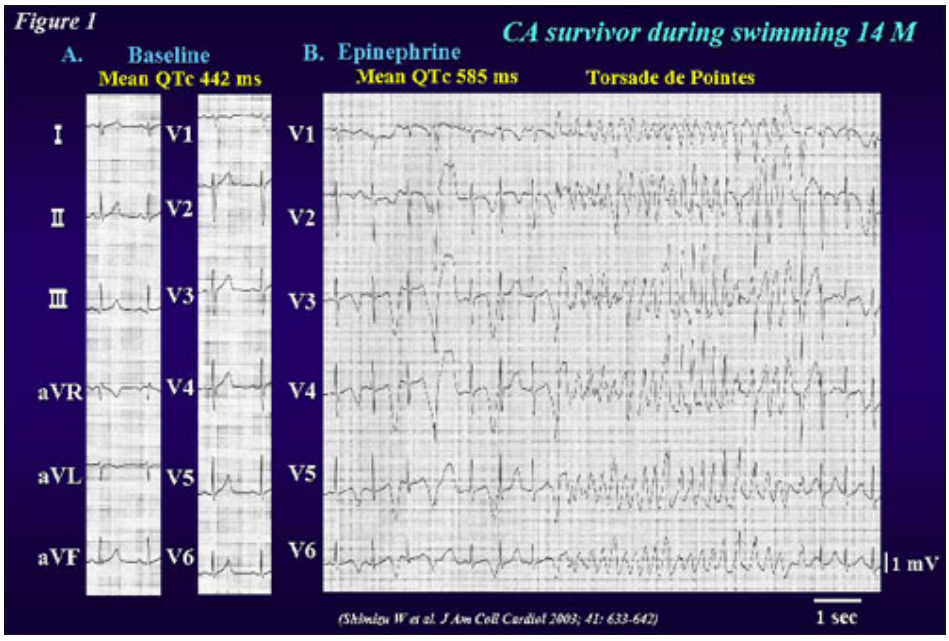
Usefulness of Epinephrine Test in the Congenital Long QT Syndrome

Wataru Shimizu M.D., Ph.D.

CASE PRESENTATION

A 14-year old Japanese boy was successfully resuscitated from cardiac arrest (near drowning) during swimming and referred to the National Cardiovascular Center for evaluating his diagnosis and treating him. He had had no previous history of syncope. Physical examination and laboratory data were normal on admission. None of chest radiographs and echocardiograms detected abnormal findings. His baseline 12-leads ECG showed borderline prolonged corrected QT (QTc) interval (442 ms) (**Figure 1A**).[1] Family study including his parents and two younger sisters showed neither history of syncope or cardiac arrest nor QT prolongation in their baseline 12-leads ECG.

Epinephrine test using our own protocol (bolus injection of 0.1 μg/kg followed by continuous infusion 0.1 μg/kg/min) was conducted. Epinephrine prolonged the QTc remarkably (585 ms), and induced spontaneously terminating torsade de pointes (TdP) (**Figure 1B**),[1] suggesting that he may be affected with congenital form of long QT syndrome (LQTS), especially LQT1 syndrome, which is most sensitive to sympathetic stimulation among several forms of LQTS. Molecular screening for LQT1 gene, *KCNQ1*, was first performed, and we could confirm successfully his molecular diagnosis as LQT1 syndrome. Oral β-blocker therapy (propranolol 1mg/kg) was started, and he has been symptom free for 7 years.



