Long QT Interval Syndrome
A New Look at an Old Electrocardiographic Measurement—The Power of the Computer

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The quest to improve the predictability of the long QT interval syndrome has been high on the research agenda of many investigators because the syndrome has a potential malignant end point of sudden death. Unfortunately, much of the data has been sparse and anecdotal. Most recently, Ward1 has written a critical and witty evaluation and summary of the reports written on the long QT interval syndrome during the past decades. His opinion may be summarized by his introductory commentary: “The definition and significance of this abnormality has become obfuscated by confused and conflicting reports concerned with this simple notion.”

The first problem is the origin of the number used as the upper limit of normal for the corrected QT interval of 440 msec. A major reference appears to be the Electrocardiographic Text Book,2 in which the normal adult range of the QT interval corrected is given as 0.35–0.44 second. Of interest, only three references were used to support this QT interval: two from studies in children and a third that was unpublished at the time. Therefore, there had been no formal reason or basis for such “normal” values. Most recently, however, a large electrocardiogram database from more than 1,300 apparently healthy Caucasians living in the west of Scotland were collected in tabular and digital form by Macfarlane and Lawrie.3 The data are divided by sex and age. The upper limits of the QTc (Bazett) at the 96% confidence limit ranged from 463 msec (men, 18–29 years old) to 506 msec (women, more than 50 years old). Because these data demonstrated a great variance in the normal QTc, the QT interval must be corrected not only for heart rate but also for age and sex. The following fundamental concept emerges from these studies: If predictability is the goal, not only must the QT, be related to a normal stratified data base but it must also be related to a homogeneous data base of patients with a well-documented pathological end point such as ventricular fibrillation or ventricular tachycardia. If one merely examines a normal data base of QT in relation to an individual case, one can only state that the case in question is, for example, three standard deviations from the normal and therefore can be called abnormal, but not necessarily pathological.

A second important theme evolved from the literature is the need to subset the long QT interval into the actual disease entity studied. For example, in the congenital long QT interval, the QT intervals are usually markedly prolonged, often more than 515 msec.4–8 Furthermore, there are other characteristic diagnostic changes in the electrocardiogram, including T wave inversion, late coupled ventricular extrasystoles, and sinus bradycardia. The actual diagnosis of these syndromes includes not only the electrocardiogram but also the clinical family histories. In the case of post–myocardial infarction, the summary of the papers reveals that the results are divergent and inconclusive.9,10 Unfortunately, many of the studies report corrected QT intervals rather than the actual QT interval,11 and raw heart rate data are not reported. One of the problems in the use of the correction formulas is that at slow heart rates, especially those less than 60 beats/min, practitioners may tend to undercorrect (reduce), and at faster rates they may overcorrect (increase), the measured QT interval by the nature of the correction formula. One of the major criticisms of these reports is the lack of formal analysis of survival using defined end points and actuarial methods; they fail to account for other possible risk factors such as poor left ventricular function, ventricular arrhythmias, and residual ischemia by their failure to use multivariate techniques. Of importance, I conclude that neither the measured QT interval nor any form of corrected value can be used to determine risk or prognosis in patients with coronary artery disease, myocardial infarction, mitral leaflet prolapse, or any other acquired cardiac abnormality. The risk in these abnormalities should be stratified using other means. Certainly, new and creative research is needed. Consequently, after a review of the literature to date, the presentation of a
study with a new approach to the comprehension of the long QT syndrome is a breath of fresh air.

The article by Benhorin et al in a recent issue of Circulation, “The Long QT Syndrome: New Electrocardiographic Characteristics,” represents a study from a group who have had a long experience in the study of patients with the long QT syndrome. This article represents a potentially important step forward because it ushers in the dynamic use of the computer to obtain new insights into the understanding of the clinical and physiological meaning of the electrocardiogram waveforms. Using the power of having the electrocardiogram in digital form, the investigators were able to dissect out and test the waveform components of the QT interval: 1) duration (SoTmc), the heart rate–corrected S wave offset (So) to T wave absolute maximal amplitude (Tm) interval; 2) late duration (TmTo): Tm to T wave offset (To) interval; and so on. These variables were identified as independent diagnostic predictors of this group of patients with long QT intervals. Five measurements had the highest diagnostic performance, with an excellent sensitivity of 95% and specificity of 96%. Of significance, one of the predictors (SoTmc) had a very high specificity of 95% and a reasonable sensitivity of 81%. The major advantage of this measurement is that it is easy for the reader of the electrocardiogram as well as the computer to make this measurement. Furthermore, this measurement has been demonstrated to have a very high reproducibility by the computer and may be better than the measurement of the QT interval.

