

Early repolarization syndrome: A case report focusing on dynamic electrocardiographic changes before ventricular arrhythmias and genetic analysis



Vern Hsen Tan, MBBS, MRCP,^{*†} Henry Duff, MD,^{*†} Brenda Gerull, MD,^{*} Glen Sumner, MD^{*}

From the ^{*}Department of Cardiac Sciences, Libin Cardiovascular Institute of Alberta, University of Calgary, Alberta, Canada, and [†]Cardiology Department, Changi General Hospital, Singapore.

Introduction

Early repolarization pattern is characterized by the presence of J-point elevation ≥ 1 mm in ≥ 2 contiguous inferior and/or lateral leads of a standard 12-lead electrocardiogram (ECG).¹ Early repolarization syndrome (ERS) is diagnosed in a patient resuscitated from otherwise unexplained ventricular fibrillation (VF) or polymorphic ventricular tachycardia (PMVT) in the presence of these same ECG criteria.^{1–5} We describe an interesting case of a young patient with multiple episodes of recurrent VF in the context of ERS. We focus on the dynamic nature of both the surface ECG and intracardiac electrogram findings just before onset of the patient's observed ventricular arrhythmias. In addition, we review potentially novel genetic findings associated with this case.

Case report

A 32-year-old woman of Asian descent with no known cardiac history presented initially with a left middle cerebral artery embolic stroke in November 2009. Investigation of her stroke revealed paroxysmal atrial fibrillation on Holter monitoring and a patent foramen ovale. Dose-adjusted warfarin was initiated. No residual neurologic deficits were present. Subsequently, in March 2010, she presented with an out-of-hospital VF arrest. The documented rhythm before VF was PMVT. The event occurred while the patient was at rest. She had no antecedent symptoms of palpitations, presyncope, or chest pain.

KEYWORDS Early repolarization syndrome; Ventricular arrhythmias; Genetic analysis

ABBREVIATIONS AKAP = A-kinase anchor protein; ECG = electrocardiogram; ERS = early repolarization syndrome; ICD = implantable cardioverter-defibrillator; PMVT = polymorphic ventricular tachycardia; PVC = premature ventricular complex; VF = ventricular fibrillation (Heart Rhythm Case Reports 2015;1:213–216)

Address reprint requests and correspondence: Dr. Glen Sumner, Department of Cardiac Sciences, Libin Cardiovascular Institute of Alberta, Calgary, Alberta, Canada T2N 2T9. E-mail address: gsumner@ucalgary.ca.

The patient's other past medical history included migraine headaches, previous cosmetic breast surgery with bilateral breast implants, and remote history of bulimia nervosa. She had no history of substance abuse. She was adopted, so her family history was unknown.

A 12-lead ECG recorded at rest during the patient's initial presentation in 2010 (after VF arrest) is shown in [Figure 1A](#). At presentation, she was found to have hypokalemia (2.0 mmol/dL) in the setting of laxative and multiple types of herbal and Chinese supplement intake. No other reversible causes were identified. The serum potassium level was subsequently corrected, and a repeat ECG showed the same findings as documented initially. Hypokalemia did not recur after the initial replacement. A full cardiac workup including transthoracic echocardiography, cardiac magnetic resonance, coronary angiography, and epinephrine/procainamide challenge yielded no specific diagnosis. A dual-chamber implantable cardioverter-defibrillator (ICD) was implanted. A dedicated bipolar ICD lead was positioned at the right ventricular apex. Subsequently, she developed multiple recurrent episodes of VF that led to appropriate ICD shocks. The episodes of VF were frequently preceded by premature ventricular complexes (PVCs) that triggered PMVT ([Figure 1B](#)). Accordingly, PVC ablation was attempted, but the procedure was aborted because no spontaneous or inducible PVCs were observed during the electrophysiologic study. She was empirically started on beta-blocker therapy (metoprolol, then nadolol) as well as disopyramide. Despite this combination of therapies, she continued to experience very frequent episodes of spontaneous VF. She was admitted to the hospital in the fall 2012 with recurrent VF that was not responsive to amiodarone or lidocaine infusions. Her condition was stabilized by isoproterenol infusion with no further ventricular ectopy or VF. Her intracardiac electrograms at the time of the arrhythmia events showed episodes of PMVT that were preceded by PVCs characterized by a short–long–short sequence ([Figure 2](#)). Further analysis of the intracardiac near-field electrogram (RVtip to RVring) revealed an inverted J-wave sinus beat after a relatively long cycle length (> 850 ms) that immediately preceded PMVT

