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Flow-Mediated Vasodilation and Reactive Hyperemia Index in Heart Failure with Reduced or Preserved Ejection Fraction

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Vascular endothelial dysfunction is part of the underlying pathophysiology of heart failure. However, there are no reports in which vascular endothelial function of both conduit arteries and microvasculature was assessed in patients with heart failure. This study was aimed to assess vascular endothelial function separately in heart failure with reduced (HFrEF) and preserved ejection fraction (HFpEF). We performed simultaneous measurement of both flow-mediated vasodilation for endothelial function of conduit arteries and reactive hyperemia-peripheral arterial tonometry for that of microvasculature in 88 consecutive patients with chronic heart failure. In 55 patients with ischemic heart disease as an underlying cause of heart failure, flow-mediated vasodilation value was comparable between the two groups of HFrEF (left ventricular ejection fraction < 50%, n = 31) and HFpEF (left ventricular ejection fraction ≥ 50%, n = 24). Reactive hyperemia index measured by reactive hyperemia peripheral arterial tonometry, however, was lower in HFrEF patients compared to HFpEF patients (P = 0.014). In contrast, among 33 patients with non-ischemic heart disease, the degree of flow-mediated vasodilation was lower in HFpEF patients (n = 18) compared with HFrEF patients (n = 15) (P = 0.009), while reactive hyperemia index was comparable between the two groups. The clinical and pathophysiological significance of endothelial function in heart failure differs between conduit artery and microvasculature, and these differences may contribute to the underlying pathophysiology of HFpEF and HFrEF, as well as in ischemic heart disease and non-ischemic heart disease.

Keywords: heart failure; heart failure with preserved ejection fraction; heart failure with reduced ejection fraction; ischemic heart disease; vascular endothelial function
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Introduction

Heart failure (HF) is a complicated syndrome characterized by final pathway for various heart disease and affects 1-2% of the population worldwide. The incidence of HF-associated deaths and hospitalizations is increasing in aging populations (Coats 2019). A complex of structural and functional alterations accounts for the genesis and progression of HF. However, the exact mechanisms underlying this disease remain poorly delineated. In the past few years, breakthroughs for further clinical benefit require a deeper understanding of the relevant pathophysiology. In addition, HF with preserved ejection fraction (HFpEF) is increasing worldwide and currently accounts for > 50% of all heart failure cases (Kalogirou et al. 2020). It is important to note that HFpEF differs from HF with reduced ejection fraction (HFrEF) regarding the pathophysiology and clinical significance (Bhatia et al. 2006; Lee et al. 2009).

Vascular endothelial dysfunction is associated with the pathogenesis and progression of HF (Ino-oka et al. 2001; Marti et al. 2012). Several studies using flow-mediated vasodilation (FMD), which represents vascular endothelial function of a conduit artery, have demonstrated that endothelial dysfunction is associated with symptom severity and clinical outcomes in patients with HF (Fischer et al. 2005; Meyer et al, 2005; Katz et al. 2005). On the other hand, prior studies on reactive hyperemia index (RHI) measurements via reactive hyperemia-peripheral arterial tonometry

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(RH-PAT), which reflects endothelial function of the microvasculature (i.e., resistance vessels) (Hamburg et al. 2011), yielded limited information about its association with HF (Fujisue et al. 2015). Although both FMD and RHI measurements can predict cardiovascular events, the clinical significance of these two vascular endothelial function tests in patients with cardiovascular diseases may be different, as these methods measure vascular function in different vessels (conduit arteries or microvasculature). Using a method of simultaneous measurement, we recently reported that both FMD and RHI were not correlated in patients with ischemic heart disease (IHD) (Tajima et al. 2020). However, there have been no previous reports on vascular endothelial function of both conduit arteries and microvasculature measurements via FMD and RHI in patients with HF. In addition, there are no reports in which vascular endothelial function was assessed separately in HFrEF and HFpEF.

The present study was conducted to elucidate vascular endothelial function of both conduit arteries and microvasculature in patients with chronic HF and compared between HFrEF and HFpEF patients.

Methods

Subjects and study outline

We performed simultaneous measurement of FMD and RHI in 88 consecutive patients with chronic HF. HF was defined based on the Framingham Heart Failure Diagnostic Criteria (McKee et al. 1971) and all patients underwent echocardiography and cardiac catheterization study including coronary angiography at the Dokkyo Medical University Hospital. Patients were excluded if they had severe HF, defined as New York Heart Association (NYHA) class IV, acute coronary syndrome, atrial fibrillation/flutter, permanent pacemaker implantation, aortic dissection, malignancy, chronic liver disease, or were on hemodialysis. The Dokkyo Medical University review board approved the study protocol, and written informed consent was obtained from each patient.

