

# Evaluation of Restitution Slopes Using a Quasi-stationary Exercise Protocol

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## Abstract

Cardiac electrical restitution is an important tool for evaluating risk of cardiac arrhythmias. Restitution slopes are used to quantify the rates of  $QT$  and  $DI$  (diastolic) interval adaptation in response to abrupt changes in cardiac cycle or  $RR$  intervals. These slopes can be either measured experimentally using invasive stepwise pacing procedures or assessed clinically from surface ECG. However, acquiring restitution slopes from surface ECG recordings may be complicated due to the presence of significant variations in  $QT$  and  $DI$  intervals. In this paper, we suggest a novel signal processing method, which overcomes these difficulties by implementing quasi-stationary exercise testing with modulated beat-to-beat  $QT/DI$  interval variations.

## 1. Introduction

As the load changes in the course of exercise protocol the amplitude of high frequency  $QT/DI$  interval fluctuations becomes smaller than corresponding changes in low-frequency  $QT/DI$  interval trend. Such modulation suggests that the magnitudes of  $QT/DI$  intervals are practically constant during each load step and resemble dynamics of  $QT/DI$  intervals in response to invasive step-wise pacing. A typical example of such behavior demonstrates that in the course of a quasi-stationary exercise protocol  $QT$  and  $DI$  interval variations gradually decrease during step-wise changes in exercise load [1].

This property can be used to simplify quantification of  $QT$  and  $DI$  interval adaptation. Although restitution slopes can be easily determined using controlled step-wise pacing protocol in invasive experiments, it is difficult to analyze similar large variations in  $QT/DI$  intervals non-invasively since under these conditions surface ECG measurements are associated with significant exercise related interval detection errors. In this paper we describe a novel algorithm of measuring the restitution slopes from modulated fluctuations and trends using  $RR$  and  $QT$  interval data sets acquired from surface ECG during quasi-stationary exercise testing.

Cardiac restitution properties are characterized by three different types of  $QT-DI$  restitution slopes which are determined by responses to specific step-wise changes in  $RR$  intervals [2]. The first type is S1-S2 restitution which characterizes fast  $QT$  interval changes in response to abrupt deviations of  $DI$  intervals from one given steady state to another. The second type is a basic cycle length (BCL) restitution which reflects long term  $QT$  interval adaptation to its steady state at a new fixed value of  $RR$  interval. The third one is a steady-state restitution which is a functional relation between steady-state values of  $QT$  and  $DI$  intervals.

Experimental findings have shown that slopes of different restitution curves are linked to cardiac instabilities [2]. It has been also demonstrated that fitting computer models of cardiac electrical activity to restitution slopes may be instrumental in making predictions for the onset of cardiac instabilities [3, 4]. However, a majority of existing electrophysiological methods to acquire restitution slopes is based on invasive pacing which presents significant difficulties for clinical implementation of restitution analysis in primary care offices. Our algorithm overcomes this limitation by implementing a quasi-stationary exercise protocol and relies only on surface ECG measurements.

## 2. Methods

We resampled original  $QT$  and  $RR$  interval data sets at a sufficiently high frequency  $F_s$  in order to obtain equidistant discrete  $QT_s(n)$  and  $RR_s(n)$  sequences. The discrete form of the diastolic interval  $DI_s(n)$  was computed as  $DI_s(n) = RR_s(n) - QT_s(n)$ . Fast fluctuations  $QT_f$  and  $DI_f$  were obtained by high pass filtering of  $QT_s$  and  $DI_s$  at a cut-off frequency  $f_h$ . Similarly, low frequency  $QT_l$  and  $DI_l$  ( $DI_l$ ) interval trends were separated by low pass filtering at a cut-off frequency  $f_l$  (Fig. 1).

We implemented an adaptive least-mean square (LMS) algorithm to estimate  $QT$  interval fluctuations ( $QT_{lms}$ ) that were physiologically related to  $DI_f$ . The input and output signals in the LMS algorithm were  $DI$  and  $QT$  fluctuations, respectively. By minimizing the mean square difference

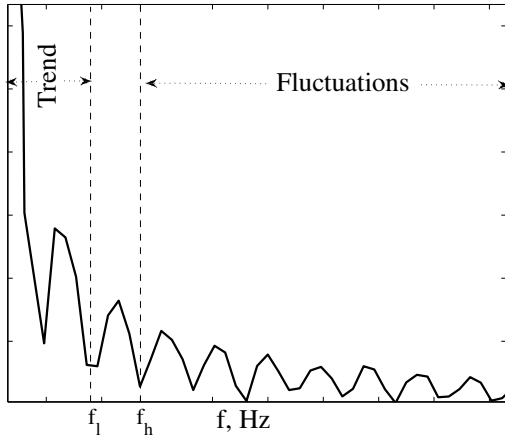


Figure 1. Frequency spectrum of an RR signal. Frequencies to the left of the first dashed line constitute the trend ( $f < f_l$ ). Frequencies to the right of the second dashed line constitute the fluctuations ( $f > f_h$ ).

between  $QT_f$  and  $QT_{lms}$  we determined the optimal parameters of the adaptive filter which allowed us to reduce uncorrelated  $QT_f$  noise. Other parameters of the algorithm were similar to those described in [5].

