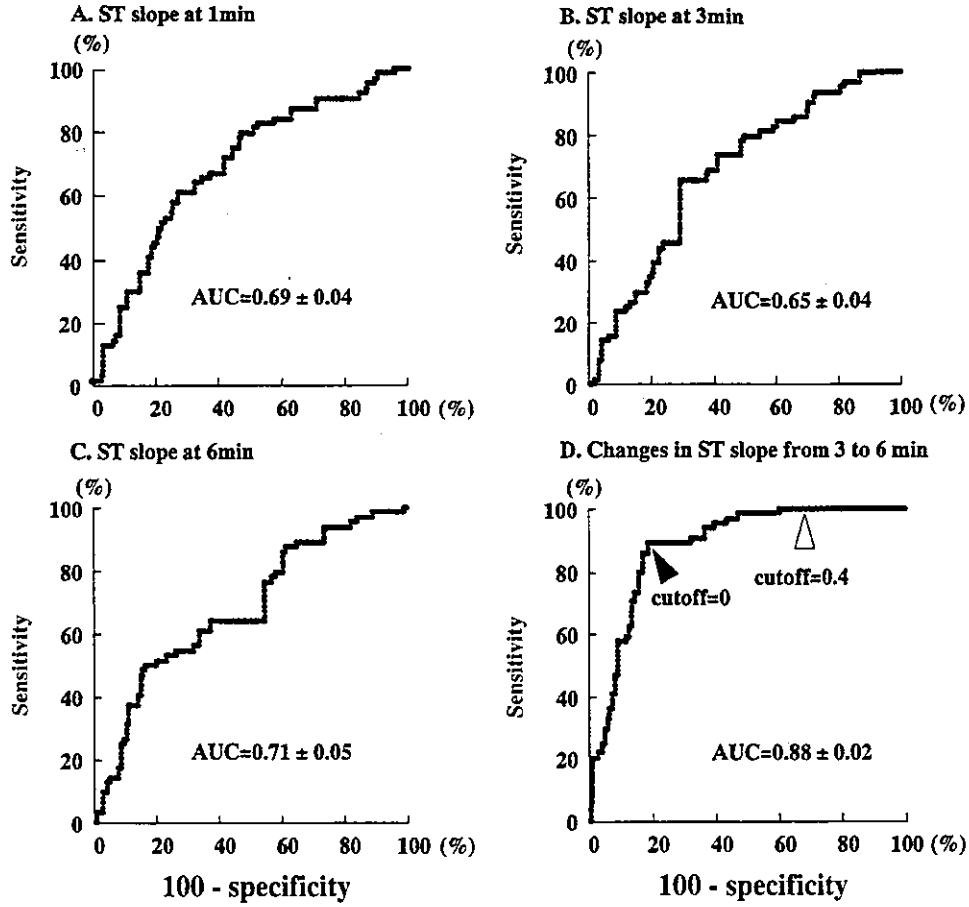

Fig 7. The receiver operating curve (ROC) for the ST slope at postexercise 1-min (A), 3-min (B) and 6-min (C), and for ΔST slope (D). The area under the ROC (AUC) for D was significantly greater than each AUC for A, B, or C ($p<0.001$, all). In (D), closed arrow indicates the diagnostic values (sensitivity 88%, specificity 81%) by using ΔST slope of <0.0 mV/s as the criterion for false-positive subjects. Open arrow indicates the values (sensitivity 37%, specificity 100%) by using ΔST slope of ≥0.4 mV/s as the criterion for true-positive patients.

Discussion

We have demonstrated that computer analysis of the recovery time-course of the ST slope is a simple, reliable method of discriminating FP from TP ST-segment responses. The accuracy using ΔST slope <0.0 mV/s as the criterion for FP response is considered to substantially improve the diagnostic value of exercise ECG. Furthermore, the finding that ΔST slope ≥0.4 mV/s could correctly identify TP responses without exception is important for the interpretation of the exercise ECG. One can consider that an exercise-induced ST-segment depression followed by an ST slope increase from post-exercise 3 to 6 min would credibly strengthen the diagnosis of CAD. To our best knowledge, there have been few studies conducted specifically to differentiate FP from TP ST-segment responses using a simple ECG marker in a relatively large population.

Diagnostic Value of ST Slope

To improve the accuracy of the exercise ECG, various indices have been proposed, including the degree of ST-segment depression[1,16,17] R wave amplitude changes[18,19] ST/HR slope[20,21] ST index[21,22] QT dispersion[2,23] ST slope[1,7,16,24,25] and concomitant changes in hemodynamic parameters[1,17] Each has been reported to improve accuracy; however, only a few are in clinical use, presumably because there has not been a dramatic increase in accuracy, the method is complicated or time-consuming, or both.

Downsloping or horizontal ST-segment depression is more specific for CAD than upsloping depression[1,7] Furthermore, the downsloping pattern has been reported as a marker for severe ischemia[26,27] Thus, the ST slope offers some useful diagnostic information. Also, in CAD patients, exercise-induced ST-segment depression often changes from an upsloping or horizontal pattern during exercise to a downsloping pattern in recovery[7,8] Therefore, because the ST-segment usually returns to baseline between 6 to 10 min postexercise, the ST-T time-course of CAD patients (ie, the TP response) can be characterized by a transient decrease in the ST slope soon after exercise with a gradual increase toward baseline in late recovery[7,8]

Unlike the characteristic time-course of the ST slope in CAD patients, individuals with FPD often show several patterns[5,8] one of which was observed in the present FP subjects. In it, the magnitude of ST-segment depression remained almost constant and the ST slope rather decreased from postexercise 3- to 6-min, whereas, in TP patients, both ST-segment depression and ST slope recovered toward baseline during this period. The directionally opposite ST slope changes emphasized the intergroup difference, contributing to accurate differentiation of the FPs from the TPs.

Different Recovery Time-Courses of the ST Slope in the TP and FP Groups

Despite the potential usefulness of ST-T time-course for diagnosis, few studies have focused on this possibility, especially in conjunction with the ST slope[5,8] In our analysis, the postexercise ST slope in TP patients progressively decreased up to 3 min, at which time it reached the lowest value of less than zero (downsloping) and gradually increased until 6 min. The mechanism(s) for this postexercise transient ST slope decrease in CAD is uncertain, but it could be, at least partially, explained by the effect of heart rate dependent J-point depression[7] In many CAD patients, tachycardia-induced J-point depression would lower the initial portion of ST-segment (ie, draw the ST-segment upward) during exercise, thereby obscuring or masking the downsloping depression, and the slowing of the heart rate following exercise would readily unmask the downsloping configuration. The subsequent progressive increase in ST slope from 3- to 6-min postexercise reflects the recovery process of the ischemia-induced electrophysiological impairment.

On the other hand, we observed a progressive decrease in the ST slope from 1- to 6-min postexercise in the FP subjects. After becoming negative at 4 min, the ST slope further decreased until 6 min, at which time the FP group eventually had a lower ST slope with a greater ST-segment depression than the TP group. This recovery time-course in FP subjects, characterized by the inappropriately late aggravation of ST-T abnormalities, has also been reported by Malcom et al who examined patients with mitral valve prolapse, a condition prone to FPD[5] The mechanism for this late aggravation is unknown. Although the FP group included many females (47%), in agreement with previous reports[1-3] it is noteworthy that the prevalence of hypertension was considerably high (44%) compared with that in the general population. In the presence of hypertension, implicated as one potential cause of FPD[9,10] strenuous exercise may acutely induce electrophysiological changes with late ST-segment aggravation by a mechanism such as the reduction of coronary flow reserve documented in those patients[6]

Advantages of Computer Analysis

Our computer analysis method using an 8-lead ECG ensures high-resolution analysis as well as objective and reproducible measurements; in particular, in terms of the J-point determination. Because it is difficult to precisely determine the J-point in a single lead with ST-segment depression, which may seriously affect the ST slope, we incorporated the QRS information of all 8 leads in a single complex (algebraic sum). Like other available systems, our stress system yields the ST slope in mV/s to one decimal place (eg, 0.3 mV/s). However, those values were not used for the analysis in the present study because the resolution was considered insufficient. More importantly, the measured values are occasionally inaccurate because of erroneous determination of the Q-Q baseline or J-point. Although ΔST slope could accurately differentiate FP from TP patients (Fig 6), the absolute values were very small in most subjects. We believe that high-resolution analysis can contribute to accurate diagnosis of the presence or absence of inducible ischemia by detecting the subtle ECG changes that are otherwise undetectable by conventional methods such as by a simple categorical judgement of the ST-segment shape[1,7]

Potential Limitations

First, FPD are frequently seen in patients with abnormal resting ECGs such as those with LVH[4,6] valvular disease[1,4,5] or cardiomyopathy[8] Because we examined subjects with a normal resting ECG, our findings cannot be extrapolated to those other categories of patients. Second, only patients with both angiographically and scintigraphically documented abnormalities were enrolled into the TP group because the diagnostic accuracy of SPECT is not perfect. This is probably the reason why the positive predictive value (68% = 134/198) for our entire population seems to be slightly lower than that previously reported. Furthermore, FPD was based on the normal exercise SPECT imaging, and 70% of FP subjects did not undergo angiography. Although the changes in ST slope from postexercise 3- to 6-min were similar in FP subjects with and without angiographic results, we cannot completely exclude the possibility that a number of FP subjects might have angiographical CAD.

Conclusion

Our study has demonstrated that a simple observation of the ST slope recovery time-course is very useful for discriminating FP from TP ST-segment depressions. Although our findings are currently confined to subjects with a normal resting ECG, they should enhance the diagnostic value of the exercise ECG and serve to reduce the number of more costly, time-consuming and invasive procedures.

