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Mode of Onset of Torsade de Pointes in Congenital Long QT Syndrome

SAMI VISKIN, MD,* SRINIVASA R. ALLA, MD, HAL V. BARRON, MD, KARIN HELLER, MD, LESLIE SAXON, MD, ILAN KITZIS, MD, GEORGE F. VAN HARE, MD, FACC, MARY J. WONG, MSN, MICHAEL D. LESH, MD, FACC, MELVIN M. SCHEINMAN, MD, FACC

San Francisco, California

Objectives. **We sought to describe the mode of onset of spontaneous torsade de pointes in the congenital long QT syndrome.**

Background. **Contemporary classifications of the long QT syndrome (LQTS) refer to the congenital LQTS as "adrenergic dependent" and to the acquired LQTS as "pause dependent." Overlap between these two categories has been recognized, and a subgroup of patients with "idiopathic pause-dependent torsade" has been described. However, it is not known how commonly torsade is preceded by pauses in the congenital LQTS.**

Methods. **We reviewed the electrocardiograms (ECGs) of all our patients with congenital LQTS evaluated for syncope or sudden death (30 patients). Documentation of the onset of torsade de pointes was available for 15 patients. All these patients had "definitive LQTS" by accepted clinical and ECG criteria.**

Results. **Pause-dependent torsade de pointes was clearly documented in 14 of the 15 patients (95% confidence interval 68% to 100%). The cycle length of the pause leading to torsade was 1.3 ± 0.2 times longer than the basic cycle length, and most pauses leading to torsade were unequivocally longer than the preceding basic cycle length (80% of pauses were >80 ms longer than the preceding cycle length).**

Conclusions. **The "long–short" sequence, which has been recognized as a hallmark of torsade de pointes in the acquired LQTS, plays a major role in the genesis of torsade in the congenital LQTS as well. Our findings have important therapeutic implications regarding the use of pacemakers for prevention of torsade in the congenital LQTS.**

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Torsade de pointes is a rapid polymorphic ventricular tachycardia that occurs in the setting of the long QT syndrome (LQTS) (1–3). Prolongation of the QT interval may be due to any of several inherited disorders (*congenital* LQTS) (4,5) or may be *acquired* (secondary to metabolic abnormalities, bradyarrhythmias or the use of drugs that prolong ventricular repolarization) (1).

Contemporary classifications of the LQTS refer to the congenital LQTS as "adrenergic dependent" and to the acquired LQTS as "pause dependent" (1,6,7). The rationale behind this grouping relates to 1) the long-recognized association between enhanced adrenergic (stressful) states and precipitation of symptoms in patients with the congenital LQTS (8); and 2) the mode of onset of torsade de pointes, which is invariably preceded by a relatively long cycle length (i.e., a pause) in the acquired LQTS (9,10). The possibility of overlap in the mode of tachycardia initiation has been recognized (1,2,6,11) since Jackman et al. (1) described a group of patients with "idiopathic pause-dependent torsade." However, the frequency of this phenomenon (i.e., the incidence of pause-dependent torsade in the congenital LQTS) is unknown. In fact, because of the sporadic nature of symptoms in patients with the congenital LQTS, the mode of onset of spontaneous torsade de pointes has not been defined in series of consecutive patients with congenital LQTS.

Methods

Patients. We reviewed the medical records of all our patients with congenital LQTS and a history of syncope or cardiac arrest (total 30 patients). The diagnosis of congenital LQTS was based on accepted clinical and electrocardiographic (ECG) criteria (5). Briefly, a patient receives points when predetermined clinical (i.e., history of cardiac arrest, syncope, documented familial LQTS) and ECG criteria (e.g., corrected QT interval [QTc] magnitude, QTU configuration) are present and a "high probability for LQTS" category is assigned to patients with a total score of four or more points (5). Data for some of the present patients have been reported in previous publications (12–15). Electrocardiographic documentation of

From the Section of Cardiac Electrophysiology, Department of Medicine and Cardiovascular Research Institute, University of California San Francisco, School of Medicine, San Francisco, California.

