The Long QT Syndrome

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Major progress has taken place, and at a very rapid pace, in the understanding of the congenital long QT syndrome (LQTS). This has been the direct consequence of the identification of several of the genes responsible for LQTS and of the studies that have followed, at both basic and clinical levels. A key issue is represented by the fact that all LQTS genes identified so far encode for ionic channels involved in the control of repolarization. The expression studies of the mutated genes have allowed identification of the specific electrophysiologic consequences of the specific mutations and have demonstrated alterations in the NA^+ and in K^+ currents sufficient to explain the prolongation of action potential duration and, hence, of the QT interval.

Ongoing studies in the selected LQTS patients, for whom the specific mutations are known, are allowing a unique understanding of the complex genotype-phenotype correlation. These studies indicate the existence of what appear to be gene-specific patterns in many clinically important features such as the response to therapeutic interventions, the response to increases in heart rate, and in the factors that precipitate the life-threatening arrhythmias typical of this intriguing disease.

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For several years, the congenital long QT syndrome (LQTS) has been either ignored or regarded by most cardiologists as an oddity, as an infrequently encountered disease of modest practical interest. Then something happened, and the pendulum started to swing in the opposite direction.

It is indeed unusual for an unusual disease to generate and attract, all of a sudden, a great deal of attention among clinicians and scientists with a multiplicity of areas of expertise, ranging from clinical cardiologists to molecular biologists, from basic electrophysiologists to geneticists, and from pediatricians to experts in channel cloning and in transgenic animals. However, this is exactly what has happened since early 1995 for the congenital LQTS.

The LQTS is an uncommon clinical disorder that has progressively attracted the interest of many clinicians and of many investigators because of several peculiar aspects. Since 1975,[1] it includes under the unifying name of the "LQTS" two hereditary variants, one with and one without deafness.

There are several reasons for what has become a widespread interest for LQTS. One is represented by the dramatic manifestations of the disease, namely the occurrence of syncopal episodes, often resulting in cardiac arrest and sudden death, usually in conditions of either physical or emotional stress and in otherwise healthy young individuals, mostly children and teenagers. A most important one is the fact that, while LQTS is a disease with a very high lethality among untreated patients, very effective therapies are available; this makes unacceptable and inexcusable the existence of symptomatic and undiagnosed patients. Another reason is the progressive realization that behind the surface of an infrequent disease may lie the key to understanding the mechanisms by which sympathetic activation may trigger life-threatening arrhythmias in nonischemic hearts. Finally, clinical cardiologists and basic scientists are now pursuing a more complete understanding of LQTS, because the identification of some of the responsible genes and the impressive correlation between specific

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mutations and critical alterations in the ionic control of ventricular repolarization is making this syndrome a unique model. This allows a correlation between genotype and phenotype, thus providing a direct bridge between molecular biology and clinical cardiology.

The focus of the present article is primarily to review the amazing progress made in the molecular biology of LQTS and to discuss how these findings have not only modified our understanding of the disease but are also opening new strategies for effective management. This requires a brief synopsis of the most important clinical aspects of LQTS.

CLINICAL PRESENTATION

The typical clinical presentation of the LQTS is the occurrence of syncope or cardiac arrest, precipitated by emotional or physical stress, in a young individual with a prolonged QT interval on the surface ECG. If these patients remain untreated, the syncopal episodes will recur and eventually prove fatal in the majority of cases.

When the family screening is performed, a prolongation of the QT interval can often be detected; a history of spells or of sudden unexpected deaths in early age is not seldom recorded within the family.

Two variants have been initially identified: the original Jervell and Lange-Nielsen surdo-cardiac syndrome with congenital deafness and a recessive pattern of inheritance,[2] and the more frequent Romano-Ward syndrome,[3,4] with similar cardiac features but normal hearing and autosomal dominant inheritance. It has also become evident[5] that there is a significant number (approximately 20%-30%) of sporadic cases, i.e., patients with syncope and a prolonged QT interval but without evidence for a familial involvement. Since 1975,[1] familial and sporadic cases are grouped under the definition of "congenital LQTS."

The clinical history of repeated episodes of loss of consciousness under emotional or physical stress is so stereotyped and unique as to be almost unmistakable, provided that the physician is aware of LQTS. However, the clinical presentation is not always so clear, and sometimes the diagnosis may be less than certain. Data from the few quantitative studies and the personal experience with quite a large number of LQTS patients have contributed to the development of diagnostic criteria.[6,7]

There are two cardinal manifestations of LQTS, the electrocardiographic abnormalities and the syncopal episodes.

The electrocardiographic abnormalities are multiform[7] and besides the QT prolongation, which in approximately 5% of patients is absent[8,9] include several features: sinus pauses; notches on the T wave[10]; episodes of T wave alternans[11]; a lower than normal heart rate[1]; and an increase in QT dispersion, particularly in the patients who remain symptomatic despite therapy.[12]

The syncopal episodes are due to torsades de pointes often degenerating into ventricular fibrillation. They are characteristically associated with sudden increases in sympathetic activity, such as during strong emotions (particularly fright, but also anger) or physical activity (notably swimming).[13] Sudden awakening (alarm clock, telephone ring, and thunder) is an almost specific trigger for some patients. A higher incidence of syncope in correspondence with menses[13] and also in the postpartum period[14] has also been noted.