Acknowledgments

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Clinical research

Classification and mechanism of *Torsade de Pointes* initiation in patients with congenital long QT syndrome

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KEYWORDS
Torsade de Pointes;
Long QT syndrome;
Premature ventricular contraction;
Onset

Aims To examine the initiating mode of *Torsade de Pointes* (TdP) in patients with congenital long QT syndrome (LQTS).

Methods and results We evaluated 111 episodes of TdP recorded on the electrocardiograms of 24 patients with congenital LQTS, and clarified the initiating mode, the three consecutive preceding RR intervals defined as C_2, C_1, and C_0, the timing of initiating premature ventricular contraction (PVC) and the cycle length (CL) of TdP. Three different initiating patterns were observed: (1) a "short-long-short" sequence (SLS) pattern (23 patients, 72 TdP, 65%) defined as one or more short–long cardiac cycles followed by an initiating short-coupled PVC ($C_1 > C_2$ and C_0), (2) an "increased sinus rate" (ISR) pattern (8 patients, 28 TdP, 25%) defined as a gradual increase in sinus rate with or without T-wave alternans ($C_2 \geqq C_1 \geqq C_0$), and (3) a "changed depolarization" (CD) pattern (5 patients, 11 TdP, 10%) defined as a sudden long-coupled PVC or fusion beat followed by short-coupled PVC. The C_0 was shorter in ISR than SLS and CD (mean C_0: 488 vs. 587 and 603 ms, respectively; $P < 0.05$). Therefore, the initiating PVC appeared near the T-wave peak of the last beat before onset in ISR, while it occurred after the T-wave peak in SLS and CD. The CL of TdP was shorter in ISR than in SLS (256 vs. 295 ms, $P < 0.05$).

Conclusions Our data show the existence of three predominant initiating modes of TdP in patients with congenital LQTS and suggests a differential mechanism of initiation of TdP for each mode.

Introduction

Torsade de Pointes (TdP) is a distinct polymorphic ventricular tachycardia appearing as a twist around the isoelectric line.[1] TdP occurs under various pathophysiological states including either acquired or congenital,

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long QT syndrome (LQTS), which sometimes degenerates into ventricular fibrillation and results in sudden cardiac death.[2–6]

Previous experimental observations suggest several hypotheses about the mechanism responsible for TdP. TdP is proposed to arise from premature ventricular contraction (PVC) due to triggered activity, especially early after depolarization (EAD) and to be perpetuated by a re-entrant mechanism as a result of the increased dispersion of repolarization.[7,8]

In the clinic, some reports have described a typical mode of onset of TdP in patients with acquired LQTS as a "short-long-short sequence" (SLS), a so-called "pause dependent" phenomenon, which shows RR interval oscillations. With regard to the initiating mode of TdP in patients with congenital LQTS, Viskin et al.,[9] suggested that SLS plays a major role in the genesis of TdP. However, data from the Registry of LQTS shows that SLS occurs as the mode of onset in half of all patients with congenital LQTS.[10]

The present study was designed to classify the initiating mode of TdP, the timing of the initiating PVC, and the cycle length (CL) of TdP in patients with congenital LQTS at a single centre.

Methods

Patient characteristics

We reviewed the medical records of consecutive 24 patients affected with congenital LQTS in whom one or more episodes of TdP were recorded at the National Cardiovascular Center, Suita, Japan. They were composed of 4 males and 20 females ranging in age from 1 to 60 years (mean of 28 ± 17 years). All patients had a history of syncope and were diagnosed with congenital LQTS based on the diagnostic criteria of Schwartz et al (score ≧4).[11]

Definition of arrhythmia and analysis parameters

TdP was defined as a polymorphic ventricular tachycardia consisting of more than five consecutive beats during which the peaks of QRS complexes twisted above and below the isoelectric line.[4,9] Measurements were taken from Holter electrocardiograms, or monitoring electrocardiograms which detected the onset of TdP. We defined the three consecutive preceding RR intervals before the onset of TdP as C_2, C_1, and C_0; C_2 = the second preceding RR interval before onset, C_1 = the first preceding RR interval before onset, C_0 = the coupling interval of the initiating PVC. The CL of TdP was calculated by averaging 10 beats of TdP. When the TdP did not last more than 10 beats, all of the beats were averaged. The QT intervals were measured by the tangential method, and bifurcated T-waves and pathological U waves were included as part of the measurements of QT intervals. If the initiating PVC appeared before the peak of the T-wave so that we could not measure the QT intervals, the previous QT intervals were referred to. The values of the absolute QT intervals (QTe) and the preceding RR intervals that could be precisely measured were used for the analysis. The Q–T peak interval (QTp) was defined as the interval between the QRS onset and the peak of the T-wave at the last beat before the onset of TdP. The corrected QT interval (QTc) was defined as the QT interval divided by the square root of the preceding RR intervals.

We evaluated the initiating mode of TdP on the basis of the relationship between the preceding RR intervals (C_2, C_1, and C_0), the timing of initiating PVC, and the CL of TdP.

Classification of the initiation mode of TdP

The initiating mode of TdP was classified into three different patterns: an SLS pattern, an "increased sinus rate" (ISR) pattern and a "changed depolarization" (CD) pattern. The SLS pattern was defined as one or more short–long cardiac cycles followed by an initiating short-coupled PVC, and the relationship between the three consecutive preceding RR intervals was $C_1 > C_2$ and C_0. Fig. 1(a) shows that a PVC led to a post-extrasystolic pause (C_1 = 920 ms), which changed the QTU of the following beat and culminated in TdP. The preceding RR intervals of TdP fulfilled the criteria of C_1 (920 ms) > C_2 (540 ms) and C_0 (580 ms). The ISR pattern was defined as a gradual increase in the sinus rate with or without T-wave alternans, and the relationship between the preceding RR intervals was $C_2 \geqq C_1 \geqq C_0$. Fig. 2(a) illustrates a gradual increase in the sinus rate with T-wave alternans resulting in TdP. The preceding RR intervals of TdP fulfilled the criteria for C_2 (520 ms) $\geqq$ C_1 (520 ms) $\geqq$ C_0 (360 ms). The CD pattern was defined as a sudden long-coupled PVC or fusion beat followed by a short-coupled PVC, and the relationship between the preceding RR intervals was $C_1 \geqq C_2 > C_0$. This pattern was different from the SLS pattern, in that the last beat before the onset of TdP was PVC or a fusion beat, and resulted in a change of repolarization (QT interval) of the last beat.[12] Fig. 3(a) represents a sudden long-coupled PVC as the last preceding beat of TdP, resulting in marked QT prolongation and subsequent TdP. The preceding RR intervals of TdP fulfilled the criteria for C_1 (820 ms) $\geqq$ C_2 (760 ms) > C_0 (560 ms).

Statistical analysis

We took possible correlations between a patient's different episodes into account. Therefore, when a patient had more than two episodes with the same initiation mode, we adopted mean values of the parameters in all episodes of each mode as a representation of each patient, and performed statistical analyses using these values. Continuous variables were expressed as the

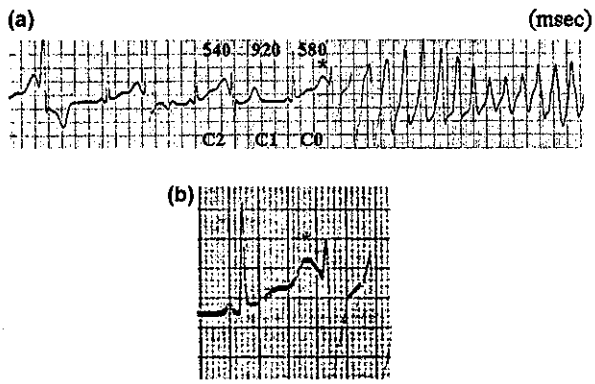

Fig. 1 The "short-long-short sequence" (SLS) pattern as an initiating mode of *Torsade de Pointes* (TdP). (a) The monitoring electrocardiogram shows that TdP is induced by the short-long cardiac cycles followed by an initiating short-coupled premature ventricular contraction (PVC). The relationship between the 3 consecutive preceding RR intervals fulfills the criteria for C_1 (920 ms) > C_2 (540 ms) and C_0 (580 ms). (b) The initiating PVC appears after the T-wave peak of the last beat before the onset of TdP.

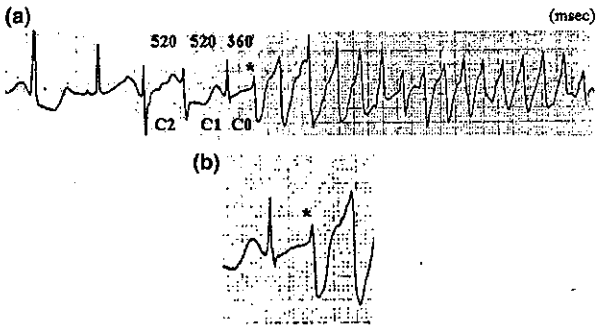

Fig. 2 The "Increased sinus rate" (ISR) pattern as an initiating mode of *Torsade de Pointes* (TdP). (a) The monitoring electrocardiogram indicates that TdP is induced by a gradual increase in the sinus rate with T-wave alternans, and that the relationship between the preceding RR intervals fulfills the criteria for C_2 (520 ms) $\geqq$ C_1 (520 ms) $\geqq$ C_0 (360 ms). (b) The initiating premature ventricular contraction occurs before the T-wave peak of the last beat before the onset of TdP.

