Low Serum Eicosapentaenoic Acid Level is a Risk for Ventricular Arrhythmia in Patients with Acute Myocardial Infarction: A Possible Link to J-waves

(低血清エイコサペンタエン酸は急性心筋梗塞患者における心室性不整脈のリスクである(虚血性J波への関与))

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Abstract

Backgrounds: Eicosapentaenoic acid (EPA) has antiarrhythmic effects. The J-wave on ECG is associated with a high incidence of ventricular tachycardia/fibrillation (VT/VF). We evaluated relationships between EPA and J-wave and their involvement in the occurrence of VT/VF in acute myocardial infarction (AMI).

Methods and Results: Consecutive 200 patients undergoing successful percutaneous coronary intervention within 12 hours after AMI onset were enrolled. Serum EPA level and J-waves at admission were evaluated. The patients were divided into two groups according to the optimal cutoff value (2.94) of serum EPA level (% of total fatty acids): LOW (<2.94, 61 ± 11 years, n=103) and HIGH groups (≥ 2.94, 70 ± 13 years, n=81). J-waves were observed more frequently in LOW (36/103, 35%) than in HIGH group (16/81, 20%) (p=0.020). The 30-day incidence of VT/VF including those occurring before admission was higher in LOW (19.5%) than in HIGH group (6.2%) (p=0.009). The patients with J-waves showed a higher incidence of VT/VF (23.1%) than those without J-waves (9.9%) (p=0.019). Kaplan-Meier analysis showed that the highest incidence of VT/VF was observed in LOW with J-wave group (27.8%), followed by LOW without J-wave (15.0%), HIGH with J-wave (12.5%) and HIGH without J-wave (4.6%) (p=0.013). Cox proportional hazard analysis revealed that Killip grade and low serum EPA level or presence of J-waves were significantly associated with the incidence of VT/VF.

Conclusions: Low serum EPA level is a risk for incidence of VT/VF in acute phase of MI. Involvement of J-wave and its possible link with EPA in the pathogenesis of ischemia-induced VT/VF were suggested.

Introduction

Sudden cardiac death (SCD) is one of the most common causes of death, and the majority of SCD is directly caused by ischemia-related acute ventricular arrhythmias such as ventricular tachycardia and ventricular fibrillation (VT/VF). It is urgently required to develop an effective strategy for preventing ischemia-induced VT/VF in the early phase of acute myocardial infarction (AMI).

The consumption of fish oil containing large amounts of n-3 polyunsaturated fatty acids (PUFAs), including eicosapentaenoic acid (EPA, C20:5) and docosahexaenoic acid (DHA, C22:5), was shown to reduce the risk of cardiovascular events and death [1]. The GISSI-Prevenzione trial found a 45% reduction in sudden death in patients consuming n-3 PUFAs [2]. Furthermore, the JELIS trial showed that EPA combined with statin significantly reduced major coronary events in hypercholesterolemic patients with established coronary artery disease [3, 4]. N-3 PUFAs were also shown to have antiarrhythmic effects on animal and human studies [5, 6, 7]. However, the detailed mechanisms by which n-3 PUFAs exert their beneficial effects on SCD and ischemia-induced VT/VF have not been fully elucidated.

The J-wave is an electrocardiogram (ECG) waveform defined by a "notching" or "slurring" at the terminal point of the QRS complex. While the J-wave had been regarded as a benign finding in healthy individuals, recent studies showed that it is a finding suggestive of the development of idiopathic VF such as a coved type ST elevation seen in Brugada syndrome [8]. Furthermore, several reports showed that the J-wave is seen commonly in patients with acute ischemia complicated by VT/VF [9, 10], suggesting an important causative role of the J-wave in not only idiopathic but

ischemia-induced VT/VF.

It is well known that ATP-sensitive potassium channel (K_{ATP} channel) is activated by ischemia, and the appearance of the J-wave is affected by K_{ATP} channel activity [11, 12]. Recently, EPA has been shown to inhibit K_{ATP} channel activation in the swine model of myocardial ischemia [13]. Thus, there may be some associations among the acute ischemia-induced VT-VF, low serum EPA level, and the presence of the J-wave, but there have been no reports investigating these associations in clinical cases. The purpose of this study was to examine whether the acute phase incidence of VT/VF is related to the serum EPA level and appearance of the J-wave in patients with AMI. We further discuss a possible link of the serum EPA level with the J-wave in the pathogenesis of VT/VF via ischemia-induced activation of K_{ATP} channels.

Methods

Study patients

The consecutive 200 patients with AMI who were transferred to Hirosaki University Hospital within 12 hours after the symptom onset and underwent successful emergent percutaneous coronary intervention (PCI) from August 2010 to March 2012 were enrolled. Those showing pacemaker rhythm (n=4) and left or right bundle branch block (n=12) were excluded. After admission, all patients underwent 12-lead ECG recording and venous blood sampling to measure serum PUFAs concentrations and blood chemistry. The diagnosis of AMI was made by the chest pain consistent with ongoing myocardial ischemia, ischemic ECG changes, and increases in the serum creatine kinase MB isoform (CK-MB) level $\geq$2 times of the normal upper limit and cardiac troponin T

level ≥0.1 ng/ml. PCI was done mostly with the use of bare metal stent. In all patients, clinical events during the first 30 days after the onset were carefully observed. This study protocol was approved by the Ethical Committee on Human Research of our institution.

