Relationship Between Serum Eicosapentaenoic Acid Levels and J-Waves in a General Population in Japan

Analysis of the Iwaki Health Promotion Project

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Summary

We previously showed that J-waves were found more frequently in patients with low levels of serum eicosapentaenoic acid (EPA) in the acute phase of myocardial infarction, and were associated with the incidence of ischemia-related ventricular arrhythmias. However, the relationship between J-waves and serum EPA levels in a general population remains to be elucidated.

The Iwaki Health Promotion Project is an ongoing community-based health promotion study in Iwaki, Hirosaki, which is in northern Japan. A total of 1,052 residents (mean age, 53.9 ± 15.4 years; 390 men) who participated in this project in 2014 were studied. A standard 12-lead electrocardiogram (ECG) was recorded and serum EPA levels were measured to evaluate the relationship between J-waves and serum EPA levels. J-waves were found in 52 (5%) subjects and were observed more frequently in male than female subjects (44 [11%] versus 8 [1%), P < 0.0001). More than half of the J-waves were the notched type (60%), and J-waves were detected most frequently in inferior leads on ECG (52%). The RR interval was longer and QTc duration shorter in subjects with J-waves than those without. No significant difference was found in serum EPA levels between subjects with and without J-waves (70 [49-116] versus 65 [41-106] μg/mL, P = 0.40). In multivariate analysis, male gender and RR interval were independent factors associated with the presence of J-waves.

There was no significant relationship between J-waves and serum EPA levels in this general population in Japan. Various mechanisms for manifestation of the J-waves are suggested.

Key words: Early repolarization, n-3 polyunsaturated fatty acids

J-waves, visible as positive deflections at the end of the QRS complex on an electrocardiogram (ECG), have been considered a benign finding. However, recent studies have shown that J-waves are associated with the incidence of ventricular arrhythmias in patients with Brugada syndrome, myocardial infarction, and non-ischemic cardiomyopathy.1,7,8

Consumption of fish oil containing large amounts of n-3 polyunsaturated fatty acids (PUFAs) including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) has been shown to reduce cardiovascular events and death.9 A 45% reduction in sudden cardiac death was reported with the consumption of n-3 PUFAs in the GISSI-Prevenzione trial,9 and EPA combined with statin therapy significantly reduced major coronary events in hypercholesterolemic patients with established coronary artery disease in the JELIS trial.10,11 Moreover, n-3 PUFAs were shown to have antiarrhythmic effects in several studies.7,12-13

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Recently, we showed that J-waves were found more frequently in the acute phase of myocardial infarction in patients with low levels of serum EPA, and were associated with the incidence of ischemia-related ventricular arrhythmias.7 Other investigators showed that early EPA treatment after percutaneous coronary intervention in the acute phase of myocardial infarction reduced the incidence of ventricular arrhythmias.12 These data suggest a possible relationship between low serum EPA levels and the presence of J-waves in the pathogenesis of ischemia-
related ventricular arrhythmias. However, this relationship remains to be elucidated in non-ischemic subjects. Therefore, we tested the hypothesis that serum EPA levels are associated with the prevalence of J-waves without ischemia in a general population.

**Methods**

**Study population:** This study was part of the Iwaki Health Promotion Project, which is an ongoing community-based health promotion study of Japanese people over 20 years of age that aims to prevent lifestyle-related diseases and prolong lifespans.\(^7\) The study has been conducted annually since 2005 in the Iwaki area of the city of Hirosaki in Aomori Prefecture, which is located in northern Japan. All study subjects participated voluntarily in response to a public announcement and approximately 600 items were collected from each participant, including a standard 12-lead ECG, body weight, medical history, cardiovascular risk factors, and blood chemical analysis results. We evaluated 1,052 residents (mean age, 53.9 ± 15.4 years; 390 men) who participated in the Iwaki Health Promotion Project in 2014 in the current study. The study protocol was approved by the Ethics Committee of the Hirosaki University Graduate School of Medicine, and written informed consent was obtained from all participants.

