Early repolarisation abnormality associated with sudden cardiac death

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Sudden cardiac death is an important cause of death, accounting for between 300 000 and 400 000 deaths in the United States alone each year. Moreover, approximately 10% of all deaths are unaccounted for, with autopsies revealing structurally normally hearts. Even with post-mortem genetic testing, specifically for long QT syndrome, 96% of young males who have died due to sudden cardiac death have no attributable cause. Although a number of genetic syndromes that can result in ventricular fibrillation (VF) have been identified, such as Brugada syndrome and arrhythmogenic right ventricular dysplasia (ARVD), there remains a large population of young, otherwise healthy patients who die due to idiopathic VF, that we are unable to diagnose.

In this issue of the *Polish Heart Journal* Kukla and Jastrzębski give a comprehensive review of early repolarisation, i.e. elevation of the J point, also known as Osborn waves, and the evidence that supports its association with sudden cardiac death. Our recent work suggests that early repolarisation, a common finding in the general population, is not as benign as was once thought [1]. In a large population of patients who were resuscitated from sudden cardiac death, early repolarisation was found in 31% of patients compared to only 5% of a matched control population.

Early repolarisation

Early repolarisation is seen at the end of the QRS complex at the start of the isoelectric ST. Instead of ending abruptly there is a notch at the end of the QRS. This is manifest as an elevation at the J point, and an arbitrary value of >0.1 mvV (1 mm) is regarded as early repolarisation. The widely held assumption is that early repolarisation is due to a potential difference between the ventricular epicardium and endocardium at the start of repolarisation (Figure 1). The arrhythmogenicity of this syndrome is thought to be related to heterogeneity of action potentials (spike and dome morphology in epicardial tissue) across the ventricular wall at the end of phase 1. Any perturbation in the balance of currents may amplify the disparity in voltage gradient and precipitate local re-entries and polymorphic ventricular arrhythmias, providing both the trigger and substrate of VF. As the accompanying article by Kukla and Jastrzębski explains in greater detail, this difference may be related to relative changes in either inward or outward currents, mediated by potassium, sodium, and calcium channels. Experimentally sodium and calcium channel blockers, activation of IK-ATP, hypercalcaemia, and hypothermia

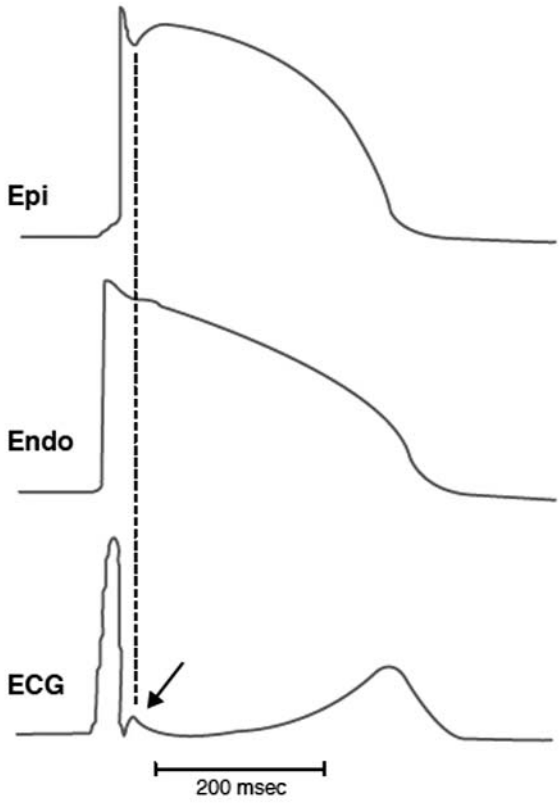

Figure 1. Pathophysiology of early repolarisation. At the start of repolarisation there is a potential difference (gradient) between the ventricular endo- and epicardium

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increase the electrical gradient and are arrhythmogenic [2]. Clinically, the exogenous precipitating factors and underlying genetic abnormality are unknown; however, the increased incidence of death during rest or sleep in our study indicates an augmenting role of increased vagal tone. Although early repolarisation is commonly seen in athletes and blacks, it typically is localised to leads V_1 to V_3, whereas in our study the early repolarisation was seen in the inferolateral leads.

