広島大学学術情報リポジトリ
Hiroshima University Institutional Repository

Title	Short-term Effects of Eicosapentaenoic Acid on P Wave Signal-Averaged Electrocardiogram in Patients with Coronary Artery Disease
Auther(s)	Kurisu, Satoshi; Kato, Yasuko; Mitsuba, Naoya; Ishibashi, Ken; Dohi, Yoshihiro; Nishioka, Kenji; Kihara, Yasuki
Citation	International journal of cardiology , 154 (2) : 200 - 202
Issue Date	2012
DOI	10.1016/j.ijcard.2011.10.068
Self DOI	
URL	http://ir.lib.hiroshima-u.ac.jp/00034795
Right	(c) 2012 Elsevier Ireland Ltd. All rights reserved.
Relation	

Hiroshima University Institutional Repository

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

Department of Cardiovascular Medicine, Hiroshima University Graduate School of Biomedical Sciences, Hiroshima, Japan

Satoshi Kurisu, Yasuko Kato, Naoya Mitsuba, Ken Ishibashi, Yoshihiro Dohi, Kenji Nishioka, Yasuki Kihara

Short title: EPA and P-wave SAECG

Correspondence to:

Satoshi Kurisu, MD

1-2-3, Kasumi-cho, Minami-ku,

Hiroshima, 734-8551, Japan

Phone:+81-82-257-5540

Fax:+81-82-257-1569

E-mail: skurisu@nifty.com

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.

REFERENCES

[1] Kang JX, Leaf A. Evidence that free polyunsaturated fatty acids modify Na+ channels by directly binding to the channel proteins. Proc Natl Acad Sci USA. 1996;93:3542-6.

[2] Christensen JH, Gustenhoff P, Korup E, et al. Effect of fish oil on heart rate variability in survivors of myocardial infarction: a double blind randomised controlled trial. BMJ 1996;312:677-8.

[3] Christensen JH, Korup E, Aaroe J, et al. Fish consumption, n-3 fatty acids in cell membranes, and heart rate variability in survivors of myocardial infarction with left ventricular dysfunction. Am J Cardiol 1997;79:1670-3.

[4] Leaf A, Kang JK, Xiao YF, Billman GE. Clinical prevention of sudden cardiac death by n-3 polyunsaturated fatty acids and mechanism of prevention of arrhythmias by n-3 fish oils. Circulation 2003;107:2646-52.

[5] Mozaffarian D, Stein PK, Prineas RJ, Siscovick DS. Dietary fish and omega-3 fatty acid consumption and heart rate variability in US adults. Circulation 2008;117:1130-7.

[6] Mozzaffarian D, Psaty BM, Rimm EB, et al. Fish intake and risk of incident atrial fibrillation. Circulation 2004;110:368-73.

[7] Guidera SA, Steinberg JS. The signal averaged P wave duration: a rapid and noninvasive marker of risk of atrial fibrillation. J Am Coll Cardiol 1993;21:1645-51.

[8] Montereggi A, Marconi P, Olivotto L, at al. Signal-averaged P-wave duration and risk of paroxysmal atrial fibrillation in hyperthyroidism. Am J

Cardiol 1996;77:266-269.

[9] Yamada T, Fukumani M, Shimonagata T, et al. Prediction of paroxysmal atrial fibrillation in patients with congestive heart failure: a prpspective study. J Am Coll Cardiol 2000;35:405-13.

[10] Darbar D, Jahangir A, Hammill SC, Gersh BJ. P wave signal-averaged electrocardiography to identify risk for atrial fibrillation. PACE 2002;25:1447-53.

[11] Tamura Y, Hirai A, Terano T, et al. Clinical and epidemiological studies of eicosapentaenoic acid (EPA) in Japan. Prog Lipid Res 1986;25:261-66.

[12] Yokoyama M, Origasa H, Matsuzaki M, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet 2007;369:1090-1097.

[13] Yli-Jama P, Meyer HF, Ringstad J, Pedersen JI. Serum fatty acid pattern and risk of myocardial infarction: A case-control study. J Intern Med 2002;251:19-28.

[14] Kaluzny MA, Duncan LA, Merritt MV, Epps DE. Rapid separation of lipid classes in high yield and purity using bonded phase columns. J Lipid Res 1985;26:135-140.

[15] Folsh J, Lees M, Sloane M, Stanley G. A simple method for the isolation and purification of total lipids from animal tissues. J Biol Chem 1957;226:497-509.

[16] Hoshi M, Williams M, Kishimoto Y. Esterification of fatty acids at room temperature by chloroform-methanolic HCL-cupric acetate. J Lipid Res

1973;14:599-601.

[17] Li GR, Sun HY, Zhang XH, et al. Omega-3 polyunsaturated fatty acids inhibit transient outward and ultra-rapid delayed rectifier K^+ currents and Na^+ current in human atrial myocytes. Cardiovasc Res 2009;81:286-293.

[18] Kitamura K, Shibata R, Tsuji Y, Shimano M, Inden Y, Murohara T. Eicosapentaenoic acid prevents atrial fibrillation associated with heart failure in a rabbit model. Am J Physiol Heart Circ Physiol 2011;300:H1814-H1821.

[19] Michellucci A, Toso A, Mezzani A, et al. Noninvasive recording of sinus node activity by P wave triggered SAECG. Validation using direct intra-atrial recording of sinus node electrogram. Am J Noninvasive Cardiol 1993;7:132-137.

