Relationship Between Coronary Plaque Vulnerability and Serum n-3/n-6 Polyunsaturated Fatty Acid Ratio

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Background: A low ratio of serum eicosapentaenoic acid to arachidonic acid (EPA/AA) has been associated with cardiovascular events. Higher-grade yellow color coronary plaques are associated with higher plaque vulnerability and higher thrombogenic potential. Therefore, the association between EPA/AA ratio and yellow color grade of coronary plaques was examined.

Methods and Results: Consecutive patients (n=54) who underwent percutaneous coronary intervention were enrolled in this study. The serum EPA/AA ratio was examined on admission. All patients underwent an angioscopic examination of the culprit vessel to examine the color grade of yellow plaques (0, white; 1, slight yellow; 2, yellow; and 3, intense yellow) and the presence of thrombus. Excluding 16 patients with acute coronary syndrome (ACS), 38 patients with stable angina were divided into 2 groups according to their EPA/AA ratio: the low EPA/AA group (n=19, EPA/AA ratio <0.37 [median]) and the high EPA/AA group (n=19, EPA/AA ratio ≥0.37). The maximum color grade (2.5 ± 0.5 vs. 1.9 ± 0.9 ; $P=0.01$) of yellow plaques was significantly higher and the number of non-culprit yellow plaques with thrombus (1.7 ± 0.8 vs. 1.2 ± 1.1 ; $P=0.06$) tended to be higher in low EPA/AA than in high EPA/AA stable angina patients. Multivariate analysis revealed that the serum EPA level (odds ratio=0.98, 95% confidence interval=0.96–0.99, $P=0.03$) was associated with the presence of grade-3 yellow plaques.

Conclusions: A low serum EPA level and a low EPA/AA ratio was associated with high vulnerability of coronary plaques. (*Circ J* 2011; **75**: 2432–2438)

Key Words: Angioscopy; Eicosapentaenoic acid to arachidonic acid ratio; Plaque vulnerability; Thrombus; Yellow plaque

Previous reports have shown that consumption of fish or fish-oil could protect against cardiovascular events, especially acute coronary syndrome (ACS). Epidemiological and clinical evidence suggests that long-term intake of long-chain n-3 polyunsaturated fatty acids, especially eicosapentaenoic acid (EPA), plays an important role in improving mortality associated with coronary artery disease.^{1–3} A high serum ratio of EPA to arachidonic acid (AA; long-chain n-6 polyunsaturated fatty acids) has been associated with a lower incidence of future cardiovascular events and a better outcome.^{1,2,4–6} Furthermore, medication with purified EPA has been demonstrated to reduce future cardiovascular events.^{7–10}

A major cause of ACS is the disruption of vulnerable plaques and thrombosis. The vulnerability of coronary plaques is determined mainly by the thickness of the fibrous cap; and the yellow color grade of plaques is inversely associated with the thickness

of the fibrous cap and is also directly associated with the frequency of plaques with thrombus.^{11–13} Furthermore, the disrupted yellow plaques are detected at the ACS culprit lesions in >90% of cases and thus, yellow plaques are supposed to include both rupture-prone and erosion-prone vulnerable plaques.^{14–16}

Therefore, in the present study, we examined the association between the serum EPA/AA ratio and plaque vulnerability evaluated by coronary angiography.

Methods

Study Patients

Consecutive patients (n=54) who underwent percutaneous coronary intervention (PCI) and a coronary angiographic examination from April 2009 to March 2010 were included in this study. Excluding 16 ACS patients, we divided patients with stable angina into 2 groups according to their serum EPA/AA

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Table. Patient Characteristics

