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CLINICAL RESEARCH

TP-fusion at peak exercise: a novel marker for the recognition of unsuspected long QT syndrome patients

Carlo Boeri [1†], Patrizio Sarto [2†], Paolo Cerea [3], Lia Crotti [3,4], Federica Dagradi [3], Fulvio L.F. Giovenzana [3], Chiara Alberio [3], Giulia Meneguzzo [2], Daniela Lucini [1,5], Giulia Musu [3], Carla Spazzolini [3], and Peter J. Schwartz [3*]

[1]BIOMETRA Department, University of Milan, via Vanvitelli 32, 20129 Milano, Italy; [2]Sports Medicine Unit, Regional Referral Center for Exercise Prescription in Young Patients with Heart Diseases, AULSS 2, Via Castellana 2, 31100 Treviso, Italy; [3]Center for Cardiac Arrhythmias of Genetic Origin and Laboratory of Cardiovascular Genetics, Istituto Auxologico Italiano IRCCS, Via Pier Lombardo 22, 20135 Milano, Italy; [4]Department of Medicine and Surgery, University of Milano-Bicocca, Piazza dell'Ateneo Nuovo 1, 20126 Milano, Italy; and [5]Exercise Medicine Unit, Istituto Auxologico Italiano IRCCS, Via Pier Lombardo 22, 20135 Milano, Italy

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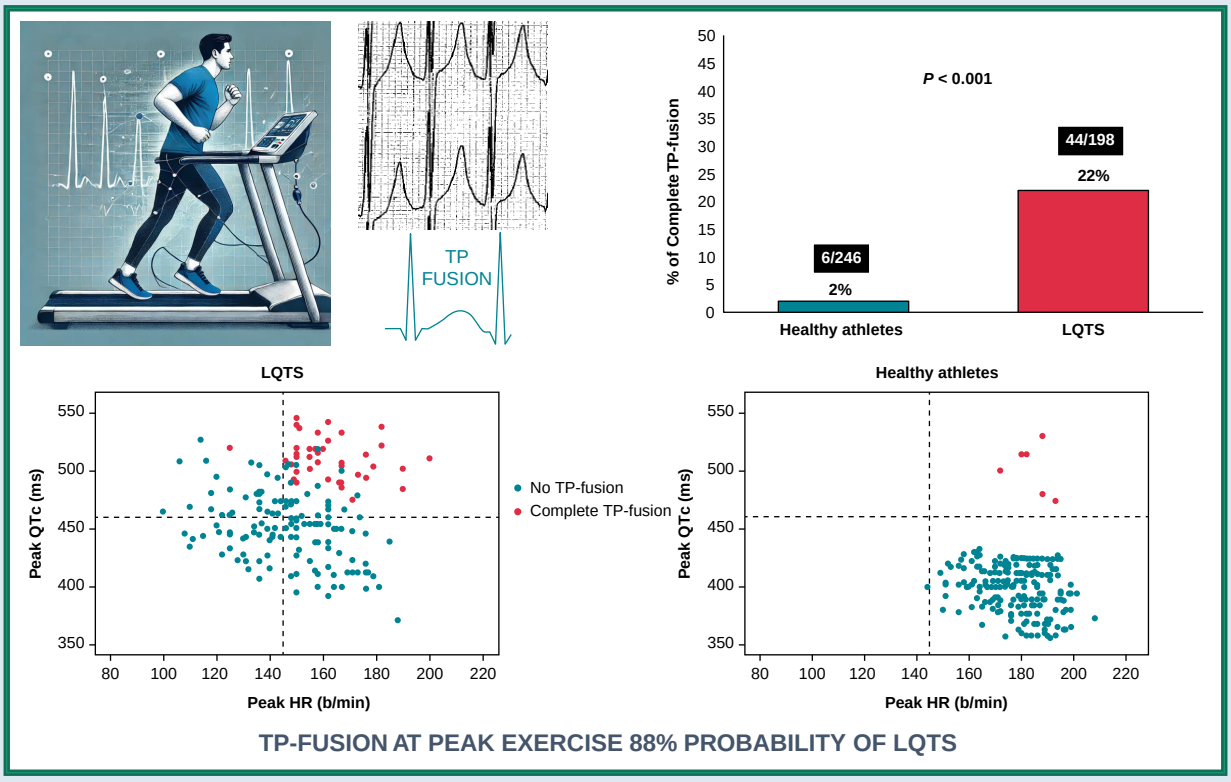
Aims The frequent occurrence of sudden death as the sentinel event in the long QT syndrome (LQTS) forces the search for still asymptomatic patients. We tested our hypothesis that complete fusion of the T and P waves (TP-fusion) at peak exercise might be a marker of likely LQTS.

Methods and results A maximal exercise stress test, off-therapy, was performed by healthy athletes and genotype-positive LQTS patients. TP-fusion had to be complete in all precordial leads except V1. The study population ($n = 578$) included 310 healthy athletes (all with QTc <430 ms) and 268 LQTS patients. To deal only with clear-cut phenotypes, 64 athletes and 70 patients with incomplete TP-fusion were excluded. TP-fusion was present in 2% of controls and in 22% ($P < 0.001$) of the 198 LQTS patients. By limiting the analysis to subjects below age 25 ($n = 262$), the prevalence of TP-fusion increased to 3% in healthy athletes and to 32% in LQTS ($P < 0.001$). TP-fusion depends on the combination of QTc prolongation and fast heart rates; either alone is not sufficient. The appearance of TP-fusion predicted an 88% probability of being affected by LQTS. Importantly, of the 44 LQTS patients with TP-fusion, 24 (55%) had a borderline/normal baseline QTc (<460 ms).