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Present address and address for correspondence: Dr. Sami Viskin, Department of Cardiology, Tel Aviv Medical Center, Weizman 6, Tel Aviv 64239, 209 Israel.

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Abbreviations and Acronyms

AV = atrioventricular
ECG = electrocardiogram, electrocardiographic
LQTS = long QT syndrome
QTc = corrected QT interval

the initiation of spontaneous torsade de pointes was available for the 15 patients who comprise the study group. These patients were comparable in age and gender to the remaining 15 patients with symptomatic congenital LQTS evaluated at our institution.

Definitions. *Torsade de pointes* was defined as a rapid (>170 beats/min) polymorphic ventricular tachycardia lasting >5 beats and was considered "sustained" when terminated by direct current shock. An episode of torsade was considered to be *pause dependent* when the ventricular tachyarrhythmia immediately followed a pause that was longer than the basic cycle length by 20 ms. The 20-ms value was chosen on the basis of reproducibility of our measurements in ECG traces at standard gain and speed (25 mm/s) using a magnifying glass. In point of fact, the vast majority of pauses observed were considerably longer (see later). A *cascade phenomenon* (10) was considered present when at least three consecutive long–short sequences with a progressive increment in the complexity of the ventricular arrhythmias preceded an episode of torsade.

Normally distributed data are presented as mean value ± SD. Differences between continuous variables were compared using the unpaired *t* test. Percentages were compared using the chi-square test. Statistical significance was defined as $p < 0.05$.

Results

Patient characteristics. Documentation of the onset of torsade de pointes was available for 15 patients (age 28 ± 19 years, range 0 to 61) with symptomatic LQTS (Fig. 1 to 3). Twelve (66%) patients were female; 8 (53%) had a history of stress-related symptomatology; and 14 (93%) had a history of cardiac arrest. Their mean QT and QTc intervals were 558 ± 64 and 589 ± 85 ms, respectively. Their QT score ranged from 4 to 6.5 (mean 5.2) points, indicating a "high probability of LQTS" for all patients in the study group (5). All patients but one had normal left ventricular function. The sole patient with left ventricular dysfunction was a 32-year old woman with dilated cardiomyopathy and normal coronary arteries who had recurrent documented torsade de pointes (invariably during emotional stress) and a strong family history of sudden cardiac death and LQTS. In addition, either mitral valve prolapse, coronary disease or hypertensive heart disease (all with normal left ventricular function) were present in three patients. The diagnosis of congenital LQTS was made years before the performance of the present study in all but one patient.

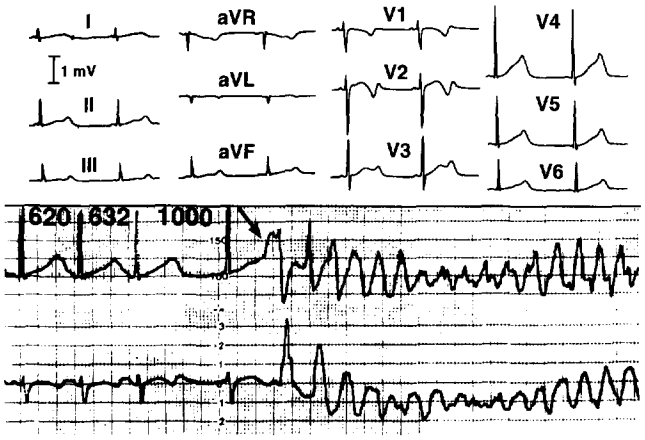

Figure 2. Electrocardiographic recordings from an 11-year old girl with congenital LQTS and recurrent syncope. **Top panel,** Twelve-lead rest ECG demonstrating biphasic and notched T waves. **Bottom panel,** Out of hospital Holter recording during a spontaneous syncopal episode triggered by sudden arousal and accompanied by seizures. The RR intervals during sinus rhythm are shown in ms. The sinus complex after the longest RR interval shows marked augmentation of TU wave amplitude (**arrow**) and is immediately followed by torsade de pointes.