Simultaneous measurement of FMD and RHI

We performed simultaneous measurement of FMD and RHI within 7 days before cardiac catheterization, as previously described (Tomiyama et al. 2014; Tajima et al. 2020). In brief, subjects were instructed to fast overnight and to abstain from alcohol, smoking, caffeine and antioxidant vitamins for at least 12 hours prior to measurements. They were asked to rest in the seated position in a quiet, dark, air-conditioned room (22°C to 25°C) for 5 minutes, followed by 15 minutes of rest in the supine position in the same room prior to the FMD and RH-PAT procedures. Blood pressure was measured in the left arm using a mercury sphygmomanometer with an appropriately sized cuff and recorded to the nearest 2 mmHg. After blood pressure was measured, a 10-MHz linear array ultrasound transducer (Unex EF 18G, UNEX Corp., Nagoya, Japan) was placed on the proximal right brachial artery to measure FMD, and the manchette was rolled at the forearm. For the RH-PAT procedure (EndoPAT-2000, Itamar Medical Ltd., Caesarea, Israel), a peripheral arterial tonometry probe was placed on the right index finger and a control tonometry probe was also placed on the left index finger to eliminate sympathetic nerve effects. The RH-PAT probes were exchanged for each patient. For FMD measurement, ultrasound longitudinal images were recorded at baseline and continuously from 30 seconds before to ≥ 2 minutes after cuff deflation following compression with a cuff pressure that was 50 mmHg above the systolic blood pressure of the right forearm for 5 minutes. The diastolic diameter of the brachial artery was determined semi-automatically using an instrument equipped with software for monitoring the brachial artery diameter. FMD was estimated as the percent change of the brachial artery diameter at maximal dilation during observation compared with the baseline value. In the RH-PAT procedure, the RHI value was calculated as the ratio of the reactive hyperemia between the two hands.

Echocardiography and coronary angiography

Transthoracic echocardiography was performed within 7 days prior to cardiac catheterization to assess left cardiac function, and images were analyzed by two experienced echocardiographers using commercially-available equipment (Vivid 9, GE Medical Systems, Horton, Norway). We measured the following parameters: left ventricular ejection fraction (LVEF) was obtained using the modified biplane Simpson's method, left ventricular end-diastolic dimension (LVDd), left ventricular end-systolic dimension (LVDs), peak early diastolic flow velocity (E), peak atrial systolic flow velocity (A), early diastolic mitral annular velocity (e'), the E to A ratio (E/A) and the E to e' ratio (E/e'). These parameters were evaluated by recording 3 cardiac cycles under stable conditions, and the mean of the measurements was used for analysis. Base on echocardiographic LVEF, we defined HFrEF as LVEF < 50% and HFpEF as LVEF ≥ 50%.

Cardiac angiographic findings were visually assessed for atherosclerotic coronary lesions by an investigator blinded to the study design. Lesion stenosis and severity was classified based on American Heart Association guidelines. Stenosis involving ≥ 75% of vessel diameter was considered a significant atherosclerotic coronary lesion.

Assessment of baseline characteristics

Prior to FMD and RH-PAT procedures, information on severity of heart failure by NYHA class, comorbidities such as hypertension, diabetes, dyslipidemia, smoking habit, stroke and chronic kidney disease and medication usage were obtained from each patient. Height and body weight were measured, and body mass index (BMI) was calculated as body weight (kg)/(height [m])^2. Blood pressure was measured prior to FMD and RH-PAT procedures using a mercury sphygmomanometer with an appropriately sized cuff. Serum creatinine level was measured using an enzymatic method, and the estimated glomerular filtration rate (eGFR) was calculated by a formula provided by the Japanese Society of Nephrology Chronic Kidney Disease Practice Guide: eGFR (mL/min/1.73 m^2) = 194 × (serum creatinine level [mg/dL])$^{-1.094}$ × (age [y])$^{-0.287}$. The product of this equation was multiplied by a correction factor of 0.739 for women (Matsuo et al. 2009). Chronic kidney disease (CKD) was defined as an eGFR < 60 mL/min/1.73 m^2. Total cholesterol and triglyceride levels were determined using enzymatic methods, high-density lipoprotein (HDL)-cholesterol was measured using the precipitation method and low-density lipoprotein (LDL)-cholesterol was calculated using the Friedewald formula: LDL-cholesterol = total cholesterol – HDL-cholesterol – (triglyceride/5). The LDL-cholesterol could not be calculated in those patients with a triglyceride level over 400 mg/dL. Hemoglobin A1c was measured by high-performance liquid chromatography and values were expressed according to the National Glycohemoglobin Standardization Program. Plasma brain natriuretic peptide (BNP) level was measured by an automated chemiluminescent enzyme immunoassay analyzer exclusive kit (Shionogi, Osaka, Japan) using specific antibodies for human BNP.