Conclusion TP-fusion, a qualitative trait more easily assessable at peak exercise than QTc prolongation, especially outside referral centres, unmasks a high probability of LQTS, even in subjects with normal baseline QTc. Further clinical assessment and genetic screening allow life-saving prophylactic therapy.

* Corresponding author. Tel: +3902619113408; fax: +3902619113411. *E-mail address*: p.schwartz@auxologico.it; peter.schwartz@unipv.it
† Co-equal first author.

Graphical Abstract



At the peak of an exercise stress test, it is sometimes possible to observe a complete fusion of the T and P waves (upper left panel). This phenomenon is rare among healthy athletes, but it is much more frequent among LQTS (upper right panel). TP-fusion characteristically appears when both heart rate is fast and QTc is prolonged. The different patterns between LQTS patients and controls are self-evident (lower panels). Clinically relevant is the fact that the presence of TP-fusion at peak exercise indicates an 88% probability of being affected by LQTS.

Keywords Long QT syndrome • Electrocardiogram • Exercise stress test • Sudden cardiac death • QTc • Sport medicine

What's new?

- Complete fusion of T and P waves (TP-fusion) at the peak of an exercise stress test is rare (2%) among healthy individuals but relatively frequent among LQTS patients (22%).
- Its appearance predicts an 88% probability of being affected by LQTS.
- Of the LQTS patients with complete TP-fusion, 55% have a borderline/normal basal electrocardiogram (ECG).
- This novel and easily detectable ECG marker may allow the identification of previously unsuspected LQTS patients and guide further diagnostic assessment.
- Detection of TP-fusion during an exercise stress test is a red flag that should prompt referral to a specialized LQTS centre.

Introduction

The clear evidence that the efficacy of the available therapies has reduced mortality of patients affected by the long QT syndrome (LQTS) from 50% to 0.5–1% during the last 50 years,[1–3] combined with the critical fact that the majority of sudden deaths occurs as first episode,[4] has highlighted the importance of an early diagnosis in still asymptomatic patients. However, this remains a challenging task with the necessary requirement of some sort of screening in unselected cohorts. The proposal for a widespread electrocardiographic screening in newborns,[5] despite being supported by a strong rationale,[6] has been implemented in a few centres only, pointing to the need for new additional approaches. Albeit involving smaller numbers, the fact that many countries require the performance of an exercise stress test to allow sport participation might offer another possibility of identifying subjects with LQTS.[7] Lack of QT interval shortening during heart rate (HR) increases in LQT1 patients and QT interval prolongation at the 4th minute post-exercise, among both LQT1 and LQT2 patients, had been noted before,[8,9] but these are parameters looked at solely in cardiology centres when LQTS is already suspected. Indeed, sport physicians usually do not continue to record the electrocardiogram (ECG) after the first 2 min following cessation of exercise.

When one of us (P.S.), expert in sport medicine, told our research group to have observed that the very few 'healthy' youngsters who, at peak exercise, showed a complete fusion of the T with the P wave had been later found by our genetic screening to carry an LQT1-causing variant, this was received with considerable scepticism. Nonetheless, we designed a rigorous and specific study with the objective to blindly examine, in a large cohort of LQTS patients still off-therapy and in a similarly large cohort of healthy athletes, whether this phenomenon was, or not, associated with the probability of being affected by LQTS.

The results were quite clear, certainly unexpected by some of us, and showed how serendipity can still lead to the discovery of a finding which carries significant health implications.

Methods

Study population

The study population included a total of 578 subjects, 268 affected by LQTS and 310 healthy athletes. All patients were genotype-positive for LQTS-related variants in the *KCNQ1*, *KCNH2*, and *SCN5A* genes, who underwent an exercise stress test during their initial cardiological evaluation at our Center in Milan and before initiating β-blocker therapy and mexiletine, if necessary. The athletes performed the exercise stress test, required by law in Italy during the pre-participation screening necessary to obtain the certificate for competitive sports, at the Center in Treviso. They all had a QTc at rest <430 ms without morphological abnormalities suggestive for LQTS. Furthermore, 185/310 (60%) were genetically screened in a separate ongoing research project sponsored by the Italian Ministry of Health and tested genotype-negative.

All exercise stress tests were performed on a stationary cycle ergometer. The protocol for the healthy athletes below age 35 started with a workload of 2–3 W/kg (females–males) with load adjustments, if necessary, until reaching at least 85% of the maximum HR according to age, or higher if tolerated.[7] Athletes over age 35 performed a graded exercise test until exhaustion. The LQTS patients performed a graded exercise stress test with a starting workload of 25 W, with subsequent stepwise increments of 25 W until exhaustion.

None of the subjects, patients and athletes, had atrioventricular and intraventricular conduction delays or sinus node dysfunction. The following variables were collected for each patient: demographics, genetic and clinical characteristics (age, gender, proband/relative, genotype, previous clinical history), exercise test characteristics (protocol of exercise, maximal load, cause of interruption), and ECG findings (HR at rest and at peak exercise, QTc at rest and at peak). HR and QT intervals were manually measured in two precordial leads between V2 and V5. The QT interval was corrected for HR (QTc) according to the Bazett formula, proven to be useful also at high heart rates.[10] The longest QTc value was used for the analyses. During the initial phase of the study, we had collegial meetings to define what would be a complete TP-fusion; once we reached a consensus and after a number of internal checks to maximize consistency, one of the co-authors (P.C.) was given the responsibility of blindly labelling the various tracings and of defining whether they were negative for TP-fusion, or positive, partially or completely.

This study was approved by the Ethical Committees of the two centres in Treviso (686/CE-AULSS2) and Milan (2018_01_30_08).

