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【 ORIGINAL ARTICLE 】

Aortic Stiffness Is Associated with Coronary Microvascular Dysfunction in Patients with Non-obstructive Coronary Artery Disease

Takahiro Muroya[1], Hiroaki Kawano[2], Seiji Koga[2], Satoshi Ikeda[2], Fumi Yamamoto[3] and Koji Maemura[2]

Abstract:

Objective Associations between aortic stiffness and cardiovascular disease events are mediated in part by pathways that include coronary microvascular dysfunction (CMD) and remodeling. However, the relationship between aortic stiffness and CMD remains unclear.

The present study aimed to determine whether aortic stiffness causes CMD as evaluated by the hyperemic microvascular resistance index (hMVRI) in patients with non-obstructive coronary artery disease (CAD).

Methods The intracoronary physiological variables in 209 coronary arteries were evaluated in 121 patients with non-obstructive CAD (fractional flow reserve >0.80) or reference vessels. The cardio-ankle vascular index (CAVI) as a measure of aortic stiffness and atherosclerotic risk factors were also measured.

Results Univariate analyses showed that hMVRI correlated with age (β=0.24, p=0.007), eicosapentaenoic acid (EPA; β=-0.18, p=0.048), EPA/arachidonic acid (AA) (EPA/AA) ratio (β=-0.22, p=0.014) and CAVI (β=0.30, p=0.001). A multivariate regression analysis identified CAVI (β=0.25, p=0.007) and EPA/AA ratio (β=-0.26, SE=0.211, p=0.003) as independent determinants of hMVRI.

Conclusion Aortic stiffness may cause CMD in patients with non-obstructive CAD via increased coronary microvascular resistance. Aortic stiffness is associated with CMD which is evaluated as hyperemic microvascular resistance in patients with non-obstructive CAD.

Key words: aortic stiffness, hyperemic microvascular resistance index, cardio-ankle vascular index, coronary flow reserve

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Introduction

The Framingham Heart Study showed that abnormal aortic stiffness and increased pressure pulsatility are associated with blunted microvascular reactivity to ischemic stress (1). Furthermore, abnormal aortic stiffness is accompanied by microcirculatory structural or functional remodeling beyond that explicable by contemporaneously measured risk factors for cardiovascular disease (CVD) (2) and is associated with left ventricular diastolic dysfunction and heart failure (3).

Aortic stiffness can be evaluated by pulse wave velocity (PWV) and the cardio-ankle vascular index (CAVI), both of which are useful for predicting cardiovascular risk and as markers for the severity of atherosclerotic vascular damage in general populations (4). In particular, CAVI can measure vascular stiffness without being influenced by blood pressure (5).

Several studies have reported coronary microvascular dysfunction (CMD) to be an independent predictor of future adverse cardiovascular events in healthy volunteers, patients with non-obstructive coronary artery disease (CAD), and patients with ST-elevation myocardial infarction (6-11). Both the hyperemic microvascular resistance index (hMVRI) and

[1]Circulatory Division, Sasebo City General Hospital, Japan, [2]Department of Cardiovascular Medicine, Nagasaki University Graduate School of Biomedical Sciences, Japan and [3]Department of Cardiology, Ureshino Medical Center, Japan
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Correspondence to Dr. Hiroaki Kawano, hkawano@nagasaki-u.ac.jp

the index of microvascular resistance (IMR) are readily available, quantitative, and reproducible measures of coronary microvascular resistance in the cardiac catheterization laboratory (7-11). We have previously reported a relationship between eicosapentaenoic acid (EPA), which is associated with reduced incidences of cardiovascular events and sudden cardiac death as an ω3-polyunsaturated fatty acid, and CMD as evaluated by hMVRI (12). However, little is known about the relationship between aortic stiffness and CMD. The aim of the present study was to investigate the relationships between aortic stiffness and hMVRI, as an indicator of CMD, in patients with non-obstructive CAD.

Materials and Methods

Patient population

We evaluated adult patients with clinically suspected coronary ischemia based on the presence of angina pectoris, using elective coronary angiography (CAG) to rule out obstructive CAD (>75%). In patients with nonobstructive CAD (i.e., ≤25% on CAG), fractional flow reserve (FFR) was measured to assess the significance of physiological stenosis. Moreover, in patients without significant stenosis (FFR >0.80, which indicates a functionally nonsignificant stenotic lesion), invasive measurement of hMVRI was conducted to evaluate microvascular dysfunction for the diagnosis of microvascular angina using modified criteria from previous study reports (11-14).