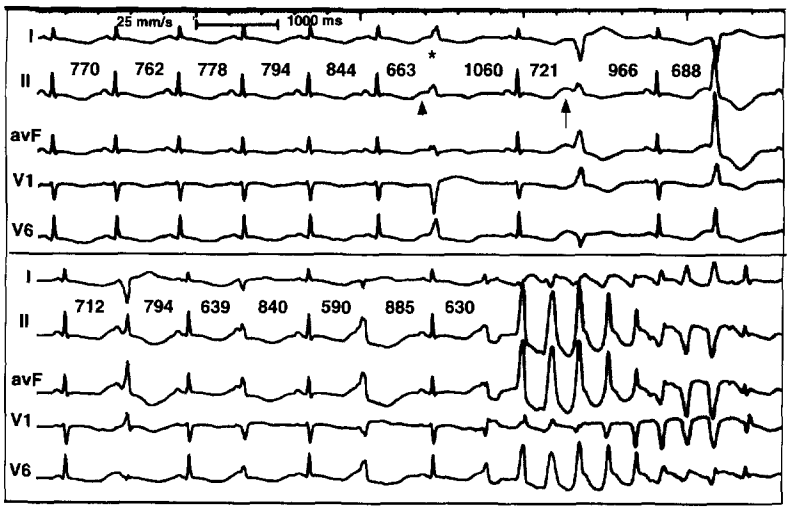

Figure 1. Electrocardiographic documentation of in-hospital initiation of torsade de pointes in a 31-year old woman with congenital LQTS. The RR intervals are shown in ms. **Top panel,** Progressive increment in RR interval due to sinus arrhythmia. The sixth sinus complex, which follows the longest RR interval (844 ms), has TU wave changes (**arrowhead**) from which the first premature ventricular complex originates (**asterisk**). A post-extrasystolic pause (1,060 ms) is followed by a sinus complex with marked post-extrasystolic augmentation in the TU wave complex (**arrow**). **Bottom panel,** Perpetuation of the long–short sequence by ventricular bigeminy, eventually leading to torsade de pointes. Top and bottom panels represent continuous recording.

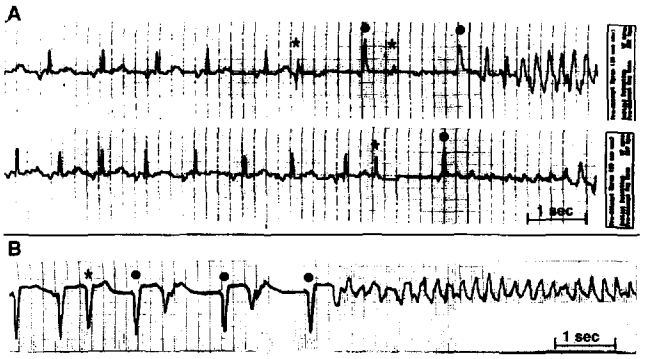

Figure 3. Examples of torsade de pointes in patients with ventricular pacemakers. **Panel A,** Two stored endocardial recordings from an automatic defibrillator implanted in a 32-year old woman with congenital LQTS, dilated cardiomyopathy and history of ventricular fibrillation. The patient reported two successive shocks during an altercation. Interrogation of the device revealed 12 recent arrhythmic events. The device settings included shock therapy for heart rate >190 beats/min and ventricular VVI pacing at 55 beats/min. **Top trace,** Five sinus complexes followed by a premature ventricular complex **(asterisks)**. The ensuing post-extrasystolic pause is terminated by a paced beat **(circles)**. A similar short–long sequence is followed by torsade. **Bottom trace,** Sinus rhythm (eight complexes) followed by a short–long sequence due to a premature ventricular complex **(asterisk)** and an escape paced beat **(circle)** leading to torsade. **Panel B,** In-hospital telemetry recordings of torsade de pointes in a 20-year old woman with implanted pacemaker for recurrent syncope despite beta-blockade. The first two complexes are probably fusion of conducted sinus beats and pacing (VVI pacing 75 beats/min). A premature ventricular complex **(asterisk)** initiates a series of short–long sequences; **circles** denote paced complexes. The RR interval between the last premature ventricular complexes and the following paced beats suggest either undersensing or late sensing of the last two premature beats. The first premature ventricular beat **(asterisk)** is sensed correctly.

