Genetic and environmental factors in cardiac sodium channel disease

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Influence of meals on variations of ST-segment elevation in patients with Brugada syndrome


ABSTRACT

Background
Glucose-induced insulin secretion is one of contributing factors to fluctuation of ST-segment elevation in Brugada syndrome.

Objectives
The purpose of this study was to explore the influence of meals on variations of ST elevation in Brugada syndrome.

Methods
We assessed changes of ST-segment elevation in lead V1-3 on ECG before and after taking meals, at midnight and at 3:00 a.m. in 20 patients with Brugada syndrome. Plasma glucose, insulin and K+ concentrations were measured. Variations of ST elevation were defined as morphological changes and/or augmentation of ST-segment level by >1.0 mm.

Result
Variations of ST segment morphology or elevation level after meals were observed in 15 of 20 patients (75%). ST elevation was augmented most markedly after dinner (3.3 ± 1.7 mm) and decreased both at midnight (2.6 ± 1.3 mm: P < 0.01 vs after dinner) and at 3:00 a.m. (2.4 ± 1.2 mm: P < 0.01 vs after dinner). Morphologic changes and elevation levels of ST segment were associated with changes in glucose-induced insulin levels after meals, being highest after dinner (47 ± 33 μU/ml) and decreasing significantly at midnight (7 ± 4 μU/ml) and at 3:00 a.m. (5 ± 2 μU/ml). There were no correlations between ST elevation and changes in serum K+ level or heart rate.

Conclusions
The present findings suggest that variations of ST elevation are frequently associated with meals. Aggravation of ST elevation is most prominent in the evening to night after dinner rather than the period between midnight and early morning. This information may help to predict event times at high risk for life-threatening arrhythmias in Brugada syndrome.
INTRODUCTION

After the first report by Brugada and Brugada\(^1\), the patients with Brugada syndrome are widely recognized at high risk for sudden cardiac death due to ventricular fibrillation (VF)\(^2\)\(^\text{-}^6\). A specific type of ST-segment elevation (coved-type or Type 1) in patients with Brugada syndrome is assumed to be diagnostic and to represent a sign for high risk of arrhythmic events\(^2\)\(^\text{-}^6\)\(^,\)\(^7\)\(^,\)\(^9\)\(^,\)\(^10\). The level and morphology of ST elevation in these patients, however, spontaneously fluctuate by time, and typical ECG changes do not exhibit a stable expression, but undergo variable changes in the degree and shape\(^3\)\(^\text{-}^4\)\(^,\)\(^6\)\(^,\)\(^7\)\(^,\)\(^9\)\(^,\)\(^10\). Multiple factors are thought to influence ST-segment elevation and such factors include changes in heart rate, body temperature, autonomic imbalance, sodium channel blockers and others\(^3\)\(^,\)\(^4\)\(^,\)\(^10\)\(^\text{-}^13\). We have recently reported that ST-segment elevation is associated with increased plasma insulin levels during oral glucose tolerance test in patients with Brugada syndrome. Glucose-induced insulin secretion is a key factor for variation of ST-segment elevation\(^14\)\(^,\)\(^15\). Furthermore, a recent report suggests that ECG abnormalities in patients with Brugada syndrome are unmasked by the full stomach test taking large meals\(^16\).

There have been, however, no studies as to variations of ST-segment elevation associated with taking meals in comparison with midnight and early morning on 12 lead ECG in patients with Brugada syndrome. This study was designed to examine the influence of meals and vagal influence after food intake on ST-segment elevation, and to explore possible link between insulin secretion after meals and variations of ST-segment elevation.

METHODS

Study Patients

The study population included 20 consecutive patients with Brugada syndrome (18 men; mean age 54 ± 14 years, range 31 to 78 years) who had either persistent or transient ST-segment elevation (≥ 2 mm) of coved type (type 1) in leads V1-V3. ST-segment elevation includes spontaneous appearance and the one induced by intravenous administration of sodium channel blocker (pilsicainide 1 mg/kg body weight). The study protocol was approved by the ethic committees at the Yokohama Minami Kyosai Hospital and the Tokyo Metropolitan Hiroo General Hospital. Written informed consent was obtained from all the subjects.

