Recurrent ventricular fibrillation in a patient with inferolateral early repolarization and higher testosterone level

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Introduction
An early repolarization (ER), defined as a J-wave elevation in inferolateral leads, is usually considered benign, because it is often observed in 1%–10% of healthy individuals, such as young people and athletes.1 Several studies, however, indicated that an ER pattern was associated with the development of ventricular fibrillation (VF) in patients with idiopathic VF.2,3 On the other hand, a recent study reported that an ER pattern was associated with life-threatening ventricular arrhythmias in patients with vasospastic angina (VSA).4 Therefore, early repolarization syndrome (ERS) may be related to the occurrence of VF in a certain number of patients with VSA. Testosterone, which modulates L-type calcium channel current, is reported to regulate cardiac repolarization and influences ST segment,5 and may be related to male predominance in Brugada syndrome.6

Here, we report the case of a patient who was initially diagnosed with VSA and demonstrated recurrent VF and inferolateral ER pattern. A pilsciaainide provocation test induced peculiar J-wave and ST-segment elevation, and both L-type calcium channel blockers and higher testosterone level could exacerbate the occurrence of VF.

Case report
A 22-year-old man who was implanted with an implantable cardioverter-defibrillator (ICD) was admitted to our hospital for the management of several episodes of VF and ICD shocks in the early morning (from 5 AM to 8 AM). At the age of 20 years, he had experienced the first episode of syncope after exercise at 11 PM. An acetylcholine provocation test during coronary angiography showed a positive result and he was diagnosed with VSA at a local hospital. He was implanted with an ICD and was started on nifedipine (20 mg/day). However, he had experienced 2 episodes of appropriate ICD shocks for VF during the 2 years after ICD implantation and several episodes of VF on the day of the admission even though nifedipine was administered.

On admission to our hospital, his height, weight, and body mass index were 173 cm, 60 kg, and 20.05, respectively. A 12-lead electrocardiogram demonstrated J wave followed by descending ST segment in inferior leads and notched-type J wave in lateral leads, and slightly shortened QT interval (QTc was 357 ms in V4 lead) (Figure 1). Two-dimensional transthoracic echocardiography revealed normal left ventricular systolic function (ejection fraction 61%) with normal left ventricular wall motion and failed to detect any organic heart diseases. Intravenous administration of pilsciaainide (50 mg) accentuated J-wave and ST-segment elevation, and both L-type calcium channel blockers and higher testosterone level could exacerbate the occurrence of VF.

KEY TEACHING POINTS
- A young man with early repolarization syndrome exhibited peculiar J-wave and ST-segment elevation after pilsciaainide provocation.
- Cilostazol attenuated both J-wave and ST-segment elevation, and effectively suppressed ventricular fibrillation (VF) recurrence.
- Both calcium channel blockers and higher testosterone level could exacerbate the occurrence of VF recurrence.

KEYWORDS Ventricular fibrillation; Early repolarization; J wave; Testosterone; Cilostazol

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exercise test, J-wave and ST-segment elevation decreased, as demonstrated in the isoproterenol provocation test.

According to these findings, ERS was suggested to be the main cause of recurrent VF in this patient. Therefore bepridil (100 mg/day), which is a calcium antagonist with fast kinetic block of sodium current that inhibits most types of potassium currents, including Ito, was started. However, 100 mg of bepridil did not affect J-wave and ST-segment elevation in inferolateral leads, and he experienced an appropriate ICD shock for VF recurrence at 2 AM 1 month after an initiation of bepridil. Hence, cilostazol (150 mg/day) was added and it attenuated J-wave and ST-segment elevation in inferior leads and J-wave elevation in lateral leads (Figure 3A).

We performed a genetic test and he carried a KCNA5 frameshift mutation, which related to atrial fibrillation. However, he did not carry CACNA1C, CACNB2, CAVN3A2D1, KCNJ8, and KCND2 mutations, which had been reported as the ERS-associated variants. Because his mother’s uncle died suddenly at the age of 20 years and there were only a few men among his mother’s relatives (Figure 1C), some gene mutations associated with the sex hormones were supposed to play a causative role in this case. Therefore, we checked genes related to the sex hormones, including androgen receptor, and no mutations were detected. We did not perform genetic test of his mother and her relatives, because they did not consent to the test. We also checked his sex hormones and a higher level of total testosterone (1020 ng/mL) was detected. After the administration of cilostazol, he has not experienced any ICD shocks for over 1 year.

