A Case of Brugada Syndrome in Which Diurnal ECG Changes Were Associated With Circadian Rhythms of Sex Hormones

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Summary

We describe a thought-provoking case of Brugada syndrome in which a relationship between the diurnal electrocardiogram (ECG) changes and sex hormone levels was observed. A 36-year-old man who experienced cardiac arrest was referred to our hospital. He had a family history of sudden cardiac death. The 12-lead ECG exhibited a mild coved type ST-segment elevation in leads V1 and V2, which was enhanced by intravenous pilocarpine injection. Hence, this case was diagnosed as Brugada syndrome. The circadian rhythm of the serum testosterone level revealed low levels in the daytime (1.66-1.99 ng/mL) and high levels (2.52-3.42 ng/mL) in the nighttime. Interestingly, augmentation of the ST segment elevation and widening of the P wave were observed at around 2:00 AM, when the serum testosterone was recorded at its highest. Our report discusses the influence of the circadian rhythms of sex hormones on the ECG changes in Brugada syndrome. (Int Heart J 2009; 50: 669-676)

Key words: Brugada syndrome, Testosterone, Diurnal electrocardiogram changes

It has been reported that Brugada syndrome occurs predominately in males compared to females. In the cellular electrophysiological field, it has been shown that there are gender-related differences in cardiac repolarization, and gonadal steroids have direct effects on repolarizing potassium currents. In addition, androgen receptors have been identified in the myocardium and it has been suggested that testosterone may augment outward repolarizing currents such as the IK1 and IKr currents, and the expression of Ito may also be regulated by testosterone. Moreover, a case report demonstrating that the Brugada type ECG...
pattern disappeared following surgical castration was recently published by Matsuo, et al.\(^3\)

Recently, Shimizu, et al demonstrated that Brugada males had a significantly higher testosterone level and lower body mass index, and speculated that
the higher testosterone level associated with a lower visceral fat mass might play a significant role in the Brugada phenotype and male predominance of Brugada syndrome. Thus, much attention has been focused on the gender-dependent differences in Brugada syndrome.

We experienced a case of Brugada syndrome in which a relationship between the diurnal ECG changes and sex hormone levels was observed. In this report, we discuss the influence of sex hormones on the specific ECG changes in Brugada syndrome.

**Case Report**

A 36-year-old man presented with palpitations lasting for 2 years. He had no history of fainting or syncope, or a family history of sudden cardiac death. On June 7, 2004 he experienced a cardiac arrest just after defecation and was admitted to Asahikawa Red Cross Hospital, and cardiopulmonary resuscitation was successfully performed. A 12-lead ECG after the cardioversion revealed a mild coved type ST-segment elevation in leads V1 and V2 and its enhancement was induced by pilsicainide administration in the chronic stage, and hence, this case was diagnosed as Brugada syndrome (Figures 1 and 2). Thereafter, he was referred to Asahikawa Medical College Hospital for close examination and

![Diurnal changes in total testosterone level](image)

**Figure 3.** Diurnal changes in total testosterone level. The circadian rhythm of the testosterone level is shown. As shown in the panel, analysis of the diurnal rhythm of the total serum testosterone level revealed low levels in the daytime (166-199 ng/mL) and high levels (252-342 ng/mL) at nighttime. The peak testosterone level in this case was recorded at 2:00 AM, which was close to the time of the spontaneous ventricular fibrillation attack episode.
Figure 4. Diurnal ECG changes. The circadian changes in the ECG in this patient are demonstrated. Note that augmentation of the ST segment elevation and widening of the P wave were observed at 2:00 AM when the highest value of the serum testosterone level was recorded.

Figure 5. Relationship between the diurnal ECG changes and sex hormone levels.
implantation of an implantable cardioverter defibrillator (ICD). Analysis of the diurnal rhythm of the total serum testosterone level revealed low levels in the daytime (1.66-1.99 ng/mL) and high levels (2.52-3.42 ng/mL) at nighttime (Figure 3). Interestingly, although the absolute value of the serum testosterone was relatively low in this patient (the reference range of testosterone in Japanese male adults has been reported to be 2.01-7.50 ng/mL), augmentation of the ST segment elevation and widening of the P wave were observed at 2:00 AM when the highest value of the serum testosterone level was recorded (Figures 4 and 5).

Figure 6 shows the diurnal serum testosterone changes observed in 4 patients with Brugada type-ECGs without any Vf. This figure shows the typical diurnal

<table>
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<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Familial history of sudden cardiac death</th>
<th>ECG</th>
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<tr>
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<td>(-)</td>
<td>coved type ST elevation in V1</td>
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<tr>
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<td>(-)</td>
<td>coved type ST elevation in V1 after pilsicainide</td>
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<tr>
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<td>male</td>
<td>(-)</td>
<td>coved type ST elevation in V1</td>
</tr>
<tr>
<td>4</td>
<td>56</td>
<td>male</td>
<td>(-)</td>
<td>coved type ST elevation in V1</td>
</tr>
</tbody>
</table>

**Table.** Characteristics of Four Patients With Brugada-Type ECG Without any Vf
changes in the serum testosterone level (highest early in the morning, and lowest late in the afternoon) in patients with asymptomatic Brugada syndrome, whose pattern was compatible with a previous report in healthy subjects.\(^6\)

ICD implantation was performed in this patient since he had a history of a cardiac arrest and family history of sudden cardiac death, and his pilscainide provocation test was positive. After 5 years and 6 months of follow-up, the patient has been asymptomatic without any ICD delivery events.

