

# Mechanisms Underlying QT Interval Adaptation Behind Heart Rate During Stress Test

Rubén Cebollada<sup>1</sup>, Cristina Pérez<sup>1</sup>, Konstantinos A Mountris<sup>1,2</sup>, Juan Pablo Martinez<sup>1,2</sup>, Pablo Laguna<sup>1,2</sup>, Esther Pueyo<sup>1,2</sup>

<sup>1</sup> BSICoS Group, I3A, University of Zaragoza, Spain, IIS Aragón, Zaragoza, Spain

<sup>2</sup> Centro de Investigación Biomédica en Red - Bioingeniería, Biomateriales, y Nanomedicina (CIBER-BBN), Zaragoza, Spain

## Abstract

*QT interval adaptation lag after heart rate (HR) has been proposed as an arrhythmic risk marker. The delay between QT and HR in a stress test has been shown to progressively reduce when approaching the stress peak, but the underlying mechanisms are yet unclear.*

*We used a cell model coupling an electrophysiological human ventricular cardiomyocyte model with a  $\beta$ -adrenergic signaling model to gain insight into these mechanisms. We paced the cell according to HR time series measured from patients' stress test recordings and we searched for the  $\beta$ -adrenergic stimulation pattern making the action potential duration (APD) response to HR changes best replicate the corresponding QT response.*

*After adjusting the  $\beta$ -adrenergic stimulation pattern, the simulated APD trends presented similar behavior to the measured QT trends for the same HR time series. The optimal pattern involved a sharp increase in  $\beta$ -adrenergic stimulation close to the stress test peak. During stress test recovery, the almost constant delay between QT and HR could be explained by a fast return from high  $\beta$ -adrenergic stimulation to baseline levels.*

*In conclusion, time-varying  $\beta$ -adrenergic stimulation patterns with high stimulation levels around the stress peak contribute to explain the characteristics of QT adaptation to HR during stress tests.*

## 1. Introduction

In the last decades, a myriad of markers derived from the electrocardiogram (ECG) have been proposed to stratify patients according to their risk of suffering from ventricular arrhythmias and sudden cardiac death. One of these markers measures the time for adaptation of the QT interval to changes in heart rate (HR) [1]. Its potential for arrhythmic risk stratification in post-myocardial infarction patients has been established [2]. On top of HR, there

are other factors that influence QT interval measurements [3, 4]. Among such factors, an important one is the autonomic nervous system (ANS), which innervates the ventricular myocardium. The ANS can play a role in the response of the QT interval to changes in HR, contributing to modulate the so-called QT/RR hysteresis.

While most previous studies have analyzed QT interval adaptation to a sudden step-like change in HR, recent investigations have proposed evaluation of the response to a more gradual, ramp-like increase in HR [5]. In first-order systems, the response to both inputs, i.e. step and ramp, is characterized by the same time constant. Measuring the adaptation to ramp-like changes is practically easier, as stress tests recordings could be used for that purpose.

By measuring the QT lag behind HR changes in stress test recordings from coronary artery disease (CAD) patients, a progressive lag reduction was observed when approaching the stress peak. This led to tiny delays around the stress peak. The mechanisms underlying such a reduction are unclear yet. Based on studies showing the adaptation time of ventricular repolarization to be progressively reduced in response to increasingly higher  $\beta$ -adrenergic stimulation levels [6], we hypothesized that  $\beta$ -adrenergic stimulation could be playing a role.

We investigated different patterns of  $\beta$ -adrenergic stimulation and we evaluated which of them led to better reproduction of the QT adaptation pattern to HR changes measured from CAD patients performing a stress test. To that aim, we simulated human ventricular cells subject to constant and to time-varying  $\beta$ -adrenergic stimulation. We evaluated the response of the action potential (AP) duration (APD) to HR time series obtained from stress test recordings. We calculated the APD adaptation lags and we compared them with those measured from the patients.

## 2. Methods

### 2.1. QT and RR intervals from patients

We analyzed ECG recordings acquired at Tampere University Hospital, Finland, from CAD patients performing a stress test in a bicycle ergometer [7]. A set of 9 patients were randomly selected, three from each of the groups classified according to Coronary Artery Disease (CAD) degree: low-, mild- and high-CAD.