	ACS	Stable angina			P value*
		All	Low EPA/AA	High EPA/AA	
Number of patients	16	38	19	19	
Male gender, n (%)	12 (75)	30 (79)	14 (73)	16 (84)	0.42
Age, years	66±9	69±8	67±7	70±8	0.32
Coronary risk factors, n (%)					
Current smoking	12 (75)	28 (73)	15 (79)	13 (68)	0.46
Hypertension	8 (50)	27 (71)	12 (63)	15 (79)	0.28
Dislipidemia	11 (68)	28 (73)	13 (68)	15 (79)	0.46
Diabetes mellitus	3 (18)	18 (47)	11 (58)	7 (36)	0.19
Prior history of ACS, n (%)	2 (13)	18 (47)	9 (47)	9 (47)	1.0
Medications, n (%)					
Aspirin	2 (12)	28 (73)	13 (68)	15 (79)	0.46
Ticlopidine/Clopidogrel	1 (6)	17 (45)	8 (42)	9 (47)	0.74
Statin	3 (18)	24 (63)	15 (79)	13 (68)	0.46
ACEI/ARB	1 (6)	20 (52)	9 (47)	11 (58)	0.51
β-blocker	1 (6)	18 (47)	8 (42)	10 (52)	0.51
Serum lipid profile, mg/dl					
Total cholesterol	211±39	176±24	171±19	182±27	0.15
LDL cholesterol	133±30	99±21	102±21	95±22	0.32
HDL cholesterol	45±10	45±9	44±8	46±9	0.43
Triglyceride	166±90	185±127	148±62	221±62	0.07
LDL/HDL ratio	3.03±0.86	2.24±0.58	2.36±0.56	2.11±0.59	0.19
Polyunsaturated fatty acid, μg/ml					
EPA	63.0±41	68.1±40	36.3±15	99.9±30	<0.001
AA	147±307	165±30	170±26	160±34	0.31
DHA	186±30	139±50	112±34	166±50	<0.001
DHLA	33±10	37±10	41±10	32±9	0.002
EPA/AA ratio	0.46±0.34	0.42±0.26	0.21±0.08	0.63±0.20	–
C-reactive protein, mg/dl	0.21±0.23	0.19±0.31	0.22±0.37	0.17±0.24	0.58
Culprit vessel, n (%)					0.35
LAD	11 (69)	12 (32)	4 (21)	8 (42)	
LCX	0 (0)	3 (8)	2 (10)	1 (5)	
RCA	5 (31)	23 (60)	13 (69)	10 (53)	
Culprit lesion					
Diameter stenosis (%)	97±4	88±15	88±15	87±16	0.82
AHA/ACC classification type B2/C, n (%)	11 (69)	25 (66)	13 (68)	12 (63)	0.73
Diagnosis, n (%)					–
Stable angina	0 (0)	38 (100)	19 (100)	19 (100)	
Unstable angina	5 (31)	0 (0)	0 (0)	0 (0)	
NSTEMI	4 (25)	0 (0)	0 (0)	0 (0)	
STEMI	7 (44)	0 (0)	0 (0)	0 (0)	

*Patients with low vs. high EPA/AA ratio among stable angina patients.

ACS, acute coronary syndrome; EPA/AA, eicosapentaenoic acid (EPA) to arachidonic acid (AA); ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; LDL, low-density lipoprotein; HDL, high-density lipoprotein; DHA, docosahexaenoic acid; DHLA, dihomogamma-linolenic acid; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; NSTEMI, non-ST segment elevation myocardial infarction; STEMI, ST segment elevation myocardial infarction.

ratio: patients with a low EPA/AA ratio (n=19, EPA/AA ratio <0.37 [median]) and patients with a high EPA/AA ratio (n=19, EPA/AA ratio ≥0.37 [median]). Angioscopic findings were compared between these 2 groups. The data of ACS patients were also presented as a reference.

Blood samples were acquired from all patients in a fasting state on admission to measure polyunsaturated fatty acids, that is, EPA, AA, docosahexaenoic acid (DHA), and dihomogamma-linolenic acid (DHLA). The measurement was performed by gas chromatography at the central laboratory (SRL,

Tokyo, Japan) using a gas chromatograph (GC-2010; Shimadzu, Kyoto, Japan) and a capillary column (BPX90; Wako, Osaka, Japan).

ACS includes acute MI defined by The Joint European Society of Cardiology/American College of Cardiology Committee and unstable angina, defined according to the Braunwald classification. Hypertensive patients were defined as those with a systemic arterial pressure of >140/90 mmHg or those already taking anti-hypertensive drugs. Diabetic patients were defined as those with a fasting blood glucose of >126 mg/dl or those

Figure 1. A representative case from the acute coronary syndrome patient group, the low eicosapentaenoic acid to arachidonic acid (EPA/AA) stable angina patient group, and the high EPA/AA stable angina patient group. **(A)** An angioscopic image of a stented culprit lesion (red arrow) in the patients with anterior acute myocardial infarction (AMI). Grade-3 yellow plaque with red thrombus was observed at the culprit lesion in the proximal left anterior descending coronary artery. The maximum yellow color grade was 3 and the number of non-culprit yellow plaques with thrombus was 6. The EPA/AA ratio was 0.30. **(B)** An angioscopic image of a stented culprit lesion (red arrow) in the stable angina patients with a high EPA/AA ratio. A white (grade-0) vessel wall was observed and no yellow plaque was detected in the vessel. The maximum yellow color grade was 0 and the number of non-culprit yellow plaques with thrombus was 0. The EPA/AA ratio was 0.82. **(C)** An angioscopic image of yellow plaque in the non-culprit segments (yellow arrow) in the stable angina patients with a low EPA/AA ratio. Grade-3 yellow plaque with thrombus was observed in the non-culprit segment. The maximum yellow color grade was 3 and the number of non-culprit yellow plaques with thrombus was 1. The EPA/AA ratio was 0.23.

