Abnormal epicardial electrophysiologic substrate in patients with early repolarization pattern and reduced left ventricular systolic function: A report of two cases

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Introduction

Early repolarization pattern (ERP) in the electrocardiogram (ECG) refers to ST-segment elevation above the isoelectric line in the absence of chest pain and/or to terminal QRS slurring or notching in $\geq$2 contiguous inferior and/or lateral leads.[1-3] The underlying electrophysiologic mechanism of ERP remains elusive and is likely heterogeneous. The latter is supported by the fact that although ERP is commonly observed in the general population and has long been considered as a benign ECG finding, some recent data suggest its link (albeit weak) to increased risk of sudden cardiac death.[4-6] In addition, different ECG markers of ERP may carry diverse prognostic significance while inferior J-point elevation of $\geq$2 mm appears to be the most strongly linked to arrhythmic death.[1,5,6] Finally, the electrophysiologic mechanism of ERP may vary in patients with and without a structural heart disease.[7]

In this report, we describe electrophysiologic substrate in 2 patients with mild idiopathic left ventricle (LV) systolic dysfunction and terminal QRS notching (J-point elevation) in inferolateral leads.

Case report

Case 1

A 63-year-old man, an avid marathon runner with no prior cardiac history, presented with recent-onset exertional lightheadedness and 1 episode of syncope. His ECG revealed terminal notching of the QRS complex (J-point elevation) in the inferior leads (Figure 1A). He had no family history of sudden death. Echocardiogram showed global hypokineses of the LV with an estimated ejection fraction of 40%. A coronary angiogram revealed normal coronary arteries. An electrophysiology study was remarkable for reproducibly inducible ventricular tachycardia (VT). He subsequently underwent placement of an implantable cardioverter-defibrillator (ICD) and was started on metoprolol. Four years later, after a period of relative quiescence, he was referred for ablation owing to multiple ICD shocks for frequent VT refractory to a number of antiarrhythmic regimens. A preprocedure contrast-enhanced cardiac computed tomography revealed global hypokinesis and mildly reduced left ventricular ejection fraction of 43%, whereas structure and function of the right ventricle (RV) were normal.

The patient presented to the electrophysiology laboratory in atrial-paced rhythm at a rate of 60 beats per minute. The AH interval was 80 ms and HV interval was 60 ms. An intracardiac ultrasound probe (CartoSound, Biosense Webster, Inc, Diamond Bar, CA) and an electroanatomic mapping (EAM) system (CARTO 3, Biosense Webster, Inc) were used to create endocardial geometries of the ventricles.

Endocardial EAM of the RV and LV in sinus rhythm (SR) demonstrated normal voltage (>1.5 mV) and electrogram morphology, whereas epicardial EAM revealed a small area with low amplitude (<1 mV) and fractionated electrograms involving the apical aspect of the LV with extension to the RV. In addition, there was a large area with sharp/high-frequency delayed potentials but relatively preserved signal amplitudes in the inferolateral LV (Figure 1B and C). Sites with abnormal electrograms were tagged on the map. A monomorphic VT (MVT) with left bundle branch block/northwest axis and negative precordial concordance QRS morphology (cycle length of 365 ms) was reproducibly induced with programmed ventricular stimulation (Figure 2A). Presystolic local electrograms during VT were noted in the area with delayed potentials in SR (Figure 2B). Detailed activation and entrainment mapping was not feasible because of rapid hemodynamic compromise and lack of consistent pacing capture in the epicardium of the LV. VT terminated during ablation at a site showing presystolic local electrograms (Figure 2C). Additional ablation was then performed in SR targeting sites with delayed potentials. At the

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KEY TEACHING POINTS

- Early repolarization pattern (ERP) in the electrocardiogram has been linked to increased risk of sudden death.
- The electrophysiologic mechanism underlying ERP remains debatable and most likely varies in patients with and without a structural heart disease.
- In our patients with mild idiopathic left ventricular systolic dysfunction and ERP (terminal QRS notching), epicardial electroanatomic mapping revealed abnormal left ventricular (LV) electrophysiologic substrate, whereas endocardial mapping was normal.
- Our report suggests that in a subset of patients with a structural heart disease, terminal QRS notching in inferolateral leads in the electrocardiogram is a manifestation of an abnormal LV epicardial electrophysiologic substrate, which can cause monomorphic ventricular tachycardia.

end of the procedure, VT was no longer inducible. After a 2-year period of relative quiescence following ablation, he had another episode of MVT with different QRS morphology (right bundle branch block/superior axis, positive precordial concordance), which has been managed with sotalol.

