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Auditory Stimuli as a Trigger for Arrhythmic Events Differentiate HERG-Related ($LQTS_2$) Patients From KVLQT1-Related Patients ($LQTS_1$)

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OBJECTIVE This study was performed to identify a possible relationship between genotype and phenotype in the congenital familial long QT syndrome (cLQTS).

BACKGROUND The cLQTS, which occurs as an autosomal dominant or recessive trait, is characterized by QT-interval prolongation on the electrocardiogram and torsade de pointes arrhythmias, which may give rise to recurrent syncope or sudden cardiac death. Precipitators for cardiac events are exercise or emotion and occasionally acoustic stimuli.

METHODS The trigger for cardiac events (syncope, documented cardiac arrhythmias, sudden cardiac death) was analyzed in 11 families with a familial LQTS and a determined genotype.

RESULTS The families were subdivided in KVLQT1-related families ($LQTS_1$, n = 5) and HERG (human ether-a-gogo-related gene)-related families ($LQTS_2$, n = 6) based on single-strand conformation polymorphism analysis and sequencing. Whereas exercise-related cardiac events dominate the clinical picture of $LQTS_1$ patients, auditory stimuli as a trigger for arrhythmic events were only seen in $LQTS_2$ patients.

CONCLUSIONS Arrhythmic events triggered by auditory stimuli may differentiate $LQTS_2$ from $LQTS_1$ patients. (J Am Coll Cardiol 1999;33:327–32) © 1999 by the American College of Cardiology

The congenital familial long QT syndrome (cLQTS), which can occur as an autosomal dominant or recessive trait, is characterized by QT-interval prolongation on the electrocardiogram (ECG) and polymorphic ventricular arrhythmias (torsade de pointes). Torsade de pointes, syncope or sudden death usually occurs in relation to exercise or emotion, but occasionally also acoustic stimuli have been reported to elicit torsade de pointes (1–3). Based on linkage analysis, cLQTS is a genetically heterogeneous disease. Five loci have been identified (4–9). As LQTS families have been described that are not linked to these loci, additional loci must exist. Four genes have been identified: all these genes encode proteins that form (part of) ion channels (10,11). On chromosome 11p15.5 the gene KVLQT1 (or in the novel nomenclature KCNQ1) is located that encodes I_{Ks}, the slowly activating component of the delayed rectifier ($LQTS_1$; 4,8). On 7q35-36 HERG (human ether-a-gogo-related gene) resides encoding I_{Kr}, the rapidly activating delayed rectifier ($LQTS_2$; 5) and on 21q21.1-22.2 the KCNE gene is located whose product co-assembles with that of KVLQT1 to form the I_{Ks} channel ($LQTS_5$; 9). On chromosome 3p21-24 the gene for the Na^+ channel α-subunit, SCN5A involved in $LQTS_3$, is found (6). Mutations in these genes result in abnormal prolonged repolarization, either by diminishing the repolarizing outward K^+ currents or by an increase in the plateau inward (Na^+-) current (10,11).

As ion channels have different time and voltage characteristics, the ECG-phenotype may be indicative for the gene involved. In particular, the late-appearing T-wave preceded by a long isoelectric segment in $LQTS_3$ patients can be distinguished (12). The ECGs of HERG-related $LQTS_2$ patients are characterized by low-amplitude T-waves in the extremity leads (12,13). In addition, preliminary data from the LQT international registry demonstrate that the precipitator for arrhythmic episodes may also be genotype-specific (14). Exercise-related events seem to dominate the

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Abbreviations and Acronyms

cLQTS = congenital long QT syndrome
EAD = early afterdepolarization
ECG = electrocardiogram
HERG = human ether-a-gogo-related gene
PCR = polymerase chain reaction
SCD = sudden cardiac death
SSCP = single-strand conformation polymorphism

clinical picture in $LQTS_1$ (14). In contrast, cardiac events during sleep predominantly occur in $LQTS_3$ and are very rare in $LQTS_1$ (14,15). The $LQTS_2$ patients display a mixed pattern of triggers for arrhythmic events (14). Acoustic stimuli have not separately been implied in these analyses. It is feasible that these clinical features correlate with the characteristics of the ionic currents affected.

In this study we analyzed the trigger for cardiac events (syncope, documented cardiac arrhythmias, sudden cardiac death [SCD]) in 11 families with a familial LQTS and a confirmed genotype. Whereas exercise-related cardiac events dominate the clinical picture of $LQTS_1$ patients, auditory stimuli as a trigger for arrhythmic events were only found in $LQTS_2$ patients. Hence, auditory stimuli may differentiate $LQTS_2$ from $LQTS_1$ patients.