All patients were in sinus rhythm before the onset of torsade. Five patients had pacemakers at the time of torsade documentation (Fig. 3): One patient, with recurrent syncope previously diagnosed as "sick sinus syndrome," had a permanent ventricular pacemaker (VVI mode); two had an implanted defibrillator with VVI pacing capabilities; one had a temporary pacer (AAI mode); and one had a permanent pacemaker (VVI mode) that was inserted in an attempt to prevent recurrent torsade. None of these five patients had evidence of atrioventricular (AV) conduction disturbances. In addition, one patient had functional 2:1 AV block (16) (see later). Hypokalemia was recorded in one patient and was ascribed to prolonged resuscitation (17). This patient had recurrent documented torsade after correction of electrolyte imbalance. Other causes for acquired QT prolongation (1) were not present in any patient. At the time of torsade documentation, one patient was receiving phenobarbital and diphenylhydantoin, one was receiving digoxin and nifedipine, and six were receiving beta-adrenergic blocking agents. Nine patients had documentation of the onset of torsade in the absence of drugs (including two of the six patients who also had torsade documentation during beta-blocker treatment).

Mode of onset of torsade de pointes. Pause-dependent torsade in the absence of AV block was clearly documented in 14 (93%) of the 15 patients (95% confidence interval 68% to 100%). These patients had 39 documented episodes (3 ± 2.3 episodes/patient). All 39 episodes of torsade de pointes were preceded by pauses, including 11 episodes eventually terminated by direct current shock and 28 episodes that terminated spontaneously after 1.4 to 36 s. The nature of the pauses leading to torsade de pointes varied among episodes. The first identified pause was related to sinus arrhythmia or sinus pause, at least once, in four patients. Generally, a long cycle due to sinus arrhythmia initiated a series of long–short sequences in the form of ventricular bigeminy until an episode of torsade followed a pause (Fig. 1). However, in one patient, the sinus beat following a single pause related to sinus arrhythmia had marked postpause QTU changes and was immediately followed by torsade de pointes (Fig. 2). In five patients the first identified rhythm disturbance was a premature complex (atrial premature complex in one patient, ventricular premature complex in four). This premature ventricular complex led to a post-extrasystolic pause that started a series of long–short sequences culminating in torsade de pointes. In the remaining patients, torsade de pointes was also pause dependent and followed a series of long–short sequences related to premature ventricular complexes. However, the rhythm disturbance leading to the first pause could not be identified because all available traces preceding the onset of torsade showed ventricular bigeminy. The "cascade phenomenon" was observed in 9 of the 15 patients.

The only patient in whom torsade was not consistently pause dependent was a baby girl with LQTS diagnosed at the time of birth. In this patient (who has been described in detail elsewhere [12]), functional 2:1 AV block would occur after a premature ventricular complex. This functional AV conduction block probably happened when the relatively rapid sinus rate encroached on the ventricular refractoriness, which had increased due to the post-extrasystolic pause (12). This 2:1 AV conduction pattern was further complicated by ectopic ventricular bigeminy and multiple episodes of torsade. This patient was the only one in whom the post-extrasystolic pause (the "long cycle") was not always clearly longer than the coupling interval of the premature ventricular complex (the "short cycle"). However, this finding could be related to the difficulty in determining the QRS onset of the premature beat originating from the large U wave of the post-extrasystolic beat. Of note, 2:1 AV block invariably preceded the torsade episodes, and DDD atrioventricular pacing was dramatically beneficial in this patient (12).

