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Exercise Training-Induced Repolarization Abnormalities Masquerading as Congenital Long QT Syndrome

Editorial, see p 2416

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BACKGROUND: The diagnosis of long QT syndrome (LQTS) is rather straightforward. We were surprised by realizing that, despite long-standing experience, we were making occasional diagnostic errors by considering as affected subjects who, over time, resulted as not affected. These individuals were all actively practicing sports—an observation that helped in the design of our study.

METHODS: We focused on subjects referred to our center by sports medicine doctors on suspicion of LQTS because of marked repolarization abnormalities on the ECG performed during the mandatory medical visit necessary in Italy to obtain the certificate of eligibility to practice sports. They all underwent our standard procedures involving both a resting and 12-lead ambulatory ECG, an exercise stress test, and genetic screening.

RESULTS: There were 310 such consecutive subjects, all actively practicing sports with many hours of intensive weekly training. Of them, 111 had a normal ECG, different cardiac diseases, or were lost to follow-up and exited the study. Of the remaining 199, all with either clear QTc prolongation and/or typical repolarization abnormalities, 121 were diagnosed as affected based on combination of ECG abnormalities with positive genotyping (QTc, 482±35 ms). Genetic testing was negative in 78 subjects, but 45 were nonetheless diagnosed as affected by LQTS based on unequivocal ECG abnormalities (QTc, 472±33 ms). The remaining 33, entirely asymptomatic and with a negative family history, showed an unexpected and practically complete normalization of the ECG abnormalities (their QTc shortened from 492±37 to 423±25 ms [P<0.001]; their Schwartz score went from 3.0 to 0.06) after detraining. They were considered not affected by congenital LQTS and are henceforth referred to as "cases." Furthermore, among them, those who resumed similarly heavy physical training showed reappearance of the repolarization abnormalities.

CONCLUSION: It is not uncommon to suspect LQTS among individuals actively practicing sports based on marked repolarization abnormalities. Among those who are genotype-negative, >40% normalize their ECG after detraining, but the abnormalities tend to recur with resumption of training. These individuals are not affected by congenital LQTS but could have a form of acquired LQTS. Care should be exercised to avoid diagnostic errors.

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Clinical Perspective

What Is New?

- Among young people participating in sports, some manifest QT interval prolongation and repolarization abnormalities to an extent that strongly suggests that they are affected by long QT syndrome (LQTS).
- Besides the genotype-positive patients diagnosed with LQTS, there are genotype-negative patients, some of whom are diagnosed as affected on clinical grounds; however, almost 40% normalize their ECG after detraining and are not affected, but their return to sport activity can induce major repolarization abnormalities again.
- This genotype-negative group presents similarities with drug-induced LQTS and may represent a new form of acquired LQTS where the "offending" stimulus is exercise training with excessive intensity.

What Are the Clinical Implications?

- To avoid diagnostic errors when examining young athletes with QT prolongation and typical repolarization abnormalities, the possibility of normalization after detraining should be considered, especially if they are genotype-negative.
- These genotype-negative subjects do not have congenital LQTS, but should be managed as if they had drug-induced LQTS, meaning that without knowing their long term follow-up data, it would seem reasonable to allow them to practice their sport, but at an intensity that does not trigger reappearance of repolarization abnormalities.
- These genotype-negative individuals have a propensity to lengthen their QT interval in response to certain stimuli, possibly myocardial stretch, and should avoid taking I_{Kr} blocking drugs if possible.

The importance of correctly diagnosing the congenital long QT syndrome (LQTS) cannot be overemphasized.[1] Missing the diagnosis in an affected patient may lead to a tragedy and incorrectly labeling a healthy person as affected is likely to severely disrupt his/her life. Exercise training may sometime become a confounder.

It is common knowledge that athletes may show repolarization abnormalities including some degree of QT prolongation,[2] usually modest, but this has not been related directly to LQTS. Given that we have long been a referral center for LQTS,[3] we are often consulted whenever the presence of this life-threatening disease[4] is suspected. In Italy, the law mandates that anyone who wishes to practice any type of competitive sport activity must undergo a clinical evaluation and obtain yearly eligibility by a sport medicine specialist.[5] Because of these 2 factors, our center is uniquely positioned to receive a large number of young athletes in whom LQTS has been suspected; this provides conditions that allow for the emergence and recognition of unforeseen patterns.

Over the years, we have been impressed by the number of times in which, despite an undeniable experience,[6] we have had to reconsider our initial diagnosis made in young athletes. These were cases in which we had confidently diagnosed LQTS based on a clear and typical ECG during our first visit, and recommended that the athlete stop their usually heavy physical training. A few months later, during control visits, we also noted marked changes in their ECGs with normalization of a previously prolonged QT interval. Subsequently, and with growing numbers showing a similar pattern, we realized that these subjects had other features in common, in addition to the ECG normalization that occurred after detraining; namely, they were all genotype-negative and completely asymptomatic, with a negative family history. Consequently, we could no longer consider these individuals as truly affected by congenital LQTS.

The significant clinical implications of these observations did not escape us; we decided to quantify these initial anecdotal observations and verify whether this is a real clinical entity. Here, we report the results of our study.

METHODS

The retrospective collection of data and waiver of informed consent was approved by the Institutional Review Board of the Istituto Auxologico Italiano. Requests to access the dataset from qualified researchers trained in human subjects confidentiality protocols may be sent to the corresponding author.

Study Population

This observational retrospective study included 310 consecutive subjects who were referred to our center on suspicion of LQTS by sport medicine doctors during the yearly mandatory preparticipation screening for the concession of the certificate necessary to practice sports in Italy. The majority were competitive athletes; the remaining subjects required a noncompetitive sport certificate (eg, for gym or pool membership). The ECG features prompting the suspicion of LQTS, and thus hindering eligibility for sports, were QT interval prolongation and/or T wave abnormalities (negative/diphasic or notched T waves not explained by age). During the preparticipation screening (or sport visit), all participants had a 12-lead ECG. After this first clinical examination, all subjects referred to our center underwent a comprehensive evaluation, as subsequently detailed.