All patients were admitted for the study and followed at either the Yokohama Minami Kyosai Hospital or Tokyo Metropolitan Hiroo General Hospital between April 2003 and October 2006. Six of 20 patients had a history of aborted cardiac arrest or unexplained
syncope. Three patients had a family history of sudden cardiac death of unknown etiology. All patients had no evidence of structural heart diseases revealed by echocardiogram, ventriculography, radionuclide examination, and coronary angiography, including provocation test for vasospastic angina using infusion of acetylcholine into the coronary artery. All 20 patients were subjected to provocation of ST elevation on 12-lead ECG by an oral glucose tolerance test. Thirteen of 20 patients had morphologic changes in ST-T wave and/or augmentation of ST elevation (>1.0 mm) in leads V1 to V3 after the glucose load. Fifteen patients underwent an invasive electrophysiological study during fasting state, involving programmed ventricular stimulation (PVS) from two sites of the right ventricular apex and right ventricular outflow tract applying up to triple extrastimuli at basic cycle lengths of 600 and 400 msec. VF was induced in all 15 patients by PVS with 2 to 3 extra stimuli.

The patients in this study had negative results on physical examination and demonstrated no overt diabetes mellitus, renal disease, nor endocrine disorders. Also excluded were subjects with a systolic blood pressure >140 mmHg, a diastolic blood pressure >85 mmHg, a total cholesterol >12.2 mmol/liter (220 mg/dl), a triglyceride >8.3 mmol/liter (150 mg/dl), a high-density lipoprotein cholesterol <2.2 mmol/liter (40 mg/dl) or a body mass index >25kg/m².

**Plasma glucose, insulin and K⁺ level during a period of 24 hours**

Blood samples were taken for measurement of plasma glucose (mgl/dL), plasma immunoreactive insulin concentration (IRI: μU/mL) and K⁺ level (mEq/L) before and after breakfast, lunch, and dinner, at midnight and at 3:00 a.m. All patients took a dairy diet of about 1800 calories. The volume and calories were divided equally into breakfast, lunch and dinner. We examined all parameters at 60 minutes after taking meals, since our previous observations confirmed the peak value of plasma glucose and prominent changes in ST-T waves at 60 minutes after glucose load. Plasma samples were stored at -20°. Each sample was assayed for glucose and IRI. Plasma glucose was determined with an autoanalyser using a glucose oxidase method. IRI was assessed by radioimmunoassay method using an antihuman insulin antibody.

**ST-segment elevation and ST-T wave changes in V1-V3 of 12-lead ECG**

ST-segment elevation and ST-T wave changes were measured in all 12-leads of ECG recorded at a paper speed of 25 mm/second for two consecutive cardiac cycles before and 60 minutes after each meal, at midnight and at 3:00 a.m. The electrodes in precordial leads were placed on the fixed positions in order to prevent electrode displacements during the whole day of study and 12-leads of ECG were recorded in the fixed supine position.
The variations of ST-segment were considered positive when augmentation (>1.0 mm) of ST elevation or development of morphologic change of ST-T waves in lead V1 to V3. A positive morphologic change of ST-T waves was defined as transformation from normal ST segment or saddle-back type to coved-type ST elevation or vice versa. Amplitude of ST-segment elevation at the J point in lead V1 to V3 was also measured at each occasion. Two independent experienced observers who were unaware of the clinical data performed the measurement and analysis.

**STATISTICAL ANALYSIS**

Data are expressed as a mean value ± SD, except for those shown in Figure 1, which are expressed as mean ± SEM. Multiple comparisons of continuous variables were performed by analysis of variance (ANOVA), coupled with Scheffe's test. Pearson chi-square test was used for comparison among noncontinuous variables. Variations of ST-segment morphology during the whole study period were analyzed by Friedman's test. A P value < 0.05 was considered significant.