ECG signals were filtered to remove baseline wander, high-frequency noise and artifacts. A spatially-transformed lead derived from Periodic Component Analysis ( $\pi$ CA) was calculated and a wavelet-based algorithm [8] was applied onto it to obtain the beat-to-beat series of RR and QT intervals. The values of those time series deviating by more than  $\pm 5\%$  from the running median computed over 80 beats were replaced with the median value [5]. Finally, the time series were interpolated at 4 Hz to obtain uniformly sampled  $RR(n)$  and  $QT(n)$  series.

### 2.2. In silico coupled electrophysiological and $\beta$ -adrenergic signaling model

The O'Hara et al. AP model [9] was used to represent the electrophysiology of a human ventricular cell by including descriptions of the main ionic current and fluxes:

$$C_m \frac{dV}{dt} + \sum_s g_s (V - E_s) + \sum_b I_b + \sum_i I_i + I_{stim} = 0 \quad (1)$$

where  $C_m$  is the membrane capacity,  $V$  is the transmembrane potential,  $g_s$  is the specific conductance of each of the channel families,  $E_s$  is the equilibrium potential of the ion  $s$ ,  $I_b$  is the current through pump  $b$ ,  $I_i$  is the current through exchanger  $i$  and  $I_{stim}$  is the stimulus current.

The electrophysiological model was coupled with the Gong et al. model of  $\beta$ -adrenergic receptor signaling [10]. The model describes the AP response to different doses of the  $\beta$ -adrenergic agonist isoproterenol by computing each ionic current or flux as a weighted average of the phosphorylated and nonphosphorylated fractions.

### 2.3. Repolarization adaption

To model the dependence of  $QT(n)$  ( $APD(n)$ , respectively) with HR, or equivalently  $RR(n)$ , linear and hyperbolic regression models were used:

$$\begin{aligned} \text{Linear (Lin)} \quad \widehat{QT}(n) &= \beta + \alpha RR(n) \\ \text{Hyperbolic (Hyp)} \quad \widehat{QT}(n) &= \beta + \frac{\alpha}{RR(n)} \end{aligned}$$

For each patient and each of the two regression models, the pairs of values  $[QT(n), RR(n)]$  ( $[APD(n), RR(n)]$ , respectively) were fitted and the values of the parameters

$\alpha$  and  $\beta$  were estimated. Specifically, we fitted the values in three windows considered as “stationary periods”: one at the beginning of the test (40 s), a duplicated one around the stress peak (20 s) and another one at the end of the test (40 s) [5]. The regression model leading to the lowest regression residuum was selected and the corresponding  $\widehat{QT}(n)$  time series was calculated.

To estimate the QT (APD, respectively) lag behind HR changes, a measure of the delay between  $\widehat{QT}(n)$  and  $QT(n)$  time series, in predefined intervals along the stress test (see [5]), was computed. For that purpose, the optimal delay value  $\tau^*$  was searched for by using a Mean Square Error (MSE) criterion to minimize the difference between  $QT(n)$  and  $\widehat{QT}(n - \tau^*)$  separately in the exercise and recovery phases of the stress test. These delays were denoted as  $\tau_e$  and  $\tau_r$ , respectively.

### 2.4. Simulated $\beta$ -adrenergic stimulation patterns

The APD response to HR changes was first analyzed for a constant level of  $\beta$ -adrenergic stimulation. This corresponded to an isoproterenol concentration of  $0.005 \mu\text{M}$ , considered as a basal level.

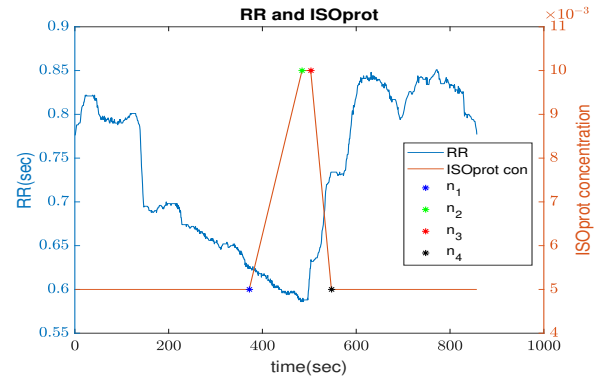


Figure 1: Time-varying isoproterenol concentration determined from  $\widehat{QT}(n)$  and  $QT(n)$  time series.