ECG evaluation

The standard 12-lead ECG recorded at admission was used for the analyses of the baseline RR interval, QRS duration, J-wave, and QT and QTc intervals. As reported previously [8, 14], the J-wave was defined as a notching (a positive J-deflection inscribed on the S wave) or slurring (a smooth transition from the QRS segment to the ST segment), and was considered to be present when its amplitude was >0.1 mV above the isoelectric line either in at least two consecutive inferior leads (II, III, aVF), left precordial leads (V4-6), or high lateral leads (I, aVL) (Figure 1). The isoelectric line was defined as a level of the preceding TP segment [8, 14]. The amplitude of the J-wave was measured in the five-fold magnified ECG tracing, and the maximal amplitude was evaluated. Detection of VT/VF was made by the documents by continuous ECG monitoring in the ambulance or in the ward. VT encompassed sustained VT, defined as lasting >30 seconds and at least 150 bpm, and/or complicated by hemodynamic compromise requiring cardioversion.

Measurement of plasma fatty acids

The plasma fatty acid levels at the time of admission were measured by the external laboratory (SRL, Tokyo, Japan). Briefly, plasma lipids were extracted by Folch's procedure, and then fatty acids (tricosanoic acid, C23:0, as the internal standard) were methylated with boron trifluoride and methanol. The methylated fatty

acids were then analyzed using a capillary gas chromatograph (GC-2010, Shimadzu, Kyoto, Japan). The serum EPA level (%) was expressed as a percentage of the total fatty acids [3, 15].

Statistical analysis

Continuous variables were listed as mean±standard deviation (SD) and were compared using Student's t-test. Categorical variables were compared using χ^2 test. The optimal cutoff point for serum EPA level was determined by receiver operating characteristic (ROC) curves for distinguishing patients with VT/VF. Analyses of cumulative incidence of VT/VF were performed according to the Kaplan-Meier method and the curves were compared using the log-rank test. Univariate Cox regression analysis and multivariate Cox proportional hazard analysis were performed to identify hazard ratios (HR) and 95% confidence intervals (CI). Probabilities of less than 5% were considered statistically significant. All analyses were performed using the statistical software package SPSS version 18.0 (SPSS, Chicago, IL, USA).

Results

Patient profiles

The patients were divided into two groups based on the optimal cutoff value for serum EPA level (2.94, sensitivity=80% and specificity=48%): LOW group with the level <2.94 (n=103) and HIGH with the level ≥2.94 (n=81). The baseline characteristics of the two group patients are summarized in Table 1. The mean age in LOW group was significantly lower than that in HIGH (61±11 vs 70±13 years, $p<0.001$). Total fatty acids were significantly higher in LOW group than in HIGH. As expected, a significantly

lower level of serum EPA was found in LOW group than in HIGH. In contrast, the serum arachidonic acid (AA) level was significantly higher in LOW group than in HIGH. This resulted in a significantly lower EPA/AA ratio in LOW group than in HIGH. Regarding the plasma lipid levels, total cholesterol and triglyceride in LOW group were significantly higher than those in HIGH group. EPA medication was not prescribed in almost all patients before admission.

ECG analysis and relationship between serum EPA level and J-wave

The RR interval, QRS duration, and QT and QTc intervals on the baseline ECG were all similar between the two groups (Table 2). Importantly, the J-wave was observed in 52 patients (28%) of all patients, and the incidence was more frequent in LOW group than in HIGH (36/103, 35% vs 16/81, 20%, p=0.02). This was further confirmed by the finding that the serum EPA level was significantly lower in the 52 patients with the J-wave than in the other 132 without J-wave (2.47 ± 1.47 vs 3.04 ± 1.66, $p = 0.03$).

A detailed analysis of the J-wave is summarized in Table 3. Except for the incidence, there were no significant differences in the mean amplitude and morphology, notched or slurred type, of the J-wave between the two groups. The J-wave was observed most often in the inferior leads on the ECG (34/52, 65%).

Incidence of ventricular arrhythmias during the acute phase

VT/VF occurred in 25 cases (VT; 3 cases, VF; 18 cases, VT and VF; 4 cases), and more frequently in LOW group than in HIGH within 30 days after the onset of AMI (p=0.009 by log-rank test)(Figure 2A). The first episode of VT/VF mostly occurred before admission in both groups (13/19 in LOW group and 4/6 in HIGH). When the incidence of VT/VF was compared between the patient groups with and without the

J-wave, it was higher in the group with the J-wave than in the group without the J-wave (p=0.019 by log-rank test)(Figure 2B). These Kaplan-Meier analyses suggest that the low serum EPA level and the presence of J-wave are both associated with the increased incidence of VT/VF.