A resting ECG was recorded in all subjects, and heart rate (HR) was calculated. The QT and RR intervals were measured in leads II and V3. The QT interval was corrected for HR (QTc) according to the Bazett formula because of its widespread use, and in consideration of its reliability for identifying abnormal values and subjects with LQTS even at

fast HRs.[7] The longest QTc value was used for all the analyses.[8,9] All ECG tracings were measured by the same cardiologist (F.D.) experienced in QT measurements. This was done during the first visit when genotype was unknown and there was no possible bias. Subsequently, F.D. blindly reanalyzed all ECGs, and results were essentially the same. At that point, a series of random ECG tracings were measured blindly by S.C. and by P.J.S.

A multistage fatigue-limited exercise stress test was performed on a bicycle ergometer in the upright position. The initial workload was 25 W, with subsequent stepwise increments of 25 W every 2 minutes at a pedaling rate of 60 rpm; peak workload was followed by a 5-minute cool-down period. HR and QTc were determined before and during the test, and at minutes 1 and 4 during recovery.

Each subject underwent a 24-hour 12-lead Holter monitoring (Mortara Instrument Europe) and the patients' data were analyzed with the H-Scribe Software. The QT intervals were manually measured and the maximum QTc was reported. The T wave morphology was assessed, taking into account the age of the subjects.

In all subjects the classic diagnostic criteria were ascertained by the Schwartz score, which grades each patient or athlete by the presence or absence of symptoms, family history, QTc duration, and repolarization abnormalities to quantify the likelihood of congenital LQTS.[10,11]

After referral by the sport medicine doctors, the subjects underwent complete clinical assessments during (1) the first visit at our center; (2) after 3 to 6 months (also depending on logistics, including the geographic area of residence of the patient) after a planned detraining period; and (3) at an additional follow-up during the study period.

Genetic Testing

All patients gave their written informed consent to undergo genetic analyses. Genetic testing of the principal LQTS genes (*KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2*) was performed through next-generation sequencing (TruSeq Custom Amplicon panel, Illumina) on a MiSeq platform (Illumina). Raw sequencing data were processed through an in-house bioinformatics pipeline. Read alignment to the human genome reference assembly hg19 was performed with the Burrows-Wheeler Aligner software, whereas variant calling was achieved with the genome analysis toolkit algorithm. Variant annotation was obtained through custom scripts and ANNOVAR (http://www.openbioinformatics.org/annovar/). All variants of interest were then confirmed with Sanger sequencing and were classified in accordance with the American College of Medical Genetics and Genomics guidelines.[12] A genotype-positive status was assigned to all patients carrying pathogenic or likely pathogenic variants, as well as to LQTS affected patients with variants of uncertain significance which are either novel (ie, absent from all publicly available exome/genome databases and literature), or are ultrarare (minor allele frequency <0.005%) with no evidence whatsoever against pathogenicity. A genotype-negative status was assigned to all patients with a negative genetic test result, or patients carrying likely benign variants and variants of uncertain significance with minor allele frequency >0.005% and contradictory evidence of a potential causative role.

Statistical Analysis

Data are presented as mean and SD or as median and interquartile range ([IQR] 25th–75th percentile) whenever their distribution was skewed. Absolute and relative frequencies are reported for qualitative variables. Group comparisons of continuous variables were performed with the Student *t* test. To analyze the effect of detraining on ECG parameters with respect to the baseline mean values recorded while on training, paired *t* test and repeated-measures ANOVA, with post hoc Bonferroni correction for multiple comparisons, were used. The nonparametric McNemar test was used to assess changes in the frequency of repolarization abnormalities associated with detraining. Two-sided *P* values <0.05 were considered statistically significant. SPSS Statistics version 23 (IBM Co, Armonk, NY) was used for computation.

RESULTS

Study Population

The baseline characteristics of the study population are summarized in Table 1. Males were 65%, mean age at presentation was 18±10 years [median, 14 (IQR, 12–18)], ranging from 6 to 56 years (19 subjects >40 years of age). Most (81%) were competitive athletes, whereas for 19% physical activity was limited to recreational sports. Three subjects (1%) reported a prior syncope, and 25 (8%) had a positive family history for LQTS, cardiac events (syncope, aborted cardiac arrest) and/or sudden cardiac death ≤40 years; all 28 were eventually diagnosed as affected by LQTS.

Clinical and Genetic Status

Based on the findings from the ECG evaluation and genetic testing, the study population was subdivided in 4 groups (Figure 1).

Non-LQTS

This group included 111 subjects (36%). Eight (3%), all genotype-negative, never returned for follow-up and were excluded from the study. The initial suspicion of LQTS was not confirmed in 103 (33%) subjects either because of a QT interval consistently within the normal range together with a negative genotype (labeled as "normal ECG"; n= 77; QTc, 438±26 ms) or because we had diagnosed other cardiac diseases (n=26; QTc, 452±27).

LQTS Genotype-Positive

In 121 clinically affected subjects (39%) an LQTS-causative variant in the 5 screened LQTS genes was identified. There were 77 (64%) LQT1, 29 (24%) LQT2,

Table 1. Baseline Characteristics of the Study Population

Variable	Value
Total no. of referrals	310
Sex, male	202 (65%)
Median age at presentation, y (IQR)	14 (12–18), range, 6–56
Training level	
Competitive	81%
Leisure, recreational	19%
Basal QTc ms	
All referrals (n=310)	468±38
Non-LQTS (n=111)	444±28
LQTS, genotype-positive (n=121)	482±35
LQTS, genotype-negative (n=45)	472±33
All LQTS (n=166)	479±35
Cases (n=33)	492±37

Cases indicates subjects with an ECG reversible pattern after detraining; IQR, interquartile range; and LQTS, long QT syndrome.

