Clinical diagnosis of long QT syndrome: back to the caliper

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Online publish-ahead-of-print 20 February 2007

This editorial refers to 'Diagnostic criteria for congenital long QT syndrome in the era of molecular genetics: do we need a scoring system?'¹ by Hofman et al., on page 575

In the last 10 years, the management of cardiac arrhythmias has evolved to an impressive pace, thanks to the development of highly sophisticated technologies for diagnosis and treatment. Mapping of the site of origin of arrhythmias, ablation, and implant of defibrillators have reduced the importance of the traditional approaches based on electrocardiographic reading and prescription of drugs. In this context, inherited arrhythmic diseases such as long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia, short QT syndrome, and Brugada syndrome represent the exception in which the ECG has remained the pivotal diagnostic tool. When approaching the diagnosis of one of these diseases, the cardiologist has to leave fancy computer screens and go back to the ‘ruler and caliper’ to measure the duration of an ‘interval’ or the elevation of an electrocardiographic ‘segment’. This apparently simple diagnosis, however, is far from being easy and even ‘experts’ in the field may face substantial diagnostic dilemma.

The diagnosis of the LQTS, for example, ‘simply’ requires the measurement of QT interval duration on a standard ECG recording and the correction of the duration for ‘heart rate’ using the Bazett’s formula. In real-life, however, the diagnosis is far from being straightforward and it is often more elusive than anticipated for a variety of reasons that encompass the difficulty to define the ‘end’ of the T-wave, the lack of linear behaviour of the Bazett’s formula at slower and faster heart rates, and the arbitrary definition of the gender-based diagnostic cut off values that define an abnormally prolonged QTc (QTc > 440 ms for males and QTc > 460 ms for females).² A large body of literature has been dedicated to the discussion of limitations of manual and automatic QT interval measurement²,³ thus promoting the interest in the development of new diagnostic criteria for LQTS. Two point score systems have been developed in an effort to enhance the diagnostic reliability of clinical parameters and have become quite popular even if their accuracy has not been systematically investigated. The Keating criteria are a binary combination of QTc values with LQTS-related symptoms.⁴ The Schwartz score incorporates, besides QTc, other electrocardiographic features of the LQTS in addition to the patient’s clinical and familial characteristics.⁵ At the end, scoring systems allow for an estimation of a certain probability of the LQTS. The specificity of these scoring systems is rather good but the low sensitivity has been a matter of dispute.

The advent of molecular diagnosis has provided the unique opportunity to address this debate allowing to compare the accuracy of the different diagnostic strategies in patients in whom genetic analysis has confirmed or dismissed the presence of the disease. This is the exercise that Hofman et al.⁶ have performed in the attempt to compare the diagnostic accuracy of QT interval measurement vs. the use of the 1993 Schwartz⁵ criteria or the Keating⁵ criteria in the diagnosis of LQTS.

Hofman et al.⁶ studied 513 relatives of 77 LQTS probands with a known disease-causing mutation. All family members were more than 10 years of age and both scores were obtained blinded to the result of genetic testing. The Schwartz⁵ criteria identified ‘high probability of LQTS’ (score > 4) in 41 of 208 mutation carriers, yielding 19% sensitivity and 99% specificity. The Keating⁵ criteria detected more mutation carriers, yielding 36% sensitivity and 99% specificity. The authors conclude that, despite high specificity, the sensitivity of both criteria is probably too low to be adopted in clinical practice. In a second part of the study, the authors sought to determine the diagnostic accuracy of different values of QT duration based on the manual measurement of QTc obtained using Bazett’s formula. Interestingly, a QTc ≥ 430 ms was identified as the optimal value to distinguish carriers (≥ 430 ms) from non-carriers (< 430 ms), yielding 72% sensitivity and 86% specificity.

Before we comment on the practical implications of these results, few considerations on the limitations of the study are needed. First of all, the study has been performed in family members of positively genotyped patients thus excluding probands. As a practical consequence, the results of the study cannot be applied to the clinical evaluation of an individual without family history of the disease. A...
second limitation derives from the fact that the authors have excluded children < 10 years of age because of the age-dependency of the QTc. This choice is rather arbitrary and profoundly limits the applicability of results because very often the diagnosis of LQTS has to be made in the paediatric population that therefore cannot benefit of the data provided by this study.

Bearing these limitations in mind, the study by Hoffman et al.\(^6\) raises the important point that the use of the more complex scoring systems is unlikely to improve diagnostic accuracy when compared with the simple measurement of the QT interval. On the contrary, the score systems increase the number of the ‘missed’ diagnosis (false negatives) that of course represents a major drawback to the use of the scoring systems.

In support to the data presented by Hoffman et al.\(^6\) are the results of a similar study that we performed in our cohort of genotyped LQTS patients in 2003\(^7\) in a group of 1209 individuals including 254 probands, 443 genetically affected, and 512 genetically non-affected family members. Our objective was to define sensitivity and specificity of QTc measurement (using Bazett’s formula) and of the use of the 1993 Schwartz’s criteria\(^5\) in identifying LQTS affected individuals. No limitations of age were used in our study and probands were also included in the analysis. The study showed that the performance of QTc interval measurement was better than that of the Schwartz’s score and the best cut off to call an individual as affected by the disease was a QTc > 440 ms that had an 81% sensitivity and 90% specificity. The best performance of the score system was found for a cut off ≥ 2 (76% sensitivity and 90% specificity). Interestingly, the same cut off was also the most accurate in the study by Hoffman et al.\(^6\) (Figure 1).

Taking the data of Napolitano and Hofman together, we come to the conclusion that (1) there is no benefit to introduce the use of the scores in the clinics and (2) genetic analysis is the only method to identify the relatively high proportion of silent carriers of disease causing mutations. In practical terms, when molecular diagnosis is available in a family, there is no question that all members should be screened to define if they carry the disease causing mutation or not.

In this respect, we do not agree with Hofman et al.\(^6\) when they propose that it may be worthwhile to use clinical criteria to select individuals suitable for molecular screening. When the mutation is known, DNA analysis to search for a single mutation is rather cheap and provides results within few days and therefore it is perfectly reasonable to offer this test to all family members irrespective of their clinical phenotype. Our data\(^6,9\) have suggested that at ~ 30% of genotyped individuals have a completely normal QT interval and a non-diagnostic score. Therefore, it is wrong to limit access to genotyping based on phenotypical characteristics.

Accordingly, we feel that every first-degree relative should be offered genetic screening when the causal mutation has been detected in the proband. This service should even be strongly encouraged in the light of the prominent 10% risk of major cardiac events when silent gene carriers are left untreated.\(^6\) To accomplish a service of providing a fast and reliable test result without substantial costs for fully-informed and prepared individuals, the call of Hofman et al.\(^6\) for a centralization of the care of patients with inherited cardiac arrhythmias in specialized cardio genetic facilities should be fully endorsed. In centres specialized in the care of patients with inherited arrhythmogenic diseases, the expertise of trained staff in accurate and reproducible ECG reading is expected to be able to identify a high proportion of ‘probands’ suitable for genetic testing, thus optimizing the cost–benefit ratio of molecular diagnostic.

Conflict of interest: none declared.

References


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**Figure 1** Sensitivity and specificity of the different cut off values for QTc (Bazett’s formula) (Panel A) and for the 1993 Schwartz’s score (Panel B) calculated on the basis of the ability to correctly detect as ‘affected’ or ‘non-affected’ by long QT syndrome based on the results of genotyping. Data from Napolitano et al.\(^2\).