

Important Developments in Long QT Syndrome

Not Only for Arrhythmia Specialists

Article, see p 2405

Sami Viskin, MD

Long QT syndrome (LQTS) can no longer be viewed as a medical curiosity, of interest only to arrhythmia specialists. With a prevalence of 1:2500, the congenital form, which can be easily recognized on a simple ECG, has an excellent prognosis with appropriate therapy but may result in sudden death at young age if left untreated. Moreover, with >200 medications—most with noncardiac indications—known to have arrhythmogenic QT-prolonging capabilities, it is imperative that physicians in all fields of medicine become familiar with LQTS. The article by Dagradi et al¹ in this issue of *Circulation*, describing excessive QT prolongation in a selected group of athletes, provides an occasion for reviewing recent developments in LQTS.

Important advances have been made in LQTS. In terms of diagnosis, 2 years ago, the group from Amsterdam published the largest series comparing the QT interval of patients with and without LQTS in *Circulation*.² The study confirmed that the QTc intervals of affected individuals, and those of healthy controls, have a normal distribution with significant overlap between the 2 distribution curves.² This means that there is not a single QTc value that distinguishes all normal from all abnormal ECGs. The authors provided an online calculator that computes the QTc from the measured QT and heart rate (<https://www.qtcaculator.org>).² This is important because too many physicians do not know how to calculate the rate-corrected QTc interval. The beauty of the calculator is that results are reported also as percentiles, thus providing information on the likelihood that a LQTS is present for the obtained QTc value.²

The ongoing coronavirus disease 2019 (COVID-19) pandemic has raised awareness of the issue of drug-induced LQTS because some of the medications proposed to treat COVID-19 can be QT-prolonging and as a result, potentially arrhythmogenic.^{3,4} It is important to recall that the risk of drug-induced torsades de pointes (for any QT-prolonging medication) is much higher for female patients, so much so that documentation of drug-induced torsades de pointes in a male patient without additional risk factors should prompt an investigation for possible hypogonadism,⁵ a treatable condition. It is worth remembering that potassium supplementation may reduce the risk of drug-induced torsades de pointes without diminishing the desired effects of the same medication.⁶

In terms of therapy, the recognition that an increased late-sodium current (I_{Na-L}), and not only blockade of the I_{Kr} —potassium current, plays an important arrhythmogenic role in drug-induced LQTS,⁷ paving the way for the use of mexiletine, a rather specific blocker of I_{Na-L} ,⁸ to treat torsades de pointes caused not only by different forms of congenital LQTS,^{9,10} but also by the more common drug-induced LQTS.¹¹

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Sports-Induced LQTS

In this issue of *Circulation*, Dagradi et al¹ present what could prove to be a new form of LQTS. ECG screening of athletes is mandatory in Italy. This screening led to the identification of 310 athletes who were referred to a specialty center in Milan to rule out LQTS.¹ Of those referred, 111 (35%) were excluded, mainly because their QT was normal. It should come as no surprise that 1 out of 3 athletes referred for suspected LQTS never had it; both underdiagnosis and overdiagnosis of LQTS are rampant. After further evaluation of the remaining 199 athletes with presumed congenital LQTS, 121 (60%) had genetic confirmation of the diagnosis, whereas 78 (40%) were originally considered to have congenital LQTS without genetic confirmation, also referred to as phenotype+/genotype– LQTS.¹

The genotype+/phenotype– group has always intrigued LQTS specialists, who ponder about the “missing gene.” In a recent multicenter study involving ≈1800 nonathletes identified as patients with congenital LQTS,¹² 11% had no identifiable mutations in any of the disease-causing genes. Patients with genotype-negative long QT had longer QT intervals and a similar clinical course, in terms of life-threatening arrhythmic events, as genotype-positive patients, demonstrating that the absence of genetic confirmation does not make a well-diagnosed case of LQTS any less dangerous.¹² The authors used genome-wide association analysis in all patients with LQTS and ≈10 000 healthy controls and reported fascinating results. Rather than mutations in a single missing gene, patients with phenotype+/genotype– LQTS had overrepresentation of genetic variants in several different genes. None of these variants (also present in healthy controls) functions as a standalone disease-causing genetic alteration. Yet, when inherited in combination, these genetic variants act as a polygenic risk factor, increasing the likelihood of clinically significant LQTS. The higher the burden of specific genetic variants in association, the higher the risk.¹²

Moving back to the athletes with abnormal QT referred to Milan,¹ let us focus on the phenotype+/genotype– long-QT group of athletes. Of 78 patients in this category, 33 athletes (representing 16% of the entire cohort of athletes with long QT) shared characteristics that would be considered unusual for a familial LQTS: they were all asymptomatic and their family history was invariably negative. Furthermore (and this is the novel finding), their abnormal QT normalized after a law-mandated disqualification from sports led to 3 to 6 months of detraining.¹ Last, resumption of intense sport activities in a few of these athletes led again to abnormal QT prolongation. In a way, these observations fulfilled revised Koch postulates of causality for the proposed entity of sports-induced LQTS.

