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Endothelial dysfunction and abnormal vascular structure are simultaneously present in patients with heart failure with preserved ejection fraction☆

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ABSTRACT

Background: Endothelial dysfunction and abnormal vascular structure may be involved in the pathogenesis of chronic heart failure (HF). The purpose of this study was to evaluate simultaneously vascular function and vascular structure in patients with heart failure with preserved ejection fraction (HFpEF).
Methods: We measured flow-mediated vasodilatation (FMD) and nitroglycerine-induced vasodilation as indices of vascular function and intima-media thickness (IMT) as an index of vascular structure of the brachial artery in 41 patients with HFpEF (23 men and 18 women; mean age, 66 ± 12 yr) and 165 patients without HF (95 men and 70 women; mean age, 54 ± 16 yr).
Results: FMD was significantly smaller in patients with HFpEF than in patients without HF (2.9 ± 2.1% versus 4.6 ± 2.7%, $P = 0.0002$). Nitroglycerine-induced vasodilation was significantly smaller in patients with HFpEF than in patients without HF (9.3 ± 4.1% versus 12.9 ± 4.9%, $P < 0.0001$). Brachial artery IMT was significantly larger in patients with HFpEF than in patients without HF (0.35 ± 0.06 mm versus 0.31 ± 0.07 mm, $P = 0.0002$). After adjustment for age, sex, hypertension, dyslipidemia, and diabetes mellitus, the associations remained significant between HFpEF and FMD (odds ratio, 0.79; 95% confidence interval, 0.66–0.92; $P = 0.0032$), nitroglycerine-induced vasodilation (odds ratio, 0.88; 95% confidence interval, 0.80–0.96; $P = 0.0039$), and brachial artery IMT (odds ratio, 1.08; 95% confidence interval, 1.01–1.17; $P = 0.033$).
Conclusions: These findings suggest that both endothelial dysfunction and abnormal vascular structure may contribute to the pathogenesis and maintenance of HFpEF. Endothelial function and vascular structure may be potential therapeutic targets for HFpEF.

1. Introduction

The prevalence of heart failure (HF) patients with preserved ejection fraction (HFpEF) is increasing, and patients with HFpEF have higher mortality rates than those in age- and sex-matched subjects without HF [1]. An effective treatment for HFpEF has not been established since the etiology and pathophysiology of HFpEF are still unclear. It has been reported that global cardiovascular reserve function, including endothelial function, is impaired in patients with HFpEF [2]. Recently, Akiyama et al. [3] demonstrated that peripheral endothelial dysfunction determined by using reactive hyperemia-peripheral arterial tonometry was an independent predictor of future cardiovascular events in patients who have HF with normal left ventricular ejection fraction (LVEF). In addition, it has been shown that carotid arterial stiffness is increased in patients with HFpEF [4]. It is likely that HFpEF is closely related to vascular function and structure.

Measurement of flow-mediated vasodilation (FMD) as an index of endothelium-dependent vasodilation and nitroglycerine-induced

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vasodilation as an index of endothelium-independent vasodilation in the brachial artery using high-resolution ultrasound has been widely used as a method for assessing vascular function [5,6]. Endothelial function is initially impaired in the pathogenesis of atherosclerosis [7,8]. Measurement of FMD is noninvasive and reflects nitric oxide (NO) production. In addition, growing evidence has shown that endothelial function assessed by FMD can serve as an independent predictor of cardiovascular events [9,10].

Findings concerning the relationship between intima-media thickness (IMT) and HFpEF and the relationship between FMD and HFpEF have been controversial [2–4,11]. In previous studies, different vascular beds were used for the assessment, i.e., common carotid artery for IMT and brachial artery for FMD. Measurements of IMT, FMD and nitroglycerine-induced vasodilation in the brachial artery offer the opportunity to investigate the interrelation between morphologic and functional parameters within the same artery by a single examination. There is no information on vascular function and structure in the same artery in patients with HFpEF. Therefore, the purpose of this study was to evaluate simultaneously vascular function and vascular structure in patients with HFpEF.

2. Methods

2.1. Subjects

Between June 2007 and July 2015, we studied 261 patients with symptoms or signs of HF who underwent FMD and echocardiography and 200 patients without symptoms or signs of HF who underwent FMD and echocardiography. We enrolled 261 consecutive patients with HF and 200 consecutive patients without HF who agreed to participate in this study during the study period. Two hundred and twenty of the 261 patients who had symptoms or signs of HF, including 42 patients with reduced LVEF, 37 patients with valvular disease, 29 patients with atrial fibrillation, 15 patients with cardiomyopathy, 4 patients with severe renal dysfunction, 31 patients with the presence of regional wall motion abnormality, 7 patients with neoplasms, and 55 patients who did not meet diagnostic criteria, were excluded. Finally, 41 patients who had symptoms or signs of HF were enrolled from Hiroshima University Hospital. We defined patients with no symptoms, no signs of HF and either normal NT-proBNP or normal echocardiography on the basis of the diagnostic criteria of the European Working Group for HF as patients without HF [12]. Thirty-five of the 200 patients without HF who did not meet the diagnostic criteria were excluded. Finally, 165 patients without symptoms or signs of HF were enrolled from Hiroshima University Hospital.

