Low Serum Levels of Eicosapentaenoic Acid and Docosahexaenoic Acid are Risk Factors for Cardiogenic Syncope in Patients with Brugada Syndrome

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Summary
The n-3 polyunsaturated fatty acids (PUFAs), including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have antiarrhythmic effects, possibly via modulation of the cardiac ion channels. Nevertheless, it is unknown whether low serum levels of n-3 PUFAs are risk factors for ventricular fibrillation in patients with Brugada syndrome (BrS). We retrospectively reviewed data from 62 men with BrS and evaluated their serum levels of EPA and DHA, and the risk factors for sudden cardiac death, including a history of cardiogenic syncope. Nineteen patients had a history of cardiogenic syncope, and their EPA and DHA levels were significantly lower than those of the patients without syncope. Multivariate logistic regression analysis revealed that low EPA and DHA levels were associated with the incidence of syncope. The receiver-operator characteristic curve showed the area under the curves of EPA and DHA for history of syncope were 0.84 and 0.72, respectively. In conclusion, low levels of EPA and DHA are risk factors for cardiogenic syncope in patients with BrS, which suggests that n-3 PUFAs play important roles in preventing ventricular fibrillation in BrS.

Key words: n-3 polyunsaturated fatty acids, Antiarrhythmic effects, Sudden cardiac death, Ventricular fibrillation

Brugada syndrome (BrS) is a genetic disease that is partially caused by a mutation in the cardiac sodium channel gene (SCN5A), and is characterized by a coved-type ST segment elevation in the right precordial leads and right bundle branch block in the patient’s electrocardiogram (ECG). This syndrome may lead to sudden cardiac death (SCD) due to ventricular fibrillation (VF). In addition, a history of syncope is confirmed predictors of adverse outcomes. Therefore, symptomatic patients of BrS should receive an implantable cardioverter defibrillator. Pharmacologic therapies, including quinidine, have been proposed to reduce the risk of life-threatening arrhythmias; however, no confirmed strategy for preventing SCD has been determined due to the lack of evidence.

The GISSI-Prevenzione trial has demonstrated that dietary supplementation with n-3 polyunsaturated fatty acids (PUFAs) reduced the rate of sudden death in patients with recent myocardial infarction. In addition, the relative risk of SCD is related to baseline blood levels of n-3 PUFAs. Furthermore, the n-3 PUFAs, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have antiarrhythmic effects, possibly via the modulation of cardiac ion channels. Therefore, low levels of n-3 PUFAs could be potential therapeutic targets for SCD in patients with BrS.

However, it is currently unknown whether low serum levels of n-3 PUFAs are risk factors for VF (as indicated by cardiogenic syncope) in patients with BrS. Therefore, the present study aimed to investigate the association between a history of syncope in patients with BrS and their PUFAs levels, including EPA and DHA. We hypothesized that low levels of n-3 PUFAs, including EPA and/or DHA, would be associated with the prevalence of cardiogenic syncope as represented by a history of syncope.

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The pathophysiology of BrS is not completely understood, although the depolarization hypothesis and the repolarization hypothesis have been proposed. EPA and DHA measurements were 1.3 and 3.3 %, and 1.5 and 2.2 %, respectively.

This study protocol was approved by the Tokushima University Hospital Ethics Committee and Shikoku Central Hospital Ethics Committee.

**Statistical methods:** Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as percentage. The associations between SCD risk factors, which include age, a family history of syncope, and a spontaneous type 1 ECG, were evaluated using Student’s t-test or Pearson’s correlation analysis. Multivariate logistic regression analysis was used to assess the degree of association between the level of EPA and DHA and the history of cardiac syncope. Levels of EPA and DHA for history of syncope were evaluated by the receiver-operating characteristic (ROC) curve.

All statistical analyses were performed using JMP software (version 10; SAS, Cary, NC, USA) for Student’s t-test and multivariate logistic regression analysis, and MedCalc (version 11; MedCalc software, Maria-kerke, Belgium) for ROC curve. Statistical significance was defined as a P value of < 0.05.

### Methods

We retrospectively reviewed data from 62 men (20-85 years old) with BrS and whose serum levels of EPA and DHA were measured in the Department of Cardiovascular Medicine at Tokushima University Hospital and in the Department of Internal Medicine at Shikoku Central Hospital between April 2013 and March 2015.

BrS was defined as a patient with ST-segment elevation with type1 morphology ≥ 2 mm in ≥ 1 lead among the right precordial leads V1, V2, positioned in the 2nd, 3 rd, or 4th intercostal space occurring either spontaneously or after provocative drug test with intravenous administration of Class I antiarrhythmic drugs, based on the 2013 consensus report. A history of cardiac syncope was considered present when the patient experienced an episode of syncope that was judged as likely being caused by ventricular arrhythmia. We excluded cases with syncope that was likely due to vasovagal events, such as those that occurred during abrupt postural changes, exposure to heat and dehydration, or emotional reactions. A family history of syncope was defined as an episode of sudden death that was judged as likely being caused by ventricular arrhythmia.