DISCUSSION

Low Penetrance in Congenital LQTS

Congenital LQTS is a hereditary disorder characterized by prolonged QT interval in the 12-leads electrocardiogram (ECG) and a polymorphic ventricular tachycardia, TdP.[2] The clinical diagnosis of LQTS is based on the baseline QTc interval, cardiac events such as syncope, aborted cardiac arrest and sudden cardiac death, and a family history of apparent LQTS.[3] However, the hypothesis that electrocardiographic diagnosis could miss patients affected by LQTS had already been proposed before the genetic bases of the disease were known. These initial observations were based on the evidence that syncopal events could occur among family members with a "normal" QT interval.[4] Vincent et al. reported that 5 (6 %) of 82 mutation carriers from 3 LQT1 families had a normal QT interval.[5] Priori and co-workers have reported a very low penetrance (38 %, 9/24) in 9 families with only 1 clinically affected individual of LQTS.[6] They recently conducted a large study of genotyped LQTS, demonstrating that penetrance was significantly lower in the LQT1 (64%) than in the LQT2 (81%) or the LQT3 (90%) syndromes.[7] These findings strongly suggest the need for novel tools to unveil concealed mutation carriers of LQTS, especially those with LQT1syndrome. The identification of patients with concealed LQTS enables the physicians to initiate potentially life-saving pharmacotherapies and healthstyle modifications.

The Epinephrine Test in Congenital LQTS

Provocative tests using catecholamine or exercise testing have long been considered to unmask some forms of congenital LQTS.[8] Treadmill or ergometer exercise testing has been used to confirm the clinical diagnosis in patients with latent LQTS.[9,10] However, it is often difficult to measure the QT interval precisely because of motion artifacts in the ECG recordings during exercise. As a catecholamine challenge test, isoproterenol has been used as a provocative testing.[9] However, the recent major insights have been gleaned from using epinephrine.

The two major protocols developed for epinephrine test include the bolus injection followed by brief continuous infusion developed by our group,[1,11-13] and the escalating-dose protocol by Ackerman's group (the Mayo protocol).[14-16] Both protocols are extremely useful and safe, and overall are well tolerated. Each protocol has some advantages and disadvantages with respect to the other.

1. Bolus Protocol (Bolus Injection Followed by Brief Continuous Infusion)

We used bolus protocol (bolus injection of epinephrine 0.1μg/kg followed by continuous infusion of epinephrine 0.1μg/kg/min) (**Figure 2**) and suggested that epinephrine test produced genotype-specific responses of the QTc interval in patients with LQT1, LQT2 and LQT3.[1,11-13] Epinephrine

remarkably prolonged the QTc interval at peak effect when the heart rate was maximally increased (1 – 2 minutes after the bolus injection), and the QTc remained prolonged during steady-state epinephrine effect (3 – 5 minutes) in patients with LQT1 (**Figure 3**).[1,12] The paradoxical QT response, i.e. the longer absolute QT interval even though the shorter preceding RR interval during epinephrine infusion, was often observed in patients with LQT1 syndrome (**Figure 3**).[12] In patients with LQT2, the QTc was also prolonged at peak epinephrine effect (during bolus), but returned to close to the baseline levels at steady state epinephrine effect (**Figure 3**).[12] On the other hand, the QTc was less prolonged at peak epinephrine effect in the LQT3 patients than in the LQT1 or LQT2 patients, and was abbreviated below the baseline levels at steady state epinephrine effect (**Figure 3**).[12] The differential responses of the QTc interval to our bolus protocol explain why the LQT1, LQT2, and LQT3 patients exhibit genotype-specific triggers for cardiac events.[17]

The experimental studies employing arterially-perfused canine left ventricular wedge preparations also showed a differential responses of action potential duration (APD) and QT interval to sympathetic stimulation with isoproterenol between the LQT1, LQT2 and LQT3 models, suggesting the cellular basis for genotype-specific triggers for cardiac events.[18] The LQT1 model using a specific I_{Ks} blocker, chromanol 193B, showed a persistent prolongation of APD and QT interval at steady state conditions of isoproterenol infusion. Under baseline conditions, β-adrenergic stimulation is expected to increase net outward repolarizing current, due to larger increase of outward currents, including I_{Ks} and Ca^{2+}-activated chloride current ($I_{Cl(Ca)}$), than that of an inward current, Na^{+}/Ca^{2+} exchange current ($I_{Na\text{-}Ca}$), resulting in an abbreviation of APD and QT interval. A defect in I_{Ks} as seen in LQT1 could account for failure of β-adrenergic stimulation to abbreviate APD and QT interval, resulting in a persistent and paradoxical QT prolongation under sympathetic stimulation. In the LQT2 model using an I_{Kr} blocker, d-sotalol, isoproterenol infusion initially prolonged but then abbreviated APD and QT interval probably due to an initial augmentation of $I_{Na\text{-}Ca}$ and a subsequent stimulation of I_{Ks}. In the LQT3 model using ATX-II, an agent that slows the inactivation of the sodium channel, isoproterenol infusion constantly abbreviated APD and QT interval as a result of a stimulation of I_{Ks}, because an inward late I_{Na} was augmented in this genotype.

