CLINICAL STUDY

Lower Circulating Omega-3 Polyunsaturated Fatty Acids Are Associated with Coronary Microvascular Dysfunction Evaluated by Hyperemic Microvascular Resistance in Patients with Stable Coronary Artery Disease

Takahiro Muroya,[1,2] MD, Hiroaki Kawano,[2] MD, Seiji Koga,[2] MD, Satoshi Ikeda,[2] MD, Fumi Yamamoto,[1] MD, Takashi Miwa,[1] MD, Yusuke Kohno,[1] MD and Koji Maemura,[2] MD

Summary

The consumption of omega-3 polyunsaturated fatty acids (PUFAs) reduces the incidence of cardiovascular events and sudden cardiac death. Coronary microvascular dysfunction (CMD) is a predictor of cardiac mortality, but little information is known on the relationship between CMD and omega-3 PUFAs. This study aimed to identify the relationship between the serum levels of omega-3 PUFAs and the CMD evaluated by the hyperemic microvascular resistance index (hMVRI) to assess coronary microvascular function in patients with stable coronary artery disease (CAD).

Intracoronary physiological variables (fractional flow reserve (FFR), hMVRI, mean distal coronary pressure (Pd), and average peak velocity (APV)) were measured in 108 patients. These parameters were evaluated in 150 coronary arteries with stenosis of intermediate severity and without significant ischemia (FFR > 0.80). The PUFA levels and atherosclerotic risk factors were also measured. Univariate analysis shows that hMVRI was negatively correlated with eicosapentaenoic acid (EPA)/arachidonic acid (AA) ratio ($\beta = -0.31$, $P = 0.001$) and EPA ($\beta = -0.25$, $P = 0.009$) and was positively correlated with dihomo-γ-linolenic acid ($\beta = 0.26$, $P = 0.006$). Multivariate regression analysis shows that the EPA/AA ratio was the only independent determinant of hMVRI ($\beta = -0.234$, SE = 0.231, $P = 0.024$). Furthermore, hMVRI decreased significantly from the lowest to highest tertiles of the EPA/AA ratio ($P = 0.007$). The EPA/AA ratio was positively correlated with APV at hyperemia ($\beta = 0.26$, $P = 0.008$) but not with Pd at hyperemia.

A lower serum EPA/AA ratio may cause CMD in patients with stable CAD.

(Int Heart J 2018; 59: 1194-1201)

Key words: Eicosapentaenoic acid/arachidonic acid (EPA/AA) ratio, Hyperemic microvascular resistance index

The dietary intake of omega-3 polyunsaturated fatty acids (PUFAs) including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from fish and alpha-linolenic acids in plants,[1] which are important components of cell membranes and are involved in cell function,[2] decreases the risk of cardiovascular disease and sudden cardiac death.[3-12] Variations in omega-3 PUFA compositions are associated with anti-inflammatory,[3] vasodilatory,[4] antiarrhythmic,[5] and antihyperlipidemic[6] effects, as well as the reduction of platelet aggregation[7] and stabilization of coronary plaque.[8] The GISSI-Prevenzione trial showed that dietary omega-3 PUFA intake significantly prevented cardiovascular death and sudden death in patients with a recent myocardial infarction (< 3 months),[9] and the Japan EPA Lipid Intervention Study (JELIS) showed that concurrent therapy with purified EPA and statins reduced the incidence of coronary events more than statins alone.[10]

Several studies reported that coronary microvascular dysfunction (CMD) is an independent predictor of future adverse cardiovascular events.[11,13-17] However, there has been only one report on the relationship between EPA and CMD evaluated by phase-contrast cine cardiovascular magnetic resonance.[18] Moreover, there has been no report on the relationship between omega-6 PUFAs including dihomo-γ-linolenic acid (DGLA) and CMD.

The hyperemic microvascular resistance index (hMVRI) and the index of microvascular resistance (IMR) as measures of coronary microvascular resistance are readily available, quantitative, and reproducible in a cardiac catheterization laboratory, and a wire-based method for invasively assessing coronary microvascular function is independent of epicardial artery stenosis.[13-17,19-25]

The aim of this study is to investigate the relation-

From the [1]Department of Cardiology, Ureshino Medical Center, Ureshino, Japan and [2]Department of Cardiovascular Medicine, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan.

Address for correspondence: Hiroaki Kawano, MD, Department of Cardiovascular Medicine, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki, Nagasaki 852-8501, Japan. E-mail: hkawano@nagasaki-u.ac.jp

Received for publication August 9, 2017. Revised and accepted January 18, 2018.