11 (9%) LQT3, with the residual 3% accounted for by *KCNE1* and by compound heterozygous mutations. Their mean QTc at rest during the sport visit was 482±35 ms. Their diagnostic Schwartz score at baseline while on training was 3.6±1.3 points.

LQTS Genotype-Negative

Among the athletes referred for suspicion of LQTS, 78 were genotype-negative. Of them, 45 (QTc, 472±33 ms) were diagnosed as affected by LQTS based on standard clinical criteria despite the absence of a positive genotype. Their diagnostic Schwartz score at baseline while on training was 3.2±1.2 points. All 45 of these athletes were evaluated again after detraining and the overall picture remained the same, with just minor changes (Figure 2A). On this basis, they were diagnosed as affected by LQTS.

The remaining 33 showed a unique ECG pattern which led us to classify them as cases and to make of them the focus of our study, whereas all other subjects (n=166; 121+45; Figure 1) diagnosed as affected by LQTS are referred to as controls. The cases are characterized by a long QT interval at baseline and/or by an abnormal ventricular repolarization evident either on the basal ECG, on the Holter recording, or during the exercise stress test. Their distinguishing feature is the reversibility of the ECG abnormalities after detraining. Of note, the QTc of the cases (492±37 ms) was prolonged slightly more than that (479±35 ms; P=0.06) of all the LQTS patients (controls, n=166) independently of their genotype (Figure 2A). Their diagnostic Schwartz score at baseline while on training was 3.0±1.2 points.

Cases

Among the 33 cases, all asymptomatic, there was an overrepresentation of men (82%). The mean age, at the time of the sport eligibility visit, was 16±8 years (median, 14 [IQR, 12.5–16]). The ECGs of their parents was normal.

A QTc ≥470 ms while on training was present in 26 of 33 subjects (79%), whereas 29 of 33 subjects (88%) had ventricular repolarization abnormalities; one or the other abnormality was present in all 33 (100%). During both the preparticipation visit and the initial visit at our center QTc was markedly prolonged, slightly more during the former (492±37 versus 471±46 ms; P=0.17) (Table 2). After detraining, there was a dramatic QTc shortening to 423±25 ms (P<0.001) (Table 2 and Figures 2A and 3). Detraining was also associated with a significantly smaller proportion of cases showing a QTc ≥470 ms and repolarization abnormalities compared with the initial presentation (P<0.001). This change in the pattern of QT prolongation and of T wave abnormalities observed

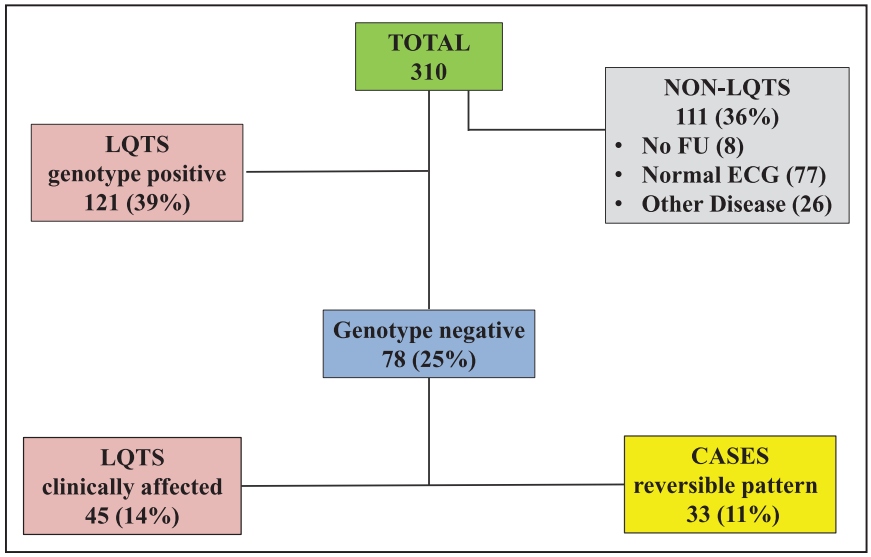

Figure 1. Study population.
Outline of the study population involving 310 subjects who participate in sport activities and were referred for a suspicion of long QT syndrome. ECG indicates electrocardiogram; FU, follow-up; and LQTS, long QT syndrome.