A few families have been reported in which cardiac arrests occur almost exclusively either at rest or, more frequently, during sleep[15,16]; we have also seen several sporadic cases with these features. As discussed below, recent data suggest that the propensity to develop life-threatening arrhythmias under stress or at rest may be influenced by specific genetic mutations.[17]

MOLECULAR BIOLOGY OF LQTS

Genes Identification and Expression Studies

The last few years have witnessed dramatic progress in the molecular biology of LQTS. The impact of these discoveries on the understanding not only of LQTS but also of other diseases in which control of the cardiac action potential is important has been recently reviewed by a multidisciplinary task force.[18]

As pointed out in two recent editorials,[19,20] this successful endeavor was based on the synergistic efforts and partnership of basic scientists and clinical investigators with established experience in LQTS. Special credit for making the first major breakthrough and for following with a quite impressive series of discoveries goes to Keating and his group in Salt Lake City, who began by studying a large family of Mormon descent followed for many years by Vincent. Significant contributions were also made by Towbin, who demonstrated the existence of genetic heterogeneity, and by Sanguinetti, who in a series of elegant studies clarified

the electrophysiological consequences of the mutations on the HERG gene which encodes for a potassium channel. Finally, it is fair to add that a critical role was played by the availability of an extraordinarily large number of LQTS families with a very well-characterized phenotype thanks to the International Registry coordinated by Moss and Schwartz who, since 1991, fully cooperated with the molecular biologists and who performed the first two studies on the genotype-phenotype correlation.[17,21]

Everything started in 1991 when Keating et al.[22] demonstrated tight linkage of LQTS to the Harvey *ras*-1 gene locus on the short arm of chromosome 11 in one large family. This was soon followed by evidence of linkage also on chromosomes 7, 3, and 4[23,24] (Fig. 1). Definite proof for genetic heterogeneity was provided by Towbin et al.,[25] who demonstrated that a significant number of families appear linked to none of these chromosomes. The most exciting discoveries, the identification of three of the responsible genes, took place within 9 months between 1995 and 1996. It was then that the genes for LQT1 (LQTS linked to chromosome 11), for LQT2 (LQTS linked to chromosome 7), and for LQT3 (LQTS linked to chromosome 3) were identified.[26-28]

The gene for LQT1 is KvLQT1 which, when coexpressed with minK, produces the I_{Ks} current.[29,30] The gene for LQT2 is HERG, a potassium channel that carries the I_{Kr} current. I_{Kr} and I_{Ks} are the two major components of the delayed rectifier I_K, a current that plays a fundamental role in the completion of repolarization.

The gene for LQT3 is SCN5A, the cardiac sodium channel gene and the three mutations described so far,[26,31] affect a region thought to be important for sodium inactivation (Fig. 2). Two are point mutations (N/S and R/H) while the third, probably the most important, results in the deletion of three amino acids (ΔKPQ).

The mutated genes for LQT2 and LQT3 have

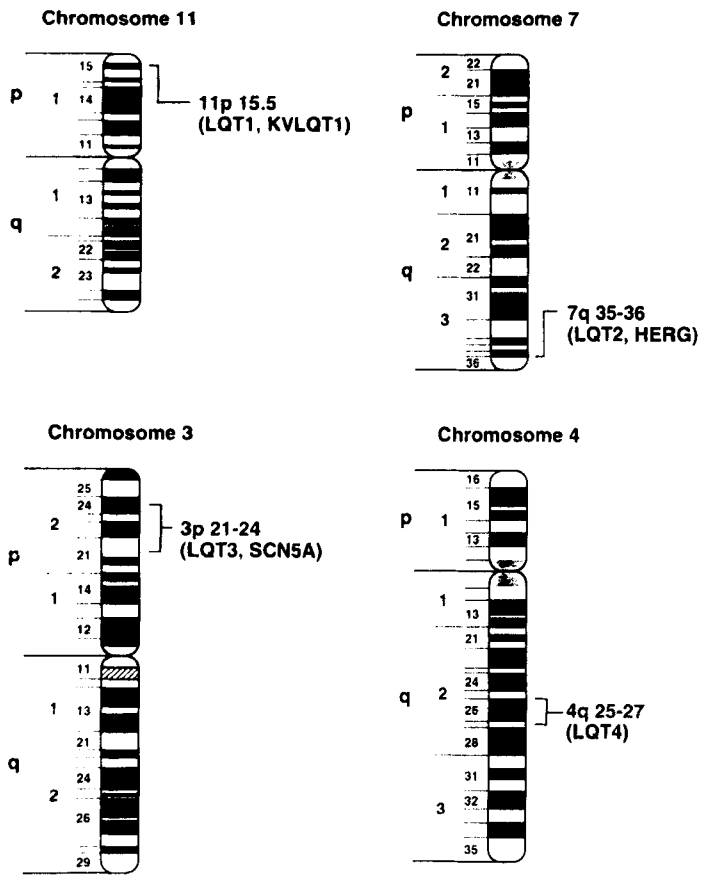

Figure 1. Genes in LQTS chromosomal location. Ideograms of chromosomes 11, 7, 3, and 4 showing the locations of the LQT1-4 genes. (From ref. 18)