Released in advance online on J-STAGE October 10, 2018.

doi: 10.1536/ihj.17-459

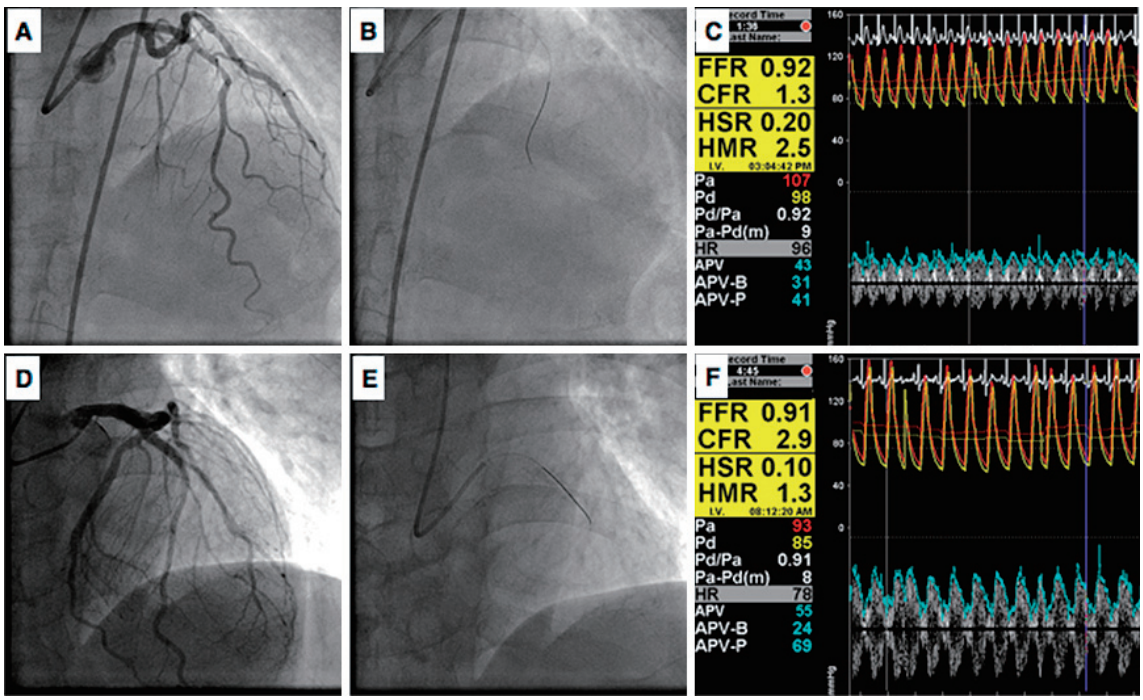

Figure 1. Representative cases with low EPA/AA ratio (0.17) and hMVRI (2.5) (**A-C**) and with high EPA/AA ratio (1.14) and low hMVRI (1.3) (**D-F**). **A** and **D:** CAG of the left coronary artery. **B** and **E:** Insertion of Doppler flow guide wire into the left coronary artery. **C** and **F:** FFR and hMVRI measurements by Doppler flow guide wire at hyperemia. EPA/AA indicates eicosapentaenoic acid/arachidonic acid; hMVRI, hyperemic microvascular resistance index; and FFR, fractional flow reserve.

ships between omega-3 or omega-6 PUFA levels and hMVRI (as an indicator of CMD) in patients with stable coronary artery disease (CAD).

Methods

Patient population: We evaluated adult patients with a clinical suspicion of coronary ischemia based on the presence of angina pectoris by using elective coronary angiography (CAG).

A CAG was performed to rule out obstructive CAD (> 75%). In patients with nonobstructive CAD, 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, an invasive measurement of hMVRI was conducted to evaluate microvascular dysfunction for the diagnosis of microvascular angina by using the modified criteria of previous study reports.[17,26,27] The Ethics Committee of Ureshino Medical Center approved the protocol for this study, which was conducted according to the Declaration of Helsinki (approval number 10-10). It has recently been reported that the coronary microvascular resistance of the right coronary artery was higher than that of the left anterior descending artery (LAD) or left circumflex artery (LCX).[20,21] Thus, we evaluated the hMVR in LAD and LCX to exclude the effect of the difference in coronary vessels in this study.

Cardiac catheterization procedure: After CAG, aortic pressure was measured via a 5- or 6-F guiding catheter placed in the coronary ostium by the radial approach or femoral approach. Intracoronary pressure and coronary flow velocity were measured with a 0.014" pressure sensor-equipped guidewire (Volcano Corp, San Diego, CA) (Figure 1). Hyperemia was induced by injecting papaverine hydrochloride into the coronary artery (12 mg into the left coronary artery over 15 seconds), and blood pressure was recorded at 20 seconds after the end of administration. FFR was defined as the ratio of mean distal coronary pressure (Pd) to mean aortic pressure in the target vessels beyond the lesion during maximal hyperemia.

Patients without significant stenosis (FFR > 0.80), which indicates a functionally nonsignificant stenotic lesion, 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 both the LAD and LCX in the same patient, the average hMVRI of the LAD and LCX was used for this study.

Measurement of PUFAs: Fasting blood samples were collected early in the morning after the patients had fasted for 12 hours overnight. The serum levels of EPA, DHA, arachidonic acid (AA), and DGLA were measured by capillary gas chromatography (SRL Inc., Tokyo, Japan).