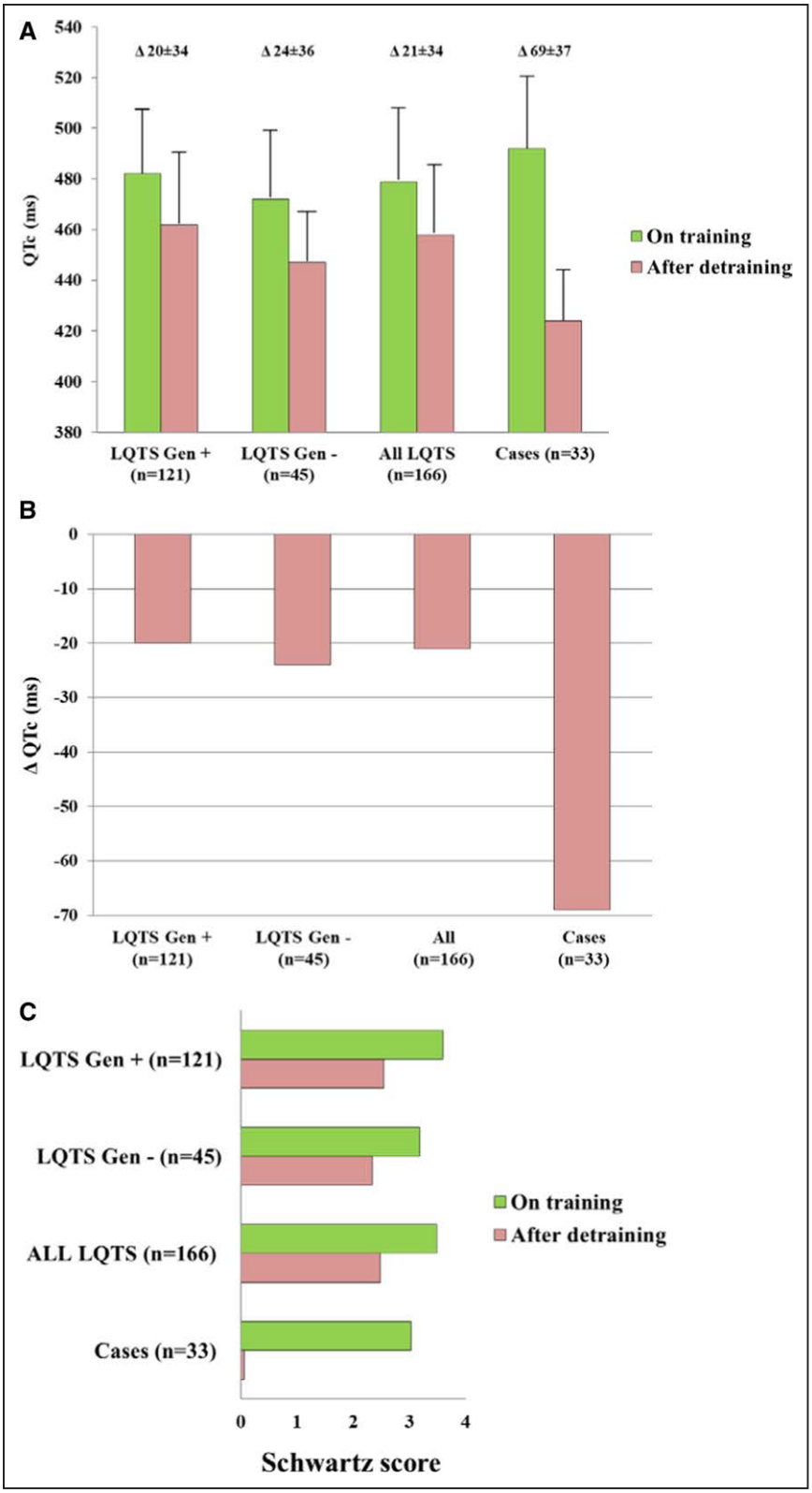

Figure 2. Effect of detraining on QTc and on the Schwartz score.
QTc and Schwartz score changes after detraining in the study subgroups. **A,** Mean QTc shortening at basal ECG. **B,** Magnitude of ΔQTc shortening, ranging from –20 to –24 ms among the LQTS patients, either genotype-positive or genotype-negative, and up to –69 ms in the cases. **C,** Comparison of the Schwartz scores calculated at the initial sport visit and at the postdetraining evaluation. The difference between the cases and all LQTS groups is large and statistically significant (*P*<0.001). Gen + indicates genotype-positive; Gen –, genotype-negative; and LQTS, long QT syndrome.

on the baseline ECG was present also on Holter monitoring and exercise stress test. The impressive QTc shortening observed after detraining was evident also on the Holter recordings and during the exercise stress test (QTc_{max} from 497±32 to 454±23 ms and QTc at minute 4 of recovery from 465±57 to 422±23 ms; *P*<0.001 for both) (Table 2).

Of major significance for understanding the factors underlying our observation is the fact that in 7 cases the resumption of physical training (after the clear

Table 2. ECG Measurements in Cases

Basal ECG	
HR (bpm)	
Sport visit	69±12
Our center 1st visit	68±9
Postdetraining visit	68±11
QTC (ms)	
Sport visit	492±37
Our center 1st visit	471±46
Postdetraining visit	423±25*
Holter	
HR_{min} (bpm)	
Our center 1st visit	42±5
Postdetraining visit	42±5
HR_{max} (bpm)	
Our center 1st visit	132±16
Postdetraining visit	125±22
HR_{mean} (bpm)	
Our center 1st visit	71±13
Postdetraining visit	72±20
QTc_{max} (ms)	
Our center 1st visit	497±32
Postdetraining visit	454±23†
Exercise stress test	
HR_{basal} (bpm)	
Our center 1st visit	78±10
Postdetraining visit	81±18
HR_{peak} (bpm)	
Our center 1st visit	169±11
Postdetraining visit	165±21
$HR_{1st\text{-}rec}$ (bpm)	
Our center 1st visit	133±25
Postdetraining visit	139±26
$QTc_{4th\text{-}rec}$ (ms)	
Our center 1st visit	465±57
Postdetraining visit	422±23†

Cases indicate subjects with an ECG reversible pattern after detraining; ECG, electrocardiogram; HR, heart rate; $HR_{1st\text{-}rec}$, heart rate at first minute of recovery; and $QTC_{4th\text{-}rec}$, QTc at fourth minute of recovery.

*P<0.001 vs preparticipation screening and vs. first visit to our center.

†P<0.001 vs first visit to our center.

normalization that followed detraining) reproduced the initial LQTS-like pattern with a marked worsening of the ECG features (QT prolongation, repolarization abnormalities) (Figures 4 and 5). Specifically, QTc increased again from 437±25 ms to 477±40 ms (*P*=0.017), with an average increase of 40 ms, and repolarization abnormalities were evident in 5 of the 7 cases. This fact rules out the possibility that the changes observed were time related, regression toward the mean, or simply a fluke, and point directly to physical training as the culprit of the abnormalities observed in these young athletes. The degree of new worsening seemed to be related to the level of intensity of retraining. In contrast, some subjects resumed sport activity but at much lower intensity and did not manifest recurrence of the abnormalities.

The changes in HR between on- and off-training were modest and not significant, despite a trend toward lower HR_{max} during Holter monitoring (125±22 versus 132±16 bpm) and toward higher $HR_{1st\text{-}rec}$ during stress test (139±26 versus 133±25 bpm) after detraining (Table 2).

