Benign Premature Ventricular Complexes from the Right Ventricular Outflow Tract Triggered Polymorphic Ventricular Tachycardia in a Latent Type 2 LQTS Patient

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Abstract

A 57-year-old woman showed frequent premature ventricular complexes (PVCs) originating from the right ventricular outflow tract (RVOT), and some of the PVCs triggered polymorphic ventricular tachycardia (PVT). Structural heart diseases were ruled out by conventional cardiac examinations. Radiofrequency catheter ablation was successful in eliminating the PVCs and subsequent PVT. However, epinephrine infusion unmasked her prolonged QT interval, and a genetic analysis revealed a $KCNH2$ mutation (R694H) as the cause of latent type-2 long QT syndrome (LQTS). This case suggests that latent LQTS may work as an arrhythmogenic substrate of PVT triggered by a benign form of RVOT-PVCs in patients with a structurally normal heart.

Key words: polymorphic outflow VT, latent long QT syndrome, catheter ablation

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Introduction

Premature ventricular complexes (PVCs) and ventricular tachycardia (VT) originating from the right ventricular outflow tract (RVOT) in patients with a structurally normal heart usually show a monomorphic VT-QRS complex. Although these arrhythmias are considered to be benign (1, 2), PVCs from RVOT triggers polymorphic VT (PVT) and/or ventricular fibrillation (VF) in some specific patients with structurally normal hearts, and this is known as “malignant RVOT tachyarrhythmia” (3, 4). However, the details of the mechanisms and characteristics of arrhythmogenic substrate of the malignant RVOT tachyarrhythmia have not been well clarified. This report presents a patient with several syncope attacks, and PVT developed following frequently observed RVOT-PVCs. Epinephrine and isoproterenol infusion unmasked the prolonged QT interval and a genetic analysis revealed the presence of a $KCNH2$ mutation (R694H) as the cause of latent type 2 long QT syndrome (LQTS).

Case Report

A 57-year-old woman was admitted for further study of the history of syncope attacks that occurred while she was at rest and/or while washing her face, but were not associated with exercise. A 12-lead electrocardiogram (ECG) showed frequent PVCs originating from the RVOT, but neither ST-T segment deviation nor QT interval prolongation was observed (Fig. 1A). A 24-hour Holter ECG demonstrated that the total number of PVCs was 25,000 beats per day, and self-terminating PVT was sometimes triggered by the PVCs with a relatively steady coupling interval (420-460 ms; Fig. 1B). Twelve episodes of non-sustained PVC (4-5 QRS complexes) were recorded on the Holter ECG. A morphologically similar QRS complex, suggesting an RVOT origin continued during the first few beats (Fig. 1B lower panel) in 3 episodes while a second and subsequent QRS complex showed a very different QRS morphology from that of the first beat (Fig. 1B upper panel) in the other 9
episodes. Her physical examination, echocardiogram, brain and cardiac magnetic resonance imaging, head-up tilt test and biochemical tests, including serum electrolyte levels, were all normal. A cardiac catheterization and an electrophysiologic study were performed after obtaining informed consent. Coronary angiography and both-sided ventriculograms were normal. The target PVCs developed less frequently both before and after administration of isoproterenol (0.01 μg/kg/min), but her QTc interval was prolonged from 400/420 to 460/480 ms by the isoproterenol infusion. Endocardial mapping did not demonstrate any abnormal local potential, and neither VT nor VF was induced by programmed ventricular stimulation from two sites in the RV. A best pace-mapping was obtained from the anterior septum of the RVOT (Fig. 1A), but no PVT was reproduced by electrical stimulation (1-2 extrastimulation and rapid stimulation up to 210 bpm) from the site. Five radiofrequency applications using a standard 4 mm tip catheter (20-30 W with a temperature limit 55°C) were delivered to the site. Continuous ECG monitoring did not show any RVOT-PVCs or subsequent PVT after the radiofrequency catheter ablation (RFCA).