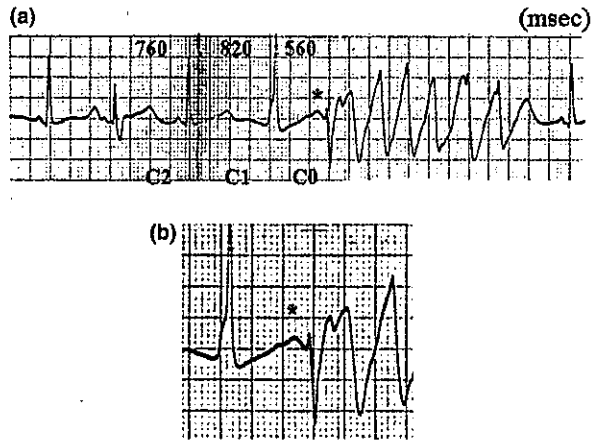

Fig. 3 The "changed depolarization" (CD) pattern as an initiating mode of *Torsade de Pointes* (TdP). (a) The monitoring electrocardiogram shows that TdP is induced by a sudden long-coupled premature ventricular contraction (PVC) followed by a short-coupled PVC. The relationship between the 3 consecutive preceding RR intervals fulfills the criteria for C_1 (820 ms) $\geqq$ C_2 (760 ms) > C_0 (560 ms). (b) The initiating PVC appears after the T-wave peak of the last beat before the onset of TdP.

group mean value ± SD. We used two-sided tests and compared using one-way ANOVA followed by Scheffe's test. A value of $p < 0.05$ was regarded as being significant.

Results

Clinical characteristics

Table 1 shows the clinical characteristics of the 24 patients with congenital LQTS. Molecular screening showed that three patients were affected with the LQT1 syndrome, and 10 patients with the LQT2 syndrome. Seven patients had a familial history of sudden death. The episodes of TdP occurred while on β-blockers in 11 patients, while 13 patients had TdP episodes while off β-blockers. Eight patients had a serum potassium concentration of less than 3.5 mEq/litre during the TdP episodes.

Initiating mode of TdP

A total of 111 episodes of TdP were observed with a median of three episodes. Seventy-two TdP events (65%) in 23 patients showed an SLS pattern as the initiating mode, 28 TdP events (25%) in nine patients exhibited an ISR pattern, and 11 TdP events (10%) in five patients exhibited a CD pattern. All three initiating mode patterns were observed in three patients, and two patterns were observed in seven patients. The initiating modes of TdP were not correlated with age, gender, genotype, or the level of serum potassium. However, the CD pattern was only observed in five patients while on β-blockers.

Table 2 represents comparisons of the ECG parameter between the three initiating patterns. There were no significant differences in the QTp, QTe, and QTc between the three initiating patterns.

Timing of initiating PVC

The coupling intervals of the initiating PVC (C_0) were significantly shorter in the ISR pattern than in the SLS and CD patterns (488 ± 72 ms vs. 587 ± 65 ms and 603 ± 24 ms; $p = 0.010$ and 0.035, respectively). The C_1 was significantly longer in the SLS pattern than in the ISR pattern (1038 ± 188 ms vs. 634 ± 146 ms, $p = 0.001$), while the C_2 was significantly shorter in the SLS pattern than in the ISR pattern (582 ± 65 ms vs. 732 ± 176 ms, $p = 0.016$). The initiating PVC appeared before or near the T-wave peak of the last beat before the onset of the ISR pattern (Fig. 2(b)), while it occurred after the T-wave peak for the SLS pattern (Fig. 1(b)) and CD pattern (Fig. 3(b)). Fig. 4(a) illustrates a comparison of the values of C_0-QTp between the three patterns. The C_0-QTp was significantly smaller in the ISR pattern than in the SLS pattern (9 ± 38 ms vs. 60 ± 34 ms; $p = 0.040$). It was also smaller in the ISR pattern compared with the CD pattern, but this difference was not significant (9 ± 38 ms vs. 53 ± 8 ms; $p = 0.219$).

CL of TdP

Fig. 4(b) shows a comparison of the CL of TdP between the three patterns. The CL was significantly shorter in the ISR pattern compared with the SLS pattern (256 ± 25 ms vs. 295 ± 36 ms; $p = 0.042$). It was also shorter in the ISR pattern compared with the CD pattern, but this difference was not significant (256 ± 25 ms vs. 279 ± 10 ms; $p = 0.547$). The CL of TdP was not correlated with age, gender, or genotype.

Discussion

Classification of the initiating mode of TdP

TdP is a distinct polymorphic ventricular tachycardia with a twisting QRS morphology most often associated with QT prolongation in congenital and acquired forms

Table 1 Clinical characteristics of 24 patients with congenital long QT syndrome

Pt. No.	Age (years)	Sex	Genotype	No. of TdP episodes	FH	β-Blockers	*K* (mEq/litre)
1	21	F	LQT2	8	–	+	3.8
2	22	F	LQT2	3	–	–	3.4
3	60	F	NA	2	–	–	2.6
4	28	F	LQT2	10	+	+	4.1
5	47	F	NA	3	+	–	3.4
6	19	F	NA	2	+	+	4
7	29	F	NA	2	–	–	3.7
8	49	F	LQT1	12	–	–	2.6
9	12	M	NA	10	–	+	3.9
10	29	F	NA	1	–	–	3.8
11	1	M	NA	11	–	–	3.3
12	41	F	LQT2	1	–	+	3.6
13	21	F	LQT2	4	–	+	NA
14	15	F	LQT1	6	–	+	3.1
15	59	F	NA	4	+	+	4
16	24	F	NA	3	–	–	3.5
17	21	F	LQT2	4	–	+	3.5
18	17	M	LQT2	3	+	–	3.7
19	26	F	LQT2	1	–	–	3.9
20	14	F	NA	2	+	–	2.8
21	14	F	LQT2	9	–	+	3.6
22	6	M	LQT2	6	–	+	3.5
23	29	F	NA	3	–	–	3.1
24	60	F	LQT1	1	+	–	3.5
	26 ± 16			3(2–6.5)			3.5 ± 0.4
	Mean ± SD			Median (interquartile range)			Mean ± SD

F, female; FH, family history of sudden death; K, serum potassium concentration; M, male; NA, not available; TdP, *Torsade de Pointes*; +, present and –, absent.

Table 2 Comparisons of ECG parameters between three initiating patterns

	SLS	ISR	CD
C_2 (ms)	582 ± 65[a]	732 ± 176	729 ± 74
C_1 (ms)	1038 ± 188[a]	634 ± 146	823 ± 132
C_0 (ms)	587 ± 65[a]	488 ± 72	603 ± 24[a]
QTp (ms)	533 ± 48	490 ± 59	551 ± 32
QTe (ms)	696 ± 53	631 ± 70	681 ± 32
QTc (ms)	685 ± 58	746 ± 60	773 ± 55

CD, changed depolarization pattern; C_2, the second preceding RR interval before onset; C_1, the first preceding RR interval before onset; C_0, the coupling interval of the initiating premature contraction; ECG, electrocardiogram; ISR, increased sinus rate pattern; QTc, corrected QT interval just before the onset of *Torsade de Pointes*; QTe, absolute QT interval just before the onset of *Torsade de Pointes*; QTp, absolute Q-T peak interval just before the onset of *Torsade de Pointes* and SLS, short-long-short sequence pattern.
[a] $p < 0.05$ vs. ISR.

of LQTS. The initiating mode of TdP in the congenital form of LQTS is still unclear. While the SLS pattern was reported to be predominant in congenital LQTS,[9] an investigation of the LQTS Registry showed that this pattern appeared as the mode of TdP onset in 20 out of 44 patients with congenital LQTS (45%).[10] The present study of a single centre showed that the SLS pattern appeared in 72 (65%) out of 111 TdP episodes, the ISR pattern in 28 (25%), and the CD pattern in 11 (10%), which is in agreement with the latter report. Viskin et al., recently suggested the difference in the clinical characteristics between "pause dependent" and "non-pause dependent" TdP. "Pause dependent" TdP was associated with females, and "non-pause dependent" TdP, especially after sinus tachycardia, with T wave alternans and was seen predominantly in infants.[13] In our study, the initiating mode of TdP and the CL of TdP were not correlated with age, gender, or genotype. In fact, three patients (pts No. 1, No. 4, and No. 21) affected with LQT2 had all three patterns of TdP. However, the present study examined a small number of patients, especially a small number of infants or genotyped patients. Furthermore, the deviation of gender could have biased our results. Therefore, larger study populations are needed to make a definitive conclusion about the relation between the initiating mode of TdP and age, gender, or genotype.

We classified the initiating mode of the TdP into three patterns based on the relationships with the preceding RR intervals and the supposed mechanisms of TdP. The CD pattern seems another variation of the SLS pattern from a point of preceding RR patterns. However, the TdP in the CD pattern was always preceded by long-

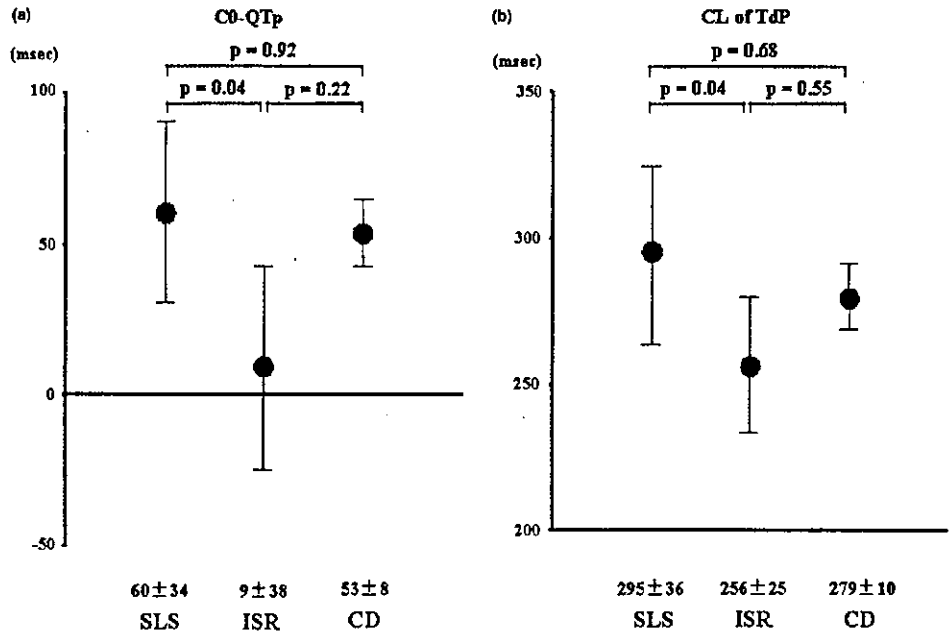

Fig. 4 Comparison of the values of the subtraction of Q-T peak intervals (QTp) from C_0 at the last beat before the onset of *Torsade de pointes* (TdP) (a) and the cycle length (CL) of TdP (b) between the "short-long-short sequence" (SLS), "increased sinus rate" (ISR), and "changed depolarization" (CD) patterns. The C_0-QTp values were significantly smaller in the ISR pattern than in the SLS pattern. The CL of TdP was also significantly shorter in the ISR pattern than in the SLS pattern.

coupled PVC or fusion beats and was only observed in five patients on β-blockers. We speculate that beta-blocker-induced sinus bradycardia may produce long-coupled PVC or fusion beats, leading to TdP in the CD pattern, and this mechanism may be different from that in the SLS pattern.