KEY TEACHING POINTS

- Early repolarization syndrome (ERS) is characterized by J-point elevation on the ECG and is associated with sustained ventricular arrhythmias that may lead to sudden death. J waves become more prominent during periods of heightened vagal tone, manifested as relative bradycardia. In atrial fibrillation (also a feature of ERS), J-point elevation becomes more prominent on a beat-to-beat basis associated with longer R-R intervals.
- Coincident with the appearance of J waves on the ECG, the intracardiac electrogram inscribes an inverted J wave that reflects the endocardial-to-epicardial electrical gradient consistent with the location of the pace/sense electrode and the physiology of ERS.
- The genetics of ERS are only partially characterized. Our patient may have a genetic profile that contributed to her phenotype in a modifier role.

(Figure 3). Recognition of intermittent J waves on careful review of both her ECGs as well as intracardiac electrograms led to a decision to initiate therapy with oral quinidine (200 mg 4 times daily). Since the initiation of quinidine therapy she has been free of any further recurrent VF events and has tolerated the quinidine therapy well.

Genetic testing of 30 genes previously associated with inherited arrhythmias was performed, including a screen for *KCNJ2*, a mutation associated with ERS. No known genes associated with ERS or idiopathic VF were identified. However, 2 variants of uncertain significance were found that could potentially contribute to the patient's phenotype. One nucleotide variant, c.7438C>T, was found in the A-kinase anchor protein (*AKAP*). This gene variant is otherwise known as Yotiao gene and leads to a premature stop codon (p.Gln2480Stop). Another nucleotide variant of uncertain significance was found in *SCN5A*. This variant codes for the protein p.Arg1193Gln. None of these genetic variants have been definitively associated with our patient's observed phenotype. However, we hypothesize that these variants may have contributed to our patient's phenotype in a genetic modifier role.

Discussion

ERS is a rare clinical entity and is difficult to diagnose in view of the highly variable, intermittent ECG features and lack of other specific diagnostic tests. Moreover, early repolarization pattern is most often an incidental finding and has a relatively high prevalence in the general population without associated ventricular arrhythmias. This pattern is estimated to occur in 1% to 13% of the general population.^{2,3,6,7} Inscription of a J wave (between the junction of

QRS complex and ST segment on ECG) is considered to be due to transmural dispersion of repolarization in the early phases of the action potential (phases 1 and 2). The ventricular epicardium often displays action potentials with a prominent I_{to} -mediated notch. Alternatively, a "spike and dome" action potential pattern may be observed. These findings are believed to be the direct result of a transmural voltage gradient during early repolarization between the endocardium and epicardium that ultimately manifests as a J wave on ECG.^{8,9}

Observational studies have shown that the amplitude of the J-wave may be absent during periods of relative physical activity but becomes progressively augmented immediately before VF events in the setting of increased vagal tone with the resultant associated bradycardia.^{2,10} This is likely due to inherent I_{to} kinetics whereby the channel is slow to recover from inactivation. I_{to} activity is reduced after an increase in heart rate. This results in a decrease in the magnitude of the J-wave.¹¹ In addition, as observed in our patient, there may be clear evidence of J-point elevation that exhibits beat-to-beat variation during atrial fibrillation, especially during long R-R intervals (Figure 2).

Upon review of the intracardiac electrograms (Figure 3), inverted J waves occurred in sinus beats with a long cycle length. This is in contrast to the absence of J waves during relatively shorter cycle length sinus beats (Figure 3). We postulate that the beat-to-beat variance in J-wave shape and vector of the intracardiac electrogram is consistent with heterogeneity of transmural gradients during repolarization recorded *in vitro*.^{8,9} In the present patient, beat-to-beat changes in the vector of the J wave during sinus rhythm frequently preceded episodes of VF. Additionally, because the ICD right ventricular lead is situated in an endocardial position, the vector of transmural dispersion during repolarization is away from the lead (ie, from endocardial to epicardial). Thus, an inverted J wave is inscribed (Figure 3). This finding is in contrast to the observed J-wave "upright" elevation on surface ECG (Figure 1A).

PVCs that triggered PMVT showed short-long-short sequences with relatively short coupling intervals likely via a phase 2 reentrant mechanism. Phase 2 reentry occurs when the epicardial action potential "dome" propagates from sites where it is present to regions where it has been lost. This gives rise to closely coupled extrasystoles that trigger PMVT.

