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Original article

Low eicosapentaenoic acid to arachidonic acid ratio is associated with thin-cap fibroatheroma determined by optical coherence tomography

Yasushi Wakabayashi (MD)[a], Hiroshi Funayama (MD, PhD)[a,*], Yusuke Ugata (MD)[a], Yosuke Taniguchi (MD)[a], Hirotaka Hoshino (MD)[a], Junya Ako (MD, PhD, FJCC)[b], Shin-ichi Momomura (MD, PhD, FJCC)[a]

[a] Department of Cardiovascular Medicine, Saitama Medical Center, Jichi Medical University, Saitama, Japan
[b] Department of Cardiovascular Medicine, Kitasato University Hospital, Sagamihara, Japan

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ABSTRACT

Background: A low eicosapentaenoic acid (EPA)/arachidonic acid (AA) ratio is known to be associated with cardiovascular events. However, the relationship between the EPA/AA ratio and coronary plaque vulnerability assessed by optical coherence tomography (OCT) has not been examined thoroughly. This study examined the relationship between the EPA/AA ratio and coronary plaque vulnerability assessed by OCT in patients with acute coronary syndrome (ACS).

Methods: We evaluated 59 ACS patients who had undergone percutaneous coronary intervention using OCT. We divided them into 2 groups according to OCT findings—those with and without thin-cap fibroatheroma (TCFA)—and compared the EPA/AA ratio between the groups.

Results: We identified 32 and 27 patients with and without TCFA, respectively. The EPA/AA ratio was significantly lower in patients with TCFA than in those without TCFA [0.35, interquartile range (0.21–0.44) vs. 0.54, interquartile range (0.42–0.70); $p < 0.001$]. In multivariate logistic regression analysis, the EPA/AA ratio was an independent predictor of TCFA (odds ratio, 0.09; 95% confidence interval, 0.007–0.99; $p = 0.049$). The EPA/AA ratio and fibrous cap thickness showed a significant positive correlation (Spearman $\rho = 0.46$; $p < 0.001$). Furthermore, receiver operating characteristic curve analysis showed that an EPA/AA ratio < 0.46 could predict TCFA (81.3%, sensitivity; 74.1%, specificity).

Conclusions: A low serum EPA/AA ratio is significantly associated with coronary plaque vulnerability assessed by OCT in ACS patients.

Introduction

Eicosapentaenoic acid (EPA) is a member of a group of n-3 polyunsaturated fatty acids (PUFAs) derived from fish or fish oil. Epidemiologic data suggest that long-term intake of n-3 PUFAs plays an important role in reducing the occurrence of adverse cardiovascular events [1]. Furthermore, administration of purified EPA has been shown to be effective in the prevention of major coronary events [2]. On the other hand, arachidonic acid (AA) is classified under the category of n-6 PUFAs, and a low EPA/AA ratio is associated with a higher incidence of cardiac events [3,4]. In addition, the increment of EPA/AA ratio is reported to be associated with a reduction in the brachial-ankle pulse wave velocity that is a surrogate marker of atherosclerosis [5].

Acute coronary syndrome (ACS) is a critical cardiac event that leads to sudden cardiac death. Pathological studies suggest that ACS is caused by thrombotic coronary occlusion after the rupture of vulnerable plaques [6,7]. One of the morphological traits typically associated with vulnerable plaques is a thin fibrous cap, sized around <65 μm that is heavily infiltrated with macrophages and inflammatory cells [8]. Vascular inflammation is considered to play a key role in plaque vulnerability, and previous studies have found that serum inflammatory markers, such as high sensitive-C reactive protein (hs-CRP), are associated with the presence of vulnerable plaques [9–11]. In addition, consumption of n-3 PUFAs such as EPA has been reported to decrease plasma concentrations of inflammatory biomarkers [12].

Optical coherence tomography (OCT) is a safe and effective modality for visualizing various features of vulnerable plaques,

* Corresponding author at: 1-847 Amanuma, Omiya-ku, Saitama City, Saitama 330-8503, Japan. Tel.: +81 48 647 2111; fax: +81 48 648 5188.
E-mail address: funahiro@omiya.jichi.ac.jp (H. Funayama).

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including thin-cap fibroatheroma (TCFA) [13], and a lower EPA/AA ratio is reported to be associated with higher plaque vulnerability assessed by OCT in patients with stable angina pectoris [14]. However, the relationship between EPA/AA ratio and plaque vulnerability assessed by OCT in ACS patients has not been examined in detail. The purpose of this study was to compare the serum EPA/AA ratio between patients with and without TCFA as determined by OCT, and to investigate the relationship between the EPA/AA ratio and plaque vulnerability in patients with ACS.

