Validity of flow-mediated dilation and reactive hyperemia index in coronary artery disease based on the new definition of Japan Society for Vascular Failure

Keijiro Kitahara,[1] Masashi Sakuma,[1] Nishino Setsu,[1]

Shichiro Abe,[1] Teruo Inoue,[2] Shigeru Toyoda,[1]

*1 Department of Cardiovascular Medicine, Dokkyo Medical Univers*ity School of Medicine, Mibu, Japan

2 Center for Advanced Medical Science Research, Dokkyo Medical University School of Medicine, Mibu, Japan

Running title: FMD and RHI in CAD based on New Definition of Vascular Failure

For correspondence: Masashi Sakuma, M.D., Ph. D.

Department of Cardiovascular Medicine, Dokkyo Medical University School of Medicine

880 Kitakobayashi, Mibu, Tochigi, Japan 321-0293

TEL: 81-282-86-1111

FAX: 81-282-86-5633

E-mail: masakuma@dokkyomed.ac.jp

Abstract

Background: Flow-mediated dilation (FMD) and reactive hyperemia-peripheral arterial tonometry (RH-PAT) are both established methods to assess vascular endothelial function. Recently Japan Society for Vascular Failure proposed a new definition for the values of FMD (≥7.0%: normal, 7.0%> and ≥4.0%: borderline, 4.0%≥: abnormal) and reactive hyperemia index (RHI) by RH-PAT (≥2.10: normal, 2.10≥ and >1.67: borderline, 1.67≥: abnormal). In this study, we assessed the clinical significance of FMD and RHI values in coronary artery disease (CAD), based on the new definition.

Methods: We performed simultaneous measurement of FMD and RH-PAT in 131 patients undergoing coronary angiography for the suspicion of CAD. The patients were divided into subgroups, according to the normal, borderline and abnormal values for FMD and RHI in the new definition.

Results: There was no significant correlation between FMD and RHI values in the overall patients. In each group of normal FMD/normal RHI, normal FMD/abnormal RHI, abnormal FMD/normal RHI and abnormal FMD/abnormal RHI, the prevalence of multi-vessel CAD was 0%, 25%, 36%, 56% (P=0.038) respectively. Furthermore, in borderline FMD/ borderline RHI group, the multi-vessel CAD was seen in 17%, and the prevalence showed significant difference among 3 groups of normal FMD/normal RHI, borderline FMD/borderline RHI and abnormal FMD/abnormal RHI (P=0.006). A multivariate logistic regression analysis showed the abnormal FMD/abnormal RHI was an independent predictor for multi-vessel CAD (odds ratio: 3.172, 95% confidence interval: 1.012-7.336, P=0.042).

Conclusions: The evaluation of simultaneously measured FMD and RHI values based on the

new definition would be advantageous to predict the severity of CAD.

Key Words: flow-mediated dilation, reactive hyperemia-peripheral arterial tonometry, reactive hyperemia index, vascular endothelial function, coronary artery disease

Introduction

In 2006, a clinical entity 'vascular failure', defined as the integration of all vascular abnormalities, was proposed[1)]. Vascular failure is not an anatomical disease, but rather a comprehensive syndrome of abnormal vascular function. Vascular failure extends from risk factors to established atherosclerotic diseases and further to calcification of the vessel wall or thromboembolic occlusion that may be caused by plaque rupture. The initial stage of angiopathy that causes vascular failure is endothelial dysfunction. The endothelial cells play various biological roles, such as maintaining vascular tone and structure, regulating intravascular hemostasis and permeability, protecting against oxidative stress, and inhibiting cell adhesion and migration[2)]. The endothelial cells release a large number of vasoactive substances, including nitric oxide (NO) and endothelium-derived hyperpolarization factor (EDHF), both of which protect vasculature. Decreased reactivity of NO and EDHF lead to impair endothelium-dependent vasodilation, which represents the functional manifestation of endothelial dysfunction[1)]. Endothelial dysfunction is known to be associated with cardiovascular events to cause atherogenic changes in the vascular wall[1, 2)].