Figure 2

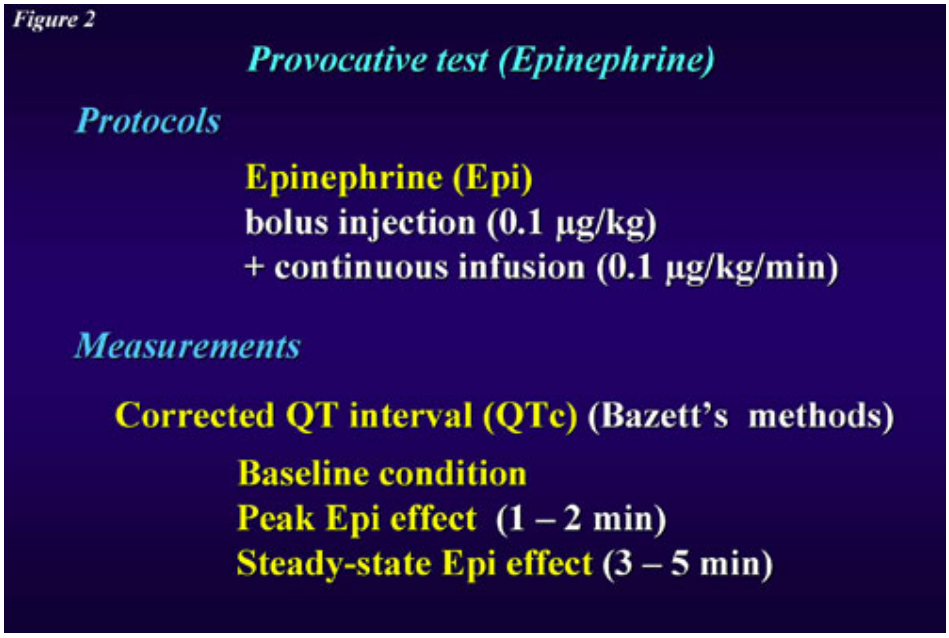
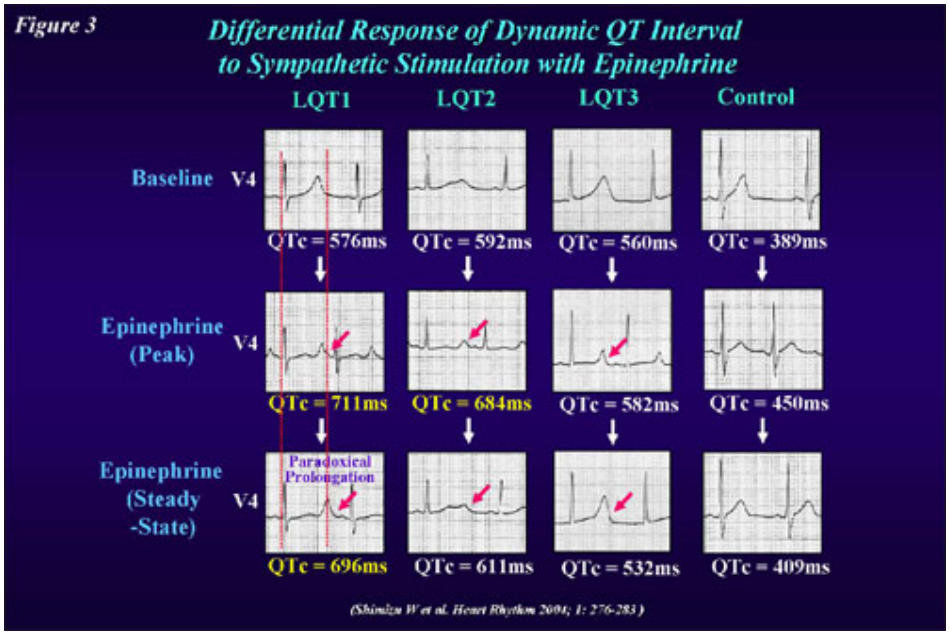
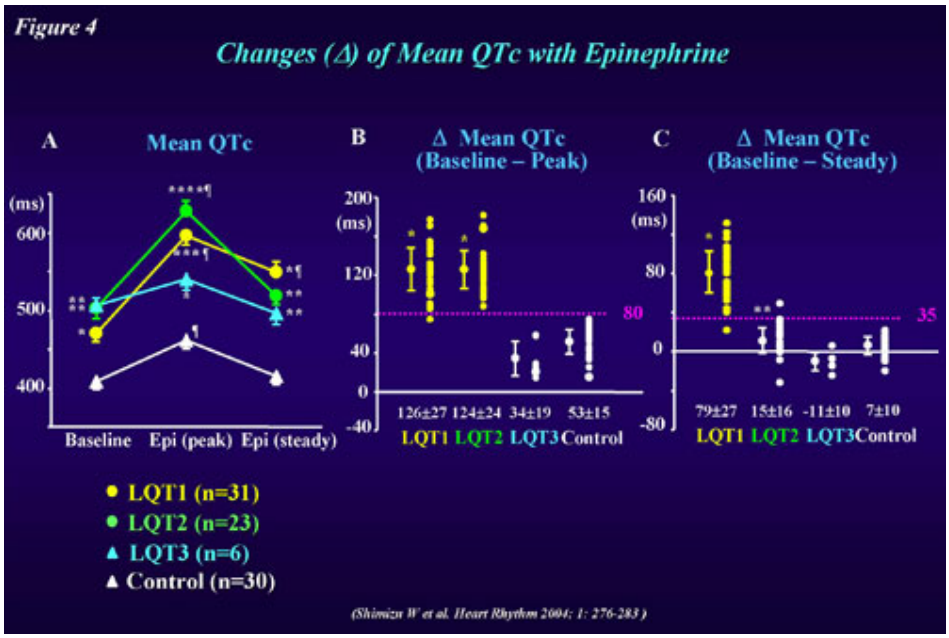