The ECG changes were mimicking LQTS so impressively and so ominously that in 12 cases, treatment with β-blockers was started without waiting for the results of the genetic testing. When it became evident that their genotype was negative and, moreover, that their ECG had normalized, the β-blockers were progressively withdrawn.

The overall analysis allowed the realization that QTc shortening with detraining is not exclusive for the cases. Irrespective of their genotype, all LQTS patients shortened their QTc after the reduction in physical activity that accompanies the diagnosis; however, this change was much more modest compared with that observed among the cases (21±34 ms versus 69±37 ms; *P*>0.001) (Figure 2A and 2B).

Although the Schwartz score calculated at the initial presentation on training was similar across all the study subgroups, after detraining it reduced to almost zero only among the cases (from 3.0±1.2 to 0.06±0.24); the mean reduction in the Schwartz score after detraining was significantly (*P*<0.001) greater compared with that of the LQTS subjects, either genotype-positive (from 3.6±1.3 to 2.5±1.5) or genotype-negative (from 3.2±1.2 to 2.3±1.1) (Figure 2C).

Given the importance of the different diagnosis between the 2 genotype-negative groups (LQTS patients and cases), Table 3 compares their QTc at basal ECG, during the Holter recording, and during the exercise stress test. In all 3 of these conditions, there were significant differences at the postdetraining visit, given that the cases consistently shortened their QTc more than the genotype-negative LQTS patients.

DISCUSSION

The main novelty of the current findings is the unquestionable evidence that among the many individuals that practice sports—especially young people—there are some in whom regular physical exercise produces an array of repolarization abnormalities so typical to mislead even experienced clinicians into incorrectly diagnosing LQTS. The most obvious repolarization abnormality is a clear prolongation of the QT interval and the frequent

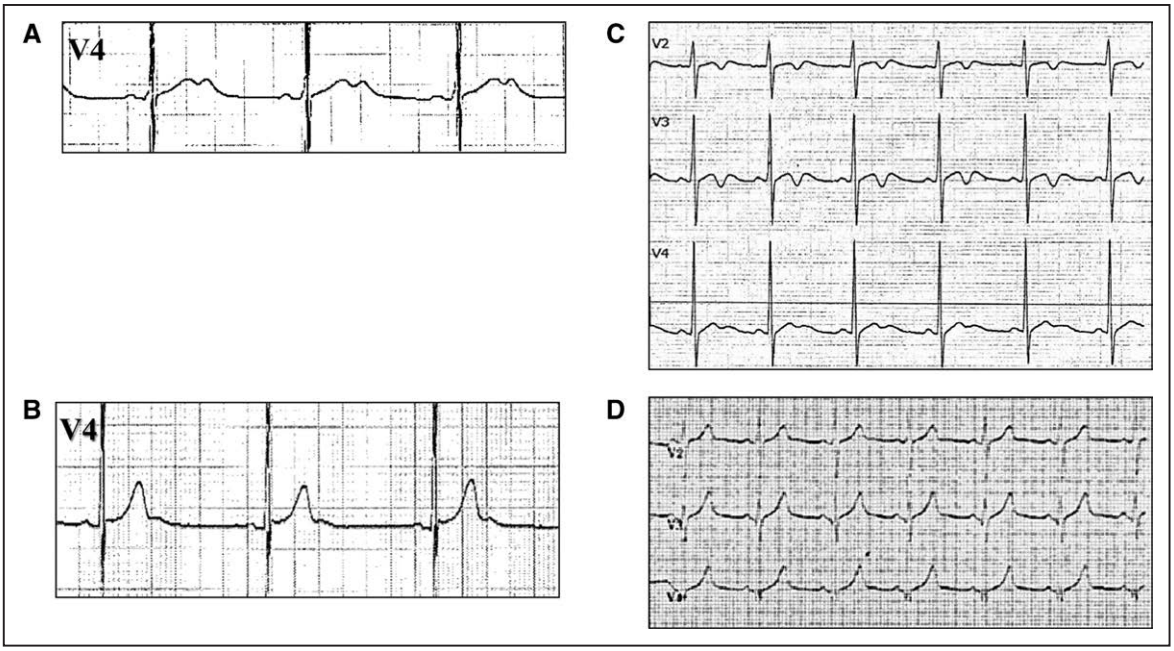

Figure 3. Effect of detraining on ECG abnormalities.
Left, Male, 17 years old, plays rugby at competitive level. **A,** Our center: QTc, 495 ms; detraining was recommended. **B**, Our center (after 4 months of detraining): QTc, 380 ms. **Right**, Male, 15 years old, swimming at competitive level. **C,** At preparticipation screening: QTc, 536 ms in V3; heart rate, 83 bpm. **D**, Our center (after 7 months of detraining): ECG with a normal morphology, QTc, 447 ms in V4; heart rate, 76 bpm.

appearance of LQTS-associated T wave abnormalities, such as notched and biphasic T waves.[13] The unexpected, distinctive, and clinically relevant, feature of these abnormalities is that they are reversible with detraining.

The most important clinical implication is that, when visiting a sport-practicing person with QT interval prolongation and repolarization abnormalities, care should be taken before jumping to the diagnosis of LQTS. The present data force a reassessment of the current diagnostic procedures with the specific need to reassess—in all genotype-negative subjects—the initial preliminary diagnosis after an adequate period of detraining.

Clinical Facts

During the yearly control visits performed on our LQTS patients in the past several years, it was occasionally observed that their QTc had normalized. The initial reactions were to repeat the measurements, but upon retesting, measurements were found to be accurate. As in the subsequent years we were confronted with a growing number of similar cases, the reaction changed and we realized that the phenomenon was real. From the beginning it looked as it was associated with a reduction in sports activities, but these clinical impressions needed to be quantified. This is how our study started, without any hypothesis or bias, just based on the repeated observations of unexpected findings. We were favored by the rather unique situation of having become, in the many years since the mid-1970s, the leading referral center for LQTS in Italy and of working in a country in which—by law—everyone who wants to practice sporting activities must obtain an eligibility certificate that is granted after a visit to a sports medicine specialist that also involves an ECG. It is from this large group of regularly exercising young people undergoing ECGs that an adequate number was suspected of having LQTS and was referred to us.