Patients with HFpEF: patients presented with symptoms or signs of HF and were diagnosed with HFpEF at the Hiroshima University Hospital. HFpEF was defined according to the diagnostic criteria of the European Working Group for HFpEF [12]. Exclusion criteria were significant valvular disease, atrial fibrillation, cardiomyopathy, severe renal dysfunction, LVEF <50% and the presence of regional wall motion. Severe renal dysfunction was defined as estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2.

Patients without HF: patients had normal LVEF, did not present with symptoms of HF, and either had normal NT-proBNP or normal echocardiography, and had never been diagnosed with or treated for HF. The patients also met the exclusion criteria of the European Working Group for HFpEF.

Hypertension was defined as systolic blood pressure of >140 mmHg or diastolic blood pressure of >90 mmHg, in a sitting position, on at least three different occasions. Normotension was defined as systolic blood pressure of <140 mmHg and diastolic blood pressure of <90 mmHg. Diabetes was defined according to the American Diabetes Association or a previous diagnosis of diabetes [13]. Dyslipidemia was defined according to the third report of the National Cholesterol Education Program [14]. The ethical committees of our institutions approved the study protocol. Written informed consent for participation in the study was obtained from all of the subjects.

2.2. Study protocol

We measured vascular responses to reactive hyperemia and IMT in the brachial artery and echocardiograms in all subjects. Subjects fasted the previous night for at least 12 h prior to the measurements. The study began at 8:30 AM. The subjects were kept in the supine position in a quiet, dark, air-conditioned room (constant temperature of 22 °C–25 °C) throughout the study. A 23-gauge polyethylene catheter was inserted into the left deep antecubital vein to obtain blood samples. Thirty minutes after maintaining the supine position, brachial-ankle pulse wave velocity (baPWV), FMD, IMT, and nitroglycerine-induced vasodilation were measured. The observers were blind to the form of examination.

Thirty minutes after remaining in the supine position, Rho-associated kinase (ROCK) activity and fasting serum concentrations of total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, blood urea nitrogen, creatinine, glucose, and N-terminal pro-brain natriuretic peptide (NT-proBNP) were measured.

2.3. Measurement of FMD and nitroglycerine-induced vasodilation

Vascular response to reactive hyperemia in the brachial artery was used for assessment of endothelium-dependent FMD. A high-resolution linear artery transducer was coupled to computer-assisted analysis software (UNEXEF18G, UNEX Co., Nagoya, Japan) that used an automated edge detection system for measurement of brachial artery diameter [15]. Please see the online data supplement for additional details.

2.4. Measurement of brachial IMT

Before FMD measurement, baseline longitudinal ultrasonographic images of the brachial artery, obtained at the end of diastole from each of 10 cardiac cycles, were automatically stored on a hard disk for off-line assessment of IMT with a linear, phased-array high-frequency (10-MHz) transducer using an UNEXEF18G ultrasound unit (UNEX Co.) [16]. Please see the online data supplement for additional details.

2.5. Measurement of baPWV

Aortic compliance was assessed noninvasively on the basis of Doppler ultrasound measurements of PWV along the descending thoracoabdominal aorta, as previously published and validated [17]. Please see the online data supplement for additional details.

2.6. Echocardiography

Echocardiograms were obtained by using a Philips iE33 (Philips Co. Ltd., Bothell, WA, USA) with a 1.0 to 5.0 MHz transducer (S5-1). Please see the online data supplement for additional details.

2.7. Measurement of ROCK activity

ROCK activity was assayed in peripheral blood leukocytes as the amount of phospho-Thr853 in the myosin-binding subunit of myosin light chain phosphatase (MLCPh), because the myosin-binding subunit on MLCPh is one of the downstream targets of ROCK. Please see the online data supplement for additional details.

2.8. Statistical analysis

Results are presented as means ± SD for continuous variables and as percentages for categorical variables. Statistical significance was set at a level of $P < 0.05$. Continuous variables were compared by using ANOVA for multiple groups. Categorical variables were compared by means of the χ^2 test. Relationships between variables were determined by Pearson correlation coefficients analysis. Multivariable regression analysis was performed to assess the association between vascular function and HFpEF in risk factors. In addition, we created matched pairs (1 patient with HFpHF to 1 control) in the supplemental data. Paired *t*-test was used for comparison of mean values of continuous variables between the 2 groups. Correlations between continuous variables were estimated with the use of Pearson correlation coefficients. The data were processed using the software package Stata, version 9 (Stata Co., College Station, TX).

3. Results

3.1. Baseline clinical characteristics

The baseline clinical characteristics of the 165 patients without HF and 41 patients with HFpEF are summarized in Table 1. Age, systolic blood pressure, NT-proBNP, and prevalence of hypertension were significantly higher in patients with HFpEF than in patients without HF. eGFR was significantly lower in patients with HFpEF than in patients without HF. There was no significant difference in other parameters between patients without HF and patients with HFpEF.

3.2. Echocardiographic parameters

Echocardiographic parameters of the 165 patients without HF and 41 patients with HFpEF are summarized in Table 2. Left atrial (LA) diameter, interventricular septal thickness, posterior LV wall thickness, late (A) diastolic mitral inflow velocity, deceleration time of E velocity, early (E) diastolic mitral inflow velocity to late diastolic mitral annulus velocity (E/E′) ratio, LA volume index, and LV mass index were significantly higher in patients with HFpEF than in patients without HF. The ratio of early to late peak velocities (E/A), E′ velocity of septal and lateral wall, and mean E′ velocity of septal and lateral wall were significantly lower in patients with HFpEF than in patients without HF. There was

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