TP-fusion definition

We defined TP-fusion to be complete when a broad positive T wave ends just before the onset of the QRS complex, completely incorporating and hiding the P wave. We considered positive for TP-fusion those 12-lead ECGs in which this pattern was observed in all precordial leads, excluding V1. Limb leads were not considered since they are more frequently disturbed by motion artefacts during the final part of the exercise. When these criteria were not satisfied and the P wave was clearly distinguishable by the previous T wave, the ECG was considered negative for TP-fusion. To minimize the risk of misclassification and of subjectivity, we labelled as 'partial fusion', and then excluded from the analysis, all those ECGs in which the phenomenon was not evident in all precordial leads or was incomplete, due to the presence of a small notch on the descending limb of the T wave which we interpreted as a P wave. Accordingly, the analysis was limited to the subjects, patients and athletes, with a clear-cut phenotype either positive or negative. As this study relies entirely on visual assessment and pattern recognition, clear examples of the three phenotypes are shown in *Figure 1*.

Statistical analyses

Statistical analyses were performed with GraphPad Prism version 10.0.1 and IBM SPSS Statistics version 29. Categorical variables were expressed as absolute and relative frequencies and compared by χ^2 test and Fisher's exact test. Continuous variables were summarized as mean ± standard deviation (SD) and compared by the Mann–Whitney *U* test or Kruskal–Wallis test. Bonferroni correction for multiple comparisons was applied. To assess the association of complete TP-fusion with being LQTS affected, odds ratio (OR) with 95% confidence intervals (CI) was estimated by logistic binary regression. A *P*-value of <0.05 was regarded as statistically significant.

Data availability statement

Data are available upon reasonable request to the corresponding author.

Results

Study subjects

The entire study population, including 310 healthy subjects and 268 LQTS, is summarized in the flowchart depicted in *Figure 2*. After the predefined exclusion of those presenting incomplete TP-fusion

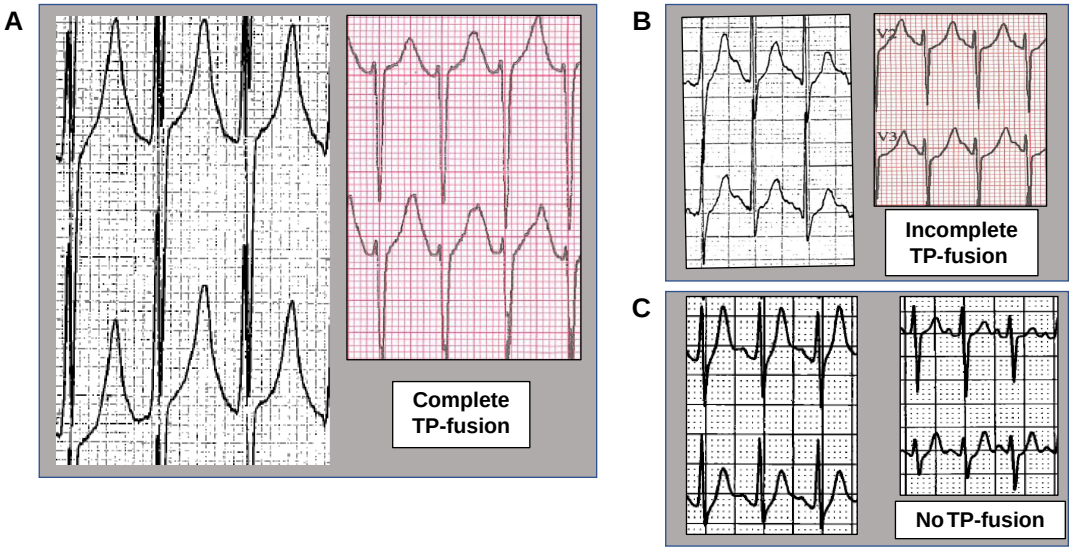


Figure 1 Representative ECGs at peak exercise displaying: in (*A*) complete TP-fusion in two LQTS patients; in (*B*) incomplete TP-fusion in two LQTS patients; and in (*C*) no TP-fusion in two healthy athletes. ECGs, electrocardiograms; LQTS, long QT syndrome.