Subsequently, a time-varying pattern of  $\beta$ -adrenergic stimulation was proposed to simulate an increase in the stimulation as the stress peak was approached. This pattern started from the basal isoproterenol concentration of  $0.005 \mu\text{M}$ . At a time point  $n_1$  during exercise, isoproterenol concentration started to linearly increase until reaching a concentration of  $0.01 \mu\text{M}$  at the stress peak ( $n_2$ ). This concentration value was kept constant at the start of the recovery until time point  $n_3$ . From that point, isoproterenol started to linearly drop until time point  $n_4$ , where it returned to the basal concentration. This is illustrated in Figure 1.

To determine the four points defining the  $\beta$ -adrenergic stimulation pattern, we departed from the  $QT(n)$  and

$RR(n)$  time series of each patient and we computed the  $\widehat{QT}(n)$  time series. The four points were obtained as:

- $n_1$ : closest point to the stress peak, happening before it, where the slopes of  $QT(n)$  and  $\widehat{QT}(n)$  are equal.
- $n_2$ : point corresponding to the stress peak.
- $n_3$ : first point during recovery where the difference between  $QT(n)$  and  $\widehat{QT}(n)$  slopes presents a local maximum.
- $n_4$ : first point after  $n_3$  where  $QT(n)$  and  $\widehat{QT}(n)$  slopes are equal.

### 3. Results and Discussion

#### 3.1. QT and APD adaptation to HR

Figure 2 shows fitted regression models to the  $[QT(n), RR(n)]$  data from a patient of the study (2a) and to the  $[APD(n), RR(n)]$  data calculated for a constant level of  $\beta$ -adrenergic stimulation (2b) and for a time-varying pattern of  $\beta$ -adrenergic stimulation (2c) when the input is the  $RR(n)$  time series of the patient.

Figure 3 illustrates the repolarization adaptation to HR for the same patient shown in Figure 2. As can be observed from the left panel, the QT lag is remarkably larger during the exercise phase of the stress test ( $\tau_e$  around 97 s) as compared to the recovery ( $\tau_r$  around 32 s), which is associated with the larger area between the  $QT(n)$  and  $\widehat{QT}(n)$  time series. Of note, when approaching the stress peak, the QT lag behind HR became progressively reduced.

When APD was simulated in response to the same  $RR(n)$  time series while keeping  $\beta$ -adrenergic stimulation constant, the APD lag did not reproduce the corresponding QT lag but a much shorter delay in the repolarization response was found, particularly during exercise ( $\tau_e$  around 48 s). This is illustrated in Figure 3, middle panel.

Following application of the time-varying  $\beta$ -adrenergic stimulation pattern proposed here, we observed an increase in the APD lag behind HR, as shown in Figure 3, right panel. The delay  $\tau_e$  increased to nearly 90 s, which is close to the value measured for the QT interval. During the recovery phase, small differences in  $\tau_r$  were measured between the QT interval from the patient and the simulated APD for either constant or time-varying  $\beta$ -adrenergic stimulation.

Table 1 presents average values of  $\tau_e$  and  $\tau_r$  after pooling the data from the patients in each study subgroup. As can be observed from the table, application of the proposed time-varying  $\beta$ -adrenergic stimulation increased the mean value of the APD delays, making them closer to the delay measured for the QT interval as compared to the values obtained for constant  $\beta$ -adrenergic stimulation. This effect can be better appreciated in the delay during the exercise phase,  $\tau_e$ , than during the recovery phase,  $\tau_r$ .

These results points to a relevant role of  $\beta$ -adrenergic stimulation in contributing to repolarization adaptation, in agreement with previous studies in the literature [6]. Future studies on larger study populations and simulated data should be conducted to confirm the outcomes of this work. Simulations could extend the ones presented here to model electrical propagation in ventricular fibers and tissues so as to account for additional effects on repolarization.