Possible mechanisms of TdP in the three initiating patterns

Previous experimental observations suggested that the initiating PVC of TdP is due to triggered activity arising from phase 2 or phase 3 EADs.[14–18] Clinical observations using monophasic action potential recordings indicated phase 3 EADs during the SLS sequence as a mechanism responsible for initiating PVC of TdP.[19–22] Burashnikov et al., suggested that phase 2 EADs were predominantly induced during a transient acceleration of the pacing rate, but that phase 3 EADs developed as the rate of stimulation was slowed.[23] The present study showed that the coupling interval of initiating PVC of TdP was significantly shorter in the ISR pattern than in the SLS pattern. Therefore, it is reasonable that the initiating PVC of TdP is related to phase 2 EADs in the ISR pattern and phase 3 EADs in the SLS pattern. On the other hand, experimental studies employing whole heart[24–26] and arterially perfused wedge preparations[27–29] presented evidence in support of the hypothesis that TdP is maintained by a re-entrant mechanism. El-Sherif and co-workers used tridimensional analysis of the kinetics of cardiac repolarization and showed that an increased transmural dispersion of repolarization (TDR), due to a more prominent prolongation of local repolarization in M regions than in epicardial or endocardial regions, resulted in functional block and slow conduction. This leads to re-entry in the "SLS" initiating pattern of TdP. [24,25] Shimizu et al., used LQTS models employing wedges and also showed that the increase in TDR was mainly due to the prolongation of action potential duration (APD) of M cells in the initiation of TdP associated with the "SLS" pattern.[27,28] They also found that the large fluctuations of TDR were mainly due to the oscillation of APD in the M regions during T-wave alternans, which were induced by an abrupt acceleration in rate similar to the "ISR" pattern, and were associated with the induction of TdP.[29] Based on these observations, we believe that TdP is at least maintained by a re-entrant mechanism resulting from increased TDR of the two initiating modes of the SLS and ISR patterns. On the other hand, these experimental studies using whole heart[26] and perfused wedge preparations[29] also showed that the initiating PVC due to triggered activity is not always required for the initiation of TdP. In other words, TdP may occur as a result of large fluctuations in the transmural and spatial dispersion of repolarization of the preceding beat, leading to local functional block and circulating wave fronts inducing the first re-entrant excitation at the fast pacing rate similar to the "ISR" initiation pattern.

Costard–Jackle et al., reported that the short-term change in ventricular activation did not allow for the accurate adaptation of ventricular APD. It produced a dispersion of repolarization, leading to TdP.[30] Kurita et al.,[12] also reported that a sudden change in the depolarization pattern was related to marked QT prolongation and the induction of TdP in a patient with a pacemaker implantation. These observations could explain a possi-

ble mechanism of TdP seen in the CD pattern. The change in the depolarization pattern of the last beat before the onset of TdP (i.e., PVC or fusion beat) resulted in the increased dispersion of repolarization, thus possibly leading to TdP due to a re-entrant mechanism.

Limitations

Our study included two 60-year-old patients, in whom their arrhythmias might be polymorphic ventricular arrhythmias rather than TdP. However, we believe that the episodes of our patients were due to TdP because these two patients had QT prolongation and prior episodes of syncope suggesting TdP in their young age. In addition, all patients showed no structural heart disease in their echocardiogram and no ischaemic ST changes during exercise testing.

We adopted mean values of the parameters in all episodes of each mode as a representation of each patient. When a patient has episodes in different initiation modes, the underlying assumption of independence is violated. However, it is clinically important to report the fact that the different initiating patterns exist in the same patient. Therefore, we performed the statistical analyses using these values.

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Mutation Site-Specific Differences in Arrhythmic Risk and Sensitivity to Sympathetic Stimulation in the LQT1 Form of Congenital Long QT Syndrome

Multicenter Study in Japan

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OBJECTIVES We sought to compare the arrhythmic risk and sensitivity to sympathetic stimulation of mutations located in transmembrane regions and C-terminal regions of the *KCNQ1* channel in the LQT1 form of congenital long QT syndrome (LQTS).

BACKGROUND The LQT1 syndrome is frequently manifested with variable expressivity and incomplete penetrance and is much more sensitive to sympathetic stimulation than the other forms.

METHODS Sixty-six LQT1 patients (27 families) with a total of 19 transmembrane mutations and 29 patients (10 families) with 8 C-terminal mutations were enrolled from five Japanese institutes.

RESULTS Patients with transmembrane mutations were more frequently affected based on electrocardiographic (ECG) diagnostic criteria (82% vs. 24%, $p < 0.0001$) and had more frequent LQTS-related cardiac events (all cardiac events: 55% vs. 21%, $p = 0.002$; syncope: 55% vs. 21%, $p = 0.002$; aborted cardiac arrest or unexpected sudden cardiac death: 15% vs. 0%, $p = 0.03$) than those with C-terminal mutations. Patients with transmembrane mutations had a greater risk of first cardiac events occurring at an earlier age, with a hazard ratio of 3.4 ($p = 0.006$) and with an 8% increase in risk per 10-ms increase in corrected Q-Tend. The baseline ECG parameters, including Q-Tend, Q-Tpeak, and Tpeak-end intervals, were significantly greater in patients with transmembrane mutations than in those with C-terminal mutations ($p < 0.005$). Moreover, the corrected Q-Tend and Tpeak-end were more prominently increased with exercise in patients with transmembrane mutations ($p < 0.005$).

CONCLUSIONS In this multicenter Japanese population, LQT1 patients with transmembrane mutations are at higher risk of congenital LQTS-related cardiac events and have greater sensitivity to sympathetic stimulation, as compared with patients with C-terminal mutations. (J Am Coll Cardiol 2004;44:117–25) © 2004 by the American College of Cardiology Foundation

Congenital long QT syndrome (LQTS) is a hereditary disorder characterized by a prolonged QT interval on the electrocardiogram (ECG), commonly associated with polymorphic ventricular tachycardia known as torsade de pointes (TdP), often leading to severe symptoms, such as syncope and sudden cardiac death (1,2). Genetic studies have so far identified seven forms of congenital LQTS caused by mutations in genes of the potassium and sodium channels or the membrane adapter located on chromosomes 3, 4, 7, 11, 17, and 21 (3–5). Among the seven forms, LQT1 syndrome is one of the two most common genetic variants of LQTS and accounts for approximately 25% of genotyped patients (6). Mutations in *KCNQ1* are responsible for defects in the slowly activating component of the delayed rectifier potassium current (I_{Ks}) underlying LQT1 syndrome (7). The LQT1 syndrome is frequently manifested with variable expressivity and incomplete penetrance (8–10) and is much more sensitive to sympathetic stimulation than the other forms (11,12).

Examination of the genotype-phenotype correlation is important for the management and treatment of patients with congenital LQTS, especially in the LQT1, LQT2, and LQT3 forms, which constitute approximately two-thirds of genotyped LQTS (13). More recently, mutation site-specific differences in the severity of phenotype have been

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Abbreviations and Acronyms

APD	= action potential duration
DNA	= deoxyribonucleic acid
$I_{Cl(Ca)}$	= Ca^{2+}-activated chloride current
I_{Kr}	= fast component of the delayed rectifier potassium current
I_{Ks}	= slow component of the delayed rectifier potassium current
$I_{Na\text{-}Ca}$	= Na^+/Ca^{2+} exchange current
LQTS	= long QT syndrome
LZ	= leucine zipper
PCR	= polymerase chain reaction
TdP	= torsade de pointes
Tpeak-end	= interval between Tpeak and Tend

evaluated in each genotype. Moss et al. (14) have suggested that LQT2 patients with mutations in the pore region of the *KCNH2* gene were at markedly increased risk of arrhythmia-related cardiac events, as compared with patients with non-pore mutations, in the International Long-QT Syndrome Registry. With regard to the LQT1 syndrome, Donger et al. (15) initially suggested that the missense mutation, R555C, located in the C-terminal region of the *KCNQ1* gene was associated with a less severe phenotype than the mutations in the transmembrane regions. Since then, more than 20 mutations located in the C-terminal region of the *KCNQ1* gene have been reported, but neither the severity nor the function of the mutations has been fully determined. In the present study, we compared the arrhythmic risk and sensitivity to sympathetic stimulation with exercise between LQT1 patients with mutations located in the transmembrane regions and those with mutations in the C-terminal regions of the *KCNQ1* gene.