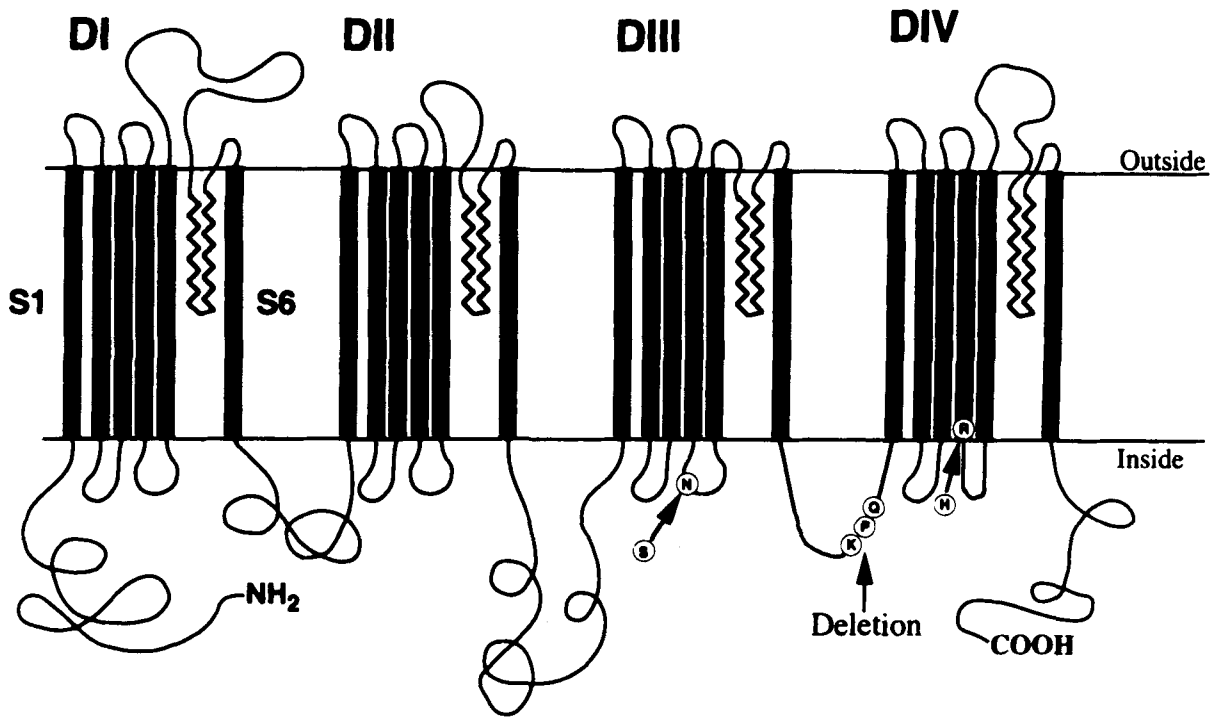

Figure 2. A model for the cardiac sodium channel and location of LQT mutations. The channel consists of four putative membrane-embebbed homologous domains (DI-DIV), joined to cytoplasmic linkers IDI-II, IDII-III, and IDIII-IV. Each domain has six putative transmembrane segments (S1-S6). (From ref. 31)

been expressed in *Xenopus oocyte*[32-34] and in the human embryonic kidney[35]; this has represented a major step forward, because it has allowed the first demonstration of an alteration in function due to specific mutations.

Expression of the mutant SCN5A genes[32,33] has shown that they produce a gain of function. Indeed, these mutations result in a small, sustained inward current (Fig. 3), which is likely to be sufficient to disrupt the normal balance between inward and outward currents during the plateau phase, and hence prolong cardiac action potentials. Single-channel recordings have allowed the demonstration that the N/S and R/H mutations show dispersed reopenings after the initial transient whereas the ΔKPQ mutation shows both dispersed reopenings and long-lasting bursts. This is the reason for the fact that the amount of persistent current is greater for the ΔKPQ mutation (Fig. 4).

It has practical importance demonstrated by the fact that this persistent inward current is blocked by mexiletine (Fig. 5), a Na^+ channel blocker,[33] and by lidocaine.[35] Similarly, in a cellular model mimicking the SCN5A and HERG defects present in LQTS, it has been observed that mexiletine corrects and almost normalizes the action potential prolongation induced by anthopleurin, a blocker of Na^+ channel inactivation used to mimic LQT3, but not that induced by dofetilide, a I_{Kr} blocker used to mimic LQT2[36] (Fig. 6). In these guinea pig isolated myocytes, during rapid pacing action, potential duration shortened more in the anthopleurin-treated than in the dofetilide-treated cells[36] (Fig. 7). These experimental observations have been reproduced to a large extent by the clinical findings in LQT2 and LQT3 patients.[17]

Expression of the mutant HERG genes has led to the identification of two main consequences.[34] Some of the mutant proteins do not form functional channels and interact with normal HERG channel when expressed in *Xenopus oocytes*. This implies that patients with these mutations will probably express half of the normal number of channels carrying I_{Kr}. Other mutant channels do not express detectable currents but cause a dominant negative suppression of the normal HERG function; thus, patients with these mutations will have a major reduction in I_{Kr} with a large effect on ventricular repolarization.