The ethics committee of Ureshino Medical Center approved the protocol for this study, which was conducted according to the Declaration of Helsinki.

Cardiac catheterization procedure

After CAG, aortic pressure was measured via a 5- or 6-Fr guiding catheter placed in the coronary ostium by a radial or femoral approach. Intracoronary pressure and coronary flow velocity were measured with a 0.014" pressure sensor-equipped guidewire (Volcano, San Diego, USA). Hyperemia was induced by injecting papaverine hydrochloride into the coronary artery (12 mg into the left coronary artery, 8 mg into the right coronary artery over 15 seconds), and blood pressure was recorded 20 seconds after the end of administration. FFR was defined as the ratio of mean distal coronary pressure (Pd) to mean aortic pressure (Pa) in the target vessels beyond the lesion during maximal hyperemia. Patients without significant stenosis (FFR>0.80) were selected. The hMVRI was calculated as Pd divided by the distal average peak velocity (APV) during maximal hyperemia. When hMVRI could be measured in two coronary arteries in the same patient, then the average hMVRI was used for this study.

Measurement of CAVI

CAVI was obtained using a VaSera CAVI instrument (Fukuda Denshi, Tokyo, Japan) equipped with electrocardiography, phonocardiography, and mechanocardiography functions. CAVI was recorded in patients after 5 minutes of rest in the supine position. The calculation of CAVI was based on blood pressure and heart-ankle PWV, monitoring of heart sounds, and electrocardiography. Heart-ankle PWV was calculated by dividing the distance from the aortic valve to the ankle artery by the sum of time intervals between aortic valve closure sound (first part of the second heart sound) and the notch of the brachial pulse wave, and between the rise of the brachial pulse wave and the ankle pulse wave.

$$CAVI=a[2\rho/(Ps-Pd)\times\ln(Ps/Pd)\times haPWV2]+b$$

where Ps and Pd are systolic and diastolic blood pressure, respectively; ρ is blood density; and a and b are constants. CAVI was taken as the average of the right and left CAVI values.

Measurement of polyunsaturated fatty acids

Fasting blood samples were collected early in the morning after the patient had fasted for 12 hours overnight. The serum levels of EPA, docosahexaenoic acid (DHA), arachidonic acid (AA), and dihomo-γ-linolenic acid were measured by capillary gas chromatography (SRL, Tokyo, Japan).

Echocardiography

All echocardiographic examinations were performed using commercially available ultrasound machines (Hi Vision Preirus ultrasonography system; Hitachi, Chiba, Japan). In all subjects, cardiac chamber quantification by 2-dimensional echocardiography was performed according to the American Society of Echocardiography Guidelines (15).

Statistical analysis

All data are expressed as the mean±standard deviation or number (percentage) of patients. Associations between the hMVRI value and variables were evaluated using a univariate linear regression analysis. The non-parametric Wilcoxon rank-sum analysis was used to analyze relationships between hMVRI and categorical data. A multivariate regression analysis was used to determine independent determinants associated with hMVRI among factors showing values of $p<0.05$ based on a univariate analysis.

Values of $p<0.05$ were considered to be significant. The data were analyzed statistically using the JMP software program version 10 (SAS Institute, Cary, USA).

Results

Patient characteristics

Between December 2010 and April 2016, we evaluated adult patients with clinically suspected coronary ischemia based on the presence of angina pectoris using elective CAG, which was performed to assess the significance of physiological stenosis and the microvascular function for each intermediate stenosis and the reference vessels. A total of 163 patients with non-obstructive CAD without signifi-

Table 1. Background Characteristics of Patients.