In Figure 2 is an ECG from a young man who presented with a cardiac arrest during sleep. He was successfully resuscitated, and on arrival at the emergency department again went into VF. Following successful cardioversion, a number of investigations ruled out all known causes of VF, with angiographically normal coronary arteries, a normal cardiac MRI scan, an Ajmaline test ruled out Brugada syndrome, and an isoprenaline infusion did not result in any other arrhythmia. The only abnormality that could be found was early repolarisation, seen best in the inferior leads.

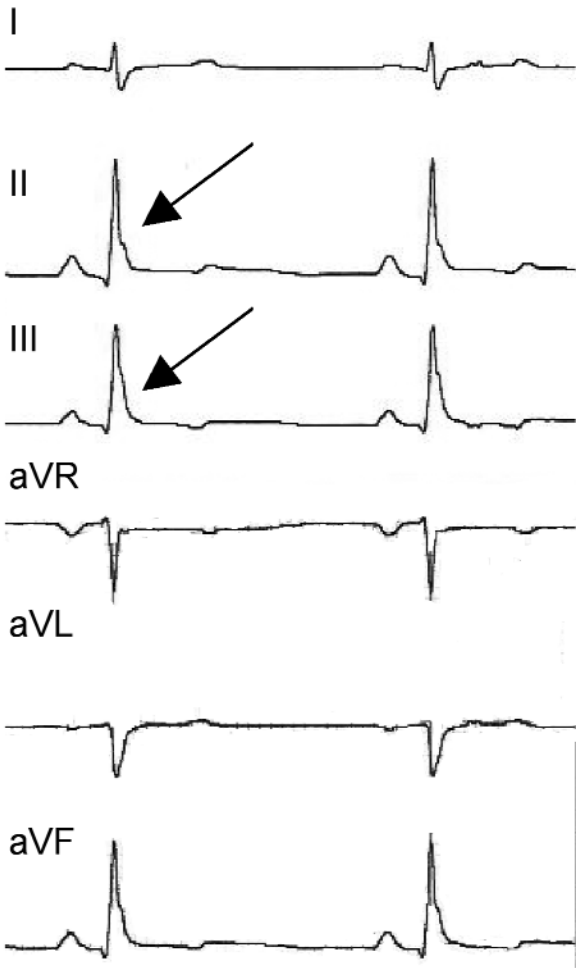

Figure 2. The ECG from a 37 year old man who suffered VF whilst asleep. Early repolarisation (arrowed) is seen at the terminal portion of the QRS in the inferior leads

Another example is presented in Figure 3; in this case a 39-year old lady had a pre-operative ECG for a gynaecological procedure. Early repolarisation can be seen in the inferior leads. A year later, this lady suffered from VF whilst working at her computer, and was successfully resuscitated by the paramedics. Again all cardiac investigations were normal.

Multicentre study of patients with idiopathic VF

In our multicentre study, we investigated 206 patients who had been resuscitated from sudden cardiac death, and who had all known causes of VF excluded. These were compared to a matched population (age, sex, sporting activity and ethnicity). In the study group 31% of patients had early repolarisation in the inferolateral leads (defined as an elevation of greater than 0.1 mV in a minimum of two leads, excluding leads V_1-V_3) compared to only 5% in the control group. Additionally, the amplitude of the early repolarisation was higher in the subjects who had suffered from VF (2.15±1.2 vs. 1.5±0.2 mm).

During a mean follow-up of 5 years, patients with early repolarisation suffer more recurrences of ventricular arrhythmia than patients without early repolarisation (42% compared to 23% respectively). Thus it appears that in these patients early repolarisation is not only a marker of VF but is related to the pathological process. In other words, it is a primary and secondary risk factor. Furthermore, interrogation of the ECG from the implantable cardiac defibrillator in these patients has shown that the arrhythmia is always VF and not ventricular tachycardia, and that the early repolarisation pattern is labile, often increasing prior to VF (Figure 4). Invasive electrophysiological study at the time of electrical storm demonstrated that the origin of arrhythmia initiating ectopy from the region of abnormal repolarisation further supports this hypothesis.