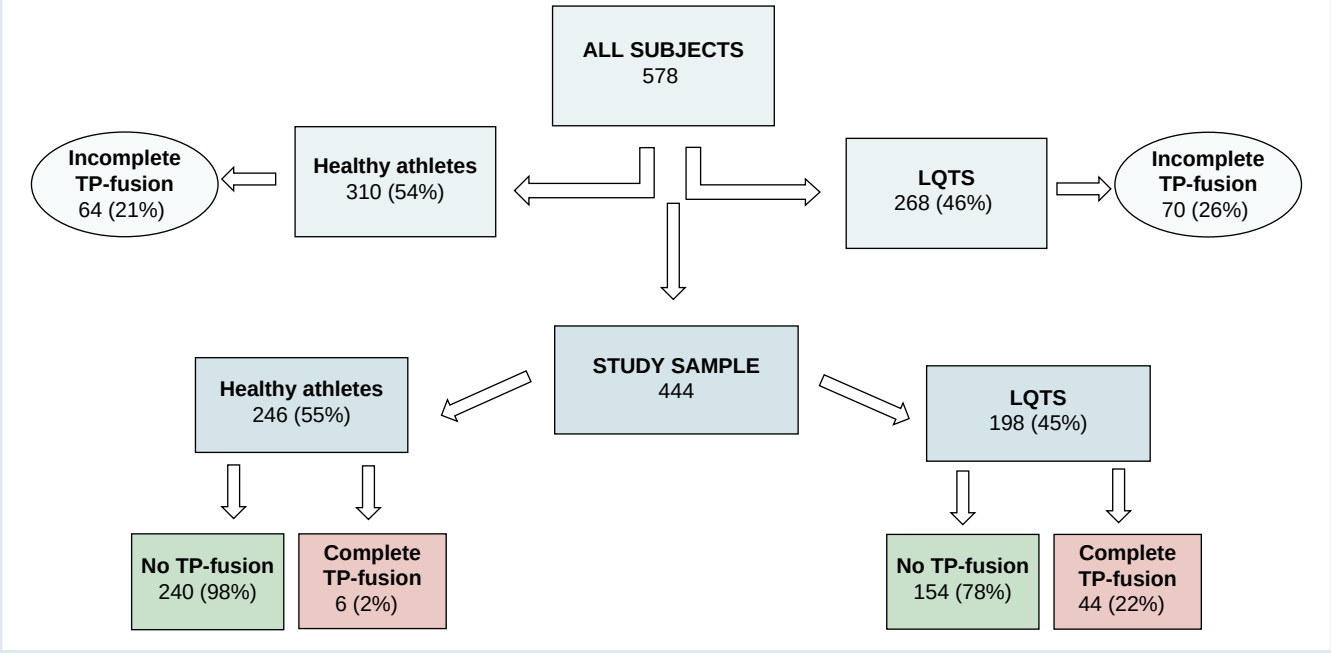


Figure 2 Study population according to genotype and to the appearance of TP-fusion at the peak of the exercise stress test performed off β-blocker and mexiletine therapy.

Table 1 Characteristics of the study sample

	Healthy athletes	LQTS	*P*	LQT1	LQT2	LQT3	*P*
n	246	198		136	48	14	
Age at test, years	25 ± 14	27 ± 16	0.41	29 ± 16	25 ± 14	21 ± 14	0.12
Males, *n* (%)	139 (57%)	87 (44%)	0.008	54 (40%)	26 (54%)	7 (50%)	0.20
Baseline HR (b.p.m.)	69 ± 10	82 ± 14	<0.001	83 ± 13	79 ± 15	84 ± 15	0.22
Baseline QTc (ms)	402 ± 15	448 ± 30	<0.001	445 ± 27	458 ± 34	442 ± 27	0.14
Peak HR (b.p.m.)	178 ± 12	150 ± 19	<0.001	148 ± 17	152 ± 23	160 ± 16	0.04
Peak QTc (ms)	403 ± 24	464 ± 37	<0.001	471 ± 36	450 ± 31	434 ± 38	<0.001 [a]
QTc 4th min recovery (ms)		477 ± 39		488 ± 38	455 ± 34	444 ± 18	<0.001 [a]
QTc 4th min recovery ≥480 ms, *n* (%)		87/183 (48%)		75/130 (58%)	11/41 (27%)	1/12 (8%)	<0.001
Total TP-fusion	6 (2%)	44 (22%)	<0.001	34 (25%)	8 (17%)	2 (14%)	0.37
Δ $HR_{peak-baseline}$	109 ± 12	68 ± 19	<0.001	66 ± 17	73 ± 23	76 ± 17	0.05
Δ $QTc_{peak-baseline}$	1 ± 29	15 ± 39	<0.001	26 ± 37	−8 ± 32	−8 ± 37	<0.001 [a]

HR, heart rate; LQTS, long QT syndrome.
[a]$P < 0.01$ LQT1 vs. LQT2 and vs. LQT3

[observed with a similar frequency in 64/310 (21%) and in 70/268 (26%)], the two groups were comparable by age, but males were more frequent among athletes. They differed, as expected, for a number of ECG variables. Compared to healthy athletes, LQTS patients had higher HR and QTc values at baseline (82 ± 14 vs. 69 ± 10 b.p.m.; 448 ± 30 vs. 402 ± 15 ms, $P < 0.001$) and longer QTc but lower HR at peak exercise (464 ± 37 vs. 403 ± 24 ms; 150 ± 19 vs. 178 ± 12 b.p.m., $P < 0.001$) (*Table 1*). Within the LQTS group, while no differences were observed among the three genetic subtypes in the ECG parameters at baseline, LQT1 patients showed longer QTc at peak exercise compared to LQT2 and especially to LQT3 (471 ± 36 vs. 450 ± 31 vs. 434 ± 38 ms, respectively, $P < 0.001$) and also at the 4th minute recovery (488 ± 38 vs. 455 ± 34 vs. 444 ± 18 ms, respectively, $P < 0.001$) (*Table 1*). Interestingly, there was a rather striking difference in the prevalence of patients with a QTc >480 ms at 4th recovery between LQT1 (58%) and LQT3 (8%), $P < 0.001$, despite a very similar baseline QTc (445 ± 27 and 442 ± 27 ms).

The change from baseline of HR and QTc at peak exercise confirmed the same different pattern between healthy subjects and patients, also across LQTS subtypes (*Figure 3*).