Statistical analysis

Data were expressed as the mean ± standard deviation (SD) or median and interquartile range. Normality for distribution of continuous variables was assessed using the Shapiro-Wilk test. Intra-group comparisons were performed using unpaired t-tests for normally distributed continuous variables and Mann-Whitney *U* tests for skew-distributed continuous variables. Chi-squared test was applied for intra-group comparisons between categorical variables. The correlation between two variables was determined by Pearson's correlation coefficient. All statistical analyses were performed using the statistical package for Social Science (SPSS II for Windows, SPSS Inc., Tokyo, Japan) and a P < 0.05 was considered significant.

Results

Patient characteristics

IHD was the underlying cause of HF in 55 of our 88 patients. Non-IHD accounted for the other 33 patients, including 11 patients with dilated cardiomyopathy, 6 with hypertrophic cardiomyopathy, 4 with hypertensive heart disease, 4 with valvular heart disease, and 8 with other cardiac disease causes. Forty-six patients had HFrEF and 42 had HFpEF. Baseline characteristics were compared between patients with HFrEF and those with HFpEF (Table 1). Heart failure severity as shown by NYHA class distribution and usage rate of beta blockers, aldosterone antagonists and loop diuretics were higher in the HFrEF group compared to the HFpEF patients.

Table 1. Patient characteristics.

	HFrEF (n = 46)	HFpEF (n = 42)	P value
Age; years	67 ± 14	69 ± 11	0.505
Male sex; n (%)	34 (74)	30 (71)	0.794
BMI; kg/m^2	23 ± 4	24 ± 3	0.452
NYHA class; n (%)			0.008
I	22 (48)	31 (74)	
II	17 (37)	11 (26)	
III	7 (15)	0 (0)	
Underlying disease; n (%)			0.321
IHD	31 (67)	24 (57)	
non-IHD	15 (33)	18 (43)	
IHD profile; n (% of IHD)			
multi-vessel disease; n (%)	19 (61)	14 (58)	0.824
PCI; n (%)	24 (77)	17 (71)	0.578
CABG; n (%)	9 (29)	7 (29)	0.991
Comorbidities; n (%)			
Hypertension	18 (39)	21 (50)	0.305
Diabetes	18 (39)	16 (38)	0.921
Dyslipidemia	21 (46)	15 (36)	0.344
Stroke	5 (11)	2 (5)	0.290
Chronic kidney disease	27 (59)	20 (48)	0.298
Smoking	33 (72)	23 (55)	0.098
Medications; n (%)			
ACE inhibitors/ARBs	29 (63)	29 (69)	0.553
Beta blockers	31 (67)	10 (24)	< 0.0001
Aldosterone antagonists	27 (59)	7 (17)	< 0.0001
Loop diuretics	38 (83)	19 (45)	0.0002
Statins	32 (70)	29 (69)	0.958
Anti-diabetic drugs	16 (35)	14 (33)	0.886

HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; BMI, body mass index; NYHA, New York Heart Association; IHD, ischemic heart disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers.

Comparison of laboratory data between HFrEF and HFpEF patients

BNP level was higher in the HFrEF group compared to the HFpEF group. Echocardiographic findings showed that LVDd and LVDs were larger in the HFrEF patients than in the HFpEF patients. As expected, LVEF was lower in the HFrEF patients than in the HFpEF patients. Regarding vascular endothelial function tests, FMD was comparable between the two groups of HFrEF and HFpEF. RHI tended to be lower in the HFrEF patients than in the HFpEF patients, though not statistically significant (Table 2).

Comprehensive assessment for vascular endothelial function parameters

FMD and RHI were positively correlated together in all 88 patients (R = 0.252, P = 0.018). When patients were placed into distinct HFrEF and HFpEF groups, the correlation between FMD and RHI was observed in HFrEF

Table 2. Laboratory data.

	HFrEF (n = 46)	HFpEF (n = 42)	P value
Heart rate; /min	66 ± 15	65 ± 11	0.521
Systolic blood pressure; mmHg	121 ± 22	129 ± 19	0.067
Diastolic blood pressure; mmHg	72 ± 13	73 ± 10	0.618
LDL-cholesterol; mg/dL	89 ± 31	87 ± 29	0.698
HDL-cholesterol; mg/dL	53 ± 14	52 ± 16	0.843
Triglyceride; mg/dL	105 ± 52	111 ± 57	0.644
FBS; mg/dL	114 ± 29	108 ± 27	0.387
HbA1c; %	6.4 ± 1.0	6.1 ± 0.6	0.114
eGFR; mL/min/1.73 m^2	56 ± 18	60 ± 20	0.360
BNP; pg/mL	168 (107-296)	77 (55-155)	0.0001
Echocardiographic parameters			
LVDd; mm	58 ± 7	47 ± 6	< 0.0001
LVDs; mm	49 ± 9	31 ± 6	< 0.0001
LVEF; %	35 ± 9	61 ± 7	< 0.0001
E/A	1.33 ± 1.02	1.03 ± 0.63	0.111
E/e'	17.6 ± 11.2	14.3 ± 9.3	0.161
FMD; %	4.98 ± 2.38	4.14 ± 2.24	0.093
RHI	1.60 (1.42-2.10)	1.81 (1.60-2.25)	0.059

HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; LDL, low-density lipoprotein; HDL, high-density lipoprotein; FBS, fasting blood glucose; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; LVDd, left ventricular diastolic dimension; LVDs, left ventricular systolic dimension; LVEF, left ventricular ejection fraction; E/A, ratio of peak early diastolic flow velocity by peak atrial systolic flow velocity; E/e', ratio of peak early diastolic flow velocity by early diastolic mitral annular velocity; FMD, flow-mediated vasodilation; RHI, reactive hyperemia index.

patients (R = 0.356, P = 0.015) but not in HFpEF patients (R = 0.214, P = 0.174) (Fig. 1).

Next, we compared vascular endothelial function parameters between patients with IHD and those with non-IHD. FMD and RHI tended to be correlated in non-IHD patients (R = 0.326, P = 0.064), but was not correlated in IHD patients (R = 0.194, P = 0.156) (Fig. 1). Comparing patients with IHD to non-IHD, the degree of FMD was found to be lower in the IHD group compared to the non-IHD group (4.18 ± 1.91 vs. 5.25 ± 2.83 %, P = 0.036), whereas RHI was comparable between the two groups [1.67 (1.44-2.01) vs. 1.84 (1.54-2.24), P = 0.401] (Fig. 2).

Among patients with IHD, the degree of FMD was comparable between those with HFrEF and HFpEF (4.19 ± 1.26 vs. 4.15 ± 2.55 %, P = 0.945). Additionally, RHI was lower in HFrEF patients compared to HFpEF patients [1.53 (1.42-1.94) vs. 1.77 (1.67-2.16), P = 0.014]. In contrast, among non-IHD patients, the degree of FMD was lower in the HFpEF group compared to the HFrEF group (4.12 ± 1.82 vs. 6.61 ± 3.26 %, P = 0.009), whereas RHI was comparable between the two groups of HFrEF and HFpEF [1.78 (1.48-2.24) vs. 1.94 (1.55-2.25), respectively, P = 0.942] (Fig. 3).

Finally, we assessed association between other background factors and the values of FMD and RHI in all 88 patients. Consequently, the degree of FMD was lower in patients who received loop diuretics compared to those who did not, and RHI was lower in patients with CKD compared to those without CKD. The other factors including prevalence of atherosclerotic risk factors such as hypertension, diabetes, dyslipidemia and smoking habit were not associated with both FMD and RHI values (Table 3). In addition, the degree of FMD was negatively correlated with age and fasting blood glucose level and positively correlated with diastolic blood pressure, LVDd and LVDs. The RHI was positively correlated with systolic blood pressure. The other parameters for atherosclerotic risk factors including lipid profiles and those for left ventricular systolic and diastolic function such as LVEF, E/A and E/e' were correlated neither with FMD nor with RHI values (Table 4).

Discussion

In the present study, we assessed vascular endothelial function parameters via FMD and RHI measurements (Tomiyama et al. 2014; Tajima et al. 2020) in patients with HFrEF and HFpEF. As a result, the degree of FMD was comparable between the two groups of HFrEF and HFpEF. However, RHI tended to be lower in the HFrEF patients than in the HFpEF patients, though not statistically significant. When assessed based on the underlying etiology of HF, specifically IHD and non-IHD, we found that the degree of FMD was lower in IHD patients compared to non-IHD patients, while RHI was comparable between both groups. In patients with IHD, the degree of FMD was comparable among patients with HFrEF and HFpEF, but RHI was lower in HFrEF patients compared to HFpEF patients. In contrast, in patients with non-IHD, the degree of FMD was lower in HFpEF patients than in the HFrEF patients, whereas RHI was comparable between the two groups of HFrEF and HFpEF. These results suggest that the clinical significance of FMD and RHI measurements in patients with HF may differ depending on whether the HF is secondary to IHD or to non-IHD and HFrEF or HFpEF.