**ECG analyses:** J-waves were defined as the notched type (a positive J-deflection inscribed on the S wave) or slurred type (a smooth transition from the QRS segment to the ST segment) on a standard 12-lead ECG, and considered to be present when the amplitude was > 0.1 mV above the isoelectric line in at least two consecutive inferior leads (II, III, aVF), left precordial leads (V4-V6), or high lateral leads (I, aVL; Figure 1).\(^1,7,18,19\) The isoelectric line was defined as the level of the TP segment.\(^1,7,18,19\) The amplitudes of J-waves were measured using 5-fold magnification, and maximum amplitude was evaluated.\(^3\) We also evaluated the RR interval and QT/QTc duration because slow heart rates and short QTc duration are considered to be factors associated with J-waves.\(^5,20\)

**Serum EPA and DHA levels and basic characteristics:** Blood samples were collected in the morning under fasting conditions from peripheral veins of participants in a supine position.\(^17\) The serum EPA and DHA levels were measured by an external laboratory (LSI Medience, To-kyo). Diabetes was defined according to the 2010 Japan Diabetes Society criteria.\(^26\) Hypertension was defined as blood pressure ≥ 140/90 mmHg or receiving treatment for hypertension. Dyslipidemia was defined as total cholesterol ≥ 220 mg/dL, triglycerides ≥ 150 mg/dL, or receiving treatment for dyslipidemia. Smoking habits were determined from questionnaires.

**Statistical analysis:** Subjects were divided into two groups by the presence or absence of J-waves, and differences between the two groups were compared. Analysis of normal distribution was conducted using Shapiro-Wilk’s W test. Differences between the two categories were compared using the t-test or Wilcoxon test. Categorical variables were compared using the chi-square test. Significant factors by univariate analysis were included in a multivariate analysis to evaluate independent factors associated with J-waves. Results are presented as the odds ratio (OR) and 95% confidence interval (CI). A \(P < 0.05\) was considered statistically significant. Data were analyzed using the statistical software JMP (version 11.0) and are expressed as the mean ± SD, median (interquartile range), or \(n (\%)\).

**Results**

**Baseline characteristics of the study population:** J-waves were observed in 52 of 1,052 (5%) subjects and were more frequent in male than female subjects (44 of 390 [11%] versus 8 of 662 [1%], \(P < 0.0001\)). The baseline characteristics of the study population are shown in Table I. Compared with the group without J-waves, the group with J-waves was characterized by male predominance and more current smokers. There were no differences in age, body mass index, hypertension, diabetes mellitus, and dyslipidemia between subjects with and without J-waves.

**Morphology of J-waves and ECG findings:** The notched type accounted for 60% of all J-waves, and the slurred type for the remainder (40%). J-waves were found most frequently in inferior leads (52%), followed by left precordial leads (29%), multiple leads (14%), and high lateral leads (6%) (Table II). The RR interval was significantly longer in subjects with J-waves than those without J-waves (1014 [934-1094] versus 924 [839-1003] ms, \(P < 0.0001\)) (Table III). There was no significant difference in QT duration between subjects with and without J-waves (402 [387-418] versus 397 [380-417] ms, \(P = 0.15\)). How-

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**Figure 1.** Two types of J-wave on an electrocardiogram: the notched type and the slurred type. Arrows indicate J-waves.
ever, QTc duration was significantly shorter in subjects with J-waves than in those without J-waves (401 [389-419] versus 414 [402-428] ms, \( P < 0.0001 \)).

**Serum EPA and DHA levels:** As shown in Figure 2, no significant difference was found in serum EPA levels between subjects with and without J-waves (70 [49-116] μg/mL, \( P = 0.4 \)). Similarly, there was no significant difference in serum DHA levels between subjects with and without J-waves (157 [110-190] versus 142 [110-176] μg/mL, \( P = 0.27 \)).

There were no significant differences in serum EPA levels between subjects with and without J-waves both in male and female subjects (Figure 3A and B). Similarly, there was no difference in serum EPA levels between subjects with the notched type and those with the slurred type (87 [52-114] versus 57 [39-118] μg/mL, \( P = 0.22 \)) (Figure 3C).