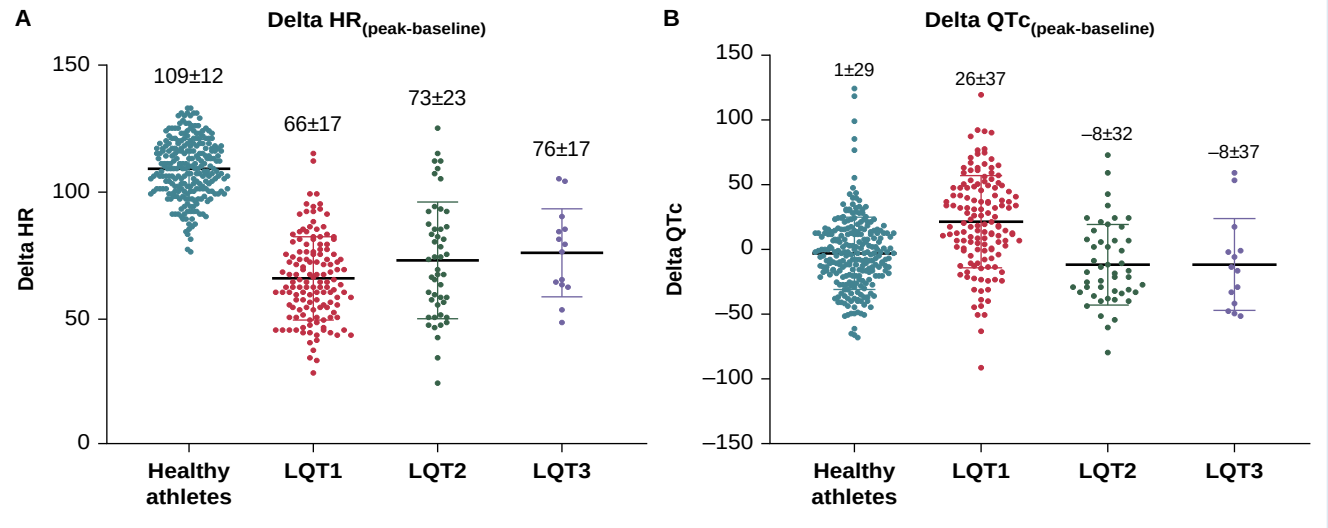


Figure 3 Changes during the exercise stress test among healthy athletes and LQT1, LQT2, LQT3 patients. (*A*) Difference (Δ) between peak and baseline heart rate, healthy athletes vs. LQT1, LQT2, and LQT3 patients, $P < 0.001$. No significant differences across genotypes. (*B*) Difference (Δ) between peak and baseline QTc, LQT1 vs. all other groups, $P < 0.001$.

Table 2 Characteristics of the LQTS patients with or without TP-fusion

	No TP-fusion	TP-fusion	*P*
n	154	44	
Age at test, years	30 ± 16	19 ± 12	<0.001
Males, *n* (%)	54 (35%)	33 (75%)	<0.001
History of syncope, *n* (%)	7 (5%)	3 (7%)	0.70
Baseline HR (b.p.m.)	82 ± 14	82 ± 14	0.99
Baseline QTc (ms)	446 ± 29	457 ± 29	0.06
Peak HR (b.p.m.)	147 ± 18	162 ± 14	<0.001
Peak QTc (ms)	450 ± 29	511 ± 17	<0.001
QTc 4th min recovery (ms)	473 ± 40	493 ± 33	<0.001
QTc 4th min recovery ≥480 ms, *n* (%)	58/142 (41%)	29/41 (70%)	0.001
Δ $HR_{peak-baseline}$	65 ± 18	79 ± 18	<0.001
Δ $QTc_{peak-baseline}$	4 ± 34	54 ± 30	<0.001

LQTS, long QT syndrome.

TP-fusion

A complete TP-fusion at peak exercise was present in 50 of the 444 (11%) subjects under study, with a striking difference between its occurrence among controls (only 6/246, 2%) and among LQTS patients (44/198, 22%, $P < 0.001$). Indeed, of all the observed TP-fusions, 44/50 (88%) occurred among LQTS patients, without significant differences across genotypes (LQT1, 34/136, 25%; LQT2, 8/48, 17%; LQT3, 2/14, 14%, $P = 0.37$).

Table 2 shows the characteristics of the LQTS patients with or without TP-fusion. Those with fusion were predominantly males (75 vs. 35%, $P < 0.001$) and significantly younger (19 ± 12 vs. 30 ± 16, $P < 0.001$). Their PR interval was within the normal range (min 120–max 180) with no significant difference between LQTS patients (146 ± 20 ms) and healthy athletes (155 ± 25 ms). At baseline, HR was identical in the two groups (82 ± 14), while QTc was slightly longer in those subsequently showing TP-fusion (457 ± 29 vs. 446 ± 29 ms, $P = 0.06$); at peak exercise, both HR and QTc values were significantly higher in patients with TP-fusion (162 ± 14 vs. 147 ± 18 b.p.m.; 511 ± 17 vs. 450 ± 29 ms). Furthermore, the QTc at the 4th minute recovery in 183/198 (92%) LQTS patients was significantly more prolonged among patients with a complete TP-fusion compared to those without it (493 ± 33 vs. 473 ± 40 ms, $P < 0.001$). Importantly, 70% of the LQTS patients with complete TP-fusion also had a QTc ≥480 ms at the 4th minute recovery, showing an important concordance between the two ECG markers, thus reinforcing the value of TP-fusion in pointing to the possibility of LQTS.

TP-fusion appeared concomitantly with a relatively higher peak HR (>145 b.p.m.) and a longer peak QTc (>460 ms) in all genotypes (*Figure 4*). Of major clinical relevance, among the 44 LQTS patients with a complete TP-fusion, the majority (24, 55%) had at baseline a QTc <460 ms and 15 (34%) even a QTc <440 ms (*Figure 5*). This highlights the usefulness of TP-fusion as a marker of 'likely LQTS' in otherwise 'normal' or borderline subjects. Similarly to LQTS patients, the six healthy subjects (all males), who showed complete TP-fusion, did it at a significantly longer peak QTc compared to the remaining athletes (499 ± 18 vs. 400 ± 19 ms, $P < 0.001$) but at a similarly high peak HR (184 ± 7 vs. 178 ± 12 b.p.m., $P = 0.16$), which in none of these six subjects was below 170 b.p.m. (*Figure 5*). Focusing on a subset of young patients and athletes all below age 25, the prevalence of TP-fusion among the LQTS patients increased from 22% (in the entire LQTS cohort) to 32%, and the difference in comparison to that present in the athletes (3%) becomes even more striking. In this subgroup of subjects homogeneous for age at exercise stress test (15 ± 3 vs. 15 ± 4 years) and for gender prevalence (males, 55 vs. 47%), it was quite evident that the significantly higher peak HR of athletes does not parallel a correspondingly larger frequency of TP-fusion.

