QT Interval Adaptation to Changes in Autonomic Balance

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Abstract

Variability in the RR interval has long been used to assess the state of the autonomic nervous system (ANS), with rapid changes being mediated by the action of the parasympathetic branch and slower variations through a combination of the sympathetic and parasympathetic branches. By contrast, the action of the ANS on QT variability may primarily be affected through the sympathetic branch. This motivates us here to assess QT interval variation during changes in autonomic balance.

To detect the QT interval, we implemented a pair of detection algorithms based on the curve-length transform. These were tested against cardiologists' annotations of 102 records in the PhysioNet QT database. Our QT interval measurements achieved a mean error ($\pm$ standard deviation) of -3.0 (± 39.8) ms, comparable with the variability between the annotations of two cardiologists, and better than the -16.1 (± 52.9) ms of the archived PhysioNet annotations associated with these records.

Our algorithms were applied to archived ECG records of nine subjects undergoing tilt-table experiments. The interventions included passive rapid tilt-up, passive slow tilt-up and active stand-ups. The RR intervals responded quickly to each change in posture, while the QT intervals showed a distinctly slower response, with characteristics of a first-order exponential, exhibiting time constants in the range of $40 - 140$ s across subjects.

1. Introduction

The brain controls heart function through neural feedback mechanisms. Higher order brain centers, such as the insular cortex, can also influence cardiac function. In humans, intraoperative stimulation of the insular cortex produces substantial changes in arterial pressure and heart rate. Stimulation of the right insular cortex results in sympathetically dominated cardiovascular responses (increased blood pressure and heart rate), whereas left insular cortex stimulation results in parasympathetically dominated effects (bradycardia) [1]. Regional brain injury can therefore lead to dysregulation of the brain-heart axis by affecting the connection between higher order brain centers and the autonomic nervous system. In patients with ischemic stroke involving the insular cortex, altered repolarization of the ventricular muscle (as shown by changes in the QT interval on the electrocardiogram), decreased heart rate variability, and decreased baroreceptor reflex sensitivity are observed [1]. In such patients, alterations in cardiac regulation might therefore be used as indicators of injury exacerbation and serve as a real-time monitoring modality in neurocritical care.

The QT interval is measured as the time interval between the onset of the QRS complex and the end of the T-wave. It represents the duration of ventricular depolarization and repolarization. The cardiac cycle length is customarily measured by the RR interval, which is the time difference between successive R-waves.

A lengthened QT interval has been associated with increased risk of ventricular tachyarrhythmias and sudden cardiac death [2]. However, variations in cardiac cycle length are a major determinant of QT interval duration, causing clinicians to correct the QT interval for the RR interval in deciding whether a QT interval is prolonged [2]. The dependence of the QT interval on RR interval is also not instantaneous. The QT adaptation dynamics to abrupt changes in heart period has been termed the QT-RR adaptation dynamics [3]. It has been shown that, for rapid transient increases in RR interval, the lengthening of the QT interval lags behind the fall in heart rate [4].

Studies have shown a difference in response between the QT interval and the RR interval under conditions that induce the stimulation of the sympathetic nervous system. For example, Yamada *et al.* [5] reported that the QT interval had a slower response to changes in posture when compared to the response of the RR intervals. Porta *et al.* [6] also reported a progressive increase in QT variability independently of heart period under postural changes.

Our paper is aimed at assessing QT interval variations with acute changes in autonomic balance in response to tilt table experiments. We use an algorithm based on the curve-length transform to determine the QT interval, and assess its performance against the PhysioNet QT database. This algorithm is then used to extract QT intervals during

tilt table transients, and to compare them with the associated RR intervals. Our immediate objective is to characterize the differences in the adaptation dynamics of QT versus RR intervals. Our longer-term objective is to determine the potential for QT variability to serve as a component modality in bedside monitoring.

2. Materials and Methods

2.1. QT detection algorithm

The QT detection algorithm implemented here in Matlab is based on work by Zong *et al.* [7], who used the forward curve-length transform (CLT) for the detection of the Q-onset, and the backward CLT for detecting the end of the T-wave. This approach was chosen because of the ease of implementation, the low computational cost and the possibility for real-time execution. Furthermore, it is insensitive to baseline wander, wave polarity, and high frequency noise.