Figure 3



Based on the clinical and experimental data mentioned above, the epinephrine test in patients with congenital LQTS is expected to presumptively diagnose the LQT1, LQT2, and LQT3 genotype by monitoring the temporal course of the QTc to epinephrine at peak effect following bolus injection and at steady-state effect during continuous infusion, (**Figure 4**).[12] as well as to unmask concealed patients with LQTS.



The clinical ECG diagnosis (sensitivity) was improved by using the steady state epinephrine effect from 68% to 87% in the 31 LQT1 patients, from 83% to 91% in the 23 LQT2 patients, but not in the 6 LQT3 patients from 83% to 83% (**Figure 5**) in our cohort .[12] The bolus protocol of epinephrine effectively predicts the underlying genotype of the LQT1, LQT2 and LQT3.[12] The **prolongation of QTc ≥ 35 ms at steady state epinephrine** effect could differentiate LQT1 from LQT2, LQT3 or control patients with a predictive accuracy ≥ 90 % (**Figure 6**). The **prolongation of QTc ≥ 80 ms at peak epinephrine effect** could differentiate LQT2 from LQT3 or control patients with predictive accuracy of 100% (**Figure 7**). A flow chart to predict LQT1, LQT2, LQT3 and control patients with the epinephrine test is illustrated in the **Figure 8**.

