European Heart Journal (2007) **28**, 2944–2949
doi:10.1093/eurheartj/ehm404

Prevalence and significance of an isolated long QT interval in elite athletes

Sandeep Basavarajaiah[1], Matthew Wilson[2], Gregory Whyte[3], Ajay Shah[1], Elijah Behr[4], and Sanjay Sharma[1]*

[1]*University Hospital Lewisham/King's College Hospital, London SE5 9RS, UK;* [2]*Olympic Medical Institute, London, UK;* [3]*Liverpool John Moores University, Liverpool, England, UK; and* [4]*St. George's Hospital Medical School, London, UK*

Received 9 July 2007; revised 15 August 2007; accepted 27 August 2007; online publish-ahead-of-print 18 October 2007

See page 2825 for the editorial comment on this article (doi:10.1093/eurheartj/ehm491)

KEYWORDS
Congenital long QT syndrome;
Elite athletes;
Polymorphic ventricular tachycardia;
Competitive sports

Aims Identification of a prolonged, corrected QT (QTc) interval in athletes may be a recommendation for disqualification from competitive sports. However, the prevalence and diagnostic significance of an isolated prolonged QTc in asymptomatic athletes without familial disease is unknown.
Methods and results Between 1996 and 2006, 2000 elite athletes (mean age, 20.2 years) underwent 12-lead ECG and 2-D echocardiography. The QT interval was corrected for heart rate (QTc). Athletes with QTc $>$ 460 ms underwent 48 h Holter monitor and an exercise stress test. All athletes with a prolonged QTc interval were offered genetic testing and first-degree relatives were invited for ECG. The QTc was prolonged in seven (0.4%) athletes ranging from 460 to 570 ms. Three athletes had a QTc value of $>$500 ms and all exhibited one of: paradoxical prolongation of QTc during exercise, a confirmatory genetic mutation, or prolonged QTc in a first-degree relative. In contrast, none of the athletes with a QTc value of $<$500 ms had any other features to indicate long QT syndrome (LQTS).
Conclusion The prevalence of prolonged QTc in elite athletes is 0.4%. A QTc of $>$500 ms is highly suggestive of LQTS. A QTc of $<$500 ms in the absence of symptoms or familial disease is unlikely to represent LQTS in elite athletes.

Introduction

Congenital long-QT syndromes (LQTS) are recognized as a cause of adrenergic-mediated polymorphic ventricular tachycardia (VT) and have been implicated in exercise-related sudden cardiac deaths in young athletes.[1–5] The identification of a prolonged QT interval corrected for heart rate (QTc) in an athlete raises the potential diagnosis of congenital LQTS and issues relating to disqualification from competitive sporting disciplines involving moderate- and high-intensity strenuous exertion,[6,7] however, an isolated prolonged QTc interval *per se* does not fulfil the proposed criteria for congenital long-QT syndrome.[8,9]

Although there are numerous electrocardiographic studies relating to athletes,[10–12] the prevalence, and more importantly, the significance, of a prolonged QTc interval has never been addressed in elite athletes.

The aim of this study was to identify the prevalence of prolonged QTc interval in a large cohort of elite British athletes and to evaluate the significance of prolonged QTc interval utilizing Holter monitoring, exercise testing, cardiovascular evaluation of first-degree relatives, and genetic testing in consenting individuals.

*Corresponding author. Tel: +44 20 3299 8370; fax: +44 20 3299 3489.
E-mail address: ssharma21@hotmail.com

Methods

Setting

The death of several professional sports persons from inherited structural or electrical disorders has called for screening of all athletes for potentially sinister cardiovascular disorders prior to selection for competition.[13] However, in the UK as in many other developed countries, a comprehensive screening programme is not possible because of constraints on financial resources, personnel and administrative infrastructure. Nevertheless, certain sporting bodies such as British Lawn tennis association, Premiership football and rugby league, and the national swimming and boxing squads have adopted self-financed mandatory pre-participation screening programmes comprising of history, physical examination, 12-lead ECG, and echocardiography with view to further investigations, if necessary.

The senior author has been responsible for performing and supervising cardiovascular evaluation in elite athletes in these sporting disciplines since 1996 at St George's Hospital Medical School, the Olympic Medical Institute (Northwick Park Hospital), University Hospital Lewisham and Kings College Hospital.

Athletes

Between 1996 and 2006, 2000 elite athletes aged between 14 and 35 years (mean, 20.2 years) were evaluated as part of mandatory pre-participation cardiovascular screening; of which, 1260 (70%) elite athletes were males and 540 (30%) were females. The athletes

participated in 15 different sports, but the vast majority of the study group (70%) represented football, rugby, tennis, and swimming (*Table 1*). All athletes competed at least at regional level and ~50% of them were playing at a National level during the study period. Written consent was obtained from individuals aged >16 years and from a parent/guardian for those aged <16 years.