Flow-mediated dilation (FMD) and reactive hyperemia-peripheral arterial tonometry (RH-PAT) are both established methods to assess vascular endothelial function. The FMD value reflects endothelial function of the large conduit arteries[3)] and depends greatly on the NO, while the reactive hyperemia index (RHI) value measured by RH-PAT reflects endothelial function of the resistance vessels (microvasclatures)[4)] and depends more on EDHF than NO[5)]. Both values of FMD and RHI has a prognostic value to predict future cardiovascular events that may exceed the predictive ability of traditional risk factors[6, 7)]. However, their clinical and

pathophysiological significance may be different because of difference in measured vessel size (conduit artery vs. resistance vessel).

We previously assessed the clinical significance of simultaneously measured FMD and RH-PAT, in patients with coronary artery disease (CAD)[8]. We divided the patients into 4 groups based on cutoff values of FMD (≥6.0%: normal, 6.0%>: abnormal) and RHI (≥1.67: normal, >1.67: abnormal) could stratify the risk for severe CAD. Moreover, multiple regression analysis showed that having abnormal values of both FMD and RHI could be an independent predictor of multi-vessel CAD.

Recently Japan Society for Vascular Failure proposed a new definition for the values of FMD (≥7.0%: normal, 7.0%> and ≥4.0%: borderline, 4.0%≥: abnormal) and reactive hyperemia index (RHI) by RH-PAT (≥2.10: normal, 2.10≥ and >1.67: borderline, 1.67≥: abnormal) **(Fig. 1)** [9, 10]. In this study, based on the new definition, we re-evaluated the clinical significance of FMD and RHI values in CAD.

Methods

Subjects and study outline

We re-analyzed data of our previous study[8], where the simultaneous measurement of both FMD and RH-PAT was performed in 131 consecutive patients, who underwent diagnostic coronary angiography due to suspicion of CAD, including stable angina pectoris, old myocardium infarction, coronary spastic angina and chest pain syndrome in Dokkyo Medical University Hospital. Detailed inclusion and excluded criteria have been previously reported[8].

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 described a simultaneous measurement method of both FMD and RHI in our previously study[8]. In really brief, we performed the measurement in the morning of the day before coronary angiography. Subjects were instructed to fast overnight and to abstain from alcohol, smoking, caffeine and antioxidant vitamins for at least 12 hr before the measurement. They rested in the sitting position in a quiet, dark, air-conditioned room (22°C to 25°C) for 5 min and rested again for at least 15 min in the supine position in the same room before the FMD and RH-PAT procedures. After blood pressure was measured in the left arm, 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. For simultaneous measurement, ultrasound longitudinal images for FMD were recorded at baseline and continuously from 30 sec 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. FMD was estimated as the percent change of the brachial artery diameter at maximal dilation during hyperemia compared with the baseline value. The RHI value was calculated as the ratio of the reactive hyperemia between the two hands.

Assessment of coronary angiography

We described also an assessment method of coronary angiography in our previous study[8]. The angiographic findings were visually assessed for all of the atherosclerotic coronary lesions by an investigator who was unaware of the study design. According to the classification of the American Heart Association, the percent diameter stenosis was evaluated for each lesion and the lesion location was assessed. We assessed the number of affected vessels, considering that ≥75% diameter stenosis was a significant atherosclerotic coronary lesion. If there were no significant stenotic lesions, acetylcholine test was performed to diagnose of coronary spastic angina. The patients who had a negative acetylcholine test were diagnosed with chest pain syndrome.

Coronary risk factor assessment

In our previously study, we also described how to assess coronary risk factors[8]. Information on coronary risk factors such as hypertension, diabetes, dyslipidemia and smoking habit were obtained from each patient, as well as information on medication usage. Height and body weight were measured, and body mass index (BMI) was calculated as body weight (kg)/ (height [m])^2. Blood pressure was measured using a mercury sphygmomanometer with an appropriately sized cuff and recorded to the nearest 2 mmHg. Just after the FMD and RH-PAT procedures, peripheral blood samples were taken via the antecubital vein. 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 (CKD) 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. 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.

