The Long QT Interval Syndrome
A Rosetta Stone for Sympathetic Related Ventricular Tachyarrhythmias

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The long QT interval syndrome (LQTS) has a low incidence in the general population, but, like the Wolff-Parkinson-White (WPW) syndrome, it has a major impact. While the WPW syndrome is the Rosetta stone of reentry, the LQTS may be the Rosetta Stone for ventricular tachyarrhythmias dependent on sympathetic stimulation.

Present Study
In a recent issue of Circulation, Schwartz et al\(^1\) provided further evidence of this sympathetic link by demonstrating the beneficial effects of left-sided cardiac sympathetic denervation in 85 patients, 84 of whom (91\%) continued to have syncope or cardiac arrest before denervation despite receiving \(\beta\)-adrenoceptor blockade. After surgery, the number of patients with cardiac events, the number of cardiac events per patient, and the number of patients with five or more cardiac events all decreased significantly. However, there still were seven (8\%) sudden deaths, reducing the 5-year survival to 94\%.

Importance
Despite criticisms of study design—no controls, lack of uniform surgical procedure, continued oral therapy with \(\beta\)-adrenoceptor blockers in 84\% of patients after surgery, and no reliable proof that all patients worldwide who underwent this procedure were included in the data analysis (e.g., did many physicians not report their surgical failures to the international registry?)—the study is important from several standpoints. First and foremost, it provides the most complete and important data found anywhere on a therapeutic modality for patients with symptomatic LQTS. Second, it offers a clue to the arrhythmogenic role of sympathetic stimulation (see below). Last, it is a fine example of international cooperation in medicine.

Long QT Interval Syndrome
The idiopathic LQTS comprises three groups of patients with a congenital disorder characterized by abnormally prolonged ventricular repolarization that contributes to the development of ventricular tachyarrhythmias, often torsades de pointes. The Jervell-Lange-Nielsen syndrome is transmitted as an autosomal recessive pattern and includes congenital neural deafness. Patients with the Romano-Ward syndrome have normal hearing and autosomal dominant transmission, whereas the sporadic form comprises a nonfamilial group with normal hearing.\(^2,3\)

Hypotheses
Any hypothesis put forth to explain this syndrome must account for all of its features, namely the long QT interval and abnormal T or TU waves, T wave alternans, a lower than normal heart rate especially in children, sinus pauses, and ventricular tachycardia, particularly torsades de pointes, that is usually precipitated by physical or emotional stress and causes syncope and sudden cardiac death.\(^2,3\) Of the several hypotheses proposed,\(^2,3\) cardiac sympathetic imbalance and an intrinsic myocardial abnormality of repolarization appear most plausible. Other neurocardiological mechanisms may be operative in occasional patients.\(^4\)

ECG Changes and Sympathetic Imbalance
The sympathetic imbalance concept proposes that reduced right cardiac sympathetic innervation (presumably on a congenital basis) results in reflex elevation of left cardiac sympathetic activity.\(^3\) This hypothesis can account for the sinus node abnormalities and perhaps the beneficial effects of left-sided cardiac sympathetic denervation\(^1\) but, in the view of this writer, inadequately explains the remaining features.

The justification for sympathetic imbalance causing QT prolongation is rooted in a 25-year-old observation in dogs showing that left stellate ganglion stimulation and right stellate ganglion interruption prolong the QT interval. The opposite did not occur. That is, left stellate ganglion interruption and right stellate ganglion stimulation produced no measurable change in the QT interval.\(^5\) In that pivotal study, the QT interval was measured in only one electro-
cardiogenic lead and increased in all but one dog by 20–40 msec after right stellate ganglion interruption and by 46 msec (mean), for 1–5 minutes, after termination of left stellate ganglion stimulation. Because sympathetic stimulation is well recognized to shorten ventricular repolarization, the authors explained the QT prolongation by the unmasking of previously cancelled repolarization forces, a concept incompletely validated.

Several years later, one of the original authors, reinvestigating these observations, showed (again recording one ECG lead) that 1–3 seconds of either left or right sympathetic stimulation prolonged the QT interval 10–30 msec, for up to several minutes, usually in the 10–30-second period after termination of stimulation. Stimulation of right or left sympathetic nerves for 30 seconds to 5 minutes, such as might be expected to occur in an exercising patient with the LQTS, always shortened the QT interval, at times after transient prolongation. Rapid injection of norepinephrine and epinephrine transiently prolonged and then shortened the QT interval while slow, prolonged infusion shortened it. These data show, at most, that neural or intravenous adrenergic stimulation can transiently prolong the QT interval, followed by shortening, and offer no evidence that reduced right and increased left cardiac sympathetic activity are responsible.