Impairment of vascular endothelial function, represented by endothelium-dependent vasodilatory capacity, plays an important role in the pathogenesis, disease progression, disease severity, and prognosis of coronary artery disease (Inoue and Node 2006). Vascular endothelial function also plays a central and significant contributory role in the pathophysiology of HF (Remme 1986). FMD measurement and RH-PAT are both effective noninvasive methods of evaluating vascular endothelial function, but have some physiological and clinical differences that depend on the vessels evaluated with each method. Endothelial function contributes to the maintenance of vasodilator tone via endothelium-derived relaxing factors (EDRFs), such as nitric oxide (NO) and endothelium-derived hyperpolarizing factor (EDHF) (Vanhoutte and Mombouli 1996; Nohria et al. 2006). Endothelium-dependent vasodilation in the conduit

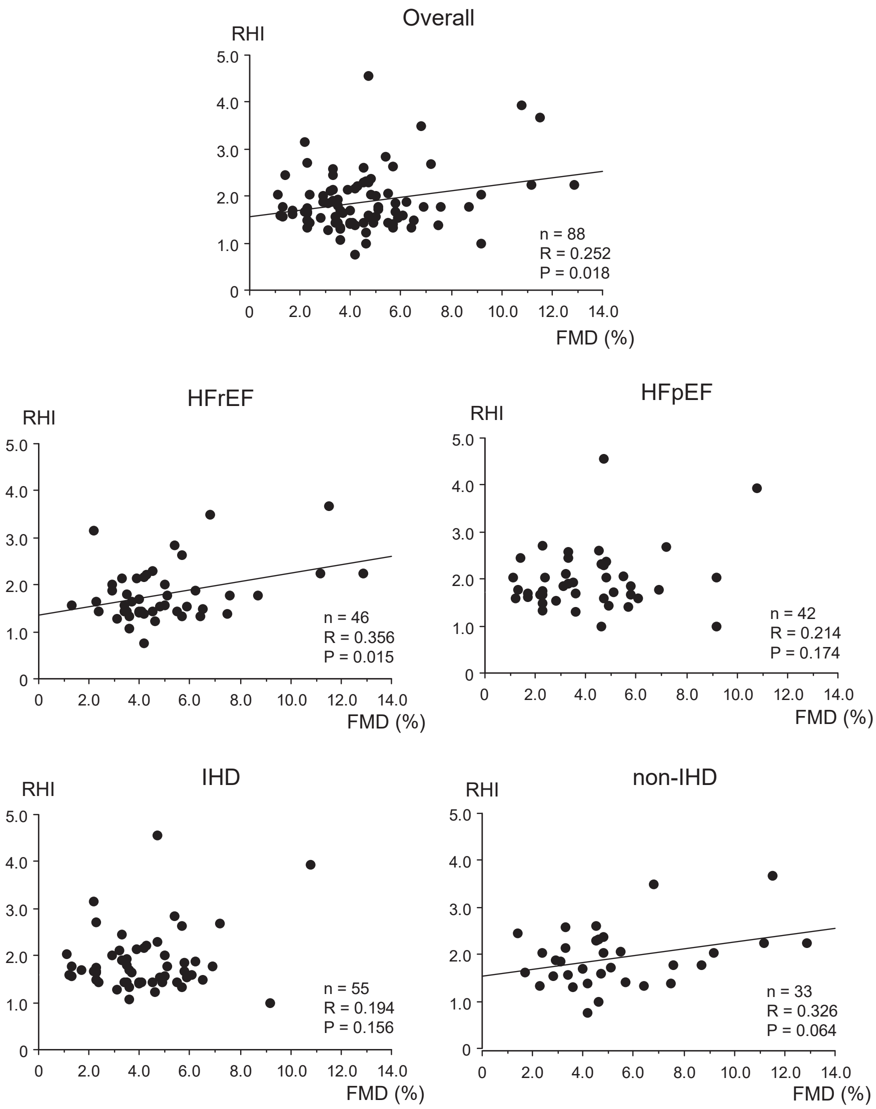

Fig. 1. Relationship between the degree of FMD and RHI.
FMD, flow-mediated vasodilation; RHI, reactive hyperemia index; IHD, ischemic heart disease; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction.

artery, as evaluated by FMD, is mediated mainly by NO, whereas the dilation of resistance vessels, as evaluated by RH-PAT, is mediated by both NO and EDHF (Schiffrin 2002).

Chronic HF patients exhibit excessive systemic vasoconstriction and reduced peripheral tissue perfusion. Impaired vascular endothelial function worsens the already existing vasoconstriction, leading to an increase in afterload, and ultimately augmentation of myocardial damage. Systemic vascular endothelial dysfunction represents coronary vascular endothelial dysfunction. Decreased coronary endothelium-dependent vasodilation impairs myocardial perfusion, reduces coronary flow, worsens left ventricular function, and decreases cardiac output. The decrease in cardiac output culminates in endothelial shear stress, which stimulates endothelial NO synthase (eNOS) expression. In patients with HF, once eNOS expression is down-regulated, NO production is suppressed and consequently systemic endothelium-dependent vasodilation is inhibited, resulting in concomitant vasoconstriction (Giannitsi et al. 2019). In this way, vascular endothelial dysfunction and left ventricular dysfunction may repeat a vicious cycle.