Case 2

A 57-year-old man with no prior medical history presented with recurrent syncopal MVT (Figure 3A). He had no family history of sudden death. Twelve-lead QRS morphology of the tachycardia suggested its epicardial origin (QS waves in lead I, pseudo-delta wave of 85 ms, and maximum deflection index of 0.75). His ECG in SR was remarkable for terminal notching of the QRS complex in the lateral leads (I and aVL), which was intermittently augmented after long post-ventricular extrasystolic pauses in lead II (Figure 3B). His cardiac magnetic resonance imaging showed global hypokinesis of the LV (left ventricular ejection fraction of 45%) with normal structure and function of the RV. There was no evidence of late gadolinium enhancement. A coronary angiogram revealed normal coronary arteries. The patient was referred for electrophysiology study and possible VT ablation.

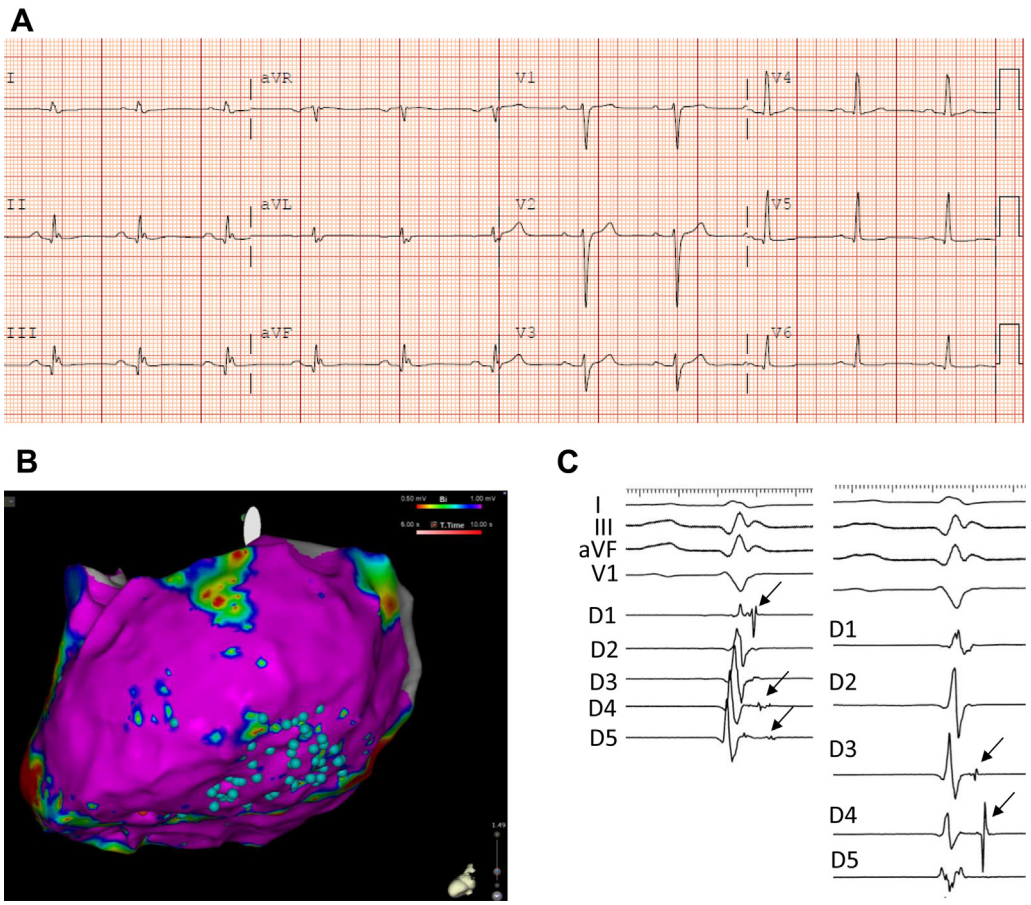

Figure 1 **A:** Twelve-lead electrocardiogram in sinus rhythm shows terminal QRS notching (J-point elevation) in leads II, III, and aVF. **B:** Epicardial electroanatomic voltage map in sinus rhythm. Sites with delayed potentials in the inferolateral left ventricle are marked with blue spheres. **C:** Examples of delayed potentials (*arrows*) recorded at the epicardial sites marked on the electroanatomic map in panel B with blue spheres. Note that timing of these potentials coincides with the terminal QRS notch in leads III and aVF.