What do these new measurements mean? The authors do not offer any explanation for these new measurements, but put forth the hope that they may improve our understanding of the abnormalities that occur in the long QT interval syndrome. Figure 1 of that article represents an intriguing opportunity for speculation. The pronounced malalignment of the six precordial T waves in this patient with long QT interval syndrome is suggestive of a high degree of dispersion of repolarization. This high degree of dispersion may be a possible clue to the detection of the postulated dispersion of refractory periods—electrophysiology of the architecture for reentry arrhythmias. In summary, this new look at an old electrocardiographic measurement holds the promise of obtaining exciting new insights into the mechanisms of sudden death.

The major hope of Benhorin et al was for the development of new electrocardiographic criteria that can better predict the malignant end points of ventricular arrhythmias that may indeed lead to sudden death. Unfortunately, these new variables did not predict the patients who were symptomatic in this data base. A possible explanation is that the data are from a very broad range of patients, from patients who actually had sudden death to relatives of patients with sudden death. As the authors themselves state, there is a need for a larger data base so that these important variables can be subsetted to determine the power of each one of them in the prediction of malignant arrhythmias.

Statistics

Another important contribution of this investigation is the use of sophisticated statistical methods. The following comments regarding Benhorin et al are those of Gregory Campbell, PhD (Research Mathematician Statistician, Division of Computer Research and Technology, Laboratory of Statistical and Mathematical Methodology, National Institutes of Health; personal communication).

At issue is the use of the statistical procedure known as the bootstrap. The bootstrap is a particular statistical technique in a class of procedures known as sample reuse or resampling plans; another member is the jackknife. The bootstrap is a device that can be used in a wide variety of situations and for almost any statistic. By sampling repeatedly from the same data that are used to form the statistic, a sampling distribution and an associated standard deviation can be calculated with very few distributional assumptions; this highly computational approach is inherently nonparametric. The data enable one to “pull oneself up by one’s bootstrap.”

The bootstrap and the jackknife have been used successfully in statistical classification (also called discriminant) analysis. Both have been touted as alternatives to the tried and true method of splitting the data into two groups, a training set and a test set. In contrast to that method, the bootstrap uses all the data simultaneously. Studies in this area have demonstrated that the bootstrapped estimates of the misclassification rates compare favorably with those one would obtain from a test set. The bias is surely reduced (but not necessarily eliminated) compared with using the same data to develop the classification rule and to test it. Of course, the bootstrap is still no substitute for an independent confirmation of the results with a second set of data. What is less clear is whether the bootstrap is inferior or superior to the approach of splitting the current data into two groups, a training and a test sample. The bootstrap trades unbiasedness of the two-group approach for the power in terms of smaller standard deviations which the bootstrap ensures. Studies of the mean square error, which attempts to combine the bias and the variance, can compare these approaches in a variety of settings.

In this article the bootstrap is used in the estimation of the error rates associated with logistic regression models in Table 5 and in Figure 2. As expected in Figure 2, the bootstrapped receiver operating characteristic (ROC) curve reduces the upwardly biased ROC curve based on the crude estimates. In addition, one can see the confidence intervals, if so desired, on the curve. If one were to have doubts about the approach, one could appeal to a second test set of data or one could resort to a simulation experiment to check whether the bootstrap performs well in a similar setting where the truth is known.
**Summary**

Because clinical studies frequently include only a marginal number of patients, these relatively new, robust statistical techniques will have increased use. The utilization of ROC curves will be more commonplace because they permit the comprehension of the data in a more dynamic mode than merely the reporting of sensitivities and specificities.

**References**


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