JACC Vol. 26, No. 5
November 1, 1995:1299–309

Effects of Verapamil and Propranolol on Early Afterdepolarizations and Ventricular Arrhythmias Induced by Epinephrine in Congenital Long QT Syndrome

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Objectives. **This study used monophasic action potentials to investigate the effects of verapamil and propranolol on epinephrine-induced repolarization abnormalities in congenital long QT syndrome.**

Background. **Early afterdepolarizations have been suggested to play a significant role in QT prolongation and ventricular arrhythmias in congenital long QT syndrome. Calcium channel blocking as well as beta-adrenergic blocking agents are reported to be effective in the management of this syndrome.**

Methods. **Monophasic action potentials from 2 to 4 sites were recorded simultaneously in eight patients with the long QT syndrome (22 sites) and in eight control patients (23 sites) and were obtained during constant atrial pacing 1) before epinephrine infusion; 2) during epinephrine infusion (0.1 μg/kg body weight min); 3) after verapamil injection (0.1 mg/kg) during epinephrine infusion; and 4) after both propranolol (0.1 mg/kg) and verapamil injections.**

Results. **Early afterdepolarizations were recorded in two of the eight patients (2 of 22 sites) during the control state. During epinephrine infusion, early afterdepolarizations were recorded in six patients (six sites), and ventricular premature complexes were induced in three and torsade de pointes in one. Epinephrine prolonged 90% monophasic action potential duration from 348 ± 48 (mean ± SD) to 381 ± 49 ms (22 sites, $p < 0.0005$) and increased the dispersion of action potential duration (difference between the longest and shortest action potential duration) from 36 ± 20 to 64 ± 34 ms ($p < 0.005$). Verapamil eliminated (two sites) or reduced (four sites) early afterdepolarizations and abolished ventricular premature complexes in two of the three patients as well as suppressing torsade de pointes. Verapamil shortened the action potential duration to 355 ± 28 ms ($p < 0.01$ vs. epinephrine) and decreased the dispersion to 44 ± 19 ms ($p < 0.05$ vs. epinephrine). Propranolol further eliminated (two sites) or reduced (two sites) early afterdepolarizations, abolished ventricular premature complexes in the remaining one patient and further shortened the action potential duration to 337 ± 32 ms ($p = 0.09$ vs. verapamil). In the control patients, none of the early afterdepolarizations, ventricular arrhythmias or marked prolongations of action potential duration were induced by epinephrine, and neither verapamil nor propranolol changed repolarization variables.**

Conclusions. **These results indicate that both verapamil and propranolol can improve repolarization abnormalities induced by epinephrine in congenital long QT syndrome.**

(J Am Coll Cardiol 1995;26:1299–309)

Early afterdepolarizations and triggered activity have been shown to play a significant role in the genesis of QT prolongation and ventricular arrhythmias in several experimental models of the long QT syndrome (1–7). In addition, some clinical studies using monophasic action potentials have demonstrated direct evidence of early afterdepolarizations in patients with both congenital (8–12) and acquired (13–15) long QT syndrome. In congenital long QT syndrome, sympathetic stimulation, or catecholamines, are known to produce QT prolongation and ventricular arrhythmias, which are often linked to syncope or sudden death. Moreover, some recent studies (11,12,16,17) using monophasic action potentials have shown that catecholamine-enhanced early afterdepolarizations are associated with ventricular arrhythmias. Commensurate with the influence of catecholamines, beta-adrenergic blocking agents are widely reported to reduce the incidence of syncope and sudden death (18,19). In addition, calcium channel blocking agents (e.g., verapamil) have recently been reported (10,12,17,20) to be effective in the suppression of early afterdepolarizations and ventricular arrhythmias in some patients with the congenital long QT syndrome. The present study sought to 1) examine the influence of epinephrine (alpha- and

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Manuscript received January 11, 1995; revised manuscript received April 14, 1995, accepted June 7, 1995.

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0735-1097/95/$9.50
0735-1097(95)00313-S

Table 1. Clinical Characteristics of Eight Patients With the Long QT Syndrome and Eight Control Patients

Pt No.	Age (yr)/ Gender	Diagnosis	Symptoms		ECG Findings				Serum Electrolytes	
			Syncope With Stress	TdP	Sinus Cycle Length (ms)	QTc ($ms^{1/2}$)	Notched T Wave in Three Leads	T Wave Alternans	K (mEq/liter)	Mg (mg/dl)
Pts with LQTS										
1	19/F	RW	+	−	760	670	+	−	4.0	2.1
2	23/F	RW	+	+	1,180	650	+	+	4.1	2.1
3	18/F	Idp	+	−	940	580	−	−	4.0	1.9
4	24/F	RW	+	+	820	620	−	−	4.0	2.2
5	12/M	RW	+	−	1,000	600	+	−	4.3	2.0
6	11/M	RW	+	+	700	570	−	−	4.6	1.9
7	3/M	RW	+	+	740	740	+	+	4.1	2.2
8	6/M	RW	+	+	880	600	−	+	4.0	1.9
Control pts										
1	44/M	Con WPW	−	−	770	400	−	−	4.2	2.0
2	57/M	Con WPW	−	−	1,000	410	−	−	4.3	2.1
3	57/M	Con WPW	−	−	970	420	−	−	4.1	2.0
4	40/F	Con WPW	−	−	780	430	−	−	4.2	2.2
5	55/F	Con WPW	−	−	960	390	−	−	4.0	2.2
6	36/F	Con WPW	−	−	820	410	−	−	4.1	1.9
7	42/F	Con WPW	−	−	720	410	−	−	4.3	2.1
8	25/F	Con WPW	−	−	840	410	−	−	4.1	2.0

Con WPW = concealed Wolff-Parkinson-White syndrome; ECG = electrocardiographic; F = female; Idp = idiopathic; LQTS = congenital long QT syndrome; M = male; QTc = corrected QT interval; Pt = patient; RW = Romano-Ward syndrome; TdP = torsade de pointes; + = present; − = absent.

beta-adrenergic stimulation) on early afterdepolarizations, ventricular arrhythmias and action potential duration in patients with the congenital long QT syndrome; and 2) investigate the effects of verapamil and propranolol (beta-blocker) on these variables.

Methods

Subjects. Congenital long QT syndrome was defined according to the new diagnostic criteria of Schwartz et al. (21): 1) a corrected QT (QTc) interval ≥450 $ms^{1/2}$; 2) a history of syncope with stress; 3) polymorphic ventricular tachycardia characteristic of torsade de pointes; and 4) family members with definite congenital long QT syndrome. Eight consecutive patients with the congenital long QT syndrome were entered into the study between January 1992 and June 1994 (four female, four male; mean age [±SD] 15 ± 8 years, range 3 to 24) (Table 1). One patient (Patient 2) was described in an earlier case report (12). The long QT syndrome was familial (Romano-Ward syndrome) in seven patients and idiopathic in one. All eight patients had a history of stress-induced syncope, and torsade de pointes was documented in six. Four patients had notched T wave in three leads, and T wave alternans was present in three. All eight patients had a mean QTc interval of 629 ± 56 $ms^{1/2}$ (range 570 to 740) that was observed spontaneously in response to emotional stress or exercise and was unrelated to antiarrhythmic agents, electrolyte abnormalities or any other causes leading to QT prolongation. Therefore, all eight patients had a score >4 points (range 5 to 8.5 points, mean 6.8 ± 1.1) according to the new diagnostic criteria of Schwartz et al. (21), indicating a high probability of congenital long QT syndrome. Eight control patients with concealed Wolff-Parkinson-White syndrome and a normal QT interval were also studied after successful radiofrequency catheter ablation for accessory atrioventricular connections to evaluate the effects of epinephrine, verapamil and propranolol on monophasic action potentials (five women, three men; mean age 45 ± 11 years, range 25 to 57; mean QTc interval 410 ± 12 $ms^{1/2}$) (Table 1).