For clarity of phenotypes, we had limited the QTc of the control group to below 430 ms. In theory, this could have reduced the probability of these athletes to develop TP-fusion. Accordingly, we performed another analysis by focusing on an additional 50 athletes

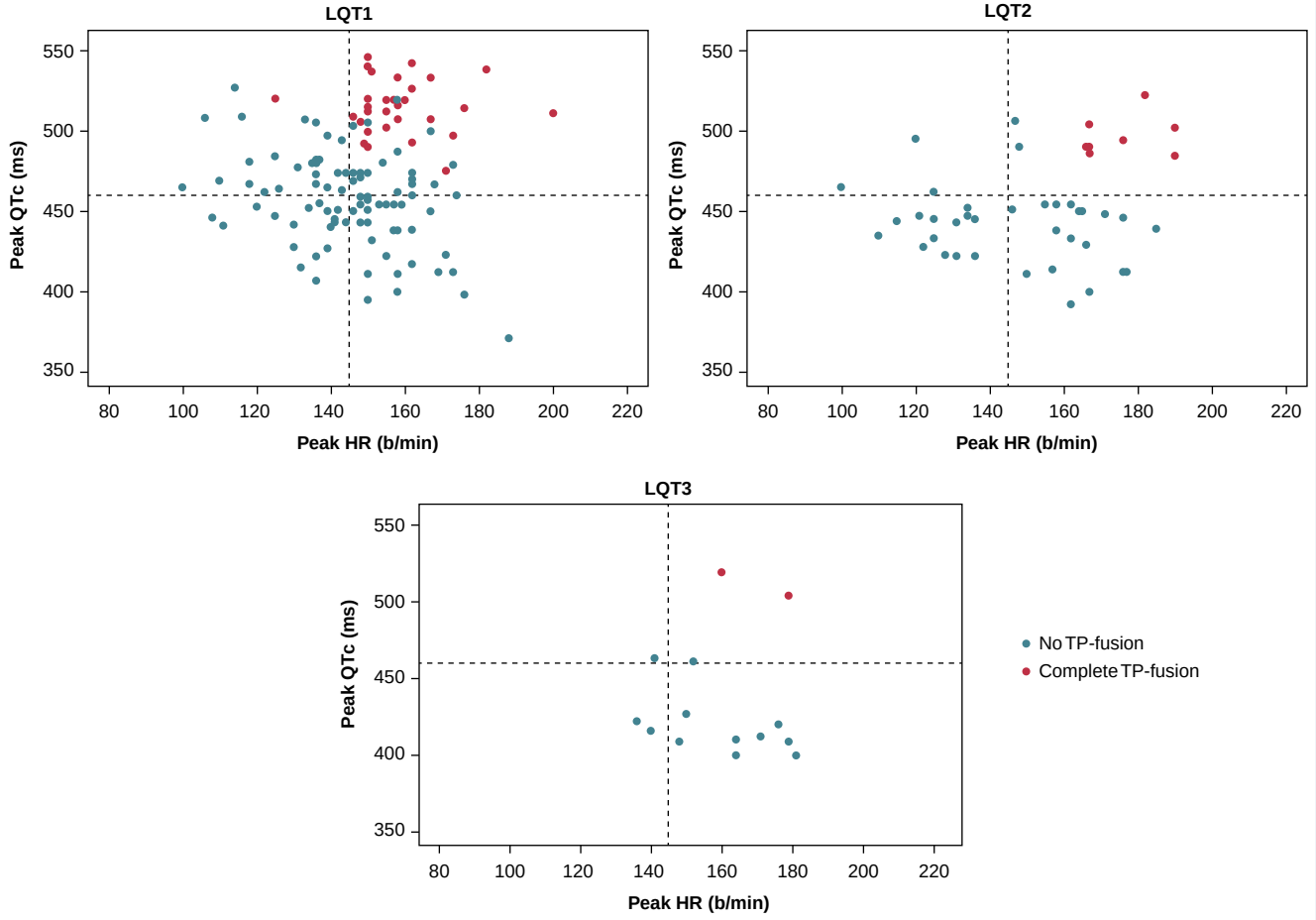


Figure 4 Scatterplot showing the distribution of individual HR and QTc values at peak exercise in the three LQTS subtypes. Dashed horizontal and vertical lines provide arbitrary cutoff points (460 ms and 145 b.p.m.) to facilitate data analysis and interpretation. It is evident, especially in the more numerous LQT1 group, that TP-fusion occurs primarily when there is the combination of prolonged QTc and of fast heart rates; in the presence of only one of these two factors, it is rare to observe the fusion. LQT1, long QT syndrome type 1; LQT2, long QT syndrome type 2; LQT3, long QT syndrome type 3.

whose baseline QTc was between 430 and 460 ms, to match that of the borderline LQTS patients: in not a single one was TP-fusion observed.

TP-fusion as a marker of long QT syndrome

Irrespective of the baseline QT interval, a complete TP-fusion at the peak of an exercise stress test had a low sensitivity (22%) and a very high specificity (98%). Importantly, the positive predictive value (PPV) for LQTS was 88% and the negative predictive value (NPV) was 61%. When focusing on all subjects presenting with a baseline QTc <460 ms, PPV and NPV values were 80 and 69%, respectively. This shows the importance of TP-fusion for the identification of those LQTS patients who would not be recognized because their baseline QTc is within normal limits. The probability of being affected by LQTS with the positive finding of TP-fusion corresponded to an unadjusted OR of 11.4 (95% CI 4.94–25.5, $P < 0.001$).

