Exercise, Stand Up, Flip a Coin, or Just Say No Provocative Testing in the Child With Borderline QTc

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The 2011 challenge in considering a diagnosis of long-QT syndrome (LQTS) is best viewed as having 4 distinct clinical scenarios. The first and most straightforward is the family member with a genotyped kindred in whom, within a month, a relatively firm diagnosis can be obtained by family-specific testing, along with an ECG. The second, the genotype-negative index patient with otherwise unexplained, repeated, markedly prolonged QTc (>480), is similarly straightforward. The third scenario comprises family members of those same patients with unambiguous LQTS but no available gene. For those patients, their prior probability of having LQTS is estimated by careful pedigree analysis, with ECG findings combined with other clinical evaluation to help characterize the potential phenotype. The likelihood of making the diagnosis is relatively large (50%, 25%, 12.5%), depending on distance from an affected individual. The most challenging scenario is the young person with the “borderline” test obtained either for unrelated symptoms or during screening efforts before sports or medication without a clear family history. For that patient, the prior probability of having LQTS may as low or lower than the estimated gene prevalence of ≈1 in 2000 (0.05%). Indeed, in that setting, even genetics sometimes leaves the clinicians challenged when the result returns with a variant of unknown significance, requiring further pedigree analysis. In that context, the careful descriptive study of exercise QT dynamics by Berger and colleagues in this issue of Circulation: Arrhythmia and Electrophysiology adds useful information to this challenge.

The study itself is straightforward: 94 boys and girls, 8 to 17 years old, were recruited for a bicycle exercise test, which was performed using a standard ramp protocol. QT and heart rate were manually measured in lead II, using the well-accepted technique of extrapolating the primary downward deflec of the T wave to the baseline. Analysis was performed by focusing on baseline, peak exercise, and recovery, using Bazett, Fridericia, and Hodge correction techniques. Analysis included parallel examinations of the effect of time and heart rate. By 5 minutes in recovery, QT and heart rates had settled, with little subsequent change. Despite clear differences between sexes for exercise and recovery heart rate patterns, the rate-corrected QTcs were nearly comparable in recovery, and sex did not affect the ΔQTc. Their Table 3 has the most salient findings, both that >40% had recovery QTcb ≥450 ms and 14% to 15% had QTcb ≥470 5 to 6 minutes after the test. The frequency of elevated QTc declines with further waiting but remains at 5% to 10% even with prolonged recovery. The QTcb ≥470 corresponds to a 35-ms increase in QTcb, which is the 95 percentile. There are different patterns of QT recovery using different correction techniques, but the core physiology of delayed QT hysteresis remains. Heart rate, resting QT, and exercise duration dominated the multivariate influences on these findings.

Berger and colleagues focus on the normal behavior of the QT and QTc in response to exercise in subjects specifically screened to be normal. In doing so, they focus on the specificity of exercise testing and the implied likelihood of false-positives or possibly more appropriately, “physiological” positives.

Berger and colleagues’ findings are comparable to other recent analyses in adults, using both exercise and standing. Those studies have used provocative tests in both a small group of normal control subjects and in genotyped LQTS patients (and in the Viskin et al study, also including a small number with genotype-unavailable clinical LQTS). In the Wong et al study, comparison of control subjects with LQT51 and LQT52 used essentially identical measurement techniques, with an estimated sensitivity and specificity of 67%, for a 30-ms increase with standing and a sensitivity of 50% for a ΔQTc of 35 ms, corresponding with a specificity of 81% for the exercise hysteresis phenomenon used by Berger. This is also similar to the standing test proposed by Viskin and colleagues, in which normal control subjects had a 50-ms increase compared with 89 ms in confirmed LQTS patients, in whom at 90% sensitivity there was a 75% specificity for the QTc interval at maximal heart rate.

The insight that Berger and colleagues emphasize is to remind the clinician both of the frequency of these “abnormal” findings and the relatively low frequency of LQTS in the general clinic setting. None of these tests are used diagnostically for patients with incidentally identified QTc of 410 ms. Rather, they are used for those with QTc ≥440 to 470 ms, so that the 86 percentile of postexercise QTc will be around 480 to 490 ms.

For illustration of the potential value of this sort of testing, we will use a cutoff of 480 ms and Berger and colleagues’ false-negative rate of 14%, for a specificity of 74%, with an estimated sensitivity of 70%. For the family with unambig-
uous LQTS, the risks to an individual can be estimated as 50%, 25%, or 12.5%. This contrasts to the patient with a borderline finding (ie, a Schwartz score of 2 to 3) with no family history of LQTS. In that scenario, the risk can be argued to range from 1 in 4000 (0.025%) for the skeptic to possibly 1% for illustrating a high frequency in that setting. The Table summarizes the positive and negative predictive values, using those assumptions.

There is no debate that each “tie-breaker” test proposed has somewhat different test characteristics, both in how the test is performed and how different genotypes respond to the provocation. Those details probably are important in understanding QT dynamics in families with LQTS. From a diagnostic perspective, all share sensitivities that range from 50% to 80% and specificities that have a similar range. What these tests also share is that the positive predictive value of the test nearly disappears once there is no clear family history of LQTS. At the same time, the negative predictive value of a normal test can have exceptional predictive value in the low-incidence setting. This insight is gaining currency, with an increasing recognition of how important context is to interpreting both the baseline ECG and every test that is generated from that.

The implications of this logic are clear and force the clinician to place all testing in full context. For those with a clear family history, a negative predictive value of 88% may be insufficient, triggering choices to start β-blockers, avoid QT prolonging agents, and possibly restrict sports. For that patient, the testing provides nuance, may assist in anticipating genotype, and, if markedly abnormal (50-, 80-, or 200-ms increases, depending on the test), some confidence in the diagnosis, but may not change the clinical choices. For the patient without a family history and borderline resting QTc, the critical aspect of any of these tests may be that the negative predictive value of a ΔQTc of 10 to 30 ms is a potent finding in helping exclude the diagnosis. Those with “positive” tests will remain a challenge, though their likelihood of actually having LQTS remains very low. With the increasing recognition of how limited the “tie breakers” are in these low-likelihood patients, it may be that accepting ambiguity is more accurate than presuming false precision in making a firm diagnosis. Berger and colleagues’ data serve as an important reminder that LQTS is a disease that continually requires caution, skepticism, and indeed, some humility regarding our ability to be precise at the edges.

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Disclosures
None.

References

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Table. Positive and Negative Predictive Values for Different Incidences of LQTS With Test Demonstrating Sensitivity of 70% and Specificity of 74%

<table>
<thead>
<tr>
<th>Prior Probability of LQTS</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>50%</td>
<td>83%</td>
<td>74%</td>
</tr>
<tr>
<td>25%</td>
<td>47%</td>
<td>88%</td>
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<tr>
<td>12.5%</td>
<td>28%</td>
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<td>1%</td>
<td>2.6%</td>
<td>99.6%</td>
</tr>
<tr>
<td>0.1%</td>
<td>0.27%</td>
<td>99.9%</td>
</tr>
<tr>
<td>0.05%</td>
<td>0.13%</td>
<td>99.9%</td>
</tr>
<tr>
<td>0.025%</td>
<td>0.07%</td>
<td>99.9%</td>
</tr>
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