*Figure 1.* Variations of ST-segment morphology in 20 patients. Changes in ST-segment morphology indicate transformation from normal ST segment or saddle-back-type ST elevation to coved-type or vice versa. Coved = coved-type, saddle-back = saddleback-type, normal = normal ST segment. Solid arrow lines indicate aggravation of ST-segment morphology (saddle-back to coved type, or normal to saddle-back type), whereas broken arrow lines represent the improvement of morphology (coved to saddle-back type and to normal, or saddle-back type to normal). The same interpretation of arrows applied to this and following figures. Numbers in the squares indicate numbers of cases that showed types of ST elevation indicated on the left (normal, saddle-back and coved). Numbers along arrows represent numbers of cases in which changes in ST-segment before and after meals, at midnight and at 3:00 a.m. were seen. Thick solid and broken arrows indicate changes observed most prominently after dinner and midnight (P < 0.01).
RESULTS

Morphological changes in ST-segment associated with meals

Variations of ST-segment morphology (coved, saddle-back or normal) were observed in 10 of 20 patients (50%). Their changes associated with meals are summarized in Figure 1. ST-segment morphology changed from saddle-back to coved type after meals in 6 cases; one case from normal to saddle-back type was also observed after meals. Coved-type ST-segment elevation after breakfast and lunch among 4 cases returned to saddle-back type before lunch in one and before dinner in another one case. Four of 6 cases with coved type after dinner changed to saddle-back type ST-segment elevation at midnight and another one to normal type at 3:00 a.m.

Thus, there was a significant correlation in ST-segment morphology changes among time periods before and after meals, at midnight and at 3:00 a.m. ($P < 0.01$). Typical examples showing morphological changes in ST-segment from saddle-back to coved type after breakfast and after dinner, returning to saddle-back at midnight and at 3:00 a.m. are shown in Figures 2 and 3.

Therefore, taking meals appeared to induce transformation of ST-segment morphology from saddle-back to coved type or normal to saddle-back type. ST-segment

![Figure 2](image.png)

**Figure 2.** A typical case presentation showing morphological variations of ST-segment associated with taking meals. Saddle-back type ST-segment before each meal changed to coved type after breakfast, lunch and dinner. ST-segment morphology returned to saddle-back type at midnight and at 3:00 a.m. from coved-type. Please note that the changes are most markedly present in lead V2.
morphism after meals shifted in an opposite direction of transformation at the times before meals, midnight and 3:00 a.m. in 10 (50%) patients.

**Changes in ST-segment elevation, plasma glucose, insulin and K⁺ levels, and heart rate**

In addition to changes in ST-segment morphology, changes in ST elevation levels after meals were also observed in many patients. To quantify changes in ST-segment associated with taking meals, we evaluated variations of ST elevation levels. The most prominent augmentation of ST elevation was observed in lead V2 in all patients and, therefore, the level of ST elevation was measured at J point in lead V2. Positive variation in ST elevation level (>1.0 mm) was observed in 14 (70%) of 20 patients. Mean values of amplitude of ST elevation were 2.9 ± 1.4 mm before breakfast and 3.1 ± 1.4 mm after breakfast. Those values for lunch were 2.9 ± 1.4 and 3.0 ± 1.4 and for dinner were 3.0 ± 1.6 and 3.3 ± 1.7 mm, respectively. ST elevation increased after each meal, with the most prominent elevation after dinner (P < 0.05 vs before dinner). ST elevation decreased at midnight (2.6 ± 1.3 mm; P < 0.01 vs after dinner) and at 3:00 a.m. (2.4 ± 1.2 mm; P < 0.01

**Figure 3.** Another example showing morphological variations of ST-segment associated with taking meals. Typical coved-type ST-segment appeared after breakfast and after dinner returning to saddle-back type at midnight and at 3:00 a.m. in lead V2.
vs after dinner). In individual cases, the maximal degree of ST elevation was observed after breakfast in 7 (35%) and after dinner in 12 (60%) patients. The minimal level of ST elevation was recorded at midnight or at 3:00 a.m. in 17 (85%) patients.

Changes in ST elevation level associated with meals were compared to measured values of serum glucose and IRI (Figure 4A, B and C). ST levels increased after meals and decreased at midnight and 3:00 a.m. Changes in plasma glucose and IRI showed similar tendency of changes to those of ST levels. Plasma glucose and IRI level increased significantly after meals and decreased significantly at midnight and at 3:00 a.m., compared to those after dinner. The maximal plasma glucose level was observed after breakfast in 8 (40%) and after dinner in 10 (50%) patients. The maximal IRI level was seen after breakfast in 11 (55%) and after dinner in 8 (40%) patients. The minimal plasma glucose level was before breakfast in 7 patients, but was detected at any times before other meals, midnight and 3:00 a.m. in the remaining 13 patients. The minimal IRI level was observed at midnight and/or 3:00 a.m. in 12 (60%) patients.