Discussion

The main finding of the present study is represented by the fact that an electrocardiographic feature, hitherto completely ignored, has a high probability to lead to the identification of patients genetically affected by LQTS but who would otherwise escape diagnosis because of a borderline/normal phenotype. The complete fusion of the T and of the P waves in the V2–V6 precordial leads at peak exercise is an uncommon but easily recognizable phenomenon which can contribute first to suspect and then, following genetic confirmation, to diagnose LQTS in apparently normal subjects. Given the high risk of sudden death as the sentinel event, by leading to a previously unsuspected diagnosis of an unrecognized LQTS patient and allowing the initiation of prophylactic therapy, this novel finding can save lives.

ECG markers of long QT syndrome

Until 1995, in the pre-genetic era, the diagnosis of LQTS was entirely based on one single ECG feature complemented by a typical clinical presentation. Indeed, a marked prolongation of the QT interval was obviously regarded as the essential and necessary feature of LQTS. However, in 1980, on a purely theoretical basis, it was proposed that there might have been patients affected by the disease but having a normal QT interval.[11] This unorthodox hypothesis was not well received by the cardiological community, and it was only 20 years later that it became accepted on the basis of the molecular findings showing LQTS-causing variants in subjects with a normal QT,[12] which led to

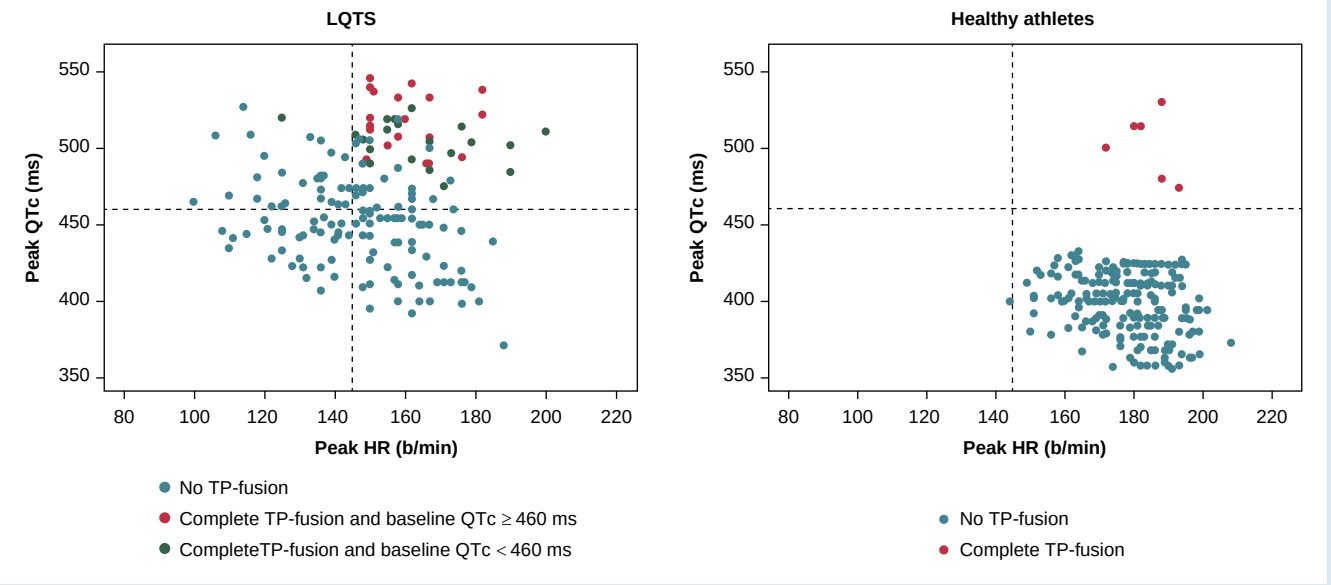


Figure 5 Scatterplot showing the distribution of individual HR and QTc values at peak exercise in all LQTS patients and in healthy athletes. Dashed horizontal and vertical lines provide arbitrary cutoff points (460 ms and 145 b.p.m.) to facilitate data analysis and interpretation. By looking at all LQTS patients independently of their genotype, the difference with the athletes is self-evident and, within the athletes, it becomes very clear that the rare onset of TP-fusion does not depend on fast heart rates alone. Of special clinical relevance is the evidence that more than half of the LQTS patients showing TP-fusion had a baseline QTc <460 ms, a value likely to escape medical attention. HR, heart rate; LQTS, long QT syndrome.

the currently established concept of genotype-positive/phenotype-negative patients.[13]

In 1975, a second ECG feature was identified to be closely associated with LQTS and to carry important prognostic information.[14] Macroscopic T wave alternans (TWA) is a rare phenomenon, highly characteristic of LQTS, which can precede the onset of Torsade-de-Pointes ventricular tachycardia or of ventricular fibrillation and which is a marker of high cardiac electrical instability. The fact that TWA could be triggered by stimulation of the left-sided cardiac sympathetic nerves[14] demonstrated their tight connection with the onset of life-threatening arrhythmias and provided a strong rationale for the use of left cardiac sympathetic denervation in the management of LQTS.[15,16]

In the early 90s, the recurrent anecdotal reports of notches on the T wave in some LQTS patients[17] were quantified,[18] and it became evident that notched T waves are important for multiple reasons: they should raise the suspicion of LQTS, they are associated with increased arrhythmic risk and with mechanical abnormalities,[19] and they are more common among LQT2 patients.[20]

The novel ECG feature of LQTS, identified in the present study, i.e. the complete fusion of the T and P waves at peak exercise, represents another turning point because it carries the unique characteristic of becoming manifest also in LQTS patients who otherwise would not be identified, as their baseline QTc can be borderline or normal.