The expression studies that have succeeded in

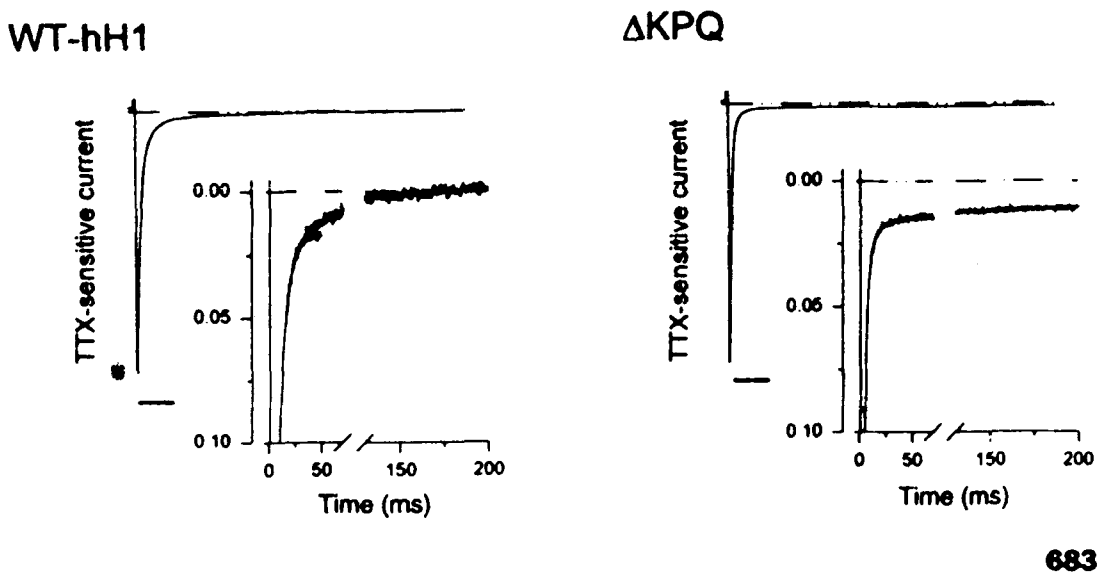

Figure 3. Sodium currents recorded in *Xenopus oocytes* expressing either WT-hH1 or ΔKPQ. Representative current traces obtained in the presence or absence of 30 μM TTX and recorded during a 200-ms test depolarization to −20 mV from a holding potential of −120 mV (left panels). Peak current amplitudes are normalized to that obtained in the absence of TTX. The result of subtraction of currents obtained in presence from those in the absence of TTX are shown in the right panels. The same subtracted data are shown on an expanded scale in the insets. Sodium-current expression was similar in WT and ΔKPQ RNA-injected oocytes. (From ref. 32)

comparing different mutations[32,33] indicate that the magnitude of the effect on repolarization varies according to the specific mutation. It will be interesting to determine if there is a correlation in the severity of the clinical manifestations and the spectrum of either HERG or SCN5A dysfunction in patients with LQT2 and LQT3. [See Addendum]

Clinical Correlation and Therapeutic Implications

The three different mutations appear to produce a different electrocardiographic phenotype.[21] Indeed, a different shape of the T wave has been reported by Moss et al.[21] to be present in LQT1, LQT2, and LQT3 patients, with the latter group being more obviously recognizable because of a distinctive, late appearing T wave, often with a biphasic morphology (Fig. 8). However, a certain degree of overlap exists, particularly between LQT1 and LQT2.

On the basis of the initial information on the two LQTS genes identified in March 1995 and on the observations made in the cellular model for LQTS developed by Priori et al.,[36] a first attempt to correlate the various mutations and clinical responses to different interventions provided in December 1995 novel information.[17] However, the very limited size of the population under study calls for caution in the extrapolation of the results.

The Na^+ channel blocker mexiletine appears to produce a considerable shortening of the QT interval in most LQT3 patients, but only a modest one in LQT2 and LQT1 patients (Fig. 9). This is the picture emerging from group data. However, by looking at the individual data and as the number of genotyped patients tested with mexiletine increases, it becomes evident that a small number of outliers (LQT1 and LQT2 patients who exhibit a significant QT shortening with mexiletine) does exist. This seems to be particularly true for LQT2 patients, as we are now finding an increasing number of them who respond to mexiletine with a clear shortening. Thus, definite conclusions on the expected effect of mexiletine on the QT interval in patients with mutations on chromosomes 3, 7, and 11 must await data on a larger population. Nonetheless, and even though QT shortening is by no means a guarantee of protection from life-threatening arrhythmias, these data suggest that it may be appropriate to test the potential value of mexiletine specifically in the patients with the SCN5A mutations.

