Oral adrenergic agents produced Ventricular fibrillation and QT prolongation in an elderly patient carrying an *RYR2* variant.

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Abbreviations: AED = automated external defibrillator, CPVT = catecholaminergic polymorphic ventricular tachycardia, ECG = electrocardiogram, RyR2 = cardiac ryanodine receptor, QTc = corrected QT interval

Abstract

Mutant cardiac ryanodine receptor channels (RyR2) are “leaky,” and spontaneous Ca^{2+} release through these channels causes delayed afterdepolarizations that can deteriorate into ventricular fibrillation (VF). *RYR2* is a causative gene of type 1 catecholaminergic polymorphic ventricular tachycardia (CPVT). Some patients carrying *RYR2* mutations in CPVT exhibit QT prolongation and are initially diagnosed with long QT syndrome. However, none have been reported to cause drug-induced VF in patients with *RYR2* variants. We describe the first case of an elderly woman with drug-induced QT prolongation and VF who carried a novel *RYR2* variant but no other mutations related to long QT syndrome.

Case report

An 84-year-old woman was hospitalized at an outside institution for repeated loss of consciousness over 3 days. She had been treated for diabetes mellitus and heart failure with preserved ejection fraction due to hypertension. She had a history of knee osteoarthritis and coronary sclerosis, and had received a painkiller drug (duloxetine, a serotonin–norepinephrine reuptake inhibitor, 40 mg per day) for several months and an antiplatelet drug (cilostazol, 100 mg per day) for 1 year. Her family history was unknown because she was adopted during childhood, and she had no children. On admission, the results of brain computed tomography and magnetic resonance imaging and magnetic resonance angiography were unremarkable. However, when the patient lost consciousness in the hospital, an automated external defibrillator (AED) detected VF. After six AED shocks, sinus rhythm was restored and the patient was transferred to our hospital. One year before starting duloxetine and cilostazol, a 12-lead ECG showed normal sinus rhythm and a normal QT interval (QT/corrected QT [QTc], 438/432 ms) (**Figure 1A**).

On admission, the patient had a normal level of consciousness. Her plasma potassium level was low, at 3.5 mEq/L (normal range: 3.6–4.8 mEq/L). Her 12-lead ECG exhibited sinus rhythm (63 beats/min), QT prolongation (QT/QU/QTc, 600/760/614 ms), and negative T and U waves in the lateral leads (**Figure 1B**). Shortly after admission, bedside continuous single-lead ECG monitoring demonstrated spontaneous VF with initial "short–long–short" sequences, which are typical in torsades de pointes (TdP) (**Figure 1D**). The adrenergic agents cilostazol and duloxetine were discontinued, and the patient's serum potassium level was maintained within a normal range by oral administration of spironolactone. She was also treated with overdrive transvenous ventricular pacing. VF was transiently suppressed. However, when the ventricular pacing rate was reduced, premature beats appeared. Because these premature beats may cause TdP, the patient received a permanent pacemaker with atrial overdrive pacing (75 pacing/min). Bradycardia was avoided by overdrive pacing, and premature ventricular beats were completely suppressed. After these therapies, no VF or TdP occurred. Coronary angiography showed no significant stenoses of the coronary arteries.

After obtaining the consent for genetic analysis approved by our institutional review board, we performed genetic screening for inherited arrhythmia syndromes using a gene panel that included all reported genes related to long QT syndrome, but found no relevant mutations. However, we did identify a novel missense variant (c.14098T>A, p.S4700T) in *RYR2* (**Figure 2**). The variant had not previously been reported in the gnomAD Browser (https://gnomad.broadinstitute.org/) or in several databases, including those containing data of Japanese individuals (e.g., TOGOVAR, https://togovar.biosciencedbc.jp). According to the pathogenesis prediction software systems PolyPhen2, SIFT, and CADD, the variant was evaluated as "tolerated" to "possibly damaging" (**Table 1**).