METHODS

Patient population. The study population consisted of 95 patients from 37 unrelated Japanese LQT1 families enrolled from five institutes in Japan: the National Cardiovascular Center, Kyoto University Graduate School of Medicine, Kanazawa University, Niigata University Graduate School of Medical and Dental Science, and Okayama University Graduate School of Medicine and Dentistry. The *KCNQ1* mutations were confirmed in all patients by using standard genetic tests. Briefly, genomic deoxyribonucleic acid (DNA) was isolated from leukocyte nuclei by conventional methods. Screening for mutations of *KCNQ1, KCNH2, SCN5A, KCNE1,* and *KCNE2* was performed by using polymerase chain reaction (PCR)/single-strand conformation polymorphism or denatured high-performance liquid chromatography analyses. For aberrant PCR products, DNA sequencing was conducted with a DNA sequencer (3700 DNA Analyzer, PE Applied Biosystems, Foster City, California). If the patients had double mutations within the *KCNQ1* gene or accompanying additional mutations in other genes, they were excluded from the present study. Genotyping of LQTS was reviewed and approved according to each Institutional Review Board's guideline, and written, informed consent was obtained from all patients. No patients were taking beta-blockers at the time of the baseline ECG and exercise treadmill test.

Clinical characterization. Routine clinical and ECG parameters were usually obtained at the time of first admission to each institute for evaluation of LQTS, and thereafter at the time of at least yearly follow-up contact.

CLINICAL DIAGNOSIS. We evaluated two major clinical ECG criteria for diagnosing LQTS-affected individuals. The ECG diagnostic criteria of Keating et al. (16), included a corrected QT (QTc) interval ≥470 ms in asymptomatic individuals and a QTc interval >440 ms for males and >460 ms for females, were associated with one or more of the following: 1) stress-related syncope; 2) documented TdP; or 3) a family history of early sudden cardiac death. The LQTS was also diagnosed by the diagnostic criteria (score ≥4) of Schwartz et al. (17).

BASELINE 12-LEAD ECG MEASUREMENTS. Baseline 12-lead ECG parameters included the RR, Q-Tend, Q-Tpeak, and Tpeak-end (Q-Tend − Q-Tpeak) intervals as an index of transmural dispersion of repolarization. The Q-Tend, Q-Tpeak, and Tpeak-end intervals were also corrected using Bazett's method. These parameters were measured manually in three leads (II, V_2, and V_5), with quantitative repolarization values reported for lead V_5, because the measurements were similar in all three leads. Q-Tend was defined as the interval between the QRS onset and the point at which an isoelectric line intersected a tangential line drawn at the minimum first derivative (dV/dt) point of the positive T-wave or at the maximum dV/dt point of the negative T-wave. When a bifurcated or secondary T wave fusing the first component appeared, it was included as part of the measurement of Q-Tend, but a normal U-wave, which was apparently separated from a T-wave, was not included. Q-Tpeak was defined as the interval between the QRS onset and the peak of the positive T-wave or the nadir of the negative T-wave. Measurements were carried out by two investigators who were unaware of the subjects' genetic status. There were no significant differences in the measured data between the two (data not shown). In addition, TdP and T-wave alternans on the ECG were assessed.

CARDIAC EVENTS, THERAPY, AND FOLLOW-UP. Congenital LQTS-related cardiac events were defined as syncope, aborted cardiac arrest, or unexpected sudden cardiac death without a known cause. Cardiac events, which brought the probands to medical attention but were secondary to apparent causes known to prolong repolarization, such as antiarrhythmic drugs, electrolyte abnormalities, or bradycardia, were excluded from the analysis of congenital LQTS-related cardiac events. Such secondary cardiac events were documented in one patient with C-terminal mutation (hypokalemia 1) and one patient with transmembrane mutation

(hypokalemia 1). Therapy, including beta-blockers, pacemakers, sympathectomy, and defibrillator, was also evaluated. Follow-up was censored at age 50 years to avoid the influence of coronary artery disease on cardiac events in the Japanese population.

EXERCISE TREADMILL TESTING. Forty-nine of the 95 patients were included for the analysis with exercise treadmill testing. All patients were in sinus rhythm, and none had atrioventricular or bundle branch block during the exercise testing. Exercise treadmill testing was performed using the standard Bruce protocol. Twelve-lead ECGs were recorded every 1 min from the baseline condition through the maximal exercise to the recovery phase for 8 min. The ECG measurements before exercise were obtained in the standing position before exercise, and those after exercise were usually obtained within 2 min after stopping exercise to avoid noise in the measurement.

Genetic characterization. Genetic mutations of the *KCNQ1* amino acid sequence were characterized by a specific location and coding effect (missense, splice site, frameshift, or deletion). The transmembrane regions were defined as six transmembrane segments (S1 to S6, amino acid residues 112 through 354), including cytoplasmic and extracellular linkers as well as the pore region. The pore region of the *KCNQ1* channel was defined as the area extending from S5 to the mid-portion of S6 involving amino acid residues 301 through 320.

Statistical analysis. Data are expressed as the mean value ± SD. Repeated measures two-way analysis of variance (ANOVA), followed by the Scheffé test, was used to compare data between mutations located in the transmembrane regions and those in the C-terminal regions, as well as to compare measurements made before and after exercise (STATISTICA, 1998 edition). Repeated measures one-way ANOVA, followed by the Scheffé test, was used to compare changes (Δ) in the measurements with exercise between the groups. Differences in frequencies were analyzed by the chi-square test. A two-sided p value <0.05 was considered to indicate significance. The cumulative probability of a first cardiac event was assessed by the Kaplan-Meier method and log-rank statistic. The multivariate Cox proportional hazards survivorship model (adjusting for mutation locations, age, and gender) was used to evaluate the independent contribution of clinical and genetic factors to first cardiac events from birth through to age 50 years. Clinical data were also compared between transmembrane mutations and C-terminal mutations for the probands and non-probands, separately. Because the non-probands (family members) in this study were mainly relatives in the first or second degree of the probands, the non-probands in each family were equally handled in the analysis.

RESULTS

Genetic characteristics. Table 1 illustrates the numbers of LQT1 patients by mutation and location (18–24). We identified 27 *KCNQ1* mutations among the 95 LQT1 patients, with 19 mutations located in the transmembrane regions and eight mutations in the C-terminal regions. Four mutations were located at the pore region in the transmembrane domain. Twenty-three of the 27 mutations were missense mutations; 2 were frameshift mutations; 1 was a deletion mutation; and 1 was a splice mutation. Thirteen mutations (seven in the transmembrane regions and six in the C-terminal regions) were novel. Functional effects by cellular electrophysiologic tests have been reported in eight of the 27 mutations (Table 1).

Clinical characteristics. Sixty-six patients from 27 unrelated families had mutations located in the transmembrane regions, and 29 patients from 10 unrelated families had mutations located in the C-terminal regions. Table 2 illustrates the clinical characteristics of the patient population. No significant differences were observed with regard to gender, percentage of proband, and age at baseline ECG recordings. The LQTS-affected individuals were more frequently diagnosed in patients with transmembrane mutations than in those with C-terminal mutations. The LQTS diagnostic score of Schwartz et al. (17) was significantly higher in patients with transmembrane mutations. The Q-Tend, Q-Tpeak, and Tpeak-end intervals, both uncorrected and corrected, were significantly greater in patients with transmembrane mutations than in those with C-terminal mutations (Figs. 1A and 1C). Although the frequency of TdP was no different, that of T-wave alternans was higher in patients with transmembrane mutations. Patients with transmembrane mutations had more frequent LQTS-related cardiac events (all cardiac events, syncope, and aborted cardiac arrest or unexpected sudden cardiac death) than did those with C-terminal mutations. More therapy with beta-blockers for LQTS was initiated in patients with transmembrane mutations.

Clinical course by mutation location. Figure 2A illustrates Kaplan-Meier cumulative cardiac event curves from birth through to age 50 years for a total of 95 patients with mutations located in the transmembrane regions ($n = 66$) and C-terminal regions ($n = 29$). The difference in the clinical course by mutation location was significant (log-rank, $p = 0.005$), with a greater risk of first cardiac events in patients with transmembrane mutations than in those with C-terminal mutations. Most of the first cardiac events occurred before age 15 years in LQT1 patients with transmembrane mutations, whereas half of the LQT1 patients with C-terminal mutations had their first cardiac events after age 15 years. Multivariate Cox proportional hazards regression analysis revealed that patients with transmembrane mutations had a greater risk of first cardiac events, with a hazard ratio of 3.4 (95% confidence interval 1.4 to 8.2, $p = 0.006$). The corrected Q-Tend modulated the risk among patients with transmembrane mutations, with an 8% increase in risk per 10-ms increase in corrected Q-Tend, but had no effect on risk among patients with C-terminal mutations. Figures 2B and 2C illustrate Kaplan-

Table 1. *KCNQ1* Mutations by Location, Amino-Acid Coding, Type of Mutation, and Reported Functional Effects

Location and Coding	No. of Families	No. of Subjects	Position	Exon	Type	Functional Effect in Expression Studies
Transmembrane domains						
Pore region						
G306R	1	2	Pore	6	Missense	Dominant negative (18)
I313K*	1	1	Pore	7	Missense	
G314A*	1	1	Pore	7	Missense	
G314S	1	1	Pore	7	Missense	Dominant negative (19,20)
Non-pore region						
R174H	1	2	S2/S3	2	Missense	
F193L	1	4	S2/S3	3	Missense	Loss of function (21)
A226V*	1	3	S4	4	Missense	
R237P*	1	1	S4/S5	5	Missense	
R243C	2	4	S4/S5	5	Missense	Loss of function (22)
R243I*	1	2	S4/S5	5	Missense	
V254M	2	3	S4/S5	5	Missense	Dominant negative (18)
R259C	1	1	S4/S5	5	Missense	Loss of function (23)
G269S	3	6	S5	6	Missense	
S277L*	2	4	S5	6	Missense	
G325R	1	4	S6	7	Missense	
delF339	1	2	S6	7	Deletion	
A341V	4	19	S6	7	Missense	Loss of function (18)
A344sp	1	4	S6	7	Splice site	
A344E*	1	2	S6	7	Missense	
C-terminus region						
R451Q*	1	1	C-term.	10	Missense	
I517T*	1	3	C-term.	12	Missense	
A525V*	2	2	C-term.	12	Missense	
L572fs/20*	1	3	C-term.	14	Frameshift	
T587M	2	2	C-term.	15	Missense	Trafficking abnormality (24)
R591H	1	6	C-term.	15	Missense	
D611Y*	1	10	C-term.	16	Missense	
H637fs/28*	1	2	C-term.	16	Frameshift	

*Novel mutation.
del = deletion; sp = last unaffected amino acid before predicted splice mutaion; fs = first amino acid affected by a frameshift (number after fs is number of amino acids before termination); term. = terminus.