There are several studies whereby endothelial function of conduit vessels was evaluated in patients with chronic HF. Shah et al (2010) found that FMD was impaired in patients with HF of non-IHD etiology. Similarly, Klosinska et al. (2009) demonstrated that FMD was more attenuated in HF patients with IHD compared to those with non-IHD, consistent with our result. Kishimoto et al. (2017) proved that endothelial dysfunction measured by FMD was significantly smaller in patients with HFpEF compared to individuals without HF. Impairment of vascular endothelial function possibly extends to microvasculature in chronic HF. Although there are only a few reports in which RHI

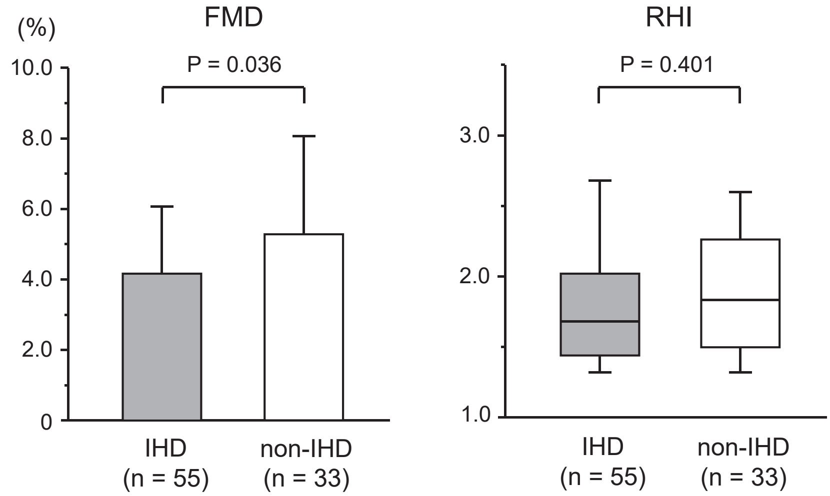

Fig. 2. Comparison of FMD and RHI between HF with IHD vs. non-IHD.
The graph shows mean ± standard deviation.
FMD, flow-mediated vasodilation; RHI, reactive hyperemia index; HF, heart failure; IHD, ischemic heart disease.

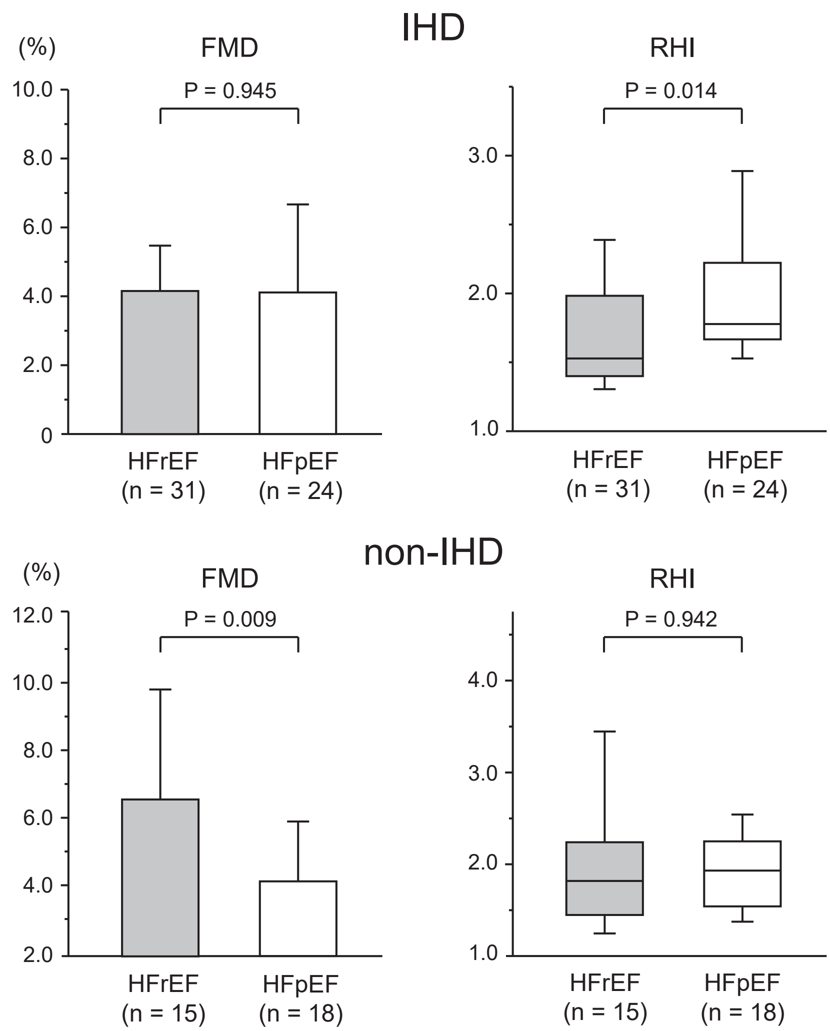

Fig. 3. Comparison of FMD and RHI between HFrEF vs. HFpEF, separately in IHD and non-IHD.
The graph shows mean ± standard deviation.
FMD, flow-mediated vasodilation; RHI, reactive hyperemia index; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; IHD, ischemic heart disease.