**DISCUSSION**

Recently, much attention has been focused on the gender-dependent differences in cardiac repolarization and the effects of sex hormones on repolarizing potassium currents since the phenotype and symptoms of Brugada syndrome are predominately observed in males. The cellular basis for the male predominance of Brugada syndrome has mainly been studied by Antselevitch and coworkers. They demonstrated that no sex differences were observed in the left ventricular epicardial cells whereas the Ito density was smaller in the epicardial cells isolated from female rather than male right ventricles, and thereby the phase 1 amplitude was significantly smaller in males than in females.\(^7\) Since a prominent Ito-mediated epicardial action potential notch is thought to be a prerequisite for Brugada syndrome and recently an Ito-related genetic disorder has also been reported,\(^8\) it is expected that testosterone induced Ito changes might be one of the main mechanisms for the male predominance of Brugada syndrome, and the susceptibility to phase 2 reentry might also be caused by the differences in the amplitude of phase 1 and the shortened action potential duration in male epicardial cells due to the gender-dependency of Ito currents.

It has recently been shown that androgen receptors exist in the myocardium.\(^1\) In addition, in the cellular electrophysiological field, it has been suggested that testosterone may augment outward repolarizing currents, such as the IK1 and IKr currents, and the expression of the Ito current may also be regulated by testosterone.\(^1\) Furthermore, the Ito current has been shown to mainly be dependent on the KV4.2/4.3 channel activity, and recent experimental evidence has suggested that the Kv4.2 channel exhibits a characteristic circadian pattern in its gene expression, namely, the Kv4.2 mRNA level tends to be larger at Zeitgeber time 6 than at Zeitgeber time 18.\(^9\)

In the present case, the time of the spontaneous ventricular fibrillation (Vf) attack episode and time of the peak testosterone level were very close. Furthermore, the Brugada-type ST-segment changes were more pronounced at midnight when the highest value of the serum testosterone level was recorded. In addition, as shown in Figure 6, while patients with Brugada type-ECG without any
Vf attacks exhibited typical diurnal changes in the serum testosterone level (the value was the highest early in the morning, and lowest late in the afternoon), the present case with a Vf attack exhibited different diurnal changes in which the serum testosterone level was the highest in the middle of the night.

Diurnal changes in the electrocardiographic indices such as the P wave duration, P-R interval, QRS duration, and QT interval have been reported in healthy subjects. In addition, rate-dependent right bundle branch block (RBBB) has occasionally been noted in the clinical setting. In our case, the augmentation of the ST segment elevation observed at 2:00 AM shown in Figure 5 was not associated with deep S waves in the left precordial leads or significant heart rate changes, suggesting that those changes were considered to be elevation of the J wave rather than rate-dependent RBBB, which was consistent with Brugada-type ECG changes.

In Brugada syndrome, it has been shown that spontaneous augmentation of the ST elevation in daily life occurs along with an increase in the vagal activity. Therefore, the night-predominance of the circadian pattern of the Brugada-type ECG observed in this case may be partially explained by the parasympathetic activity which may have caused enhanced acetylcholine-sensitive K channel activity or suppression of the Ca channel activity. On the other hand, evidence is accumulating that sex hormones exert nongenomic actions - actions that are too rapid to be accounted for by the activation of RNA and protein synthesis. Since nongenomic actions are frequently associated with the activation of various protein-kinase cascades, there is a possibility that sex hormones may act as multichannel blockers. Furthermore, it has recently been shown that estradiol inhibits HERG-mediated potassium and SCN5A-mediated sodium currents, whereas epiandrosterone blocks L-type calcium channels. Hence, it is speculated that there is another possibility that the ST segment elevation may correlate with the ion channel activity influenced by the testosterone level and subsequent changes in the gene expression and nongenomic actions as discussed above.

In conclusion, it is suggested that the diurnal Brugada-type ECG changes may be modulated by not only the autonomic nervous tone, but also (at least in part) the diurnal changes in the testosterone level.

Limitations: Since our report was based on only a few cases, we could not conclude anything about the relationship between the diurnal ECG changes and circadian rhythms of sex hormones. Furthermore, not only sex hormones but also parasympathetic activity and other multi-factors might have contributed to the genesis of ventricular fibrillation in Brugada syndrome. Further studies from the basic and clinical points of view will be needed to clarify those points.
References