The basic RR interval (before any cycle length disturbance) in the 14 patients with pause-induced torsade was 830 ± 67 ms (range 640 to 960), which is equivalent to a heart rate of 74 ± 7 beats/min (range 62 to 94). The coupling interval of the premature beats (short cycle) initiating short–long sequences was 584 ± 88 ms (range 440 to 720, $p < 0.01$ vs. basic cycle length). Finally, the mean RR interval of the pauses leading to increased ventricular ectopic beats culminating in torsade de pointes was 1,068 ± 206 ms (range 760 to 1,560 ms, $p < 0.01$ vs. basic cycle length). The great majority of documented pauses leading to torsade were unequivocally longer than the

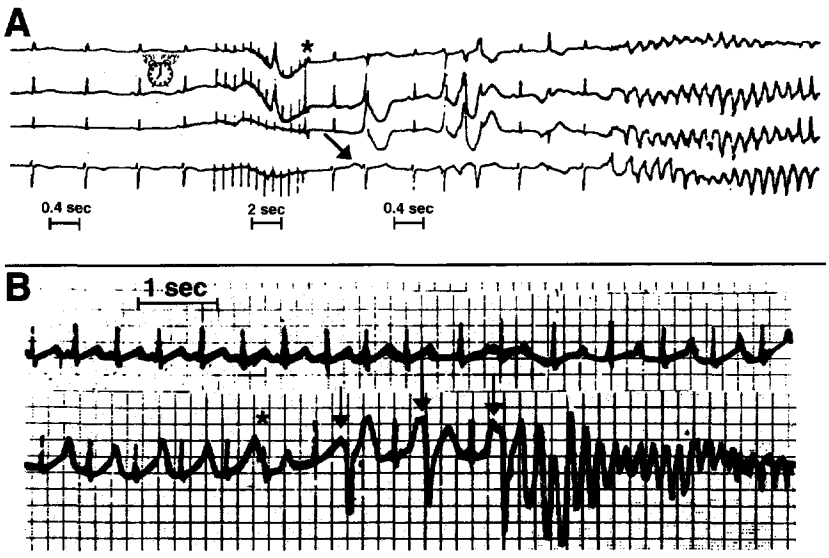

Figure 4. Two examples of adrenergic-mediated (also pause dependent) torsade from published English-language reports. **Panel A,** Initiation of torsade in a 18-year old woman by an auditory stimulus **(alarm clock),** as reported by Wellens et al. (33). Although the paper speed was changed at the time of the actual recording, it can be appreciated that a premature ventricular complex **(asterisk)** leads to marked post-extrasystolic TU changes **(arrow)** and begins a series of long–short sequences eventually culminating in torsade. **Panel B,** Traces from a 3-year old boy with congenital LQTS and onset of symptoms at 20 months of age. At the time of this report by Garza et al. (23), the child had anoxic brain damage after prolonged resuscitation from ventricular fibrillation. This tracing was recorded after intravenous injection of epinephrine (5 μg/kg body weight). After epinephrine administration, there is a marked increase in U wave amplitude. Eventually, a premature ventricular complex **(asterisk)** begins a series of long–short sequences culminating in torsade. Note the marked post-extrasystolic TU changes **(arrows).** Reprinted with permission.

preceding basic cycle length: 96%, 90% and 80% of pauses were >40, >65 and >80 ms longer than the preceding cycle length, respectively. On average, the cycle length of the pause (long cycle) leading to torsade was 1.3 ± 0.2 times longer than the basic cycle length.

Discussion

The long–short sequence has been recognized as a hallmark of torsade de pointes in the acquired LQTS (1,2,6,7,18). However, our study shows that the long–short sequence plays an important role in the genesis of torsade in patients with the congenital LQTS as well. Moreover, review of the published reports in English reveals that in 16 (80%) of the 20 published illustrations of torsade in patients with congenital LQTS, torsade de pointes is preceded by a pause (Fig. 4, Table 1) (3,19–36).