The exclusion criteria were structural cardiac abnormalities (observed via transthoracic echocardiography), untreated coronary arterial disease, a history of myocardial infarction, and the use of fish oil supplements or drugs that contained n-3 fatty acids. In addition, we excluded patients with symptomatic active malignant disease, electrolyte abnormalities, or liver/kidney dysfunction (aspartate aminotransferase levels of > 100 IU/L, alanine aminotransferase levels of > 100 IU/L, and serum creatinine levels of > 2.0 mg/dL).

Serum fatty acid composition, including levels of EPA and DHA was measured using gas-liquid chromatography at a commercial laboratory (SRL, Tokyo, Japan). The intra- and inter-assay coefficients of variation for the

### Results

The patients’ clinical characteristics: The patients’ characteristics with/without syncope are shown in Table I. There were no significant differences between the two groups except a spontaneous type1 ECG.

**Correlation between n-3 PUFAs levels and a history of syncope:** The serum levels of EPA and DHA are shown in Figure 1. The serum levels of EPA and DHA in patients with syncope (EPA 36 ± 16 μg/mL, DHA 108 ± 36 μg/mL) were significantly lower than those in patients without syncope (EPA 71 ± 38 μg/mL, DHA 143 ± 48 μg/mL).

Multivariate logistic regression analysis was used to identify the independent determinants of a history of syncope (Table II). The serum level of EPA and DHA were negatively associated with a history of syncope, but not age, family history, and spontaneous type 1 ECG.

The ROC curves of EPA and DHA for history of syncope are shown in Figure 2. The area under the curves of EPA and DHA for history of syncope was 0.84 and 0.72, respectively.

### Discussion

Our results indicate that low serum level of EPA and DHA was associated with cardiac events, which were representative by a history of syncope in patients with BrS. Previously, Okamura et al. have reported that a history of syncope in BrS was the most powerful predictive factor for arrhythmic events among their proposed risk factors, which included a spontaneous type 1 Brugada ECG and the inducibility of VF. Therefore, reducing the risk of syncope may significantly improve efforts to prevent SCD in BrS.

The pathophysiology of BrS is not completely understood, although the depolarization hypothesis and the repolarization hypothesis have been proposed. The depo-
The etiology of BrS is multifactorial, and involves genetic, environmental, and hormonal components.16-18) Numerous animal/clinical reports have described the secondary prevention of SCD/ventricular arrhythmias after myocardial infarction or heart failure using n-3 PUFAs.19) In addition, epidemiological studies have demonstrated that dietary fish oil intake is associated with a low risk of myocardial infarction or heart failure using n-3 PUFAs.14) Secondary prevention of SCD/ventricular arrhythmias after myocardial infarction or heart failure using n-3 PUFAs.14) The present study had several limitations. First, we used a retrospective design with a small sample size at two centers. Second, we did not show evidence of VF in the patients labeled as cardiogenic syncope. Third, we could not evaluate the level of EPA/DHA at the time of syncope. Therefore, larger clinical cohort studies are needed to clarify the effects of n-3 PUFAs on VF in patients with BrS.

Table II. Logistic Multiple Regression Analysis for Determinants of History of Syncope in Brugada Syndrome

<table>
<thead>
<tr>
<th>Variables</th>
<th>Coefficient</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motel *</td>
<td>0.03</td>
<td>-0.01 to 0.08</td>
<td>0.20</td>
</tr>
<tr>
<td>Age, years</td>
<td>0.03</td>
<td>-0.01 to 0.08</td>
<td>0.20</td>
</tr>
<tr>
<td>Family History</td>
<td>0.35</td>
<td>-0.44 to 1.18</td>
<td>0.39</td>
</tr>
<tr>
<td>Spontaneous Type 1 ECG</td>
<td>-0.43</td>
<td>-1.15 to 0.26</td>
<td>0.23</td>
</tr>
<tr>
<td>EPA, µg/mL</td>
<td>-0.07</td>
<td>-0.12 to -0.03</td>
<td>0.004</td>
</tr>
<tr>
<td>Model 2**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>0.03</td>
<td>-0.01 to 0.07</td>
<td>0.19</td>
</tr>
<tr>
<td>Family History</td>
<td>0.31</td>
<td>-0.46 to 1.09</td>
<td>0.42</td>
</tr>
<tr>
<td>Spontaneous Type 1 ECG</td>
<td>-0.51</td>
<td>-1.20 to 0.15</td>
<td>0.13</td>
</tr>
<tr>
<td>DHA, µg/mL</td>
<td>-0.02</td>
<td>-0.04 to -0.01</td>
<td>0.02</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; ECG, electrocardiogram; EPA, eicosapentaenoic acid; and DHA, docosahexaenoic acid. *r² = 0.30; P < 0.0001, **r² = 0.18; P < 0.0001.

Figure 1. A comparison of the levels of EPA and DHA with and without a history of syncope (*P < 0.001). EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid.

Figure 2. Receiver-operator characteristic curves for history of syncope in Brugada syndrome. AUC: area under the curves; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid.
Conclusion

Low serum levels of EPA and DHA are risk factors for cardiogenic syncope in patients with BrS, which suggests that EPA and DHA play important roles in preventing VF.

Acknowledgments

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Disclosures

Conflicts of interest: The authors declare that they have no conflicts of interest to disclose.

References