### 4. Conclusion

$\beta$ -adrenergic stimulation modulates ventricular adaptation to HR in stress tests. A time-varying pattern of  $\beta$ -adrenergic stimulation explains the adaptation lag of repolarization duration after HR changes in exercise and recovery with higher accuracy than a constant stimulation level.

### Acknowledgments

This work was supported by projects ERC-StG 638284 (ERC), PID2019-105674RB-I00 and PID2019-104881RB-I00 (Ministerio de Ciencia e Innovación) and European Social Fund (EU) and Aragón Government through BSICoS group T39\_20R. Computations were performed by ICTS NANBIOSIS (HPC Unit, U. Zaragoza).

### References

- [1] Pueyo E, Malik M, Laguna P. A dynamic model to characterize beat-to-beat adaptation of repolarization to heart rate changes. *Biomedical Signal Processing and Control* 2008; 3(1):29–43.
- [2] Pueyo E, Smetana P, Caminal P, De Luna AB, Malik M, Laguna P. Characterization of QT interval adaptation to RR interval changes and its use as a risk-stratifier of arrhythmic mortality in amiodarone-treated survivors of acute myocardial infarction. *IEEE Transactions on Biomedical Engineering* 2004;51(9):1511–1520.
- [3] Ahnve S, Vallin H. Influence of heart rate and inhibition of autonomic tone on the QT interval. *Circulation* 1982; 65(3):435–439.
- [4] Bexton R, Vallin H, Camm A. Diurnal variation of the QT interval–influence of the autonomic nervous system. *Heart* 1986;55(3):253–258.
- [5] Pérez C, Pueyo E, Martínez JP, Viik J, Laguna P. Characterization of impaired ventricular repolarization by quantification of QT delayed response to heart rate changes in stress test. In *2020 Computing in Cardiology. IEEE*, 2020; 1–4.
- [6] Sampedro-Puente DA, Fernandez-Bes J, Szentandrassy N, Nánási P, Taggart P, Pueyo E. Time course of low-frequency oscillatory behavior in human ventricular repolarization following enhanced sympathetic activity and relation to arrhythmogenesis. *Frontiers in Physiology* 2020;10:1547.
- [7] Aiemenin T, Lehtinen R, Viik J, Lehtimäki T, et al. The Finnish Cardiovascular Study (FINCAVAS): characterising patients with high risk of cardiovascular morbidity and mortality. *BMC Cardiovascular Disorders* 2006;6(1).

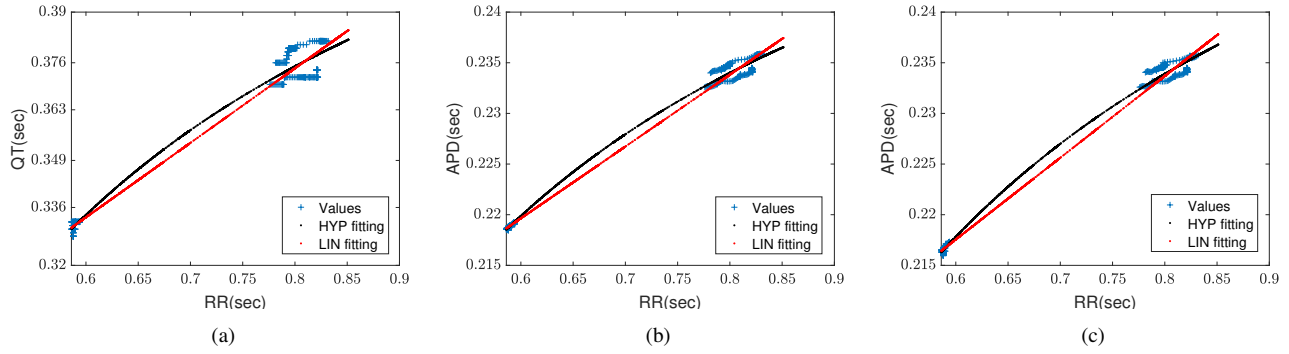


Figure 2: Linear and hyperbolic fitting obtained for QT and RR series of a patient (a) and for simulated APD with constant (b) and time-varying (c)  $\beta$ -adrenergic stimulation under the same RR series as in (a).

