Endocardial Arrhythmogenic Mechanisms of Torsades de Pointes in Patients with the Congenital Long QT Syndrome

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Abstract

We injected acetylcholine (Ach) into the coronary artery to ascertain whether coronary vasospasm contributed to the syncopal events or chest oppression suffered by 3 patients with long QT syndrome (LQTS). During the test, a quadripolar electrode catheter was placed in the right ventricle and the activation-recovery interval was reanalyzed from the stored data. Intracoronary Ach transiently prolonged the QT intervals in all 3 patients without inducing coronary vasospasm. The Ach-induced QT prolongation was associated with enhanced spatial and temporal dispersion of intra-ventricular repolarization. The electrophysiological abnormalities were consistent with the putative arrhythmogenic mechanisms identified in experimental studies of LQTS.

Key words: Long QT syndrome, torsades de pointes, activation-recovery interval, repolarization dispersion

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Introduction

The congenital long QT syndrome (LQTS) is characterized by a prolonged QT interval and development of torsades de pointes (Tdp) (1-6). Previous experimental studies have shown that the arrhythmogenesis of LQTS is based on a prolonged action potential duration and premature ventricular complexes (PVC) due to early afterdepolarization infringing on a markedly heterogeneous ventricular repolarization and triggering reentrant ventricular tachyarrhythmias (7-9). However, whether these arrhythmogenic mechanisms identified in basic experiments are applicable to clinical events has not been confirmed, because Tdp and intracardiac repolarization are infrequently mapped during the actual events or during electrophysiologic studies.

We retrospectively reanalyzed the intracardiac electrograms recorded in 2 patients presenting with congenital type 2 LQTS and 1 patient with type 1 LQTS, before and after the intracoronary injection of acetylcholine (Ach). This Ach test was performed to ascertain whether coronary vasospasm contributed to the syncopal and/or chest pain events suffered by all 3 patients (10).

Patients and Methods

The 3 patients were admitted to our hospital after having each suffered several episodes of syncope and/or chest oppression (Table 1). The screening hematological and biochemical analyses, chest roentgenogram, two-dimensional echocardiogram, electroencephalogram and electrocardiologic study in a single procedure, after they were explained about its possible complications and after they or their immediate relatives had granted their informed consent. The protocol of electrophysiologic study and intracoronary Ach administration in patients with prolonged QT interval (including LQTS) and with syncope/chest pain episodes is approved by the Ethics Committee of Niigata University School of Medicine.

The electrophysiologic studies were performed in the non-sedated, post-absorptive state to study whether bradyarrhythmia and/or tachyarrhythmias were the cause of their syncope episodes. Three 6F quadripolar electrode catheters with 5-mm interelectrode distance were placed at right atrium, His-
Table 1. Demographic Characteristics, Genotypes and Outcomes of Acetylcholine Tests in the 3 Study Patients

<table>
<thead>
<tr>
<th>Patient no</th>
<th>Age (y)/sex</th>
<th>Genotype</th>
<th>Dose (μg)</th>
<th>Before</th>
<th>After</th>
<th>Tdp induced</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>59/F</td>
<td>LQTS2</td>
<td>20</td>
<td>480/518</td>
<td>640/691</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>10/M</td>
<td>LQTS1</td>
<td>20</td>
<td>370/501</td>
<td>470/637</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>21/F</td>
<td>LQTS2</td>
<td>50</td>
<td>500/540</td>
<td>680/734</td>
<td>Yes</td>
</tr>
</tbody>
</table>

F = female; M = male; LQTS1 = type 1 long QT syndrome; LQTS2 = type 2 long QT syndrome; Tdp = torsades de pointes