To further investigate the relationships, the patients were divided into four groups according to the serum EPA level and the presence of J-wave: LOW with the J-wave (LOW-JW (+), n=36), LOW without the J-wave (LOW-JW (-), n=67), HIGH with the J-wave (HIGH-JW (+), n=16), and HIGH without the J-wave (HIGH-JW (-), n=65). Kaplan-Meier analysis showed that the highest incidence of VT/VF was observed in LOW with J-wave group (27.8%), followed by LOW without J-wave (15.0%), HIGH with J-wave (12.5%) and HIGH without J-wave (4.6%) (p=0.013). Additionally, we performed the Kaplan-Meier analysis using the absolute EPA value (optimal cutoff value, 85.7 μ g/mL) as well as the serum EPA level expressed as a percentage of the total fatty acids, and found similar Kaplan-Meier curves (p=0.014 by log-rank test).

Incidence of ventricular arrhythmias evaluated by serum EPA/AA ratio

Serum EPA/AA ratio is known as a predictive marker for coronary death and AMI [4]. Therefore, we performed the Kaplan-Meier analysis for the other four groups which were divided according to the optimal cutoff value for the serum EPA/AA ratio (0.47, sensitivity=72%, specificity=53%) and appearance of the J-waves. As shown in Figure 3B, we found similar Kaplan-Meier curves (p=0.015) as in Figure 3A.

Predictors for ventricular arrhythmias

The results of univariate and multivariate Cox proportional hazard analyses to elucidate the predictors for the development of VT/VF are shown in Table 4. Univariate

analysis showed that the Killip grade II-IV (HR, 4.22; 95%CI, 1.92-9.26, p=0.001), presence of J-waves (HR, 2.39; 95%CI, 1.09-5.24, p=0.028), low serum EPA level <2.94 (HR, 3.246; 95%CI, 1.22-8.70, p=0.020), and low serum EPA/AA ratio < 0.47 (HR, 2.34; 95%CI, 1.01-5.41, p=0.042) were significantly associated with the occurrence of VT/VF. DHA and AA did not influence the incidence of VT/VF when patients were divided into two groups based on their optimal cutoff values (6.88 and 6.26, respectively) obtained from ROC curve analysis. The univariate predictors with $p<0.05$ were subsequently entered into multivariate Cox proportional hazard analysis. Because of a significant relationship between presence of J-waves and serum EPA level, those valuables were added separately. Model 1 showed that the Killip grade II-IV (HR, 3.68; 95%CI, 1.69-8.13, p=0.001) and presence of J-waves (HR, 2.23; 95% CI, 1.02-4.90, p=0.046) were independent predictors for the occurrence of VT/VF. Similarly, model 2 showed that the Killip grade II-IV (HR, 4.03; 95%CI, 1.83-8.93, p=0.001) and low serum EPA level (HR, 2.72; 95% CI, 1.01-7.23, p=0.048) were independent predictors for the occurrence of VT/VF.

Discussion

The present study showed that the low serum EPA level is a risk factor for VT/VF during the acute phase of MI, and the J-wave, more frequently found in the patients with the low serum EPA level, is associated with the increased incidence of VT/VF as estimated by the Kaplan-Meier analysis. These indicate a significant importance of the low serum EPA level and the J-wave in the pathogenesis of VT/VF during the acute phase of MI, and further suggest a possible mechanistic link between

the low serum EPA level and presence of the J-wave in the patients presenting VT/VF in the acute phase of AMI.

Beneficial effect of n-3 PUFAs on the occurrence of VT/VF and its possible mechanism

N-3 PUFAs have been shown to exert beneficial effects on long-term cardiovascular events after AMI [15]. However, there have been few studies that examined their favorable effects on the lethal arrhythmic events during the acute phase of AMI. Aarsetøy et al showed that the plasma levels of n-3 PUFAs were significantly lower in patients having VF event during the acute phase AMI than in those without such an event [16]. This supports our finding that VT/VF occurred more frequently in LOW group than in HIGH within 30 days after the onset of AMI. We further showed a significant importance of the low serum EPA level as an independent predictor for the occurrence of VT/VF by multivariate analysis. Although the higher concentration of total fatty acid and triglycerides in LOW group may affect the incidence of ventricular arrhythmia, the results of three Kaplan-Meier analyses using serum EPA level expressed as a percentage of the total fatty acids, the absolute value of EPA, and EPA/AA ratio, support an important role of low serum EPA levels in the incidence of ventricular arrhythmia in patients with AMI.

The underlying mechanism by which the high serum EPA level exerts a protective effect on the occurrence of VT/VF during the acute phase AMI is of great interest. N-3 PUFAs exert their antiarrhythmic effects possibly due to modulation of ion channels, particularly voltage-gated sodium, potassium, and L-type calcium channels [17]. Experimental animal studies indicated that a dietary supplementation of n-3 PUFA significantly reduced the incidence and severity of ventricular arrhythmias occurring

after coronary artery occlusion in a canine model by inhibiting the rapid accumulation of intracellular calcium following ischemia [5]. In the human electrophysiologic study, the infused or dietary n-3 PUFA decreased the inducibility of VT in patients with implantable cardioverter defibrillator at risk of SCD [6]. Although these animal and clinical studies clearly described the antiarrhythmic effects of n-3 PUFAs, its precise mechanism in the setting of acute ischemia has not been fully elucidated.

