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Evaluation of T-wave Time-Warping Dynamics in Patients with Long QT Syndrome.

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***Abstract*—In this work, we use a T-wave time-warping-based morphology variation index, d_w, quantifying ventricular repolarization dispersion (VRD), and assess its performance in classifying long QT syndrome (LQTS) patients and healthy control (CG) individuals, as well as LQTS patients who experienced syncope (LQTS-SG) and those who did not (LQTS-NSG). The values of d_w were obtained by quantifying the morphological differences between the mean warping T-wave (MWTW), estimated from each 10-second ECG recording and a reference MWTW estimated from the UK Biobank cohort. In CG, d_w had median (IQR) values of 9.32 (5.53) ms, while larger changes were noted in LQTS patients, with median (IQR) values of 20.93 (12.67) ms. Neither d_w nor the QT interval presented significant differences when comparing LQTS-SG and LQTS-NSG. A p-value near significance was found for d_w in lead II. $d_{w,\mathrm{T}_{pe}}$ marker, restricting the analysis to the final T-peak to T-end part, reached significance when comparing LQTS-SG with LQTS-NSG in Lead I. In conclusion, larger d_w values in LQTS patients as compared to CG allows LQTS idnetification more significnatly than QT interval. Distintion between LQTS-SG and LQTS-NSG patients becomes unconclusive, both with d_w and $d_{w,\mathrm{T}_{pe}}$ as well as QT interval suggesting further work.**

***Index Terms*—time-warping, repolarization, long QT syndrome, T-wave morphology**

I. Introduction

Long QT syndrome (LQTS) is one of the most common inherited syndromes associated with sudden death. The characteristic manifestations are prolongation of the QT interval and T-wave abnormalities on the ECG associated with syncope and sudden death, resulting from the ventricular tachyarrhythmia torsade de pointes (TDP) [1]. Studies have analyzed the QT-RR coupling [2], genotype-phenotype correlation as a trigger for life-threatening arrhythmias [3], QT-interval duration, T-wave parameters, and their relation to heart rate (HR) changes [4]. However, there is a lack of undestanding on the the characterization of T-wave markers quantifing exclusively morphological variations within the T wave, and their behavior in symptomatic and asymptomatic patients with LQTS.

In this study we evaluate a novel time-warping-based marker, d_w, aiming to surrogately quantify ventricular repolarization dispersion (VRD) changes on the T wave. The aim of this work was to analyze d_w marker on LQTS patients and to test whether it could distinguish between control and LQTS patients and between LQTS patients who experienced syncope and those who did not.

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II. Materials and Methods

The study population included the following data cohorts. First, ECGs from a set of 142 patients (LQTS group – LQTS-G), of which 67 patients had syncope (Syncope group – LQTS-SG) and the remainder did not (Non-syncope group – LQTS-NSG), together with clinical information from a LQTS congenital study, available at the database (E-HOL-03–0480-013) from the Telemetric and Holter ECG Warehouse (THEW: www.thewproject.org) [5]. Second, 52 healthy controls from the PTB Diagnostic ECG Database [6] (Control group - CG) from the freely-available repository PhysioNet. Finally, a normal reference T-wave morphology cohort of middle-aged subjects without a history of cardiovascular events, matched for sex, heart rate and specific lead, from the UK Biobank. [7].

ECG epochs of 10 seconds were extracted from the diurnal part of each ECG recording from control and LQTS patients. Proper ECG signal quality were ensured by visual inspection. ECG pre-processing included a band-pass linear filtering with a sixth order Butterworth filter, 0.5 to 40-Hz bandwidth. ECG delineation was performed using a wavelet-transform-based single-lead method.

The T-wave morphology changes was quantified by the time-warping d_w index proposed by Ramírez in [8]. For each 10-seconds ECG recording and each available lead, T waves were extracted and a mean warped T-wave (MWTW) was computed $\boldsymbol{f}^s(\boldsymbol{t}^s) = [f^s(t^s(1)), ..., f^s(t^s(N_s))]^T$, where $\boldsymbol{t}^s = [t^s(1), ..., t^s(N_s)]^T$. Analogously, a reference MWTW was taken from the corresponding sex-, heart rate–, and specific-lead from the Biobank cohort [7], $\boldsymbol{f}^r(\boldsymbol{t}^r)$, so that d_w represents the T-wave morphological changes of a LQTS patient T wave $\boldsymbol{f}^s(\boldsymbol{t}^s)$ relative to the normal T-wave morphology $\boldsymbol{f}^r(\boldsymbol{t}^r)$ from Biobank taken as reference. The marker d_w is estimated as the temporal reparametrization between the previous two waves and represents the mean warping needed to minimise the time domain differences among the two different MWTW.

d_w **estimation:** Let $\gamma(\boldsymbol{t}^r)$ be the warping function that relates $\boldsymbol{t}^r$ and $\boldsymbol{t}^s$ such that the composition

$[\boldsymbol{f}^s \circ \gamma](\boldsymbol{t}^r) = \boldsymbol{f}^s(\gamma(\boldsymbol{t}^r))$ denotes the re-parameterization, or time-warping, of the $\boldsymbol{f}^s(\boldsymbol{t}^s)$ using $\gamma(\boldsymbol{t}^r)$. The optimal warping function, $\gamma^*(\boldsymbol{t}^r)$, is the one that minimizes the amplitude difference between the square-root slope functions of $\boldsymbol{f}^r(\boldsymbol{t}^r)$ and $\boldsymbol{f}^s(\gamma(\boldsymbol{t}^r))$.