Electrophysiologic studies. All protocols were reviewed and approved by our Ethical Review Committee, and written informed consent was obtained from all patients or their parents. (Because four patients were minors, the purpose of the study [that the effects of verapamil and propranolol on the action potential were to be examined directly using the monophasic action potential] was explained, and informed consent was obtained from the parents.) Electrophysiologic studies were performed in the nonsedated, postabsorbed state in all but two patients with the long QT syndrome (Patients 7 and 8) who received sodium pentobarbital (3 mg/kg body weight) and diazepam (0.3 mg/kg) as sedation. All antiarrhythmic medications were discontinued for at least five drug half-lives.

Two or three 6F or 7F monophasic action potential catheters (monophasic action potential–pacing combination catheter, EP Technologies) were introduced through a femoral vein and advanced into the right ventricle under fluoroscopic guidance to record the right ventricular monophasic action potentials. Another 6F or 7F catheter was also introduced through a femoral artery and advanced into the left ventricle to

record the left ventricular monophasic action potential. A standard 6F bipolar electrode catheter with 10-mm interelectrode spacing (USCI) was positioned in the right atrial appendage for atrial pacing.

Recordings of monophasic action potentials. Monophasic action potentials from two to four sites on the right and left ventricular endocardium were recorded simultaneously in each patient by the contact electrode technique described previously (11,12,22–25). A total of 22 sites were recorded in eight patients with the long QT syndrome and 23 in eight control patients. Monophasic action potential signals (amplified and filtered at a frequency of 0.05 to 500 Hz), six surface electrocardiographic (ECG) leads and the radial artery pressure were displayed simultaneously on a 16-channel Mingograf strip chart recorder (Siemens-Elema) at a paper speed of 25 or 100 mm/s. Monophasic action potentials were obtained during both sinus rhythm and constant atrial pacing (cycle length 600 ms) after placement of the catheter electrode in a position providing continuous recordings with a stable amplitude, smooth configuration and isopotential diastolic baseline (phase 4) that persisted for at least 10 min. Once the contact catheter was stabilized, monophasic action potentials could be recorded continuously from the same endocardial site for long periods without additional catheter manipulation.

Early afterdepolarizations were defined as depolarizing afterpotentials that interrupted or delayed repolarization of the action potential (11). The *amplitude* of early afterdepolarizations was defined as follows: When early afterdepolarizations showed reversal of depolarization, the amplitude was defined as the difference between the maximal diastolic potential during phase 4 and the maximal positive deflection of the early afterdepolarizations. When early afterdepolarizations did not show reversal of depolarization, the amplitude was defined as the difference between phase 4 and the first deviation of the smooth repolarization phase. The amplitude of early afterdepolarizations was expressed as a percent of the monophasic action potential amplitude (*percent early afterdepolarization amplitude*). The monophasic action potential duration was determined at 90% repolarization (*90% monophasic action potential duration*), which included early afterdepolarizations if present. The *dispersion* of 90% monophasic action potential duration was defined as the difference between the longest and shortest 90% monophasic action potential duration for each patient. The *QT(U) interval* was defined as the time between QRS onset and the point at which the line of maximal downslope of the T wave, or the late component of the T(U) complex, if present, crossed the baseline before the isoelectric UP interval (24,26).

Protocol. Constant right atrial pacing at a cycle length of 600 ms was performed with 2-ms rectangular stimuli at twice diastolic threshold delivered from a programmable stimulator (SEC-3102, Nihon Kohden). Monophasic action potentials were recorded before epinephrine infusion (control state) during constant atrial pacing for at least 3 min until the monophasic action potential duration reached a new steady state (27). The mean 90% monophasic action potential duration and QT(U) interval >3 consecutive beats during constant atrial pacing were used for analysis.

Epinephrine infusion. Epinephrine was infused at a constant rate of 0.1 μg/kg body weight per min in both patient groups. After a steady state was achieved, the effect of epinephrine on ventricular arrhythmias was studied during sinus rhythm, and monophasic action potentials were recorded during constant atrial pacing (cycle length 600 ms), as described earlier (Protocol).

Verapamil injection. Verapamil (0.1 mg/kg) was injected for 3 min during continuous epinephrine infusion in both patient groups, and the effect of verapamil on ventricular arrhythmias induced by epinephrine was investigated. Monophasic action potentials were recorded during constant atrial pacing (cycle length 600 ms) 5 min after verapamil injection, and the effect of verapamil on early afterdepolarizations and on monophasic action potential duration was investigated.

Propranolol injection. Propranolol (0.1 mg/kg) was also injected for 3 min during continuous epinephrine infusion at ~20 min after verapamil injection to assess the effect on ventricular arrhythmias in both groups of patients. Monophasic action potentials were recorded during constant atrial pacing (cycle length 600 ms) 5 min after propranolol injection, and the effect of propranolol on early afterdepolarizations and on monophasic action potential duration was investigated.

Statistical analysis. Data are reported as mean value ± SD. A repeated measures analysis of variance followed by the Scheffé test was used to compare measurements made before and after serial drug administration. The Student *t* test for unpaired data was used to compare differences between patients with the long QT syndrome and control patients. A p value <0.05 was considered significant.

Results

Sinus cycle length and systolic blood pressure. Epinephrine significantly shortened the sinus cycle length in both patient groups (from 759 ± 85 to 648 ± 49 ms [$p < 0.05$] in patients with the long QT syndrome and from 858 ± 105 to 739 ± 87 ms [$p < 0.005$] in control patients). Injection of verapamil during continuous epinephrine infusion did not change the sinus cycle length in either patient group (629 ± 23 and 730 ± 100 ms in patients with the long QT syndrome and control patients, respectively). Addition of propranolol during continuous epinephrine infusion significantly prolonged the sinus cycle length in both groups (848 ± 137 and 946 ± 80 ms [both $p < 0.0005$ vs. verapamil] in patients with the long QT syndrome and control patients, respectively). Epinephrine significantly increased systolic blood pressure during constant atrial pacing (cycle length 600 ms) in both groups (from 113 ± 12 to 139 ± 18 mm Hg [$p < 0.0005$] in patients with the long QT syndrome and from 129 ± 13 to 146 ± 17 mm Hg [$p < 0.05$] in control patients). Injection of verapamil during continuous epinephrine infusion significantly decreased systolic blood pressure in both groups (119 ± 19 and 125 ± 15 mm Hg