Ethical approval for the study was sought from the Harrow Research Ethics Committee by the Cardiac Risk in the Young (CRY), Centre of Sports Cardiology.

Health questionnaire

All athletes filled out a questionnaire that comprised of enquires regarding cardiovascular symptoms, with particular emphasis on the relationship with physical exertion, past medical history, regular medications and a family history of inherited cardiovascular conditions, premature sudden cardiac death (SCD), epilepsy or unexplained deaths in first-degree relatives from drowning or road traffic accidents.

Electrocardiography

Standard 12-lead EGC were recorded using a Marquette Hellige recorder (Milwaukee, WI, USA) with a paper speed of 25 mm/s and amplification of 0.1 mV/mm.[14] The QT interval was measured in all leads from the onset of QRS complex to the end of T wave, defined as the intersection of iso-electric line and the tangent of the maximal downward limb of the T wave.[15] The U-wave was excluded during the measurement of the QT interval, except when the T wave was biphasic or in the presence of T–U complexes where the identification of the termination of the T wave was difficult. In such cases, the U-wave was included if it exceeded 50% of the T-wave amplitude.[15] In the presence of biphasic T waves, we have also assessed the QT interval in other leads that did not exhibit biphasic T waves. The lead with the longest QT interval was used to obtain an average QT over three to five consecutive beats. The QTc values were derived using Bazett's formula,[16] which has been most widely used in all large studies evaluating patients with LQTS. All ECGs were analysed independently by three independent cardiologists with a clinical and academic interest in LQTS. According to internationally accepted guidelines, males with a QTc value of >440 ms and females with a QTc value of >460 ms were considered to have an abnormally prolonged QTc interval.[13]

Table 1 Number of athletes from various sporting disciplines

Type of sport	Number of athletes	Percentage
Football	520	26
Tennis	450	22.5
Rugby	256	12.8
Swimming	202	10.1
Rowing	88	4.4
Hurling	40	3
Cycling	64	3.2
Athletics	64	3.2
Netball	52	2.6
Basketball	52	2.6
Badminton	54	2.7
Triathlon	52	2.6
Boxing	42	2.1
Fencing	32	1.6
Speed skating	32	1.6
Total	2000	

Further investigations

Athletes with a prolonged QTc interval were detrained for 6 weeks and underwent repeat ECG and further assessment with 48 h ECG monitoring and exercise stress testing to identify additional phenotypic features of congenital LQTS.

48 h ECG

Athletes were encouraged to continue with usual (non-athletic) life activities while undergoing ECG monitoring. The 48 h ECG recordings were analysed specifically for episodes of polymorphic VT.

Exercise stress test

An upright exercise stress test was performed in accordance with the standard Bruce Protocol[17] and athletes were encouraged to the point of achieving maximal age-predicted heart rate (maximal heart rate of 220 − age). Continuous 12-lead ECG recordings were obtained throughout the test looking for episodes of polymorphic VT. ECG tracings were printed for the QTc calculation at heart rate increments of 10 beats per minute up to a heart rate of 130 beats per minute during exercise and heart rate decrements of 10 beats per minute from a heart rate of 130 beats per minute to baseline heart rate during recovery. The QT interval was not measured at heart rates above 130 beats per minute, as the Bazett's correction is deemed inaccurate at high heart rates.

Assessment of first-degree relatives

The first-degree relatives of the athletes with prolonged QTc intervals (parents and siblings) were invited to undergo 12-lead ECG to help identify evidence of familial disease.

Genetic testing

All athletes with prolonged QTc interval were offered genetic testing for all genetic mutations commonly implicated in LQTS type 1–3 (KCNQ1, HERG, and SCN5A). Genetic testing was performed following counselling and after obtaining informed consent. Mutations were identified using standard genetic tests.[18–20]