The level of warping represents the amount of time stretching needed to optimally fit the wave under study relative to the reference one. The d_w biomarker quantifies this level of warping required as the average of the absolute difference value between $\gamma(\boldsymbol{t}^r)$ and $\boldsymbol{t}^r$:

$$d_w = \frac{1}{N_r} \sum_{n=1}^{N_r} |\gamma^*(\boldsymbol{t}^r(n)) - \boldsymbol{t}^r(n)|. \tag{1}$$

d_w was calculated in each lead both for control and the LQTS patients. The computation of d_w when restricting the analysis to the second half of the T wave, T-peak to T-end (T_{pe}) interval [9] and the QT interval were also estimated for comparative purposes. Results were compared between the control and LQTS-G and between LQTS-SG and LQTS-NSG using the Kruskal-Wallis test. Statistical significance was assumed when p-value ≤ 0.05.

III. Results and Discussion

No significantly different from cero d_w values were found in CG, [median: 9.32, IQR: 5.53], pointing to the fact that the small d_w values in control conditions just reflect natural ECG variability. On the contrary, larger changes measured by d_w are found for LQTS, resulted from T-wave width increaments in LQTS patients [median: 20.93, IQR: 12.67], Fig. 1(a).

The d_w and $d_{w,\mathrm{T}_{pe}}$ magnitudes measured in lead I and II, clustered for Syncope and Non-syncope group (b and c, respectively) are presented in Fig. 1(b-c). The median [IQR] values for each lead and and patient group with p-values isshown in Table I, together with the QT values.

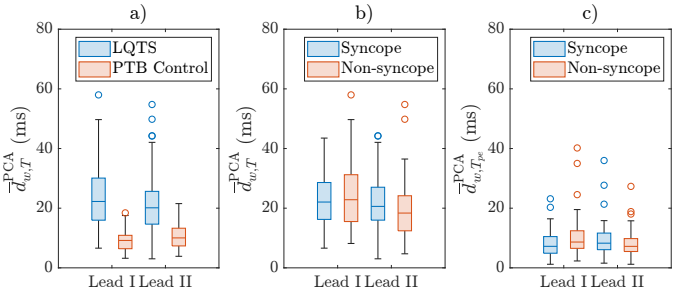

Fig. 1. Box plots distributions of d_w (a and b) and $d_{w,\mathrm{T}_{pe}}$ (c) for the LQTS (blue) and CG (red) in (a) and for LQTS-SG (blue) and LQTS-NSG (red) in (b and c), measured in leads I and II.

The d_w magnitude was significantly higher for LQTS-G than in the CG for both leads, having lower p-values than for the QT interval comparison. However, neither d_w nor QT interval presented significant differences when comparing LQTS-SG and LTS-NSG. The lowest value of p-value were found for d_w in lead II. The above suggest that d_w marker could capture some spatial heterogeneity and should be more deeply analyzed to see if it really can go beyond the temporal prolongation information provided by the QT interval. Furthermore, the $d_{w,\mathrm{T}_{pe}}$ marker was slightly significantly different when studing Lead I, pointing in the same direction.

TABLE I
Median [IQR] in ms and p-value for d_w, QT and $d_{w,\mathrm{T}_{pe}}$ indices segregated by comparison groups

Index	Group	Lead I	Lead II
d_w	CG	9.19 [4.48]	10.04 [5.94]
	LQTS-G	22.25 [14.11]	20.13 [10.99]
	p-value	$< 10^{-18}$	$< 10^{-11}$
	LQTS-SG	22.06[12.37]	20.06 [11.04]
	LQTS-NSG	22.84[15.7]	18.37[11.75]
	p-value	0.50	0.05
QT	CG	376 [36]	378 [41]
	LQTS-G	410 [68]	408 [60]
	p-value	$< 10^{-6}$	$< 10^{-5}$
	LQTS-SG	420[78]	417 [60]
	LQTS-NSG	405[58]	403 [51]
	p-value	0.15	0.06
$d_{w,\mathrm{T}_{pe}}$	LQTS-SG	7.21 [5.58]	8.27 [5.57]
	LQTS-NSG	8.65 [5.89]	7.02 [4.33]
	p-values	0.03	0.25

IV. Conclusions

The T-wave time-warping-based shape markers present large and significant differneces betwewen normals and LQTS subjects, as does QT interval, but with higher significance. When distinguishing patients prone to syncope from those non-prone no remarkable added value of the warping parameters with respect to QT is obtained. Differences in lead location from standard 12 lead in the reference ECG to Holter ECG recording in the LQTS database can also play a role which deserved further studies.

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