg/dl, and/or a high-density lipoprotein cholesterol value of <40 mg/dl. Chronic kidney disease was defined as an estimated glomerular filtration rate (GFR) <60 ml/min/1.73 cm^2 [21]. Estimated GFR was measured by the Modification of Diet in Renal Disease formula [21]. Anemia was defined as hemoglobin of <12.0 g/dl in females and <13.0 g/dl in males [4]. A smoker was defined as a person who had smoked any cigarettes in the past three months. Patients were followed up for cardiac events (including cardiac death and/or progressive heart failure), non-cardiac death, and all-cause mortality. Cardiac death included death due to ventricular fibrillation or worsening HF. Progressive HF was defined as re-hospitalization due to worsening HF based on the Framingham criteria [18]. Non-cardiac death included death due to respiratory failure, infection, sepsis, cancer, digestive hemorrhage, etc. Status and dates of deaths were obtained from the patients' medical records. If these data were unavailable, status was ascertained by a telephone call to the patient's referring hospital physician. Written informed consent was obtained from all study subjects. The study protocol was approved by the Ethical Committee of Fukushima Medical University.

Pulmonary function test

Pulmonary function test was performed using a spirometer (CHESTAC-8900, Chest, Tokyo, Japan) when patients were in a relatively stable phase, or during an euvolumic phase before discharge. Spirometry was defined by standard indices: FEV_1, FVC, FEV_1/FVC, vital capacity, %vital capacity, and peak expiratory flow. COPD (obstructive disorder) was defined by a reduced FEV_1/FVC ratio of <70% [19,20]. COPD was graded as stage I (mild: $FEV_1 \geq 80\%$ of expected for age and gender corresponded), stage II (moderate: $50\% < FEV_1 \leq 80\%$), stage III (severe: $30\% < FEV_1 \leq 50\%$), and stage IV (very severe: $FEV_1 < 30\%$) as demonstrated in the GOLD criteria [19]. Restrictive disorder was characterized by reduced lung volumes (%vital capacity < 80%).

Flow-mediated dilatation

Endothelial function was evaluated blindly by means of flow-mediated dilatation [22]. After fasting overnight, patients were required to lie at rest for at least 15 min, and flow-mediated dilatation was assessed in the right arm in a supine position in a quiet temperature-controlled room using high-resolution ultrasound (UNEXEF18G, UNEX Corporation, Nagoya, Japan). Flow-mediated dilatation was calculated as the percentage of change in diameter from the baseline value before cuff release to the peak value after cuff release: %Flow-mediated dilatation = [(vessel diameter reactive hyperemia − vessel diameter at rest) × 100]/vessel diameter at rest [22].

Cardio-ankle vascular index

Cardio-ankle vascular index (CAVI) as an index of arterial stiffness was measured blindly using a Vasera VS-1000 device (Fukuda Denshi, Tokyo, Japan) as previously reported [23], while the subjects were awake between 08:00 h and 12:00 h. CAVI reflects the stiffness of the aorta, femoral arteries, and tibial arteries as a whole [23].

Signal averaged ECG

The signal averaged ECG was recorded using bipolar orthogonal leads as previously reported [15]. Recordings were performed in the supine position with CardioStar FCP-7541 (Fukuda Denshi). Three parameters were computed: RMS40, the root-mean-square voltage of the signals in the last 40 ms; LAS40, the duration of the low-amplitude signal after the voltage decreased to less than 40 μV; and fQRS, filtered QRS-duration. Late potential positive was defined as two of three parameters (RMS40, LAS40, fQRS) showing positive.

Echocardiography

Echocardiography was performed blindly by an experienced echocardiographer using the standard techniques. Echocardiographic parameters investigated included interventricular septum thickness, left ventricular (LV) dimension, posterior wall thickness, LV volume, LV ejection fraction (LVEF), left atrial volume, and the ratio of early transmitral flow velocity to mitral annular velocity (mitral valve E/E'), inferior vena cava diameter, peak systolic pulmonary artery pressure (SPAP), right atrial diameter, right ventricular (RV) diameter, RV area, RV fractional area change (RV-FAC), Doppler-derived tricuspid lateral annular systolic velocity (tricuspid valve S'), etc. [24]. The LVEF was calculated using a modification of the Simpson's method. Mitral valve E/E' was calculated by transmitral Doppler flow and tissue Doppler imaging. SPAP was calculated by adding the right atrial pressure (estimated by the diameter and collapsibility of the inferior vena cava) to the systolic trans tricuspid pressure gradient [12,24]. The RV-FAC, defined as (end diastolic area-end systolic area)/end diastolic area × 100, is a measure of RV systolic function [24]. All recordings were performed on ultrasound systems (ACUSON Sequoia, Siemens Medical Solutions USA, Inc., Mountain View, CA, USA).

Statistical analysis

Normally distributed data are presented as mean ± SD, non-normally distributed data are presented as median (interquartile range), and categorical variables are expressed as numbers and percentages. We used the one-way repeated-measures analysis of variance (ANOVA) followed by Tukey's post hoc test. Non-normally distributed data were analyzed by the Kruskal–Wallis test. The chi-square test was used for categorical variables among the three