Table 2. Electrophysiologic Data for Eight Patients With the Long QT Syndrome

	Control					Epinephrine				
Recording Site	%EAD Amp (%)	$MAPD_{90}$ (ms)	Dispersion of $MAPD_{90}$ (ms)	QT (ms)	Ventricular Arrhythmias	%EAD Amp (%)	$MAPD_{90}$ (ms)	Dispersion of $MAPD_{90}$ (ms)	QT (ms)	Ventricular Arrhythmias
Pt 1										
RV ant	—	330	35	380	—	+56%	360	70	450	—
RVOT	—	295				—	290			
Pt 2										
LV inf	+22%	420	80	490	—	+53%	485	135	530	VPCs
RV ant	—	340				—	350			
RV sep	—	365				—	350			
Pt 3										
RV ant	—	275	40	350	—	—	315	50	440	—
LV lat	—	315				—	365			
Pt 4										
LV lat	—	280	10	350	—	+14%	400	75	520	VPCs
RV sep	—	290				—	325			
Pt 5										
LV inf	—	375	40	430	—	+64%	435	70	480	—
RV ant	—	360				—	390			
RV sep	—	335				—	365			
RVOT	—	340				—	375			
Pt 6										
LV lat	—	325	20	380	—	—	345	20	440	—
RV ant	—	335				—	365			
RV sep	—	315				—	345			
Pt 7										
LV lat	—	410	35	490	—	—	410	55	520	VPCs TdP
RVOT	—	435				—	455			
RV sep	+53%	445				+78%	465			
Pt 8										
LV lat	—	375	30	430	—	—	400	40	480	—
RVOT	—	345				+56%	415			
RV apex	—	355				—	375			

%EAD Amp = percent early afterdepolarization amplitude; LV inf = left ventricular inferior wall; LV lat = left ventricular lateral wall; $MAPD_{90}$ = monophasic action potential duration at 90% repolarization; RV ant = right ventricular anterior wall; RV sep = right ventricular septum; RVOT = right ventricular outflow tract; VPCs = ventricular premature complexes; other abbreviations as in Table 1.

[both $p < 0.005$ vs. epinephrine] in patients with the long QT syndrome and control patients, respectively). The addition of propranolol had no further effect on systolic blood pressure in either patient group (116 ± 15 and 136 ± 17 mm Hg in patients with the long QT syndrome and control patients, respectively).

Early afterdepolarizations. *Patients with long QT syndrome (Table 2).* Before epinephrine infusion (control state), early afterdepolarizations were recorded in two of the eight patients with the long QT syndrome (2 of 22 recording sites) and were consistent with the late component of the T(U) wave. During constant atrial pacing (cycle length 600 ms), the mean percent early afterdepolarization amplitude was 38 ± 22% (two sites) (Fig. 1A). Epinephrine increased the percent early afterdepolarization amplitude to 66 ± 18% (two sites) in association with an increase in the amplitude of the late component of the T(U) wave (Fig. 1B). Epinephrine also induced new early afterdepolarizations in another four patients with the long QT syndrome (four recording sites). Therefore, early afterdepolarizations were recorded in six of eight patients with the long QT syndrome (6 of 22 recording sites) during epinephrine infusion (mean percent early afterdepolarization amplitude 54 ± 21%, (6 sites). Injection of verapamil during continuous epinephrine infusion eliminated early afterdepolarizations in two of six patients with the long QT syndrome (two of six recording sites) and reduced the percent early afterdepolarization amplitude slightly to 37 ± 23% in the remaining four (four recording sites) (Fig. 1C). Addition of propranolol during continuous epinephrine infusion eliminated early afterdepolarizations in two of the remaining four patients with the long QT syndrome (two of four recording sites) and reduced the percent early afterdepolarization amplitude to 24 ± 3% in the other two (two recording sites) (Fig. 1D).

Recordings of early afterdepolarizations were stable during the same protocol, and the shape and amplitude of early afterdepolarizations were constant during constant atrial pacing (constant RR interval) in patients with the long QT syndrome. Moreover, the amplitude of early afterdepolariza-

Verapamil During Epinephrine					Propranolol During Epinephrine				
%EAD Amp (%)	$MAPD_{90}$ (ms)	Dispersion of $MAPD_{90}$ (ms)	QT (ms)	Ventricular Arrhythmias	%EAD Amp (%)	$MAPD_{90}$ (ms)	Dispersion of $MAPD_{90}$ (ms)	QT (ms)	Ventricular Arrhythmias
+45%	350	60	450	—	+22%	335	50	390	—
—	290				—	285			
+38%	420	70	500	—	+26%	415	70	490	—
—	350				—	345			
—	350				—	350			
—	315	40	440	—	—	295	40	360	—
—	355				—	335			
+5%	365	40	500	VPCs	—	275	25	360	—
—	325				—	300			
+58%	410	65	460	—	—	390	55	450	—
—	380				—	370			
—	345				—	335			
—	355				—	335			
—	345	20	440	—	—	330	20	390	—
—	365				—	335			
—	345				—	315			
—	370	35	390	—	—	320	20	380	—
—	375				—	335			
—	340				—	340			
—	365	20	430	—	—	365	20	420	—
—	345				—	345			
—	355				—	355			

tions recorded in patients with the long QT syndrome was bradycardia dependent and increased after a long preceding RR interval after atrial pacing (Fig. 2). These characteristics of early afterdepolarizations were consistent with those of experimentally induced early afterdepolarizations.

Control patients. In contrast, no early afterdepolarizations were recorded during the entire protocol in any control patient.

Ventricular arrhythmias. No ventricular arrhythmias occurred during either sinus rhythm or constant atrial pacing in the control state in both patient groups (Fig. 3A).

Patients with long QT syndrome. Epinephrine induced ventricular premature complexes in three of eight patients with the long QT syndrome (Fig. 3B). In one of these three patients, ventricular premature complexes originated from the peak of early afterdepolarizations that were augmented by epinephrine, suggesting that these arrhythmias were closely related to the early afterdepolarizations (Fig. 3B). Moreover, in another of the three patients, epinephrine induced torsade de pointes (Fig. 4). Injection of verapamil during continuous epinephrine infusion abolished ventricular premature complexes in two of the three patients (Fig. 3C) and also suppressed subsequent torsade de pointes. Addition of propranolol during continuous epinephrine infusion abolished ventricular premature complexes in the remaining patient.

Control patients. In contrast, no ventricular arrhythmias were induced during the entire protocol in any control patient.

Ninety-percent monophasic action potential duration. The mean 90% monophasic action potential duration was significantly longer in patients with the long QT syndrome (22 sites) than in control patients (23 sites) during constant atrial pacing (cycle length 600 ms) in the control state (348 ± 48 vs. 246 ± 14 ms, $p < 0.0005$) (Fig. 5).

Patients with the long QT syndrome. In patients with the long QT syndrome, epinephrine prolonged the 90% monophasic action potential duration markedly to 381 ± 49 ms ($p < 0.0005$ vs. control state), whereas injection of verapamil during continuous epinephrine infusion shortened it to 355 ± 28 ms ($p < 0.01$ vs. epinephrine). Addition of propranolol during continuous epinephrine infusion slightly shortened it further to 337 ± 32 ms ($p = 0.09$ vs. verapamil) (Fig. 1 and 5A).