Discussion

This is a case report of a young patient with VSA and inferolateral ER pattern, who showed peculiar ST-T change during the pilsicainide provocation test. On the other hand, he demonstrated a higher testosterone level, as reported in patients with Brugada syndrome. The peculiar ST-T change after pilsicainide provocation could have some relationship with a higher testosterone level in this case.

Initially, VSA was assessed as the cause of VF in this case, because he demonstrated the first VF episode at midnight and also had subsequent VF episodes after smoking and/or drinking. In patients with VSA, angina attacks mainly occur between midnight and early morning, and the ER pattern could be associated with the development of VF. In the present case, it was uncertain whether the cause of VF was ERS or VSA, and therefore we prescribed 100 mg/day of bepridil, which is a calcium antagonist with fast kinetic block of sodium current that inhibits most types of potassium currents including Ito, with abstinence from smoking and drinking. However, VF recurred despite these measures, and ERS rather than VSA was diagnosed as the main cause of VF. Accordingly, we added 150 mg/day of cilostazol and VF did not recur.

He had 2 episodes of appropriate ICD shocks for VF during the 2 years after ICD implantation and several episodes of VF on the day of the admission even though nifedipine was administered for the prevention of VSA. Moreover, VF recurred 1 month after an initiation of bepridil. Both L-type calcium channel blockers exacerbated the VF recurrence. In contrast, cilostazol, which increases cellular cAMP levels and L-type calcium channel current, resulting in the inhibition of Ito currents, like isoproterenol, effectively suppressed VF recurrence in this case. In patients with ERS, J-point elevation has been reported to be exacerbated during bradycardia and ameliorated during tachycardia, reflecting the characteristics of potassium (Ito), calcium, and sodium currents. Shinohara and colleagues showed that calcium channel blockers, such as verapamil, increase J-point elevation; in contrast, disopyramide, which suppresses the Ito current and increases sympathetic nerve activity as well as calcium channel currents, reduced J-point elevation. In the present case, J-point elevation in this patient decreased...
during both isoproterenol provocation and treadmill test, but increased with edrophonium, which stimulates parasympathetic nerve activity. A distinctive feature of this case was that pilsicainide obviously induced ST-segment elevation in addition to J-wave elevation in inferior leads and J-wave elevation in lateral leads. However, in a previous study,}

**Figure 2** Intravenous administration of pilsicainide (50 mg) accentuated J-wave and ST-segment elevation in inferior leads and J-wave elevation in lateral leads (arrow). However, typical coved-type ST elevation was not induced in right precordial leads, even in the third intercostal space (right panel).

**Figure 3** A: A 12-lead electrocardiogram demonstrated J-wave and ST-segment elevation in inferior leads and notched type J-wave elevation in lateral leads (arrow) before cilostazol administration. B: These J-wave and ST-segment elevations were attenuated (arrowheads) after cilostazol administration.
J-wave and ST-segment elevation in inferolateral leads were attenuated by pilsicainide administration in patients with ERS and Brugada syndrome. The present case demonstrated higher total testosterone level (1020 ng/dL), which was reported in patients with Brugada syndrome. In that report, hyperandrogenemia was defined as serum levels >700 ng/dL. Testosterone reduces calcium channel currents, and testosterone levels were reported to be associated with an inferolateral ER pattern with a rapidly ascending ST segment. Both calcium channel blockers and higher testosterone level could be related to peculiar J-wave and ST-segment elevation in this case.

Conclusion
In this report, a young man with VSA and J wave in inferolateral leads and ST-segment elevation in inferolateral leads was diagnosed as ERS. Cilostazol not only reduced J-wave and ST-T elevation and effectively suppressed VF recurrence. We postulated that both calcium blockers and higher testosterone levels could exacerbate VF recurrence in this patient.

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