Variable	Value	Variable	Value
Age, y	69.8±9.6	CAD	
Male sex, n (%)	82 (67.8)	Prior MI, n (%)	22 (18.2)
Height, cm	159.0±8.8	Recent AMI	4 (3.3)
Weight, kg	62.3±11.4	Prior PCI, n (%)	57 (47.1)
BMI, kg/m^2	24.6±8.8	Hemodialysis	1 (0.8)
Risk factors		UCG findings	
Hypertension, n (%)	81 (66.9)	LVDd	47.3±3.8
Dyslipidemia, n (%)	82 (67.8)	LVDs	30.0±3.9
Diabetes mellitus, n (%)	51 (42.1)	IVS	9.7±1.3
Current smoking, n (%)	32 (26.4)	LVPW	10.0±4.0
Laboratory findings		LVEF (%)	66.1±6.3
Total cholesterol (mg/dL)	176±34	Coronary artery	
HDL-C (mg/dL)	54±15	LAD	90
LDL-C (mg/dL)	103±32	LCX	62
Triglycerides (mg/dL)	135±82	RCA	57
Uric acid (mg/dL)	5.9±5.1	Vessel numbers/Patient	1.73
FBS	112±40	Medication, n (%)	
Serum creatinine (mg/dL)	0.8±0.6	β-blockers	17 (14.1)
HbA1c, %	6.0±1.1	Calcium channel blockers	64 (52.9)
BNP (pg/dL)	45±67	ARB or ACE inhibitors	54 (44.6)
PUFA		Statins	70 (57.9)
DGLA (μg/mL)	34.7±11.6	CAVI	9.00±1.4
AA (μg/mL)	172.6±43.0		
EPA (μg/mL)	78.7±43.0		
DHA (μg/mL)	146.3±44.8		
EPA/AA ratio	0.48±0.29		
ABI	1.1±0.1		

Values presented as n (%) or means±SD.

BMI: body mass index, FBS: fasting blood sugar, BNP: brain natriuretic peptide, PUFA: polyunsaturated fatty acids, DGLA: dihomo-γ-linolenic acid, AA: arachidonic acid, EPA: eicosapentaenoic acid, DHA: docosahexaenoic acid, CAD: coronary artery disease, MI: myocardial infarction, AMI: acute myocardial infarction, PCI: percutaneous coronary intervention, UCG: ultrasoundcardiography, IVS: interventricular septum, LVPW: left ventricular posterior wall, ACE: angiotensin-converting enzyme, ARB: angiotensin receptor blocker, CAVI: cardio-ankle vascular index, ABI: ankle brachial pressure index

cant stenosis (FFR>0.80) were assessed using a Doppler velocity and pressure-equipped guidewire. Only two patients had atrial fibrillation. Patients with hypertrophic cardiomyopathy or left ventricular hypertrophy (n=5), moderate-to-severe heart valve disease (n=4), a left ventricular ejection fraction <50% due to prior myocardial infarction or complete left bundle branch block (n=13), culprit vessel of myocardial infarction (<6 weeks before screening) (n=5), visible collateral development to the perfusion territory of interest (n=3), and peripheral arterial disease [ankle brachial index (ABI) <0.9 or history of endovascular treatment; n=12] were excluded. As a result, 209 coronary arteries in 121 patients were included in the present study. There were no significant procedure-related complications such as coronary dissection, coronary perforation, myocardial infarction, life-threatening arrhythmia, major bleeding, or death.

The mean age of study participants was 69.8 years. Overall, 22 patients had prior myocardial infarction, 57 patients had prior percutaneous coronary intervention, and the remaining patients were suspected to have CAD based on chest pain, dyspnea or coronary stenosis on coronary computed tomography. All patient characteristics are presented in Table 1. In these patients, the frequencies of the following coronary risk factors were: hypertension, 66.9%; dyslipidemia, 67.8%; diabetes mellitus, 42.1%; and current smoking, 26.4%. A total of 90 left anterior descending arteries (LADs), 62 left circumflex arteries (LCXs) and 57 right coronary arteries (RCAs) were examined; the mean number of coronary arteries examined in each patient was 1.7.

Coronary physiological values and characteristics

All coronary physiological measurements are presented in Table 2. The mean FFR and hMVRI values in all coronary arteries were 0.91 and 1.97 mmHg/cm/s, respectively. The mean APV at rest and APV at hyperemia were 17.9 cm/s and 37.8 cm/s, respectively.

Associations between hMVRI and the variables according to a univariate analysis

Univariate analyses showed that hMVRI correlated with

Table 2. Coronary Physiological Values.

Variable	Value
FFR	0.91±0.05
Pa at rest (mmHg)	88.4±11.9
Pa at hyperemia (mmHg)	76.9±11.5
Pd at rest (mmHg)	79.8±15.6
Pd at hyperemia (mmHg)	58.8±19.5
APV at rest (cm/s)	17.9±8.1
APV at hyperemia (cm/s)	37.8±11.7
hMVRI (mmHg/cm/s)	1.97±0.69

Values presented as n (%) or means±SD. FFR: fractional flow reserve, hMVRI: hyperemic microvascular resistance index, APV: average peak blood flow velocity, Pa: mean proximal coronary pressure, Pd: mean distal coronary pressure

Table 4. Association between hMVRI and Risk Factors.