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. Multiple group comparisons were performed using one-way analysis of variance followed by post-hoc Bonferroni test for continuous variables and Fisher's exact test for categorical variables. The correlations between the 2 variables were examined by the officially approved correlation coefficient of Pearson. Logistic regression analyses were performed for predicting multi-vessel CAD using variables including age, gender and biomarkers for coronary risk, and the prevalence of abnormal FMD and/or abnormal RHI values. First, we selected candidate predictors by a univariate regression model, and then performed multivariate regression analysis using these candidates. All statistical analyses were performed using the statistical package for Social Science (Dr. SPSS II for Windows, SPSS Inc., Tokyo, Japan). $P<0.05$ was considered significant.

Results

As shown also in the previously report[8], there was no significant correlation between FMD and RHI (R=0.119) in all 131 patients. Then, according to the three categories for FMD and RHI values (normal, borderline and abnormal) in the new definition of Japan Society for Vascular Failure **(Fig. 1)**[9, 10], the patients were divided into subgroups. Among these subgroups, we first focused on the 4 groups: patients with normal FMD and normal RHI (normal FMD/normal RHI group), those with normal FMD but abnormal RHI (normal FMD/abnormal RHI group), those with abnormal FMD but normal RHI (abnormal FMD/normal RHI group) and those with abnormal FMD and abnormal RHI (abnormal FMD/abnormal RHI group). As a result, the number of patients was 7 (5%), 4 (3%), 25 (19%), and 16 (12%) in each group of normal FMD/normal RHI, normal FMD/abnormal RHI, abnormal FMD/normal RHI, and abnormal FMD/abnormal RHI, respectively **(Fig. 2)**. Baseline characteristics compared among these 4 groups were shown in **Table 1**. Hemoglobin A1c value and the use of statins showed statistically significant difference among the 4 groups and serum creatinine level showed a trend for difference. The other baseline characteristics parameters were comparable among the 4 groups. **Table 2** showed characteristics of CAD compared among the 4 groups. Proportion of the patients with no coronary stenotic lesion (i.e., coronary spastic angina or chest pain syndrome) and those with multi-vessel coronary artery disease showed statistically significant difference among the 4 groups. The number of patients with no stenotic lesion was 2 (29%), 0 (0%), 7 (36%) and 0 (28%) patients in each group of normal FMD/normal RHI, normal FMD/abnormal RHI, abnormal FMD/normal RHI and abnormal FMD/abnormal RHI, respectively (P=0.036). The multi-vessel CAD was observed in 0 (0%), 2 (25%), 9 (36%) and

9 (56%) patients in each group of normal FMD/normal RHI, normal FMD/abnormal RHI, abnormal FMD/normal RHI and abnormal FMD/abnormal RHI, respectively (P=0.038) **(Fig. 3)**. The other CAD characteristics were comparable among the 4 groups.

Next, we performed additional analysis, considering borderline values, which are included in the new definition of Japan Society for Vascular Failure[9, 10]. In the 131 patients, 23 (18%) had borderline FMD and borderline RHI (borderline FMD/borderline RHI group). In the borderline group, the multi-vessel CAD was observed in 4 (17%) patients. When the prevalence of multi-vessel CAD was compared among the 3 groups of normal FMD/normal RHI, borderline FMD/borderline RHI and abnormal FMD/abnormal RHI, significant difference was observed (P=0.006). Also, regarding number of percutaneous coronary intervention (PCI), multiple PCI was performed in 0 (0%), 4 (17%), 9 (56%) patients in the normal FMD/normal RHI, borderline FMD/borderline RHI and abnormal FMD/abnormal RHI groups, respectively, and significant difference was observed (P=0.006) **(Table 3)**.

Finally, we performed univariate and multivariate logistic regression analysis to assess whether the values or FMD and/or RHI could be independent predictors for the multi-vessel CAD. In the univariate regression model, among variables including age, gender and biomarkers for coronary risk, and the prevalence of abnormal FMD and/or abnormal RHI values, candidates of independent predictors were abnormal FMD (odds ratio: 2.508, 95% confidence interval: 1.124-5.598, P-0.025), abnormal RHI (odds ratio: 3.384, 95% confidence interval: 1.398-8.192, P-0.007) and abnormal FMD/abnormal RHI (odds ratio: 4.629, 95% confidence interval: 1.568-13.666, P-0.006). Multivariate logistic regression analysis showed that only the prevalence of abnormal FMD/abnormal RHI was an independent predictor of multi-vessel CAD (odds ratio: 3.172, 95% confidence interval: 1.012-7.336, P-0.042) **(Table 4)**.