Heart rate increase produced a rather marked

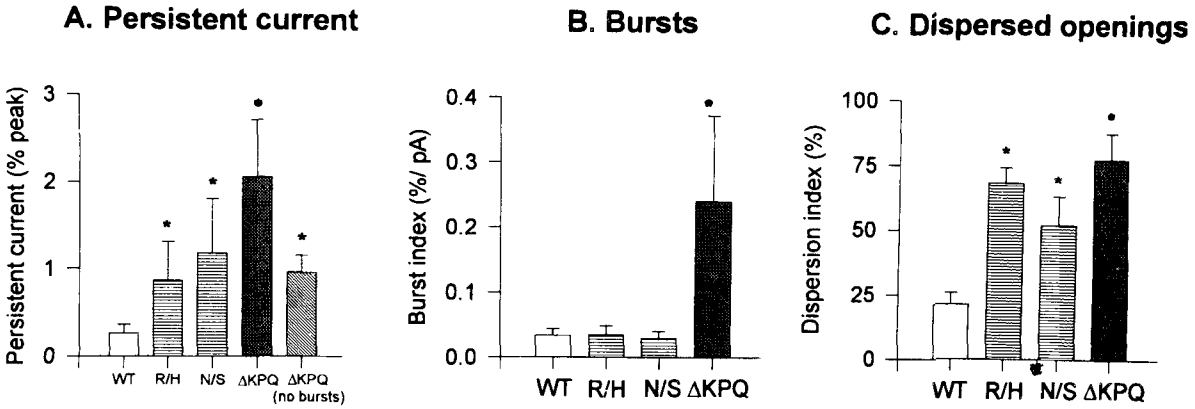

Figure 4. Summary of single-channel data. The relative amount of persistent current (A) was obtained by measuring the average current in the ensemble of idealized recordings from each patch over the 30- to 140-ms range after the start of the pulse. Each trace was corrected for nonzero baseline in a two-step procedure: leakage currents were offset by digital subtraction of recordings with no openings, and then before idealization, each recording was adjusted to a zero baseline by an automatic baseline correction method that removes slow drift during the test pulse. The average persistent current was normalized by dividing by the peak current in the 0- to 25-ms range after the start of the pulse and was expressed as a percentage. The occurrence of traces containing bursts (B) and dispersed openings was obtained by identifying bursts according to the following procedures: a closed time histogram was constructed from a collection of traces containing obvious bursts and fit to a biexponential distribution. It was observed that 90% of the area was described by a time constant of 0.2 ms; the remaining events, by a time constant of 11 ms. The shortest time constant was taken as the closest interval between events within the burst, and a burst was defined as a sequence of three or more openings separated by intervals no longer than 0.6 ms. A burst index (B) was calculated from the ratio of traces containing bursts to the total number of traces. The ratio was corrected for differences in the number of channels in the patch (unitary amplitude, 1.0 pA) by normalizing to the maximum peak current. Panels A and B show pooled data from 9 WT, 5 R/H, 7 N/S, and 5 ΔKPQ patches. Traces containing dispersed openings were identified by the criterion that a dispersed opening was a single open event separated from its neighbors by a closed interval longer than 0.6 ms. The dispersion index (C) was calculated as the percent of traces in which dispersed openings were observed in patches selected to have similar numbers of channels. * $P < 0.05$ versus WT (From ref. 33)

shortening of the QT interval among LQT3 patients; surprisingly, but in agreement with the experimental observations in isolated myocytes,[36] this effect was much less evident among LQT2 and LQT1 patients (Fig. 10). A potential practical inference would be that LQT3 patients might be at lesser risk of syncope during physical exercise, when in these patients the progressive heart rate increase may allow appropriate QT shortening. These patients may also be those less likely to be protected by beta-blockers that would produce an excessively low heart rate and would prevent an adequate heart rate increase during exercise.

Additional support for this concept seems to come from preliminary data on the circadian changes in QT_c among genotyped patients, particularly in the nighttime hours. It appears that LQT1 patients have a modest shortening or no change compared to the day hours, and that LQT2 patients have considerable interindividual variability. In what looks like a startling contrast, LQT3 patients rather uniformly seem to have a significant QT_c prolongation in the hours associated with sleep.[37] Should these preliminary observations be confirmed, they would also point to a greater risk for LQT3 patients while at rest or during sleep.

Finally, this pilot study provided the first opportunity to look at potentially different associations between triggering events and the various genotypes. The preliminary data published in 1995 are currently being greatly expanded and appear to provide rather striking information. We now have data available on over 130 genotyped patients. The factors associated with syncope or cardiac arrest have been divided into three main groups: exercise; emotions; and events occurring during either sleep or at rest with and without arousal. Exercise represents the cleanest group, because there can be no misinterpretation about this association. The events at rest are more difficult to interpret correctly; for instance, it is impossible to know whether a patient found dead in his bed had any

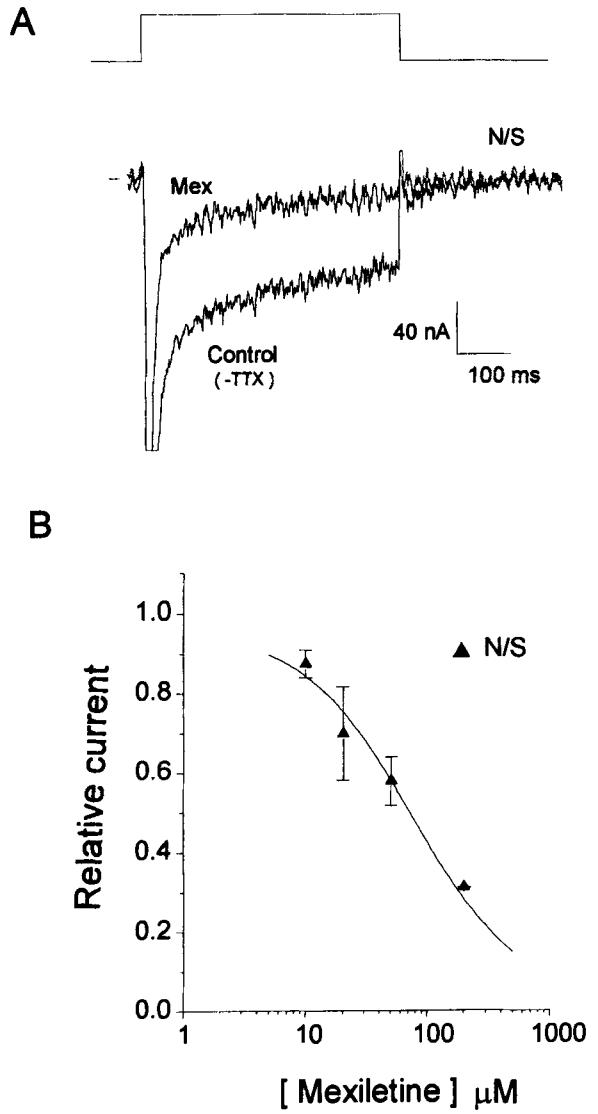

Figure 5. Sensitivity of the late current to mexiletine. (A) Currents elicited by 500-ms pulses to − 10 mV showed a 69% block of the N/S late current (control TTX), at 300 ms (dotted line), after extracellular application of 200 μmol/L mexiletine (Mex). (B) Dose-response curve for the block of the late Na^+ current by Mex. The remaining TTX-sensitive current after subtraction of the Mex-sensitive component was normalized to the maximal TTX-sensitive current. Data from three experiments were averaged, and their mean values were plotted against drug concentration. The data, fit to the Hill equation for a 1:1 binding kinetics, yielded an apparent K_d of 59.9 μmol/L (Hill coefficient = 0.93). (From ref. 33)

