Characterization of impaired repolarization by quantification of the QT delay in response to heart rate changes from stress test recordings

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Abstract— **Increased spatio-temporal heterogeneity in the repolarization of the ventricles is related to cardiac instabilities. Slowed adaptation of the QT interval to sudden abrupt changes in heart rate (HR), measured with the time constant of a first-order-like response, has been identified as a biomarker for arrhythmic risk. Since abrupt HR changes are difficult to induce in patients, an exercise stress test, where ramp-like HR variations are observed, is considered. The time lag between the QT response and the expected HR-dependent QT time series is characterized by a time constant, hypothesized to have the same value as in the case of the step response. The delay is estimated by minimizing the Mean Square Error on the stress and recovery phases, in 14 high-risk patients of the FINCAVAS database, reaching average values of 26.3 and 40.6 seconds, respectively, comparable with the time lags measured in response to sudden step-like HR changes.**

I. INTRODUCTION

In recent years, different biomarkers for stratification of patients according to their risk of suffering from ventricular arrhythmias and Sudden Cardiac Death (SCD) have been proposed. A review of the most robust methods shows that the study of spatio-temporal repolarization dispersion is pivotal for SCD prediction [1]. Intrinsic electrophysiological heterogeneities in the ventricular myocardium lead to ventricular repolarization dispersion, which can be exacerbated in response to changes in heart rate (HR) due to the fact that different ventricular cells present distinct patterns of repolarization adaptation to the HR change. During these transient situations in which there is an increase in ventricular repolarization dispersion, the vulnerability to the appearance of ventricular arrhythmias is enhanced. The adaptation time of the QT interval to sudden changes in HR has been identified as a biomarker of arrhythmic risk [2], subsequently corroborated by electrophysiological experimental and simulated studies [3]. This phenomenon occurs on top of beat-to-beat variability, commonly quantified under stationary conditions, and can provide complementary information.

Previous studies have highlighted the importance of determining normal and abnormal ranges of QT adaptation dynamics in response to sudden changes in HR as a possible way to characterize the risk for cardiac arrhythmias and SCD [4]. Obtaining adaptation time lags in patients' daily life is difficult, since inducing an abrupt HR change implies a difficult maneuver, and therefore not easily observed in Holter recordings. Conversely, ramp-like HR changes are more feasible to be obtained from stress test recordings.

The ramp-response of a first-order system is theoretically characterized by the same time constant as the step response. Its characterization would provide the same clinical information. The advantage is ramp-like inputs are typically observed in the common exercise stress tests, where the cardiac system is subject to an approximately linear HR input both during the exercise and recovery phases of the test.

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II. MATERIALS AND METHODS

A. Database

This study evaluated stress test ECG recordings using a bicycle ergometer sampled at 500Hz from 14 patients from the high likelihood for Coronary Artery Disease (CAD) group of the FINCAVAS database recorded to characterize patients with high risk of cardiovascular morbidity and mortality [5].

B. Signal Preprocessing

Considering a transformed lead derived from applying spatially Principal Component Analysis (PCA) over the 8 independent standard leads, a wavelet-based algorithm [6] was used to delineate both QT(i) and RR(i) beat-to-beat intervals series. Outlier values of both series were defined as those deviating more than 0.5% from the median of each series computed in a running window of 50 beats, and these were replaced with the corresponding median value. Also, these series were interpolated to a sampling frequency of 4 Hz to have uniformly spaced RR(n) and QT(n) time series.

C. Expected HR-dependent QT series by hyperbolic fit

To estimate the expected stationary HR-dependent QT interval series, $\widehat{QT}(n)$, the values of the parameters α and β of a hyperbolic regression model were estimated by jointly fitting the $[QT(n), RR(n)]$ data pairs of all three different windows: at onset (40 seconds), at end (40 seconds) and at the peak (20 seconds) of the stress test, which are assumed to be stationary and representative of the subject QT-to-RR dependency. The first two windows were kept as they were, while the last one was replicated twice to have equal weight in each of the three areas marked inside the red rectangles in Fig. 1, used to fit the next model:

$$\widehat{QT}(n) = \beta + \frac{\alpha}{RR(n)}$$

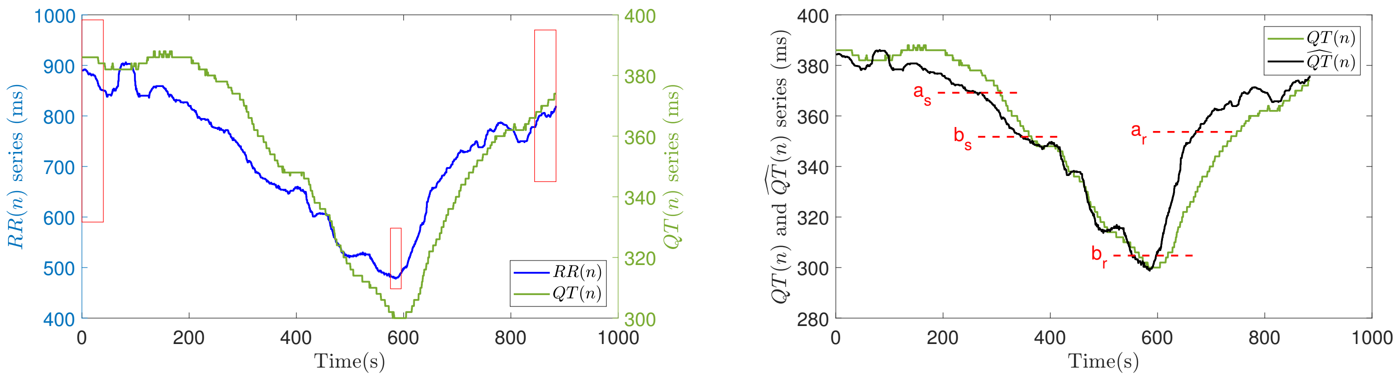

Fig. 1: **Left panel:** delimited regions in RR signal used to calculate expected heart rate HR-dependent QT time series by fitting a hyperbolic regression model. **Right panel:** HR-dependent QT time series is compared to real QT time series during exercise and recovery phases to determine delays. Stress ramp was delimited by (a_s,b_s) and the recovery one by (a_r,b_r).

The assumption of stationary at the stress peak is clearly questionable, but it is included to account for the whole excursion of the RR in evaluating the RR-to-QT dependency. Considering that the window is symmetric around the peak, including ascending and descending HR phases, a compensation for the dynamics is expected.

D. Time lag estimation

The time lag between $\widehat{QT}$ and real QT time series, illustrated in Fig. 1 for one of the analysed recordings, was estimated by a Mean Square Error (MSE) fit between the QT ramp and the $\widehat{QT}$ ramp, compensated for its delay until minimum MSE was reached. This was done separately in the exercise (stress delay, τ_s) and recovery phases (recovery delay, τ_r), using the marked intervals in Fig. 1.

III. RESULTS AND DISCUSSION

The average time lags across subjects (mean$\pm$standard deviation) at the stress phase and at the recovery with the $\alpha = -0.10 \pm 0.01$ and $\beta = 0.51 \pm 0.04$ values estimated to generate the expected $\widehat{QT}(n)$ series, and the root mean square error (ε_{RMS}), are shown in Table I. Values estimated from the here proposed ramp-like test were 26.3 s for stress and 40.6 s for recovery (p=0.09, Wilcoxon signed-rank test). These values are in order of magnitude comparable to those reported in [2], where the time constants estimated from a step-like response methodology reached values ranging from 35 to 57 seconds, depending on the patient subgroup studied. In previous studies the time constant for HR acceleration, $\tau_s = 34.8 \pm 13.6$ s, was lower than for HR deceleration, $\tau_r = 48.4 \pm 25.3$ s [3] [7]. The same behavior can be seen in this research using a hyperbolic fit. As a particular observation, $\widehat{QT}$ and QT became overlapped with no significant delay time when approaching the stress peak, and it may be explained by different autonomic modulation of ventricular electrical activity in stress tests. This is in agreement with recent findings showing the time for ventricular repolarization adaptation to sympathetic provocation becomes progressively reduced for increasingly higher levels of beta-adrenoceptors' estimulation [8], as occurs when approaching the stress peak. The dependence of time lag values as a function of the chosen QT/RR model should be explored. This study shows it is possible to measure QT hysteresis in response to gradual HR changes, as in stress test, advocating for further studies to explore its value as a sudden cardiac death predictor.

TABLE I: Mean and standard deviation for the time delay in exercise, τ_s, and recovery, τ_r, and for the error ε_{RMS}.

$\varepsilon_{RMS}(s)$	$\tau_s(s)$	$\tau_r(s)$
$3.4 \cdot 10^{-3} \pm 2.3 \cdot 10^{-3}$	26.3 ± 22.2	40.6 ± 15.2

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