EDITORIAL COMMENT

Sudden Death by Stress

How Far Under the Nerves Should We Dig to Find Out Why LQT1 Patients Die?*

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Since the very first description, in its homozygous variant known as the Jervell and Lange-Nielsen syndrome (1,2), of the congenital long QT syndrome (LQTS) (3), it had been evident that the most critical trigger for sudden death was represented by an abrupt activation of the sympathetic nervous system. Indeed, the tragic deaths of those 3 little siblings occurred while they were running, playing, or swimming (1). The recognition of the much more common heterozygous form, initially called Romano-Ward syndrome before the introduction in 1975 of the acronym LQTS (4), brought together the concept that the single most important trigger for lethal arrhythmias in LQTS was sympathetic hyperactivity (4). This partial truth was the consequence of the fact that in the pre-genetic era, most of the few diagnoses made were in severe cases with the striking association between collapse and physical or emotional stress and that probably most of them were in patients who would now be labeled LQT1. Not by chance, already in 1985, the possibility was surmised that “the basic defect in LQTS is an unknown intracardiac abnormality that decreases electrical stability and makes the myocardium more vulnerable to the effect of sympathetic discharges. In this case the sympathetic nervous system, acting mostly through the quantitatively dominant left stellate ganglion, would merely represent the trigger for the ventricular tachyarrhythmias that lead to the death of patients with LQTS” (5). This hypothesis, advanced 10 years before the identification of the first LQTS genes, also strengthened the concept that therapy should involve antiadrenergic interventions such as beta-blockers and left cardiac sympathetic denervation, which still represent the key to proper management (6).

The identification of KvLQT1 as the gene for LQT1 (7) shifted the focus to a specific current, I_Ks, and represented a giant leap forward in the search for underlying mechanisms. I_Ks is activated by fast heart rates and by catecholamines, and it shortens ventricular repolarization, thus providing a physiological protection against the possibility of arrhythmias at fast rates. This may help explain why, compared with LQT2 and LQT3 patients, LQT1 patients are at much higher risk during exercise. Because of their malfunctioning I_Ks channels, it is expected that their hearts shorten their QT intervals during tachycardia less effectively than the hearts of normal individuals do. Indeed, when the triggers for lethal events where subdivided between exercise, emotion, and rest, it turned out that 90% of LQT1 patients had these events during exercise or emotion (8). That study on 670 symptomatic patients of known genotype established that sympathetic activation is the main arrhythmogenic trigger for LQT1 patients (8).

As the genotype-phenotype correlation studies evolved, it became evident that the site of the mutation (e.g., transmembrane versus C-terminal), the type of mutation (missense versus nonmissense), the biophysical effect (dominant-negative versus haploinsufficiency), and mutation-specific characteristics could all have important clinical impacts. However, neither the localization of a mutation nor its cellular electrophysiological effect is sufficient to consistently predict the impact on clinical manifestations.

The most striking example of mutation-specific behavior is probably that of KCNQ1-A341V, a relative hotspot mutation characterized by unusual clinical severity demonstrated by 80% of the patients being symptomatic, with >30% experiencing cardiac arrest or sudden death (9,10). What is puzzling is that A341V is only a mildly dominant-negative versus haploinsufficiency, and mutation-specific characteristics could all have important clinical impacts. However, neither the localization of a mutation nor its cellular electrophysiological effect is sufficient to consistently predict the impact on clinical manifestations.

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Interestingly, the phosphomimetic substitution KCNQ1-S27D (known to enhance wild-type I_Ks just like natural cAMP stimulation (13)) rescued the loss of up-regulation conferred by KCNQ1-A341V through a mechanism requiring the presence of the A-kinase anchoring protein Yotiao (11). These data nicely illustrate the intricate regulation of I_Ks by multiple elements of its macromolecular channel complex. In principle, defects at any level may cause loss-of-function, as exemplified by the identification of a LQTS-causing mutation in Yotiao, which inhibits the functional response of I_Ks to cAMP (14). Contemporary studies of the molecular-biophysical defects underlying LQTS thus focus on the regulatory mechanisms of ion-channel expression and function, much beyond the characterization of basal current only.