Figure 5 *Accuracy of ECG Diagnosis Before and After Epinephrine*

	Baseline		Epinephrine (Steady state)	
	Sensitivity (%) (Penetrance)	Specificity (%)	Sensitivity (%) (Penetrance)	Specificity (%)
LQT1				
ECG criteria*	21/31 (68)	30/30 (100)	27/31 (87)	30/30 (100)
Score ≥ 4**	21/31 (68)	30/30 (100)	25/31 (81)	30/30 (100)
LQT2				
ECG criteria*	19/23 (83)	30/30 (100)	21/23 (91)	30/30 (100)
Score ≥ 4**	19/23 (83)	30/30 (100)	21/23 (91)	30/30 (100)
LQT3				
ECG criteria*	5/6 (83)	30/30 (100)	5/6 (83)	30/30 (100)
Score ≥ 4**	3/6 (50)	30/30 (100)	3/6 (50)	30/30 (100)

* A QTc > 470 ms in asymptomatic individuals and a QTc > 440 ms for males and > 460 ms for females associated with ≥ 1 of the following: (1) stress-related syncope, (2) documented TdP, or (3) family history of early sudden cardiac death.

** Diagnostic criteria by Schwartz et al.

(Shimizu W et al. Heart Rhythm 2004; 1: 276-283)

Figure 6

Prediction of Genotype with Epinephrine Test (Δ QTc)

	Se	Sp	PPV	NPV	Accuracy
LQT1 vs. LQT2	97%	96%	97%	96%	96%
Δ QTc ≥ 35 ms (Steady – Baseline)	(90%)	(83%)	(88%)	(86%)	(87%)
LQT1 vs. LQT3	94%	100%	100%	95%	97%
Δ QTc ≥ 35 ms (Steady – Baseline)	(90%)	(100%)	(100%)	(67%)	(92%)
LQT1 vs. Control	97%	100%	100%	97%	98%
Δ QTc ≥ 35 ms (Steady – Baseline)	(90%)	(97%)	(97%)	(91%)	(93%)

NPV, negative predictive value. PPV, positive predictive value. Se, sensitivity. Sp, specificity. Percentages in parenthesis indicate those calculated by data measured simply from lead V5.

(Shimizu W et al. Heart Rhythm 2004; 1: 276-283)

Figure 7

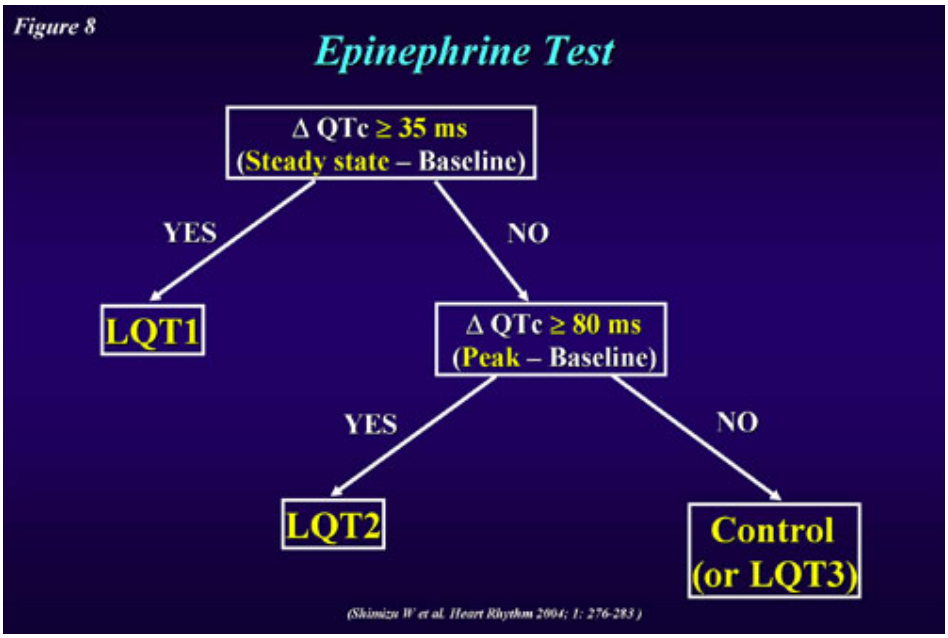
Prediction of Genotype with Epinephrine Test (Δ QTc) (Continued)

	Se	Sp	PPV	NPV	Accuracy
LQT2 vs. LQT3 Δ QTc ≥ 80 ms (Peak – Baseline)	100% (91%)	100% (100%)	100% (100%)	100% (75%)	100% (93%)
LQT2 vs. Control Δ QTc ≥ 80 ms (Peak – Baseline)	100% (91%)	100% (90%)	100% (88%)	100% (93%)	100% (91%)

NPV, negative predictive value. PPV, positive predictive value. Se, sensitivity. Sp, specificity. Percentages in parenthesis indicate those calculated by data measured simply from lead V5.

