The quest to facilitate the diagnosis of the long-QT syndrome (LQTS) and even to predict genotype is never ending. The study by Sy et al published in the current issue of Circulation adds a new piece to the puzzle and has the potential to be very useful.

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Since the early days, diagnosis of the long-QT syndrome (LQTS) has undergone several levels of progressive upgrade. Initially, the diagnosis was made only in the presence of multiple factors, such as very bizarre T waves and marked prolongations of the QT interval in a child or teenager or abrupt loss of consciousness during emotional or physical stress, and it also required one of the few medical doctors who had heard about LQTS. The first attempt to provide diagnostic criteria for LQTS came in 1985 and, in their simplicity, they are still useful now for a first assessment (Table 1). As the disease became better known, as was bound to happen given its prevalence (1 in 2000), a new set of more specific diagnostic criteria to discriminate between subjects likely or unlikely to be affected by LQTS was proposed and provided a quantitative score.

Those criteria, subsequently referred to as the “Schwartz criteria,” were developed before the genetic revolution, which has progressively led to the identification of 13 LQTS disease-causing genes. As a consequence, a lot of weight has been placed on the actual duration of the QT interval. By the early 1990s, it had been recognized that the highest risk was for patients who had already suffered 1 cardiac event. It was thus essential not to miss the diagnosis in these patients; hence, weight was given to previous symptoms. Also, it was obvious that the disease had a genetic origin; it was running in families, and this prompted giving weight to the presence of a family member already diagnosed with certainty as affected by LQTS.

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The idea that patients might have LQTS with a normal QT interval was then just an unsupported hypothesis advanced in 1980 on the basis of much speculation and very little evidence. Eventually, this hypothesis was confirmed by evidence that, in LQTS, penetrance can be low and that several patients genetically affected may have a normal or borderline QT interval. Indeed, we now know that these silent mutation carriers are actually rather common, accounting for 36% of LQT1 patients, 19% of LQT2 patients, and 10% of LQT3 patients. Thus, the Schwartz criteria were not meant for and cannot be used to identify silent mutation carriers. Based on the growing clinical evidence, in 2006 there was an update, and the Schwartz score, ie, the number associated with a high probability of LQTS, was lowered from 4 to 3.5, which increased the sensitivity without reducing the specificity, thus reducing the number of false negatives. Unfortunately, 4 points are still often used as a cutoff, thus lowering the sensitivity of the score. Its best use is in identifying patients with a reasonably high probability of being affected and in selecting those who should undergo genetic testing. It has no use for patients with a normal or borderline QT interval.

In the current issue of Circulation, Sy et al propose that QTc prolongation at 4 minutes of recovery after an exercise stress test could be used for the diagnosis of LQTS among asymptomatic relatives of affected individuals. They also propose that their algorithm allows discrimination between LQT1 and LQT2 patients. In 69 relatives of genotyped LQT1 or LQT2 patients, they found that the combination of resting QTc with QTc at 4-minute recovery could predict a positive genetic result. Subsequently, they validated their findings in a second cohort of 152 relatives and in an independent third cohort of 45 probands with borderline LQTS who were subsequently confirmed to have a disease-causing mutation in the KCNQ1 or KCNH2 genes. They suggested a 3-step algorithm, with an initial evaluation of the basal ECG; patients with a normal or borderline QTc were selected for the second step analysis, consisting of evaluation of the QTc during the recovery phase of an exercise stress test. A QTc ≥445 ms during the fourth minute of recovery was identified as the optimal cutoff to distinguish between mutation and nonmutation carriers. This three-step approach led to a sensitivity of 0.9 and a specificity of 0.9 in the first cohort, which were essentially confirmed in the second and third cohorts. Additionally, the authors suggest considering QTc in the first minute of recovery to distinguish between probable LQT1 and probable LQT2 patients. They propose that this 3-step approach could be an alternative and more readily available tool to detect LQTS in first-degree relatives when...
genetic testing is not available or as an interim test while awaiting formal genetic results.

The study, conducted by a large group including several recognized experts, has merit, and the findings are convincing. There are some clinically relevant recommendations that can be drawn from this interesting study, even beyond what the authors actually propose.

The concept that further increases in QTc during the recovery phase of an exercise stress test could be useful for a diagnosis of LQTS was first suggested almost 30 years ago by Locati et al. In 1991, Vincent et al observed that LQTS patients were not able to shorten the QT interval normally during heart rate increases and suggested that QT adaptation during exercise could be useful for the diagnosis of borderline cases. Subsequently, many articles supported these initial findings, and, at the dawn of molecular genetics for LQTS, a gene-specific behavior during exercise was reported. In 1995, Schwartz et al observed that LQT3 patients shortened their QT interval much more than LQT2 patients and more than healthy controls in response to increases in heart rate, a finding also confirmed in comparison with LQT1 patients. A few years later, Swan et al observed that, during exercise, the QT interval shortens more in LQT2 than in LQT1 patients, and an exaggeration of QT prolongation is observed after physical effort mainly in LQT1 patients. The authors’ conclusions were that the recovery phase of the test may enhance the diagnostic accuracy in LQT1 and LQT2 patients, and they also attempted to combine resting QTc together with QTc during the recovery of exercise to increase diagnostic sensitivity and specificity. Very recently, Horner et al analyzed 243 subjects (82 LQT1, 55 LQT2, 18 LQT3, and 88 genotyped negative cases regarded as normal) using an exercise stress test and observed that a paradoxical increase in QTc during the recovery phase distinguishes LQTS patients, particularly LQT1, from controls and found that LQT2 patients also lengthen their QTc from the third minute of recovery.