Rosso et al¹² reported that the combination of J waves with ST segment elevation during sinus rhythm improves the ability to distinguish patients with benign (upsloping ST segment) from malignant (horizontal/descending ST segment) early repolarization patterns. In our patient, the ST segment was upsloping (after the J-wave in sinus rhythm) in lead II, V₅, and V₆, whereas leads III and aVF showed horizontal ST-segment elevation. Overall, we classified this patient's early repolarization pattern to be predominantly of the horizontal ST-segment type. This variant carries a stronger association with malignant arrhythmias.¹² The inverted J-wave on the local intracardiac electrogram

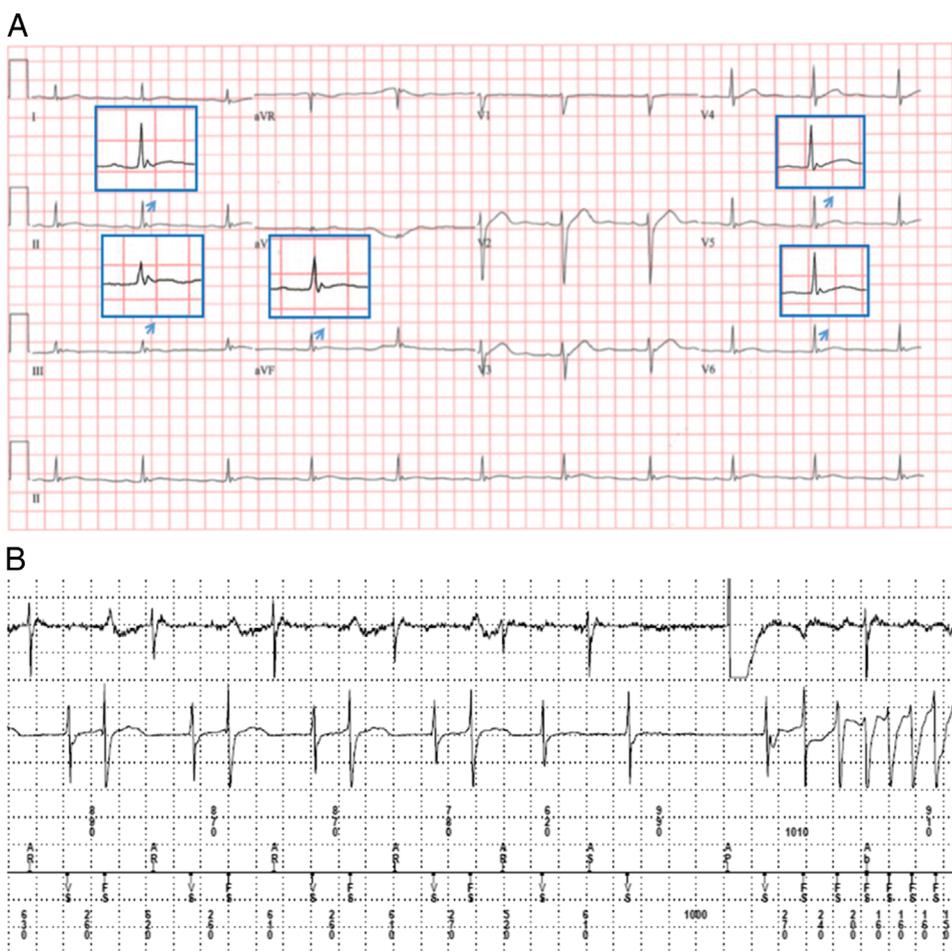


Figure 1 A: Twelve-lead ECG (with magnification of inferolateral single beat) showing J-point elevation (1 mm) in leads II, III, aVF, V₅, and V₆ associated with upsloping ST segment. B: Polymorphic ventricular tachycardia triggered by relatively short coupling premature ventricular complex (270 ms) with short–long–short interval before the arrhythmia event.

corroborates with the upright J-wave on the surface ECG. These findings together with the clinical presentation further establish the diagnosis of ERS in this patient.