(Shimizu W et al. Heart Rhythm 2004; 1: 276-283)

Figure 8



2. Mayo Protocol (Incremental, Escalating Epinephrine Infusion)

Ackerman et al. have used the Mayo protocol (incremental, escalating infusion protocol for 25-minute, 0.025 to 0.3 μg/kg/min) in the LQT1, LQT2, LQT3 patients and genotyped-negative patients.[14-16] The median change of the QT interval was 78 ms in LQT1, -4 ms in LQT2, -58 ms in LQT3, and -23 ms in the genotype-negative patients by epinephrine infusion at low-dose of ≤ 0.1μg/kg/min.[15] A **paradoxical QT prolongation, defined as a 30-ms increase in the QT** (not QTc) interval during low-dose epinephrine infusion, was specifically observed in the LQT1 patients (92%), but not in the LQT2 (13%), the LQT3 (0%), and the genotype-negative patients (18%).[15] A sensitivity, specificity, positive predictive value, and negative predictive value with the paradoxical QT prolongation for LQT1 vs. non-LQT1 status was 92.5%, 86%, 76%, and 96%, respectively.[15] Therefore, the Mayo protocol provides a presumptive, pre-genetic clinical diagnosis of LQT1 genotype. Major advantages of the escalating infusion protocol are better patient tolerance and a lower incidence of false-positive responses. They also reported that epinephrine-induced notched T wave was more specifically observed in patients with LQT2 syndrome.[16]

Molecular diagnosis is still unavailable to many institutes and requires high costs and is time-consuming. The presumptive, pre-genetic diagnosis of either LQT1, LQT2, or LQT3 based upon the response to epinephrine would facilitate molecular screening by targeting suspected genes. Moreover, a clinical diagnosis of concealed LQTS by the epinephrine test enables to limit exposure of the individuals to potentially dangerous conditions such as participation into competitive sport and use of drugs known to prolong repolarization, thus reducing the risk of life threatening cardiac arrhythmias. Furthermore, the identification of the QT or QTc response to epinephrine test like that in LQT1, LQT2, or LQT3 patients can guide gene-specific treatment strategies, even though the individuals can not be genetically diagnosed.

It is noteworthy that the induction of TdP or ventricular fibrillation (VF) should be always taken into account during the epinephrine test. Therefore, it goes without saying that epinephrine test should only be done by cardiologists under enough preparation of intravenous β-blockers as well as direct cardioverter for unintentionally induced VF. However, the induction of TdP or VF is extremely uncommon. In over 400 studies conducted using the Mayo protocol and our bolus protocol

respectively, only two episodes of TdP (10 beats and 20 beats) and one episode of macroscopic T wave alternans have been observed (**Figure 1B**).[1]