Acute treatment of electrical storms

Electrical storm, defined as ≥3 episodes of VF within a 24-hour period, occurs in a minority of patients implanted with an ICD but can result in death or require extreme measures such as heart transplantation to save the patient's life. In a further study in an expanded population of patients with early repolarisation we have confirmed the severity of electrical storm in association with early repolarisation and have investigated the role of specific antiarrhythmic agents [3]. In this study we have shown that continuous infusion of isoproterenol successfully treats electrical storm and consistently restores normal ECG in this particular patient population. This efficacy has also been reported in a preliminary study including the same condition [4] as well as in Brugada syndrome or in torsades de pointes associated with [5-7]. Isoproterenol is thought to be effective probably by increasing the I Ca-L current and thus decreasing the electrical gradient and possibly by increasing heart rate and reducing inactivation of I_{to} [2].

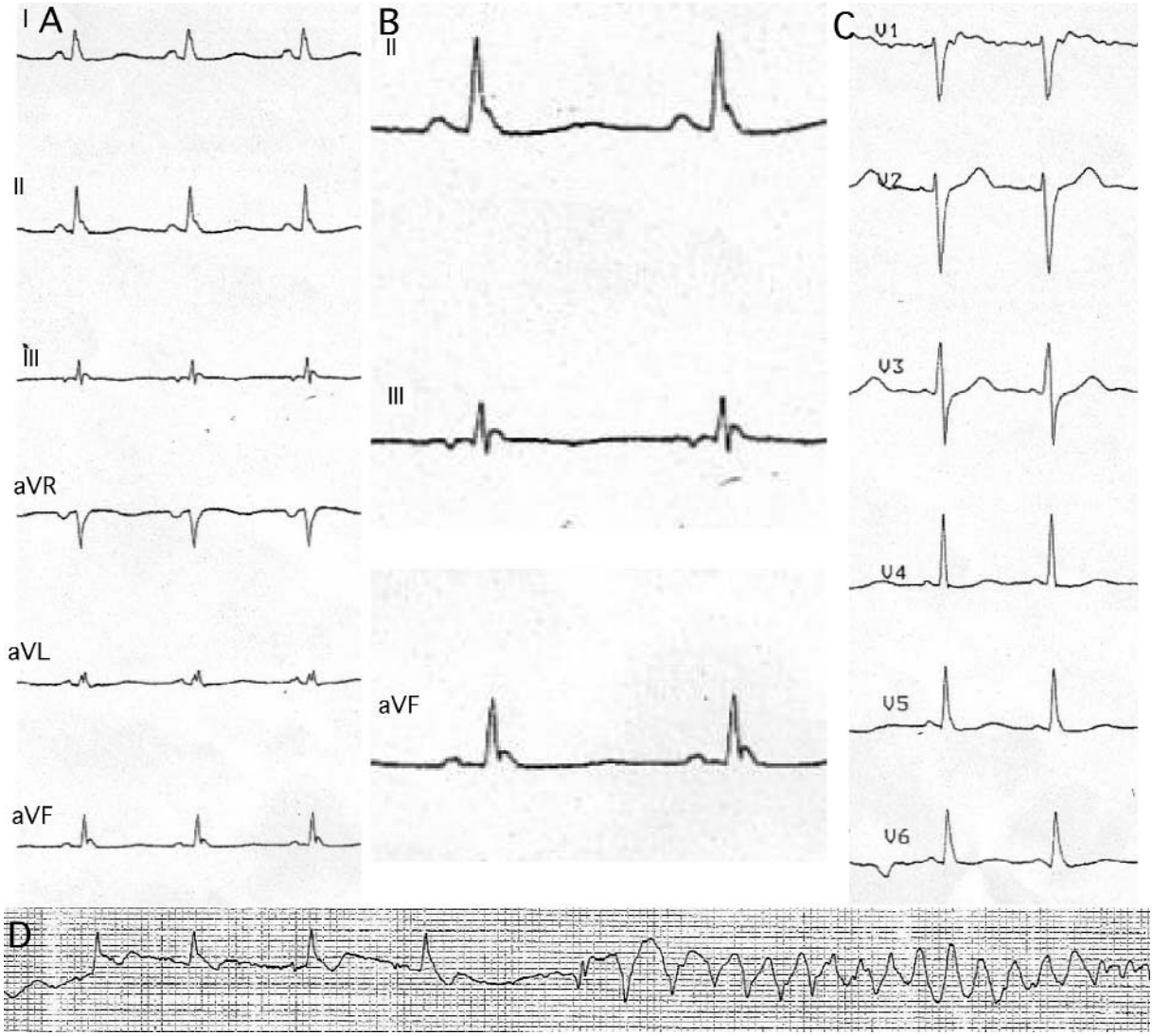

Figure 3. The ECG (**A** and **C**) from a 39 year old lady who initially presented for a routine gynaecological procedure. A year later this lady suffered from recurrent VF (Panel **D**), in panel **B** the inferior leads have been enlarged, and the early repolarisation pattern is clearly seen