Echocardiography: All echocardiographic examinations were performed with commercially available ultrasound machines (Hi Vision Preirus ultrasonography system, Hitachi, Chiba, Japan). Cardiac chamber quantification by 2D echocardiography was performed in all subjects according to the guidelines of the American Society of Echocardiography.[28]

Table I. Patient Characteristics

Characteristic	Value
Age, years	69.1 ± 9.5
Male sex	75 (69.4)
Height, (cm)	159.3 ± 9.0
Weight (kg)	62.5 ± 11.4
BMI (kg/m^2)	24.6 ± 4.0
SBP (mmHg)	125 ± 13
DBP (mmHg)	75 ± 10
HR (beats/minute)	70 ± 13
Coronary risk factor	
Hypertension	73 (67.6)
Dyslipidemia	76 (70.4)
Diabetes mellitus	47 (43.5)
Current smoking	28 (25.9)
Prior history of comorbidities	
Prior MI	23 (21.3)
Prior PCI	48 (44.4)
Peripheral vascular disease	10 (9.3)
Hemodialysis	2 (1.8)
Coronary artery	
LAD	86
LCx	64
Laboratory finding	
Total cholesterol (mg/dL)	174 ± 32
HDL-C (mg/dL)	54 ± 65
LDL-C (mg/dL)	102 ± 28
Triglycerides (mg/dL)	137 ± 96
Uric acid (mg/dL)	5.5 ± 1.2
FBS	110 ± 31
Serum creatinine (mg/dL)	0.88 ± 0.86
HbA1c, %	6.0 ± 1.1
BNP (pg/dL)	32 ± 33
CRP	0.16 ± 0.22
PUFA	
DGLA (μg/mL)	34.7 ± 11.6
AA (μg/mL)	173.0 ± 43.1
EPA (μg/mL)	80.9 ± 44.6
DHA (μg/mL)	146.9 ± 45.4
EPA/AA ratio	0.50 ± 0.30
UCG findings	
IVS (mm)	9.7 ± 1.3
LVPW (mm)	9.6 ± 1.0
LVEF (%)	66.2 ± 6.2
Medication	
β-blockers	15 (13.9)
Calcium channel blockers	56 (51.9)
ARB or ACE inhibitors	46 (42.6)
Statins	66 (61.1)
Diuretics	5 (4.6)
Antiplatelet agents	107 (99.1)

Values are presented as *n* (%) or mean ± SD. BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; MI, myocardial infarction; PCI, percutaneous coronary intervention; LAD, left anterior descending branch; LCX, left circumflex branch; FBS, fasting blood sugar; BNP, brain natriuretic peptide; CRP, C-reactive protein; PUFA, polyunsaturated fatty acids; DGLA, dihomo-γ-linolenic acid; AA, arachidonic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; IVS, interventricular septum; LVPW, left ventricular posterior wall; ACE, angiotensin-converting enzyme; and ARB, angiotensin receptor blocker.

Statistical analysis: All data are expressed as mean ± standard deviation or number (percentage) of patients. The associations between the hMVRI value and variables were evaluated using univariate linear regression analysis. Nonparametric Wilcoxon rank-sum analysis was used to analyze the relationships between hMVRI and categorical data. Kruskal-Wallis analysis was used to compare hMVRI by the tertile of the EPA/AA ratio.

Multivariate regression analysis was used to determine the independent determinants associated with hMVRI among factors whose *P* values were less than 0.05 on univariate analysis.

P values < 0.05 were considered significant. Data were analyzed statistically by using JMP 10 (SAS Institute Inc., Cary, NC, USA).

Results

Patients' characteristics: Between December 2010 and April 2016, a total of 160 patients with stable CAD were assessed using a Doppler velocity and pressure-equipped guidewire. Patients with hypertrophic cardiomyopathy or left ventricular hypertrophy (n = 8), moderate to severe heart valve disease (n = 3), left ventricular ejection fraction < 50% due to prior myocardial infarction (Prior MI) or complete left bundle brunch block (n = 7), coronary artery bypass graft surgery (n = 1), atrial fibrillation (n = 7), cardiac pacemaker to control complete atrioventricular block (n = 6), myocardial infarction (< 6 weeks before screening) (n = 13), visible collateral development to the perfusion territory of interest (n = 3), coronary spastic angina (n = 2), and left main trunk disease (stenosis > 50% or stent insertion) (n = 2) were excluded. Thus, 108 patients were included in this 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 the study population was 69.1 years. Overall, 23 patients had Prior MI, 48 patients had prior percutaneous coronary intervention (PCI), and the remaining patients were suspected to have CAD because they had chest pain or coronary stenosis on coronary computed tomography. Table I shows the patient characteristics. In these patients, the following coronary risk factors were observed: hypertension (67.6%), dyslipidemia (70.4%), diabetes mellitus (43.5%), and current smoking (25.9%). A total of 86 LADs and 64 LCXs were examined, and the mean number of examined coronary arteries was 1.4 per person.