Using the output of the adaptive LMS algorithm we determined S1-S2 and BCL restitution dependencies. Firstly, we computed a moving average window cross correlation signal,  $CC(n)$ , between  $QT_{lms}$  and  $DI_f$  as

$$CC(n) = \frac{1}{\|QT_{lms}\| \|DI_f\|} \sum_{j=n-p}^{n+p} QT_{lms}(j) DI_f(j) \quad (1)$$

where  $p$  is the number of sample points in the moving window.

Secondly, using a threshold  $\eta$ , we determined periods of exercise during which  $QT_{lms}$  and  $DI_f$  were either correlated ( $CC > \eta$ ) or anti-correlated ( $CC < -\eta$ ) for at least five consecutive RR intervals. Each correlated and anti-correlated strip were considered as S1-S2 and BCL restitution dependencies, respectively. In order to approximate corresponding restitution slopes we performed linear regression between corresponding values of  $QT_s$  and  $DI_s$  intervals within each of these strips. Local steady state values of  $QT$  interval and  $DI$  intervals were determined at the intersections of BCL regression lines and  $QT_t-DI_t$  trend.

### 3. Results

The algorithm was applied to  $QT/RR$  data sets collected during physiological exercise from seventeen normal volunteers. Exercise testing was performed in our laboratory using GE Case 8000 treadmill system. Each subject

exercised on a treadmill with a pre-programmed quasi-stationary ramp-up/ramp-down exercise protocol. Speed and elevation were changed gradually in one-minute steps with 1 MET increments of exercise load. Using GE Workstation software (Version 1.8) we computed beat-to-beat 4-point median  $QT$  and  $RR$  intervals and exported them in ASCII format for post-processing. We evenly re-sampled these intervals at  $F_s = 7$  Hz using linear interpolation and computed  $DI_s$  as the difference between  $RR_s$  and  $QT_s$ .

An example of  $RR$  and  $QT$  interval profiles recorded for one subject is shown in Figures 2 and 3, respectively. Interval trends were computed by filtering corresponding signals using a low pass filter at  $f_l = 0.008$  Hz.  $DI$  and  $QT$  fluctuations were separated from discrete signals  $DI_s$  and  $QT_s$  at a cut-off frequency  $f_h = 0.03$  Hz. As explained above, the estimates of  $QT_{lms}$  were computed from  $DI_f$  using the adaptive LMS algorithm.

The upper panel in Fig. 4 shows  $DI_f$  and  $QT_{lms}$  signals determined within a five minute period of exercise from 750 to 1050 seconds as depicted in Fig. 2. Correlation signal between these portions is shown in the lower panel of the same figure. This signal was computed using a six second moving average window (Eq. 1,  $p = 21$ ). Strips of either correlated or anti-correlated fluctuations were determined using a threshold of  $\eta = 0.8$ .

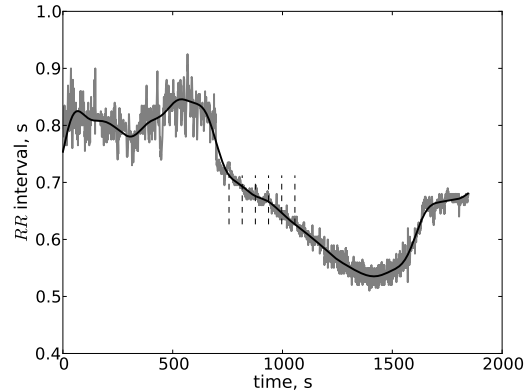


Figure 2. Evenly sampled  $RR_s$  signal (gray) and corresponding trend  $RR_t$  (black). Duration of the test for this example is 25 minutes including the pre-test resting period of 9 minutes. Dotted vertical lines delineate 5 one-minute stages of exercise used to compute restitution slopes.

Figure 5 shows a set of S1-S2 ( $S_{S1-S2}$ ) and BCL ( $S_{BCL}$ ) restitution slopes determined for the stages of exercise depicted in Fig. 2. The steady state restitution curve is traced by the  $QT_t-DI_t$  trend (dashed line) which connects steady state points (black diamonds) located at intersections with BCL regression lines shown in black. S1-S2 restitution slopes are depicted by gray regression lines.

Circular markers correspond to the actual values of  $QT$  and  $DI$  intervals.

