QUESTION:

In a patient with different QT intervals, which one will give the highest prognostic accuracy?

REPLY:

First, there are two possibilities: I) It is not known, if the patient (subject) presented in the question has the congenital Long QT Syndrome (LQTS), or II) It is already known that the patient has LQTS. Several factors influence and have to be taken into account when considering the prognostic accuracy of QT intervals with different lengths in the patient. From the prognostic point of view, it is most important to know, if the subject has LQTS. This will be dealt first. For simplifying the question, the prognostic accuracy of QT intervals with different lengths in patients (subjects) without the congenital LQTS, such as in patients with the acquired LQTS, with a previous myocardial infarction, or in general population, is not specifically discussed here.

I

The following ECG criteria based on a standard 12-lead have been proposed to discriminate LQTS patients and unaffected subjects: age from 1 to 15 years: QT interval corrected for heart rate by Bazett's formula (QTc) >0.46 sec = affected, QTc <0.44 sec = unaffected; men: QTc >0.45 sec = affected, QTc <0.43 sec = unaffected; and women: QTc >0.47 sec = affected, QTc <0.45 sec = unaffected (Moss et Robinson 1992). By giving two different cutpoints that are further adjusted for age and gender, these criteria increase positive and negative predictive accuracy of QT-based diagnosis of LQTS, however, leave the subjects with QT intervals in the borderline range under uncertainty in terms of diagnostic and prognostic accuracy. This uncertainty extends also to a subject with QT intervals of different duration in different QT ranges. The diagnostic and prognostic accuracy is further

modified by several other factors that influence the length of QT interval. These factors include: 1) intra- and interindividual variability of the QT interval measurements, 2) the choice of the lead of the standard 12-lead ECG used in the QT interval measurements, 3) the QT interval measured on the Holter may be substantially longer or shorter compared to the QT interval measured using the same complex on a standard ECG, 4) the automatic methods for QT interval analysis have not yet been well standardized (particularly in patients with abnormalities of T wave morphology) and may give substantially different values than manual measurements, 5) difficulties in appropriate correction of the QT interval for heart rate due to a) sinus arrhythmia b) limitations of the heart rate correction formulas (Bazett's formula is most often used although it overcorrects QT values at high heart rates, ideally QT heart rate correction would need individual nonlinear approach) c) hysteresis phenomenon, 6) autonomic tone, 7) mechano-electric coupling (e.g., an increase in afterload shortens the action potential duration), 8) body temperature, 9) electrolyte disturbances, 10) several disease states: a) myocardial infarction b) diabetic autonomic neuropathy c) alcoholic liver disease d) primary autonomic failure e) atrial fibrillation f) adult coeliac disease g) cerebral stroke h) mitral valve prolapse, 11) various cardiac and noncardiac drugs, 12) polymorphism of the ion channel genes, 13) and importantly the genotype of the patient with LQTS.

A selected cutpoint of the QT interval for diagnostic purposes of LQTS is always a compromise in terms of balance between specificity and sensitivity, however, it is an important choice as a correct decision whether a subject has or does not have LQTS yields prognostically fundamental information. Many other factors, than those which influence the length of QT interval per se, contribute to the diagnostic accuracy of different QT intervals and QT interval cutpoints. These factors are related to the predetermined probability of LQTS in the population or in the individual studied and include: the population studied (e.g., general population or members of a family with a patient with LQTS), and clinical history of the individual (no symptoms, syncope, torsade de pointes ventricular tachycardia, congenital deafness, family history). Therefore in practice, all diagnostically relevant information in

addition to the length of the QTc interval is taken into account when considering the diagnostic accuracy of different QTc cutpoints. In other words, the diagnostic accuracy of different QTc intervals and QTc cutpoints is dependent on the subject's clinical and family history as well as other factors such as T wave morphology and occurrence of T wave alternans that have influence on the probability of LQTS in the individual. Therefore diagnostic criteria for the congenital LQTS that give scores both to several ECG findings (e.g., different scores for QTc ≥ 480 msec, 460-480 msec, or 450-460 msec [in males]) and clinical history have been developed (Schwartz et al. 1993). The total score cathegorizes a subject of having definite, intermediate or low probability of LQTS. Taken into account the abovementioned confounding factors and the fact that prolongation of the QTc interval may be variable in patients with the congenital LQTS, QTc being prolonged, intermittently prolonged, borderline in length or even normal, it is important for achieving the best diagnostic accuracy to individually adjust the cutpoint(s) for QTc based on all available information.

A standard 12-lead ECG for QT interval measurement should be obtained in controlled conditions while a subject is physically and emotionally restful. All the confounding factors should be avoided or minimized. As the length of the QT interval has spatial and temporal variability, representative cycles and a lead (preferably a lead with the maximum QT interval with distinct starting and ending points of QT) should be selected for standardized measurement of QT interval. When a subject has QTc intervals of different lengths on different ECGs obtained by standardized methods and during standardized conditions and LQTS is suspected, it would be recommended to take the longest ones into consideration for getting the highest diagnostic accuracy in terms of sensitivity. QTc ≥ 460 msec as a cutpoint yields good positive predictive value with better sensitivity than the higher cutpoints and QTc ≥ 470 msec in men and ≥ 480 msec in women excellent positive predictive value for the congenital LQTS (Vincent et al. 1992). It should be borne in mind that there are differences in the length of QTc intervals and triggers of events between patients with different genotypes. Patients with LQT3 tend to have longer QTc intervals

than patients with LQT1 and LQT2 and have high risk of events and excessive prolongation of the QT interval during sleep or at rest at slow heart rates, whereas patients with LQT1 have susceptibility to events during adrenergic triggers such as exercise and swimming.

In some patients with suspected congenital LQTS, the QTc interval is only intermittently prolonged. This may not be detected, even if repeated standard 12-lead ECGs are recorded several times on different occasions and the longest QTc intervals are taken into consideration. It has been proposed that ambulatory ECG recordings may include significant diagnostic information in the case of patients with suspected congenital LQTS (Eggeling et al. 1992). However, even healthy subjects may have QTc intervals of order of 500 msec during Holter recordings. Furthermore, temporal variability of QT is increased in patients with LQTS compared with unaffected subjects (Perkiomaki et al. 2002). Therefore the longest good quality QTc intervals from Holter recordings should be taken into consideration, and QTc values that are clearly over 500 msec may give some additional support for diagnostic purposes of LQTS. An increase in the QTc interval during moderate exercise can be a helpful diagnostic finding in congenital LQTS patients with borderline long QTc intervals at rest (Vincent et al. 1991). When the congenital LQTS is suspected and the diagnosis cannot be confirmed based on ECG and clinical criteria, genetic testing should be performed when possible.

II

In patients with confirmed diagnosis of the congenital LQTS, the genotype influences the clinical course. However, the length of QTc interval yields prognostic information independent of the genotype in these patients. It has been shown that a longer QTc is significantly associated with an increased risk of cardiac events with a hazard ratio of order of 1.06 for each 10 msec increase in QTc. Substantially higher proportion of patients with QTc between 441 msec and 500 msec than patients with QTc ≤ 440 msec, and even higher proportion of patients with QTc > 500

msec, have cardiac events (Zareba et al. 1998). In a patient with already confirmed diagnosis of the congenital LQTS, several other factors than genotype and the length of QTc interval may influence the prognosis. If the patient has reliable measurements of QTc intervals with different lengths, one could assume that taking the longest ones into consideration yields the best incremental prognostic information. However, all the confounding factors that are discussed above should be kept in mind.

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