Procedural characteristics: Table II shows the coronary physiological measurements. The mean FFR and hMVRI values in all coronary arteries were 0.90 and 1.9 mmHg/cm/second, respectively. The mean APV at hyperemia and Pd at hyperemia were 38.6 cm/second and 70.2 mmHg, respectively.

Associations between hMVRI and variables in the univariate and multivariate analyses: In the univariate analysis, the hMVRI in the coronary arteries was negatively correlated with the EPA/AA ratio (β = –0.31, P = 0.001) and EPA (β = –0.25, P = 0.009) and was positively correlated with DGLA (β = 0.26, P = 0.006). However, the traditional risk factors, including sex, Prior MI, and prior PCI, and C-reactive protein (CRP) were not cor-

Table II. Coronary Physiological Values

Variable	Value
FFR	0.90 ± 0.05
hMVRI (mmHg/cm/second)	1.9 ± 0.7
APV at hyperemia (cm/second)	38.6 ± 12.4
Pd at hyperemia (mmHg)	70.2 ± 10.6
QCA	
MLD (mm)	2.15 ± 0.69
RD (mm)	2.24 ± 0.81
Diameter stenosis (%)	38.9 ± 20.8
Lesion length (mm)	23.3 ± 13.9

Values are presented as *n* (%) or mean ± SD. FFR indicates fractional flow reserve; hMVRI, hyperemic microvascular resistance index; APV, average peak blood flow velocity; Pd, mean distal coronary pressure; QCA, quantitative coronary analysis; and RD, reference diameter.

Table III. Associations between hMVRI and Risk Factors in the Univariate Analysis

Variable	β	*P*	r^2
Age	0.12	0.218	-
Height	-0.01	0.353	-
Weight	-0.03	0.741	-
BMI	0.02	0.833	-
SBP	0.17	0.075	
DBP	0.07	0.497	
HR	0.16	0.092	-
Laboratory finding			
Total cholesterol	0.03	0.767	-
HDL-C	-0.00	0.738	-
LDL-C	0.11	0.250	-
Triglycerides	0.03	0.798	-
Uric acid	-0.09	0.367	-
Serum creatinine	-0.04	0.660	-
FBS	0.14	0.148	-
HbA1c	0.01	0.908	-
BNP	0.08	0.429	-
CRP	0.10	0.310	-
PUFA			
DGLA	0.26	0.006	0.070
AA	0.15	0.112	-
EPA	-0.25	0.009	0.054
DHA	0.01	0.943	-
EPA/AA ratio	-0.31	0.001	0.093
UCG finding			
IVS	0.09	0.356	-
LVPW	-0.00	0.998	-
LVEF	0.14	0.144	-
QCA			-
MLD (mm)	0.04	0.714	-
RD (mm)	0.07	0.073	-
Diameter stenosis (%)	-0.03	0.749	-
Lesion length (mm)	-0.04	0.714	-

The abbreviations used in this table are the same as those in Tables I and II.

related with hMVRI (Tables III, IV). In multivariate regression analysis with the EPA/AA ratio and DGLA, the EPA/AA ratio was the only independent factor related to hMVRI (β = –0.234, SE = 0.231, *P* = 0.024) (Table V). Furthermore, hMVRI decreased significantly from the lowest to highest tertiles of the EPA/AA ratio (*P* = 0.007) (Figure 2). Thereafter, the relationships of the EPA/AA ratio with APV at hyperemia or Pd at hyperemia were examined because the hMVRI was calculated as Pd and APV at hyperemia. Although the EPA/AA ratio had no significant relationship with Pd at hyperemia (*P* = 0.132), there was a significant positive correlation between the EPA/AA ratio and APV at hyperemia (β = 0.26, *P* = 0.008) (Figure 3).

Table IV. Association between hMVRI and Risk Factors

Variable	*n*	hMVRI (mmHg/cm/second)	*P*
Sex			
Male	75	1.9 ± 0.1	0.13
Female	33	2.1 ± 0.8	
Hypertension			
Yes	73	2.0 ± 0.7	0.59
No	35	1.9 ± 0.6	
Dyslipidemia			
Yes	76	1.9 ± 0.7	0.38
No	32	2.0 ± 0.6	
DM			
Yes	47	2.0 ± 0.7	0.58
No	61	1.9 ± 0.6	
Current smoking			
Yes	28	2.0 ± 0.7	0.98
No	80	1.9 ± 0.6	
Prior MI			
Yes	23	1.9 ± 0.7	0.69
No	85	1.9 ± 0.6	
Prior PCI			
Yes	48	1.8 ± 0.6	0.17
No	60	2.0 ± 0.7	

The abbreviations used in this table are the same as those in Table I.

Table V. Multivariate Regression Analysis Model for hMVRI

Variable	hMVRI		
	β	SE	*P*
EPA/AA ratio	-0.234	0.231	0.024
DGLA	0.161	0.006	0.161

The abbreviations used in this table are the same as those in Table I.