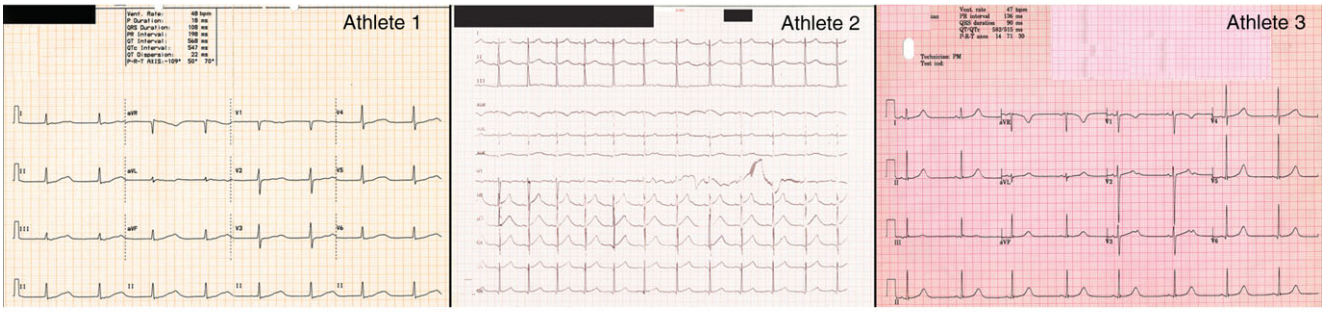
Results

The mean QTc interval in 2000 athletes measured 397 ± 28 ms and ranged from 346 to 570 ms. Of the 2000 athletes, seven (six male and one female) had a prolonged QTc interval amounting to a prevalence of 0.4%. The mean heart rate in these seven athletes was 58 beats per minute (range, 47–68 beats per minute) and the QTc ranged from 460 to 570 ms. Of the seven athletes, three had a baseline QTc value of >500 ms (*Figure 1*). All seven athletes were asymptomatic; none were taking regular medications that could be associated with a prolonged QTc interval and had family history of congenital LQTS, premature SCD, unheralded syncope, or epilepsy. None of the athletes had sensorineuronal deafness.[8,9] The characteristics of all athletes with prolonged QTc interval are shown in *Table 2*.

48 h ECG

All athletes with a prolonged QTc interval successfully completed the 48 h ECG monitoring. None of the athletes showed evidence of polymorphic VT during the recording.

A



B

Athlete no.	QT (ms)	RR-interval (s)	QTc (ms)
Athlete 1	568	1.066	550
Athlete 2	540	0.897	570
Athlete 3	582	1.277	515

Figure 1 Panel showing the 12-lead ECGs of three athletes with QTc > 500 ms.

Table 2 Characteristics of the seven athletes with prolonged QTc intervals

Athlete no.	Age	Gender	Type of sport	QT interval (ms)	RR interval (s)	QTc interval (ms)	Positive ETT	Affected first-degree family members	Genetic testing
1	17	Male	Swimming	568	1.066	550	Yes	Yes	Negative
2	19	Male	Rugby	540	0.897	570	Yes	No	Negative
3	16	Female	Swimming	582	1.277	515	No	Yes	Positive for LQT1
4	15	Male	Football	436	0.898	460	No	No	Declined
5	19	Male	Rugby	492	1	492	No	No	Declined
6	15	Male	Tennis	466	0.966	474	No	No	Negative
7	18	Male	Tennis	467	0.908	490	No	No	Negative

ETT, exercise treadmill test.

Exercise stress test

All athletes achieved at least 90% of their age-predicted heart rate during the test. None of the athletes developed episodes of polymorphic VT; however, two athletes exhibited prolongation of the QTc interval during the initial stages of exercise and immediately post exercise (*Figure 2*). Both athletes had a baseline QTc value of >500 ms.

12-Lead ECG screening of first-degree relatives

Both parents and all siblings of each of the seven athletes agreed to be evaluated with 12-lead ECG. One athlete had three siblings, two athletes had two siblings, and four athletes had one sibling. Two athletes had a first-degree relative with a long QTc. In each case, one parent and one sibling were affected (*Figure 3*). Both athletes had a baseline QTc value of >500 ms.

Genetic testing

Of the seven athletes, two declined genetic testing after counselling. The results from the genetic tests were not available before 4 months in any athlete and up to 12 months in one athlete. Only one of the five (20%) athletes who underwent genetic testing had a positive genetic diagnosis. The athlete in question had C to T nucleotide substitution at position c.691 of the *KCNQ1* gene, resulting in an amino acid exchange of arginine (R) to cysteine (C) at codon 231 (p.R231C) and his baseline QTc value of >500 ms. A genetic diagnosis was not possible in the other four athletes after screening for all the known mutations capable of causing LQT1-3.

