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Impact of vascular endothelial function on comorbid chronic kidney disease in patients with non-ischemic heart failure

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Abstract:

Background: Vascular endothelial dysfunction plays a role on pathophysiology of heart failure (HF) and chronic kidney disease (CKD), both of which are often comorbid. However, there have been no previous reports, where the vascular endothelial function was assessed focusing on comorbid CKD in the HF, especially non-ischemic HF. **Methods:** We assessed vascular endothelial function using simultaneous procedure of flow-mediated dilatation (FMD) and reactive hyperemia-peripheral arterial tonometry (RH-PAT) in 33 consecutive patients with non-ischemic HF. **Results:** The FMD value was lower in HF patients with comorbid CKD (CKD group; n=18) than in the remaining patients without CKD (non-CKD group; n=15) (4.37±1.89 vs 6.31±3.42, P=0.048). The value of reactive hyperemia index (RHI) measured by RH-PAT was also lower in the CKD group than in the non-CKD group (1.65±0.46 vs 2.24±0.65, P=0.004). Even after adjustment for confounding factors, which showed intra-group difference, the significant differences in both values of FMD (P=0.005) and RHI (P=0.003) still remained between CKD and non-CKD groups. **Conclusions:** Vascular endothelial function might be impaired more strongly in non-ischemic HF patients with comorbid CKD, compared with those without CKD. The impaired endothelial function might be associated with prevalence of CKD in patients with non-ischemic HF.

Key words:

Vascular endothelial function, Non-ischemic heart failure, Chronic kidney disease, Flow-mediated dilation, Reactive hyperemia-peripheral arterial tonometry

Introduction

Impairment of vascular endothelial function is an initial step in the pathogenesis of atherosclerosis continuum, and then imposing unfavorable clinical impact[1)]. Several studies suggested that the presence of vascular endothelial dysfunction is an independent predictor of cardiovascular events[2,3)]. Endothelial dysfunction is closely associated with the occurrence and development of a variety of atherosclerotic diseases including ischemic heart disease and stroke[4)]. On the other hand, endothelial dysfunction is also associated with the pathogenesis and progression of heart failure (HF), and the existence of endothelial dysfunction in HF patients imposes increased morbidity and mortality[5,6)].

Chronic HF is often comorbid with chronic kidney disease (CKD). Baseline renal impairment and worthening of renal function over time are frequently observed in patients with chronic HF as well as acute decompensated HF. When both HF and CKD are present, both entities relate to strongly impaired survival, with the presence of CKD showing a more consistent relationship with poor outcomes[7)]. Conversely, cardiovascular complications are the major cause of death in patients end-stage CKD. Vascular endothelial dysfunction is a crucial mediator of increased cardiovascular risk also in patients with CKD, from early-stage to end-stage CKDs. Therefore, vascular endothelial function seems to play a crucial role on pathophysiology in a perspective of cardio-renal syndrome. Common risk factors of vascular endothelial dysfunction in cardiovascular disease and CKD includes hypertension and diabetes, which is

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closely associated with atherosclerotic cardiovascular disease, so discussions regarding endothelial function in HF with CKD may tend to focus on ischemic HF. However, endothelial dysfunction is involved also in the non-ischemic HF[8-11], in which comorbid CKD is also an important contributor to pathophysiology, severity and prognosis.

In the present study, we investigated vascular endothelial function of both conduit vessels and microvasculature in patients with non-ischemic HF, and compared between those with and without comorbid CKD.

Methods

Subjects and study outline

This study was a cross sectional observational study conducted in a single center of Dokkyo Medical University Hospital. Subject included 33 consecutive patients with chronic non-ischemic HF, diagnosed based on the Framingham Heart Failure Diagnostic Criteria[12], in whom underlying heart disease was diagnosed based on echocardiography and coronary angiography, where no significant atherosclerotic stenotic lesions were observed in any coronary arteries. In all of the patients, we performed vascular endothelial function tests, using flow-mediated dilation (FMD) as an endothelial function of conduit vessels and reactive hyperemia peripheral arterial tonometry (RH-PAT) as that of microvasculature (i.e., resistance vessels). Patients were excluded if they had serious heart failure such as New York Heart Association (NYHA) class IV, atrial fibrillation/flutter, permanent pacemaker implantation, aortic dissection, malignancy or serious liver diseases, or were on hemodialysis. The Dokkyo Medical University review board approved the study protocol, and written informed consent was obtained from each patient.