Results

Patient No. 1

A 59-year-old woman was admitted to our hospital for management of recurrent episodes of chest oppression and syncope. A standard, 12-lead electrocardiogram (ECG) showed sinus rhythm, incomplete right bundle branch block, and prolongation of the QT and QTc intervals to 520 and 491 ms, respectively. At cardiac catheterization and electrophysiologic studies, the measurements of intracardiac pressures and left ventriculography were normal, and programmed RV electrical stimulation induced no ventricular tachyarrhythmia. The AH and HV intervals during sinus rhythm measured 120 ms and 50 ms, respectively, and the Wenckebach cycle length during atrial pacing was 140 bpm. The baseline coronary angiograms were normal. The intracoronary administration of Ach did not induce coronary vasospasm. However, shortly after the injection of 20 μg into the left coronary artery, the QT/QTc intervals transiently increased from 480/518 to 640/691 ms (Fig. 1). The ARI also lengthened and ARI dispersion among the 4 electrodes of the RV septal catheter increased from 9-17 to 61-64 ms during atrial pacing at 70 bpm (Fig. 2), and non-sustained Tdp developed, triggered by a short-long-short cycles sequence due to ventricular bigeminy (Fig. 3). The QT and QTc intervals and ARI returned to baseline within approximately a minute. The systemic blood pressure was 136/78 mmHg before and 142/82 mmHg after the administration of Ach. Type 2 congenital LQTS (KCNH2 mutation; G601D) was later diagnosed by genetic analysis. For a follow-up of 11 years, the patient has remained free from adverse cardiac events, on a regimen of propranolol, 60 mg daily, and mexiletine, 100 mg daily.

Patient No. 2

A 10-year-old boy was referred to our hospital for management of syncope attacks. The standard 12-lead ECG showed sinus rhythm and prolongation of the QT and QTc intervals was 500 and 472 ms, respectively. Measurements of the intracardiac pressures, baseline coronary angiograms and left ventriculography were normal, and programmed electrical RV stimulation induced no ventricular tachyar-
rhythmia. The AH and HV intervals during sinus rhythm measured 110 ms and 45 ms, respectively, and the Wenckebach cycle length during atrial pacing was 150 bpm. Ach (20 μg) injected into the left coronary artery transiently lengthened the QT/QTC intervals from 370/501 to 470/637 ms during the atrial pacing at 110 bpm without inducing coronary vasospasm. At the same time, prolongation and alternans was observed on the endocardial electrogram recordings, though it was not apparent on the surface ECG (Fig. 4). The ARI alternans was associated with prominent spatial and temporal dispersion of ventricular repolarization, and ARI dispersion increased from 32-33 to 85-116 ms (Fig. 4). The QT interval and ARI returned to baseline values within a minute without the development of ventricular tachyarrhythmias. The systemic blood pressure was 112/66 mmHg before, and 110/70 mmHg after the administration of Ach. Type 1 congenital LQTS (KCNQ1 mutation; A525V) was later diagnosed by genetic analysis. The patient has remained free from syncope on a treatment of atenolol, 25 mg daily, for a 9-year follow-up.

Patient No. 3

A 26-year-old woman with a diagnosis of type 2 LQTS (KCNH2 mutation; P1034fs22) was readmitted to our hospital for investigations of chest oppression and syncope, followed by ICD shocks. The ICD was implanted in 1998 because of the demonstration of Tdp and sufficient amounts of β-blocker could not be prescribed because of bradycardia and hypotension. Before these events, she had been clinically stable on a regimen of atenolol, 25 mg daily, mexiletine, 300 mg daily, and was paced in the atrium at 70 bpm by the ICD. On admission, the 12-lead ECG showed sinus and atrial paced rhythm, and QT/QTC intervals prolongation to 640/716 ms. Since she complained of chest oppression and was under the treatment of β-blocker, we attempted cardiac catheterization to study whether coronary vasospasm participated as a trigger of ventricular fibrillation. At cardiac catheterization, the intracardiac pressures, baseline coronary angiogram and left ventriculogram were normal. Programmed RV stimulation induced no ventricular tachyarrhythmia. The AH and HV intervals during sinus beats measured 100 ms and 45 ms, respectively, and the Wenckebach cycle length during atrial pacing was 150 bpm. Ach, injected in a dose of 50 μg into the left coronary artery, prolonged the QT interval and induced transitory Tdp triggered by ventricular bigeminy in absence of coronary vasospasm. The onset of the triggered PVC overlapped the end of the preceding T wave (Fig. 5). On the RV endocardial re-
cordings, a delay was observed between the QRS complex and onset of endocardial activation preceding the onset of Tdp (Fig. 5). The systemic blood pressure was 128/74 mmHg before and 136/80 mmHg after the administration of Ach. For a follow-up of 12 years, the patient has continued to experience sporadic recurrences of ventricular fibrillation despite treatment with bisoprolol, 5 mg daily, mexiletine, 300 mg daily, potassium chloride, 1.2 g daily, and atrial pacing at 70 bpm.

