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Relation	

Short-term Effects of Eicosapentaenoic Acid on P Wave Signal-Averaged Electrocardiogram in Patients with Coronary Artery Disease

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Short title: EPA and P-wave SAECG

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The antiarrhythmic properties of n-3 polyunsaturated fatty acids (PUFAs) have been demonstrated in experimental models and in patients with coronary artery disease [1-6]. On the other hand, the signal-averaged electrocardiogram (SAECG) of the P waves has been used to predict the development of atrial fibrillation by measuring the filtered P wave duration (FPD) as an index of atrial conduction delay with high accuracy [7-10]. In this study, we assessed whether key long-chain n-3 PUFA, eicosapentaenoic acid (EPA) affected parameters of P wave SAECG in patients with coronary artery disease.

The study population consisted of 27 patients with coronary artery disease who had episodes of suspected paroxysmal atrial fibrillation. They were treated with 1800 mg of EPA ethyl ester (EPADEL, Mochida Pharmaceutical, JAPAN) for 3 months [11,12]. Blood samples were collected before and 3 months after the administration of EPA.

Fatty acid analysis has been described in detail elsewhere [13-16]. Fatty acid composition in the methylated sample was analyzed by gas chromatography. We determined the levels of n-6 PUFAs (dihomo-γ-linolenic acid (DGLA) and arachidonic acid (AA)) and n-3 PUFAs (EPA and docosahexaenoic acid (DHA)).

The P wave SAECGs were obtained with a multipurpose electrocardiograph (FDX-6531, Fukuda Denshi Co., Tokyo) before and 3 months after the administration of EPA. P wave triggering signals for 500 beats during sinus rhythm were integrated. The P wave complexes from the three bipolar leads

were combined into a vector magnitude using the formula $(X^2+Y^2+Z^2)^{1/2}$. The onset and offset of the P waves were defined as the points where the voltage of the atrial signal exceeded 0.4 μV during the TP segment and returned to a level of 0.4 μV, respectively. The FPD and the root-mean-square voltage for the last 20 ms (RMS-20) in SAECG were measured in the vector magnitude.

Data are expressed as means±SD. The paired Student t test was used to compare the two sequential values during follow-up. Differences were considered significant at $p < 0.05$.

Patient characteristics are shown in Table 1. There were 18 male and 9 female patients with a mean age of 69±10 years. Left ventricular ejection fraction was 57.2±10.7 %. Left atrial diameter was 39.2±5.1 mm.

Serum lipid and PUFA levels before and after the treatment with EPA are shown in Table 2. The treatment with EPA increased the EPA level (51±18 μg/ml to 141±48 μg/ml, $p<0.001$). On the other hand, it decreased the GDLA level (34±12 μg/ml to 24±8 μg/ml, $p<0.001$) and the DHA level (163±38 μg/ml to 143±36 μg/ml, $p<0.001$).

There was a significant correlation between left atrial diameter and FPD before the treatment with EPA ($r=0.50$, $p<0.01$, Figure 1). The treatment with EPA did not affect FPD (122±22 ms to 123±20 ms, p=ns) as well as RMS-20 (5.12±3.21 μV to 5.12±3.00 μV, p=ns).

This study demonstrated that short-term treatment with EPA significantly

increased serum EPA level, but did not affect any parameter of P wave SAECG in patients with coronary artery disease.