Discussion

Prevalence of isolated long QTc interval on a 12-lead ECG in athletes

The diagnosis of congenital LQTS is based on the triad of prolonged QTc interval, unheralded syncope or polymorphic VT and a family history of SCD or LQTS.[8,9] On the basis of this triad, the prevalence of LQTS is between 1 in 2500 to 1 in 10 000.[21] However, genotype–phenotype correlation studies in patients with congenital LQTS show that a significant

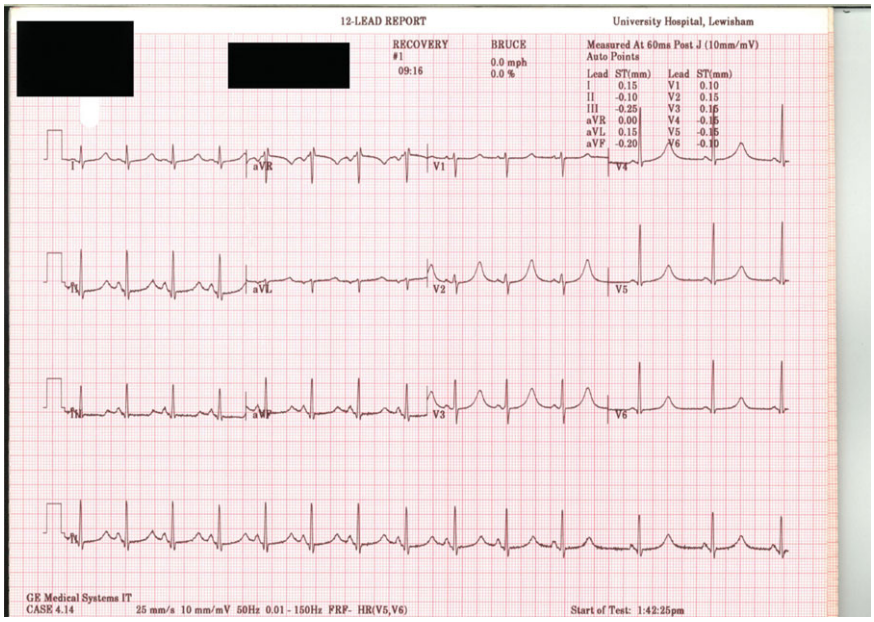


Figure 2 12-Lead ECG of an athlete (athlete 1) demonstrating paradoxical prolongation of the QTc during the recovery phase of exercise.

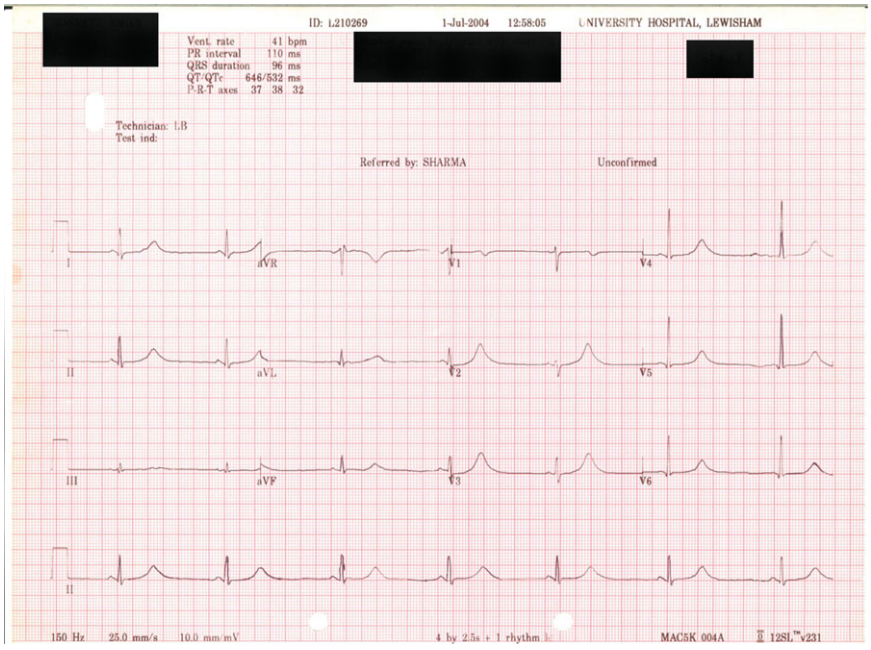


Figure 3 12-Lead ECG of the brother of an athlete (athlete 3) with a long QTc.

number of gene positive individuals may manifest as a prolonged QTc interval in isolation.

