

Relative Prolongation of the Terminal Part of the QT Segment Is Associated with Sudden Death in the Elderly

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Abstract

Holter-based QT parameters were measured in 40 matched participants (age 73.03 ± 4.51, 24 M, 8 F), 20 with SCD (sudden cardiac death) and 20 without SCD who had recordings in the Cardiovascular Health Study. Time to SCD was 6.5±2.8 years. Beat-by-beat QT_{onset}, QT_{peak}, and QT_{end} times were measured and averaged for one 2-min segment/hr and results compared between cases and controls. QT interval was significantly longer among cases (445 ± 88 vs. 405 ± 45 ms, p<0.001). Correcting the QT for heart rate did not affect this relationship. % QT in the pre-peak interval was significantly shorter in SCD cases (23.7 ± 3.1% vs. 24.2 ± 3.7%, p=0.040). % QT in the post-peak interval was significantly longer in SCD cases (23.4 ± 3.9% vs. 22.0 ± 2.5%, p<0.001). Results did not differ by the channel examined. Findings are consistent with a prolonged Holter-based QT and an additional relative prolongation of the terminal QT, in older adults with SCD.

1. Introduction

Prolongation of the QT-complex on Holter recordings has been linked to sudden cardiac death (SCD) [1]. The congenital long QT syndrome (LQTS), an inherited form, has also been associated with prolonged ventricular repolarization and Torsades de pointes (TdP), a serious polymorphic ventricular tachycardia. LQTS is a genetic abnormality caused by specific ion channel mutations [2]. However, prolonged QT is also found as a result of and is a marker for cardiovascular disease and such patients are also at higher risk of SCD [1]. Recently it has been suggested that prolongation of the terminal segment of the QT is more strongly associated with SCD and specifically TdP than overall QT prolongation, because some drugs that prolong the overall QT but do not prolong the terminal portion do not appear to be associated with increased risk of SCD [3]. Increased length of the terminal portion of the QT reflects increased

transmural dispersion of repolarization in the ventricle [4]. As a result, patients with prolongation of the terminal portion of the QT would have an increased risk of a malignant ventricular arrhythmia. The goal of this study was to investigate whether there is an association between the prolongation of the terminal portion of the Holter-based QT intervals and subsequent SCD in Holter recordings from the Cardiovascular Health Study.

2. Methods

The Cardiovascular Health Study (CHS) is an NIH-sponsored population-based longitudinal study to identify risk factors that relate to the onset and course of coronary heart disease and stroke in 5,201 men and women aged 65 years and older [5]. Participants underwent extensive testing, at baseline (starting in 1989) and during a second examination cycle (starting in 1996) to identify the presence and severity of cardiovascular risk factors and the presence of overt disease. A less extensive follow up examination was performed annually, and telephone data were collected semi-annually. Ambulatory ECG (Holter) monitoring was performed on a subset of 1,429 volunteers at baseline (yr2 cohort) and repeated in 864 during the second examination (yr7 cohort). Recordings were also made during the second examination in an additional 385 participants who entered the study during exam year 5 (minority cohort).

Of the 1,814 individuals who had at least one Holter recording in the CHS, 1,649 were in normal sinus rhythm had at least 18 hours of usable Holter data. N=49 of them suffered SCD during up to 14 years of follow up. SCD was defined as a sudden pulseless condition (presumably, but not definitely, ventricular fibrillation) due to a cardiac etiology in an otherwise stable patient. All individuals who had their event either out of the hospital or in the ER were included, but patients who were already hospitalized and nursing home patients who often have multiple comorbidities were excluded. SCD was ascertained by a cardiologist's record review of all cardiac deaths.

Each SCD case was matched on age within 5 years,

gender, beta-blocker use, history of myocardial infarction, and use of hypoglycemic medications (oral or insulin) with a control participant alive at the time of death of the case and not suffering SCD on follow up. This nested case: control approach was chosen because measurement of QT properties was extremely labor intensive and it was not feasible to do this for all of the recordings in the cohort. For the current study, 20 SCD cases were randomly selected from among the 49 who had SCD and recordings for their controls were also analyzed.

Digitized ECGs (.MIT format) outputted from the MARS 8000 Holter Analyzer (GE Medical Systems, Milwaukee, WI) were integrated with beat-to-beat files obtained from Holter scanning using ecgpuwave (www.physionet.org). This program detected the start, peak, and end time of each R-wave and T-wave. These times were used to determine the heart rate and the duration of the initial and terminal portions of each T-wave.