Meier cumulative cardiac event curves for 37 probands and 58 non-probands with transmembrane mutations and C-terminal mutations, respectively. The difference in phenotype severity based on mutation location persisted ($p = 0.007$) in the non-probands. There was no significant difference in the clinical course of the probands according to mutation site, although the number of probands was relatively small.

Exercise treadmill testing. Exercise treadmill testing was conducted in 33 patients with transmembrane mutations and 16 patients with C-terminal mutations. Table 3 illustrates the ECG measurements before and after exercise testing in both patient groups. The baseline RR and corrected repolarization parameters before exercise in both groups showed quite similar values to those evaluated in the total patients (Table 2), indicating that these patients who had exercise testing were representative of each group. The RR interval was similarly shortened with exercise between the two groups. Exercise produced a significant prolongation in the corrected Q-Tend interval, but not at all in corrected Q-Tpeak, resulting in a significant increase in corrected Tpeak-end in both groups. These changes were much more pronounced in patients with transmembrane mutations than in those with C-terminal mutations (Figs. 1B and 1D). Therefore, the increases in the corrected Q-Tend and corrected Tpeak-end intervals with exercise were significantly greater in patients with transmembrane mutations (Table 3).

When we re-analyzed the ECG measurements for the probands ($n = 26$) and for the non-probands ($n = 23$) separately, the corrected Q-Tend intervals both before and after exercise were longer in the probands than in the non-probands. However, the magnitude of differences in corrected Q-Tend for the two mutation groups persisted after this re-analysis both in the probands and non-probands (data not shown).

DISCUSSION

The major findings of the present study are: 1) LQT1 patients with mutations located in the transmembrane regions are at a higher risk of congenital LQTS-related cardiac events than are patients with C-terminal mutations; and 2) LQT1 patients with transmembrane mutations had a greater sensitivity to sympathetic stimulation than did patients with C-terminal mutations.

Table 2. Clinical Characteristics of the Study Population

	Transmembrane Domain (n = 66)	C-Terminal (n = 29)	p Value
Demographics			
Female gender (%)	41 (62%)	14 (48%)	NS
Proband (%)	29 (44%)	8 (28%)	NS
Age (yrs) at ECG (range)	32 ± 20 (6–83)	28 ± 17 (4–64)	NS
Diagnosis			
Diagnosed LQTS (Keating)	54 (82%)	7 (24%)	< 0.0001
Diagnosed LQTS (Schwartz >4)	43 (65%)	5 (17%)	< 0.0001
Schwartz score	4.4 ± 2.1	2.0 ± 1.5	< 0.0001
Baseline ECG measurements			
RR (ms)	910 ± 127	918 ± 131	NS
Q-T_{end} (ms)	472 ± 54	419 ± 46	< 0.0001
Q-T_{peak} (ms)	382 ± 46	349 ± 44	0.002
$T_{peak-end}$ (ms)	90 ± 20	71 ± 12	< 0.0001
Corrected Q-T_{end} (ms)	496 ± 46	439 ± 38	< 0.0001
Corrected Q-T_{peak} (ms)	402 ± 42	365 ± 39	0.0002
Corrected $T_{peak-end}$ (ms)	95 ± 19	74 ± 11	< 0.0001
Torsade de pointes (%)	10 (15%)	2 (7%)	NS
T-wave alternans (%)	10 (15%)	0	0.03
Cardiac events			
All cardiac events (%)	36 (55%)	6 (21%)	0.002
Age (yrs) at first events (range)	11 ± 8 (3–48)	13 ± 9 (2–25)	NS
Syncope (%)	36 (55%)	6 (21%)	0.002
Aborted cardiac arrest/SCD (%)	10 (15%)	0	0.03
Therapy			
Beta-blockers (%)	30 (45%)	6 (21%)	0.02
Pacemakers (%)	1 (2%)	0	NS
Sympathectomy (%)	0	0	NS
Defibrillator (%)	0	0	NS

Data are presented as the mean value ± SD or number (%) of subjects.
ECG = electrocardiography; LQTS = long QT syndrome; SCD = sudden cardiac death.

Mutation site-specific arrhythmic risk in LQT1 syndrome. Moss et al. (14) have recently reported that the greater risk of arrhythmia-related cardiac events in LQT2 patients with pore mutations of the *KCNH2* gene was consistent with the cellular electrophysiologic effects of the *KCNH2* mutations, with pore mutations showing a greater negative effect on the rapidly activating component of the delayed rectifier potassium current (I_{Kr}) than non-pore mutations. Although the cellular electrophysiologic effects of a small percentage of known *KCNQ1* mutations have been reported to be like those of *KCNH2* mutations, several in vitro electrophysiologic studies have reported missense mutations with dominant-negative effects on I_{Ks} in the transmembrane regions of the *KCNQ1* gene (18,19,25,26). However, Wang et al. (18) have suggested that the degree of I_{Ks} suppression by *KCNQ1* transmembrane mutations evaluated in the heterologous expression system did not correlate with severity in the clinical phenotype in LQT1 patients. There have been fewer reports on the cellular electrophysiologic effects of the C-terminal mutations of the *KCNQ1* gene. To the best of our knowledge, the electrophysiologic effects were examined in seven C-terminal mutations of the *KCNQ1* gene (R555C, R533W, R539W, Δ544, G589D, T587M, and G643S) by French, Finland, and Japanese groups (19,20,24,27–30). All seven C-terminal mutations, except for Δ544 and T587M, when co-expressed with *KCNE1*, could produce functional heteromultimeric channels and showed only a mild reduction of I_{Ks} due to a rightward voltage shift in the activation process and/or acceleration of the deactivation kinetics. Neyroud et al. (28) have reported a homozygous deletion-insertion mutation in the C-terminal region of the *KCNQ1* gene (Δ544), causing a severe phenotype—the Jervell and Lange-Nielsen syndrome. However, the heterozygotes of Δ544 clinically displayed mild or no QT prolongation, with no symptoms, mainly due to the lower dominant-negative effects of the Δ544 mutant. More recently, Larsen et al. (31) have described a severe form of Romano-Ward syndrome associated with compound heterozygosity for two C-terminal mutations (R518X and A525T) in the *KCNQ1* gene. Once again, none of the heterozygotes of the C-terminal mutations (R518X or A525T) had symptoms with minor or no QT prolongation. These previous reports on C-terminal mutations in the *KCNQ1* gene indicate a less severe phenotype in C-terminal mutations than that in transmembrane mutations in LQT1 syndrome, concordant with the findings in the present study.

It is noteworthy that most of the first cardiac events occurred before age 15 years in the LQT1 patients with transmembrane mutations, whereas half of the LQT1 patients with C-terminal mutations had their first cardiac events after age 15 years. This tendency holds up regardless

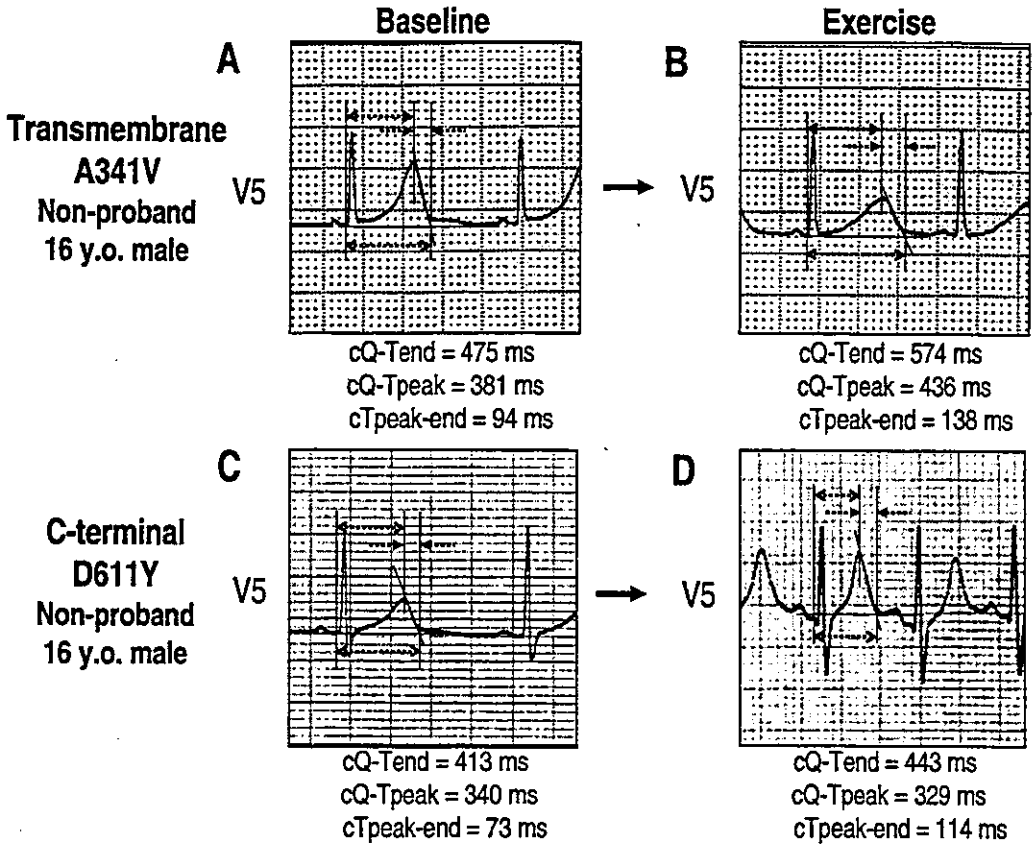

Figure 1. Electrocardiographic parameters in lead V_5 before and after exercise in LQT1 patients with mutations located in the transmembrane region (A341V, non-proband, 16-year-old male) **(A and B)** and in the C-terminal region (D611Y, non-proband, 16-year-old male) **(C and D)**. The baseline corrected Q-Tend (cQ-Tend), Q-Tpeak (cQ-Tpeak), and Tpeak-end (cTpeak-end) intervals were greater in the patient with a transmembrane mutation than in the patient with a C-terminal mutation **(A and C)**. Exercise produced more prominent increases in the cQ-Tend and cTpeak-end in the patient with a transmembrane mutation than in the patient with a C-terminal mutation **(B and D)**.