METHODS

Patients. The study was performed according to a protocol approved by the local ethics committee. Informed consent was obtained from all patients. All families came to our attention after unexpected cardiac death at a relatively young age (<40 years) in one or more family members. Both ECGs and peripheral blood samples for genotype analysis were obtained from all symptomatic individuals and from as many family members as possible. In all symptomatic patients cardiac evaluation revealed prolonged QT-intervals, and Romano-Ward syndrome was diagnosed because of normal hearing. Individuals with a positive genotype (see below) and individuals within these families who died suddenly and unexpectedly under the age of 40 years were defined as LQT patients (no ECGs were available in any of these patients)

The trigger for eventual cardiac events (syncope, documented cardiac arrhythmias, SCD) was analyzed in all individuals. Triggers were subdivided into three categories: 1) (physical) exercise; 2) stress, emotion and anger; and 3) auditory stimuli (alarm clock, telephone ring, ambulance siren, and others).

Genotype analysis. Genomic DNA was extracted from peripheral blood lymphocytes by a high-salt extraction method (16). Genomic fragments coding for the S1–S6 transmembrane domains (including the pore region) of the KVLQT1 gene (8) and the S1–S6 domains of HERG, including the pore and putative nucleotide binding domain, were amplified (5) on a Perkin-Elmer 9600 PCR (polymerase chain reaction) thermal cycler in the presence of 100 ng forward and reverse primers, 0.2 mmol/liter deoxyribonucleotide, 1 U Taq DNA polymerase (Gibco/BRL), 1.5 mmol/liter $MgCl_2$ and 100 ng genomic DNA (volume 50 μl). Subsequently, PCR fragments were screened for single-strand conformation polymorphism (SSCP) variants using the GenePhor system (Pharmacia) and GeneGel Excell gels 12.5/24. Gels were run at 10°C using manufacturer's standard conditions. The gels were silver-stained (Pharmacia PlusOne kit using an automatic stainer) and air-dried.

Amplified products with aberrant SSCP bands were purified with PCR purification kit (Qiagen). The purified fragments were sequenced in both directions using the amplification primers. They were analyzed on a ABI-377 automatic sequencer (Perkin-Elmer) using Dye Terminator Cycle sequencing kit (Perkin-Elmer). For a detailed description of the methods employed, see Van den Berg et al. (17).

Statistical analysis. The presence of a specific trigger between the two groups of patients was compared by the Fischer exact test. Values of $p < 0.05$ were considered significant.

RESULTS

Out of the 18 families controlled in our centers, the genotype could be determined in 11. This analysis revealed five KVLQT1-related families (16 male and 26 female gene carriers; mutations identified Y184S, G189R in two families with a confounder in ±1780, R130C and G345R) and six HERG-related families (8 male and 15 female gene carriers; mutations identified: A558P, R582C in two apparently unrelated families, G604S, T613M and F640L). The precipitator for syncope was evaluated in these genotyped families (Table 1). In 9 out of 15 symptomatic gene carriers in all six HERG-based families, acoustic stimuli were related to syncope. Although common, these auditory stimuli were not exclusively related to arousal. Figure 1 shows one of the episodes, triggered by an alarm clock. The arrhythmia is preceded by a "long–short" sequence based on ventricular extrasystoles. Five individuals in these HERG-related families died during sleep, one directly preceded by an acoustic stimulus and four without a known trigger (from one of them it was told that she could faint upon hearing the doorbell).

In contrast to HERG-related patients, none of the 23 symptomatic carriers of a mutated KVLQT1 gene reported syncope related to auditory stimuli ($p < 0.0001$). Instead, in $LQTS_1$ patients, exercise was the predominant trigger ($p < 0.0002$) and directly related to SCD in three young individuals (Table 1).