Incomplete TP-fusion is present among LQTS patients and healthy athletes with a similar frequency (26 and 21%), and it has no clinical significance.

Evidence

This study was designed when one of us (P.S.) reported that from his large cohort of athletes, those subsequently diagnosed by our genetic laboratory as carriers of LQT1 pathogenic variants tended to show the fusion of the T and P waves when reaching the peak of the exercise stress test, mandatory in Italy for the certificate necessary to practice competitive sports.[7] There were several aspects of the study that we regarded as essential in order to draw safe and scientifically credible conclusions. The first was to have exercise stress test data, all performed off β-blockers and mexiletine, from two large cohorts, one of genotype-positive LQTS patients, including all genotypes, and one of healthy athletes with a definitely normal QTc (<430 ms). The rationale for the latter point is based on the recognition that intense physical training can induce QT prolongation with a morphology indistinguishable from that of LQTS patients and can lead to a misdiagnosis of LQTS.[21] The second was to have a rigorous definition for the TP-fusion, which had to be complete and present in all precordial leads (except V1), in order to identify and discard from the analysis all intermediate patterns or partial fusions because clinically irrelevant and potentially confounding. Accordingly, the definitions of non-fusion, partial fusion, and complete fusion provided us with a clear black and white phenotype. Third, we had to present the readers with clear examples of our definitions to allow everyone to recognize these very different patterns.

The tight relationship between TP-fusion and the probability of being affected by LQTS is strengthened by the close association (70% concordance) between complete TP-fusion and an established ECG marker characteristic of LQTS, such as QTc >480 ms at the 4th minute recovery.

Pathophysiological considerations

The measurement of the QT interval and especially its quantification after the necessary correction for HR are burdened by a significant 'measurement error' of which one has to be aware. This is why it is important that in any QT-related study, all measurements are made by a single and expert investigator, to reduce individual variability. At low heart rates, this error is likely to be limited to ±10 ms. At fast rates, it increases significantly. At peak exercise, the error can be large. It should be obvious that if the T wave ends just before the onset of the Q wave, being fused with the P wave, the QT interval must be very long. This means that the recognition of the TP-fusion allows to

state that there is a major QT prolongation, with all the necessary clinical implications, without the need of venturing into an improbable and often unreliable quantitative QTc estimate. Additionally, it has to be recognized that, at variance with what happens in LQTS referral centres, the measurements of the QT interval during an exercise stress test are often rather cursory, especially towards peak exercise when the fast heart rates interfere with a careful reading. Thus, while the importance of QT prolongation for the identification of likely LQTS patients remains, it should be evident that the much simpler observation of TP-fusion could favour the suspicion of LQTS also by non-experts.

In theory, TP-fusion could simply be the consequence of very fast heart rates. *Figure 5* shows that this is not the case. Indeed, even though most of the athletes reached higher heart rates compared to the LQTS patients, only 2% of them showed TP-fusion, thus demonstrating that high HR *per se* is necessary but not always sufficient to generate the phenomenon. Conversely, a prolongation of the QT interval at baseline is not a requirement because TP-fusion can occur in a significant number of patients with normal/borderline QTc at baseline. A 'propensity' to prolong ventricular repolarization, combined with high heart rates and increased sympathetic activity, appears necessary. This is why TP-fusion appears exquisitely related to LQTS, where it appears to be largely independent of the specific genotype. During exercise, QTc increases among LQT1 patients (+26 ± 37 ms), whereas in contrast it shortens among LQT2 and LQT3 patients (−8 ± 32 ms, −8 ± 37 ms) (*Figure 3*). This peculiar behaviour confirms the early observation, made in a first and very tiny group of LQT3 patients, that QTc would actually decrease with increasing heart rates even more than among healthy individuals.[22]

Implications

The importance of the present findings is not so much for tertiary centres specialized in channelopathies where the diagnosis of LQTS is unlikely to be missed, even though the new knowledge that special attention should be given to the occurrence of TP-fusion when exercising a patient with possible LQTS and a borderline QT interval would certainly help avoiding diagnostic errors.

The main value of recognizing the highly specific pattern of TP-fusion concerns primarily sport physicians and any cardiologist without personal experience with LQTS who performs exercise stress tests in apparently healthy and normal people. In these situations, two things, which might prevent the correct diagnostic suspicion, happen regularly. One is that, when the T wave morphology is normal, a QTc below 460 ms or even below 470 ms is likely to escape attention. The other is that, outside referral centres, the ECG is almost never recorded for 4 min after cessation of exercise, a point in time when QTc prolongation contributes to the diagnosis of LQTS.[9,23] It is in these common situations, when mostly young people perform a standard exercise stress test in relation to their sport activity, that awareness of the implications of observing the appearance of TP-fusion becomes very important. When that happens, the responsible doctors should realize that there is an approximate 90% probability that they are dealing with an undiagnosed LQTS patient and also that an important concordance does exist between TP-fusion and QTc prolongation at the 4th minute recovery. Accordingly, if they could, they should promptly proceed with diagnostic refinements such as determining the QTc at the 4th minute of recovery of exercise[9,23] and analysing a 12-lead 24/h Holter recording,[2] being ready to proceed with genetic testing. Alternatively, and probably more wisely, they should refer the patient to an LQTS referral centre.

Conclusions

Physicians, including cardiologists and sport doctors, should become familiar with the specific and easily recognizable pattern of complete TP-fusion because, if it appears at peak exercise, it indicates a high probability of being in the presence of an LQTS patient, even if his/her QTc at baseline was normal or just borderline. TP-fusion is much more reliable to indicate a major QT prolongation than a QTc measured at very high heart rates. The clinical relevance of identifying, among apparently normal individuals, those who carry a pathogenic variant causing LQTS should not be underestimated.

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