of whether the patient was a proband. Moreover, hypokalemia, which is known to prolong repolarization, unmasked the LQTS proband in a patient with C-terminal mutation in the present study. These findings suggest that careful follow-up is needed in LQT1 patients with C-terminal mutations, despite their less severe phenotype, by limiting exposure of these patients to QT prolonging conditions.

Although the difference in the clinical course based on

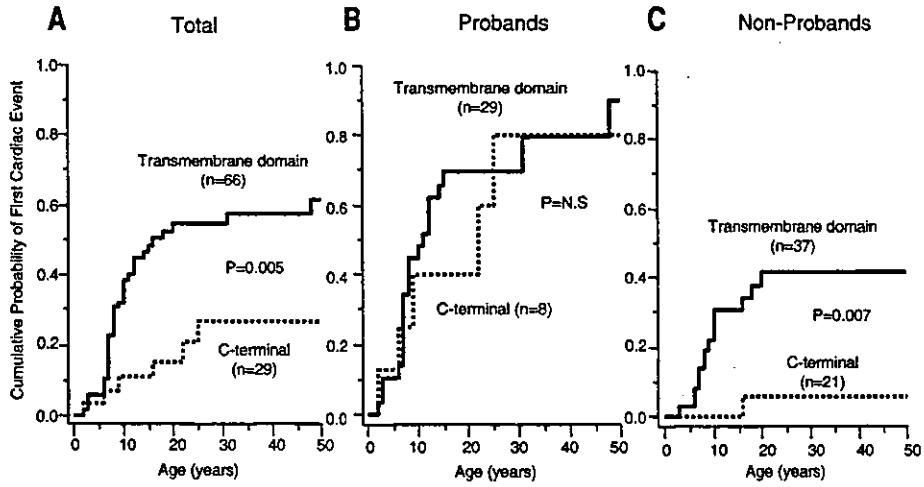

Figure 2. **(A)** Kaplan-Meier cumulative cardiac event curves from birth through to age 50 years for a total of 95 patients with *KCNQ1* mutations located in the transmembrane regions (n = 66) and C-terminal regions (n = 29). The difference in the clinical course by mutation location was significant (log-rank, p = 0.005), with a greater risk of first cardiac events in patients with transmembrane mutations than in those with C-terminal mutations. Kaplan-Meier cumulative cardiac event curves for 37 probands **(B)** and 58 non-probands **(C)** with transmembrane mutations and C-terminal mutations.

Table 3. Electrocardiographic Measurements Before and After Exercise Testing

	Transmembrane Domain (n = 33)	C-Terminal (n = 16)	p Value
Demographics			
Female gender (%)	18 (55%)	7 (44%)	NS
Proband (%)	22 (67%)	4 (25%)	0.006
Age (yrs) at ECG (range)	26 ± 16 (9–72)	27 ± 13 (6–45)	NS
ECG measurements before exercise			
RR (ms)	862 ± 128	850 ± 106	NS
Corrected Q-T_{end} (ms)	494 ± 40	435 ± 28	<0.0001
Corrected Q-T_{peak} (ms)	403 ± 37	359 ± 26	<0.0001
Corrected $T_{peak-end}$ (ms)	91 ± 12	76 ± 6	NS
ECG measurements after exercise			
RR (ms)	514 ± 87*	503 ± 74*	NS
Corrected Q-T_{end} (ms)	571 ± 45*	470 ± 39*	<0.0001
Corrected Q-T_{peak} (ms)	420 ± 38	365 ± 51	<0.0001
Corrected $T_{peak-end}$ (ms)	151 ± 34*	106 ± 17*	<0.0001
Changes in ECG measurements with exercise			
RR (ms)	349 ± 119	348 ± 137	NS
Corrected Q-T_{end} (ms)	77 ± 32	35 ± 17	<0.0001
Corrected Q-T_{peak} (ms)	17 ± 36	5 ± 30	NS
Corrected $T_{peak-end}$ (ms)	60 ± 34	30 ± 17	0.002

*$p < 0.005$ vs. before exercise. Data are presented as the mean ± SD value or number (%) of subjects. The electrocardiographic (ECG) measurements after exercise were obtained within 2 min after stopping exercise.

mutation location was obvious in the non-probands, no significant difference was observed in the clinical course according to mutation location in the probands. This is not surprising, because probands are usually brought to medical attention by their first cardiac events, especially those with a less prolonged QT interval. There indeed may be no difference in cardiac events based on mutation location for probands. This is because other modifier genes may be contributing to the more severe phenotype, which leads to the individual receiving a label of "proband."

Zareba et al. (32) recently reported on 294 LQT1 patients in the International Long-QT Syndrome Registry and analyzed the QTc interval and cardiac event rates by mutation location. In contrast to the present study, they found no significant differences in QTc or risk of cardiac events when the patients were separated into those with transmembrane mutations and those with C-terminal mutations. However, only six transmembrane mutations were overlapped between the two studies (out of 31 transmembrane mutations in the Registry and 19 transmembrane mutations in this study). Moreover, no overlap was observed in the C-terminal mutations between the two studies (out of 11 C-terminal mutations in the Registry and 8 C-terminal mutations in this study). In transmembrane regions, the S4 to S5 loop (amino acid residues 221 through 300) and the S6 segment (amino acid residues 325 through 354) are known to be important for voltage-dependent I_{Ks} function (22); thus, a more severe phenotype is expected in mutations located in the S4 to S5 loop and the S6 segment than in the S2 to S3 loop (amino acid residues 148 through 220). The transmembrane mutations in the non-pore region in the present study were located in the S4 to S5 loop and the S6 segment, except for two mutations found in the S2 to S3 loop. This may affect the result that cardiac event rates were higher in patients with transmembrane mutations in the present study than those in the Registry. Interestingly, when the patients with transmembrane mutations in the present study were separated into those with pre-pore mutations and those with pore mutations, according to the definition by Zareba et al. (32), the patients with pore mutations had a longer corrected Q-Tend than did those with pre-pore mutations (data not shown). Overall, our data present evidence that mutation site-specific differences in arrhythmic risk exist, in contrast to findings previously reported from the Long-QT Syndrome Registry. Therefore, a larger patient population per mutation and a greater spectrum of *KCNQ1* mutations by corroboration with other investigators are clearly needed to make a definitive conclusion about the mutation site-specific differences in arrhythmic risk in LQT1 syndrome.

Greater sensitivity to sympathetic stimulation in transmembrane mutations of the *KCNQ1* gene. The LQT1 syndrome is reported both clinically and experimentally to be the most sensitive to sympathetic stimulation among the seven forms of LQTS (9–12). Sympathetic stimulation is known to increase the net outward repolarizing current due to a larger increase in outward currents, including Ca^{2+}-activated I_{Ks} and Ca^{2+}-activated chloride current ($I_{Cl(Ca)}$), compared with the inward Na^+/Ca^{2+} exchange current (I_{Na-Ca}), resulting in an abbreviation of action potential duration (APD) and QT interval under normal conditions. A defect in I_{Ks} in LQT1 syndrome could account for the failure of sympathetic stimulation to abbreviate the QT interval and APD, especially in the mid-myocardial regions, resulting in a paradoxical QT prolongation and an increase in transmural dispersion of repolarization reflecting an

increase in the Tpeak-end interval under sympathetic stimulation (12). In fact, recent clinical studies have demonstrated that sympathetic stimulation with epinephrine infusion or exercise produced a more significant increase in Q-Tend and Tpeak-end intervals in LQT1 compared with LQT2 patients (33–35). More recently, the Q-Tend and Tpeak-end intervals both before and after epinephrine and prolongation of Q-Tend with epinephrine were reported to be greater in symptomatic than asymptomatic patients with LQT1 syndrome (9). In the present study, LQT1 patients with transmembrane mutations, who had more frequent LQTS-related cardiac events than those with C-terminal mutations, showed greater baseline Q-Tend and Tpeak-end intervals and a greater increase in both Q-Tend and Tpeak-end intervals with exercise than those with C-terminal mutations. The data in the present study may indicate a stricter exercise limit and a more aggressive use of beta-blockers in LQT1 patients with transmembrane mutations, but once again, we need to evaluate a larger patient population to make a definitive recommendation.

