Drug Challenge with Epinephrine or Isoproterenol for Diagnosing a Long QT Syndrome: Should We Try This at Home?

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Editorial Comment

Diagnosing a congenital long QT syndrome (LQTS) is straightforward when a prolonged QT is present in a patient with arrhythmia-related symptoms and documented torsade de pointes. More often, however, a clear-cut diagnosis is not possible because: (1) QT-related arrhythmias are only rarely documented (except for patients with arrhythmic storms), and cannot be reliably and safely provoked. (2) Accurate measurement of the QT interval is not always easy and cannot be reliably and safely provoked. (3) Accurate measurement of the QT interval is not always easy and the presence of respiratory sinus arrhythmia complicates the estimation of the rate corrected QTc because the response of the QT interval to heart rate oscillations is not instantaneous. Consequently, the QTc calculated during heart rate deceleration will be shorter than the QTc calculated, only a few beats later, when the heart rate accelerates. (3) The QTc intervals of healthy individuals and that of patients with genetically proven LQTS overlap to such extent that one third of LQTS gene carriers and a similar number of healthy individuals have “borderline QT,” that is, a QTc between 430 and 460 ms. (4) Genetic testing is obviously useful when mutations are found but, with present technology, no mutations are identified in ≥25% of patients with LQTS. Furthermore, genetic analysis is only available in selected centers and often takes months to perform. Therefore, diagnostic and therapeutic decisions are still based, at least initially, on clinical grounds.

Since symptoms in the common types of LQTS are commonly triggered by stress, it is only logical to use sympathetic stimulation, in the form of adrenaline or isoproterenol infusion, as a challenge test to unravel a LQTS in questionable cases. In fact, physicians have used such tests sporadically without rigorous control. Two groups of investigators finally evaluated the effects of an epinephrine challenge in LQTS patients in a controlled fashion. First, Ackerman studied 37 patients with LQTS (19 with LQT1, 15 with LQT2, and 3 with LQT3) as well as 27 healthy controls. Epinephrine was started at “low doses” (0.05 μg/kg/min) and the infusion rate was gradually increased to a “high dose” of 0.3 μg/kg/min. The absolute (uncorrected) QT interval increased in all patients with LQT1, decreased in LQT2/3 and increased or decreased in different controls. Since epinephrine also increased the heart rate, the rate-corrected QTc actually increased in all patient groups. This increment in QTc was greatest for LQT1 patients, intermediate for controls and smallest for LQT2/3 patients. Yet, there was significant overlap between the QTc increment of patients and controls. More useful information could be retrieved from the effects of epinephrine on the absolute (uncorrected) QT interval. LQT1 patients could be completely distinguished from healthy controls during “low dose” epinephrine infusion because the QT duration clearly increased (by 82 ± 34 ms) in LQT1 patients while it remained essentially unchanged (shortened by 7 ± 13 ms) in the controls. However, the QT response of LQT2/3 patients overlapped that of the controls. Moreover, at higher epinephrine doses the QT of some controls also increased and “high dose” (0.3 μg/kg/min) epinephrine was only useful for distinguishing LQT1 from LQT2/3 because the QT of the latter shortened. Epinephrine-induced arrhythmias were of little diagnostic value because ventricular ectopy developed in 22% of controls and 9% of LQTS patients. It should be noted that before drug challenge only nine of the LQTS patients (all with LQT1) had nondiagnostic QT prolongation (QTc <460 ms). Therefore, little could be learned about the performance of this test for the patients who need it most (i.e., those with suspected LQTS who have nondiagnostic QT interval at rest).

The value of epinephrine for patients with (nondiagnostic) borderline QT prolongation was directly addressed by Shimizu. The QT response to epinephrine was studied in 15 patients who carried a LQT1 mutation but had a baseline QTc of ≥460 ms. These patients were compared to 19 LQT1 patients with obvious QT prolongation (positive controls) and to 27 noncarriers (negative controls). Indeed, the epinephrine-induced QT changes increased the sensitivity for diagnosing LQTS without affecting specificity.

It is difficult to merge the results of Shimizu and Ackerman because the two studies varied in terms of patients selection, epinephrine doses and end-points reported. Patients with LQT2 were not included by Shimizu in this study (see below). This limitation is important because the QT response of LQT2 in the Ackerman study resembled more that of the controls. Consequently, the absence of LQT2 patients in the Shimizu study biased the results toward a more favorable distinction between LQTS patients and controls. Also, “low” (0.05 μg/kg/min) and “high” (0.3 μg/kg/min) epinephrine doses were studied by Ackerman whereas only an “intermediate” epinephrine dose (0.1 μg/kg/min) was studied by Shimizu. Finally, the uncorrected QT, which was most useful in Ackerman’s study was not reported by Shimizu.