Discussion

This study demonstrated the following: 1) Univariate analysis shows that hMVRI, which is one of the indicators of coronary microcirculation, had significantly negative associations with the EPA/AA ratio and EPA and had a positive correlation with DGLA. 2) The EPA/AA ratio was the only independent factor related to hMVRI in multivariate regression analysis. 3) The low EPA/AA group had significantly higher hMVRI than the high EPA/AA group. 4) The EPA/AA ratio had a significant relationship with APV at hyperemia but not with Pd at hyperemia. 5) The traditional risk factors and CRP were not associated

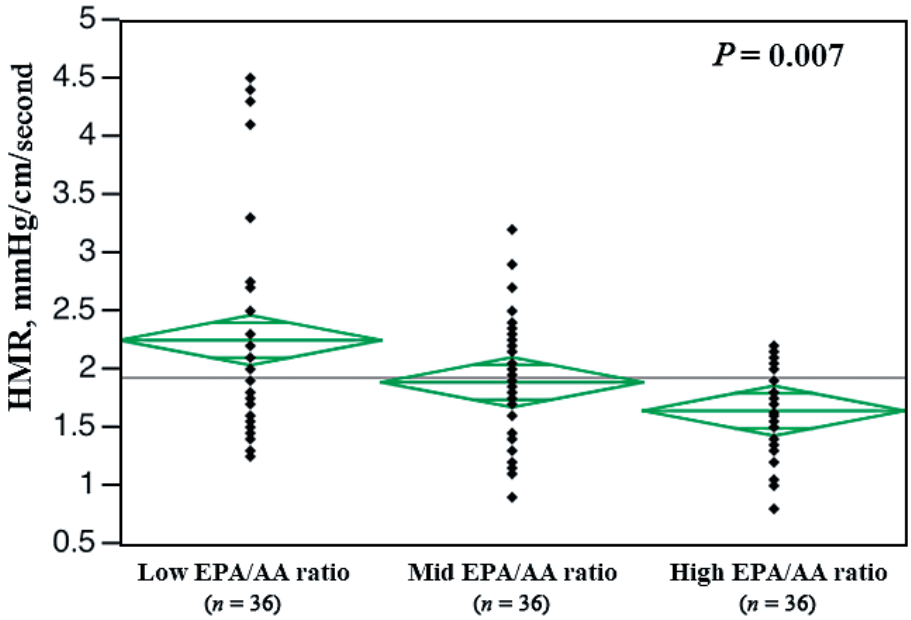

Figure 2. Comparison of hMVRI among patients by the tertiles of the EPA/AA ratio. The hMVRI increases significantly from the lowest to the highest tertiles of the EPA/AA ratio ($P = 0.01$). hMVRI indicates hyperemic microvascular resistance index; and EPA/AA, eicosapentaenoic acid/arachidonic acid.

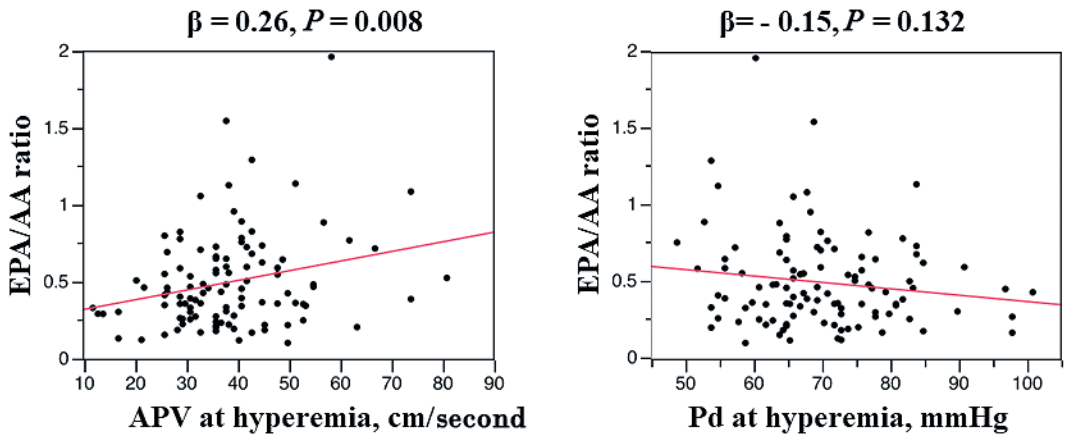

Figure 3. Association between the EPA/AA ratio and APV at hyperemia on univariate analysis. There is a significantly positive correlation between the EPA/AA ratio and APV at hyperemia, but not APV at rest and Pd at hyperemia. APV indicates average peak velocity; Pd, mean distal coronary pressure; and EPA/AA, eicosapentaenoic acid/arachidonic acid.

with hMVRI.

These results suggest that EPA (EPA/AA) may play a pivotal role in the coronary microcirculation of patients with stable CAD, exert relatively good control on the traditional risk factors, and preserve LV function.