A customized MATLAB program (Figure 1) was used to overread beat detection and exclude misdetections. As can be seen in the figure, the full-length gray line represents where the peak of the R-wave was detected, the dotted red line represents where T_{peak} was detected, and the $\frac{3}{4}$ -length gray line is where T_{end} was detected. The one green line is a marker of abnormality, and in the case of Figure 1, the green line marks that the R-wave detection was off. The program was run separately on the two channels of the Holter ECG and the one with a higher proportion of accurately detected beats was used for the analysis. A box on the right side of the screen shows the percentage of usable beats, which are beats that were readable and detected correctly in a 2-minute segment. The first 2-minute segment of each hour that had at least 80% correctly detected beats was accepted for waveform measurement. The program outputted values at the time of each measure parameter for each beat in the chosen 2-minute segment and these values were then averaged from each 2-minute segment for each hour.

In addition, the percent of the QT period in the pre- and post-peak portions was determined for each hour and QT intervals were corrected using both Bazett's and Fridericia's formulas [6]. Values were compared between groups using t-tests.

3. Results

N=4 cases and N=4 controls did not have sufficient usable QT data, but there was no difference by SCD status in age (72.6 ± 4.6 for cases vs. 73.5 ± 4.5 for controls), gender (12 males and 4 females in both the cases and the controls) or clinical parameters (history of myocardial infarction and presence of diabetes) between the remaining 16 SCD cases and 16 controls. N=346 2-minute segments were available from controls and N=353 2-minute segments were analyzed from cases. N=24

recordings were analyzed on ch1 and N=8 on ch2. Results did not differ by the channel examined. SCD occurred 6.5 ± 2.8 years (range 0.4-9.7) after the Holter recording. All of the controls were alive at the time of SCD of their matched case.

QT interval was significantly longer among cases (445 ± 88 vs. 405 ± 45 ms, $p < 0.001$). Correcting the QT for heart rate did not affect this relationship (Bazett: 473.9 ± 61.3 vs. 436.6 ± 18.4 , $p < 0.001$; Fridericia: 463.9 ± 66.2 vs. 426.4 ± 17.6 , $p < 0.001$). Both the length of the T_{onset} to T_{peak} and the length of the terminal part of the QT (T_{pe}) were significantly longer in cases (T_{onset} to T_{peak} ; 105 ± 24 for cases vs. 99 ± 16 ms for controls, T_{pe} 108.3 ± 27.0 for cases vs. 93.6 ± 13.6 ms for controls, both $p < 0.001$). Also, however, percent QT in the pre-T to the peak of the T interval was significantly shorter in SCD patients ($23.7 \pm 3.1\%$ vs. $24.2 \pm 3.7\%$, $p = 0.002$) whereas percent QT in the peak of the T to the end of the T (T_{pe}) interval was significantly longer in SCD ($24.3 \pm 3.9\%$ vs. $22.9 \pm 2.5\%$, $p < 0.001$).

4. Discussion and conclusions

Although the longer QT intervals of those who suffered SCD was not unexpected, results support the hypothesis that there is additional information in the distribution of the QT interval with respect to the peak that may also identify higher-risk individuals. Specifically, a greater prolongation, both in absolute and relative terms of the terminal portion of the QT segment which is believed to reflect increased repolarization dispersion and therefore increased vulnerability to ventricular arrhythmias was found in those who later suffered SCD. It is of interest that these abnormalities were seen long before the SCD event.

Existing commercial Holter software is already able to measure QT intervals for each heart beat, although these measures contain considerable noise and precise measurements would be time consuming and problematic for the 100,000 beats or more of the typical Holter recording. Measurement of detailed QT properties is not yet available in commercial Holter analyzers but could easily be implemented if further studies continue to support its potential value. In the current analysis, detailed measures of the T wave from 2-minute segments of each hour were carefully made. This appeared to be sufficient to identify underlying abnormalities although it is possible that a more detailed analysis of all of the T-waves on the recording could have provided increased precision.

The results support further exploration of detailed QT interval properties as a potential risk factor for SCD. The current method is relatively labor intensive and clinical application would require additional software development to make it more efficient.