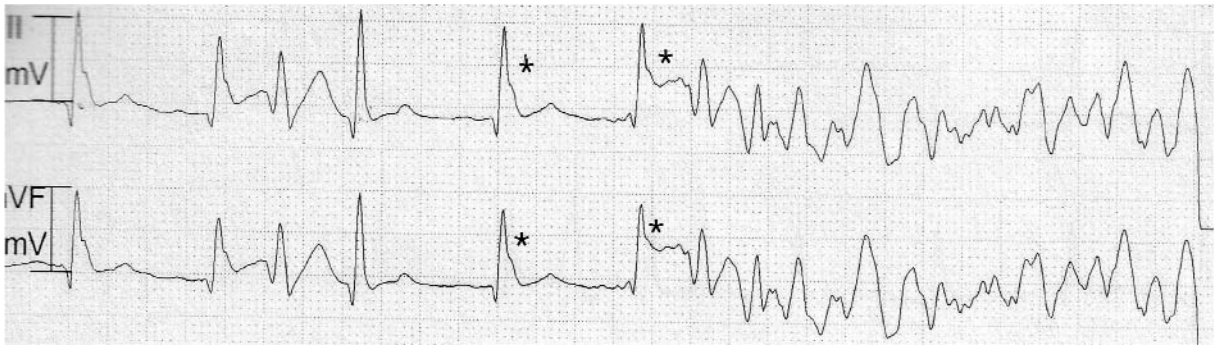

Figure 4. An ECG in a patient with early repolarisation and an episode of VF. Note the elevation of the J point prior to VF (starred)