Every person referred to our center by sport physicians, who were following the recommendations of a position statement endorsed by the European Society of Cardiology,[14] underwent the same diagnostic process to either confirm or dismiss the suspicion of LQTS. As these were all asymptomatic individuals, mostly with a completely negative family history, it was possible in the majority of cases to delay the initiation of treatment with β-blockers by a few months, while waiting for the genetic results. The genotype positive subjects, all with clear repolarization abnormalities, were obviously affected by LQTS. Among the genotype-negative patients, there were several who were nonetheless considered as affected, because of the continued presence of a clear QTc prolongation together with multiple ECG markers of LQTS, either on the Holter recordings or during the exercise stress test. However, among these genotype-negative subjects, more than 40% showed a complete or almost complete normalization of their ECGs after the 3 to 4 months of detraining (sometimes more). These individuals became our cases, and we focused our study on them.

Once we had told these subjects that, in our opinion, they did not have LQTS, most of them wanted to return to their previous sport activities; however, it became evident that with a similar workload, the abnormalities

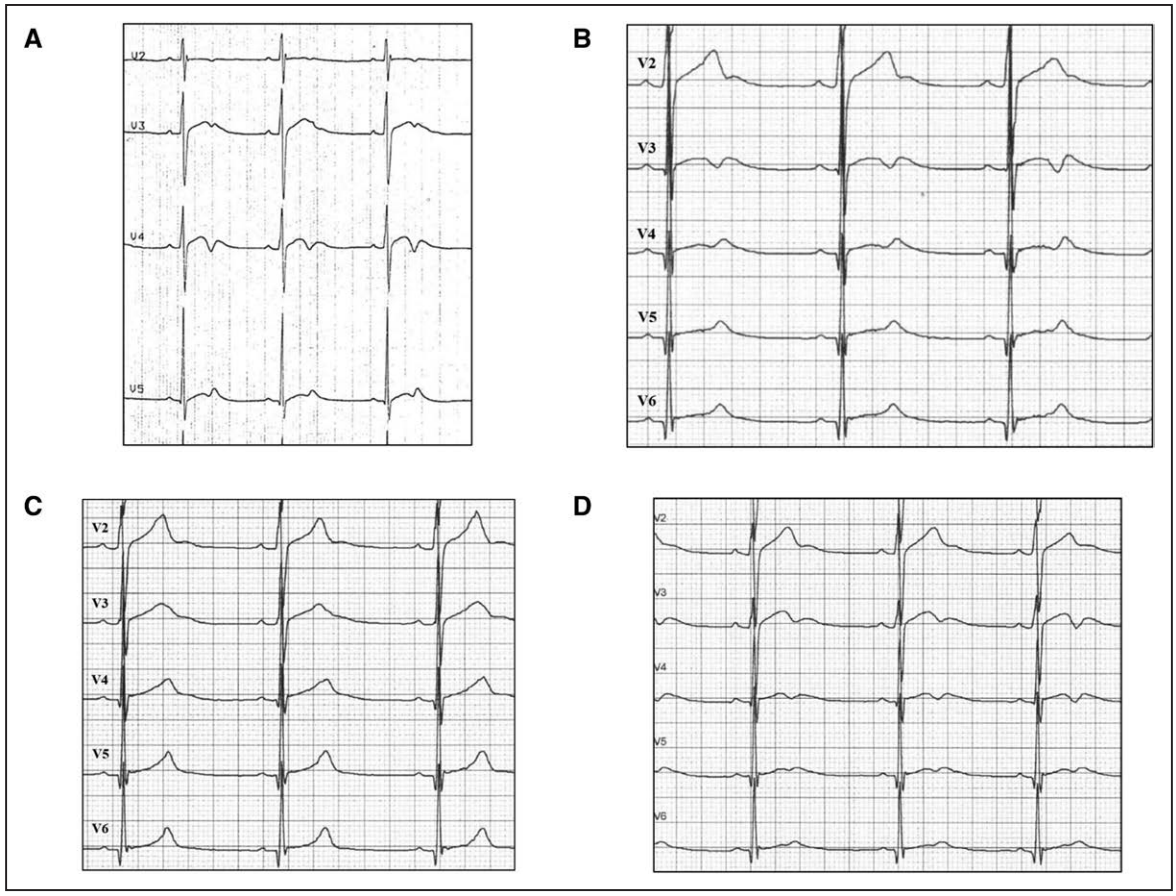

Figure 4. Effect of detraining and of returning to sport activity.
Male, 14 years old, water polo at the competitive level. **A**, At sport visit: QTc, 511 ms in V4; heart rate (HR) 50 bpm. **B,** Our center (still on training): nighttime Holter recording showing repolarization abnormalities (QTc, 547 ms in V4; HR, 47 bpm). **C**, After 4-month detraining, the nighttime Holter recording at the same HR shows QTc normalization and normal repolarization (QTc, 440 ms in V4; HR, 48 bpm). **D,** The patient returned to competitive sport and after 4 months of retraining, the repolarization abnormalities reappear, extending to V6 (QTc, 550 ms in V4; HR, 53 bpm).

reappeared in 7 cases. Other patients accepted the guidance to play with lesser intensity and remained with borderline normal values.

This study also allowed an additional valuable observation, which would have probably escaped us: all LQTS patients tend to shorten their QTc when—even if not actively participating in sports—they reduced their physical activity simply because of the psychological effect of the diagnosis and the well-known association between sympathetic activation and cardiac events.[15] All LQTS groups, both genotype-positive and negative, shortened their QTc by an average of 21 ms. Of note, most ECG studies in athletes point to longer QTc values compared with controls with a relatively modest, and clinically irrelevant, difference between 10 and 15 ms.[16] This probably accounts, at least in part, for the close to 20-ms shortening observed after the diagnosis-related reduction in physical activity among LQTS patients, who start from much longer baseline QTc values. A recent study[17] of adolescents practicing sports suggested, based on 5 subjects, that when QTc is >480 ms it does not normalize over time; our data do not support that view, provided, however, that detraining takes place.