Previous studies showed that the impairment of microcirculation was one of the important independent predictors of the prognosis of long-term cardiovascular diseases in healthy volunteers, patients with stable CAD, and patients with ST elevation myocardial infarction.[11,13-17] The microcirculation was evaluated by different methods and different indices as follows: coronary flow reserve (CFR) by perfusion positron emission tomography, phase-contrast cine cardiovascular magnetic resonance, or transthoracic Doppler echocardiography and coronary flow velocity reserve (CFVR); or hMVRI or IMR by cardiac catheterization.[11,13-25,29-31]

Chamuleau *et al.*[16] suggested that CFVR had a prognostic value that is superior to myocardial perfusion scintigraphy in stable CAD patients with moderate stenoses in multiple vessels. Moreover, Pepine, *et al.*[17] reported that in women with signs and symptoms of ischemia, coronary microvascular reactivity to adenosine was more important in the prediction of major adverse cardiac events (MACEs) than angiographic coronary artery severity or CAD risk factors.

Herzog, *et al.*[11] reported that abnormal CFR was associated with a significantly increased MACE rate com-

pared with normal CFR. Van de Hoef, *et al*.[13] reported that the discordance of CFVR with FFR originates from the involvement of the coronary microvasculature and that impaired reference CFVR in patients with stable CAD is associated with a significant increase in fatal events at long-term follow-up. However, CFVR is defined as the capacity of the epicardial coronary arteries and coronary microvascular circulation, and hMVRI, which is similar to IMR, is a quantitative and specific index for the coronary microvascular circulation. Furthermore, hMVRI almost does not change with epicardial coronary stenosis severity when collateral flow is properly taken into account.[19,20] Verhoeff, *et al*.[23] reported that the collateral flow effect on hMVRI is minimal in patients with FFR > 0.8. Thus, hMVRI was used for the evaluation of coronary microcirculation in the present study of cases with FFR > 0.8.

There have been two large previous studies on the association between the EPA/AA ratio and MACEs.[9,10] The JELIS study,[10] which evaluated the effects of the addition of EPA to statin therapy in hypercholesterolemic patients, demonstrated that a decreased EPA/AA ratio was significantly associated with increased cardiac death and that an increased EPA/AA ratio induced a 19% reduction of MACEs. Another study called the GISSI-Prevenzione trial[9] showed that dietary ω-3 PUFA intake significantly prevented cardiovascular death and sudden death in patients with recent myocardial infarction (< 3 months). Furthermore, Domei, *et al*.[32] reported that among the PUFA parameters, only high EPA/AA ratio (> 0.4037) had a significant association with low MACE incidence in patients undergoing PCI. However, although both CMD and omega-3 PUFAs are associated with MACEs in ischemic heart disease, little is known about the relationship between CMD and omega-3 PUFAs in stable CAD.

Only one report showed that CFR was significantly positively correlated with serum EPA in CAD patients with less than 50% angiographic stenosis by phase-contrast cine cardiovascular magnetic resonance induced by ATP infusion; this result shows that serum EPA plays an important role in the regulation of CFR in patients with CAD.[18] We demonstrated similar results for the association between EPA and CMD, i.e., hMVRI by coronary catheter procedure in CAD patients with FFR > 0.8. Moreover, Oe, *et al*.[31] performed transthoracic Doppler echocardiography on elderly Japanese individuals and reported that PUFA supplementation (AA and DHA) for three months increased CFVR. Shimokawa, *et al*.[33] reported that dietary omega-3 PUFAs augment endothelium-dependent relaxation to bradykinin in the coronary microvessels of a pig. Recently, O'Connell *et al*.[34] reported that omega-3 PUFAs prevent interstitial fibrosis and microvascular rarefaction via free fatty acid receptor 4. These results indicate that PUFAs are related to coronary microcirculation.

Although the relationships between CMD and coronary risk factors such as DM, dyslipidemia, and hypertension have also been reported previously,[24,29,30] hMVRI had no significant correlation with these coronary risk factors in the present study. These diseases were well controlled in patients in this study by using antihypertensive drugs including calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, statins, and anti-DM treatment. Thus, we suggested that the EPA/AA ratio is also important as a residual risk factor for CMD and epicardial CAD.[9,10,35]

The precise mechanisms of the effect of omega-3 PUFAs on the improvement of coronary microvascular function has remained unknown even though previous studies have proposed the following beneficial effects of omega-3 PUFAs on coronary microcirculation: the influence on the biophysical changes of the cell membrane to affect membrane function via ion channels and signal transduction,[36] the augmentation of endothelium-derived relaxation, and the inhibition of endothelium-derived contraction.[33]

Omega-3 PUFAs directly affect endothelial-derived vasodilatation by reducing vascular oxidative stress and inflammation and endothelial-independent vasodilatation by stimulating smooth muscle cells.[5]

This study demonstrated that the EPA/AA ratio was significantly positively associated with APV at hyperemia but not with Pd at hyperemia by using papaverine, which is known to produce vasodilatation via the direct relaxation of arteriolar smooth muscle. Furthermore, CRP was not related to microcirculation. These findings suggest that EPA (EPA/AA) may improve the reactivity of coronary microcirculation via the relaxation of arteriolar smooth muscle cells.