Control patients. In contrast, epinephrine prolonged the 90% monophasic action potential duration slightly to 250 ± 14 ms ($p < 0.05$ vs. control state) in the control patients;

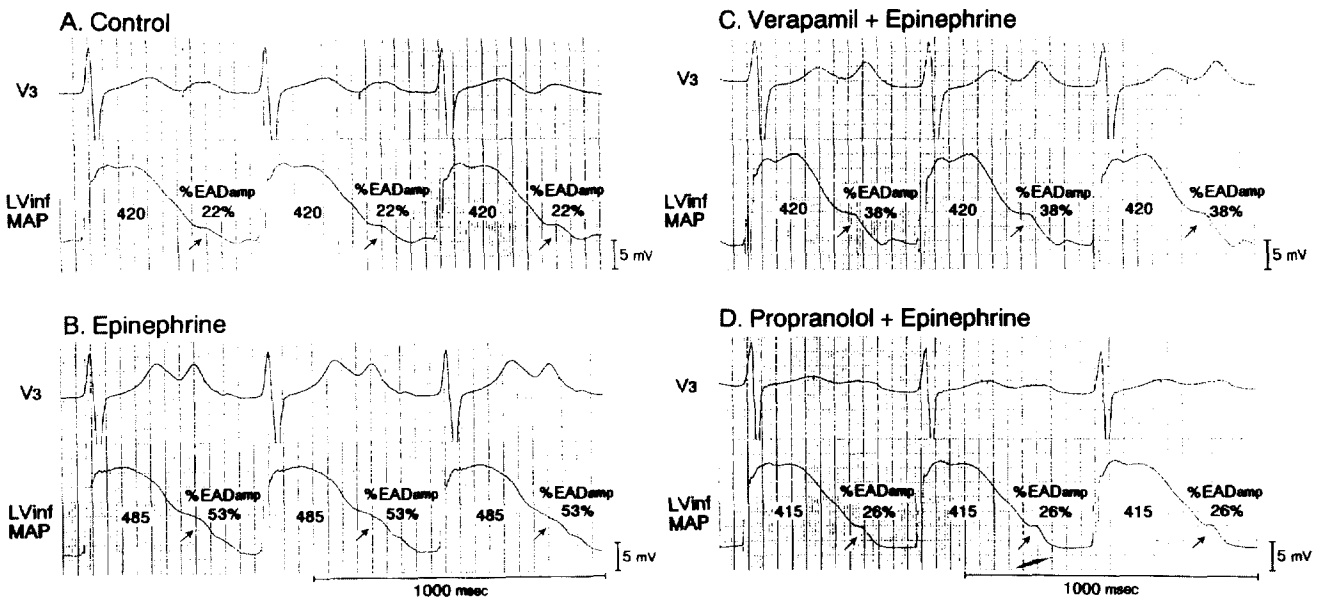

Figure 1. Recordings of monophasic action potentials during constant atrial pacing (cycle length 600 ms) before epinephrine infusion **(A)**; during epinephrine infusion (0.1 μg/kg per min) **(B)**; after verapamil injection (0.1 mg/kg) during epinephrine infusion **(C)**; and after propranolol injection (0.1 mg/kg) during epinephrine infusion **(D)** in Patient 2 with the long QT syndrome. Simultaneous recordings of electrocardiographic lead V_3 and the monophasic action potentials from the left ventricular inferior wall (LVinf MAP) are shown. In the control state, early afterdepolarizations were recorded **(arrows)** and were consistent with the late components of the T(U) wave in lead V_3 **(A)**. The amplitude of the early afterdepolarizations (%EADamp) was 22%, and the 90% monophasic action potential duration was 420 ms. Epinephrine increased the amplitude of early afterdepolarizations to 53% in association with an increased amplitude of the late component of the T(U) wave and prolonged the 90% monophasic action potential duration to 485 ms **(B)**. Verapamil injection during epinephrine infusion reduced the amplitude of early afterdepolarizations to 38% and shortened the 90% monophasic action potential duration to 420 ms **(C)**. Addition of propranolol during epinephrine infusion further reduced the amplitude of early afterdepolarizations to 26% and further shortened the 90% monophasic action potential duration to 415 ms **(D)**.

however, no change occurred after injection of verapamil and additional propranolol during continuous epinephrine infusion (verapamil 252 ± 13 ms, propranolol 251 ± 13 ms) (Fig. 5B).

Dispersion of 90% monophasic action potential duration. The mean dispersion of 90% monophasic action potential duration was significantly larger in the eight patients with the long QT syndrome than in the eight control patients during constant atrial pacing (cycle length 600 ms) in the control state (36 ± 20 vs. 18 ± 6 ms, $p < 0.05$) (Fig. 6).

Patients with long QT syndrome. In patients with the long QT syndrome, epinephrine increased the dispersion to 64 ± 34 ms ($p < 0.005$ vs. control state), whereas injection of verapamil during continuous epinephrine infusion decreased it to 44 ± 19 ms ($p < 0.05$ vs. epinephrine). Addition of propranolol during continuous epinephrine infusion did not change dispersion (38 ± 19 ms) (Fig. 6A).

Control patients. In contrast, dispersion of 90% monophasic action potential duration did not change during the entire protocol in the control patients (epinephrine 21 ± 7 ms, verapamil 20 ± 9 ms, propranolol 18 ± 9 ms) (Fig. 6B).

QT interval. The mean QT interval was significantly longer in the eight patients with the long QT syndrome than in the eight control patients during constant atrial pacing (cycle length 600 ms) in the control state (413 ± 57 vs. 318 ± 9 ms, $p < 0.0005$).

Patients with long QT syndrome. In patients with the long QT syndrome, epinephrine prolonged the QT interval markedly to 483 ± 37 ms ($p < 0.01$ vs. control state). Injection of verapamil during continuous epinephrine infusion shortened the QT interval to 451 ± 36 ms; but this difference was not statistically significant. Addition of propranolol during continuous epinephrine infusion further shortened it to 405 ± 46 ms. Although the difference between verapamil and propranolol was also not statistically significant, the difference between epinephrine and propranolol was significant ($p < 0.005$).

Control subjects. In contrast, epinephrine prolonged the QT interval slightly to 326 ± 5 ms ($p < 0.05$ vs. control state) in control patients. Injection of verapamil and additional propranolol during continuous epinephrine infusion did not change the QT interval (verapamil 328 ± 8 ms, propranolol 327 ± 7 ms).