Materials and methods

Study population

We identified 350 consecutive ACS patients who had a de novo culprit lesion and underwent percutaneous coronary intervention (PCI) between March 2008 and November 2011 at Saitama Medical Center, Jichi Medical University. Patients who did not undergo OCT ($n = 282$) were excluded, and 68 patients were selected as the study samples. They underwent OCT, which was performed by a single investigator (H. F.). Prior to performing OCT, the investigator applied the following exclusion criteria: significant left main coronary artery disease, ostial lesions, cardiogenic shock, the use of intra-aortic balloon pumping, chronic renal failure on hemodialysis, heavily calcified lesions, and failure to attain thrombolysis in myocardial infarction (TIMI) grade 3 coronary flow. We excluded 2 patients who had a history of treatment with oral purified EPA and 4 patients with missing serum PUFA data. In addition, 3 patients were excluded because we could not assess their plaque characteristics because of low-quality OCT images. Thus, data from 59 patients with ACS [ST-elevation myocardial infarction (STEMI) = 28; non-STEMI = 8; and unstable angina pectoris = 23] were used in the final analysis (Fig. 1). ACS was defined as acute myocardial infarction and unstable angina pectoris. Acute myocardial infarction was defined as elevated cardiac markers (i.e. creatine kinase-myocardial band or troponin T) along with chest pain persisting for >30 min, hospital arrival within 12 h of chest pain onset, new ST-T wave changes, or a new left bundle branch block on a 12-lead electrocardiogram [15]. Unstable angina pectoris was defined as the presence of angina at rest, occurring during the preceding 48 h with significant transient ischemic ST-segment and/or T-wave changes and without a significant increase in serum creatine kinase level (Braunwald class III-B). Hypertensive patients were defined as those with a systemic arterial pressure >140/90 mmHg or those already taking anti-hypertensive drugs. Diabetes patients were defined as those with fasting plasma glucose level >126 mg/dL, casual plasma glucose level ≥200 mg/dL, or those already taking oral drugs for diabetes mellitus or receiving insulin therapy. Patients with dyslipidemia were defined as those with levels of low-density lipoprotein cholesterol >140 mg/dL, high-density lipoprotein cholesterol <40 mg/dL, triglycerides >150 mg/dL, or those already taking lipid-lowering drugs. Patient data were obtained from medical records and analyzed retrospectively. The study protocol was approved by the Ethics Committee of Saitama Medical Center, Jichi Medical University.

Coronary angiography and intervention

Cardiac catheterization was performed via the femoral or radial artery using 6- or 7-Fr sheaths and catheters after a loading dose of oral aspirin (162 mg) and clopidogrel (300 mg) was administered. The culprit lesion was identified on the basis of coronary angiography, electrocardiography, and echocardiography findings. Intravenous heparin (100 U/kg) was administered before the coronary intervention, and an additional dose was repeated as a routine protocol in our hospital.

OCT image acquisition and analysis

OCT was performed at the culprit lesion. If the patient did not have TIMI grade 3 coronary flow, aspiration thrombectomy was performed before OCT image acquisition. We advanced a 0.016-inch OCT catheter (ImageWire; LightLab Imaging, Westford, MA, USA) to the distal end of the culprit lesion through a 4-Fr occlusion balloon catheter. In order to remove blood from the field of view, the coronary artery was occluded within 1 min using a balloon catheter at the proximal site of the artery, and Ringer's solution

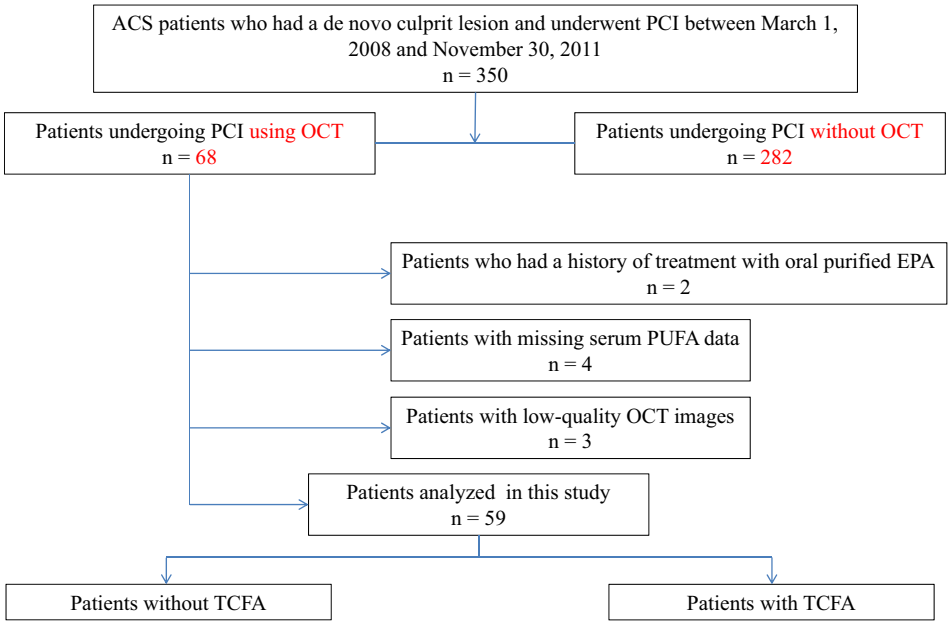

Fig. 1. Flowchart.
ACS, acute coronary syndrome; EPA, eicosapentaenoic acid; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; PUFA, polyunsaturated fatty acid; TCFA, thin-cap fibroatheroma.