In a study on the effects of stellectomy, Schwartz et al showed that right stellectomy shortened refractoriness 3–5 msec at the right ventricular apex (opposite to that found by Yanowitz et al, while left stellectomy increased refractoriness 4–7 msec, as did bilateral stellectomy. Schwartz et al explained shortening of refractoriness after right stellectomy by a reflex increase in left sympathetic activity. They postulated that the reflex increase in right sympathetic activity after left stellectomy was insufficient to counteract the loss of left sympathetic effects, and ventricular refractoriness increased. They concluded that both stellate ganglia exert qualitatively similar effects that shorten cardiac refractoriness but the left stellate exerted quantitatively greater effects. The QT interval was not mentioned.

Other experimental models have been studied. Recently it has been demonstrated that neonatal rats injected with an antiserum to nerve growth factor developed an abnormal sympathetic innervation pattern and a long QT interval. No mention was made of a right/left sympathetic imbalance pattern, however.

In the chick embryo, removal of the premigratory surface ectoderm in the area of the right nodose placode caused a 25-msec QT increase in the ECG obtained through the egg shell (and corrected by Bazett's formula) compared with control embryos, but no arrhythmias. The relevance of these models is not known.

Finally, clinical studies of sympathetic innervation patterns determined by metaiodobenzylguanidine (MIBG) scintigraphy in patients with the LQTS show conflicting patterns. We found no evidence of apparent left/right imbalance; however, another recent study noted reduced or absent MIBG uptake in the diaphragmatic part of the left ventricle in patients with the long QT syndrome.

To summarize, the often-quoted studies that purport to establish the foundation for the ECG characteristics of LQTS show that refractory period and T wave changes with stellate ganglion manipulation are small compared with the QT changes in patients with the LQTS. While T wave alternans and changes in T wave contour can be produced with left stellate ganglion stimulation, the bizarre T-U morphology commonly seen in patients with the LQTS rarely occurs. Further, discrepancies exist among the results of the different studies investigating QT and refractory period changes. In the present study, QTc shortened after left sympathectomy in patients who became asymptomatic, but not for the group as a whole. However, in another study of 10 patients with the LQTS who remained symptomatic after left stellotomy, QTc shortened 50 msec.

It is important to remember that just because patients with the LQTS have increased risk for developing ventricular tachyarrhythmias, that does not mean that all other states characterized by QT prolongation confer a similar risk. In fact, it is the aim of potassium channel blocking drugs to prolong refractoriness (and the QT interval) and thereby suppress arrhythmias. Not all QT interval prolongation is arrhythmogenic, nor is all QT interval shortening antiarrhythmic. Uniform changes in refractoriness throughout the ventricle are probably more important. Whether such dispersion in recovery of excitability causes arrhythmias in patients with the LQTS is unclear.

Arrhythmias and Sympathetic Imbalance

Sympathetic imbalance has been invoked to explain the arrhythmogenic potential of the LQTS on the basis of reflexly increased left sympathetic activity. One study showed an increased prevalence of ventricular tachycardia and fibrillation during a 10–90-second coronary occlusion in 11 dogs after right stellate ganglion blockade and a reduction of ventricular arrhythmias after left stellate ganglion blockade. However, data from subsequent studies are less convincing and can be briefly summarized: 1) in dogs subjected to 5-minute coronary occlusions, left stellate ganglion stimulation increased the number of dogs with ventricular fibrillation from one of 20 to five of 20, but left stellate ganglion interruption did not reduce ventricular arrhythmias; after right stellotomy, arrhythmias were unchanged in seven dogs, increased from none to development of premature ventricular complexes in three dogs, and increased from none to ventricular fibrillation in one dog; 2) in 72 dogs undergoing circumflex coronary occlusion, both right and left stellate ganglionectomy reduced the incidence of early and total ischemia-induced ventricular tachycardia and ventricular fibrillation and improved outcome, with left stellate ganglionec-
omy more effective than right; 3) in conscious dogs, premature ventricular complexes increased during exercise in two of 25 dogs that were normally innervated and in six of seven dogs after right stellate ganglion interruption; 4) in neonatal rats with lengthened QT intervals treated with antibody to nerve growth factor, no spontaneous ventricular arrhythmias occurred; 5) in an abstract on cats after right stelllectomy, emotion lengthened the QT interval and most commonly caused AV nodal tachycardia, with frequent premature ventricular complexes and ventricular tachycardia in some cats (no quantitative data provided or information given on the number of cats with sustained or nonsustained ventricular tachycardia); 6) in dogs, right stellate ganglion interruption reduced the ventricular fibrillation threshold 48% compared with a 72% increase following left stellate ganglion interruption; 7) in a clinical abstract, exercise-induced ventricular arrhythmias (type not specified) occurred in six of 34 patients after right stelllectomy for Raynaud’s syndrome (no prestelllectomy control results) compared with one of 32 neurally intact patients, one of 19 with left stelllectomy and none of 18 patients with bilateral stelllectomy; 8) in a more recent clinical abstract, 26 patients underwent right and then left high thoracic sympathetic interruption for primary palmar hyperhidrosis and had no arrhythmias.