Discussion

There were two major findings of the present study: 1) Epinephrine induced or augmented early afterdepolarizations, induced ventricular arrhythmias, prolonged markedly the 90% monophasic action potential duration and the QT interval and increased the dispersion of 90% monophasic action potential

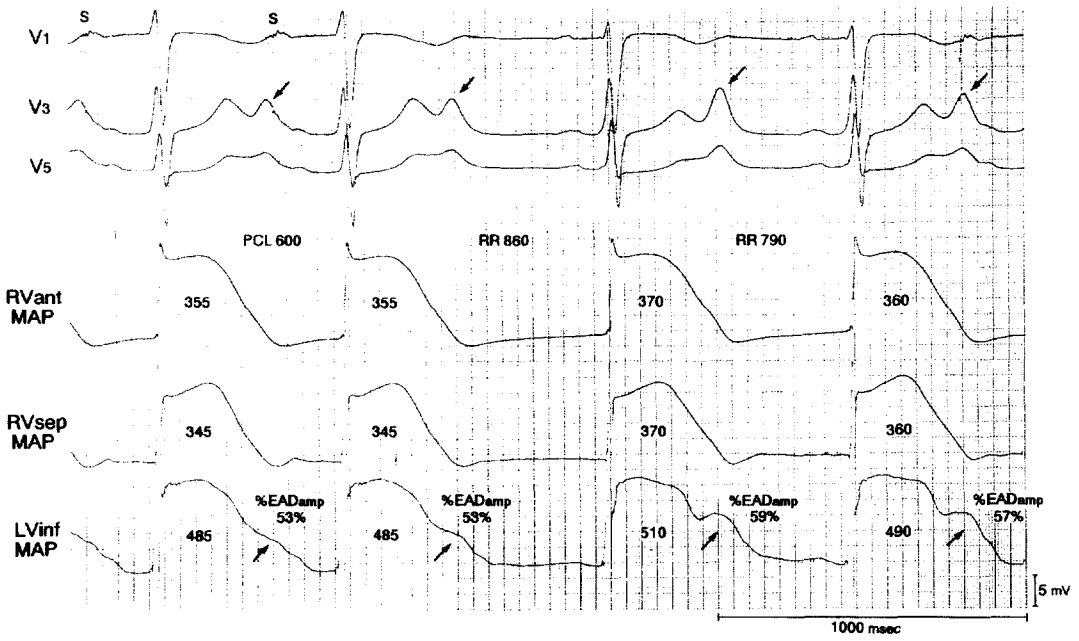

Figure 2. Simultaneous recordings of electrocardiographic leads V_1, V_3 and V_5 and the monophasic action potentials from the right ventricular anterior wall (RVant MAP), right ventricular septum (RVsep MAP) and left ventricular inferior wall (LVinf MAP) during epinephrine infusion (0.1 μg/kg per min) in Patient 2 with the long QT syndrome. Tracings show the last two beats of right atrial pacing (pacing cycle length [PCL] 600 ms) and the subsequent two sinus beats. Early afterdepolarizations were recorded in the left ventricular monophasic action potentials **(arrows)** and were consistent with the late components of the T(U) wave in lead V_3 **(arrows).** The amplitude of early afterdepolarizations (%EADamp) was 53% and the 90% monophasic action potential duration was 485 ms during atrial pacing. Note that the amplitude of early afterdepolarizations increased to 59%, and the 90% monophasic action potential duration was prolonged to 510 ms, after a long preceding RR interval (860 ms) after atrial pacing. S = atrial pacing stimulus.

duration in patients with congenital long QT syndrome. 2) Both verapamil and propranolol were effective in suppressing early afterdepolarizations and epinephrine-induced ventricular arrhythmias, in shortening the 90% monophasic action potential duration and the QT interval and in decreasing the dispersion of 90% monophasic action potential duration.

Role of catecholamines in early afterdepolarizations and ventricular arrhythmias in congenital long QT syndrome. Physical exertion and strong emotion are known to precipitate syncope and sudden death in patients with congenital long QT syndrome (28). In addition, exercise stress testing (29–31) or isoproterenol infusion (31,32) are reported to produce paradoxic prolongation of the QT interval and to occasionally precipitate torsade de pointes. Thus, sympathetic stimulation or catecholamines play an important role in the exaggeration of repolarization abnormalities in this syndrome.

Since Yanowitz et al. (33) demonstrated that left stellate ganglion stimulation and right stellate ganglion interruption prolonged the QT interval in dogs, the "sympathetic imbalance" hypothesis for congenital long QT syndrome has been proposed (28). However, experimental models based on intense stimulation of the left stellate ganglion and total interruption of the right ganglion do not produce QT prolongation and torsade de pointes as severe as those found in the clinical setting. Moreover, Calkins et al. (34) recently used positron emission tomography with carbon-11 hydroxyephedrine (HED) to demonstrate that patients with congenital long QT syndrome have a normal distribution and density of sympathetic nerve terminals.

Recently, several experimental models of long QT syndrome (1–7) and clinical studies using monophasic action potentials (8–12,16) have suggested that early afterdepolarizations and triggered activity were important in the genesis of QT prolongation and torsade de pointes in congenital long QT syndrome. Ben-David and Zipes (24) have demonstrated that ansae subclaviae stimulation or norepinephrine caused an increase in cesium-induced early afterdepolarizations and torsade de pointes in dogs. Shimizu et al. (11), using monophasic action potentials, found that isoproterenol induced early afterdepolarizations in four of six patients with congenital long QT syndrome.

In the present study, epinephrine induced or augmented early afterdepolarizations in six of eight patients with the long QT syndrome and significantly prolonged the 90% monophasic action potential duration and QT interval. Epinephrine also induced ventricular premature complexes in three of eight patients and torsade de pointes in one of these three. Moreover, the ventricular premature complexes were demonstrated to originate from the peak of the early afterdepolarizations, which were augmented by epinephrine in one of these three patients. By contrast, none of the early afterdepolarizations, ventricular arrhythmias or marked prolongation of the 90% monophasic action potential duration and QT interval were