Variable	n	hMVRI	p value
Sex			
Male	82	1.9±0.1	0.253
Female	39	2.0±0.1	
Hypertension			
Yes	81	2.0±0.1	0.201
No	40	1.8±0.1	
Dyslipidemia			
Yes	82	1.9±0.1	0.273
No	39	2.1±0.1	
DM			
Yes	51	2.1±0.1	0.112
No	70	1.9±0.1	
Current smoking			
Yes	32	2.0±0.1	0.816
No	89	2.0±0.1	
OMI and Recent MI			
Yes	26	2.0±0.1	0.382
No	95	2.0±0.1	
Prior PCI			
Yes	57	1.9±0.1	0.697
No	64	2.0±0.1	

Values presented as n (%) or means±SD. The abbreviations used in this table are the same as in Table 1. hMVRI: hyperemic microvascular resistance index, DM: diabetes mellitus, OMI: old myocardial infarction

Table 3. Associations between hMVRI and Risk Factors on Univariate Analysis.

Variable	hMVRI		
	β	p value	R^2
Age	0.24	0.007	0.059
Height	-0.11	0.238	-
Weight	-0.15	0.111	-
BMI	-0.11	0.221	-
Laboratory data			
Total cholesterol	-0.01	0.899	-
HDL-C	-0.1	0.263	-
LDL-C	-0.03	0.766	-
Triglycerides	0.04	0.683	-
Uric acid	0	0.995	-
Serum creatinine	0.02	0.853	-
FBS	0.05	0.635	-
HbA1c	0.03	0.771	-
BNP	0.06	0.526	-
PUFA			
DGLA	0.15	0.105	-
AA	0.09	0.334	-
EPA	-0.18	0.048	0.032
DHA	0.03	0.784	-
EPA/AA ratio	-0.22	0.014	0.049
UCG data			
LVDd	-0.12	0.212	-
LVDs	-0.12	0.202	-
IVS	-0.04	0.637	-
LVPW	-0.03	0.737	-
LVEF	0.1	0.305	-
CAVI	0.3	0.001	0.089
ABI	-0.09	0.328	-

The abbreviations used in this table are the same as in Table 1. hMVRI: hyperemic microvascular resistance index

age (β=0.24, p=0.007), EPA (β=-0.18, p=0.048), EPA/AA ratio (β=-0.22, p=0.014) and CAVI (β=0.30, p=0.001) (Table 3, 4).

A multivariate regression analysis model for hMVRI

The multivariate regression analysis included age, EPA/AA ratio, and CAVI (model 1) identified EPA/AA ratio (β=-0.26, SE=0.211, p=0.003) and CAVI (β=0.26, SE=0.048, p=0.007) as independent factors associated with the hMVRI (Table 5). The multivariate regression analysis included age, EPA/AA ratio, CAVI, sex, hypertension, diabetes mellitus, and current smoking (model 2) selected EPA/AA ratio (β=-0.24, SE=0.194, p=0.005), CAVI (β=0.25, SE=0.047, p=0.008), sex (β=0.22, SE=0.069, p=0.023), and hypertension (β=-0.26, SE=0.061, p=0.003) as independent factors associated with the hMVRI (Table 5).

Discussion

The present study demonstrated that: 1) hMVRI correlated positively with age and CAVI as a marker of aortic stiffness, and negatively with both EPA and EPA/AA ratio according to a univariate analysis; 2) EPA/AA ratio and CAVI, in addition to sex and hypertension, were independent determinants of hMVRI according to a multivariate regression analysis in patients showing FFR>0.8 in stable CAD. These results suggest the important relationships among aortic stiffness, CMD, and serum EPA/AA related to future adverse cardiovascular events in patients with non-

Table 5. Multivariate Regression Analysis Model for hMVRI.