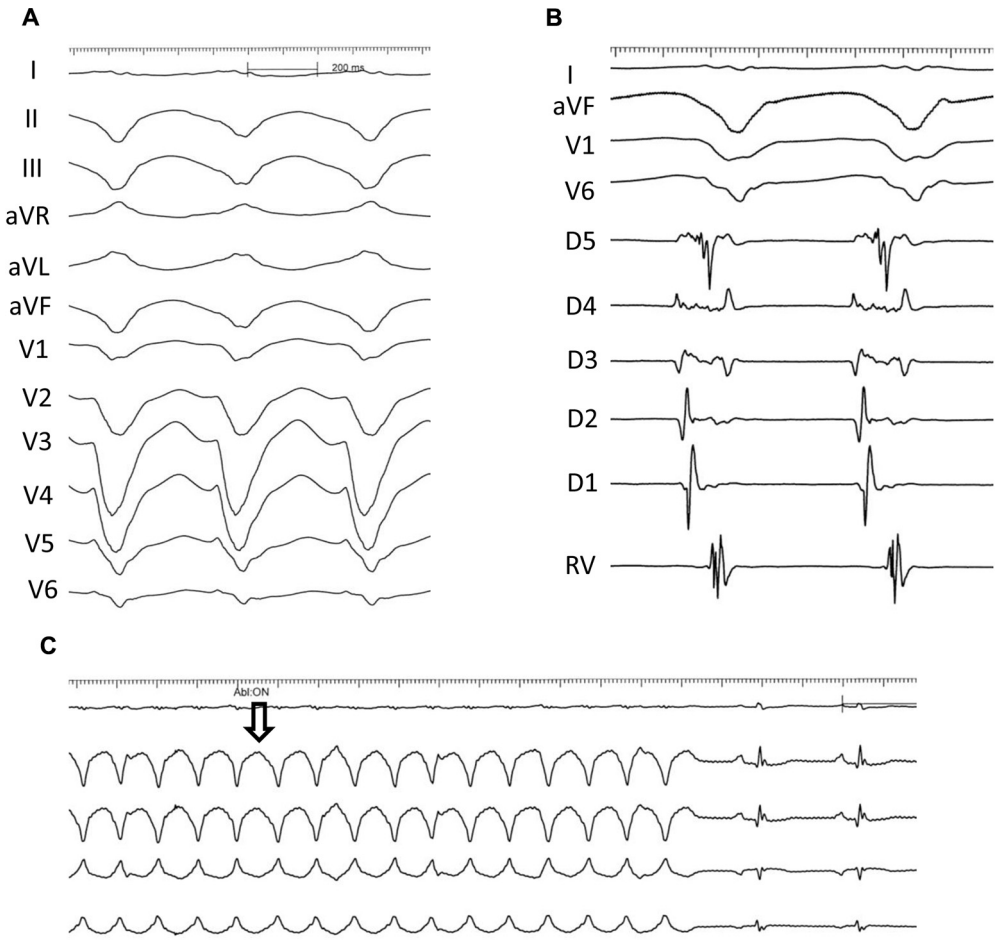

Figure 2 **A:** Twelve-lead electrocardiogram of the induced ventricular tachycardia (VT). **B:** An example of presystolic local electrograms (D3-4) recorded during VT from the epicardial region with delayed potentials in sinus rhythm (marked with blue spheres in Figure 1B). **C:** Termination of VT with ablation at the site corresponding to D3-4 in panel B.