2.2. PhysioNet QT database

The PhysioNet QT database serves as the reference for the validation of our algorithm [8],[9]. The database consists of a total of 105 records compiled from different PhysioNet databases, chosen so as to sample a wide variety of QRS and T-wave morphologies. Each record contains two ECG leads (projections), is sampled at 250 Hz, and is 15 minutes in length. Within each record, 30 to 70 representative beats were annotated by at least one cardiologist. Two cardiologists annotated eleven of the 105 records. In total, the cardiologists annotated 3,622 beats.

In addition to the manual annotations done by the cardiologists, each record has automated annotations detected using the `ecgpuwave` algorithm from PhysioNet.

2.3. Tilt-table dataset

To assess the dynamic variation in QT segment length, we applied the QT algorithm to archived recordings from subjects undergoing an orthostatic challenge test [10]. Briefly, ECGs were obtained from ten healthy subjects, who underwent changes in posture. Subjects were placed on a tilt table with foot support, and were secured to the table with straps. Each subject underwent a series of six postural changes: two active stand-ups, two rapid passive tilts and two slow passive tilts. The sequence of interventions was randomized for each subject.

2.4. Data analysis

In order to evaluate the accuracy of our QT algorithm, QT intervals were calculated from our algorithm's annotations, and cardiologist's annotations. The mean error and the standard deviation (SD) of the error between the cardiologists' measurements and our algorithm's measurements were calculated. To provide a basis for comparison, the mean error and SD of the cardiologists' and PhysioNet's measurements were also computed. To put our results into context, an inter-observer variability study was also carried out by computing the mean errors and SDs between the QT interval measurements of both cardiologists on the 11 records in which beat annotations were available from both experts.

For the dynamic QT adaptation study, we performed a least-squares fit of a single-exponential model to the QT responses for each transition in posture. The Bazett and Fridericia formulas were used to derive the corrected QT intervals (QT_c) during dynamic QT assessment. For Bazett, $QT_c[i] = QT[i]/\sqrt{RR[i]}$ and in the case of Fridericia, $QT_c[i] = QT[i]/\sqrt[3]{RR[i]}$ [11].

3. Results

3.1. Performance on PhysioNet database

On the PhysioNet QT database, our algorithm produced a mean error of -3.0 (± 39.8) ms, whereas PhysioNet's automated annotations had a mean error of -16.1 (± 52.9) ms. On average, the two expert annotations agreed to within 1.1 (± 38.9) ms for the QT interval measurements.

3.2. QT variation in tilt-table dataset

Figure 1 shows the RR interval (top) and the QT interval (bottom) tracings we obtained from a subject in the tilt database. The red lines mark the beginning or end of a transition in posture. Figure 2 shows the RR and QT interval responses from Subject 12734 before a slow tilt (before the first two red lines), during the upright position (between the second and third red lines), and in the supine position after the slow tilt (after the fourth red line). Rapid

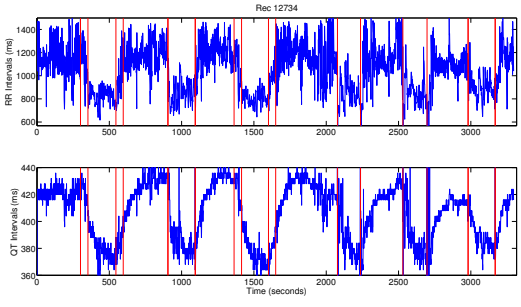

Figure 1. RR and QT interval time series for Subject 12734.

Table 1. Summary of average time constants τ obtained from interventions

	Rapid tilt (s)	Slow tilt (s)	Stand-ups (s)	Transitions to supine (s)
Mean	65.8	79.6	66.5	89.8
SD	12.4	21.7	17.0	35.2

tilt and active stand-up transitions result in faster RR interval adaptations, but similar QT interval adaptations to those shown in Fig. 2. Looking at individual transitions, it is evident that the QT intervals adapt quite slowly in comparison to the quick adaptation of the RR intervals.

The adaption of the QT interval of the subject during and after an intervention appears to exhibit mono-exponential responses. The average time constants obtained from fitting an exponential to the QT interval transients are summarized in Table 1. Figure 3 shows the fit of an exponential to a QT interval transient.