Assessment of baseline characteristics

Information on severity of heart failure by NYHA class, comorbidities such as hypertension, diabetes, dyslipidemia and stroke, smoking habit, and medication usage were obtained from each patient. Body mass index, heart rate and blood pressure were measured on the day of vascular endothelial function tests. Blood tests were performed within 7 days before or after vascular endothelial function tests. From the serum creatinine level, 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[13]. Chronic kidney disease was defined as the eGFR<60 mL/min/1.73 m^2.

Simultaneous procedure of FMD and RH-PAT

The FMD and RH-PAT was simultaneously performed in a morning, according to a method previously described[14-16]. In brief, the subjects were instructed to fast overnight and to abstain from alcohol, smoking, caffeine and antioxidant vitamins for at least 12 h before the measurements. They were asked to rest in the sitting position in a quiet, dark, air-conditioned room (22°C to 25°C) for 5 min. Then, they were asked to rest again for at least 15 min in the supine position in the same room before 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 mm Hg. After blood pressure was measured, a 10-MHz linear array ultrasound transducer (Unex EF 18 G, 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 s before to ≥ 2 min after cuff deflation following compression with a cuff pressure that was 50 mmHg above the systolic blood pressure of the right forearm for 5 min. 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 hyperemia compared with the baseline value. In the RH-PAT procedure, the reactive hyperemia index (RHI) was calculated as the ratio of the reactive hyperemia between the two hands.

Echocardiography

Transthoracic echocardiography was performed on the day within 7 days before or after vascular endothelial function tests to assess left cardiac function. We measured the following parameters: left ventricular ejection fraction (LVEF: modified Simpson 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. Based on echocardiographic LFEF, we defined heart failure with reduced ejection fraction (HFrEF) as LVEF<50% and heart failure with preserved ejection fraction (HFpEF) as LVEF≥50%.

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. For the skew-distributed continuous variables, unpaired t tests were also performed after the variables were transformed into natural logarithmic values. Chi-squared tests were applied to intra-group comparisons for categorical variables. For assessment of intra-group differences in vascular endothelial function parameters, analysis of covariance (ANCOVA) was used to adjust for confounding factors, which showed difference in the intra-group comparisons. The correlation between two variables was determined by Pearson's correlation coefficient. P<0.05 was considered significant.

Results

In total of 33 patients with chronic non-ischemic HF, comorbid CKD was observed in 18 patients. Then we performed intra-group comparisons between 18 patients with CKD (CKD group) and the remaining 15 patients without CKD (non-CKD group). Baseline characteristics are compared in **Table 1**. Patients in the CKD group were older than those in the non-CKD group. Systolic blood pressure was higher in the non-CKD group, compared with the CKD group. The other parameters including severity of heart failure as represented by NYHA class, cause of heart failure, other comorbidities and medications were comparable between the two groups of CKD and non-CKD. Major blood test parameters and echocardiographic parameters were compared in **Table 2**. As a matter of course, eGFR value was lower in the CKD group, compared with non-CKD group. However, the other parameters including lipid and glucose metabolism parameters, plasma BNP level and left ventricular systolic and diastolic function parameters were comparable between the two groups.

In all patients, FMD and RHI values tended to be correlated, although the correlation was not statistically significant (R=0.326, P=0.064) (**Figure 1**). The FMD value was significantly lower in the CKD group than in the non-CKD group (4.37±1.89 vs 6.31±3.42, P=0.048). The RHI value was also significantly lower in the CKD group than in the non-CKD group (1.65±0.46 vs 2.24±0.65, P=0.004). Next, ANCOVA was performed for intra-group comparison of FMD value, adjusted for the confounding factors such as age, systolic blood pressure and RHI value, which showed significant intra-group difference. As a result, the FMD value in the CKD group was still significantly lower than that in the non-CKD group (P=0.005). The ANCOVA for comparison of the RHI value adjusted for age, systolic blood pressure and FMD value as confounding factors also showed that the RHI value in the CKD group was still significantly lower than that in the non-CKD group (P=0.003) (**Figure 2**). Finally, for both FMD and RHI, we assessed proportion of patient number in each category of normal, borderline and abnormal values, based on the Physiological Diagnostic Criteria for Vascular Failure from the Japanese Society for Vascular Failure[17,18]. As a result, patients with the abnormal value tended to be more in CKD group than in non-CKD group for the RHI, although such a trend was absent for the FMD (**Table 2**).