Discussion

In the present study, we divided patients into subgroups, according to the cutoff values of FMD (4.0% and 7.0%) and RHI (1.67 and 2.00) in the new definition of Japan Society for Vascular Failure, in which the values were categorized as normal, borderline and abnormal[9, 10]. The major finding is that the prevalence of multi-vessel CAD was significantly different among the 4 groups of normal FMD/normal RHI, normal FMD/abnormal RHI, abnormal FMD/normal RHI and abnormal FMD/abnormal RHI. In the abnormal FMD/abnormal RHI group, the prevalence of multi-vessel CAD was 56%, while it was 0% in the normal FMD/normal RHI group **(Table 2, Fig. 3)**. The result suggests that endothelial function of both conduit arteries and microvasculature is impaired in patients with advanced CAD. In addition, logistic regression analyses to predict the multi-vessel CAD showed that the prevalence of abnormal FMD/abnormal RHI was the strongest predictor among various parameter for coronary risk in both univariate (odds ratio: 4.629) and multivariate regression models (odds ratio: 3.172). Therefore, impaired endothelial function of both conduit arteries and microvasculature might strongly represent pathophysiological features of CAD.

In our previous study[8], the patients were divided into 4 groups based on the cutoff values of FMD (6%) and RHI (1.67): normal FMD/normal RHI group, normal FMD/abnormal RHI group, abnormal FMD/normal RHI group, and abnormal FMD/abnormal RHI group. As a result, the highest incidence of multi-vessel CAD was observed in the abnormal FMD/abnormal RHI group (52%) and the lowest was in the normal FMD/normal RHI group (5%). In addition,

contrary to the result of present study, the prevalence multi-vessel CAD was lower in the abnormal FMD/normal RHI group, compared with the normal FMD/abnormal RHI group (25% vs 43%). The previous study did not set up the borderline values, like proposed by Japan Society for Vascular Failure. Therefore, in the previous study, each of the 4 groups included patients with borderline values in either FMD or RHI, or both. In this regard, the new definition of the Japan Society for Vascular Failure enabled risk stratification between high or low risk clearly by adding the borderline values. Actually, in the present study, the comparison among 3 groups of normal FMD/normal RHI, borderline FMD/borderline RHI and abnormal FMD/abnormal RHI could clearly stratified the prevalence of multi-vessel CAD as 0%, 17% and 57%, respectively **(Table 3)**.

Although there are several studies that examined the relationship between FMD and RHI based on RH-PAT, the relationship between the values of FMD and RHI is controversial. In healthy subjects, it has been shown that FMD and RHI values showed a positive correlation. In the 2 community-based epidemiological studies, the Framingham Heart Study showed no correlation[11], while the Gutenberg Heart Study showed a modest correlation[12]. However, both of these studies demonstrated that the FMD value was particularly sensitive to impairment by traditional risk factors but that the RHI value was more sensitive to metabolic risk factors, such as diabetes and obesity. Moreover, these studies indicated that the FMD value could reflect different stages of atherosclerosis, and thus, it might be more important in patients with existing atherosclerosis, whereas RHI value might be an early indicator of arteriosclerosis risk[11-13]. We believe the results of present study could support such evidence. Tomiyama et al.[14] found no correlation between the values of FMD and RHI when the 2 parameters were measured simultaneously, and their results were similar to ours. They demonstrated that autonomic

nervous activation, especially sympathetic nerve activation induced by reactive hyperemia, affected RHI value more than FMD value.