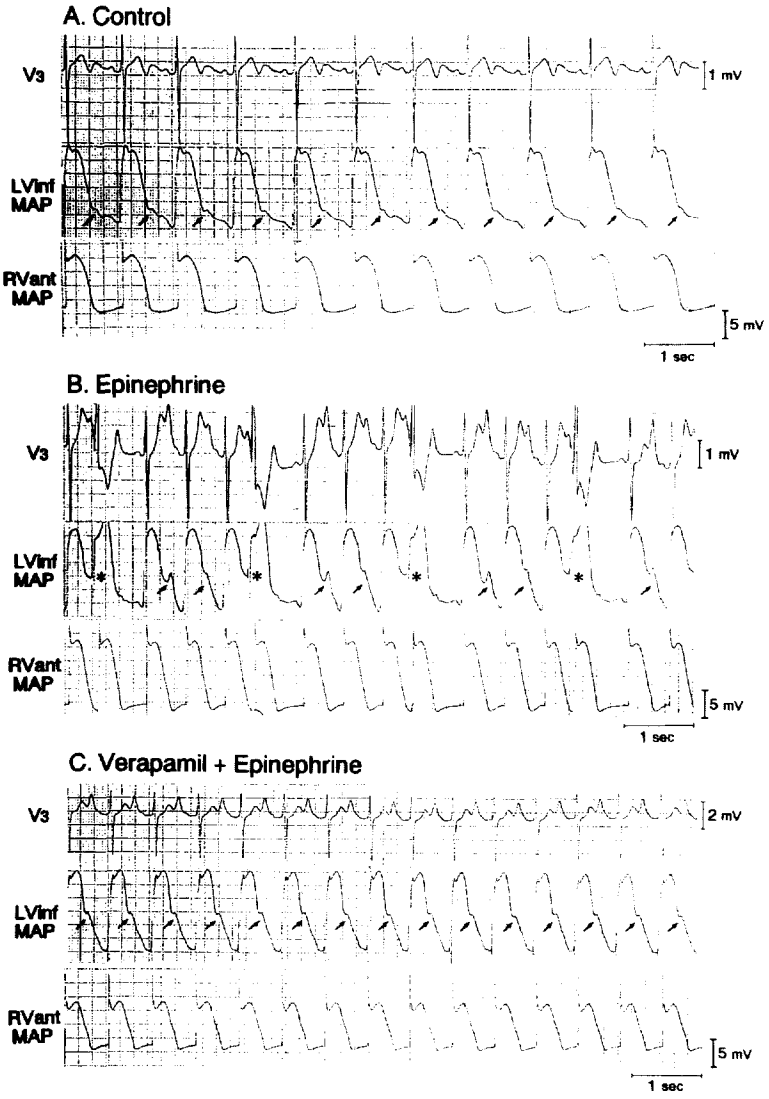

Figure 3. Recordings of ventricular premature complexes induced by epinephrine infusion (0.1 μg/kg per min) and the effect of verapamil injection (0.1 mg/kg) during epinephrine infusion on ventricular premature complexes in Patient 2 with the long QT syndrome. All tracings are from electrocardiographic lead V_3 and the monophasic action potential recordings from the left ventricular inferior (LVinf MAP) and right ventricular anterior walls (RVant MAP) during sinus rhythm. In the control state **(A)** there was no ventricular arrhythmia, although early afterdepolarizations were recorded in the left ventricular inferior wall monophasic action potentials **(arrows) (A).** Epinephrine increased the amplitude of early afterdepolarizations **(arrows)** and induced ventricular premature complexes that arose from the peak **(asterisk)** of the early afterdepolarizations, suggesting that the ventricular premature complexes were closely related to the early afterdepolarizations **(B).** Verapamil injection during epinephrine infusion abolished all ventricular premature complexes, although early afterdepolarizations were still present **(arrows) (C).**

induced by epinephrine in any control patient. These results suggest that catecholamines play a significant role in the generation of early afterdepolarizations and repolarization abnormalities and that early afterdepolarizations are closely linked to the initiating beats at least (ventricular premature complexes) of torsade de pointes in congenital long QT syndrome. However, the dispersion of 90% monophasic action potential duration was also increased by epinephrine in the patients with the long QT syndrome. Therefore, the possibility that torsade de pointes is perpetuated by a reentrant mechanism initiated by increased dispersion of repolarization cannot be excluded (35,36).

Cellular mechanism of early afterdepolarizations and effects of verapamil and propranolol in congenital long QT syndrome. There are several cellular mechanisms that are postulated to be critical in the generation of early afterdepolarizations in the long QT syndrome. These mechanisms include the sodium ion "window" or slowly inactivating current, potassium ion currents, calcium ion "window" current and the sodium/calcium exchange mechanism. Keating et al. (37) recently reported that the congenital long QT syndrome phenotype was tightly linked to the Harvey *ras*-1 gene on chromosome 11 in a large family. The Harvey *ras*-1 gene has been identified (38) and shown to have G protein functions, including signal transmitters in potassium ion channels. Therefore, Keating et al. (37,38) hypothesized that mutation of this gene in congenital long QT syndrome alters G protein function and impairs the delayed rectifier potassium ion current, causing prolongation of the action potential and QT interval (39).

However, January and co-workers (5,6), using voltage-clamped Purkinje fibers, suggested that the time- and voltage-dependent L-type calcium ion current within its "window" was important in the genesis of early afterdepolarizations after lengthening of the action potential plateau (conditioning phase). These investigators also demonstrated that calcium ion channel blockers (e.g., verapamil) directly suppressed the L-type calcium ion current and abolished early afterdepolarizations. Moreover, catecholamines are reported to enhance

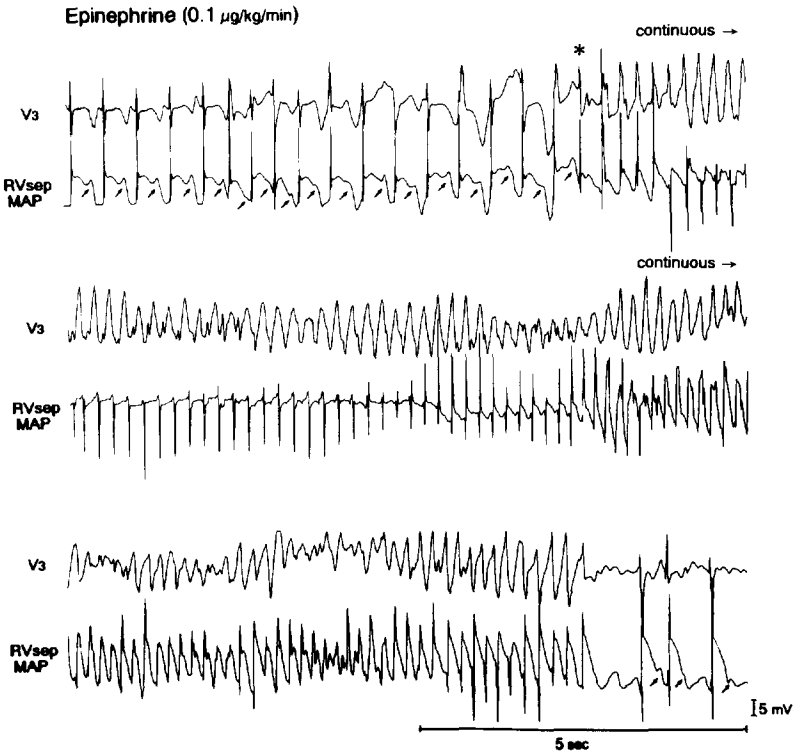

Figure 4. Torsade de pointes induced by epinephrine infusion (0.1 μg/kg per min) in Patient 7 with the long QT syndrome. Tracings are continuous recordings from electrocardiographic lead V_3 and the monophasic action potentials from the right ventricular septum (RVsep MAP) during sinus rhythm. Early afterdepolarizations were seen in the right ventricular monophasic action potentials **(arrows)**, and torsade de pointes was subsequently induced **(asterisk)**. Even after termination of torsade de pointes, the monophasic action potential recording was stable, and early afterdepolarizations were still present **(arrows)**.

the L-type calcium ion "window" current or calcium ion release from the sarcoplasmic reticulum and were shown to enhance early afterdepolarizations in several experimental studies (24,40). Therefore, propranolol (a beta-blocker) may suppress early afterdepolarizations as a result of interference with these pathways.

In the present study, both verapamil and propranolol abolished or suppressed both early afterdepolarizations and epinephrine-induced ventricular arrhythmias and also improved repolarization variables. In contrast, neither verapamil nor proranolol affected repolarization variables in any control patient. These findings are consistent with the results of experimental studies (5,6).

According to the results of the present study, patients with congenital long QT syndrome may have a primary myocardial abnormality (prolonged action potential duration) controlled by the sum of several membrane currents (e.g., congenital impairment of the potassium ion current), and catecholamines may induce early afterdepolarizations and ventricular arrhythmias as a result of an enhanced L-type calcium ion "window" current, so that both verapamil and propranolol effectively suppress early afterdepolarizations and ventricular arrhythmias.