In some of our cases, the ECG abnormalities were so striking and so closely resembling those typical of LQTS, and indeed meeting the so-called "Schwartz criteria" for "high probability of LQTS,"[10,11] that we did not only consider them as affected, but actually began treatment with β-blockers. Without the subsequent realization that these individuals were actually part of a special group of patients with features closely mimicking LQTS, but not really affected by the disease, they would have remained on treatment for a long time (the absence of symptoms being certainly interpreted as "therapeutic success"!) with the heavy psychological burden of being carriers of a genetic disorder.

One additional consideration, which might help in differentiating the cases from the genotype-negative LQTS patients, is the very different behavior of the Schwartz score after detraining (Figure 2C). A major reduction of the score to almost 0 points, would strongly suggest that the subject is not an LQTS patient.

Underlying Mechanisms

At this time, the mechanisms underlying the reversible QT prolongation caused by physical training are not known.

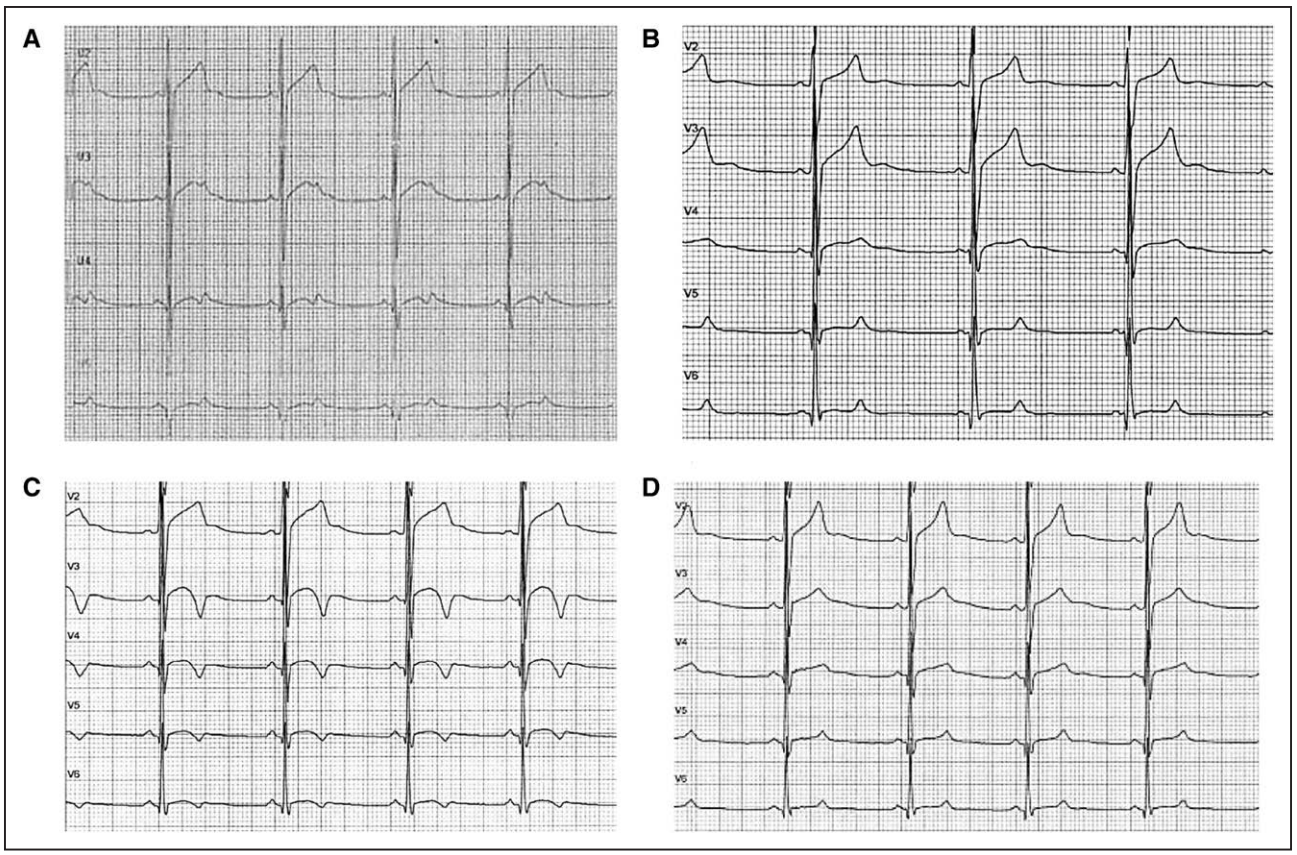

Figure 5. Reversibility of the ECG abnormalities with detraining, retraining, and detraining.
Male, 16 years old, playing competitive soccer since age 12 years. **A**, Preparticipation screening ECG: notched T waves; QTc, 490 ms in V3; heart rate (HR), 57 bpm. **B**, Our center (after 3-month detraining): ECG normalization (QTc, 419 ms in V3; HR, 54 bpm). **C,** The patient did not follow detraining and started competitive sport activity again, which led to a major worsening (QTc, 550 in V3; HR, 58 bpm). At this point, the patient accepted to really detrain. **D,** After 7 months of complete detraining, there was a complete ECG normalization (QTc, 415 ms in V3; HR, 58 bpm).