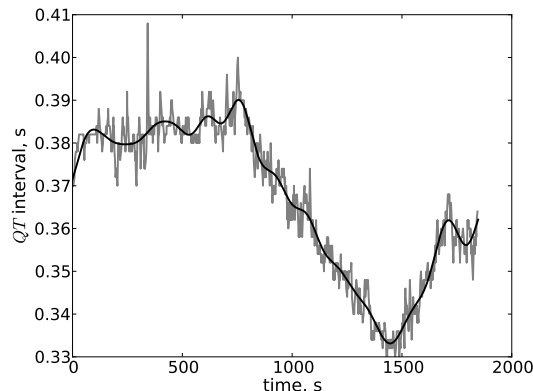


Figure 3. Evenly sampled  $QT_s$  signal (gray) and corresponding trend  $QT_t$  (black).

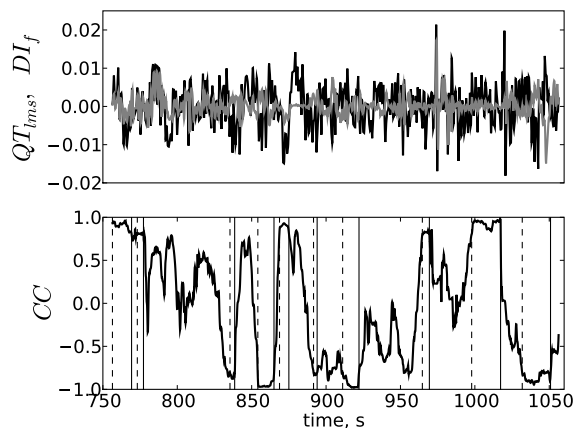


Figure 4. Portions of  $DI_f$  (black),  $QT_{lms}$  (gray) are shown in the upper panel. Correlation signal  $CC$  for the same portions is shown in lower panel. From left-to-right, dotted vertical lines mark beginnings of correlation strips and solid vertical lines denote the ends of the same strips.

Restitution slopes  $S_{S1-S2}$  and  $S_{BCL}$  were computed for all subjects at every stage of exercise protocol. A linear regression analysis demonstrated that higher heart rates ( $HR$ ) were associated with higher magnitudes of  $S_{S1-S2}$  and  $|S_{BCL}|$  slopes (Table 1). This observation was similar to that reported in [6]. We also found that there was a categorical separation of  $|S_{BCL}|$  based on a target heart rate of 100 BPM. Values of  $|S_{BCL}|$  were higher for heart rates exceeding this target (Table 2).

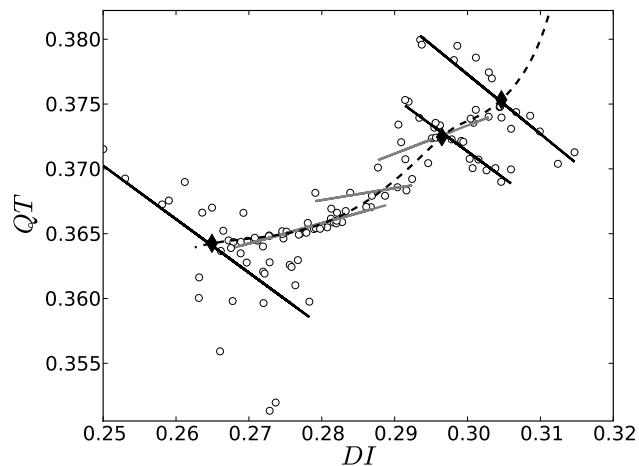


Figure 5. Restitution slopes determined for the five minute period of quasi-stationary exercise shown in Fig. 2.  $S1-S2$  regression lines are shown in gray.  $BCL$  regression lines are shown in black. The dashed line is the  $QT_t-DI_t$  trend curve. Points marked by diamonds denote steady state values of  $QT$  and  $DI$  intervals, respectively.

Table 1. Association between restitution slopes and  $HR$

Slope $Y$	$S_{S1-S2}$ and $ S_{BCL} $
Number of sample points in all subjects	184
Regression equation	$y = -0.08 + 0.0045 HR$
Significance level	$P = 0.016$

#### 4. Conclusions

In this paper, we introduced and implemented a novel non-invasive method for acquiring cardiac restitution slopes from surface ECG data recordings. We confirmed that slopes of different restitution components depend on heart rate and may be considered as an important modality in the evaluation of risk of arrhythmic events. Our algorithm can be easily integrated into existing exercise ECG devices to enhance methods of ambulatory monitoring of stability of cardiac rhythms.

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Table 2. Group-wise separation of  $|S_{BCL}|$  for target  $HR$  of 100 BPM

$S_{BCL}$	$HR < 100$ BPM	$HR > 100$ BPM
Number of sample points in all subjects	41	78
95% CI of mean	0.26 to 0.43	0.38 to 0.55
T-test	$P = 0.048$	

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