**Discussion**

The main observations made in this study were: 1) Ach-induced prolongation of the QT interval on standard surface ECG was associated with heterogeneous endocardial ARI prolongation and prominent spatial dispersion of ventricular
We have previously reported a close correlation between the mechanism of Ach-induced QT interval prolongation and the local effective refractory period, including in patients suffering from congenital LQTS (18). The quadripolar electrode catheter was placed in the septal region of the RV. Therefore, the electrograms of the catheter represented the phenomenon in the right-sided interventricular septum. Since we administered Ach into the left coronary artery, the Ach was perfused into the ventricular septum through the branch arteries from the left anterior descending coronary artery. Since the QT interval duration, QT/T alternans and short PVC falling on the terminal portion of the preceding T wave.

Correlation between surface electrocardiogram and endocardial electrograms

In patients presenting with congenital LQTS, prominent prolongation of the QT interval, QT/T alternans and short alternating with long cardiac cycles on the surface ECG are common precursors of Tdp (1-6, 15). While previous experimental studies have shown that these ECG manifestations are closely associated with the presence of prominent spatial and temporal dispersion of ventricular repolarization (16, 17), the abnormalities of repolarization visible on surface ECG and the arrhythmogenic changes recorded on the endocardial surface have not been clearly correlated in clinical cases of LQTS. This is explained by the infrequent induction of Tdp by programmed electrical stimulation in clinical studies, as well as by the inability of standard mapping techniques to measure the repolarization of a single cardiac cycle at multiple ventricular sites. We reanalyzed ARI from the stored data during the intracoronary Ach test to study the distribution of the local ventricular repolarization during the QT interval prolongation. In this case study, ARI was obtained from each electrode of a single quadripolar catheter to make simultaneous measurements at 4 sites. We have previously reported a close correlation between ARI measured from unipolar intracardiac electrograms and the local effective refractory period, including in patients suffering from congenital LQTS (18). The quadripolar electrode catheter was placed in the septal region of the RV. Therefore, the electrograms of the catheter represented the phenomenon in the right-sided interventricular septum. Since we administered Ach into the left coronary artery, the Ach was perfused into the ventricular septum through the branch arteries from the left anterior descending coronary artery. As observed in experimental studies of LQTS (16, 17), the analysis of ARI in our patients confirmed that the prolongation of the QT interval on surface ECG was correlated with a prominent spatial (marked ARI dispersion) and temporal (during ARI alternans) dispersion of RV endocardial repolarization.

Despite the challenge represented by the analysis of local activation with recordings of unipolar electrograms, a scrutiny of the records from the present patient no 3 suggested that the presence of localized, delayed RV endocardial conduction predicted the onset of Tdp. The onset of the triggered PVC coincided with the end of the preceding T wave, a timing of events consistent with the triggering of Tdp by early afterdepolarizations in LQTS (3, 5, 6). Therefore, the observations made in this study suggest that the arrhythmogenic hypotheses derived from experimental studies are applicable to clinical cases of LQTS.

Intracoronary acetylcholine and prolonged QT interval

The mechanism of Ach-induced QT interval prolongation in congenital LQTS has not been clarified. We have reported

Figure 4. ARI alternans in the unipolar endocardial electrograms in patient no 2. A. Before the injection of Ach, ARI was short and stable from beat to beat during atrial pacing at 110 bpm. B. Ach prolonged the QT interval and obvious ARI alternans was transiently observed in the unipolar electrograms. Since the duration of ARI changed on a beat-to-beat basis, a greater ARI dispersion (ARID) was associated with the cycles with longer ARI (L) and a smaller ARID with the cycles with shorter ARI (S). Other abbreviations as in Fig. 2.
previously that the Ach-induced QT interval prolongation was not observed in those control patients in whom intracoronary Ach administration was performed to examine the reasons for unexplained syncope but coronary vasospasm was not provoked by Ach injection (19). In that study, administration of Ach induced transient QTc interval prolongation in LQTS patients (from 0.519±0.029 to 0.688±0.067 second, p<0.01) but not in the control subjects (from 0.418±0.026 to 0.401±0.024 second, ns). The QT interval of the LQTS patients was not prolonged by the injection of saline, or biphasic action) to L-type Ca\(^{2+}\) current (30-34). Therefore, it is still uncertain why the intracoronary Ach administration prolonged the QT interval in these 3 patients with genotyped LQTS but not in the control subjects.