The concept that n-3 PUFAs may have antiarrhythmic effects for human atrium is supported by basic sciences. Li et al reported that EPA and DHA inhibit I_{to}, I_{kur}, and I_{Na} in human atrial myocytes using a whole-cell patch voltage clamp technique [17]. Kitamura et al recently investigated the effects of EPA on atrial fibrillation associated with heart failure in a rabbit model and demonstrated that EPA might prevent atrial remodeling through the suppression of fibrosis [18]. P wave SAECG has been demonstrated to correlate with direct intra-atrial electrocardiographic recording [19,20]. This good correlation supports the notion that FPD serves as a surrogate marker of atrial conduction time. Nomura et al previously evaluated P wave SAECG in hypertensive patients with paroxysmal atrial fibrillation, and demonstrated that there was a significant correlation between FPD and procollagen C propeptide type I as a marker of cardiac fibrosis [21]. On the basis of their results, we hypothesized that EPA might affect P wave SAECG in patients with coronary artery disease. This study showed that oral administration of EPA for 3 months did not affect PFD as well as RMS-20 of P wave SAECG. There are several possible reasons for this discrepancy between experimental and our clinical studies. First, in experimental studies, cardiac fibrosis was induced by rapid ventricular pacing in rabbits [18] or transverse aortic constriction in mice [22]. On the other hand, in our study, most patients had preserved systolic function despite of coronary artery disease, and about half of patients were receiving angiotensin-converting

enzyme inhibitor or angiotensin II type 1 receptor blocker. These agents have been demonstrated to prevent cardiac fibrosis [21,23]. Thus, there was a possibility that atrial fibrosis was mild in our patients compared with those in experimental models. Second, in experimental studies, a dose of 300 mg/kg per day was often administered [18]. This dose was markedly high compared with the usual dose in humans. A dose of 1800 mg per day has been demonstrated to prevent major coronary events in clinical studies [12], but might not be enough to prevent atrial fibrosis.

There were several limitations in this study. First, we assessed the effect of EPA for 3 months, but long-term follow-up data were not obtained. Second, we did not assess the effect of higher doses of EPA. Finally, the small sample size is a major limitation and a larger study should be performed to confirm our findings.

In conclusion, short-term treatment with EPA significantly increased serum EPA level, but did not affect any parameter of P wave SAECG in patients with coronary artery disease.

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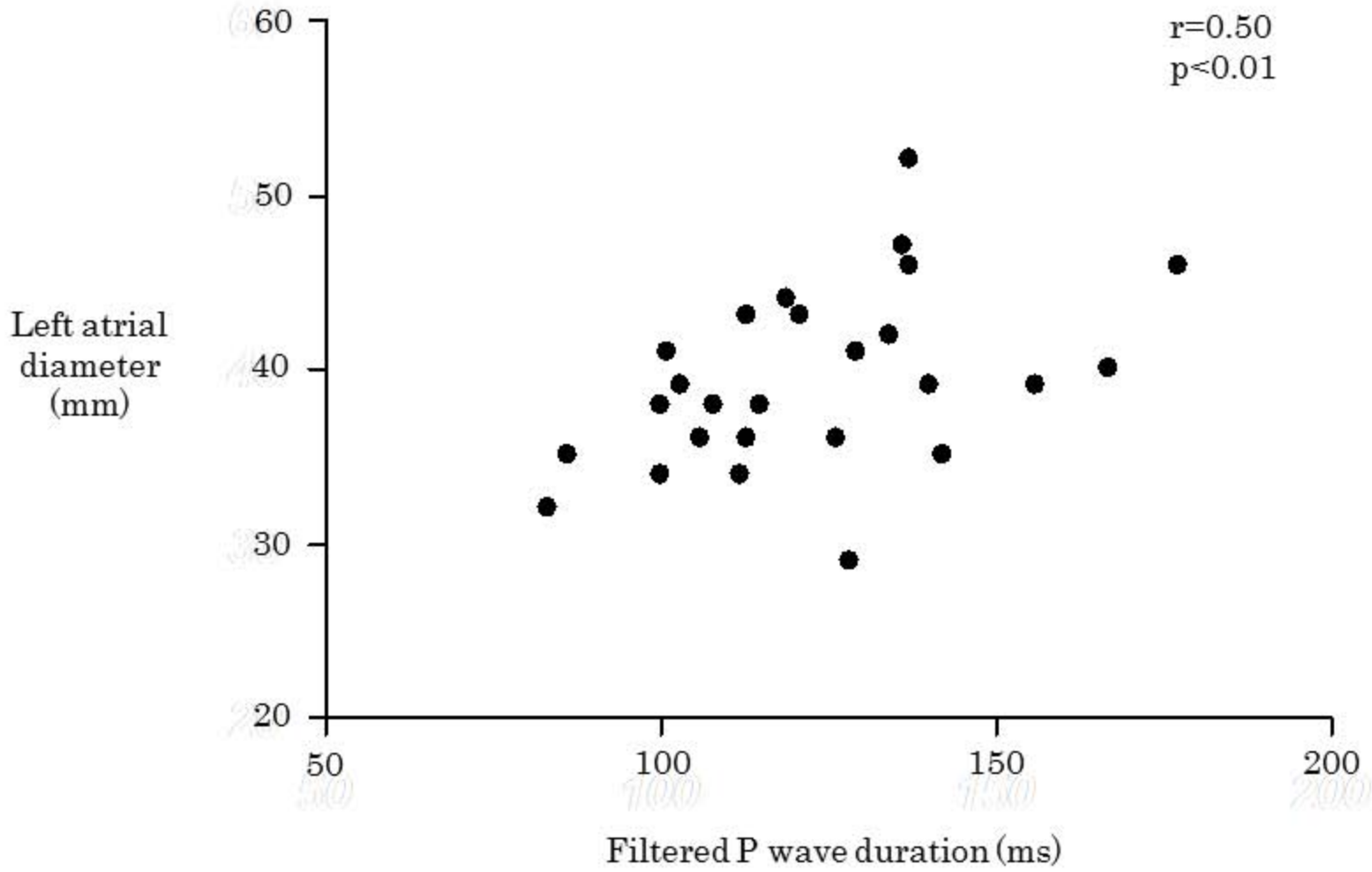
FIGURE LEGEND