Table 3. Vascular endothelial function parameters and patient characteristics.

	FMD					RHI				
	Yes		No		P value	Yes		No		P value
	n	mean ± SD	n	mean ± SD		n	median (IQR)	n	median (IQR)	
Male sex	64	4.38 ± 2.27	24	5.10 ± 2.49	0.198	64	1.68 (1.47-2.01)	24	2.04 (1.44-2.30)	0.275
NYHA II/III	35	4.50 ± 2.21	53	4.63 ± 2.44	0.810	35	1.67 (1.44-2.15)	53	1.76 (1.54-2.07)	0.520
Hypertension	39	4.33 ± 2.38	49	4.78 ± 2.32	0.376	39	1.68 (1.43-2.17)	49	1.78 (1.53-2.13)	0.798
Diabetes	34	4.29 ± 2.29	54	4.76 ± 2.38	0.366	34	1.71 (1.49-2.06)	54	1.75 (1.43-2.16)	0.925
Dyslipidemia	36	4.24 ± 2.32	52	4.81 ± 2.35	0.266	36	1.71 (1.44-2.07)	52	1.74 (1.52-2.13)	0.993
Chronic kidney disease	47	4.41 ± 2.01	41	4.77 ± 2.68	0.472	47	1.67 (1.42-2.02)	41	1.87 (1.59-2.24)	0.046
Smoking	56	4.71 ± 2.58	32	4.35 ± 1.86	0.494	56	1.68 (1.44-2.04)	32	1.82 (1.51-2.18)	0.665
ACE inhibitors/ARBs	58	4.28 ± 1.92	30	5.16 ± 2.94	0.093	58	1.75 (1.54-2.12)	30	1.63 (1.43-2.13)	0.344
Beta blockers	41	4.78 ± 2.02	47	4.40 ± 2.60	0.461	41	1.78 (1.42-2.23)	47	1.68 (1.53-2.04)	0.808
Loop diuretics	57	5.00 ± 2.26	31	3.80 ± 2.31	0.021	57	1.68 (1.43-2.13)	31	1.84 (1.57-2.17)	0.305
Statins	61	4.52 ± 2.25	27	4.70 ± 2.58	0.738	61	1.67 (1.43-2.97)	27	1.84 (1.60-2.18)	0.220
Anti-diabetic drugs	30	4.45 ± 2.23	58	4.64 ± 2.41	0.716	30	1.65 (1.43-1.92)	58	1.78 (1.53-2.16)	0.353

FMD and RHI was compared between two groups of present (yes) and absent (no) in each item for baseline characteristics represented as categorical variables. FMD, flow-mediated vasodilation; RHI, reactive hyperemia index; SD, standard deviation; IQR, interquartile range; NYHA, New York Heart Association; ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers.

Table 4. Relationship between vascular endothelial function and other background parameters.

	FMD		RHI	
	R	P value	R	P value
Age	−0.439	< 0.0001	−0.121	0.262
Heart rate	−0.051	0.635	−0.204	0.057
Systolic blood pressure	−0.064	0.554	0.266	0.012
Diastolic blood pressure	0.243	0.023	0.051	0.636
LDL-cholesterol	0.124	0.268	0.136	0.227
HDL-cholesterol	0.087	0.420	0.045	0.679
Triglyceride	0.011	0.920	−0.028	0.795
FBS	−0.296	0.005	−0.023	0.831
HbA1c	0.046	0.682	0.095	0.395
eGFR	0.120	0.266	0.042	0.696
BNP	0.133	0.218	−0.130	0.228
LVDd	0.240	0.024	−0.136	0.205
LVDs	0.258	0.015	−0.137	0.204
LVEF	−0.192	0.074	0.083	0.442
E/A	0.144	0.196	−0.077	0.493
E/e’	0.027	0.810	0.149	0.180

FMD, flow-mediated vasodilation; RHI, reactive hyperemia index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; FBS, fasting blood glucose; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; LVDd, left ventricular diastolic dimension; LVDs, left ventricular systolic dimension; LVEF, left ventricular ejection fraction; E/A, ratio of peak early diastolic flow velocity by peak atrial systolic flow velocity; E/e’, ratio of peak early diastolic flow velocity by early diastolic mitral annular velocity.