In one of the HERG families (genotype A558P) acoustic stimuli triggered loss of consciousness in three first-degree relatives; one of them died suddenly at the age of 22 upon

Table 1. Precipitator of Cardiac Events in Symptomatic $LQTS_1$ and $LQTS_2$ Carriers

	Exercise	Stress-Emotion, Anger	Acoustic	Unknown
KVLQT1 ($LQTS_1$)				
n = 23	18	9	0	2
(5 families)	78%	39%	0%	9%
HERG ($LQTS_2$)				
n = 15	2	3	9	4
(6 families)	13%	20%	60%	27%

Precipitator of syncope as derived from the patients' history. Exercise relates to physical exercise. In one individual, more triggers and/or more than one type of acoustic stimulus might be present. Male-to-female ratio was 9/14 in KVLQT1 carriers and 4/11 in HERG carriers. The precipitator is unknown in six patients. Six $LQTS_2$ patients died suddenly, five of them during sleep (see text). Three young $LQTS_1$ patients died suddenly while exercising. Note that acoustic stimuli (in five patients an alarm clock, in five the doorbell, in three the telephone, and in one an ambulance siren) are only reported by $LQTS_2$ patients ($p < 0.0001$) and that exercise-related events predominantly occur in $LQTS_1$ patients ($p < 0.0002$).

arousal from sleep by an alarm clock. Figure 2 shows the onset of a rapid polymorphic ventricular arrhythmia shortly after arousal by an alarm clock in one of these individuals. Prior to the onset of the arrhythmia a slight increase in heart rate was noted. The quality of the registration does not allow careful description of the T-wave morphology or duration measurement. The arrhythmia degenerated into ventricular fibrillation (VF) and the patient could be successfully defibrillated.

Figure 3 shows recordings (lead II, V2 and V5) of these three sibs (III-2, -3 and -4) and their father (II-5). No ECG had been recorded from the deceased patient. Markedly prolonged, terminally negative T-waves in the precordial leads were observed in patients III-2 and III-4. Individual III-3 and all other family members (not shown) were asymptomatic, and QT-intervals were all within normal range. Without exception, affected individuals met the criteria of a high probability for LQTS (18).

Treatment with beta-blockers was installed in 10 $LQTS_2$ patients and was successful in 8. Two patients developed torsades de pointes after many years (>10 years) of successful treatment (while being heavily symptomatic before treatment was installed). Seven (asymptomatic) patients were not treated at all. Fourteen $LQTS_1$ patients were treated with beta-blockers, and in all of them treatment has thus far been successful; 24 patients were not treated (or refused treatment). One patient (female 84 years) has been treated for more than 30 years with diphantoïn, and this treatment has not been changed after the genotype was established.

DISCUSSION

cLQTS-related polymorphic ventricular arrhythmias most often occur in relation to exercise and emotion. The recent molecular analysis of the LQTS indicates that both the electrocardiographic repolarization pattern and the conditions during which arrhythmias develop might be genotype-specific (12–14). All identified genes involved in the congenital LQTS code for (part of) ion channels involved in the repolarization process. They include KVLQT1 ($LQTS_1$), KCNE ($LQTS_5$) and HERG ($LQTS_2$) encoding subunits of the slowly activating delayed rectifier (I_{Ks}) and the rapidly activating delayed rectifier (I_{Kr}), respectively, and SCN5A ($LQTS_3$) encoding the Na^+ channel α-subunit (4–6,8,9). A mutation in an unknown gene on chromosome 4 is responsible for $LQTS_4$ described in a single French family

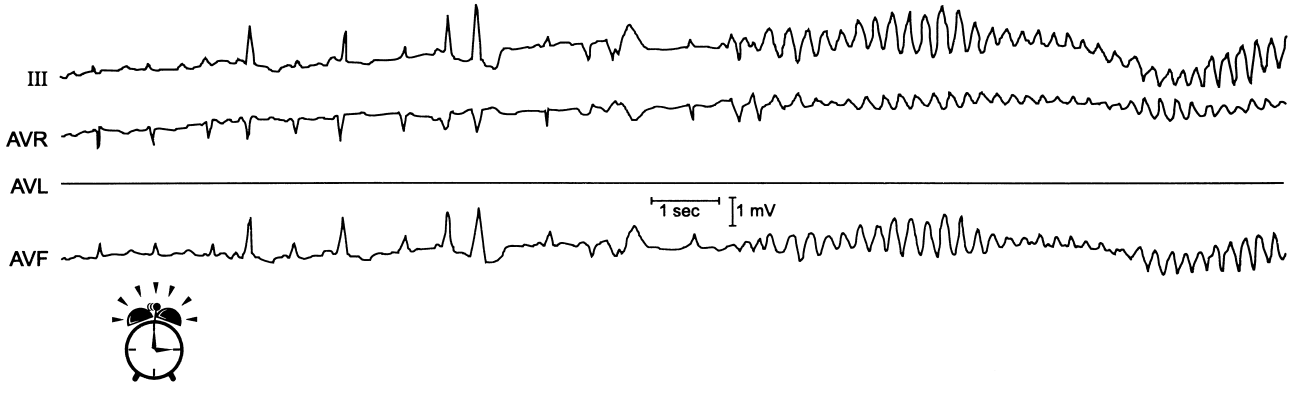

Figure 1. Extremity leads of a ventricular arrhythmia upon sudden arousal at 3:00 AM by an alarm clock. The HERG mutation in this patient was G604S.