form of arousal (sudden noise, a phase of REM sleep) just prior to the event. Thus, these conditions represent a mixed bag, including events truly occurring at rest or sleep but also arousals from sleep or rest. The important pathophysiological aspect is that they all initiate from a rather low heart rate, because of either sleep or rest; this is in marked contrast not only with exercise but also with emotions occurring during normal daily activity when heart rate is usually intermediate or elevated. The group that has events during "emotions" is probably somewhat underestimated because some events are included, as explained above, in the events occurring "at rest." Two additional caveats concern the fact that for approximately 30% of the LQT2 patients, the specific condition during which the cardiac event took place is not yet known and that the LQT3 group remains numerically limited.

With these limitations in mind, several considerations are possible. The most striking difference is the one present between LQT1 and LQT3 patients. Whereas only 1%-2% of the LQT1 patients had their cardiac events at rest or during sleep, this occurred in more than 65% of the LQT3 patients. Conversely, whereas two-thirds of the LQT1 patients had cardiac events during exercise, this occurred only in < 10% of LQT3 patients. The LQT2 patients are somewhere in the middle but their pattern, surprisingly, is more similar to LQT3 than to LQT1 patients. These data support the observation made on the response to heart rate increases by LQT3 patients and indicate that it is not exercise that is the most important risk factor for them. Thus, our findings suggest that the previously puzzling clinical observation that some LQTS patients were more at risk when they were resting than during exercise may now be explained on the basis of the specific and differential effect of the various genetic mutations. The same data also indicate that LQT1 patients are at risk almost exclusively during exercise and during emotions occurring in the awake state, when heart rate is definitively elevated. This suggests that these patients may be those in whom beta-blockers are particularly effective.

All these observations should be taken cautiously, because the relatively small number of patients studied so far does not yet allow a careful investigator to extrapolate these data to the entire population affected by LQTS. Furthermore, there is clear and growing evidence also from our own data that some degree of overlap does exist. Nonetheless, this study[17] and its ongoing extension have provided the first demonstration of differential responses of LQTS patients to interventions targeted to their specific genetic defect.

As a counterpart of the findings with mexiletine in LQT3 patients,[17] a recent report has suggested

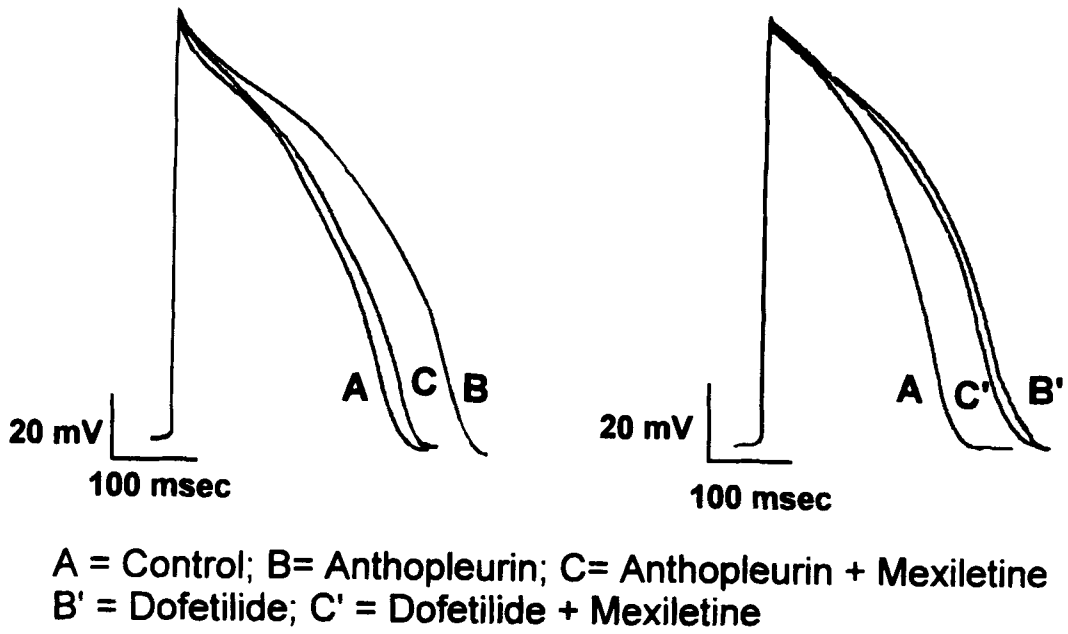

Figure 6. Example of APD prolongation induced in a control cell (A) by anthopleurin (B) and subsequent reduction of APD after combined exposure to anthopleurin and mexiletine (C) (left panel). Example of APD prolongation induced in a control cell (A) by dofetilide (B') and subsequent reduction of APD after combined exposure to dofetilide and mexiletine (C') (right panel). (From ref. 38)