Previous studies demonstrated that treatment with omega-3 PUFAs have beneficial effects on acute myocardial infarction (AMI) (e.g., reduction of myocardial infarct size)[37] and can improve left ventricular remodeling via the suppression of inflammation during the convalescent healing phase.[38] Previous reports have described the secondary prevention of sudden cardiac death and ventricular arrhythmias after myocardial infarction or heart failure via the use of omega-3 PUFAs.[39] The cardioprotective effects of ω-3 PUFAs are thought to be due to synergism among multiple mechanisms.[36]

The results of previous studies and those of the present study suggest that the improvement of coronary microcirculation by EPA may protect against microvascular ischemia or reperfusion injury when AMI occurs in patients with stable AP.

In conclusion, the EPA/AA ratio affects coronary microvascular function and epicardial coronary artery function and may play an important role in cardioprotection in patients with stable CAD.

Study limitations: First, this study involved a relatively small study population and was performed at a single facility.

Second, the effects of EPA administration on hMVRI were not examined. Further investigations are needed to elucidate the direct effects of EPA administration on hMVRI improvement and the prognosis of stable CAD patients.

Disclosures

Conflicts of interest: None.

References

1. Swanson D, Block R, Mousa SA. Omega-3 fatty acids EPA and DHA: health benefits throughout life. Adv Nutr 2013; 3: 1-7.
2. Hulbert AJ, Turner N, Storlien LH, Else PL. Dietary fats and membrane function: implications for metabolism and disease. Biol Rev Camb Philos Soc 2005; 80: 155-69.
3. Sun C, Alkhoury K, Wang YI, *et al*. IRF-1 and miRNA126 modulate VCAM-1 expression in response to a high-fat meal. Circ Res 2012; 111: 1054-64.
4. Wang Q, Liang X, Wang L, *et al*. Effect of omega-3 fatty acids supplementation on endothelial function: a meta-analysis of randomized controlled trials. Atherosclerosis 2012; 221: 536-43.
5. Din JN, Newby DE, Flapan AD. Omega 3 fatty acids and cardiovascular disease-fishing for a natural treatment. BMJ 2004; 3: 30-5.
6. Jakobsen MU, O'Reilly EJ, Heitmann BL, *et al*. Major types of dietary fat and risk of coronary heart disease: a pooled analysis of 11 cohort studies. Am J Clin Nutr 2009; 89: 1425-32.
7. Phang M, Lincz LF, Gayg ML. Eicosapentaenoic and docosahexaenoic acid supplementations reduce platelet aggregation and hemostatic markers differentially in men and women. J Nutr 2013; 143: 457-63.
8. Thies F, Garry JM, Yaqoob P, *et al*. Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: a randomized controlled trial. Lancet 2003; 361: 477-85.
9. Marchioli R, Barzi F, Bomba E, *et al*. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Soprvvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. Ciculation 2002; 105: 1897-903.
10. Yokoyama M, Origasa H, Matsuzaki M, *et al*. Effect of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomized open-label, blinded endpoint analysis. Lancet 2007; 369: 1090-8.
11. Herzog BA, Husmann L, Valenta I, *et al*. Long-term prognostic value of 13N-ammonia myocardial perfusion positron emission tomography added value of coronary flow reserve. J Am Coll Cardiol 2009; 54: 150-6.
12. Kurisu S, Shimonaga T, Iwasaki T, *et al*. Effects of ezetimibe on serum polyunsaturated fatty acids in patients with coronary artery disease. Int Heart J 2013; 54: 254-7.
13. Van de Hoef TP, van Lavieren MA, Damman P, *et al*. Physiological basis and long-term clinical outcome of discordance between fractional flow reserve and coronary flow velocity reserve in coronary stenoses of intermediate severity. Circ Cardiovasc Interv 2014; 7: 301-11.
14. Fearon WF, Low AF, Yong AS, *et al*. Prognostic value of the index of microcirculatory resistance measured after primary percutaneous coronary intervention. Circulation 2013; 127: 2436-41.
15. Van de Hoef TP, Bax M, Damman P, *et al*. Impaired coronary autoregulation is associated with long-term fatal events in patients with stable coronary artery disease. Circ Cardiovasc Interv 2013; 6: 329-35.
16. Chamuleau SA, Tio RA, de Cock CC, *et al*. Prognostic value of coronary blood flow velocity and myocardial perfusion in intermediate coronary narrowings and multivessel disease. J Am Coll Cardiol 2002; 39: 852-8.