Figure 1 There was a significant correlation between left atrial diameter and filtered P wave duration before the treatment with EPA ($r=0.50$, $p<0.01$).


r=0.50
p<0.01
Left atrial diameter (mm)
60
50
40
30
20
50
100
150
200
Filtered P wave duration (ms)

Number of patients	27
Male gender	18 (67%)
Age (years)	69±10
Diabetes	10 (37%)
Hypertension	15 (56%)
Prior myocardial infarction	8 (30%)
Prior coronary intervention	17 (63%)
Medications	
ACE-I or ARB	13 (48%)
Beta blocker	14 (52%)
Calcium channel blocker	14 (52%)
Aspirin	20 (74%)
Warfarin	4 (15%)
Statin	20 (74%)
Echocardiographic parameters	
Left ventricular end-diastolic diameter (mm	48.8±6.5
Left ventricular end-systolic diameter (mm)	34.1±8.2
Left ventricular ejection fraction (%)	57.2±10.7
Left atrial diameter (mm)	39.2±5.1

Table 1 Baseline characteristics

ACE-I, angiotensin-converting enzyme inhibitor;
ARB, angiotensin II type 1 receptor blocker.

	Before EPA ethyl ester	After EPA ethyl ester	p value
Low-density lipoprotein cholesterol (mg/dl)	96±31	92±30	ns
High-density lipoprotein cholesterol (mg/dl)	51±10	53±16	ns
Triglyceride (mg/dl)	147±78	137±87	ns
n-6 polyunsaturated fatty acid			
Dihomo-γ-linolenic acid (μg/ml)	34±12	24±8	<0.001
Arachidonic acid (μg/ml)	163±38	143±36	<0.001
n-3 polyunsaturated fatty acid			
Eicosapentaenoic acid (μg/ml)	51±18	141±48	<0.001
Docosahexaenoic acid (μg/ml)	130±37	118±46	ns
Ratio of EPA to AA	0.32±0.13	1.02±0.37	<0.001
P wave SAECG			
Filtered P wave duration (msec)	122±22	123±20	ns
Root-mean-square voltage for the last 20 ms (μ V	5.12±3.21	5.12±3.00	ns

Table 2 Serum lipid levels, polyunsaturated fatty acid levels and parameters of P wave SAECG before and after the administration of EPA ethyl ester

EPA, eicosapentaenoic acid; AA, arachidonic acid; SAECG, signal averaged electrocardiogram.