Genetic analysis of 30 genes identified a variant in AKAP9 (Yotiao) that encodes variant 9 of the AKAPs. Such a variant has been associated with long QT syndrome type 1. However, Yotiao mutations are not a well-established cause of inherited arrhythmia. There has only been 1 published report of a missense mutation in association with a long QT phenotype in 2 sisters.¹³ In this report, it has been

hypothesized that mutations in AKAP9 may lead to arrhythmia by disrupting the interaction between AKAP9 and KCNQ1-encoded potassium channels. To explain this mechanism, 2 binding regions for KCNQ1, encoded by exons 2, 9–11, and 16–19 of AKAP9, may be of particular relevance. Our patient carries a nonsense variant. Interestingly, the p. Gln2480stop variant was not found in any variant databases for the control population (dbSNP and the NHLBI exome sequencing project). However, other nonsense variants have been detected in the normal population, suggesting that

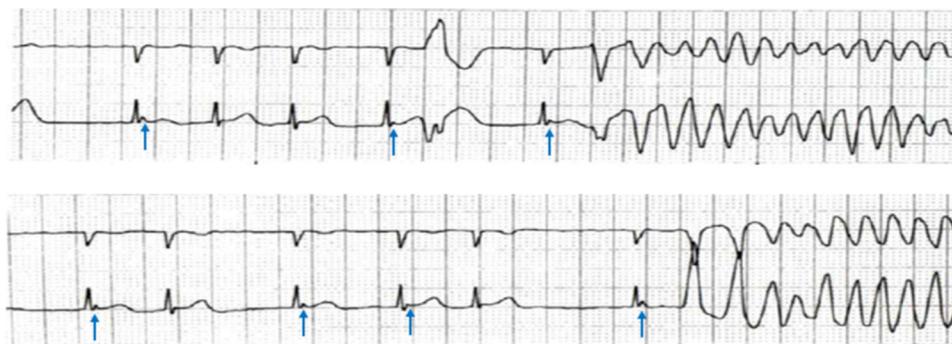


Figure 2 J-point elevation (↑) increases during atrial fibrillation with long R-R intervals.

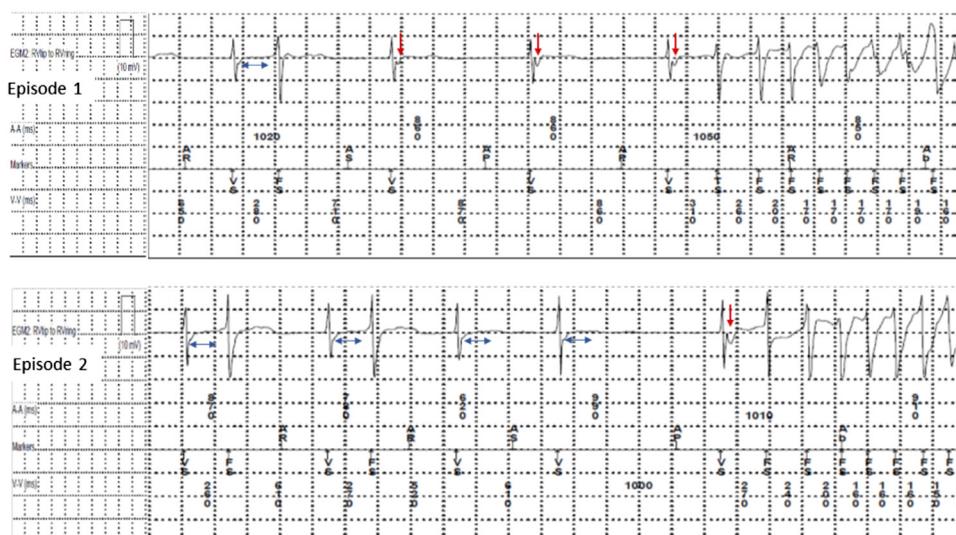


Figure 3 Intracardiac electrogram showed inverted J wave (↓) in sinus beat with long cycle length compared to absence of J wave (isoelectric ST segment, ↔) in sinus beat with short cycle length (followed by relatively short coupling premature ventricular complex). Atrial intracardiac electrograms are not shown.

nonsense variants in AKAP9 might be tolerated and are not associated with a cardiac arrhythmia phenotype. Another missense variant was found in SCN5A (c.3578G>A; p.Arg1193Gln), also named as an R1193Q variant with a minor allele frequency ranging between 0.12% (exome variant server) and 1.2% (dbSNP). This variant is prevalent in up to 12% of the Chinese population.¹⁴ Furthermore, this mutation has been shown to be associated with Brugada syndrome and long QT syndrome,¹⁵ and *in vitro* data suggest a contribution of this variant to cardiac electrical abnormalities. For example, expression of R1193Q in cultured cells followed by patch clamping shows that the sodium current has a residual noninactivating component and hence could account for prolongation of repolarization. In addition, a shift in steady-state inactivation toward more hyperpolarized voltage could account for a Brugada phenotype. However, even though our patient is of Asian ethnicity, it is unlikely that this variant explains her phenotype, and we expect that the fundamental genetic causes remain unknown.