**Multivariate analysis for detection of J-waves:** Multivariate analysis for detection of J-waves was performed after adjusting for significant factors by univariate analysis. Male gender and RR interval on ECG were independent predictors for detection of J-waves (male: OR, 8.03; 95% CI, 3.82-19.0; \( P < 0.0001 \) and RR interval: OR, 1.00; 95% CI, 1.00-1.01; \( P = 0.02 \)) (Table IV).

**Discussion**

**Major findings:** We previously showed that J-waves were found more frequently in patients with low levels of serum EPA in the acute phase of myocardial infarction, and were associated with the incidence of ischemia-related ventricular arrhythmias.26 In the present study, however, there was no relationship between serum EPA levels and the presence of J-waves in non-ischemic subjects. These findings suggest that mechanisms for manifestation of J-waves in association with serum EPS levels may differ between myocardial ischemic and non-ischemic subjects.

**Characteristics of the study population and J-wave morphology:** Recent studies have shown that the prevalence of J-waves in a general population ranges from 0.9% to 24.8%,27,28 and that male gender is a factor associated with J-waves partly through the effect of testosterone.18,29-31 Consistent with these findings, the present study results revealed that J-waves were more frequent in male than female subjects. Moreover, male gender was an independent predictor for J-wave prevalence and showed the highest OR in multivariate analysis. Although current smoking was also associated with the prevalence of J-waves in univariate analysis, it was not an independent predictor in multivariate analysis, possibly because most of the current smokers were men.

Regarding morphology on ECG, more than half of the J-waves were the notched type in the present study, which is consistent with previous reports.32,33 In univariate analysis, a long RR interval and short QTc duration were associated with the prevalence of J-waves. In general, QTc duration was shorter in male than in female subjects,34,35 and male predominance in the present study likely contributed to the short QTc duration associated with J-waves. Indeed, short QTc duration was not an independent predictor for J-wave prevalence in multivariate analysis. In contrast, a long RR interval was an independent factor for J-wave prevalence in multivariate analysis. It has been suggested that the transient outward potassium current (I\(_{\text{to}}\)), which is responsible for J-wave manifestation, is increased following a decrease in heart rate because recovery of I\(_{\text{to}}\) from inactivation is slow, resulting in an increase in the magnitude and appearance of J-waves.21,24,25,36

**Relationship between J-waves and serum EPA levels:** During myocardial ischemia, intracellular adenosine triphosphate (ATP) concentration is decreased, and K\(_{\text{ATP}}\) channels are subsequently activated.37 Activation of K\(_{\text{ATP}}\) channels or differences in distribution between epicardial
and endocardial myocardium seems to contribute to the manifestation of J-waves.\(^{38,39}\) In a previous study, we speculated that EPA inhibits K\(_{ATP}\) channel activation, thereby reducing manifestation of J-waves, and inhibiting ischemia-induced ventricular arrhythmias.\(^{7,40}\) Furthermore, n-3 PUFAs have been reported to exhibit electrophysiological effects through modulating various cardiac ion channels including I\(_{Ca}\).\(^{41}\) However, we found no significant relationship between the prevalence of J-waves and serum EPA levels in the present study. These findings indicate that without myocardial ischemia, serum EPA levels may not be associated with the manifestation of J-waves, possibly because K\(_{ATP}\) channels are not activated in this setting. Actually, the prevalence of J-waves in this study was much lower than that in our previous study in the acute phase of myocardial infarction (5% versus 28%). Furthermore, more than half of the J-waves were the slurred type in our previous study, whereas more than half of the J-waves were the notched type in the present study. These findings indicate that the mechanisms for J-wave manifestation might differ between subjects with and without myocardial ischemia.

**Study limitations:** There are some limitations in the present study. First, we evaluated J-waves at only one point in the present study, although the prevalence and morphology of J-waves are known to change with time.\(^{3,7}\) Second, because our study subjects were limited to residents of Iwaki Town in northern Japan, further studies in other areas are clearly warranted.

**Conclusions:** In a general population, no significant relationship was found between J-waves and serum EPA levels, indicating different associations between J-waves and serum EPA levels in myocardial ischemic and non-ischemic subjects.

**Disclosures**

**Conflicts of interest:** None.
References