It is, nevertheless, possible that a dynamic change in autonomic nervous activity, for example an increase in sympathetic nerve activity following parasympathetic activation nerve by Ach, may be a cause of Ach-induced QT interval prolongation in patients suffering from congenital LQTS. This is because adrenergic stimulation has been reported to lengthen the QT interval in LQT1 and LQT2 patients (16, 35). This hypothesis may be related to the observation that prolonged ARI was recorded from the electrode catheter placed in the region of the RV septum because in normal myocardium the action potential duration of the myocytes through augmentation of net outward current by increasing \(I_{\text{K,ach}}\). An indirect effect of Ach may also shorten the action potential duration through decreasing \(I_{\text{C}}\) by the antagonism of \(\beta\)-stimulation (21, 24, 25). As another possibility, intracoronary injection of Ach might affect myocardial ion currents through nitric oxide (NO) because healthy coronary endothelium releases NO in response to Ach (26, 27), and the results of coronary angiogram were normal in the 3 patients. However, action potential duration of myocardium may either be prolonged (increase of late sodium current and/or decrease of rapidly activating delayed rectifier current) or shortened (increase of slowly activating delayed rectifier current and/or inward rectifier current) by NO (28, 29). NO has been reported to show various effects (increase, decrease or biphasic action) to L-type Ca\(^{2+}\) current (30-34). Therefore, it is still uncertain why the intracoronary Ach administration prolonged the QT interval in these 3 patients with genotyped LQTS but not in the control subjects.

In this study, transient Tdp was induced in 2 patients of type 2 LQTS but not in the patient of type 1 LQTS. Since it
has been reported that an abrupt increase of the sympathetic nerve activity is more arrhythmogenic in type 2 LQTS rather than type 1 LQTS (1, 2, 6), their genetic background might be associated with the different response of the Ach injection.

Since parasympathetic nervous activity exerts few effects on the depolarization and repolarization of ventricular myocytes under baseline conditions (21, 24, 25), it is also unlikely that the intracoronary Ach injection directly triggered the PVC. On the other hand, a heightened sympathetic nervous activity following the activation of parasympathetic activity by Ach may have triggered the premature events by augmenting the myocardial calcium and sodium currents (3, 5).

Coronary vasospasm can coexist in patients with LQTS (36). Therefore, physicians need to watch for possible QT interval prolongation during intracoronary Ach administration when the test is considered to be necessary for the diagnosis of vasospastic angina in patients with LQTS.

Limitations of our study

Our analysis was limited by the sampling of a small number of unipolar RV septal electrograms in only 3 patients. Since the main arrhythmogenic substrate in LQTS is believed to be located in the LV, the magnitude of endocardial ARI dispersion in this study was probably underestimated. However, the purpose of this retrospective analysis of ventricular repolarization was not quantitative. Second, the mechanism by which intracoronary Ach prolongs the QT interval is unclear and may be different from that, which occurs spontaneously in the LQTS. Furthermore, 2 of our patients presented with type 2 LQTS and 1 patient suffered from type 1 LQTS, and the mechanism of Ach-induced QT interval prolongation in both genotypes may be different. However, there is no apparent reason why the arrhythmogenic mechanism of QT interval prolongation should be variable. The mechanism and incidence of Ach-induced QT interval prolongation are important subjects, but the purpose of this study was to analyze the endocardial electrograms during the period of QT interval prolongation and further clarification is beyond the scope of this study. We believe, nevertheless, that our observations contribute information in support of a relationship between the results of experimental electrophysiological studies and the clinical observations made in patients presenting with the congenital LQTS.

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

References