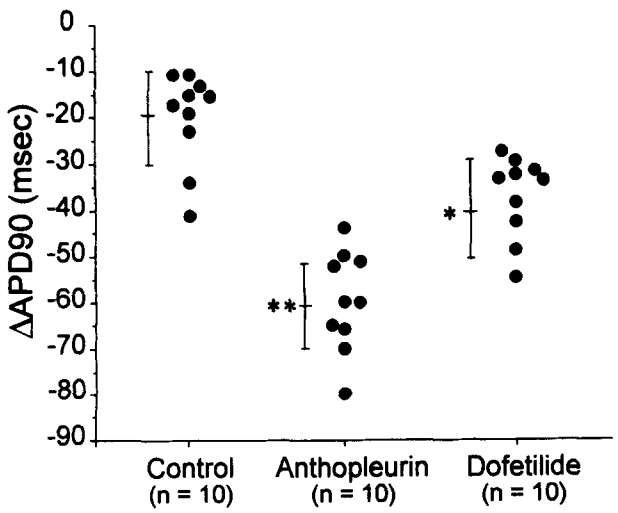

Figure 7. Individual and mean values (± SD) of the response to fast pacing (from 1–2.5 Hz) in control cells (n = 10), in anthopleurin (n = 10), and in dofetilide (n = 10) treated cells. Data are expressed as APD90 shortening in ms. ANOVA $P < 0.001$; Scheffè post hoc * $P < 0.05$ vs controls; ** $P < 0.05$ vs dofetilide and controls. (From ref. 38)

that an increase in the extracellular concentration of potassium may shorten the QT interval in LQT2 patients.[38] However, the specificity of this intervention will be demonstrated only when data will also become available for LQT1 and LQT3 patients.

Novel Approaches to the Prevention and Treatment of Arrhythmias and Sudden Death?

The long QT syndrome represents a unique model of tight correlation between specific mutations and specific alterations in function, thus representing the best example available so far of genotype-phenotype correlation. The amazing progress under development is also likely to have an impact on the management of these patients by allowing testing of novel and highly specific interventions. At this time the data available suggest that the following series of therapeutic implications may be worthy of careful testing.

In patients with SCN5A mutations (LQT3), it is reasonable to test the potential efficacy of Na^+ channel blockers. Mexiletine, available for oral use, is the most logical candidate drug at this time. New Na^+ channel blockers with specific effect on the late inward current associated with all three mutations might be useful.

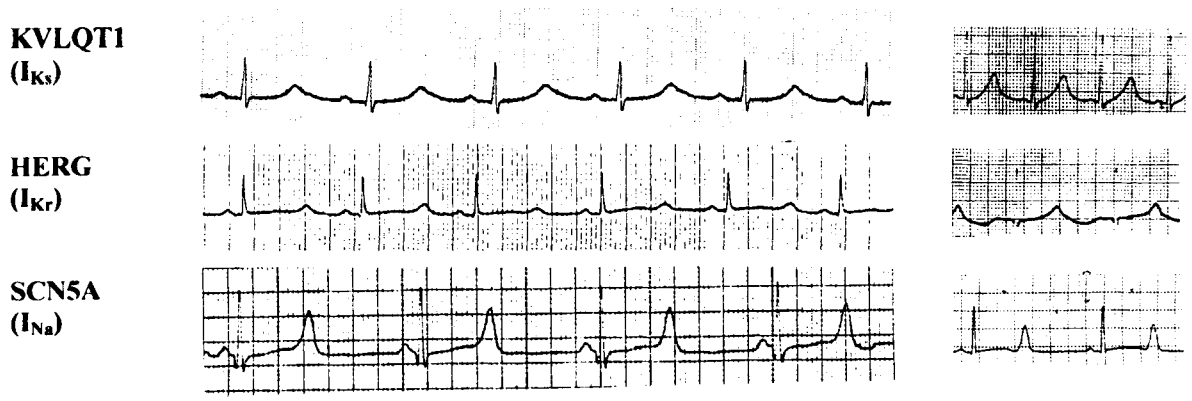

Figure 8. On the left: Distinctive T wave patterns observed in the three genotypes of LQTS. The T wave is broadest in patients with KvLQT1 mutations (top); T wave amplitude is lowest in patients with HERG (I^{Kr}) mutations (middle); and onset of the T wave is most delayed in patients with SCN5A (sodium channel) mutations (bottom). (Modified from ref. 18). On the right: ECG recordings from lead V_5 in other three patients linked to chromosomes 3, 7, and 11. None of the patients was receiving β-adrenergic blocking medication at the time the ECGs were obtained. (Modified from ref. 21)

In patients with HERG mutations, it is logical to test various ways of increasing the extracellular K^+ concentration. Potassium infusions represent only an experimental tool. Oral K^+ supplements in combination with K^+ sparing agents is worth testing, and K^+ channel openers are being tested. When available, I_{Ks} activators may represent a very rational approach for LQT1 patients.

An exercise stress test should be performed in all patients. In LQT3 patients, if exercise indeed produces a significant shortening of the QT interval, physical activity may not need to be restricted. Also, it is possible that LQT3 patients may benefit from the use of a pacemaker more than LQT1 and LQT2 patients.

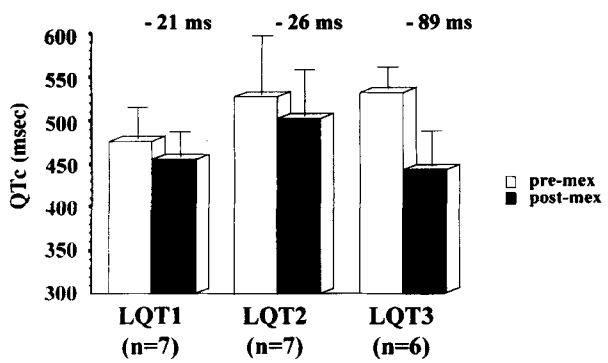

Figure 9. QT_c values in control condition and during acute oral drug testing with mexiletine in LQT3 (linked to chromosome 3, n = 6), in LQT2 (linked to chromosome 7, n = 7), and in LQT1 (linked to chromosome 11, n = 7) patients. Data are expressed as mean ± SD. (Modified from ref. 17)

Finally, it is important to remember that QT interval shortening, albeit encouraging, cannot be assumed to automatically imply protection from life-threatening arrhythmias. The use of novel and experimental therapies should not deprive the symptomatic patients of the therapies with established protective effect.