[20] Ehlert F, Gaur A, Steinberg JS. Correlation of the P-wave signal-averaged electrocardiogram to intra-cardiac atrial conduction. Circulation 1996;94:I-70.

[21] Nomura M, Kawano T, Nakayasu K, Nakaya Y. The effects of losartan on signal-averaged P wave in patients with atrial fibrillation. Int J Cardiol 2008;126:21-27.

[22] Chen J, Shearer GC, Chen Q, et al. Omega-3 fatty acids prevent pressure overload-induced cardiac fibrosis through activation of cyclic GMP/protein kinase G signaling in cardiac fibroblasts. Circulation 2011;123:584-593.

[23] Ciulla MM, Paliotti R, Esposito A, et al. Effects of antihypertensive treatment on ultrasound measures of myocardial fibrosis in hypertensive

patients with left ventricular hypertrophy: results of a randomized trial comparing the angiotensin receptor antagonist, candesartan and the angiotensin-converting enzyme inhibitor, enarapril. J Hypertens 2009;27:626-632.

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).
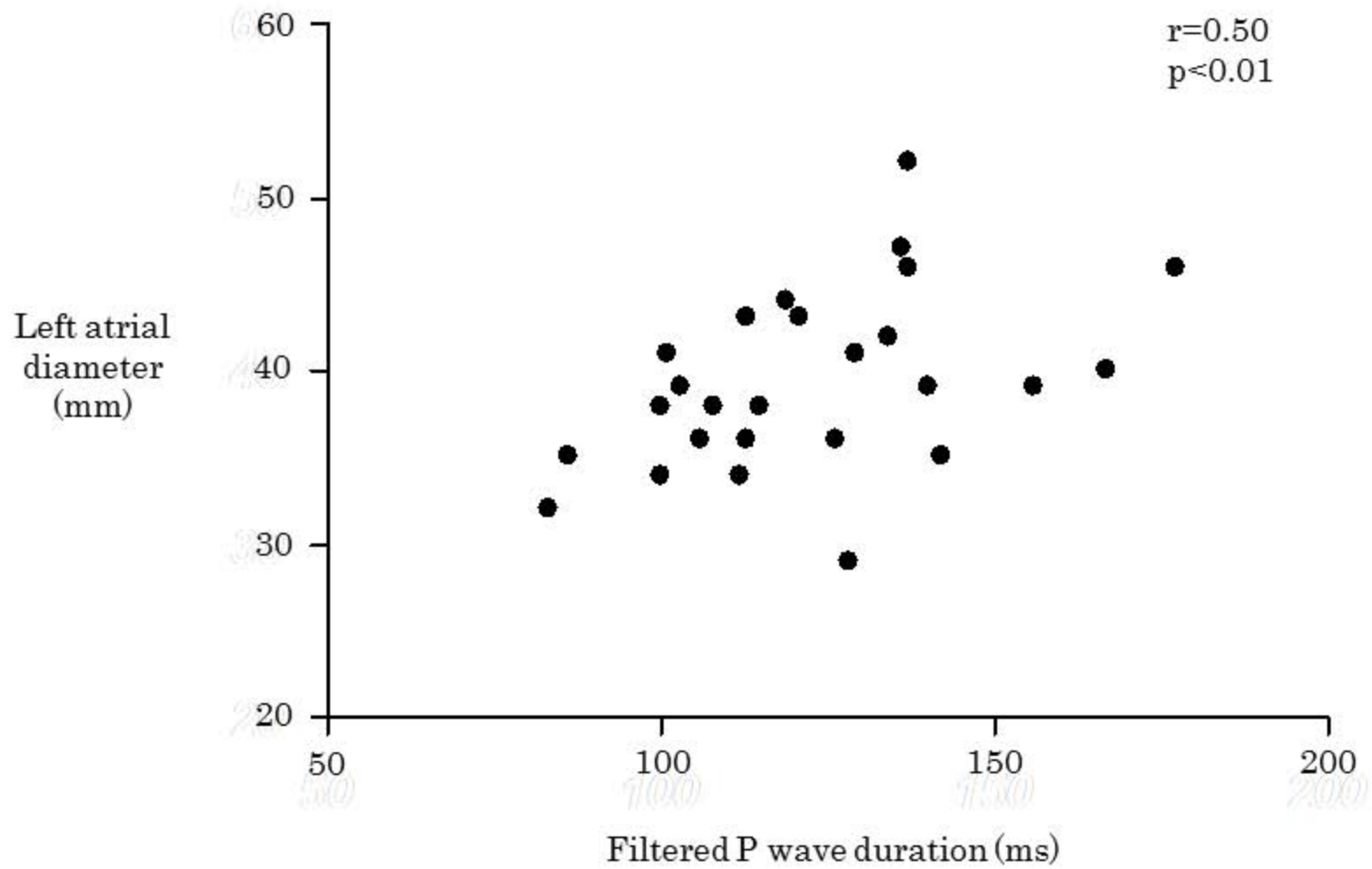
Number of patients	27
Male gender	18 (67%)
Age (years)	69±10
Diabetes	10 (37%)
Hypertension	15 (56%)
Prior myocardial infarction	8 (30%)
Prior coronary intervention	17 (63%)
Medications	
ACE-I or ARB	13 (48%)
Beta blocker	14 (52%)
Calcium channel blocker	14 (52%)
Aspirin	20 (74%)
Warfarin	4 (15%)
Statin	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 (μV)	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.