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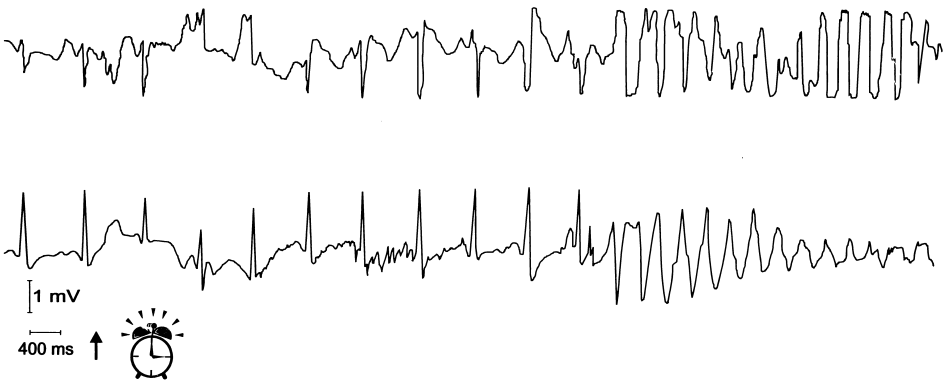

Figure 2. Ventricular arrhythmia upon sudden arousal at 3.00 A.M. by an alarm clock in a HERG patient (A558P). The leads given are (approximately) V1 and II. See text for discussion.

(7). Both $LQTS_1$ and $LQTS_2$ are the most prevalent subtypes.

Genotype-phenotype relationship. Preliminary data on the relation between genotype and the trigger for arrhythmic events in patients included in the international LQTS registry (14) reveal that, in agreement with our data (Table 1), $LQTS_1$ arrhythmic events were frequently related to exercise (14,19,20). Inadequate and transmurally nonuniform action potential shortening by β-adrenoceptor stimulation may underlie the associated high prevalence of arrhythmic events in these patients (21). In contrast, $LQTS_3$ patients, not included in this study, experienced events during sleep (15). In these patients cardiac repolarization may be fairly normal during fast rates due to the presence of normal K^+ currents. However, at rest, the incomplete inactivation of I_{Na} (as a result of the mutation in the SCN5A gene) leads to abnormal repolarization (15). Indeed, in experimental models mimicking $LQTS_3$ a fairly steep APD- and QT-rate relationship has been observed (22,23). The $LQTS_2$ patients have an equally distributed pattern of precipitators (i.e., exercise, fright and emotion, and sleep). Acoustic stimuli as a trigger for arrhythmic events are not specifically cited in any previously mentioned study.

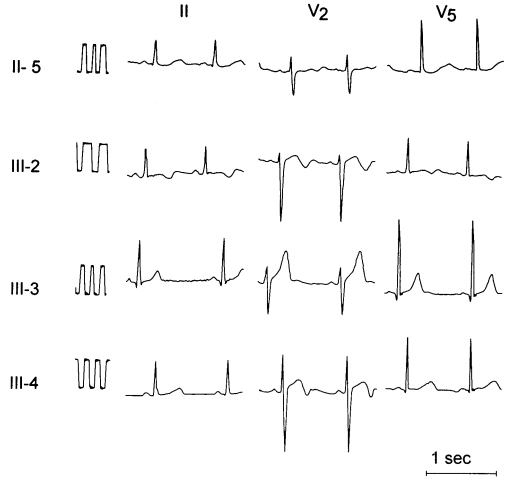

Figure 3. ECG recordings of the three sibs III-2, -3 and -4 and their father (II-5). Recordings from lead II, V2 and V5 have been selected. Abnormal, prolonged QT segments are present in patients II-5, III-2 and III-4. Calibrations are standard. The recording in Figure 2 is from patient III-2.

In this study we report on HERG-related cLQT families in which SCD, ventricular tachyarrhythmias and repeated syncope were preceded by auditory stimuli. In the patients with an auditory stimulus-related cardiac event, described in the literature, the genotype is unknown. In light of the available data on genotype specific ECG characteristics (12,13), the markedly low T-wave amplitude in the extremity leads in the patients described by Wellens et al. (1) and by Shimizu et al. (2) might indicate a HERG-related defect.