Sports-Induced LQTS: What Is it and What Should We Do About it?

Critics will claim that these athletes do not have LQTS at all, noting that athletes, in general, have longer QT intervals than the general population. However, the mean QTc of athletes with this entity (QTc 492 ms) is >99.9th percentile of QTc values of healthy controls² and is longer than the 80th percentile of QTc values recorded among patients with congenital LQTS.² Thus, their QT interval was very long. In fact, the QTc of athletes with “sports-induced LQTS” was longer than that of athletes with genetically confirmed LQTS in the same study.¹ Furthermore, ECG examples presented (Figures 2 through 4 in Dagradi et al)¹ show that the QT of these athletes was not only long, but also had abnormal morphology. This abnormal morphology included T-wave notching similar to that observed when specific I_{Kr}-potassium channels malfunction in the type II congenital form or in drug-induced or bradycardia-induced LQTS. Abnormal T-wave morphology attests to the presence of arrhythmogenic dispersion of ventricular repolarization.¹³ These observations suggest that sports-induced QT prolongation, to the degree observed here, is potentially arrhythmogenic.

An opposite argument could be that patients with sports-induced LQTS simply have genotype–/phenotype+ LQTS and that the QT shortening observed during detraining simply reflects a day-to-day variability of their QT duration that was unrelated to deconditioning. After all, the mean difference between the shortest and longest QTc values among patients with congenital LQTS undergoing repeated ECG recordings over many years is also in the 50 ms range. However, patients with sports-induced LQTS had a very low pretest probability of having a genetic disorder because they were all detected by population screening. Nevertheless, we await the report of wider genetic screening of these athletes, including reporting of their polygenic risk score.¹²

The authors speculate that sports-induced increased stretch of myocardial cells activates mechano-gated ion channels that lead to action potential prolongation.¹ Alternatively, intense sports could lead to downregulation of repolarizing potassium channels in susceptible athletes. Downregulation of potassium channels is well documented in animal models of bradycardia-induced LQTS.¹⁴ The resulting prolongation of the action potential allows for increased calcium recruitment. This is a desirable effect from the mechanical point of view because it allows for increased myocardial contractility to increase cardiac output when increasing heart rate is not possible, at the expense of a potentially arrhythmogenic QT prolongation.

Regardless of its mechanism, sports-induced LQTS should be taken seriously. In the wake of the article by Dagradi et al,¹ we at the Tel Aviv Medical Center already

recognized our first case. The patient is a competitive young athlete with QT prolongation detected by ECG screening, which is also mandatory in Israel. The patient has no personal or family history of LQTS and has a negative genetic screening, but she was diagnosed with and treated for LQTS because her QTc ranged from 461 to 473 ms (equivalent of the 97th to 99th percentile for healthy women) and her response to our quick-standing test¹⁵ was positive. She was allowed to continue competing while on β -blocker therapy. However,

the COVID-19 epidemic forced her to stop all training for 4 months. After the description from Milan, we re-evaluated her for LQTS and realized her QT had partially but significantly shortened (Figure).

The optimal therapy for athletes with sport-induced LQTS remains to be defined. Competitive sports appear to be safe for appropriately treated patients with congenital LQTS, and a similar approach could be adopted here, individualized by the degree of sports-induced QT prolongation, for those wishing to continue competing.