Since the maximal elevation of ST level and peak values of serum glucose and IRI were observed after breakfast and after dinner in most cases, the correlation among three
parameters as to the peak changes was assessed. The numbers of patients with the maximal elevation of ST level after breakfast or dinner correlated with those exhibiting the maximal glucose and IRI values at corresponding times ($P < 0.01$). There was also a correlation between the numbers of patients showing the minimal elevation of ST level and those with the minimal IRI value at midnight or at 3:00 a.m. ($P < 0.05$). However, the minimal glucose value was not statistically correlated to the minimal ST level in these patients.

**Figure 5** represents a typical example showing changes in ST-segment elevation associated with meals in a case of coved type ST morphology in whole day.

The plasma $K^+$ levels during the whole study period ranged from 3.7 to 4.4 mEq/L. The values were not significantly different among all measurements.

Heart rate increased significantly after meals, compared with the rate before each meal, and decreased at midnight ($57 \pm 8$ bpm; $P < 0.01$) and at 3:00 a.m. ($56 \pm 8$ bpm; $P < 0.01$) compared with the value after dinner (**Figure 4D**). The lowest mean heart rate was observed at 3:00 a.m. There were no correlations between the maximal or the minimal elevation of ST level and heart rate or $K^+$ level in any time.

![Figure 5](image_url)

**Figure 5.** Variations of ST elevation after taking meals in a patient showing persistent coved-type ST-segment in whole day. The morphology of ST-segment was not changed whole day, but ST elevation level after taking meals apparently increased, compared with the one before meals. At midnight and 3:00 a.m., the level of coved-type ST-segment elevation decreased.
DISCUSSION

In the present study, patients with Brugada syndrome exhibited variations of ST-segment elevation in association with meals. Augmentation and morphologic change in ST-segment elevation most prominently developed after dinner, and reduced at midnight and at 3:00 a.m. The variations were associated with food intake, especially with glucose-induced insulin level after meals. The findings suggest that variations of ST elevation become highly aggravated in the evening to night after dinner rather than at midnight to the early morning in patients with Brugada syndrome.

**Influence of meals on ST-segment abnormalities**

ST-segment elevation and its morphology in Brugada syndrome are influenced by various factors including drugs, autonomic tones, and body temperature. We recently reported that morphologic changes and augmentation of ST-segment elevation were associated with increased plasma insulin level during oral glucose tolerance test in patients with Brugada syndrome. Other study also confirmed augmented ST-segment elevation after glucose and insulin. We suppose that augmentation of ST-segment elevation associated with glucose tolerance test might be due to effects of insulin on ionic channels and transporter. Ikeda et al. reported that ST-T abnormalities in Brugada syndrome were induced by a large meal. They supposed that a stomach rapidly filled with a large meal might increase vagal tone to cause such changes in ST-segment. Therefore, in the present study, we tested the hypothesis that glucose-induced insulin secretion after taking meals might be a contributing factor to induce variations of ST-segment elevation, rather than increased vagal tone induced by stomach dilatation due to food intake. For this purpose, we divided food intake of equal quantities and calorie into three meals, while measurements of ST-segment elevation together with IRI, glucose and serum K⁺ levels were done before and after each meal, at midnight and at 3:00 a.m. In the latter two timings, when vagal activity was supposed to be increased. We found that augmentation and morphologic changes in ST-segment elevation developed after taking meal, especially after dinner followed by after breakfast, despite equal amount and calories of food intake in all three meals. The changes decreased at midnight and at 3:00 a.m. Therefore, we assumed that the changes in ST elevation after meal could be related to the timing of taking meal rather than a simple increase in vagal tone due to a large volume of food intake or vagotony during midnight to early morning. To the best of our knowledge, this study is the first to evaluate the relation between taking three meals and variations of ST-segment elevation in patients with Brugada syndrome.
Possible mechanism of variations of ST-T waves during a period of 24 hours

Arrhythmic events have been reported to occur frequently during sleep between at 10 p.m. and early-morning hours, and especially around midnight. Matsuo et al. demonstrated that VF episodes were more frequently detected at night and during sleep than in the daytime while awake in patients with Brugada syndrome who underwent ICD implantation. It was reported that increased vagal activity promoted ST-segment elevation and increased susceptibility to VF induction. It was further suggested that not only increased vagal tone but also bradycardia itself, having abnormal response of repolarization properties to heart rate changes, could contribute to manifestations of ST elevation and the initiation of arrhythmic events around midnight in symptomatic patients with Brugada syndrome.