During myocardial ischemia, intracellular ATP concentration decreases and subsequently K_{ATP} channel is activated, thereby leading to the shortening of action potential duration and heterogeneous ventricular repolarization [18]. These cause transmural differences in the early phase of cardiac action potential and eventually induce phase 2 reentry and VT [19]. In a swine model of myocardial ischemia, EPA was shown to reduce the risk of VF and mortality possibly due to attenuating of the monophasic action potential shortening [13]. In the cellular level, EPA was found to inhibit mRNA transcription and protein expression of Kir6.2, a major component of sarcolemmal K_{ATP} channels [13]. This experimental observation strongly suggests that EPA exerts an antiarrhythmic effect partly via inhibition of ischemia-induced activation of K_{ATP} channels.

Inhibition of J-wave appearance by n-3 PUFAs

Another important issue to be discussed in this study is how EPA influences the appearance of J-wave on the ECG. The J-wave was originally regarded as a benign finding in healthy individuals. However, recent reports showed that the presence of the J-waves is associated with an increased risk of VT/VF during acute myocardial ischemia [9, 10, 20], and is an independent predictor for the occurrence of VF in the very early

phase of AMI [21]. We showed that the J-wave was observed more frequently in LOW group than in HIGH and the incidence of VT/VF was also higher in LOW than in HIGH, supporting the detrimental effects of the J-wave during the acute phase AMI. Further, our findings suggest a possible interaction between the low serum EPA level and J-wave for the occurrence of VT/VF. Activation of K_{ATP} channels and/or their difference in the distribution between the epicardial and endocardial myocardium partly contribute to the manifestation of the J-wave [22, 23]. Taken together, this may logically allow us to propose a possible mechanism that EPA inhibits ischemia-induced activation of K_{ATP} channels and thereby reduces K_{ATP} channel induced-manifestation of the J-wave, which in turn leads to the decrease in the incidence of VT/VF during the acute phase AMI (Figure 4). This proposal and our finding that almost all patients in this study population were not treated with EPA before admission seem to warrant immediate EPA treatment after AMI to prevent VT/VF events in acute phase of AMI. Further experimental and large clinical studies are required to justify our speculation.

Appearance of J-wave and its morphology

As VT/VF is most commonly observed in the acute phase AMI, we analyzed the ECG and the J-wave at admission, a time as close as possible to the onset of AMI. In other clinical studies evaluating the J-wave, the ECG was recorded five or seven days after admission [24, 25]. However, PCI may have been undertaken by that time and the possibility that PCI influenced the ECG waveform cannot be completely excluded. Furthermore, the appearance of the J-wave and its morphology also change with time and the J-wave may disappear immediately in some cases [10]. Our protocol to evaluate the ECG and the J-wave on admission concurs with that used in other studies [24, 25].

The frequency of J-waves in our study (28%) and the lead location on the ECG where the J-wave was observed were both similar to those in the other studies [20, 21, 24]. Our study further showed that more than a half of the J-wave were a slurred type, whereas in the other studies the majority of the J-wave were a notched type [17, 25]. This difference in the J-wave morphology could be explained by the different timing of the observation and different genetic background of the patients.

Limitations

There are some limitations in this study. First, it is unknown whether the patients had the J-wave prior to the onset of AMI. Accordingly, although we found the association of the J-wave with the occurrence of VT/VF, we could not elucidate the behavior of the J-wave prior to the onset of VT/VF. Second, the number of patients was relatively small to determine the suitable cutoff value for the serum EPA level and to adequately examine its relationship with the incidence of VT/VF. Further large scale and prospective clinical studies are required.

Conclusions

Our study provides the evidence that the low serum EPA level is a risk factor for the occurrence of VT/VF in the acute phase of AMI and the J-wave is involved in the pathogenesis of VT/VF. More notably, a possible mechanistic link between the low serum EPA level and the appearance of the J-wave presumably through K_{ATP} channel activation is suggested to be a novel pathogenesis of ischemia-induced VT/VF. A supplementary EPA treatment might be recommended to prevent VT/VF in acute phase of AMI, especially in patients with low serum EPA level and the J-wave.

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Table 1. Baseline characteristics of LOW and HIGH EPA groups

	LOW EPA (n = 103)	HIGH EPA (n = 81)	P
Characteristics			
Age	61 ± 11	70 ± 13	< 0.001
Female	23 (20%)	23 (28%)	0.20
BMI, kg/m^2	24.1 ± 4.4	23.6 ± 3.8	0.47
Hypertension	64 (62%)	63 (69%)	0.32
Dyslipidemia	67 (65%)	53 (65%)	0.95
Diabetes mellitus	39 (38%)	30 (37%)	0.90
Current smoker	28 (27%)	31 (38%)	0.52
CKD	40 (39%)	37 (46%)	0.23
Culprit vessel			
LAD	49 (48%)	36 (44%)	
LCX	19 (18%)	10 (12%)	0.17
RCA	35 (34%)	33 (41%)	
LMT	0 (0%)	2 (2%)	
Extent of coronary artery disease			
One vessel	48 (47%)	32 (39%)	
Two vessels	36 (35%)	29 (36%)	0.38
Three vessels	19 (18%)	20 (25%)	
Severity of AMI			
LVEF (%)	45 ± 9	45 ± 10	0.81