QT intervals are often normalized to remove the dependence of the QT intervals on cardiac cycle length. While such corrections make sense under steady-state conditions, during transients the correction will mask the dynamic changes in the QT interval, as illustrated in Fig. 4.

4. Discussion

We have presented a QT interval estimation algorithm using the curve-length transform, based on the work done by Zong *et al.* [7]. Our results performed better than the automated algorithm made available by PhysioNet, and comparably with results obtained in an inter-observer study.

In the second part of our study, we assessed the dynamics of QT variability using QT and RR intervals from subjects undergoing an orthostatic challenge test. Our results show a difference in response between the QT and RR intervals under the different interventions. Compared to the

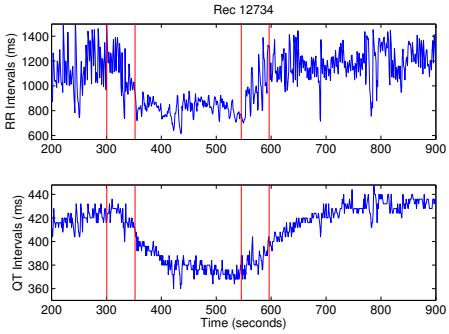

Figure 2. RR (top) and QT (bottom) interval time series for Subject 12734 during slow tilt.

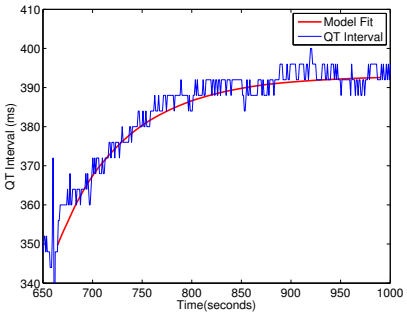

Figure 3. Exponential fit to QT response of Subject 12755, $\tau = 75.1$ s, NRMSE = 1.3%

RR intervals, the QT intervals have a slower response that is well characterized as a mono-exponential response. The time constants obtained from the fits are within the range of $40 - 141$ seconds, which is much slower than the time scale of the parasympathetic nervous system [12].

Yamada *et al.* [5] reported similar results for QT adaptation during postural changes. They suggested that in accordance with what was reported by Seed *et al.* [13] and Brownstein *et al.* [14], the response of the QT interval reflect mainly slow responses of the ventricular action potential (AP) to rapid changes in heart period. Pueyo *et al.* found similar results: the action potential duration (APD) adaptation dynamics to abrupt changes in heart period occurs in two stages, the first stage being the initial exponential rise or drop, and the second stage being the gradual settling to the asymptotic value [15] [16]. Pueyo *et al.* concluded that cellular mechanisms controlling the AP are responsible for the adaptation dynamics.

Other studies have associated QT variability with the effects of the modulation of the sympathetic nervous system (SNS) [6], [17]. It is suggested that the portion of QT variability independent of heart period is an indirect indication of SNS activity. Porta *et al.* showed that QT variabil-

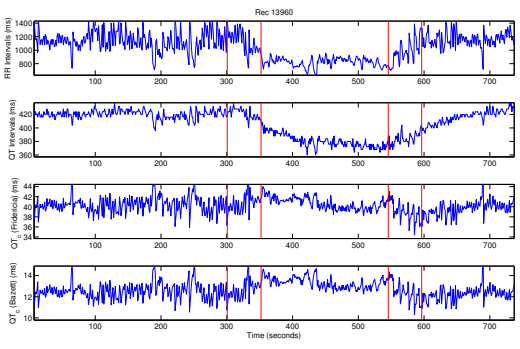

Figure 4. Unnormalized and normalized QT from Subject 13960.

ity unrelated to heart period progressively increased under the graded head-up tilt [6]. Magnano *et al.* also showed that the SNS directly affects the ventricular myocardium of healthy subjects, causing variations in QT interval that are independent of heart rate [17].

The QT interval is often associated with ventricular APD at the cellular level [4],[18]. Some of these ionic currents responsible for APD are modulated by the SNS. SNS control of cardiac electrical activity is mediated by the activation of β-adrenergic receptors that regulate the activity of select ion channels. More generally, channel conductances can be modulated by the SNS [18] and can be heart rate dependent [19]. Further work is required to understand what part of the QT adaptation is attributable to direct action of the sympathetic nervous system as opposed to dynamics associated with intracellular adaptation to RR variations.

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