Low T-wave amplitude in the extremity leads was also observed in our patients with HERG mutations (e.g., Fig. 1). Documented arrhythmic episodes followed arousal by an alarm clock at 3 A.M. (Figs. 1 and 2). These episodes and those described previously (1,3) demonstrate that arrhythmias follow the stimulus within 10 s. Between the alarm signal and the onset of the arrhythmia the T-wave might invert (1,3) and ventricular extrasystoles may appear (1,3; Fig. 1) giving rise to a "long–short" sequence resulting in more serious arrhythmias. This sequence is a common finding in LQTS patients (24).

Figure 2, however, shows that ventricular extrasystoles are not a prerequisite for the onset of potentially lethal arrhythmias. Further similarity in these patients is the predominant occurrence at night. In apparent conjunction, five individuals in HERG-related families experienced nocturnal death. A similar high incidence of nocturnal death has been observed in other HERG-related families (25–27). We found in $LQTS_1$ patients no acoustic stimuli in relation to disease-related events.

Based on the preceding evidence it is tempting to speculate that acoustic stimuli as a precipitator for arrhythmic events may differentiate $LQTS_2$ from $LQTS_1$ patients.

In physiological terms an unexpected auditory stimulus is presumably equal to sudden fright, and a role for catecholamines is suggested. The sudden onset of the arrhythmia, within seconds after the stimulus, precludes a systemic catecholamine effect or a catecholamine-related shift in the extracellular environment as basis for the arrhythmia. In agreement is the lack of changes in heart rate variability parameters just prior to the arrhythmic events (3). The arrhythmic events occur at a relatively low rate and not necessarily after a preceding sudden significant change in rate (Fig. 2; ECG recordings in 1–3). Hence, it seems fair to state that rate-dependent effects on the respective currents are not involved either.

Rather, it seems more likely that a sudden release of local catecholamines triggers the event. Indeed, the sudden onset of ventricular extrasystoles originating from the terminal part of the grossly deformed T-waves is compatible with catecholamine-induced early afterdepolarizations (EADs) at a cellular level. The EADs have been recorded in LQTS patients upon exposure to (systemic) catecholamines (2,28). Whereas in control patients isoproterenol shortens the (monophasic) action potential, a lengthening is observed in LQTS patients (28).

Electrophysiological background. Functional studies with HERG mutants expressed in *Xenopus* oocytes reveal complete loss of function for some mutants and dominant negative suppression of HERG function for others (29). In an experimental cellular model mimicking a HERG defect (guinea pig ventricular cells exposed to a selective I_{Kr} blocker), β-adrenoceptor stimulation initially further lengthens the action potential and EADs develop (22). After several minutes the action potential shortens, presumably due to catecholamine-induced I_{Ks} activation.

In contrast to I_{Ks}, I_{Kr} is insensitive to catecholamines (30). In control cells and in cells pretreated with anthopleurin aimed to mimick a SCN5A defect by blocking I_{Na} inactivation, isoproterenol shortens the action potential from the onset of exposure (22). The KVLQT1 mutants similarly exert a dominant negative effect on I_{Ks} current (31). Preliminary experimental data, using the specific (32) I_{Ks} blocker chromanol 293B, reveal evidence that β-adrenoceptor stimulation results in a dramatic increase of transmural dispersion of repolarization and the development of ventricular arrhythmias most likely as a result of a large augmentation of residual I_{Ks} in epicardial and endocardial cells, but not in M-cells where I_{Ks} is intrinsically weak (21). Computer simulation studies on the role of I_{Ks} and I_{Kr} in cardiac repolarization in a guinea-pig ventricular cell-based model reveal that a decrease in I_{Ks} conductance of $>80\%$ prevents cardiac repolarization completely (33). The I_{Kr} reduction does lengthen the action potential but does not result in EADs (33).

Based on these results, obtained in a model in which compared to human cells several important repolarizing currents are not present (among which the transient outward current), it is postulated that the ratio I_{Ks}/I_{Kr} is of particular importance with regard to the development of EADs (33). Although both currents have been shown in isolated (right) ventricular myocytes (34), no detailed information is available on its ratio and distribution.

Conclusions. The presence of acoustic stimuli as a trigger for arrhythmic events may differentiate $LQTS_2$ from $LQTS_1$ patients. The absence of SCN5A- and KCNE-related patients precludes a statement that acoustic stimuli can be considered characteristic for $LQTS_2$. Although this observation ought to be confirmed by larger studies, it seems that, based on the prevalence of the LQTS subtypes, the presence of auditory stimuli should direct molecular genetic analysis toward HERG.

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