EDVI (ml/m^2)	86 ± 31	77 ± 24	0.07
Killip grade			
I	79 (47%)	71 (87%)	
II	11 (11%)	3 (4%)	0.23
III	7 (7%)	4 (5%)	
IV	6 (6%)	3 (4%)	
Maximal CK (IU/L)	3710 ± 3382	3007 ± 2397	0.11
Maximal CK-MB (IU/L)	343 ± 306	282 ± 212	0.12
BNP (pg/mL)	206 ± 481	223 ± 390	0.79
Laboratory findings on admission			
eGFR (60 mL/min/1.73 m^2)	69 ± 30	69 ± 26	0.97
Total cholesterol (mg/dL)	196 ± 47	182 ± 36	0.02
Triglycerides (mg/dL)	151 ± 112	114 ± 85	0.01
HDL-cholesterol (mg/dL)	45 ± 14	46 ± 12	0.74
LDL-cholesterol (mg/dL)	122 ± 39	114 ± 31	0.18
UA (mg/dL)	5.8 ± 2.0	5.7 ± 1.6	0.58
Glucose (mg/dL)	164 ± 65	162 ± 93	0.88
HbA1c (%)	6.0 ± 1.3	5.9 ± 1.1	0.52
hsCRP (mg/L)	1013 ± 3163	723 ± 1607	0.45
Total fatty acids (μg/mL)	3461 ± 1067	3046 ± 818	0.004
EPA (μg/mL)	61 ± 27	127 ± 40	<0.001
DHA (μg/mL)	156 ± 56	209 ± 64	<0.001
AA (μg/mL)	195 ± 55	163 ± 42	<0.001

EPA/AA	0.32 ± 0.15	0.82 ± 0.31	<0.001
Medication before admission			
ACE-I or ARB	24 (23%)	26 (32%)	0.18
Calcium blockers	29 (28%)	30 (37%)	0.20
Beta blockers	12 (12%)	10 (12%)	0.88
Statins	12 (12%)	12 (15%)	0.52
EPA	0 (0%)	2 (2%)	0.19
Medication after admission			
ACE-I or ARB	98 (95%)	79 (98%)	0.40
Calcium blockers	4 (4%)	4 (5%)	0.72
Beta blockers	95 (92%)	74 (91%)	0.82
Statins	93 (90%)	75 (93%)	0.58

Values are expressed as mean ± SD. AA indicates arachidonic acid, ACEI; angiotensin-converting enzyme inhibitor, ARB; angiotensin II receptor blocker, BMI; body mass index, BNP; brain natriuretic peptide, CK; creatine kinase, CKD; chronic kidney disease, estimated glomerular filtration rate < 60 mL/min/1.73 m^2, CK-MB; creatine kinase-myocardial isoform, DHA; docosahexaenoic acid, EDVI; end-diastolic volume index, EPA; eicosapentaenoic acid, HDL; high-density lipoprotein, hsCRP; high sensitivity C-reactive protein, LAD; left anterior descending artery, LCX; left circumflex artery, LDL; low-density lipoprotein, LMT; left main trunk artery, LVEF; left ventricular ejection fraction, RCA; right coronary artery, UA; uric acid.

Table 2. Electrocardiographic findings in LOW and HIGH EPA groups

	LOW EPA (n = 103)	HIGH EPA (n = 81)	P
Baseline RR interval (msec)	798 ± 73	810 ± 178	0.55
QRS interval (msec)	112 ± 22	108 ± 18	0.28
QT interval (msec)	390 ± 47	393 ± 39	0.65
QTc ($msec^{1/2}$)	440 ± 35	436 ± 50	0.52
J-wave, n (%)	36 (35%)	16 (20%)	0.02

Table 3. J-wave morphology in LOW and HIGH EPA groups with J-wave (n=52)

	LOW EPA (n = 36)	HIGH EPA (n = 16)	P
J-wave amplitude (mV)	0.23 ± 0.08	0.22 ± 0.08	0.65
Type of J-waves, n (%)			
Notched type	16 (44%)	7 (43%)	
Slurred type	20 (56%)	9 (56%)	0.96
Lead location of J-waves, n (%)			
Inferior	21 (58%)	13 (81%)	
Left precordial	6 (17%)	2 (13%)	
High lateral	4 (11%)	0 (0%)	
Multiple	5 (14%)	1 (7%)	0.34
Site of MI, n (%)			
Anterior	17 (47%)	9 (56%)	
Inferior	14 (39%)	5 (31%)	0.82
Posterior	5 (14%)	2 (13%)	

ECG indicates electrocardiogram, MI; myocardial infarction.