He presented to the electrophysiology laboratory in SR at rate of 55 beats per minute. The AH interval was 110 ms and HV interval was 45 ms. An intracardiac ultrasound probe (CartoSound, Biosense Webster, Inc, Diamond Bar, CA) and an EAM system (CARTO 3, Biosense Webster, Inc) were used to create endocardial geometries of the ventricles. No sustained VT could be induced. Endocardial EAM of the RV and LV in SR showed normal electrogram morphology and amplitude. Epicardial EAM revealed 2 distinct areas with low amplitude and fractionated electrograms: outflow tract of the RV (RVOT) and mid-lateral LV (Figure 3C). Extensive pace mapping from the endocardial and epicardial LV suggested his clinical VT exit site to be in the area of the lateral epicardial LV adjacent to the abnormal electroanatomic substrate based on the direction of the QRS complex. However, exact QRS morphology of the clinical VT could not be reproduced. Empiric ablation of the epicardial substrate was not performed owing to proximity of the phrenic nerve to this area. He was subsequently implanted with an ICD and started on sotalol.

Discussion

In this report we describe epicardial arrhythmogenic electrophysiologic substrate in 2 patients with idiopathic mild LV dysfunction, recurrent MVT, and terminal QRS notching (J-point elevation) in inferolateral leads in SR. Endocardial EAM mapping of the RV and LV demonstrated normal local electrogram characteristics. Electrophysiology findings strongly suggest the origin of MVT to be from the area of the abnormal epicardial substrate in both patients.

Although ERP has long been considered a benign ECG phenomenon, this notion was first questioned by Gussak and Antzelevtich,[4] who indicated potential similarity of cellular and ionic mechanisms between Brugada ECG manifestations and ERP. Over the last 2 decades, a growing body of experimental and clinical data has linked ERP to increased risk of ventricular arrhythmia and sudden death.[4-8] Initial reports identified ERP as a risk marker of sudden death due to idiopathic VF in patients with a structurally normal heart, referred to as "early repolarization syndrome."[5,6] In a recent study by Furukawa and colleagues,[7] the presence of

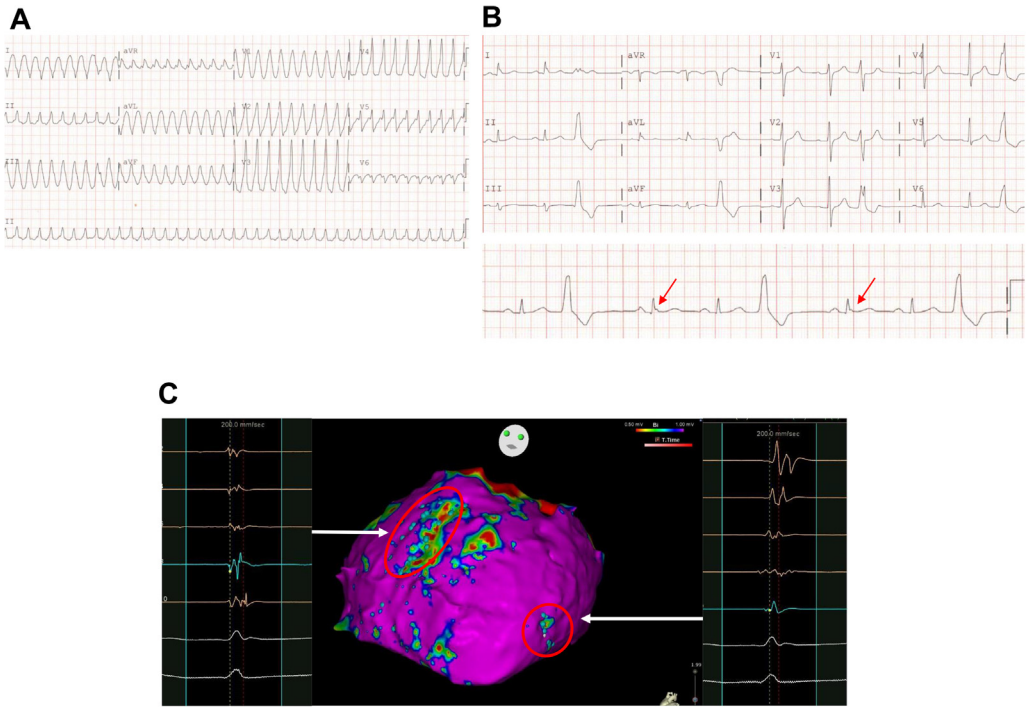

Figure 3 **A:** Twelve-lead electrocardiogram (ECG) of the clinical ventricular tachycardia. **B:** Twelve-lead ECG in sinus rhythm shows terminal QRS notching in leads I and aVL (upper panel). Note augmentation of the terminal QRS notching after postextrasystolic pause in lead II (*arrows*, lower panel). **C:** Epicardial electroanatomic voltage map demonstrates 2 areas of abnormal electrograms, right ventricular outflow tract and lateral left ventricle (delineated by *red ovals*), as well as examples of the corresponding local electrograms (*arrows*). Sites with high-frequency multicomponent electrograms are tagged on the map with blue spheres.