Current Status of Molecular Diagnosis in LQTS

The application to clinical practice of the knowledge resulting from the elucidation of the molecu-

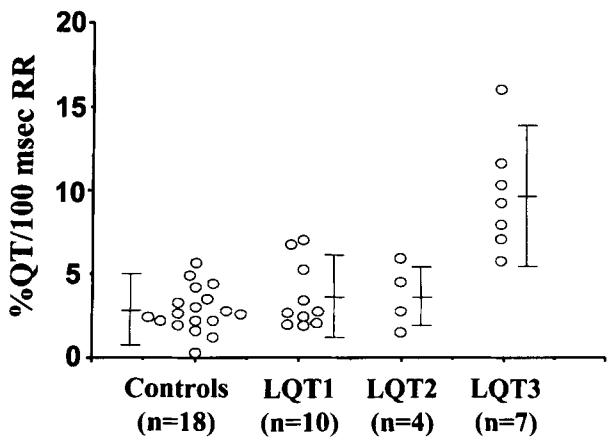

Figure 10. Individual and mean values (± SD) of the response to heart rate increase in controls (n = 18) and in LQT3 (linked to chromosome 3, n = 7), LQT2 (linked to chromosome 7, n = 4), and in LQT1 (linked to chromosome 11, n = 10) patients. Data are expressed as percent QT shortening for each 100-ms reduction in RR interval. (Modified from ref. 17)

lar basis of LQTS, in order to genotype a large number of affected families and individuals, poses several problems.[39]

The progress in molecular biology will not be immediately as helpful for the diagnosis of borderline cases as many are hoping. At this time only a few centers worldwide do the entire screening for all the already identified mutations. (Our group performs genetic screening for LQTS. Those interested for their own patients can contact P.J. Schwartz or S.G. Priori by mail or Fax +39-382-526952. Information on how to send blood will then be forwarded.)

Some of the same molecular techniques that have been used to identify the genes for LQTS can now be applied to clinical screening. Linkage analysis can be used to identify the chromosome where the mutation is located in a LQTS family. Once linkage is established, based on the data obtained in the clinically affected individuals, the information can be extended to those individuals with an intermediate phenotype and can therefore allow to define whether they are unaffected or carriers of the genetic abnormality. The major limitation of linkage analysis is the need for large families with several clinically affected individuals to obtain the statistical power (lod score) to establish the presence of linkage. As a consequence, this approach is not suitable for identifying genetic defects in small families nor in the sporadic cases in which a de novo mutation has occurred.

To investigate sporadic cases in small families or families in which collection of blood samples from different individuals is not possible, it is necessary to screen all the regions of all LQTS related genes, searching for the presence of an abnormality in the sequence of the cDNA. In our laboratory, the technique used is SSCP (Single Strand Conformation Polymorphism), that is able to identify most single or multiple base changes in DNA fragments in single patients. Alterations in the DNA sequence are visualized by this method as changes in the electrophoretic mobility of single strand DNA on nondenaturing acrylamide gels. The major limitation of this approach, when applied to LQTS, is that it is not yet possible to study the entire genes because the complete genomic structure is available only for SCN5A[40] but not for HERG or KvLQT1. As a consequence, it is currently possible to study only a fraction of the HERG and KvLQT1 genes (approximately 40%-50% of each can be studied). This implies that successful identification of the genetic defect will be successful only in a fraction of LQTS families. Specifically, one cannot exclude that an LQTS patient has a mutation on either chromosome 7 or 11. In these two chromosomes, a particularly large number of mutations has been described. In the case of chromosome 7, it even appears that every family has its own "private" mutation.

This limitation of the molecular diagnostic capabilities should always be mentioned to families, who often rely upon genetic testing to overcome the anxiety associated with the uncertain clinical identification of family members at risk.

Molecular diagnosis has its most important role in establishing conclusively or excluding the disease in those individuals presenting with a borderline phenotype. This is true, because at variance with disorders in which no therapy is available, thus limiting the value of early diagnosis, the availability of effective therapies in LQTS reinforces the importance of a correct diagnosis which, through the implementation of therapy, may prevent the occurrence of sudden death.

It is important to consider that the successful identification of the genetic defect is still far from 100%, that the identification of gene defects is expensive and time consuming, that the costs are usually not covered by national health care systems or by insurance companies, and that they are largely covered by research funds. As a consequence, the molecular diagnosis of LQTS cannot yet be considered as a routine test, and it is still performed at specialized centers mainly for research purposes. Nonetheless, given the important consequences that the identification of asymptomatic gene carriers may have, we believe that it is worth attempting molecular studies in all LQTS families, provided that the likelihood of having an inconclusive result is clearly explained to patients.

In addition to the obvious clinical value of this information, the availability of many genotyped families will make it possible to define the molecular epidemiology of LQTS, thus providing an answer to pressing questions such as the prevalence of each variant of LQTS, the severity of each of the genetic forms, and the risk for a gene carrier to become symptomatic or of dying during the first episode if left untreated.

ADDENDUM

While this article was under revision, a fifth LQTS gene has been identified on chromosome 21. The mutations on this gene produce a reduction of function in the I_{Ks} current.[41]

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