Table 4. Predictors of ventricular arrhythmia by Cox proportional hazard analysis

	Univariate	
	HR (95%CI)	*P*
Age (years)	1.002 (0.969-1.036)	0.90
Female	1.778 (0.792-3.991)	0.16
BMI	1.065 (0.945-1.201)	0.99
Killip grade II-IV	4.219 (1.923-9.259)	0.001
Multivessel disease	0.973 (0.395-2.395)	0.95
Maximal CK-MB	1.000 (0.999-1.002)	0.64
Presence of J-waves	2.392 (1.091-5.244)	0.028
EPA < 2.94 (%)	3.246 (1.219-8.695)	0.020
DHA < 6.88 (%)	2.159 (0.645-7.194)	0.21
AA < 6.26 (%)	1.003 (0.433-2.323)	0.99
EPA/AA < 0.47	2.336 (1.007-5.405)	0.042
	Multivariate (model 1)	
Killip grade II-IV	3.676 (1.658-8.130)	0.001
Presence of J-waves	2.229 (1.015-4.895)	0.046
	Multivariate (model 2)	
Killip grade II-IV	4.032 (1.834-8.928)	0.001
EPA < 2.94	2.717 (1.009-7.299)	0.048

In multivariate analysis, presence of J-waves and serum EPA level were added separately: model 1 included Killip grade II-IV and presence of J-waves, and model 2 included Killip

grade II-IV and EPA < 2.94. HR indicates hazard ratio, CI; confidence interval, Other abbreviations are shown in Table 1.

Figure Legends

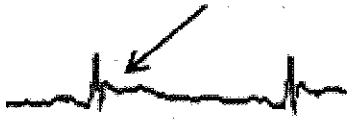
Figure 1. J-wave morphology. Representative two types of J-waves on ECG, notched and slurred types, are shown. Arrows indicate J-wave.

Figure 2. Kaplan-Meier estimates of the incidence of VT/VF divided into two groups according to the optimal cutoff value of serum EPA level (2.94)(% of total fatty acids): LOW EPA and HIGH EPA groups (A), and those based on the presence of J-waves: J-waves (+) and J-waves (-) (B).

Figure 3. Kaplan-Meier estimates of the incidence of VT/VF divided into four groups based on the optimal cutoff value of serum EPA level (2.94)(% of total fatty acids) and the presence of J-waves (A), and those based on the optimal cutoff value of serum EPA/AA ratio (0.47) and the presence of J-waves (B). LOW with the J-waves (LOW-JW (+), black solid line), LOW without the J-waves (LOW-JW (-),black dotted line), HIGH with the J-waves (HIGH-JW (+), gray solid line), and HIGH without the J-waves (HIGH-JW (-), gray dotted line).

Figure 4. Proposed mechanism by which EPA exerts an anti-arrhythmic effect on ischemia -induced VT/VF. EPA inhibits ischemia-induced activation of K_{ATP} channels and thereby reduce K_{ATP} channel induced-manifestation of J-waves. These may lead to decrease in incidence of VT/VF during the acute phase of MI.