already taking oral drugs for diabetes mellitus or receiving insulin therapy. Patients with dyslipidemia were defined as those with a LDL cholesterol >140 mg/dl, HDL cholesterol <40 mg/dl, triglyceride >150 mg/dl or those already taking lipid-lowering drugs. No patients in the present study were taking the purified EPA drug, ethyl eicosapentate. Written informed consent was acquired from all patients. This protocol was approved by the Osaka Police Hospital Ethical Committee.

Coronary Intervention and Angioscopic Examination

Catheterization was performed by a femoral, brachial, or radial artery approach using a 6- or 7-Fr sheath and catheters. Intravenous heparin (100 U/kg) was administered at the beginning of catheterization, and an additional dose was repeated at the time of PCI as a routine protocol in our hospital. An angioscopic examination was performed after stent implantation at the culprit lesion. Oral aspirin (100 mg/day) and ticlopidine (75 mg/day) were started as soon as possible in the stable angina patients. A loading dose of oral aspirin (300 mg) and ticlopidine (300 mg)

were administered before catheterization in the ACS patients.

An angioscopic examination of the whole culprit vessel was performed to evaluate yellow plaques. The angioscope RX-3310A and MV-5010A (Machida, Tokyo, Japan) and optic fiber DAG-2218LN (Machida) were used. Angioscopic observations were made while blood was cleared away from view by the injection of 3% dextran-40, as previously reported.¹⁷ The color grade of detected yellow plaques was determined according to the standard colors (0, white; 1, slight yellow; 2, yellow; and 3, intensive yellow), as previously reported.¹⁴ The number of detected yellow plaques and maximum color grade of those plaques were determined for each patient. The presence or absence of thrombus adhering to the plaques was also determined, and the number of non-culprit yellow plaques with thrombus was counted for each patient. The presence or absence of thrombus at the culprit yellow plaques was excluded from analysis as it might be influenced by the PCI procedures. Thrombus was defined as white or red material that had a cotton-like or ragged appearance or that presented fragmentation

with or without protrusion into the lumen or was adherent to the luminal surface. Angioscopic images were evaluated by 2 experienced observers who were unaware of the patients' background. In the case of disagreement, a joint reading was performed and a consensus decision was reached. The inter- and intra-observer reproducibility for the interpretation of angioscopic images was 85% and 95% for plaque color, and 90% and 100% for thrombus, respectively.

Statistical Analysis

Continuous data were presented as mean $\pm$ SD. Comparisons between low and high EPA/AA groups were done by using an unpaired Student's t-test or a chi-square test. Multivariate step-

wise logistic regression analysis was performed to analyze the factors associated with the presence of grade-3 yellow plaque (maximum color grade=3) among EPA, AA, DHA, LDL cholesterol, HDL cholesterol, and C-reactive protein. The ACS group was presented only as a reference and was not included in any statistical analysis. A P value <0.05 was regarded as statistically significant. Analysis was done with Dr SPSS II for Windows (SPSS Japan Inc, Tokyo, Japan).

Results

Patients' characteristics are presented in [Table](#). Among stable angina patients, the EPA and EPA/AA ratio and also the DHA

level was significantly lower in the low than in the high EPA/AA group. No other background factors were different between the low and high EPA/AA groups. Representative cases from 3 groups of patients (ACS patients, low EPA/AA stable angina patients, and high EPA/AA stable angina patients) are presented in [Figure 1](#).

The number of detected yellow plaques was not different between the low and the high EPA/AA ratio stable angina patients (3.1 ± 1.6 vs. 3.0 ± 2.3 , $P=0.4$), while it was 4.5 ± 2.6 in ACS patients. The maximum color grade (2.5 ± 0.5 vs. 1.9 ± 0.9 ; $P=0.01$) of yellow plaques was significantly higher in the low than in the high EPA/AA stable angina patients ([Figure 2A](#)), while it was 2.7 ± 0.5 in ACS patients. The number of plaques

with thrombus (1.7 ± 0.8 vs. 1.2 ± 1.1 ; $P=0.06$) in the non-culprit segments tended to be larger in the low than in the high EPA/AA stable angina patients ([Figure 2B](#)), while it was 2.1 ± 1.7 in ACS patients.