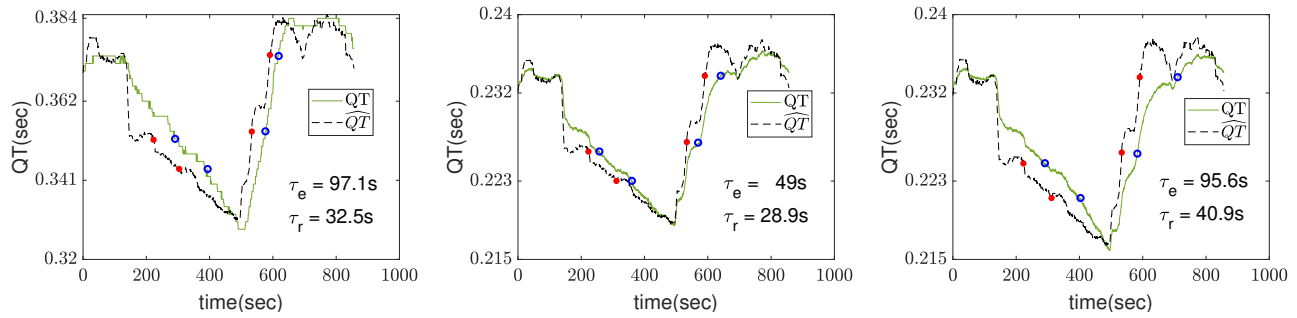


Figure 3: Left panel: Measured delay between  $QT(n)$  and  $\widehat{QT}(n)$  in exercise and recovery. Middle panel: Measured delay between  $APD(n)$  and  $\widehat{APD}(n)$  in simulated exercise and recovery for constant  $\beta$ -adrenergic stimulation. Right panel: Measured delay between  $APD(n)$  and  $\widehat{APD}(n)$  in simulated exercise and recovery for the proposed time varying  $\beta$ -adrenergic stimulation.

Table 1: Delay values  $\bar{\tau}_e$  and  $\bar{\tau}_r$  measured in patients (left columns), simulated with constant  $\beta$ -adrenergic stimulation (middle columns) and simulated with the proposed time-varying  $\beta$ -adrenergic stimulation curve (right columns).

	QT		APD with constant isoproterenol		APD with time-varying isoproterenol	
	$\bar{\tau}_e$	$\bar{\tau}_r$	$\bar{\tau}_e$	$\bar{\tau}_r$	$\bar{\tau}_e$	$\bar{\tau}_r$
<b>low-CAD</b>	$89.3 \pm 14.5$	$25.7 \pm 13.8$	$67.2 \pm 5.3$	$13 \pm 9.6$	$70.3 \pm 12.6$	$11.2 \pm 8.3$
<b>mild-CAD</b>	$65.7 \pm 17.6$	$34 \pm 3.1$	$36.7 \pm 9.2$	$26.2 \pm 13$	$62.5 \pm 27.5$	$33 \pm 21.3$
<b>high-CAD</b>	$71.2 \pm 17$	$51.8 \pm 42.5$	$39.8 \pm 11.7$	$29.4 \pm 8.3$	$49.8 \pm 2.9$	$41.4 \pm 3.2$

- [8] Martínez JP, Almeida R, Olmos S, Rocha AP, Laguna P. A wavelet-based ECG delineator: evaluation on standard databases. *IEEE Transactions on Biomedical Engineering* 2004;51(4):570–581.
- [9] O'Hara T, Virág L, Varró A, Rudy Y. Simulation of the undiseased human cardiac ventricular action potential: model formulation and experimental validation. *PLoS Computational Biology* 2011;7(5):e1002061.
- [10] Gong JQ, Susilo ME, Sher A, Musante CJ, Sobie EA. Quantitative analysis of variability in an integrated model of

human ventricular electrophysiology and  $\beta$ -adrenergic signaling. *Journal of Molecular and Cellular Cardiology* 2020; 143:96–106.

Address for correspondence:

Rubén Cebollada  
Univ. Zaragoza, Campus Río Ebro, 50018 Zaragoza, Spain  
rcebolladas97@gmail.com