This patient’s mother was incidentally admitted to another hospital in the same month, because of VF associated with hypokalemia (2.9 mEq/L) due to acute colitis. Her mother’s ECG at that admission showed prolonged QTU intervals (730 ms at 61 bpm) and low-amplitude T waves with an accentuated U wave in the V1-V6 leads. These ECG abnormalities were normalized after recovery from the colitis and hypokalemia, and her mother was considered to have suffered from a latent LQTS which was exacerbated by the hypokalemia. An epinephrine administration test (0.1 μg/kg bolus infusion followed by 0.1 μg/kg/min maintenance administration for 5 minutes) was attempted to study the possibility of the same latent LQTS in the current patient. Epinephrine prolonged the QTc interval from 437 ms at a baseline to 655 ms at the maximum effect (Figs. 2A, 2B). In addition, the normal T-wave configuration was altered into a low-amplitude bifurcated T-wave in the V1-V6 leads. The prolongation of the QTc interval and altered T-wave configuration were maintained during a steady state of epinephrine administration (QTc 620 ms, Fig. 2C). No PVC was observed during the epinephrine test. Implantable cardioverter-defibrillator (ICD) therapy was recommended, because of

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**Figure 1.** (A): Left panel shows the 12-lead electrocardiogram (ECG) of the proband and QT and QTc intervals were normal (410/431 ms) at the heart rate of 66 bpm. The center panel shows an extrasystole originating from the right ventricular outflow tract (RVOT), which frequently appeared in this patient. The right panel shows the QRS morphology that was produced by pace-mapping in the RVOT during an electrophysiological study. (B): The 24-hour Holter ECG demonstrating monomorphic extrasystoles followed by non-sustained polymorphic ventricular tachycardia. (C): Direct sequencing data from the proband show a single nucleotide mutation of G2081A in the KCNH2 gene, causing substitution of the 694th amino acid, an arginine (R) for histidine (H). (D): Alignment of amino acid sequences around the KCNH2-R694H mutation (from 690th to 698th amino acid). Amino acid sequences predicted from the nucleotide sequence of human KCNH2 (GenBank Accession No. NM_000238) were aligned with those from Chimpanzee (XM_001137384), Mouse (NM_013569), Dog (NM_001103145), Rabbit (NM_001082384), Bos taurus (NM_001099101), and Zebrafish (NM_202837).
the episodes of syncope attacks and her family history of VF, despite the successful result of RFCA for the PVC. Neither recurrence of syncope nor ICD discharge has been observed during a 23-month follow-up period. A genetic analysis of cardiac ion channel genes revealed that this patient carried a heterozygous KCNH2 missense mutation, the substitution of the 694th amino acid arginine for histidine (R694H; Fig. 1C). This mutation was not found in the single nucleotide polymorphism database (dbSNP, www.ncbi.nlm.nih.gov/projects/SNP/). A comparative genomics analysis by aligning nucleotide sequences of various species showed that the surrounding region of the mutation is evolutionarily conserved, suggesting the functional importance of this region (Fig. 1D). Functional predictions of the KCNH2-R649H mutation were assessed using bioinformatics methods encoded in the Polymorphism Phenotyping ver. 2 program (PolyPhen-2, http://genetics.bwh.harvard.edu/pph2) (5). The PolyPhen-2 reported this mutation to be “probably damaging” to proper protein function (with their score, 0.981/1). No mutation was found in other LQTS-causing genes (KCNQ1, SCN5A, KCNE1, KCNE2, or KCNJ2).

**Discussion**

The current patient (a 57-year-old female) had no structural heart disease but showed frequent PVCs originating from the RVOT. This patient was initially suspected to have malignant RVOT tachycardia, since the PVC triggered self-terminating PVT, and sustained PVT and/or sequential VF were a likely cause of her syncope episodes. Patients with malignant RVOT tachyarrhythmia are reported to be characterized by (i) the presence of syncope episodes and (ii) short coupling intervals of the PVCs (350±20 ms) (3, 4). Indeed, the patient had several syncope episodes, but the coupling interval of the PVCs (420-460 ms) was not as short as that reported in the previous reports (3, 4). The non-sustained PVT showed a morphological change between the first and following beats in the 9 events whereas similar QRS morphology continued for the first several beats in the other 3 events. The former characteristics seem to resemble the torsades de pointes arrhythmia in LQTS rather than idiopathic RVOT-PVT (3, 6).

A missense mutation (R694H) in the KCNH2 gene, which is a gene that causes type 2 LQTS, was identified in this patient. A functional prediction using the PolyPhen-2 program indicated that the KCNH2-R649H mutation would induce functional impairment of the cardiac $I_{Kr}$ channel. Furthermore, the neighboring R696C mutation in the heterozygous pattern was reported as a cause of QT prolongation and PVT (7). However, the patient showed normal QT/QTc intervals at rest and had a low probability of LQTS according to the criterion by Schwartz et al. (8); i.e., syncope episodes without stress (1 point). The QT interval prolongation and a VF episode in her mother were highly related to hypokalemia due to colitis, so this was unable to be counted as a family history of LQTS. In addition, an analyses of LQTS families show that some mutations in KCNH2 are associated with low penetration (9). Itoh et al. reported that several KCNH2 mutations are found in patients with latent type 2 LQTS, which were unmasked by the use of $I_{Kr}$ channel blockers or in the presence of hypokalemia (10). Therefore, the current patient was probably in latent type 2 LQTS, and intravenous isoproterenol and epinephrine unmasked the QT interval prolongation and low-amplitude bifurcated T-waves.
which were compatible as ECG characteristics of type 2 LQTS (11-13).