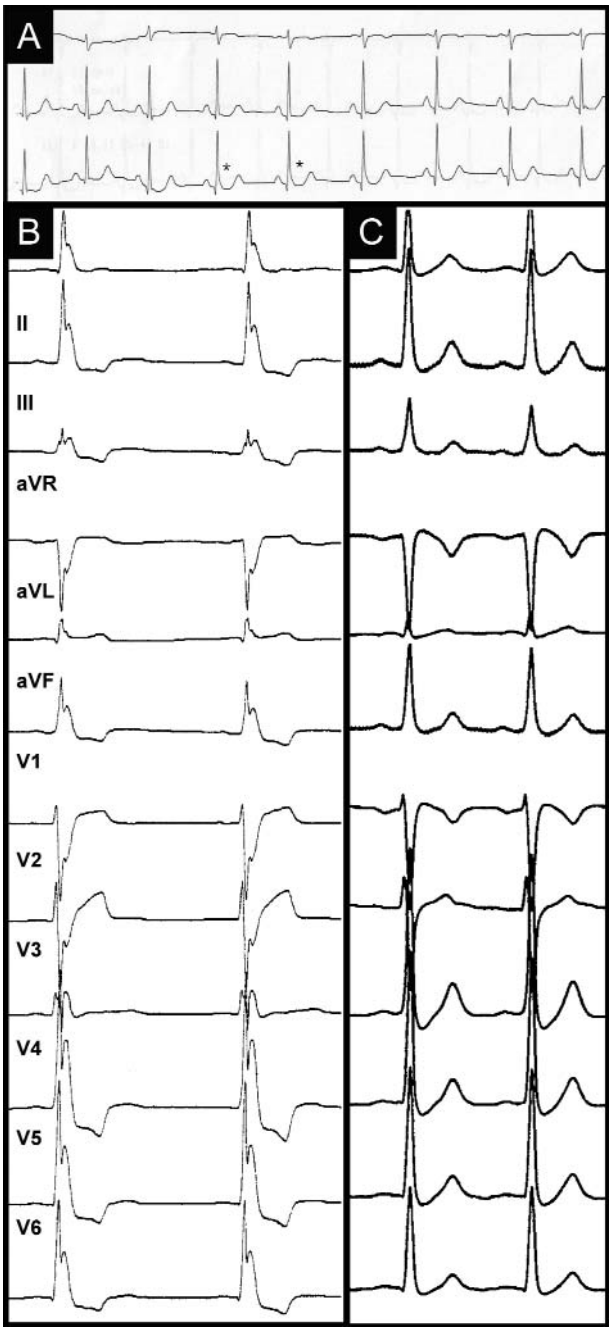

Figure 5. Fluctuation of the J point from one beat to another during a Vasalva maneuver (panel A). In panel B, the patient has a heart rate of 48 bpm and the J point elevation is marked while it decreases with the acceleration of the heart rate (102 bpm in panel C)

Maintenance antiarrhythmic therapy

We have also demonstrated that most antiarrhythmic drugs, including beta blockers, class 1c and verapamil, are ineffective in patients with early repolarisation abnormality. Previous studies have shown the efficacy of quinidine in preventing clinical recurrences of idiopathic VF, Brugada syndrome and HERG-linked short QT syndrome [5, 7-10]. In our latest study we have demonstrated that quinidine is effective in prevention of recurrence of VF associated with the early repolarisation abnormality. The patients in the study had a particularly high number of VF episodes and a long-term follow-up free of ICD interventions strongly supports the efficacy of this drug. Such results have also been reported in case reports [4, 11, 12]. As the accompanying article by Kukla and Jastrzębski explains, quinidine inhibits several currents including an effect in blocking Ito.

Nosological frontiers with Brugada syndrome

In the report from the consensus committee regarding Brugada syndrome early repolarisation is reported as a differential diagnosis [13]. Early repolarisation has the following distinct features: the ECG marker is absent in the right precordial leads, is insensitive to sodium channel blockers and is not associated with conduction defects or the SCN5A mutation; additionally VF originating from multiple locations in the right or left ventricle contrasts with Brugada syndrome, which is defined as a right ventricular (outflow tract) disease [14]. However, patients with the early repolarisation syndrome reported by ourselves share some analogous features with Brugada syndrome. The ECG abnormality occurs at the early phase of repolarisation and is associated with potential arrhythmogenicity. Additionally, the efficacy of isoproterenol and quinidine is reminiscent of their efficacy in Brugada syndrome. Though both conditions are manifestations of electrical heterogeneity during phase 1 of the action potential, they may express specific ionic current density/function in different regions of the heart while sharing a common element (for example acting in synergy with Ito current). The nosological frontier between these conditions and confusion caused by phenotypic overlap [15-24] will almost certainly benefit from genetic studies as well as studies using molecular or morphological imaging.

Practical implications

Distinguishing early repolarisation from late depolarisation is sometimes difficult. Slurring of the terminal portion of the QRS can represent late activation of a zone of myocardium. Early repolarisation can be distinguished as it can spontaneously fluctuate from one ECG to another (sometimes beat by beat, Figure 5), particular during vagal manoeuvres and with effort. Early repolarisation is accentuated with bradycardia and is diminished with tachycardia. In comparison, delayed depolarisation is much more constant and it will join readily with late potentials.

The major limitation of the new finding of the association between early repolarisation and VF is the vast number of patients with early repolarisation who will never go on to develop VF. Currently there is no pharmacological test equivalent to the Ajmaline test for Brugada syndrome, nor has any common genetic mutation been found, although we

have recently reported a novel mutation in the K_{ATP} channel in one patient. However, in those patients with early repolarisation and VF, isoproterenol infusion is an effective treatment for electrical storm, while quinidine is effective in long-term maintenance therapy.