Overall, the genetic findings in this case are inconclusive. Even so, it is interesting to speculate that the AKAP9 and/or SCN5A variants might contribute to her phenotype as genetic modifiers. The therapeutic response to both isoproterenol and quinidine in this case suggests, but does not prove, a similar arrhythmogenic substrate to that observed in Brugada syndrome.

This case illustrates that in a patient with ERS, dynamic ECG and intracardiac electrogram changes may be observed before the onset of PMVT or VF. These observed changes are consistent with the proposed mechanism of ion channel dysfunction of I_{to} that is associated with ERS. Although genetic testing in this individual was inconclusive, some genetic variants were identified that could potentially contribute to the patient's phenotype in a modifier role.

References

1. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, Blom N, Brugada J, Chiang C-E, Huikuri H. Executive summary: HRS/EHRA/APHR expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Europace* 2013;15:1389–1406.
2. Haissaguerre M, Derval N, Sacher F, et al. Sudden cardiac arrest associated with early repolarization. *N Engl J Med* 2008;358:2016–2023.
3. Tikkanen JT, Anttonen O, Junttila MJ, Aro AL, Kerola T, Rissanen HA, Reunanen A, Huikuri HV. Long-term outcome associated with early repolarization on electrocardiography. *N Engl J Med* 2009;361:2529–2537.
4. Nam GB, Kim YH, Antzelevitch C. Augmentation of j waves and electrical storms in patients with early repolarization. *N Engl J Med* 2008;358:2078–2079.
5. Rosso R, Kogan E, Belhassen B, Rozovski U, Scheinman MM, Zeltser D, Halkin A, Steinvil A, Heller K, Glikson M, Katz A, Viskin S. J-point elevation in survivors of primary ventricular fibrillation and matched control subjects: incidence and clinical significance. *J Am Coll Cardiol* 2008;52:1231–1238.
6. Klatsky AL, Oehm R, Cooper RA, Udaltsova N, Armstrong MA. The early repolarization normal variant electrocardiogram: correlates and consequences. *Am J Med* 2003;115:171–177.
7. Aizawa Y, Sato M, Kitazawa H, Aizawa Y, Takatsuki S, Oda E, Okabe M, Fukuda K. Tachycardia-dependent augmentation of “notched J waves” in a general patient population without ventricular fibrillation or cardiac arrest: not a repolarization but a depolarization abnormality? *Heart Rhythm* 2015;12:376–383.
8. Litovsky SH, Antzelevitch C. Transient outward current prominent in canine ventricular epicardium but not endocardium. *Circ Res* 1988;62:116–126.
9. Antzelevitch C, Sicouri S, Litovsky SH, Lukas A, Krishnan SC, Di Diego JM, Gintant GA, Liu D-W. Heterogeneity within the ventricular wall. *Circ Res* 1991;69:427.
10. Shinohara T, Takahashi N, Saikawa T, Yoshimatsu H. Characterization of J wave in a patient with idiopathic ventricular fibrillation. *Heart Rhythm* 2006;3:1082–1084.
11. Yan G-X, Lankipalli RS, Burke JF, Musco S, Kowey PR. Ventricular repolarization components on the electrocardiogram: cellular basis and clinical significance. *J Am Coll Cardiol* 2003;42:401–409.
12. Rosso R, Glikson E, Belhassen B, Katz A, Halkin A, Steinvil A, Viskin S. Distinguishing “benign” from “malignant early repolarization”: the value of the ST-segment morphology. *Heart Rhythm* 2012;9:225–229.
13. Chen L, Marquardt ML, Tester DJ, Sampson KJ, Ackerman MJ, Kass RS. Mutation of an A-kinase-anchoring protein causes long-QT syndrome. *Proc Natl Acad Sci U S A* 2007;104:20990–20995.
14. Hwang HW, Chen JJ, Lin YJ, Shieh RC, Lee MT, Hung SI, Wu JY, Chen YT, Niu DM, Hwang BT. R1193q of SCN5A, a Brugada and long QT mutation, is a common polymorphism in Han Chinese. *J Med Genet* 2005;42:e7; author reply e8.
15. Huang H, Zhao J, Barrane FZ, Champagne J, Chahine M. Nav1.5/r1193q polymorphism is associated with both long QT and Brugada syndromes. *Can J Cardiol* 2006;22:309–313.