In pause-dependent torsade, an escalating sequence of events, referred to as the cascade phenomenon, has been well described (10): 1) A premature depolarization generates a post-extrasystolic pause; 2) the sinus complex that follows the pause shows marked post-extrasystolic TU changes from which a subsequent ventricular extrasystole originates; 3) this extrasystole generates a new pause, which in turn is followed by more bizarre TU changes from which progressively longer and faster runs of polymorphic ventricular tachycardia originate. Clinical and experimental data (1,7) suggest that the bizarre post-extrasystolic TU changes are the ECG representation of early afterdepolarizations and that the postpause ventricular extrasystoles, including those initiating torsade de pointes, originate when the early afterdepolarizations are sufficiently large to depolarize the cell membrane. However, these observations were made mainly in relation to acquired forms of LQTS, secondary to antiarrhythmic drug therapy or bradyarrhythmias, or both (37–39). In contrast, recording of early afterdepolarizations in patients with the congenital LQTS has been accomplished mainly after isoproterenol or epinephrine infusion (31,40). Nevertheless, augmentation of early afterdepolarizations after postpacing or post-extrasystolic pauses has been documented in patients with congenital LQTS as well (1,31). Also, patients with congenital LQTS exhibit an exaggerated delay in repolarization at long RR cycle lengths (41). On the basis of these observations and our study results, it is plausible that the described association between episodes of torsade and increased catecholamine states in the congenital LQTS is the result of several synergistic mechanisms: 1) Adrenergic stimulation increases the action potential duration (40,42) as well as the dispersion of ventricular refractoriness (40,42) and facilitates the formation of early afterdepolarizations to trigger ventricular ectopic beats (40,43). 2) The premature ventricular complexes thus created, generate post-extrasystolic pauses that lead to further repolarization delay (41) and more dispersion of refractoriness (44). 3) Although the longer RR intervals of the post-extrasystolic pauses further promote the onset of triggered activity, heightened sympathetic tone facilitates conduction of these early afterdepolarizations from their site of origin to the surrounding myocardium to initiate torsade de pointes (7,45). Although adrenergic-mediated early afterdepolarizations could lead directly to the initiation of torsade de pointes, especially in cases of excessive QT prolongation or circumstances of extreme stress, our data suggest that this is the exception rather than the rule. In most cases, a long–short sequence appears to be necessary for the initiation of torsade de pointes in the congenital LQTS. Whether continuation of this polymorphic ventricular tachyarrhythmia is the result of multiple triggered waves or reentry is still under debate (1,6,7).

Table 1. Mode of Onset of Torsade de Pointes in Patients With Congenital Long QT Syndrome Reported by Others

Study*	Fig.	Pt Age (yr)†/ Gender	Mode of Onset		Nature of Pause‡
			Stress	Drug†	
James, 1967 (21)	8a,b	33/F§			SS, P/E
van Bruggen, 1969 (22)	2	8/F§			P/E
Garza, 1970 (23)	5	3/M	+	E	P/E
	9	3/M	+	E + Ph	—
	12	3/M	NR	NR	P/E
Ratshin, 1971 (24)	1	29/F	+		SS
Jervell, 1971 (25)	3	1/F§	−		—
Wellens, 1972 (33)	1	18/F	+		P/E
Bashour, 1973 (34)	2	36/F	+		P/E
Crawford, 1975 (20)	2	13/F		DH	P/E
Roy, 1976 (19)	3b	7/F	+ (EST)		—
Curtiss, 1978 (26)	2	43/F			P/E
Hartzler, 1981 (27)	2	7?M§	−	H	—
Fontaine, 1982 (3)	6	§			P/E
Medina-Ravell, 1983 (32)	6	13/M			P/E
Coumel, 1985 (28)	8c	18/M			SS, P/E
	12	18/F	+		P/E
Wilmer, 1987 (30)	1	23/F	+	BB	P/E
Eggeling, 1992 (29)	3	22/F			P/E
Zhou, 1992 (31)	1	17/F	+		SS

*Last name of first author, date (reference number). Reports of patients with congenital LQTS in whom the onset of torsade is shown; cases of congenital LQTS treated with potentially arrhythmogenic drugs (35) or with AV block (36) are not included. †At time of torsade documentation. ‡ Mechanism of pauses in long–short sequence leading to torsade de pointes. §Patient (Pt) with congenital deafness. BB = beta-blockers; DH = diphenylhydantoin; E = epinephrine; EST = exercise stress test; F = female; Fig. = figure number in the original article; H = emergence from anesthesia with halothane; L = lidocaine; NR = not recorded; P/E = post-extrasystolic pause; Ph = phentolamine; SS = sinus slowing (sinus arrhythmia or sinoatrial block); — = no evident pause.