Table 1. Baseline characteristics

	Non CKD (n=15)	CKD (n=18)	P value
Age; yr	54±17	68±12	0.010
Male gender; n (%)	11 (73)	9 (50)	0.172
BMI; kg/m^2	25±6	23±4	0.333
Heart rate	61±14	61±12	0.961
Systolic blood pressure	129±18	114±20	0.031
Diastolic blood pressure	78±13	70±11	0.074
NYHA class; n (%)			0.586
I	13 (86)	13 (72)	
II	1 (7)	3 (17)	
III	1 (7)	2 (11)	
Underlying disease; n (%)			0.320
Dilated cardiomyopathy	6 (40)	9 (50)	
Hypertrophic cardiomyopathy	1 (7)	3 (17)	
Hypertensive heart disease	1 (7)	2 (11)	
Valvular heart disease	3 (20)	0 (0)	
Others	4 (26)	4 (22)	
Comorbidities; n (%)			
Hypertension	5 (33)	6 (33)	1.000
Diabetes	3 (20)	5 (28)	0.604
Dyslipidemia	5 (33)	8 (44)	0.515
Stroke	1 (7)	1 (6)	0.894
Smoking habit	9 (60)	9 (50)	0.566
Medications; n (%)			
ACE inhibitors/ARBs	8 (53)	13 (72)	0.261
Beta blockers	9 (60)	9 (50)	0.566
Aldosterone antagonists	6 (40)	7 (39)	0.948
Loop diuretics	9 (60)	12 (67)	0.692
Statins	5 (33)	8 (44)	0.515
Anti-diabetic drugs	16 (35)	14 (33)	0.886

BMI, body mass index; NYHA, New York Heart Association; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker

Discussion

Major finding of the present study is that both FMD and RHI values were lower in non-ischemic HF patients with comorbid CKD than in those without CKD. The result suggests that impairment of vascular endothelial function was stronger in non-ischemic HF patients with comorbid CKD, compared with those without CKD.

Vascular endothelial dysfunction in patients with HF has been widely investigated. Several studies have demonstrated that reduced FMD value is associated with symptom severity and clinical outcomes in patients with HF[19,20]. There are several studies, where the FMD was shown to decrease in patients with HF even of non-IHD etiology[9,11]. Klonsinska et al.[10] demonstrated that FMD was more attenuated in patients with ischemic HF than in those with non-ischemic HF. On the other hand, there is a limiting information, in which vascular endothelial function was assessed using RH-PAT in HF patients[21], and no previous report in the limited patients with

Table 2. Laboratory data

	Non CKD (n=15)	CKD (n=18)	P value
Blood test			
LDL-cholesterol; mg/dL	99±31	97±33	0.870
HDL-cholesterol; mg/dL	56±18	52±17	0.537
Triglyceride; mg/dL	121±52	94±57	0.168
Glucose; mg/dL	100±19	98±16	0.659
Hemoglobin A1c; %	6.2±1.0	5.9±0.5	0.259
eGFR; mL/min/1.73 m^2	78±16	41±13	<0.0001
BNP; pg/mL	85 (42-176)	125 (64-362)	0.212
ln BNP; ln (pg/mL)	4.48±1.19	5.01±1.02	0.171
Echocardiography			
LVDd; mm	55±11	51±10	0.227
LVDs; mm	42±12	38±13	0.406
LVEF; %	51±15	50±16	0.794
E/A	1.36±0.93	1.18±0.95	0.598
E/e'	15.5±9.4	12.3±5.4	0.236
HFpEF; n (%)	8 (53)	10 (56)	0.898
FMD, diagnostic criteria; n (%)			0.132
Normal (FMD≥7.0)	5 (33)	2 (11)	
Borderline (7.0>FMD≥4.0)	7 (47)	7 (39)	
Abnormal (4.0>FMD)	3 (20)	9 (50)	
RHI, diagnostic criteria; n (%)			0.066
Normal (RHI≥2.10)	8 (53)	3 (17)	
Borderline (2.10>RHI≥1.67)	4 (27)	6 (34)	
Abnormal (1.67>RHI)	3 (20)	9 (50)	

LDL, low-density lipoprotein; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; enzyme; BNP, brain natriuretic peptide; ln BNP, natural logarithmic BNP; LVDd, left ventricular diastolic dimension; LVDs, left ventricular systolic dimension; LVEF, left ventricular ejection fraction, E/A, ratio of peak diastolic flow velocity by peak atrial systolic flow velocity, E/e', ratio of peak early diastolic flow velocity by early; FMD, flow-mediated dilation; RHI, reactive hyperemia index