Variable	hMVRI		
Model 1			
	β	SE	p value
Age	0.18	0.007	0.05
EPA/AA ratio	-0.26	0.211	0.003
CAVI	0.25	0.048	0.007
Model 2			
	β	SE	p value
Age	0.16	0.007	0.135
EPA/AA ratio	-0.24	0.194	0.005
CAVI	0.25	0.047	0.008
Sex	0.22	0.069	0.023
Hypertension	-0.26	0.061	0.003
Dyslipidemia	0.12	0.066	0.175
Diabetes mellitus	-0.14	0.061	0.120
Current smoking	-0.14	0.075	0.154

The abbreviations used in this table are the same as in Table 1. hMVRI: hyperemic microvascular resistance index

obstructive CAD.

Previous studies have demonstrated that increased aortic stiffness is related to CMD in metabolic syndrome, CAD, and angina in female patients without obstructive CAD (16-22). Fukuda et al. (21) showed that coronary flow reserve (CFR) correlated significantly with brachial-ankle PWV (baPWV) and age according to univariate analyses, and baPWV was an independent determinant of CFR in patients with CAD. Nichols et al. (22) also reported that CFR was inversely related to aortic PWV, an index of aortic stiffness among symptomatic women without obstructive CAD.

The present study demonstrated that CAVI was an independent determinant of hMVRI according to a multivariate regression analysis in patients with non-obstructive CAD without significant stenosis (FFR>0.80). Our data are compatible with the findings of previous studies. We used CAVI instead of PWV, because CAVI can measure vascular stiffness without being influenced by blood pressure (5). We also used hMVRI instead of CFR. CFR and hMVRI are generally considered as important surrogate markers of CMD, but neither index offers a perfectly matched marker of coronary artery microcirculatory function in patients with stable CAD (FFR>0.8) (23). CFR is thought of as the capacity of the epicardial coronary arteries and coronary microvascular circulation, whereas hMVRI is a specific quantitative index for coronary microvascular circulation. Furthermore, hMVRI remains largely unchanged with epicardial coronary stenosis severity when the collateral flow is properly taken into account (24, 25). Verhoeff et al. (26) reported that the effect of collateral flow on hMVRI is minimal in patients with FFR>0.8. As a result, hMVRI was used to evaluate coronary microcirculation in the present study of cases with FFR>0.8.

Previous studies have demonstrated that aortic stiffness may stimulate small vessel damage or remodeling leading to elevated peripheral resistance and an attenuated flow (27, 28). In patients with increased aortic stiffness, aortic impedance increases disproportionately to impedance of the peripheral muscular arteries, leading to impedance matching and a reduction in wave reflection (29, 30). This reduction in wave reflection eliminates the protective mechanism that normally buffers the peripheral microcirculation against excessive pressure and pulsatility (29, 30). Higher pulsatility leads to hypertrophic remodeling and progressive encroachment on the arterial lumen (31, 32).

We also showed that in addition to CAVI, the EPA/AA ratio was an independent determinant of hMVRI in patients with FFR>0.8 in stable CAD. To the best of our knowledge, this is the first report to show that low EPA/AA and increased aortic stiffness correlate independently with CMD.

Previous studies have suggested that a decreased EPA/AA ratio impairs arterial stiffness (33) and an increased EPA/AA ratio improves aortic stiffness (34). Moreover, borderline aortic stiffness is associated with endothelial dysfunction (35).

Taken together, CMD may be induced by the direct effects of a low serum EPA/AA ratio and increased aortic stiffness, and aortic stiffness impaired by a low serum EPA/AA ratio.

Both aortic stiffness and CMD are independent predictors of future adverse cardiovascular events (12, 36, 37). Aortic stiffness is associated with epicardial CAD and CMDR (21). Moreover, previous large studies have demonstrated that EPA therapy or the intake of ω3 polyunsaturated fatty acid may prevent cardiovascular events (38, 39). EPA therapy or ω3 polyunsaturated fatty acid intake may thus ameliorate aortic stiffness and CMD to prevent future adverse cardiovascular events in non-obstructive CAD. Further investigations are needed to elucidate the direct effects of EPA administration on hMVRI and CAVI improvement and the prognosis of stable CAD.

In conclusion, aortic stiffness and EPA/AA may cause CMD in patients with CAD via increased coronary microvascular resistance. Aortic stiffness is associated with coronary microvascular dysfunction which is evaluated as hyperemic microvascular resistance in patients with non-obstructive CAD.

Study limitations: First, this study involved a relatively small study population and was performed at a single facility. Second, this is a cross-sectional study, and the effects of EPA administration on hMVRI and CAVI were not examined.

The authors state that they have no Conflict of Interest (COI).

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