Study limitations. This retrospective descriptive analysis may have inherent biases and therefore may not be representative of the population of patients with congenital LQTS at large: 1) Although the mean age of our study group was not different from the age of the remaining patients with symptomatic congenital LQTS seen at our institution, our patients were older (at the time of torsade documentation) than the "typical" patient in large series of patients with congenital LQTS (46). 2) Electrocardiographic documentation of the onset of torsade is more likely for patients with recurrent and more severe symptoms. In addition, recent data suggest that patients with different LQTS genotypes may have different ECG characteristics at rest and in response to stress (47,48). Because data on the genotype of our patients was not available, it is possible that our findings do not apply to all the subpopulations of patients with congenital LQTS. However, review of published reports in English reveals that in the majority of case reports in which the initiation of torsade de pointes is shown, torsade follows a long–short cycle (Table 1, Fig. 4). Our patients were from 15 different families, and it is unlikely that all our patients, as well as the patients included in Table 1, fortuitously have the same genotype.

Clinical implications. Permanent pacing, in conjunction with beta-blocker treatment, has become an accepted mode of therapy for patients with the congenital LQTS (14,15,49,50). Originally, pacemakers were used to treat the symptomatic bradyarrhythmias that occur spontaneously or after beta-blocker use in young patients with the congenital LQTS (19,20). More recent evidence suggests that even in the absence of bradyarrhythmias, permanent pacing may decrease the frequency of symptoms when other modes of therapy have failed (14,15,49). Shortening of the QT interval with permanent pacing at faster rates has been proposed as a possible mechanism of the beneficial effects observed with long-term pacing (14). Although the QTc interval remains prolonged in the majority of patients during pacing (49), data on drug-induced torsade suggest that the actual (uncorrected) QT interval may be a better predictor of pause-induced torsade than the QTc interval (51). Nevertheless, recurrent syncope and sudden death have been reported (49,50) in some patients with combined beta-blocker and pacemaker therapy. The main goal of pacemaker therapy in the congenital LQTS may be the prevention of pauses that facilitate the onset of torsade. One way of achieving this goal may be to increase the programmed pacing rate. In our study, the minimal cycle length of pauses leading to torsade (excluding the infant in our series) was 760 ms. Accordingly, 80 beats/min should probably be viewed as the minimal pacing rate. However, the optimal pacing rate remains to be defined. More rapid pacing rates will shorten post-extrasystolic pauses with the potential for reducing the

risk of pause-induced torsade. However, rapid pacing will reduce pacemaker longevity, an important consideration in view of the relatively young age of most patients with congenital LQTS. Furthermore, the potential detrimental effects on left ventricular function of years of overdrive pacing at fast rates are unknown. This uncertainty stems from the fact that the minimal pacing rate that could result in tachycardia-induced cardiomyopathy (52) is unknown. The pacing rates that have been shown to be effective in the short-term prevention of drug-induced pause-dependent torsade (100 to 140 beats/min) (53) are too fast to be of practical use for the long-term management of patients with congenital LQTS.

An alternative method for preventing pause-induced torsade involves using pacing algorithms specifically designed for pause prevention. The technical capability for recognition of premature complexes is a feature present in several pacemakers (54,55). An algorithm that responds to such sensed premature events with an immediate transient increase in pacing rate could prevent post-extrasystolic pauses, which appeared to be instrumental in the induction of the vast majority of torsade episodes. To prevent postpacing pauses, this algorithm must include a gradual decrease in pacing rate to the programmed low rate (54,55). Finally, our study also has important implications for patients with congenital LQTS treated with implantable cardioverter-defibrillators. Although such devices are almost invariably effective in terminating rapid ventricular arrhythmias, any pause after the device shock and the emotional stress caused by the discharge could place patients with congenital LQTS at increased risk for immediate recurrence of torsade, potentially leading to multiple shocks (56). Thus, it seems prudent to recommend programming of the postshock pacing rate at a relatively rapid rate.

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