17. Pepine CJ, Anderson RD, Sharaf BL, *et al*. Coronary microvascular reactivity to adenosine predicts adverse outcome in women evaluated for suspected ischemia results from the national heart, lung and blood institute WISE (Women's Ischemia Syndrome Evaluation) study. J Am Coll Cardiol 2010; 22: 2825-32.
18. Kato S, Fukui K, Kawaguchi J, *et al*. Relationship between coronary flow reserve evaluated by phase-contrast cine cardiovascular magnetic resonance and serum eicosapentaenoic acid. J Cardiovasc Magn Reson 2013; 15: 106.
19. Fearon WF, Balsam LB, Farouque HM, *et al*. Novel index for invasively assessing the coronary microcirculation. Circulation 2003; 107: 3129-32.
20. Aarmoudse W, Fearon WF, Manoharan G, *et al*. Epicardial stenosis severity does not affect minimal microcirculatory resistance. Circulation 2004; 110: 2137-42.
21. Lee JM, Layland J, Jung JH, *et al*. Integrated physiologic assessment of ischemic heart disease in real-world practice using index of microcirculatory resistance and fractional flow reserve. Circ Cardiovasc Interv 2015; 8: e002857.
22. Murai T, Lee T, Yonetsu T, *et al*. Variability of microcirculatory resistance index and its relationship with fractional flow reserve in patients with intermediate coronary artery lesions. Circ J 2013; 77: 1769-76.
23. Verhoeff BJ, van de Hoef TP, Spaan JA, Piek JJ, Siebes M. Minimal effect of collateral flow on coronary microvascular resistance in the presence of intermediate and noncritical coronary stenoses. Am J Physiol Heart Circ Physiol 2012; 303: H422-8.
24. Picchi A, Limbruno U, Focardi M, *et al*. Increased basal coronary blood flow as a cause of reduced coronary flow reserve in diabetic patients. Am J Physiol Heart Circ Physiol 2011; 301: H2279-84.
25. Yamanaga K, Tsujita K, Komura N, *et al*. Single-wire pressure and flow velocity measurement for quantifying microvascular dysfunction in patients with coronary vasospastic angina. Am J Physiol Heart Circ Physiol 2015; 308: H478-84.
26. Lee BK, Lim HS, Fearon WF, *et al*. Invasive evaluation of patients with angina in the absence of obstructive coronary artery disease. Circulation 2015; 131: 1054-60.
27. Montalescot G, Sechtem U, Achenbach S, *et al*. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 2013; 34: 2949-3003.
28. Lang RM, Bierig M, Devereux RB, *et al*. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiography 2005; 18: 1440-63.
29. Kaufmann PA, Gnecchi-Ruscone T, Schäfers KP, Lüscher TF, Camici PG. Low density lipoprotein cholesterol and coronary microvascular dysfunction in hypercholesterolemia. J Am Coll Cardiol 2000; 36: 103-9.
30. Mizuno R, Fujimoto S, Saito Y, Okamoto Y. Optimal antihypertensive level for improvement of coronary microvascular dysfunction: the lower, the better? Hypertension 2012; 60: 326-32.
31. Oe H, Hozumi T, Murata E, *et al*. Arachidonic acid and docosahexaenoic acid supplementation increases coronary flow velocity reserve in Japanese elderly individuals. Heart 2008; 94: 316-21.
32. Domei T, Yokoi H, Kuramitsu S, *et al*. Ratio of serum n-3 to n-6 polyunsaturated fatty acids and the incidence of major adverse cardiac events in patients undergoing percutaneous coronary intervention. Circ J 2012; 76: 423-9.
33. Shimokawa H, Aarthus LL, Vanhoutte PM. Dietary omega 3 polyunsaturated fatty acids augment endothelium-dependent relaxation to bradykinin in coronary microvessels of the pig. Br J Pharmacol 1988; 95: 1191-6.
34. O'Connell TD, Block RC, Huang SP. ω3-polyunsaturated fatty acids for heart failure: effects of does on efficacy and novel signaling through free fatty acid receptors 4. J Mol Cell Cardiol 2017; 103: 74-92.
35. Shimada T, Kadota K, Eguchi H, *et al*. Relationship between n-3 polyunsaturated fatty acids and extent of vessel disease in patients with ST elevation myocardial infarction. Int Heart J 2017; 58: 868-73.
36. Adkins Y, Kelley DS. Mechanisms underlying the cardioprotective effects of omega-3 polyunsaturated fatty acids. J Nutr Biochem 2010; 21: 781-92.

37. Oskarsson HJ, Godwin J, Gunnar RM, Thomas JX Jr. Dietary fish oil supplementation reduces myocardial infarct size in a canine model of ischemia and reperfusion. J Am Coll Cardiol 1993; 21: 1280-5.
38. Heydari B, Abdullah S, Pottala JV, *et al*. Effect of omega-3 acid ethyl esters on left ventricular remodeling after acute myocardial infarction: The OMEGA-REMODEL randomized clinical trial. Circulation 2016; 134: 378-91.
39. Yagi S, Soeki T, Aihara KI, *et al*. Low Serum Levels of Eicosapentaenoic Acid and Docosahexaenoic Acid are Risk Factors for Cardiogenic Syncope in Patients with Brugada Syndrome. Int Heart J 2017; 58: 720-3.