The current study reveals that the prevalence of a prolonged QTc interval in elite athletes is 0.4%. This figure is not dissimilar to Mobitz type first-degree AV block, wandering atrial pacemaker and right bundle branch block that are regarded as normal variants in athletes.[10] The Italian preparticipation screening programme comprising of over 34 000 reported disqualification (0.69%) of all athletes based on the identification of a prolonged QTc interval (>440 ms in males and>460 ms in females).[22] The results of both studies could be interpreted to indicate a higher prevalence of LQTS in athletes than other disorders, such as hypertrophic cardiomyopathy, commonly implicated in exercise-related SCD in athletes.[23] If consideration is given to the fact that up to 40% of individuals with LQTS will not be identified on a single ECG, the prevalence of LQTS could be even higher.[24]

However, the current data on SCD in young athletes (<35 years) indicate that deaths in the absence of a structural cardiac abnormality are implicated in no more than 2–4% of cases.[1–5] In relation to the relatively high prevalence of a prolonged QTc interval on the 12-lead ECG in athletes, the low death rates suggest either that the vast

majority of causal mutations may be relatively benign or that most athletes with an isolated long QT interval do not actually have LQTS.

Significance of an isolated long QT interval in an athlete

The significance of an isolated prolonged QTc interval in an athlete has never been studied previously. Although the Italian pre-participation programme identified a long QTc in 0.69% athletes, there is no data relating to subsequent investigations to confirm or refute the diagnosis of congenital LQTS in these athletes.[22] An isolated long QT interval in an athlete may represent the effect of delayed repolarization as a result of increased left ventricular mass[25] or the fact that the Bazett's formula may not hold true in individuals with very slow heart rates.[26,27] Conversely, it may be the only phenotypic manifestation of a potentially fatal ion channel disorder in whom abstinence from sport of a moderate- to high-intensity nature may be compulsory to minimise the risk of SCD.

We aimed at eliminating the effects of physical training (increased left ventricular mass and slow heart rates) by re-evaluating all athletes with a prolonged QTc interval following a 6-week period of detraining based on the previous studies in athletes demonstrating regression of LV mass[28] and our own experience.[29] Our study evaluated potentially affected asymptomatic athletes ($n = 7$) for the broader phenotypic features of the disorder and evidence of familial disease. All athletes had QTc intervals that would be considered to be representative of a diagnosis of LQTS with intermediate probability according to the Schwartz score.[30] Detailed evaluations proved useful in the identification of additional phenotypic features of LQTS or evidence of familial disease and provided diagnostic clarification in three out of seven (43%) athletes.

Interestingly, all three athletes with a baseline QTc value of >500 ms either exhibited paradoxical prolongation of the QT during exercise, an additional phenotypic manifestation of LQT1 and 2,[31] or had a first-degree relative with a prolonged QTc interval. Two of the athletes scored four points on the Schwartz LQT diagnosis scoring system indicating a high probability of LQTS[30] and one had evidence of a disease causing mutation. These observations suggest that the demonstration of a QTc value of >500 ms in an athlete is indicative of unequivocal LQTS and warrants disqualification from most sports to minimise the risk of exercise related SCD. In such cases, subsequent genetic testing may be useful in confirming the genotype and facilitating cascade screening if applicable.

The grey zone

In contrast, none of the athletes with a QTc value of <500 ms (460, 474, 490, and 492 ms) had any features of congenital LQTS on exercise testing and Holter monitoring or any family members with a prolonged QTc interval. Similarly, none scored >4 points on the Schwartz scoring system to indicate a high probability of underlying LQTS.[30] Indeed, risk stratification in probands with LQTS suggests that males with QTc value of <500 ms generally represent a low-risk group.[32] However, according to the 36th Bethesda guidelines, the three athletes with a QTc value of ≥ 470 ms would have been restricted from participating in their sporting disciplines.[6] We made a clinical decision to allow these athletes to continue to participate in competitive sport and all four athletes remain well after a mean follow-up of almost 3 years. Our study indicates that the significance of an isolated prolonged QTc interval of <500 ms in athletes remains unknown but represents a low probability of LQTS or a benign group in whom close monitoring rather than disqualification may be more appropriate in the absence a genetic diagnosis.

Limitations

Our study was unable to comment on the usefulness of genetic testing in the assessment of athletes with a long QT interval and could not utilize genotyping for risk stratification purposes, since two of the seven athletes declined the test and only one tested positive for the disorder. Nevertheless, the results of this study provide convincing evidence that a QTc value of ≥ 500 ms is diagnostic of LQTS in elite athletes; subsequent genotyping may influence decision-making relating to on-going participation in sport.

Acknowledgement

The authors wish to thank the CRY Centre of Sports Cardiology, Olympic Medical Institute, Northwick Park Hospital, Watford road, Harrow, Middx HA1 3UJ, UK for enabling cardiovascular assessment of our athletes in this study.

Conflict of interest: none declared.

Funding

S.B. was funded by a research grant provided by Cardiac Risk in the Young.

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