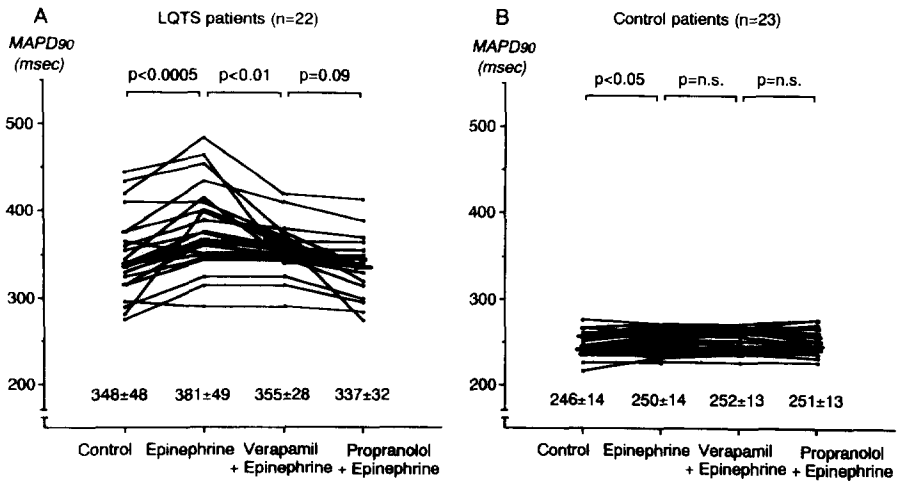

Figure 5. Plots of changes in the 90% monophasic action potential duration ($MAPD_{90}$) during constant atrial pacing (cycle length 600 ms) before epinephrine infusion (Control); during epinephrine infusion (0.1 μg/kg per min); after verapamil injection (0.1 mg/kg) during epinephrine infusion; and after propranolol injection (0.1 mg/kg) during epinephrine infusion in patients with congenital long QT syndrome (LQTS) (22 recording sites) **(A)** and control patients (23 recording sites) **(B)**.

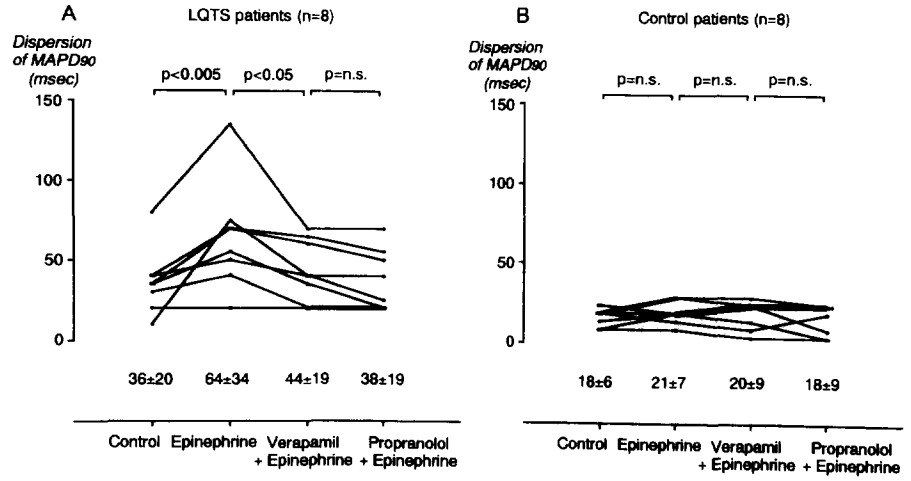

Figure 6. Plots of changes in the dispersion of 90% monophasic action potential duration (Dispersion of $MAPD_{90}$) during constant atrial pacing (cycle length 600 ms) before epinephrine infusion (Control); during epinephrine infusion (0.1 μg/kg per min); after verapamil injection (0.1 mg/kg) during epinephrine infusion; and after propranolol injection (0.1 mg/kg) during epinephrine infusion in eight patients with the congenital long QT syndrome (LQTS) (**A**) and eight control patients (**B**).

Limitations of the study. There are several limitations to the present study.

1. We cannot completely exclude the possibility that the "humps" we called early afterdepolarizations were recording artifacts. However, we assumed that they were not artifacts for the following reasons: a) all monophasic action potential recordings had a stable amplitude and configuration; b) changes in the early afterdepolarization amplitude were closely correlated with changes in the late component of the T(U) waves in patients with the long QT syndrome; c) the amplitude of early afterdepolarizations recorded in patients with the long QT syndrome was bradycardia dependent, and this characteristic is similar to that of experimentally induced early afterdepolarizations; and d) no early afterdepolarizations were recorded in any control patient.

2. Monophasic action potential recordings are reported to reflect the potential from both ventricular cells and Purkinje fibers. Sicouri and Antzelevitch (41) recently described the existence of M cells that exhibit electrophysiologic characteristics intermediate between those of ventricular cells and Purkinje fibers and have a markedly prolonged action potential duration in the canine ventricle. Therefore, it is possible that the monophasic action potential recordings may reflect the potential from such M cells with a prolonged action potential duration.

3. The monophasic action potential recordings were obtained simultaneously from only two to four sites in each patient. This small number of recording sites limits the calculation of dispersion of action potential duration across the entire ventricle, and more detailed monophasic action potential recordings are necessary to obtain a more precise dispersion value.

4. Although the effects of verapamil and additional propranolol were investigated during continuous epinephrine infusion, there were differences between responses with regard to sinus cycle length and systolic blood pressure to these drugs. Verapamil did not change the sinus cycle length despite its negative chronotropism. This finding may be due to the injection of verapamil during epinephrine infusion and also reflective of beta-adrenergic stimulation to the decreased systolic blood pressure. Additional propranolol prolonged the sinus cycle length as a result of its negative chronotropism and blocking of the circulating epinephrine. However, verapamil decreased systolic blood pressure as a result of its negatively inotropic effect. Additional propranolol during epinephrine infusion did not affect systolic blood pressure, probably because of residual alpha-adrenergic stimulation.

5. We could not evaluate the effect of propranolol alone but only the additive effect of propranolol to that of verapamil on early afterdepolarizations, ventricular arrhythmias and monophasic action potential duration. However, propranolol further improved repolarization abnormalities compared with verapamil alone. Therefore, we considered propranolol to be effective.

References

1. Brachmann J, Scherlag BJ, Rosenshtraukh LV, Lazzara R. Bradycardia-dependent triggered activity: relevance to drug-induced multiform ventricular tachycardia. Circulation 1983;68:846–56.
2. Levine JH, Spear JF, Guarnieri T, et al. Cesium chloride-induced long QT syndrome: demonstration of afterdepolarizations and triggered activity in vivo. Circulation 1985;72:1092–103.
3. Roden DM, Hoffman BF. Action potential prolongation and induction of abnormal automaticity by low quinidine concentrations in canine Purkinje fibers: relationship to potassium and cycle length. Circ Res 1985;56:857–67.
4. Davidenko JM, Cohen L, Goodrow R, Antzelevitch C. Quinidine-induced action potential prolongation, early afterdepolarizations, and triggered activity in canine Purkinje fibers: effects of stimulation rate, potassium, and magnesium. Circulation 1989;79:674–86.
5. January CT, Riddle JM, Salata JJ. A model for early afterdepolarizations: induction with the Ca^{2+} channel agonist Bay K 8644. Circ Res 1988;62:563–71.
6. January CT, Riddle JM. Early afterdepolarizations: mechanism of induction and block: a role for L-type Ca^{2+} current. Circ Res 1989;64:977–90.
7. El-Sherif N, Zeiler RH, Craelius W, Gough WB, Henkin R. QTU prolongation and polymorphic ventricular tachyarrhythmias due to bradycardia-dependent early afterdepolarizations: afterdepolarizations and ventricular arrhythmias. Circ Res 1988;63:286–305.