The maximum color grade had a weak but significant correlation with EPA ($R=-0.40$, $P=0.006$), EPA/AA ratio ($R=-0.29$, $P=0.03$), and DHA ($R=-0.40$, $P=0.007$). The correlation between maximum color grade and EPA/AA ratio is presented as scatter plot in [Figure 3](#). The number of plaques with thrombus in the non-culprit segments also had a weak but significant correlation with EPA ($R=-0.45$, $P=0.002$), EPA/AA ratio ($R=-0.37$, $P=0.01$), and DHA ($R=-0.27$, $P=0.04$).

Multivariate analysis revealed that the serum EPA level

(odds ratio=0.98, 95% confidence interval=0.96–0.99, $P=0.03$) was significantly associated with the presence of grade-3 yellow plaque (maximum color grade=3), when EPA, AA, DHA, LDL cholesterol, HDL cholesterol, and C-reactive protein were included in the analysis.

Discussion

In the present study, we evaluated coronary plaque vulnerability by the maximum color grade of yellow plaques and the number of already thrombogenic/disrupted yellow plaques in the non-culprit segments, and revealed its association with the EPA/AA ratio among stable angina patients. Additionally, the plaque vulnerability in low EPA/AA stable angina patients appeared similar to that in ACS patients.

The additive effect of EPA therapy and antiplatelet therapy has been reported.¹⁸ EPA therapy reduces serum small dense LDL and high sensitive C-reactive protein,^{19,20} and the anti-inflammatory effect of EPA is considered to be an important mechanism to protect against atherosclerotic disease.²¹ A majority of patients with stable angina were taking aspirin and statin and had a relatively low LDL cholesterol level in the present study; however, those patients with a low EPA/AA ratio had higher plaque vulnerability than those with a high EPA/AA ratio. Therefore, EPA therapy might contribute to the stabilization of coronary plaques and prevention of cardiovascular events through different mechanisms from statins or antiplatelet therapy.

Although the extent of atherosclerosis has been associated with the serum EPA level, as found by a study with coronary computed tomography,²² the present study would be the first to have examined the association between EPA/AA ratio and the level of plaque vulnerability. Judging from the result of multivariate analysis in which markers of serum fatty acid (EPA, AA, and DHA), cholesterol (LDL and HDL cholesterol), and inflammation (C-reactive protein) were included, a low serum EPA level was significantly associated with the presence of grade-3 yellow plaques, which are regarded as vulnerable plaques and compatible with thin-cap fibroatheroma.^{13,15} Although the correlation between maximum color grade and the EPA/AA ratio was weak, this weak correlation, judging from the scatter plot in [Figure 3](#), might be partly due to the lack of rather healthy patients who had low maximum color grade and a high EPA/AA ratio. Because maximum color grade is determined by multiple factors, it is not surprising that the correlation with each of them is weak. In the present study, LDL cholesterol was not significantly associated with the color grade by multivariate analysis. This might be because the level of serum LDL cholesterol was well controlled by statin treatment in the present study patients, as shown in [Table](#). We have previously demonstrated that statin treatment reduces the color grade of coronary plaques and that the reduction of color grade is not associated with the achieved LDL cholesterol level.²³ In ACS patients, all patients had rather high maximum color grades of 2 or 3, and there appeared to be no correlation between maximum color grade and EPA/AA ratio. Culprit and non-culprit yellow plaques in ACS patients are known to reduce their yellow color grade during follow up after the onset of ACS.^{14,24} Therefore, a low serum EPA level and a low EPA/AA ratio would be associated with high coronary plaque vulnerability; and EPA therapy might reduce cardiovascular events by stabilizing coronary plaques.

Study Limitations

The number of patients was too small in the present study to analyze adequately the contributing factors for the maximum

color grade. In particular, judging from the scatter plot in [Figure 3](#), healthy stable angina patients with a low maximum color grade and a high EPA/AA ratio would be required in order to strengthen our conclusion. This group of rather healthy patients who did not require PCI was not included in the present study because we included only the patients who received PCI as a study design. Therefore, our findings should be confirmed by further investigations. All 3 coronary vessels were not examined. An angiographic examination was performed after stent implantation so that the whole vessel could be observed; however, we excluded the evaluation of thrombus at the stented lesion to minimize the influence of a PCI procedure on the angiographic findings.

Conclusion

Low serum EPA level and a low EPA/AA ratio were associated with the high vulnerability of coronary plaques.

Disclosures

None.

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