However, logical hypotheses can be formulated. Our starting point is that the observed major QTc prolongation is not a normal physiological phenomenon, as it appears only in a small minority of all young people who participate in sports. It must reflect an abnormal response to training that is present in a few individuals, possibly because of a genetic predisposition. An obvious analogy is with drug-induced LQTS.[18,19] As postulated in 1982,[20] with the proof of concept obtained in 2000[21] and quantitative evidence provided in 2016,[22] it is evident that the abnormal QT interval prolongation observed in response to a large number of drugs blocking the I_{Kr} current and representing a potentially dangerous form of acquired LQTS is favored by the presence of genetic variants associated with congenital LQTS.[19] The management of drug-induced LQTS rests on the withdrawal of the offending drug and on the avoidance of drugs with similar properties.[19] On this basis, it is reasonable to consider the possibility that the repolarization abnormalities induced by exercise training might represent another form of acquired LQTS similar to that of drug-induced LQTS, ie, exercise-induced LQTS. One important distinction between these 2 acquired forms, however, is that while drug-induced LQTS can be associated with Torsades de Pointes ventricular tachycardia and cardiac arrest, such evidence does not exist at this time for exercise-induced LQTS which might be a more benign variant. Such a conclusion needs a longer follow-up.

As exercise training augments the workload of the heart and its size, we have considered an increased stretch of the myocardial cells as a possible triggering mechanism. The heart is endowed with mechanically-gated ion channels, of which the most relevant to our findings are the stretch-activated channels.[23] Stretch-activated channels increase their open probability in direct response to membrane deformation and their activation by stretch is associated with a large rise in $[Ca^{2+}]_i$.[24] In turn, this increase in $[Ca^{2+}]_i$ will prolong or delay the final phase of repolarization resulting in a prolongation of the QT interval on the surface ECG.[23]

Our current hypothesis is that the hearts of certain individuals have a predisposition (genetic or otherwise) to react to increased mechanical stretch with an increased intracellular release of Ca^{2+}, which would largely explain their abnormal ECGs. After detraining and the attendant progressive decrease in mechanical stretch, action potential duration would progressively shorten with a return toward normal ventricular repolarization. A training-induced

Table 3. QTc Comparison Between Cases and LQTS Genotype-Negative

Variable	Cases (n=33)	LQTS Genotype-Negative (n=45)
Basal ECG QTc		
Sport visit*	492±37	472±33
First visit to our center	471±46	457±37
Postdetraining visit†	423±25	447±25
Holter QTc_{max}		
First visit to our center	497±32	492±32
Postdetraining visit†	454±23	484±28
Exercise stress test $QTc_{4th\text{-}rec}$		
First visit to our center	465±57	476±52
Postdetraining visit†	422±23	471±46

Cases indicates subjects with an ECG reversible pattern after detraining; ECG, electrocardiogram; LQTS, long QT syndrome; and $QTc_{4th\text{-}rec}$, QTc at 4th minute of recovery.

*P<0.05 between groups.

†P<0.001 between groups.

chronic elevation of cell membrane stretch or increased sensitivity to stretch may originate from abnormal cellular hypertrophy, abnormally increased hemodynamic load, predisposed oversensitivity of stretch-activated channels, or combinations thereof. Hypotheses must be put forward and tested in order to be either confirmed or dismissed. We have initiated 2 specific studies designed to answer the questions raised by the present observations, and also plan to use advanced echocardiography to assess potential mechanical abnormalities which might help differentiate cases from run-of-the-mill LQTS patients.

Implications for Management

These findings unavoidably force a reappraisal of how patients suspected to be affected by LQTS should be managed. The new evidence that a certain number of subjects referred because of an ECG pattern typical of LQTS are actually not affected by congenital LQTS raises significant issues and mandates a somewhat different approach. As the problem concerns only genotype-negative patients, it follows that—as clearly spelled out[25,26] and besides the consideration of medico-legal issues[26]–genetic testing is no longer an option; put simply, it should always be performed. In this way the question would be narrowed to the "genotype-negative phenotype-positive" patients. The current data call for extra caution before labeling these individuals as "certainly affected," particularly if they are young people actively participating in sports. Before making a definitive clinical judgment with these subjects, it is now necessary to carefully examine their ECG after full detraining because some of them are likely not affected. The aforementioned pattern represents a potential diagnostic trap that must be avoided because the cost of possible medical errors, as discussed earlier, would be borne by patients and their families.

The delicate part comes after these subjects are identified as such. They should be told that they are not affected by congenital LQTS, but at the same time they should be made to understand that as with food allergy, to use an example easily understood by the patients, their hearts do not tolerate excessive physical training well and respond by lengthening the QT interval, which could be dangerous. Common sense would dictate that if, for psychological well-being, they continue to practice sporting activities, they should do it at a much lower intensity while monitoring the QT interval for possible recurrent lengthening. These subjects should realize that if their new level of exercise reproduces the ECG abnormalities, they should not continue. Furthermore, as they have already shown a predisposition to prolong the QT interval, they should be given a list of QT prolonging drugs with the advice to avoid them, if at all possible.

Limitations

We acknowledge the retrospective design, the relatively small sample size, the variability in the intensity of exercise with lack of granular data on training and detraining, and lack of long-term outcome data. This was the only way to share these unexpected findings which surfaced during normal clinical management. Despite the recognized limitations, the difference between cases and genotype-negative LQTS patients is so clear that it inspires confidence in the interpretation and conclusions.

Conclusions

The amazing progress in the unraveling of LQTS keeps increasing the complexity of the questions that the responsible physician must address. In the early days if the QT interval was normal, the diagnosis of LQTS was not even considered. In 1999, our demonstration of low penetrance in LQTS[27] made it impossible to simply assume, when dealing with LQTS families, that family members with normal repolarization were unaffected, and mandated genetic screening for all. The present findings further complicate the diagnostic process but in the opposite direction. Indeed, they show that when dealing with genotype-negative subjects practicing sports, despite repolarization abnormalities pathognomonic for LQTS, it is necessary to assess the effect of detraining before making the diagnosis. This approach, progressively less simplistic and guided by solid data, will help to avoid a number of wrong diagnoses with the attendant negative consequences. The pendulum swings.

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None.

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