From the present study, one might reason that if sympathetic imbalance were the arrhythmogenic mechanism, even partial surgical relief (assuming it was properly done) should provide a cure. One would not think that total left-sided cardiac sympathectomy would be necessary to reestablish “balance.” Yet, after surgery, six patients still had sudden death, and 27 still had syncope or cardiac arrest. A counterargument to this logic might be that sympathetic imbalance from birth creates permanent myocardial changes corrected only by complete left-sided sympathetic denervation. In a recent report, however, one patient after autotransplantation and complete cardiac denervation continued to have the long QT interval, sporadic ventricular tachyarrhythmias and, eventually, sudden cardiac death.

From these and other uncited studies (for reviews see Corr and Schwartz and Priori), it would appear reasonable to conclude that left and bilateral sympathetic interruption can be arrhythmogenic, particularly during acute myocardial ischemia and in the LQTS, and that left and bilateral sympathetic stimulation can be arrhythmogenic, but that right stelllectomy does not seem to be particularly arrhythmogenic. This conclusion would again challenge the hypothesis of sympathetic imbalance.

Intrinsic Abnormality in Repolarization

The second hypothesis, that of an intrinsic abnormality in myocardial repolarization, can explain the QT prolongation, prominent and peculiar T and U waves, T wave alternans, and ventricular tachyarrhythmias. In addition, it can serve as the mechanism for the acquired LQTS, which the sympathetic imbalance concept cannot. It might also explain the apparent sinus node abnormalities if the involved channel contributed to normal sinus node activity.

This hypothesis assumes that the cause of abnormal repolarization lies within the heart itself, perhaps an abnormal channel protein reducing or blocking an outward repolarizing potassium current or increasing an inward depolarizing calcium or sodium current. This results in afterdepolarizations, probably early afterdepolarizations, that cause triggered activity and torsades de pointes. Blockade of potassium channels or augmentation of the calcium current can produce early afterdepolarizations that lengthen repolarization and cause triggered activity and ventricular tachyarrhythmias experimentally. Antiarrhythmic agents such as the class IA drugs that provoke the acquired LQTS and torsades de pointes are potent potassium and sodium channel blockers. Magnesium suppresses the early afterdepolarizations and ventricular tachyarrhythmias in these animal models as it suppresses ventricular tachyarrhythmias in patients with the acquired LQTS. In addition, deflections consistent with early afterdepolarizations have been recorded from the hearts of patients with the idiopathic LQTS and a patient with the acquired LQTS.

Where does this leave the role of sympathetic stimulation? In the animal model of LQTS produced by cesium chloride administration, bilateral and left ansae subclaviae stimulation produces larger early afterdepolarizations and increases the prevalence of spontaneous ventricular tachyarrhythmias to a greater degree than does right ansae subclaviae stimulation. However, during norepinephrine infusion, the amplitude of early afterdepolarizations increases equivalently in both ventricles in a dose-related fashion. These findings suggest that there is nothing unique in the response of the right and left ventricles to cesium or to uniform catecholamine stimulation by drug infusion, only to left ansae subclaviae stimulation. The larger early afterdepolarization amplitude in the left ventricle during left or bilateral ansae subclaviae stimulation may simply reflect more norepinephrine released and more myocardium affected. It is known that the left ansae subclaviae innervates most of the ventricular myocardium, or at least a much larger amount of the ventricle than does the right stellate ganglion. Further, norepinephrine content is greater in the left than in the right ventricle. Finally, left stellate ganglion stimulation results in a greater overflow of norepinephrine in coronary sinus blood than does right stellate ganglion stimulation.