REFERENCES

1. Shimizu W, Noda T, Takaki H, Kurita T, Nagaya N, Satomi K, Suyama K, Aihara N, Kamakura S, Echigo S, Nakamura K, Sunagawa K, Ohe T, Towbin J A, Napolitano C, Priori S G: Epinephrine unmasks latent mutation carriers with LQT1 form of congenital long QT syndrome. *J Am Coll Cardiol* 2003;41:633-642.
2. Schwartz PJ, Periti M, Malliani A: The long QT syndrome. *Am Heart J.* 1975;89:378-390.
3. Schwartz PJ, Moss AJ, Vincent GM, Crampton RS. Diagnostic criteria for the long QT syndrome: An update. *Circulation.* 1993;88:782-784.
4. Moss AJ, Schwartz PJ, Crampton RS, Locati E, Carleen E: The long QT syndrome: a prospective international study. *Circulation.* 1985;71:17-21.
5. Vincent GM, Timothy KW, Leppert M, Keating M: The spectrum of symptoms and QT intervals in carriers of the gene for the long-QT syndrome. *N Engl J Med.* 1992;327:846-852.
6. Priori SG, Napolitano C, Schwartz PJ: Low penetrance in the Long-QT syndrome. Clinical impact. *Circulation.* 1999;99:529-533.
7. Priori SG, Napolitano C, Schwartz PJ, Grillo M, Bloise R, Ronchetti E, Moncalvo C, Tulipani C, Veia A, Bottelli G, Nastoli J: Association of long QT syndrome loci and cardiac events among patients treated with beta-blockers. *JAMA.* 2004;292:1341-1344.
8. Schechter E, Freeman CC, Lazzara R: Afterdepolarizations as a mechanism for the long QT syndrome: electrophysiologic studies of a case. *J Am Coll Cardiol.* 1984;3:1556-1561.
9. Shimizu W, Ohe T, Kurita T, Shimomura K: Differential response of QTU interval to exercise, isoproterenol, and atrial pacing in patients with congenital long QT syndrome. *PACE.*1991;14:1966-1970.
10. Takenaka K, Ai T, Shimizu W, Kobori A, Ninomiya T, Otani H, Kubota T, Takaki H, Kamakura S, Horie M: Exercise stress test amplifies genotype-phenotype correlation in the LQT1 and LQT2 forms of the long QT syndrome. *Circulation* 2003;107:838-844.
11. Noda T, Takaki H, Kurita T, Suyama K, Nagaya N, Taguchi A, Aihara N, Kamakura S, Sunagawa K, Nakamura K, Ohe T, Horie M, Napolitano C, Towbin J A, Priori S G, Shimizu W: Gene-specific response of dynamic ventricular repolarization to sympathetic stimulation in LQT1, LQT2 and LQT3 forms of congenital long QT syndrome. *Eur Heart J.* 2002;23:975-983.
12. Shimizu W, Noda T, Takaki H, Nagaya N, Satomi K, Kurita T, Suyama K, Aihara N, Sunagawa K, Echigo S, Miyamoto Y, Yoshimasa Y, Nakamura K, Ohe T, Towbin J A, Priori S G, Kamakura S: Diagnostic value of epinephrine test for genotyping LQT1, LQT2 and LQT3 forms

of congenital long QT syndrome. *Heart Rhythm* 2004;1:276-283.

13. Shimizu W: The long QT syndrome: Therapeutic implications of a genetic diagnosis. *Cardiovasc Res* 2005;67:347-356.
14. Ackerman MJ, Khositseth A, Tester DJ, Hejlik JB, Shen WK, Porter CB. Epinephrine-induced QT interval prolongation: a gene-specific paradoxical response in congenital long QT syndrome. *Mayo Clin Proc.* 2002;77:413-421.
15. Vyas H, Hejlik J, Ackerman MJ: Epinephrine QT stress testing in the evaluation of congenital long-QT syndrome: diagnostic accuracy of the paradoxical QT response. *Circulation.* 2006;113:1385-1392.
16. Khositseth A, Hejlik J, Shen WK, Ackerman MJ: Epinephrine-induced T-wave notching in congenital long QT syndrome. *Heart Rhythm.* 2005;2:141-146.
17. Schwartz PJ, Priori SG, Spazzolini C, Moss AJ, Vincent GM, Napolitano C, Denjoy I, Guicheney P, Breithardt G, Keating MT, Towbin JA, Beggs AH, Brink P, Wilde AA, Toivonen L, Zareba W, Robinson JL, Timothy KW, Corfield V, Wattanasirichaigoon D, Corbett C, Haverkamp W, Schulze-Bahr E, Lehmann MH, Schwartz K, Coumel P, Bloise R: Genotype-phenotype correlation in the long-QT syndrome : gene-specific triggers for life-threatening arrhythmias. *Circulation* 2001;103:89-95.
18. Shimizu W, Antzelevitch C: Differential response to beta-adrenergic agonists and antagonists in LQT1, LQT2 and LQT3 models of the long QT syndrome. *J Am Coll Cardiol.* 2000;35:778-786.