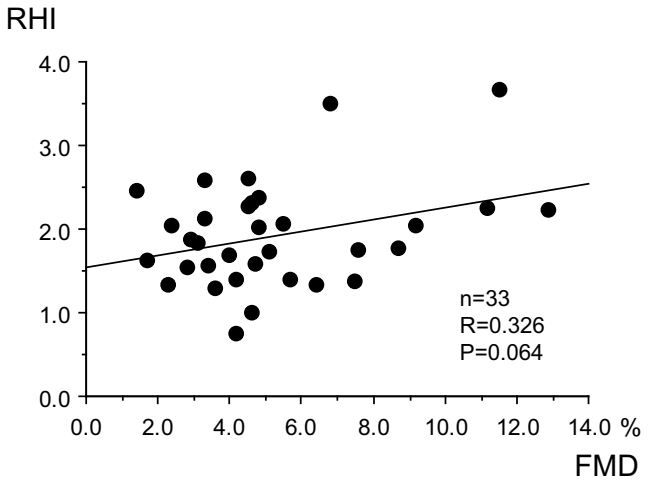

Figure 1. Relationship between flow-mediated dilation (FMD) and reactive hyperemia index (RHI) in overall patients with non-ischemic heart failure (HF) including both patient population with and without comorbid chronic kidney disease (CKD).

non-ischemic HF, and thus, the present study is the first one that evaluated RHI in non-ischemic HF patients.

In patients with chronic HF, impaired vascular endothelial function deteriorates already existing vasoconstriction, which increases afterload, and results in augment of myocardial damage. Systemic vascular endothelial dysfunction is often accompanied by endothelial dysfunction of coronary arteries, which impairs myocardial perfusion, reduces coronary flow, worsens left ventricular function, and consequently, decreases cardiac output. The decrease in cardiac output culminates endothelial shear stress which stimulates endothelial NO synthase (eNOS) expression. In HF patients, once eNOS expression is down-regulated, NO production is suppressed and consequently systemic endothelium-dependent vasodilation is inhibited, resulting in concomitant vasoconstriction[6,20]. In this way, vascular endothelial dysfunction and left ventricular dysfunction may repeat a vicious cycle.

In the present study, the prevalence of CKD was associated with impaired vascular endothelial function in patients with non-ischemic HF. Patients with chronic HF often have comorbid CKD. In large observational cohorts, CKD is observed in 30-50% of patients with HF[22-24]. In patients with HF, presence of comorbid CKD was associated with strongly reduced survival rates, independently of left ventricular function and severity of HF[25,26]. On the other hand, vascular endothelial dysfunction is accompanied with CKD

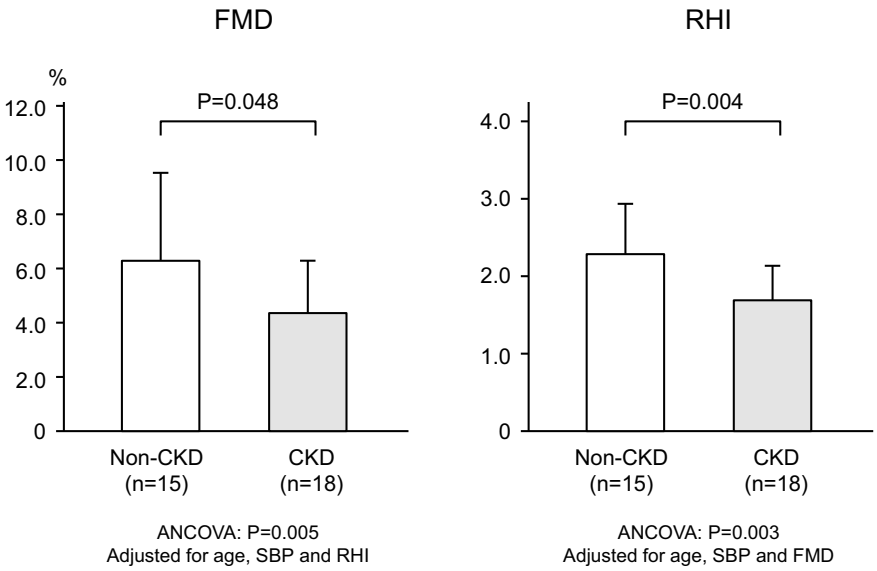

Figure 2. Comparisons of FMD and RHI between non-ischemic HF patients with (CKD group) and without (non-CKD group) comorbid CKD. Both FMD and RHI values were lower in CKD group than in non-CKD group. Even after adjustment for confounding factors, the difference in both FMD and RHI values between CKD non-CKD groups was remained.