In this study, the level of ST-segment elevation and ST-T wave changes decreased at midnight and in the early morning (3:00 a.m.) when heart rate decreased significantly, compared with those after dinner. Moreover, the maximal level of ST-segment elevation was frequently observed after dinner and after breakfast as the second predominance, although the degree of elevation was not necessarily maximal after dinner in all patients.

The minimal level of ST elevation occurred at midnight or 3:00 a.m. Therefore, we assume that high vagal tone and bradycardia cannot be major contributing factors to cause ST-segment elevation. Since variations of ST segment elevation is associated with glucose and insulin levels after meals, especially after dinner, we assume that glucose-induced insulin secretion after dinner is causally related to the development of prominent ST-segment elevation. It was not clarified from this study, however, why ST elevation became most prominent after dinner, compared with the times after other meals, in Brugada syndrome. There might be complex interactions with insulin levels and other factors to cause ST elevation. For example, dynamic changes in decreasing sympathetic tone with increasing vagal activity might be involved in the genesis of ST elevation, since abnormal MIBG-uptake indicating presynaptic sympathetic dysfunction was dominantly observed in cases with coved-type ST elevation. Further study is necessary to clarify the actual factors and their roles involved in variations of ST-segment elevation.

Insulin has been shown to cause hyperpolarization of membrane potential through activation of the Na⁺-K⁺ pump, which activated outward current during the plateau phase. Although the serum K⁺ concentrations were not changed after meals in this study, the possibility that increased K⁺ gradient across the immediate vicinity of cell membrane could affect the repolarization process or different effects between epicardial and endocardial cells of the ventricular wall could not be excluded. These factors might contribute to the ST-segment abnormalities observed in Brugada syndrome. Moreover, high glucose and insulin level after taking meals would also change the characteristics of other factors, such as autonomic tones, plasma viscosity, and other ion...
channels\textsuperscript{28,29}. Therefore, complex effects of all the above factors might influence variations of ST-segment elevation in patients with Brugada syndrome.

**CLINICAL IMPLICATION**

ST-segment elevation in patients with Brugada syndrome was most prominently aggravated in the evening to night after dinner, rather than at midnight to early morning, when a high probability to develop life-threatening ventricular arrhythmias was expected because of increased vagal tone and resultant bradycardia. Actually, VF episodes have been reported to occur in some patients from evening to midnight while awake, after taking meals\textsuperscript{10,16,18}. In this study, among 6 symptomatic patients, syncope attacks were observed after breakfast in one and after dinner in 3 patients. Another possibility is that while cellular mechanisms for developing ventricular tachyarrhythmias for the basis of increased disparity of repolarization are thought to be caused by various ionic currents, multiple factors appear to be involved in the development of cardiac events in humans. These factors include increased vagal tone, bradycardia, glucose and insulin level after meal and the timing of dinner. Further study is necessary to delineate complex interaction of these multiple factors for perpetuation from aggravated ST-segment elevation to development of life-threatening arrhythmias in patients with Brugada syndrome.

**STUDY LIMITATION**

The study population of Brugada patients was small—only 20 cases. Genetic and clinical backgrounds for possible etiological factors might not be uniform. Reproducibility of ST segment elevation and changes was not confirmed in this study. Furthermore, we didn’t clarify the relationship between variation of ST-segment elevation and the outcome of clinical symptoms, such as syncope and ventricular fibrillation. We need a large-scaled prospective study to clarify actual development of cardiac events and clinical significance of the effects of taking meals in patients with Brugada syndrome.

**CONCLUSIONS**

Augmentation and morphologic changes in ST-segment elevation occurred frequently after taking meals, especially dinner, than at midnight or in the early morning in patients with Brugada syndrome. Variations of ST elevation were associated with glucose-induced
insulin level after meal. Further study is required to clarify the clinical significance of our observations.
REFERENCES