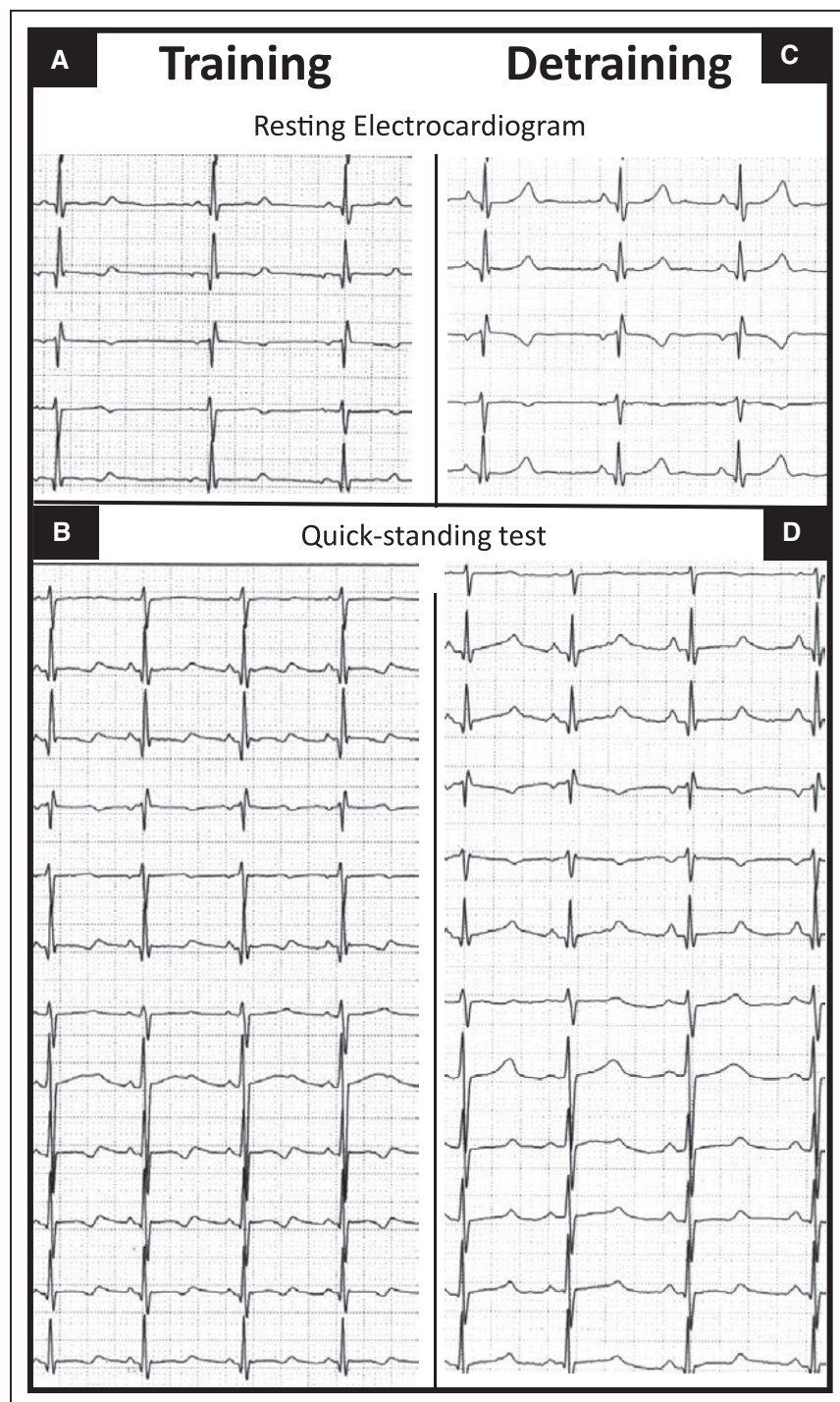


Figure. Training and detraining resting ECG and quick-standing test.

Female athlete diagnosed with congenital long QT syndrome because of a QTc in the 99th percentile (A) and a highly abnormal QT-stretching response to our quick-standing test¹⁵ (B). Note the notched and biphasic T-waves during quick standing in lead V2 and inferolateral leads, respectively (B). At repeated evaluation after 4 months of detraining, there is partial but significant QT normalization at rest (C) and in response to quick standing (D).

For those quitting sports to avoid the need for therapy, strict avoidance of QT-prolonging medications, and close ECG surveillance to verify that their normalized QT remains normal, is prudent until we learn more about this new form of LQTS.

ARTICLE INFORMATION

Correspondence

Sami Viskin, MD, Tel Aviv Sourasky Medical Center, Weizman 6, Tel Aviv 64239, Israel. Email samiviskin@gmail.com

Affiliation

Tel Aviv Sourasky Medical Center and Sackler School of Medicine, Tel Aviv University, Israel.

Disclosures

None.

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