References

1. Haïssaguerre M, Derval N, Sacher F, et al. Sudden cardiac arrest associated with early repolarization. *N Engl J Med* 2008; 358: 2016-23.
2. Yan GX, Antzelevitch C. Cellular basis for the electrocardiographic J wave. *Circulation* 1996; 93: 372-9.
3. Haïssaguerre M, Sacher F, Nogami A, et al. Characteristics of recurrent ventricular fibrillation associated with inferolateral early repolarization – role of drug therapy. *J Am Coll Cardiol* (in press).
4. Nam GB, Kim YH, Antzelevitch C. Augmentation of J waves and electrical storms in patients with early repolarization. *N Engl J Med* 2008; 358: 2078-9.
5. Jongman JK, Jepkes-Bruin N, Ramdat Misier AR, et al. Electrical storms in Brugada syndrome successfully treated with isoproterenol infusion and quinidine orally. *Neth Heart J* 2007; 15: 151-5.
6. Maury P, Couderc P, Delay M, et al. Electrical storm in Brugada syndrome successfully treated using isoprenaline. *Europace* 2004; 6: 130-3.
7. Ohgo T, Okamura H, Noda T, et al. Acute and chronic management in patients with Brugada syndrome associated with electrical storm of ventricular fibrillation. *Heart Rhythm* 2007; 4: 695-700.
8. Alings M, Dekker L, Sadee A, Wilde A. Quinidine induced electrocardiographic normalization in two patients with Brugada syndrome. *Pacing Clin Electrophysiol* 2001; 24: 1420-2.
9. Belhassen B, Glick A, Viskin S. Efficacy of quinidine in high-risk patients with Brugada syndrome. *Circulation* 2004; 110: 1731-7.
10. Probst V, Evain S, Gournay V, et al. Monomorphic ventricular tachycardia due to Brugada syndrome successfully treated by hydroquinidine therapy in a 3-year-old child. *J Cardiovasc Electrophysiol* 2006; 17: 97-100.
11. Garg A, Finneran W, Feld GK. Familial sudden cardiac death associated with a terminal QRS abnormality on surface 12-lead electrocardiogram in the index case. *J Cardiovasc Electrophysiol* 1998; 9: 642-7.
12. Otto CM, Tauxe RV, Cobb LA, et al. Ventricular fibrillation causes sudden death in Southeast Asian immigrants. *Ann Intern Med* 1984; 101: 45-47.
13. Antzelevitch C, Brugada P, Borggrefe M, et al. Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. *Circulation* 2005; 111: 659-70.
14. Mehta M, Jain AC, Mehta A. Early repolarization. *Clin Cardiol* 1999; 22: 59-65.
15. Daimon M, Inagaki M, Morooka S, et al. Brugada syndrome characterized by the appearance of J waves. *Pacing Clin Electrophysiol* 2000; 23: 405-6.
16. Horigome H, Shigeta O, Kuga K, et al. Ventricular fibrillation during anesthesia in association with J waves in the left precordial leads in a child with coarctation of the aorta. *J Electrocardiol* 2003; 36: 339-43.
17. Kalla H, Yan GX, Marinchak R. Ventricular fibrillation in a patient with prominent J (Osborn) waves and ST segment elevation in the inferior electrocardiographic leads: a Brugada syndrome variant? *J Cardiovasc Electrophysiol* 2000; 11: 95-8.
18. Ogawa M, Kumagai K, Yamanouchi Y, Saku K. Spontaneous onset of ventricular fibrillation in Brugada syndrome with J wave and ST-segment elevation in the inferior leads. *Heart Rhythm* 2005; 2: 97-9.
19. Riera AR, Ferreira C, Schapachnik E, et al. Brugada syndrome with atypical ECG: downsloping ST-segment elevation in inferior leads. *J Electrocardiol* 2004; 37: 101-4.
20. Sassone B, Sacca S, Donateo M. Paradoxical effect of ajmaline in a patient with Brugada syndrome. *Europace* 2006; 8: 251-4.
21. Shinohara T, Takahashi N, Saikawa T, Yoshimatsu H. Characterization of J wave in a patient with idiopathic ventricular fibrillation. *Heart Rhythm* 2006; 3: 1082-4.
22. Takagi M, Aihara N, Takaki H, et al. Clinical characteristics of patients with spontaneous or inducible ventricular fibrillation without apparent heart disease presenting with J wave and ST segment elevation in inferior leads. *J Cardiovasc Electrophysiol* 2000; 11: 844-8.
23. Takeuchi T, Sato N, Kawamura Y, et al. A case of a short-coupled variant of torsades de Pointes with electrical storm. *Pacing Clin Electrophysiol* 2003; 26: 632-6.
24. Ueyama T, Shimizu A, Esato M, et al. A case of a concealed type of Brugada syndrome with a J wave and mild ST-segment elevation in the inferolateral leads. *J Electrocardiol* 2007; 40: 39-42.