These data suggest that the left stellate ganglion exerts a quantitatively greater adrenergic influence on the ventricles than does the right stellate ganglion. This quantitative difference, which results in more ventricular mass being affected because of more norepinephrine being released, rather than qualitative differences between stellate ganglia or left...
and right stellate imbalance, may be the basis for the greater arrhythmogenic potential of left stellate ganglion stimulation compared with right. It also may account for the beneficial effects after surgical interruption of the left stellate ganglion. Sympathetic stimulation, primarily left, caused by physical or emotional stress could periodically increase the amplitude of early afterdepolarizations that were present because of the intrinsic repolarization abnormality, to reach threshold and provoke ventricular tachyarrhythmias. Surgical interruption of the left stellate ganglion could eliminate the arrhythmias without consistently shortening the QT interval because the early afterdepolarization would still exist, but would be subthreshold.

Analysis of the observations of Schwartz et al offers further insight into the arrhythmogenic actions of sympathetic neural stimulation. The fact that surgical interruption of the left stellate ganglion reduces the incidence of syncope and sudden death after unsuccessful treatment with β-adrenoceptor blockers underscores the potential arrhythmogenic role of α-adrenoceptor stimulation in the LQTS, because severing neural innervation provides α- as well as β-adrenoceptor interruption. That conclusion suggested a series of experiments in which we showed that α1-adrenoceptor stimulation increased and α1-adrenoceptor blockade decreased early afterdepolarization amplitude and ventricular tachycardia prevalence.35,46,47 It is possible that there are groups of patients with the long QT syndrome in whom α1 rather than β-adrenoceptor stimulation is more arrhythmogenic, or vice versa. Results from specific autonomic challenges might better direct therapy. For example, patients who have induction of large-amplitude early afterdepolarizations and replication of their ventricular tachyarrhythmias during phenylephrine infusion and not during isoproterenol infusion might be better treated with α- than β-adrenoceptor blockers. They may represent the treatment failures to β-adrenoceptor blockers. If the reverse occurred, β-adrenoceptor blockade might be preferable. Combined α- and β-adrenoceptor blockade might be tried. Recent data suggest that use of drugs that increase potassium conductance48 or even prostaglandins49 might also be considered.

In summary, the weight of the evidence suggests that an intrinsic myocardial abnormality in repolarization is responsible for the LQTS, leading to early afterdepolarizations, triggered activity, and ventricular tachyarrhythmias. It would seem reasonable that pieces of myocardium obtained at surgery or by endomyocardial biopsy could be studied by modern biochemical and electrophysiologic approaches, including voltage clamp analysis of disaggregated myocytes, patch membrane, and lipid bilayer techniques. We used the lipid bilayer method to study a myocardial biopsy from one patient with aborted sudden cardiac death caused by the LQTS. The patient had early afterdepolarizations demonstrated during epinephrine challenge but had a normally functioning calcium-activated potassium channel during the lipid bilayer study.50 We were not able to estimate the number or distribution of calcium-activated potassium channels, however.

Conclusions

The current study presents an important advance that offers therapy capable of saving many young lives. Nevertheless, cardiac events still occurred, indicating that left cardiac sympathectomy is not universally successful,13 possibly because of a mixed population of patients. For some patients, long-term pacing51 and/or implantation of a cardioverter-defibrillator may be necessary.

In the future, further attempts at understanding the electrophysiologic and genetic abnormalities should be made.52,53 Recently, a DNA marker at the Harvey ras-1 locus was shown to be linked to the long QT syndrome. This finding confirms the genetic basis of the disorder and localizes this gene to the short arm of chromosome 11.54 Either ras or a gene tightly linked to ras appears responsible. A molecular probe to the gene would unerringly be able to detect patients who have the long QT syndrome. Interestingly, the protein encoded by the gene is one of the G proteins and may help control the passage of potassium ions through membrane channels. It should be possible to identify, clone, and map the abnormal gene and even express it in transgenic mice.55 In this way, one can identify precisely the repolarization abnormality for this Rosetta stone and possibly direct therapy with more specificity than producing left-sided sympathetic denervation of the heart.

References


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