Figure 1



Notched type

Slurred type

Figure 2

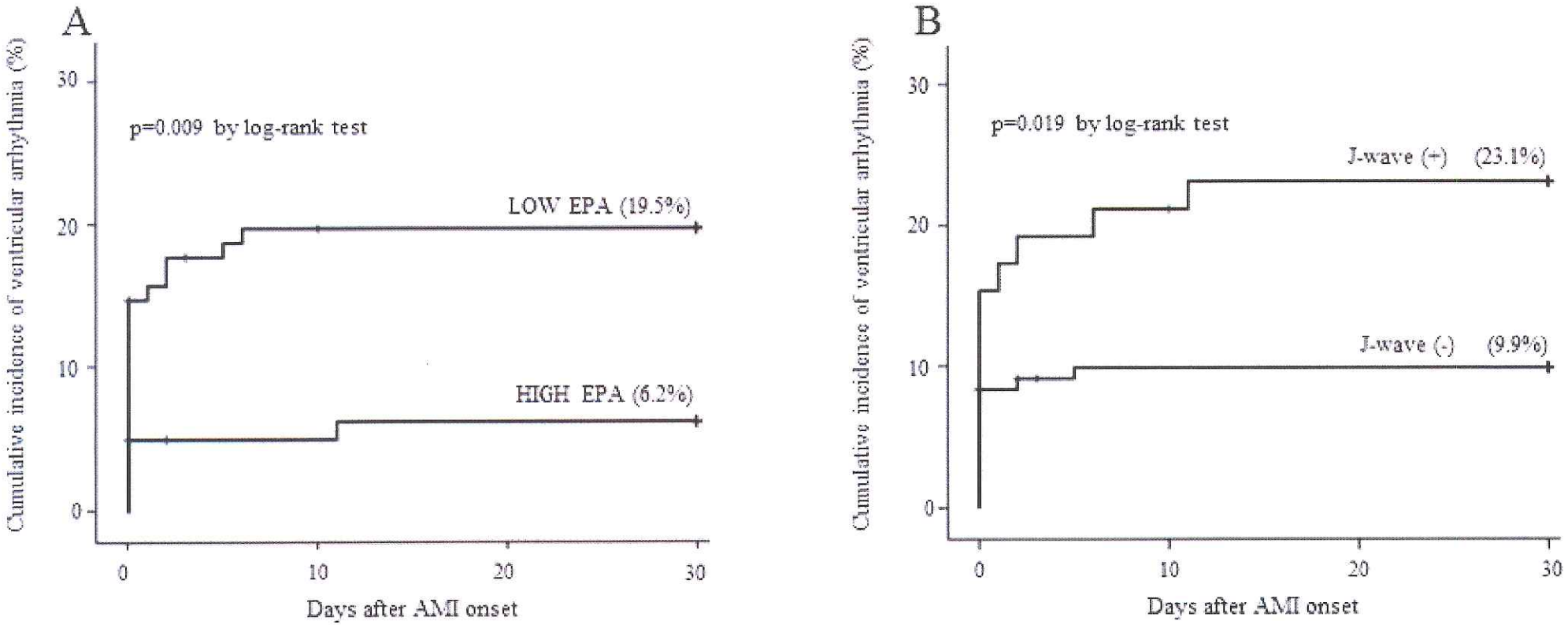

A
Cumulative incidence of ventricular arrhythmia (%)
30
20
10
0
p=0.009 by log-rank test
LOW EPA (19.5%)
HIGH EPA (6.2%)
0
10
20
30
Days after AMI onset
B
Cumulative incidence of ventricular arrhythmia (%)
30
20
10
0
p=0.019 by log-rank test
J-wave (+) (23.1%)
J-wave (-) (9.9%)
0
10
20
30
Days after AMI onset