and the relationship seems to be bidirectional, leading to a vicious circle. It has been observed that FMD value was lower in CKD patients, compared with controls[27-29], while there has been no report that assessed RHI in CKD patients. Importantly, systemic endothelial dysfunction does not only occur in patients with end-stage CKD, but also in earlier stages of CKD. Close association between microalbuminuria and systemic endothelial dysfunction renders renal vascular function an important marker for the severity of cardiovascular damage. Furthermore, changes in renal endothelium might be actively involved in the progression of renal end-organ damage[30]. In a mutual association between vascular endothelial function and CKD, an attempt has been made to understand the impact of diabetes and hypertension[31]. These components are not only risk factors of atherosclerotic cardiovascular disease but also involved in pathophysiology of non-ischemic HF. In the present study, however, prevalence of diabetes and hypertension were comparable between non-ischemic HF patients with and without comorbid CKD. On the contrary, systolic blood pressure was rather lower in patients with CKD, compared with those without CKD. In addition, the CKD patients was older than the non-CKD patients. Thus, we performed an ANCOVA analysis to compare the FMD and RHI between the two groups of non-ischemic HF patients with and without CKD after adjustment for confounding factors including age and systolic blood pressure. As a result, even after adjustment for age, systolic blood pressure and RHI value, the FMD value was still lower in patient with CKD than in those without CKD. Also, after adjustment for age, systolic blood pressure and FMD value, the RHI value was still lower in patient with CKD than in those without CKD. These results suggest that each of low values of FMD and RHI might be an independent risk of comorbid CKD in patients with non-ischemic HF.

Although both FMD and RHI can predict cardiovascular events, the clinical significance of these two vascular endothelial function parameters may be different, because they represent endothelial function in different vessels, i.e., conduit vessels or microvasculature. Endothelial function contributes to the maintenance of vasodilator tone by endothelium-derived relaxing factors (EDRFs), including nitric oxide (NO) and endothelium-derived hyperpolarizing factor (EDHF)[32,33]. Endothelium-dependent vasodilation in the conduit vessels, as evaluated by FMD, is mediated mainly by NO, whereas the dilation of microvasculature, as evaluated by RHI, is mediated by NO and EDHF together[34].

Finally, we assessed proportion of patients in each category of normal, borderline and abnormal values for FMD and RHI, based on the criteria of the Japanese Society for Vascular Failure[17,18]. As a result, the patent population belonging to abnormal category tended to be more in non-ischemic HF patients with CKD than those without CKD for the RHI value, although such a trend was absent for the FMD value. Taken together, from our results we can envision that vascular endothelial function of both conduit vessels and microvasculature might be associated with prevalence of comorbid CKD in patients with non-ischemic HF, but the association might be somewhat greater in microvascular endothelial function than that in conduit vessel endothelial function.

Limitations

The present study has several potential limitations. First, we did not perform sample size determination, and the study included small number of subjects. The study was only a

cross sectional observation study. Therefore, we could discuss the results of present study only from a perceptive of phenomenology. To discuss the pathophysiological mechanism of our results, we need further approaches. In this study, we defined CKD as the eGFR<60 mL/min/1.73 m^2. Another component, proteinuria or albuminuria is also important determinant factor for pathophysiology of CKD, so we need further assessment including association between such a component and vascular endothelial function.

Conclusion

Both FMD and RHI values were lower in non-ischemic HF patients with comorbid CKD than in those without CKD. The results suggest that impaired endothelial function might be associated with prevalence of CKD in patients with non-ischemic HF.

Abbreviations

HF=heart failure, CKD=chronic kidney disease, FMD= flow-mediated dilation, RH-PAT = reactive hyperemia-peripheral arterial tonometry, NYHA=New York Heart Association, eGFR=estimated glomerular filtration rate, RHI=reactive hyperemia index, LVEF=left ventricular ejection fraction, LVDd=left ventricular end-diastolic dimension, LVDs= left ventricular end-systolic dimension, E=peak early diastolic flow velocity, A=peak atrial systolic flow velocity, e'= early diastolic mitral annular velocity, HFrEF=heart failure with reduced ejection fraction, HFpEF=heart failure with preserved ejection fraction, ANCOVA=analysis of covariance, EDRF=endothelium-derived relaxing factors, NO= nitric oxide, EDHF= endothelium-derived hyperpolarizing factor

Authors' contributions

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Conflicts of Interest

The authors declare that they have no competing interests.

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