In the present study, the prevalence of multi-vessel CAD was higher in the abnormal FMD/normal RHI group, compared with the normal FMD/abnormal RHI group (36% vs 20%) **(Table 2, Fig. 3)**. In the logistic regression analyses, however, odds ratio for prediction of multi-vessel CAD was higher in abnormal RHI than in abnormal FMD (3.384 vs 2.508) in the univariate regression model. Therefore, it remains unclear whether FMD or RHI is more sensitive surrogate marker for severity of CAD. On the other hand, patients with no stenotic lesion, i.e., coronary spastic angina or chest pain syndrome are included in the groups of normal FMD/normal RHI and abnormal FMD/normal RHI but not in those of the normal FMD/abnormal RHI as well as abnormal FMD/abnormal RHI. These results suggest that the FMD shows abnormal values from the initial stage of atherosclerosis, and the abnormal values also appear in RHI with atherosclerosis progression. Therefore, it is presumed that during the process of atherosclerosis progression, vascular endothelial dysfunction first appears in the conduit arteries and then in the resistance vessels. It is understandable that patients with abnormal values of both FMD and RHI had more severe CAD.

Although the values of FMD and RHI have different physiological significance, they are both important markers for atherosclerotic diseases such as CAD. By measuring both, it will be clearer to understand the pathophysiology of atherosclerotic diseases, determine their therapeutic effect, and predict their prognosis. From the results of present study, we can envision that simultaneous measurement of FMD and RHI values would be advantageous to predict the severity of CAD. In addition, the definition of Japan Society of Vascular Failure would be valid, also in terms to assess the severity of CAD.

Potential limitations

The present study has several potential limitations. The biggest limitation is that the sample size was too small. Although we suggested in this study that classification into subgroups according to the cutoff values of FMD and RHI proposed by the new definition of Japan Society for Vascular Failure could succeed risk stratification for CAD, the number of patients in each group was too small. In addition, the analysis was only performed among 4 groups or 3 groups but not among all subgroups, and the subgroups of the patients with borderline value of either FMD or RHI were excluded from the analysis. Consequently, it remains unclear how much risk for CAD the patients in these subgroups have. Therefore, from the results of present study alone, we could not draw definitive conclusions. Further assessment using a larger number of patients is required. This study was only a cross- sectional study. Although we could give a certain evaluation for assessment of FMD and RHI values based on the new definition of Japan Society of Vascular Failure from this study, how to utilize it for treatment is a future issue. A prospective interventional study, using FMD and RHI values as its surrogate marker and assessing based on the new definition, would be promising. Even considering these limitations, however, we believe our study showed clinically important differences between FMD and RHI, and the advantages of the simultaneous measurement of both values based on the new definition.

Vascular stiffness markers such as pulse wave velocity and cardio ankle vascular index are also often used to assess the severity and prognosis of cardiovascular disease and their diagnostic criteria are also included in the new definition of Japan Society for Vascular Failure. Although in the present study we assessed severity of CAD using the combination of two

endothelial function tests, FMD and RHI, further evaluations combining with vascular stiffness tests could provide us more significant information.

Conclusions

Simultaneous measurement of FMD and RHI values would be promising to predict the severity of CAD. In addition, the definition of Japan Society of Vascular Failure would have rationale, also in terms to assess the severity of CAD.

Conflict of interest

The authors declare that there is no conflict of interest.

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Figure legends

Figure 1 Japan Society for Vascular Failure proposed a new definition of cutoff values for flow-mediated dilation (FMD) (≥7.0%: normal, 7.0%> and ≥4.0%: borderline, <4.0%: abnormal) and reactive hyperemia index (RHI) (≥2.10: normal, 2.10> and ≥1.67: borderline, <1.67: abnormal)[9, 10].

Figure 2 There was no significant correlation between the values of FMD and RHI in overall patients. When the patients were divided into 9 groups according to the cutoff values of FMD and RHI proposed by the new definition of Japan Society for Vascular Failure, the number of patients was 7 (5%), 4 (3%), 25 (19%), and 16 (12%) in each group of normal FMD/normal RHI, normal FMD/abnormal RHI, abnormal FMD/normal RHI, and abnormal FMD/abnormal RHI, respectively. The number of patients included in the borderline FMD/borderline was 23 (18%).

Figure 3 Multi-vessel CAD was observed in 0%, 25%, 36% 56% of the patients in each group of normal FMD/normal RHI, normal FMD/abnormal RHI, abnormal FMD/normal RHI and abnormal FMD/abnormal RHI, respectively. There was a significant difference among the 4 groups.