With regard to the sympathetic regulation of I_{Ks}, Marx et al. (36) have suggested that beta-adrenergic modulation of I_{Ks} required targeting of cyclic adenosine monophosphate (cAMP)-dependent protein kinase and protein phosphatase-1 to *KCNQ1* through the targeting protein yotiao. The binding of protein kinase and protein phosphatase-1 to the *KCNQ1* channel through yotiao is mediated by leucine zipper (LZ) motifs located in the C-terminal of the *KCNQ1* gene (amino acid residues 588 to 616). They also reported that the G589D mutant channel located in the LZ motifs of the C-terminus prevented cAMP-dependent regulation of I_{Ks}, and thus may not respond to beta-adrenergic stimulation, resulting in a defect of APD shortening and further prolonging of the APD. The G589D mutation was not included among the C-terminal mutations of the present study. Two C-terminal mutations, R591H and D611Y, located in the LZ motifs were included in the present study. However, the prolongation of the QTc interval was mild in patients with the two mutations (Fig. 1). Further clinical evaluation will be required to conclude the role of LZ motifs in the C-terminus on sympathetic modulation of the I_{Ks} channel.

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Ventricular Tachycardia with Figure Eight Pattern Originating From the Right Ventricle in A Patient with Cardiac Sarcoidosis

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NODA, T., ET AL.: Ventricular Tachycardia with Figure Eight Pattern Originating From the Right Ventricle in A Patient with Cardiac Sarcoidosis. *This case report describes VT with figure eight pattern originating from the right ventricle in a 33-year-old patient with cardiac sarcoidosis. Multiple radiofrequency linear ablation could abolish the VT, and this patient has been clinically free from symptoms of VT during a 6-month follow-up. (PACE 2004; 27:561–562)*

ventricular tachycardia, sarcoidosis, CARTO, ablation

Case Report

A 33-year-old man was referred to the hospital for recurrent episodes of ventricular tachycardia (VT). He had a history of admission to another hospital due to swelling of the bilateral hilar lymph nodes on chest X ray, and sarcoidosis was diagnosed by a transbronchial lung biopsy confirming noncaseating granulomatosis. His standard 12-lead electrocardiogram, during sinus rhythm, showed no significant changes but only inverted T waves in leads V_1 and V_2. The cardiac echocardiograms revealed the right ventricular (RV) dilatation and the reduction of the RV wall motion, but neither hypokinesia of the left ventricle (LV) nor the thinning of the basal LV wall. His coronary angiogram was normal, and the left ventriculogram showed normokinesis. Hematological and serological examinations were within the normal limit except for a slightly high serum angiotensin converting enzyme value (21.9 IU/L) and his gallium scintigraphy indicated no abnormal uptake in the myocardium. The further examination of the RV endomyocardial biopsy indicated epithelioid histiocytes suggesting as a part of noncaseating granulomatosis but no fatty degeneration. He was diagnosed cardiac sarcoidosis based on these findings and underwent electrophysiological study with a three-dimensional electroanatomic mapping system (CARTO, Biosense Webster, Johnson & Johnson, Diamond Bar, CA, USA). During sinus rhythm, the RV activation map by CARTO showed multiple delayed potentials in the anterolateral wall of the RV, and the RV bipolar voltage map indicated the diffuse area of extremely reduced voltage values (bipolar voltage amplitude $\leq$0.5 mV), so called scar area, in the anterolateral wall of the RV. Programmed electrical stimulation (PES) was performed from the RV apical site, and VT was induced by triple extrastimuli. Manifest entrainment was confirmed by a series of stimuli delivered from this site. This VT was the same morphology as the clinical VT (left bundle branch block morphology with a inferior QRS-axis deviation) and was hemodynamically well tolerated (Fig. 1A). The RV activation map during the VT represented a figure eight pattern revolving around the scar area and the pulmonary annulus (PA) (Fig 1. B–D). This circuit involved a critical isthmus between the scar area and the PA. The total activation time of the VT by CARTO fulfilled >90% of the VT cycle length. The macroreentrant VT with figure eight pattern in the RV was suggested, and radiofrequency catheter linear ablation was performed during the VT in the attempt to transect the critical isthmus between the scar area and the PA. The first linear lesion was created in the critical isthmus resulting the interruption of the VT (Fig. 1E). Then, the second liner lesion, during sinus rhythm, was created in the anatomic isthmus between the scar area and the tricuspid annulus (TA) to avoid a new VT associated with this isthmus (Fig. 1F). After the completion of the two linear lesions, scar-PA and scar-TA, PES could not induce the VT at all.

He has been clinically free from symptoms of VT during the 6-month follow-up.

Discussion

Sarcoidosis is systemic granulomatous disorder including heart. The LV wall-motion abnormality and the thinning of the basal LV wall are common features of the cardiac sarcoidosis.[1] However, a case of cardiac sarcoidosis mimicking RV

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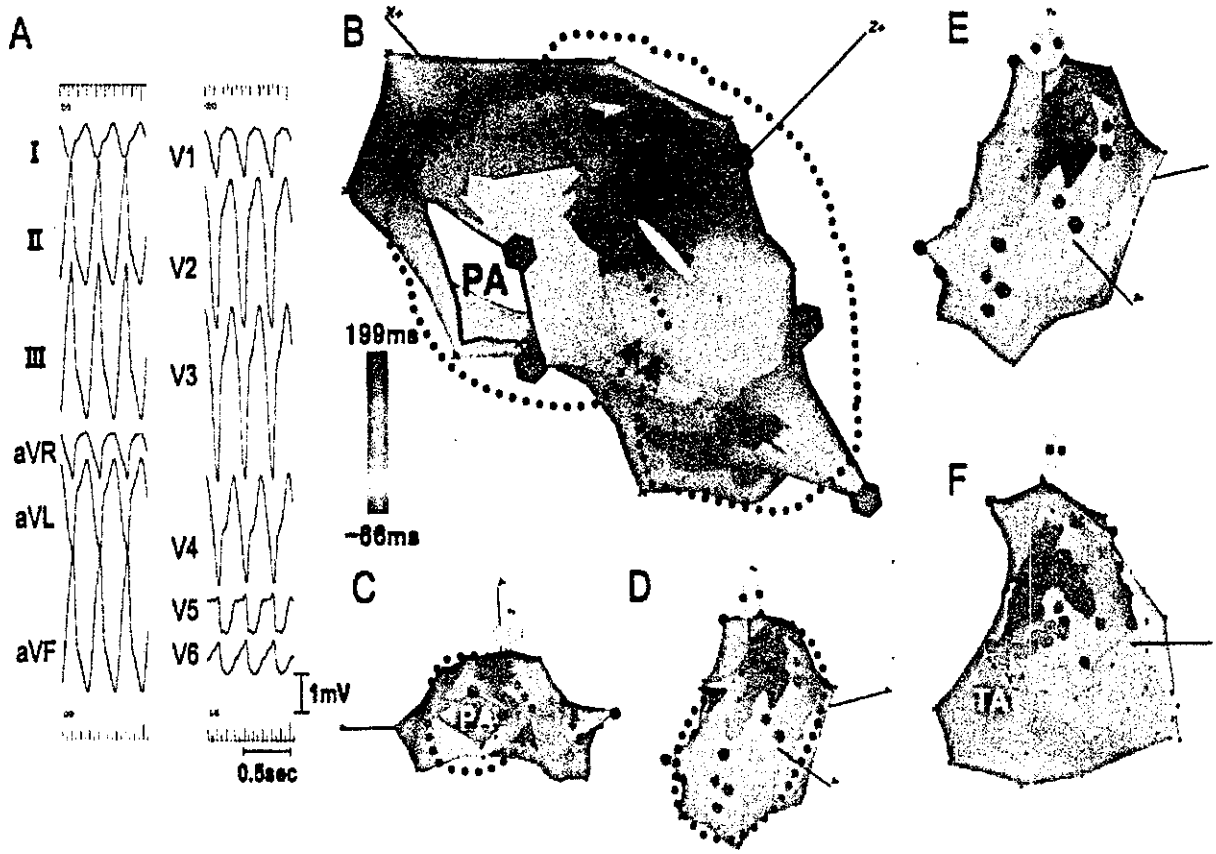

Figure 1. *(A) Twelve-lead electrocardiogram during the induced ventricular tachycardia (VT). The induced VT showed the same morphology of the clinical VT (left bundle branch block morphology with a inferior QRS-axis deviation), and the cycle length of the VT was 290 ms. (B) The cranial right posterior oblique view of the right ventricular (RV) activation map during the VT by CARTO. The RV activation map during the VT represented a figure eight pattern. Note the total activation time of the VT by CARTO fulfilled > 90% of the VT cycle length. Gray areas represent scar (bipolar voltage amplitude ≤0.5 mV). (c) The cranial posteroanterior view of the RV activation map during the VT by CARTO. The VT revolved around the pulmonary annulus (PA). (D) The cranial right anterior oblique view of the RV activation map during the VT by CARTO. The VT revolved around the scar area. (E) The location of the first linear lesion. The first linear lesion created in the critical isthmus between the scar area and the PA was shown in the cranial right anterior oblique view of the RV activation map. Red dots indicate radiofrequency applications. (F) The location of the second linear lesion. The second linear lesion created in the anatomic isthmus between the scar area and the tricuspid annulus during sinus rhythm was shown in the right oblique view of the RV activation map.*

dysplasia was recently reported.[2] Clinical manifestations of cardiac sarcoidosis also include ventricular arrhythmias leading to sudden death.[3] In the present case, it was indicated that the RV dilatation and the reduction of the RV wall motion but neither hypokinesia of the LV nor the thinning of the basal LV wall, and the VT was the first clinical manifestation of cardiac sarcoidosis. The electrophysiological study using CARTO showed that the macroreentrant VT with a figure eight pattern in the RV and radiofrequency linear ablation was performed with CARTO to transect the two isthmi, scar-PA and scar-TA, leading to abolishment of VTs.

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