One month after the cessation of cilostazol and duloxetine, the patient's QT interval shortened (QT/QTc, 372/417 ms) (**Figure 1C**) and her plasma potassium level returned to normal (4.0 mEq/L). The patient was discharged without oral adrenergic agents, and has done well with no recurrent VF during 5 years of follow-up.

Discussion

Mutations in *RYR2* cause several forms of ventricular arrhythmia, including type 1 CPVT, catecholaminergic idiopathic VF, and idiopathic VF.[1,2] These arrhythmias may lead to sudden cardiac death due to exercise or emotional stress in young people without QT prolongation.[2] *RYR2* mutations were also detected in approximately 6% of clinically diagnosed genotype-negative patients with long QT syndrome.[3] Recently, several patients carrying *RYR2* mutations in CPVT exhibited QT prolongation and were initially diagnosed with long QT syndrome in young people.[4, 5] To the best of our knowledge, there have been no reports of drug-induced VF in older patients carrying *RYR2* variants.

In the present case, marked QT prolongation and VF occurred only during oral administration of adrenergic agents; the symptoms were not identified before the administration of these agents and disappeared after they were discontinued, indicating that these agents caused QT prolongation and subsequent VF. Oral adrenergic agents are known to result in QT prolongation, as observed in carriers of *KCNQ1* mutations; however, our patient had an *RYR2* variant but no *KCNQ1* mutation; therefore, the former was possibly involved in her QT prolongation.

Our patient took two drugs: cilostazol and duloxetine. The former, an antiplatelet drug, is a selective inhibitor of phosphodiesterase III and exerts vasodilatory activity by increasing cellular cAMP levels.[6] Cilostazol is listed as a risk factor for TdP by CredibleMeds (https://www.crediblemeds.org). Duloxetine, a drug for depressive disorders, knee osteoarthritis pain, and diabetic neuropathy, is a serotonin and noradrenaline reuptake

inhibitor, and like cilostazol, it increases intracellular cAMP levels.[7] Consequently, cAMP promotes protein kinase A activity, which phosphorylates proteins essential for excitation–contraction coupling, such as L-type Ca^{2+} channels, RyR2, phospholamban, and contractile proteins. These phenomena underlie the positive inotropic and lusitropic effects of adrenergic receptor stimulation.[8] In our patient carrying the *RYR2* variant, cilostazol and duloxetine might have induced abnormalities in Ca^{2+} flux, which resulted in QT prolongation, triggered activity, and delayed afterdepolarization.

Conclusions

Oral adrenergic agents might induce QT prolongation and subsequent VF in patients carrying an *RYR2* variant. Screening for *RYR2* could be valuable in patients with suspected drug-induced long QT syndrome.

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Figure Legends

Figure 1. A. Twelve-lead ECG recorded 1 year before the administration of duloxetine and cilostazol. **B.** Twelve-lead ECG during treatment with duloxetine and cilostazol. **C.** Twelve-lead ECG 1 month after cessation of duloxetine and cilostazol. **D.** Bedside continuous single-lead ECG tracings after admission. Ventricular fibrillation spontaneously occurred with typical initial “short–long–short” sequences.

Figure 2. Electropherogram of *RYR2* gene in a control subject (**A**) and the patient (**B**), showing a heterozygous variant, p.S4700T (c. 14098T>A) .

Table 1. Prediction of the functional effect of a missense variant (S4700T) in the *RYR2* gene

PolyPhen2	SIFT	CADD
Possibly damaging	Tolerated	24.5

PolyPhen2, **Poly**morphism **Phen**otyping v**2**; SIFT, **S**ort **I**ntolerant **F**rom **T**olerant amino acid substitution; CADD, **C**ombined **A**nnotation **D**ependent **D**epletion.

Refs.: PolyPhen2: http://genetics.bwh.harvard.edu/pph2/, SIFT: http://sift.jcvi.org/, CADD: http://cadd.gs.washington.edu/score.