Shimizu et al. recently updated their experience with the epinephrine test. This time they prospectively studied all main genotypes (31 LQT1, 23 LQT2, and 6 LQT3). On the other hand, patients with LQTS and borderline QTc (the group of interest to most readers) were not reported separately. Epinephrine was injected as a bolus of 0.1 μg/kg followed by 0.1 μg/kg/min and the effects on the QT interval were assessed at two points in time: (1) At the peak effect of epinephrine (the time of maximal heart rate, shortly after thepeak effect of epinephrine (the time of maximal heart rate, shortly after the
bolus) and (2) at steady state (2–3 min later). The steady state effects reported by Shimizu in three genotypes can now be compared with those reported by Ackerman during low-dose epinephrine, whereas the peak effects of Shimizu can be taken as the equivalent of the high dose of Ackerman. Steady-state (Shimizu protocol) and low-dose epinephrine (Ackerman protocol) clearly differentiated LQT1 patients from controls because only the former developed a QTc increment of more than 35 ms. At the same stage of the test (steady state), the QTc of patients with LQT2 was also longer than the QTc of controls but only because LQT2 patients had a longer QTc to begin with (at baseline). The actual increment in QTc was similar (and therefore not diagnostic) for patients with LQT2/3 and controls. In contrast, during the peak effects of epinephrine a QTc increment of ≥80 ms discriminated between LQT2 patients and controls. The few LQT3 patients never developed sufficient QT changes to be distinguished from the controls. These observations are consistent with experimental work showing that α-adrenergic agonists amplify the dispersion of myocardial repolarization in animal models of LQT1 and LQT2 but reduce it in models of LQT3.

Although changes in T-wave morphology were not reported by Shimizu and Ackerman, it is clear from their figures that attention was paid to the T-wave changes induced by epinephrine. Furthermore, physicians performing similar epinephrine tests are likely to interpret the appearance of bizarre T-U waves during epinephrine challenge as “further proof” that a LQTS has been unraveled by sympathetic stimulation. This is because notched T waves also termed “T-wave humps” or “pathologic U waves” are considered distinctive of the LQTS when present at baseline. In this regard, the article by Nakagawa in this issue of the Journal, showing that abnormalities in T-U wave morphology are the rule (rather than the exception) in healthy women submitted to sympathetic stimulation, could not have come at a better time.

Nakagawa et al. studied 24 healthy volunteers (including 12 women). They first underwent sympathetic stimulation with isoproterenol and were later submitted to “autonomic blockade” (with propranolol and atropine). During isoproterenol infusion, the QTc of these healthy males and females increased to ≥550 ms, and ≥570 ms, respectively. Moreover, 60% of healthy females developed notched T waves while the remaining females developed biphasic T waves. Among males, 50% and 8% developed notched and biphasic T waves, respectively. These results are consistent with those reported by Magnano, who studied the effects of exercise, parasympathetic blockade (atropine) and sympathetic stimulation (isoproterenol) on the QT interval of healthy individuals. The following facts from the last two studies demonstrate that sympathetic stimulation (with isoproterenol) has a direct effect on the QT interval of healthy individuals: (1) The maximal QTc lengthening during isoproterenol infusion appeared before the maximal effect on heart rate. At identical degrees of tachycardia, every patient had more QT prolongation during isoproterenol infusion than during exercise, atropine, or atropine plus propranolol infusion. (3) Complex T-U morphology was induced by isoproterenol but not by exercise or atropine.

Since sympathetic stimulation has a direct effect on the myocardial repolarization of healthy individuals, a critical issue is quantifying the “normal” QTc response to epinephrine. The lack of QTc increment in the control group is what allowed for good discrimination between LQTS patients and healthy controls in the Shimizu studies. Yet, others report QTc increments of 450 ms and up to 500 ms among healthy controls challenged with higher doses of epinephrine. Genetic polymorphisms that are relatively prevalent in the population at large, affect the QT interval of healthy individuals, influence their response to drugs and probably affect their response to epinephrine. Since less than 100 healthy controls were included in all epinephrine studies combined, it is clear that the “normal” response of the QTc to epinephrine remains to be defined. Physicians willing to try this epinephrine-challenge test at home ought to keep this limitation in mind. It is also important to recall that most of the LQTS patients included in the epinephrine-studies (except for some LQT1 patients) had obvious QT prolongation at rest. The test may not perform as well in LQT-patients who have lesser degrees of QT prolongation at baseline. These reservations notwithstanding, it is evident that the epinephrine test can provide important information: (1) Epinephrine should first be given at low doses. Marked QT and QTc prolongation at this point would strongly suggest LQT1. Distinguishing LQT1 from other genotypes is important because these patients appear to be particularly responsive to β-blocker therapy. (2) Lack of response to low-dose epinephrine does not exclude the presence of LQT2 and LQT3 and increasing the dose of epinephrine could help reveal LQT2. However, the higher the dose the higher the likelihood of false-positive QT prolongation in a healthy individual. (3) LQT3 cannot be reliably distinguished from controls with epinephrine. However, LQT3 patients tend to have longer QT intervals than LQTS patients with other genotypes and borderline QTc at rest is only rarely seen in LQT3. Indeed, the epinephrine-challenge test appears to work best for those who need it most (LQT1 patients with borderline QTc) and worst for those who need it least (LQT3).

References

4. Vincent GM: How to make the diagnosis of long QT syndrome in patients with reduced penetrance of the prolonged QT phenotype when DNA testing is not available or is negative. Available at: http://www.lqts-symposium.org.

*Note: The dose of propranolol used by the authors (0.2 mg/kg over 30 seconds) is much larger than the usual therapeutic doses.