Figure 3

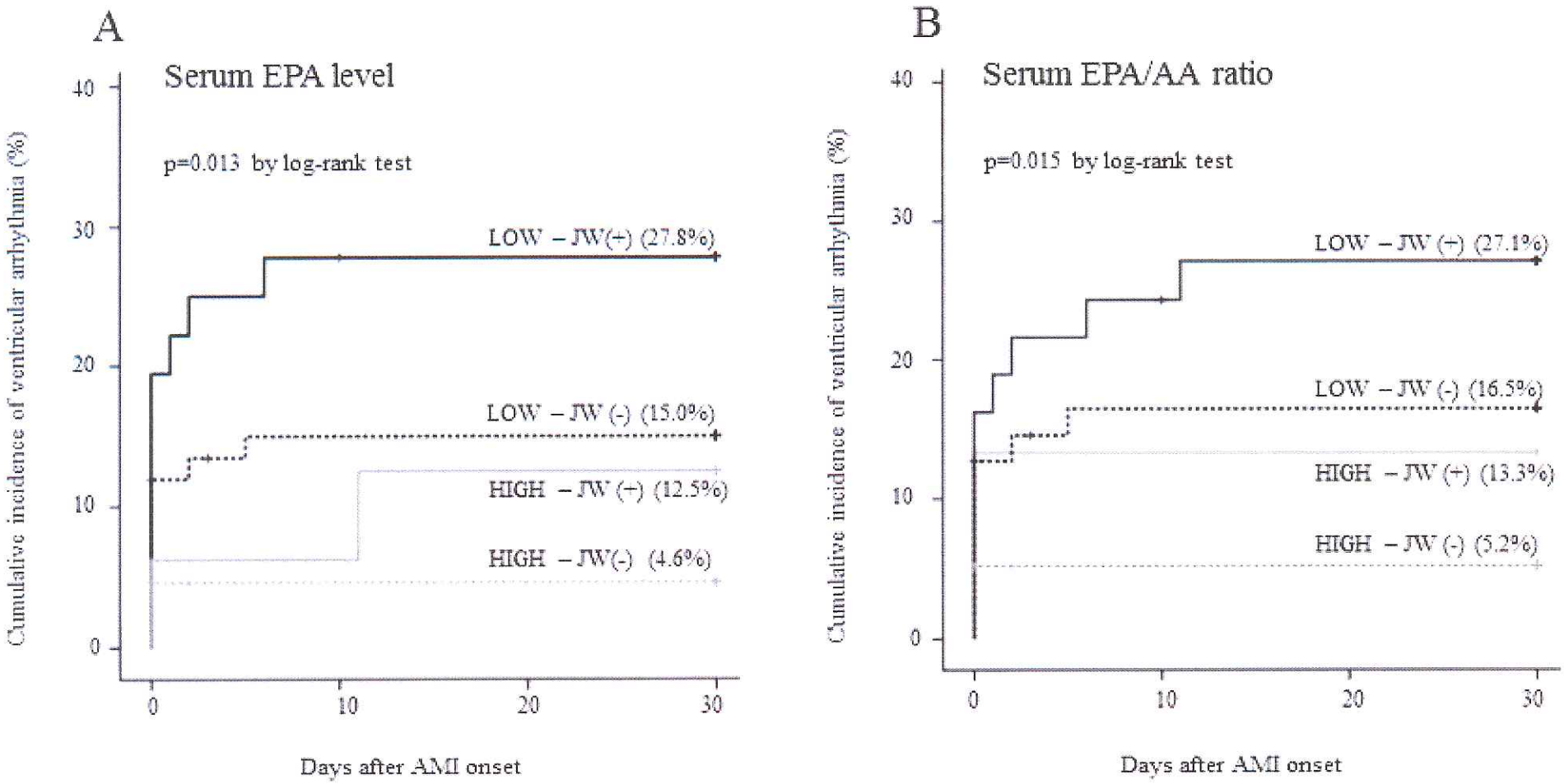
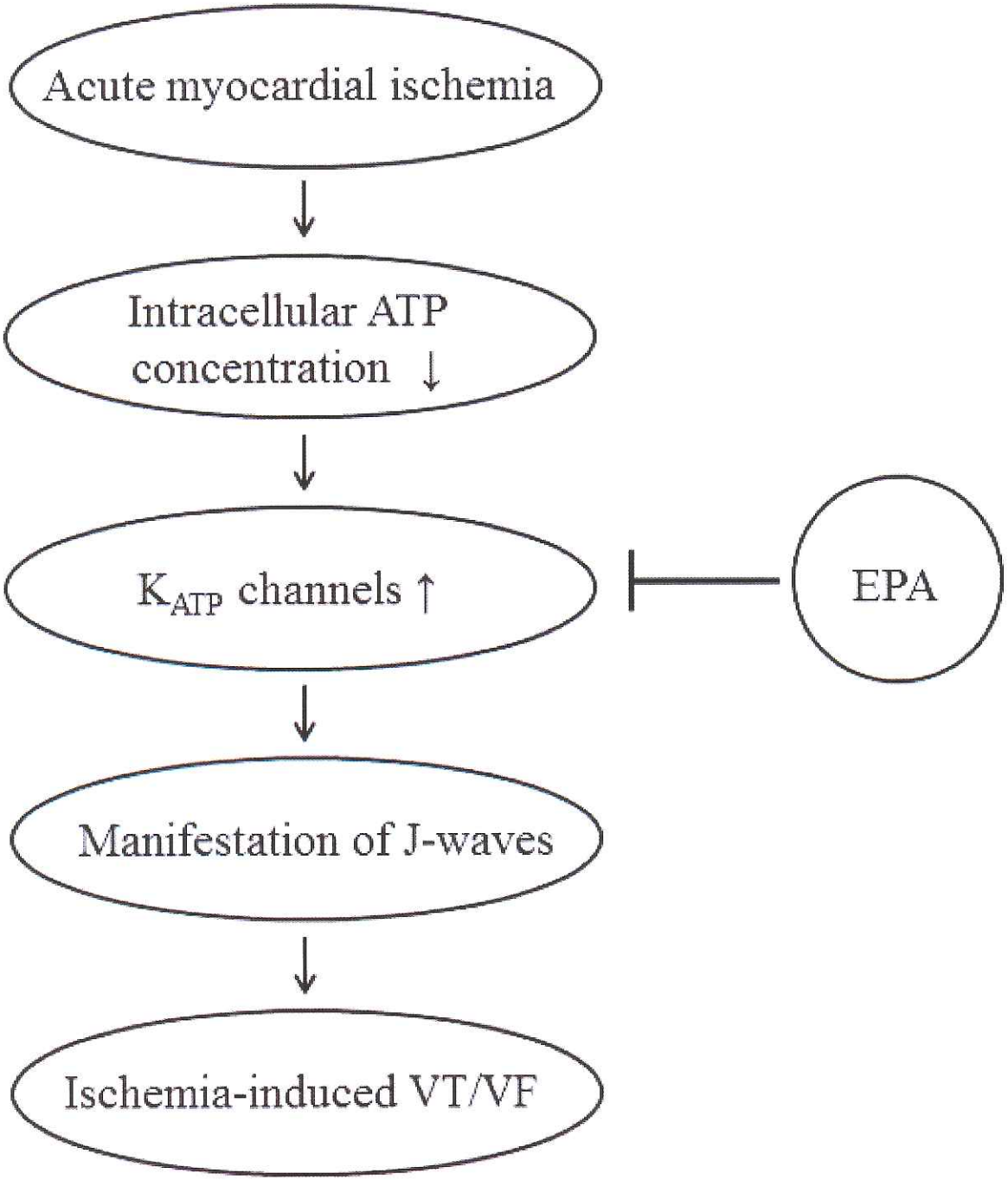

A
Serum EPA level
p=0.013 by log-rank test
LOW – JW(+) (27.8%)
LOW – JW (-) (15.0%)
HIGH – JW (+) (12.5%)
HIGH – JW(-) (4.6%)
Cumulative incidence of ventricular arrhythmia (%)
Days after AMI onset
B
Serum EPA/AA ratio
p=0.015 by log-rank test
LOW – JW (+) (27.1%)
LOW – JW (-) (16.5%)
HIGH – JW (+) (13.3%)
HIGH – JW (-) (5.2%)
Cumulative incidence of ventricular arrhythmia (%)
Days after AMI onset

Figure 4


Acute myocardial ischemia
Intracellular ATP concentration ↓
K_{ATP} channels ↑
EPA
Manifestation of J-waves
Ischemia-induced VT/VF