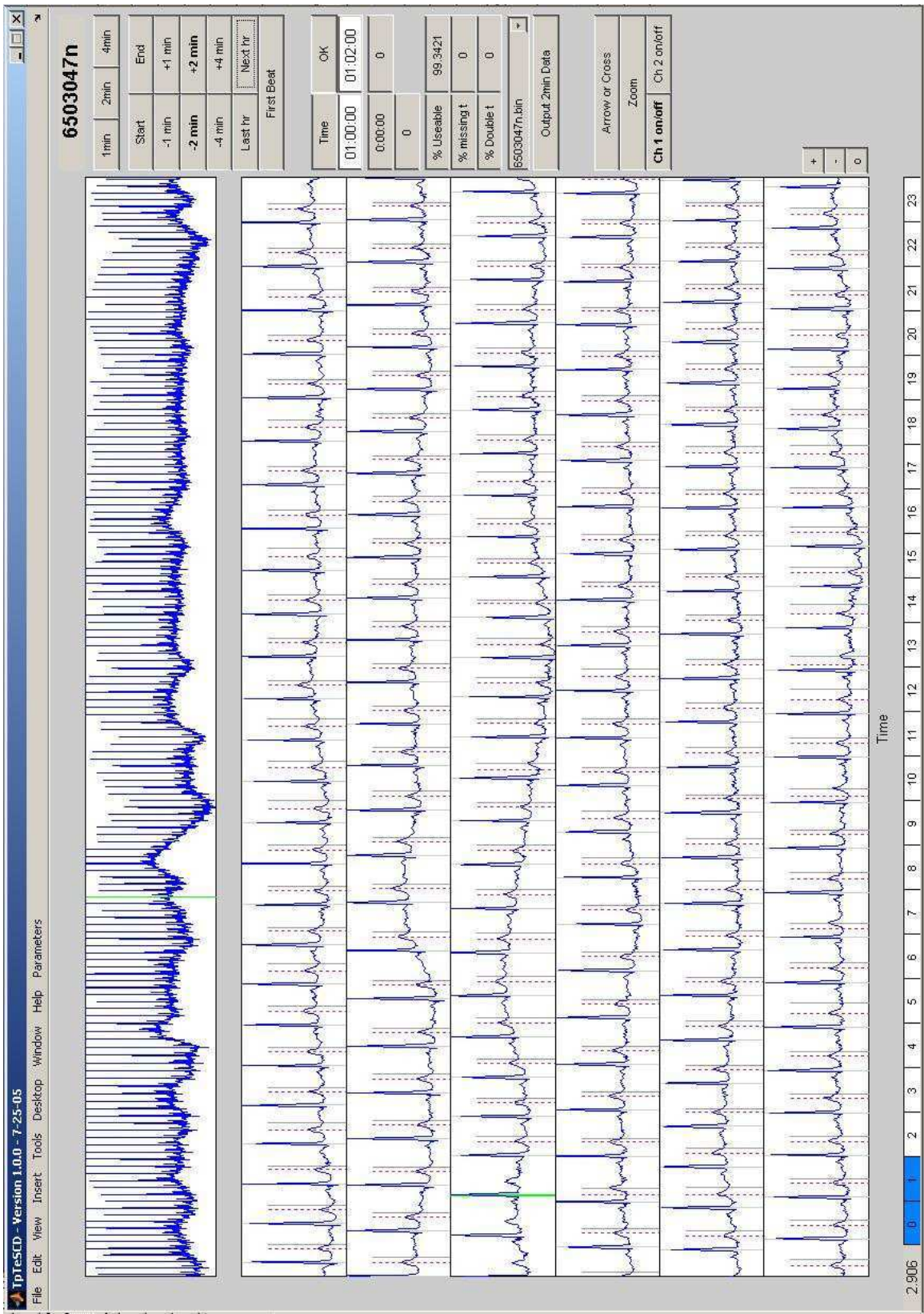


Figure 1. Screenshot of the customized MATLAB program TpTeSCD.

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References

- [1] Pfeufer A et al. Common variants at ten loci modulate the QT interval duration in the QTSCD Study. *Nat Genet* 2009;41:407-14.
- [2] Satomi K et al. Response of beat-by-beat QT variability to sympathetic stimulation in the LQT1 form of congenital long QT syndrome. *Heart Rhythm* 2005;2:149-54.
- [3] Antzelevitch C. Arrhythmogenic Mechanisms of QT Prolonging Drugs: Is QT Prolongation Really The Problem? *J Electrocardiol* 2004;37:15-24.
- [4] Kannankeril PJ et al. Rate-Independent QT Shortening During Exercise in Healthy Subjects: Terminal Repolarization Does Not Shorten with Exercise. *J Cardiovasc Electrophysiol* 2008;19:1284-8.
- [5] Stein PK et al. Holter-Based Measures are Associated with Sudden Cardiac Death in the Community-Dwelling Elderly: The Cardiovascular Health Study. *Circulation* 2008;118:S_1097.
- [6] Desai M et al. Variability of heart rate correction methods for the QT interval. *Br J Clin Pharmacol* 2002;55:511-517.

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