In this issue of the Journal, Wu et al. (15) describe the pathogenic consequences of another KCNQ1 mutation, G269S, residing in the S5 segment of the channel. The investigators have performed a meticulous study by linking the cellular characterization of basal and cAMP-inert mutant I_Ks to a thorough QT analysis in G269S carriers from 4 unrelated families. Most of the 11 carriers had normal-to-borderline corrected QT intervals at rest, but abnormal corrected QT adaptation during exercise. One family member had died suddenly and another, a 22-year-old woman, experienced syncope while dancing. She has been well on beta-blockade thereafter. Various important messages emerge from this act of modern LQT1 phenotyping. First, these data stress again how crucial it is to take good notice of the patient’s symptoms and family history, as well as to look beyond the actual QT interval in case of suspected LQTS. A borderline-normal QT may still be associated with a severe risk of arrhythmia, as postulated long ago (16). Careful examination during dynamic conditions, including exercise testing (17,18), epinephrine challenging (19), baroreflex sensitivity testing (20), or postural change (21) may be necessary to unmask the presence and severity of QT pathology in LQTS-mutation carriers. Second, at the cellular level, Wu et al. (15) elegantly present yet another example of a heterozygous KCNQ1 mutation with a dominant-negative impact on cAMP-dependent up-regulation, after A341V (11) and mutations in cytoplasmic loops S2-S3 and S4-S5 (22). It remains to be elucidated whether reduced KCNQ1 phosphorylation could underlie this loss-of-function by G269S (Is it protein kinase A-dependent? Is N-terminal S27 involved? More generally, one is curious to understand why mutations at so many different locations of the KCNQ1 protein (S2-S3 and S4-S5 loops, S5 segment, S6 segment) all confer defective regulation of I_Ks by cAMP. Finally and intriguingly, a novel molecular aspect is suggested by the observation of Wu et al. (15) that G269S-mutant I_Ks is not rescued by the phosphomimetic substitution S27D, unlike the findings for A341V (11). Which post-phosphorylation defect hinders I_Ks enhancement in this condition?

Recent studies involving in silico modeling have focused on the correlation of mutation-specific I_Ks-channel dysfunction with patient phenotype in LQT1 for the prediction of arrhythmia risk, with promising results when the patient’s corrected QT interval provided less than clear-cut information (23). Although the study by Wu et al. (15) did not incorporate computational modeling of repolarization gradients and proarrhythmic instability, the experimental addition of cAMP-dependent regulation of I_Ks and its pathological loss, beyond a thorough QT analysis, improves our possibilities to assess cardiac risk. These and other incremental understandings of the genotype-phenotype relations will eventually be incorporated in translational models for personalized management of LQTS. In this regard, improved multiscale modeling of the integrated heart is awaited. Another key to better understand phenotypic differences and outcome in LQT1 patients will be to examine the genetic mutation in its genomic context, as provided by stem-cell technology (24).

It is evident how the most recent studies are confirming the importance of neural mechanisms in the onset of stress-induced arrhythmias, thus confirming the 1985 hypothesis (5), and progressively pointing to a more complex relationship between cardiac sympathetic nerves and lethal arrhythmias in LQTS.

The question now is whether we will ultimately be able to develop diagnostic modalities by which we can recognize phenotypic signatures of ion-channel mutations at the patient level and predict clinical outcomes. In any scenario, for LQT1, such a translational approach should encompass the cellular investigation of cAMP regulation of I_Ks (i.e., a “molecular stress test”) besides basal current characteristics. At the integrative level, the patient’s responsiveness to sympathetic challenges should be examined in a safe, controlled manner. Bringing these levels together is crucial for a more thorough understanding of the genotype-phenotype interaction, and the present study by the group led by Dr. Horie represents another step forward.

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