8. Gavrilescu S, Luca C. Right ventricular monophasic action potentials in patients with long QT syndrome. Br Heart J 1978;40:1014–8.
9. Bonatti V, Rolli A, Botti G. Recording of monophasic action potentials of the right ventricle in long QT syndromes complicated by severe ventricular arrhythmias. Eur Heart J 1983;4:168–79.
10. Jackman WM, Szabo B, Friday KJ, et al. Ventricular tachyarrhythmias related to early afterdepolarizations and triggered firing: relationship to QT interval prolongation and potential therapeutic role for calcium channel blocking agents. J Cardiovasc Electrophysiol 1990;1:170–95.
11. Shimizu W, Ohe T, Kurita T, et al. Early afterdepolarizations induced by isoproterenol in patients with congenital long QT syndrome. Circulation 1991;84:1915–23.
12. Shimizu W, Ohe T, Kurita T, Tokuda T, Shimomura K. Epinephrine-induced ventricular premature complexes due to early afterdepolarizations and effects of verapamil and propranolol in a patient with congenital long QT syndrome. J Cardiovasc Electrophysiol 1994;5:438–44.
13. El-Sherif N, Bekheit SS, Henkin R. Quinidine-induced long QTU interval and torsade de pointes: role of bradycardia-dependent early afterdepolarizations. J Am Coll Cardiol 1989;14:252–7.
14. Shimizu W, Tanaka K, Suenaga K, Wakamoto A. Bradycardia-dependent early afterdepolarizations in a patient with QTU prolongation and torsade de pointes in association with marked bradycardia and hypokalemia. PACE 1991;14:1105–111.
15. Kurita T, Ohe T, Shimizu W, Hotta D, Shimomura K. Early afterdepolarization in a patient with complete atrioventricular block and torsades de pointes. PACE 1993;13:33–8.
16. Zhou JT, Zheng LR, Liu WY, et al. Early afterdepolarizations in the familial long QTU syndrome. J Cardiovasc Electrophysiol 1992;3:431–6.
17. Krause PC, Rardon DP, Miles WM, et al. Characteristics of Ca^{2+}-activated K^+ channels isolated from the left ventricle of a patient with idiopathic long QT syndrome. Am Heart J 1993;126:1134–41.
18. Moss AJ, Schwartz PJ, Crampton RS, Locati E, Carleen E. Hereditable malignant arrhythmias: the long QT syndrome: a prospective international study. Circulation 1985;71:17–20.
19. Moss AJ, Schwartz PJ, Crampton RS, et al. The long QT syndrome: prospective longitudinal study of 328 families. Circulation 1991;84:1136–44.
20. Malfatto G, Rosen MR, Foresti A, Schwartz PJ: Idiopathic long QT syndrome exacerbated by beta-adrenergic blockade and responsive to left cardiac sympathetic denervation: implications regarding electrophysiologic substrate and adrenergic modulation. J Cardiovasc Electrophysiol 1992;3: 295–305.
21. Schwartz PJ, Moss AJ, Vincent GM, Crampton RS. Diagnostic criteria for the long QT syndrome: an update. Circulation 1993;88:782–4.
22. Franz MR. Long-term recording of monophasic action potentials from human endocardium. Am J Cardiol 1983;51:1629–34.
23. Franz MR, Chin MC, Sharkey HR, Griffin JC, Scheinman MM. A new single catheter technique for simultaneous measurement of action potential duration and refractory period in vivo. J Am Coll Cardiol 1990;16:878–86.
24. Ben-David J, Zipes DP. Differential response to right and left ansae subclaviae stimulation of early afterdepolarizations and ventricular tachycardia induced by cesium in dogs. Circulation 1988;78:1241–50.
25. Shimizu W, Tsuchioka Y, Karakawa S, et al. Differential effect of pharmacological autonomic blockade on some electrophysiological properties of the human ventricle and atrium. Br Heart J 1994;71:34–7.
26. Browne KF, Zipes DP, Heger JJ, Prystowsky EN. Influence of the autonomic nervous system on the Q-T interval in man. Am J Cardiol 1982;50:1099–103.
27. Franz MR, Swerdlow CD, Liem LB, Schaefer J. Cycle length dependence of human action potential duration in vivo: effects of single extrastimuli, sudden sustained rate acceleration and deceleration, and different steady-state frequencies. J Clin Invest 1988;82:972–9.
28. Schwartz PJ. Idiopathic long QT syndrome: progress and questions. Am Heart J 1985;109:399–411.
29. Vincent GM, Jaiswal D, Timothy KW. Effects of exercise on heart rate, QT, QTc and QT/QS2 in the Romano–Ward inherited long QT syndrome. Am J Cardiol 1991;68:498–503.
30. Eggeling T, Hoeher M, Osterhues HH, Weismueller P, Hombach V. Significance of noninvasive diagnostic techniques in patients with long QT syndrome. Am J Cardiol 1992;70:1421–6.
31. 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;14:1966–70.
32. Curtiss EI, Heibel RH, Shaver JA. Autonomic maneuvers in hereditary Q-T interval prolongation (Romano–Ward syndrome). Am Heart J 1978;95: 420–8.
33. Yanowitz F, Preston JB, Abildskov JA. Functional distribution of right and left stellate innervation of the ventricles: production of neurogenic electrocardiographic changes by unilateral alteration of sympathetic tone. Circ Res 1966;18:416–28.
34. Calkins H, Lehmann MH, Allman K, Wieland D, Schwaiger M. Scintigraphic pattern of regional cardiac sympathetic innervation in patients with familial long QT syndrome using positron emission tomography. Circulation 1993; 87:1616–21.
35. Priori SG, Napolitano C, Diehl L, Schwartz PJ: Dispersion of the QT interval: a marker of therapeutic efficacy in the idiopathic long QT syndrome. Circulation 1994;89:1681–9.
36. Shimizu W, Kamakura S, Ohe T, et al. Diagnostic value of recovery time measured by body surface mapping in patients with congenital long QT syndrome. Am J Cardiol 1994;74:780–5.
37. Keating M, Atkinson D, Dunn C, Timothy K, Vincent GM, Leppert M. Linkage of a cardiac arrhythmia, the long QT syndrome, and the Harvey ras-1 gene. Science 1991;252:704–6.
38. McCormick F. ras GTPase activation protein: signal transmitter and signal terminator. Cell 1989;56:5–8.
39. Vincent GM. Hypothesis for the molecular physiology of the Romano-Ward long QT syndrome. J Am Coll Cardiol 1992;20:500–3.
40. Priori SG, Corr PB. Mechanisms underlying early and delayed afterdepolarizations induced by catecholamines. Am J Physiol 1990;258:H1796–H805.
41. Sicouri S, Antzelevitch C. A subpopulation of cells with unique electrophysiological properties in the deep subepicardium of the canine ventricle. The M cell. Circ Res 1991;68:1729–41.