ERP in inferior leads was associated with increased risk of sudden death in patients with heart failure secondary to systolic LV dysfunction.

The exact electrophysiologic mechanism underlying ECG findings in ERP is incompletely understood and may be heterogeneous. ERP most likely represents a spectrum of electrophysiologic mechanisms, from benign to highly arrhythmogenic. Its mechanism and underlying electrophysiologic substrate may be different in patients with early repolarization syndrome and those with a structural heart disease. Elegant experimental studies using a canine ventricular wedge model suggest mechanistic similarity between ERP and the Brugada ECG pattern referred to as "J-wave syndromes."[4,8,9] Based on these studies, both ECG phenomena could be recapitulated by an accentuated regional (LV lateral wall in ERS and RVOT in Brugada) transmural repolarization gradient from endocardium to epicardium caused by a net outward shift in repolarizing current in RV epicardium secondary to either increased outward currents, especially the transient outward potassium current (I_{to}), or decreased inward currents such as peak sodium-channel current (I_{Na}) or L-type calcium-channel current (I_{Ca}). In addition, both experimental ERP and Brugada ECG patterns show similar response to pharmacologic interventions.[9] Increased regional repolarization gradient is thought to constitute an arrhythmogenic substrate capable of precipitating phase 2 reentry after a closely coupled premature ventricular contraction.[8,9] However, more recently, studies using epicardial mapping in Brugada patients demonstrated RVOT regions with low-amplitude, fractionated, and delayed local electrograms consistent with slow conduction. Ablation of these epicardial regions was associated with arrhythmia suppression and attenuation of right precordial J-point elevation.[10] Data on epicardial mapping in patients with ERP are limited. Nakagawa and colleagues[11] recorded delayed local electrograms from the epicardial surface of the lateral LV using a mapping catheter advanced through a lateral coronary sinus vein in a patient with ERP and a structurally normal heart who presented with ventricular fibrillation (VF).[11] However, detailed epicardial mapping was not performed.

The pathophysiology of delayed and fractionated epicardial electrograms in Brugada patients remains debatable. Histopathologic studies in patients with Brugada syndrome found evidence of subtle structural abnormalities of the RVOT myocardium, manifested as interstitial fibrosis and reduced gap junction redistribution.[12] These findings lend support to delayed depolarization (or slow conduction) within the RVOT as a potential mechanism of the above electrophysiologic abnormalities. Recent experimental studies using a canine ventricular wedge Brugada model suggested an alternative, repolarization, mechanism of fractionated and delayed electrograms. In this model, delayed bipolar epicardial electrograms correlated with concealed phase 2 reentry in the simultaneously recorded epicardial monophasic action potentials, whereas ablation of the sites of phase

2 reentry diminished ECG Brugada manifestations.[13,14] The mechanism of delayed and fractionated electrograms in our patients with ERP remains unclear.

Pause-dependent J-point augmentation has been previously linked to increased risk of VF in patients with ERP.[15] It has been postulated that this finding is characteristic of the repolarization mechanism of J-point elevation and can help differentiate true J-point elevation from intramyocardial conduction delays (QRS fragmentation) masquerading as a J wave in patients with a cardiomyopathy.[16] Interestingly, in 1 of our patients (case 2), there was pause-dependent augmentation of terminal QRS notching after ventricular premature beats (Figure 3B).

Previous reports have linked ERP to increased risk of idiopathic VF. The prevalence of MVT in this patient population is unknown. In a recent large series of Brugada patients, 4.2% of them received appropriate ICD interventions for MVTs.[17] Our report demonstrates that MVT is one of the mechanisms of arrhythmia in ERP, and thus indicates potential mechanistic heterogeneity of this ECG pattern.

In summary, our report suggests that in a subset of patients with a structural heart disease, ERP (terminal QRS notching) is an ECG manifestation of an arrhythmogenic epicardial LV substrate, which can cause MVT.

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