It is not fully understood how the arrhythmogenic substrate of the latent LQTS was associated with the frequent RVOT-PVCs and subsequent PVT in this patient. No abnormal local electrogram was recorded from the RV, and PVT was unable to be induced by the programmed ventricular stimulations (including from the site of PVC origin). However, these electrophysiological characteristics were compatible to those of LQTS patients (14). Noda et al. also reported that non-sustained PVT or ventricular fibrillation was induced during an electrophysiological study in only in 3 of 16 patients with malignant idiopathic RVOT tachyarrhythmia (3).

Spatial (and temporal) dispersion of the ventricular repolarization would be small when the self-terminating PVTs developed (on the day of Holter ECG recording) because QT interval prolongation was not obvious in the two ECG leads of the Holter recording. However, it is still possible that the dispersion of the ventricular repolarization of this patient was greater than that in healthy subjects without a mutation of the KCNH2 gene. Surface ECG is unable to accurately represent all small spatial dispersion of ventricular repolarization in the whole ventricle. Therefore, the non-prolonged QT interval on Holter recording could not completely rule out the possibility that latent LQTS might work as an arrhythmogenic substrate of non-sustained PVT. On the other hand, early afterdepolarization might not be a mechanism of initial triggering PVC because no prolonged QT interval was observed at the time of the Holter recording. In addition, although this patient had several episodes of syncope attacks, this patient did not report syncope or fainting during the Holter recording, and all PVTs recorded on the Holter ECG self-terminated within a few seconds (not sustained for longer time or degenerated into VF) suggesting the lack of a large enough magnitude of an arrhythmogenic substrate at the time of Holter ECG recording.

Reithmann et al. reported a type 3 LQTS patient showing PVT triggered by RVOT-PVCs (15). However, this is the first report that latent type 2 LQTS due to a KCNH2 gene mutation was found in a patient with from PVT triggered by RVOT-PVC. Both the RVOT-PVC and PVT were successfully treated by RFCA. Experimental studies reported that early afterdepolarization, which arises from M-cells layer and/or endocardial Purkinje fibers in the left ventricle, is the most likely cause of the initiation of ventricular arrhythmias in LQTS patients (6). However, Birati et al. recently reported that more than half of the triggering-PVC origins of PVT are found from the right or left ventricular outflow tract in LQTS patients (including various genotypes of congenital LQTS and acquired form of LQTS) (16). The precise reasons for the discrepancy between the experimental studies and the clinical observations remain uncertain and this subject needs to be clarified in future studies.

The coupling intervals of triggered PVC in LQTS patients (probably due to early afterdepolarization) are reported to be in the range of 500-700 ms, and these values were longer than that in the current patient (420-460 ms) (16, 17). Early afterdepolarization seemed to be less likely as a mechanism of the RVOT-PVCs, because (i) a shorter coupling interval of the triggered PVC, (ii) the RVOT-PVCs occurred frequently during a period with a normal range of QT interval and (iii) epinephrine and isoproterenol infusion prolonged QT interval but did not increase the frequency of RVOT-PVCs. We think that there are two possible causes of PVT in this patient. [1] Benign PVC from the RVOT was a trigger and latent LQTS was at work as an arrhythmogenic substrate of PVT, or [2] this patient independently suffered from both a malignant form of RVOT-PVT and latent LQTS. Although it is difficult to precisely differentiate between these two possibilities, the current patient may have had benign RVOT-PVCs, and activation of the PVCs could infringe on the spatial dispersion of ventricular repolarization of the heart with latent LQTS, which resulted in the development of subsequent PVT.

Although RFCA successfully eliminated the targeted PVCs, an arrhythmogenic substrate of the latent LQTS must be present in this patient, and any other PVC may trigger PVT in the future. ICD treatment may prove to be useful to prevent a possible cardiac event in this patient. Although it might be rare, it is necessary to pay attention to the possibility of latent LQTS as an arrhythmogenic substrate of malignant arrhythmias triggered by benign RVOT-PVCs.

The authors state that they have no Conflict of Interest (COI).

References