was observed in HF patients, it has been shown that the low RHI was associated with future HF-related adverse events in patients with HFrEF (Fujisue et al. 2015). In addition, the RHI was lower in patients with HFpEF, compared with non-HF patients (Akiyama et al. 2012), and low RHI in the HFpEF patients was associated with future cardiovascular events. However, there have been no reports in which the endothelial function was compared specifically between HFrEF and HFpEF patients. In addition, there are have been no reports in which it was evaluated, separately in IHD and non-IHD as the etiology of HF. In the present study, the degree of FMD was reduced in IHD patients, compared with non-IHD patients and the degree of FMD in IHD arm were comparable between HFrEF and HFpEF. The result suggests that endothelial function of conduit vessels might be strongly impaired in advanced atherosclerotic disease such as IHD, and thus, might be independent of cardiac performance in HF patients with IHD etiology. In the non-IHD arm, however, the degree of FMD was lower in HFpEF patients than in HFrEF patients, suggesting that endothelial dysfunction of conduit vessels might play a pathophysiological role in HFpEF of non-IHD etiology, although causal relationship is unclear. On the other hand, the result of our present study that RHI was lower in patients with HFrEF than in those with HFpEF in the IHD arm while comparable between HFrEF and HFpEF patients in the non-IHD arm is puzzling. However, the result suggests that microvascular endothelial function would be affected by left ventricular systolic function in advanced atherosclerotic disease such as IHD, although the mechanisms are currently unclear.

We previously demonstrated that the degree of FMD and RHI were not correlated in patients with IHD (Tajima et al. 2020). In the present study, we also assessed the relationship in HF patients, and consequently, found that the degree of FMD and RHI were correlated. Interestingly, the correlation was absent in the IHD patients, similar to our previous observation, but a trend of correlation was present in the non-IHD patients. The results suggest that endothelial function of a conduit artery and that of microvasculature were independently associated with the pathophysiology in HF of IHD etiology, but both play a role in the pathophysiology of non-IHD etiology HF, being related each other. In addition, we also found that the correlation was present in the HFrEF patients but absent in the HFpEF patients, although we could not well explain its mechanism. Taken together, the results of our present study suggest that the pathophysiological significance of endothelial function in HF differs between the conduit artery and microvasculature and this may explain the differences in the pathophysiology of HF between HFrEF and HFpEF, as well as in IHD and non-IHD patients.

Study limitation

The present study was a cross sectional observational study, thus we could discuss our results only from a perceptive of phenomenology. To discuss the pathophysiological mechanism of our results, we need a further approach, such as changes after therapeutic interventions. We did not perform sample size determination and the sample size was small, so it cannot be denied that positive data is a type 1 error and negative data is a type 2 error. Although we performed simultaneous measurement of FMD and RHI using an established method previously described, both FMD and RHI have several confounding factors, which we could not consider in the present study. Actually, in our final analysis, FMD was associated with receiving loop diuretics, age, fasting blood glucose level, diastolic blood pressure, LVDd and LVDs, and RHI was associated with the prevalence of CKD and systolic blood pressure. In order to analyze under adjustment with these confounding factors, however, the sample size was too small. More comprehensive assessment using larger sample size would be needed in future.

Clinical perspectives

Although success of pharmacological approaches for chronic HF, including angiotensin converting enzyme inhibitors/angiotensin receptor blockers and beta blockers, have substantially improved long-term outcomes in patients with HFrEF, their effectiveness is still limited. Moreover, effective treatments to improve long-term prognosis for HFpEF has not been established. As a novel approach, vascular endothelial function-targeting treatment for HF, e.g., statin treatment, might be feasible. Statins have shown beneficial effects, in part based on their pleiotropic effects including improving vascular endothelial function, on symptoms, cardiac function and prognosis in patients with HF patients (Node et al. 2003; Takano et al. 2013). From our results, we can envision that HF treatment under the guide with vascular endothelial function assessment using FMD and/or RH-PAT methods would be promising. Specifically, FMD in patients with HFpEF of non-IHD etiology and RHI in patients with HFrEF of IHD etiology would be powerful indicators for the treatment strategies.

Conclusion

The clinical and pathophysiological significance of vascular endothelial function in HF might be different between conduit artery and microvasculature and these differences contribute to the pathophysiology of heart failure in patients with HFrEF and HFpEF, and also between IHD and non-IHD.

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Author Contributions

Ryutaro Waku, Shigeru Toyoda and Teruo Inoue contributed to study design. All authors contributed to the acquisition, analysis, or interpretation of data for the work. All authors participated in drafting or revising the manuscript, approved the final version of the manuscript, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest

The authors declare no conflict of interest.

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