Thus, many publications over the years have supported a contributory role of the exercise stress test in the assessment of a potential LQTS patient. So far, however, all previous studies have been limited by the absence of clear and easily applicable criteria validated in more than 1 cohort that could be used by clinical cardiologists without specific expertise in LQTS. The great merit of the work by Sy et al is to provide the general cardiologist with an easily implementable tool to be used whenever a LQTS case is suspected.

Sy et al propose using this 3-step algorithm for the asymptomatic family members of genotyped patients. Their rationale is that genetic testing remains unavailable to many and that there is often a significant time delay before results are available. However, if the proband has already been genotyped, genetic testing is likely to also be available to family members. Because it involves simply the confirmation of the presence of a specific mutation, the results should be available within 2 to 3 weeks. In addition, urgency is limited when dealing with asymptomatic family members. The cost for confirming a mutation is modest; in Europe, it varies between 70 and 300 Euros. If the asymptomatic family member undergoes genetic testing instead of the exercise stress test, the difference between the 2 costs will be small. In 2011, 2 consensus documents were published with the recommendations for the use of genetic testing in the clinical evaluation of genetically transmitted arrhythmogenic diseases. Both documents recommend genetic testing for family members of genetically confirmed LQTS cases regardless of symptoms or of baseline ECG. Indeed, once the disease-causing mutation is identified in the proband, molecular screening in family members is the best way to reach 100% sensitivity and specificity.

It seems to us that the ideal population in which to implement the clever algorithm proposed by Sy et al is that represented by probands, those patients who come for the first time to medical attention and are just suspected of being affected by LQTS. They are not yet genotyped, and the first
consensus documents, genetic testing is recommended when reported by Sy et al that we have decided to add it to a new probands subsequently genotyped on their algorithm works well in suspected borderline LQTS carefully designed study, Sy et al have already shown that improve sensitivity without reducing the specificity, we Sy et al. As our goal in updating the Schwartz score is to improve the Schwartz score by adding the solid parameter of evaluation of the recovery phase of exercise provided by Schwartz and Crotti Exercise, QTc, and LQTS 2183


Figure

PROBAND
G.T., 7 yrs
QTc = 630 ms

SISTER
S.T., 10 yrs
QTc = 605 ms

FATHER
V.T., 37 yrs
QTc = 584 ms

genetic testing in a family is a rather lengthy and possibly expensive procedure. In addition, it is urgent to establish whether they are indeed likely to be affected, because this may allow initiation of protection with β-blockers.7 In their carefully designed study, Sy et al have already shown that their algorithm works well in suspected borderline LQTS probands subsequently genotyped on KCNQ1 or KCNH2.

We are so convinced about the value of the finding reported by Sy et al that we have decided to add it to a new version of the Schwartz criteria (Table 2). According to the 2 consensus documents, genetic testing is recommended when the Schwartz score is ≥3½ or when LQTS is suspected based on the patient’s clinical history, family history, and ECG evaluation,19 ie, the three components of the Schwartz score. For a proband, it is true that molecular screening could not be available or could not be justified without a relatively high probability of LQTS; additionally, costs are higher, the time delay before a result can range from 2 to 8 months, and the probability of success remains around 75–80% even in patients with a clear LQTS phenotype. Thus, the time is ripe to improve the Schwartz score by adding the solid parameter of evaluation of the recovery phase of exercise provided by Sy et al. As our goal in updating the Schwartz score is to improve sensitivity without reducing the specificity, we followed the authors’ suggestion to use as cutoff 480 ms at the fourth minute of recovery, which reached 100% specificity. As this parameter, which is effective in LQT1 and LQT2 patients, is unlikely to be useful in LQT3 patients, and its role in genotype-negative patients is unknown, we consider it appropriate not to modify the scores associated with low (≤1 point), intermediate (1.5–3 points), and high probability (≥3.5 points) of LQTS.

The possibility of distinguishing genotypes based on clinical parameters is more complex. Few years have elapsed since first Moss et al20 and then Zhang et al21 proposed that genotype could be identified by specific ECG patterns. Some of them are indeed useful, but they are less than 100% correct. Examples exist that prove how very different ECG patterns can coexist within the same family.22 Figure 1 shows 3 ECG patterns for 3 members of an LQT2 family and illustrates how different inferences would have been drawn by examining only 1 member of this family. In our opinion, clinical parameters may help to make reasonable inferences but should not be used to genotype patients.

In conclusion, the article by Sy et al can usefully contribute to an early diagnosis of LQTS and could probably be even more useful in probands than in family members.

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