

CONTINUOUS ANALYSIS OF REPOLARIZATION CHARACTERISTICS DURING INSULIN INDUCED HYPOGLYCEMIA

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Abstract: Hypoglycemia has been shown to affect ECG. Reported changes are prolongation of QT-interval and increased R/T amplitude ratio. These ECG changes are suggested to be connected to so-called dead in bed syndrome. Continuous analysis of ECG changes and blood glucose values, during insulin induced hypoglycemia is presented. Altogether 22 subjects were analyzed in three different groups; 1) healthy group 2) diabetic patients diagnosed less 5 years ago and 3) chronic diabetics diagnosed over than 5 years ago. The results showed that 20 of 22 subjects' QT-time was prolonged during hypoglycemia. In addition, in group 3 changes were smaller than in groups 1 and 2.

1 INTRODUCTION

The dead in bed syndrome which refers sudden death in type 1 diabetic patients have been widely studied in past decades. Earlier studies have shown that hypoglycemia affects somehow on the autonomic nervous system and cardiac repolarization. It have been hypothesized that these hypoglycemia related changes could be connected to dead in bed syndrome. Thus cardiac repolarization characteristics have been studied and QT time prolongation and T-wave flattening during hypoglycemia have been reported (Laitinen et al., 2008). In addition a connection between hypoglycemia and vector electrocardiogram parameters such as QRS-T-angle has been found (Koivikko et al., 2008).

Repolarization characteristic have been estimated by averaging T-waves during few minutes period (Murphy et al., 2004) and then averaged T-wave sections are annotated by hand. Because normal variation of ECG parameters is very large, averaging can remove some information and thus disturb results.

We used an advanced principal component regression (PCR) based method (Lipponen et al., 2010) to analyze repolarization characteristics. By using the PCR method we can analyze ECG parameters beat-by-beat, and this enables the comparison of repolarization characteristic parameters such as QT-times and blood glucose values in given time instant.

Hypoglycemia may result in seizure or unawareness, and can thus be fatal e.g. in driving conditions (Cox et al., 1993). Since hypoglycemia seems to affect ECG, were there have been some studies which tries to predict hypoglycemic events using these ECG changes (Nguyen et al., 2008). However, in almost all studies euglycemic and hypoglycemic clamps are analyzed separately, and thus, the key information; how long hypoglycemic event should last before remarkable ECG changes occur have not yet been reported. We used continuous measurements and beat-by-beat analysis, which gives us the opportunity to compare estimated repolarisation parameters with blood glucose values continuously, and thus, hopefully answer the question is it possible to predict hypoglycemic

events using ECG changes.

Many of the earlier studies have used diabetic or/and healthy test subjects (Laitinen et al., 2008; Koivikko et al., 2008). However, it is known chronic diabetics who have suffered from diabetes for a long time have lower autonomic response to hypoglycemia than subjects with shorter history of diabetes. In this reason our dataset contains three different groups of subjects: 1). healthy normal subjects, 2). diabetics who have suffered diabetes less than 5 years and 3). chronic diabetics who have suffered from diabetes over 5 years.

2 METHODS

Advanced PCR based method was used for analyzing repolarization characteristics beat-by-beat (Lipponen et al., 2010). In the PCR method each T-wave was modeled using three optimal orthogonal basis vectors. These basis vectors were obtained as the most significant eigenvectors of correlation matrix computed from 1000 previous T-wave segments. Use of such a large number of T-wave segments was possible because no remarkable heart rate or morphology changes were present in used measurements, and on the other hand such a large amount of prior information maximizes the denoising effect of the model. Similar PCR approach was applied to model the QRS complexes.

From each estimated waveform, Q-wave onset, R-wave peak, T-wave peak and T-wave offset were then extracted. From these extracted time points QT interval, RR interval and R/T-wave amplitude ratio time series were then formed. In addition, heart rate corrected QTc time series was formed by using Friedricia's method.

For time series trend estimation, smoothness priors method was used (Tarvainen et al., 2002). Before the trend estimation each time series was transformed evenly sampled time series by using 4Hz cubic spline interpolation. Used trend estimation method reflects time-varying lowpass filter with adjustable cutoff frequency which can be changed by using a smoothing parameter α . Because in these time series the effects due to off the glucose concentration changes are shown in very low frequency range, relatively low cutoff frequency was used.

Glucose values were measured at 5 minute intervals, but values were then interpolated such that sample rate was 4 Hz, same as for all time series. Although second order and seven point Savitzky-Golay smoothing was done beforehand to reduce measurement errors, because it is highly presumable that

blood glucose value doesn't change rapidly during 5 minutes such a smoothing is recommended.

3 MATERIALS

ECG measurements were recorded in Turku University Hospital and altogether 27 subjects participated test sessions. Continuous measurements of biosignals such as ECG and EEG were acquired during the test, along with the blood glucose measurements at 5 minute intervals. In this paper, we concentrate only on analysis of ECG signal. ECG was recorded using a modified chest lead V5 with sample rate 128 Hz.

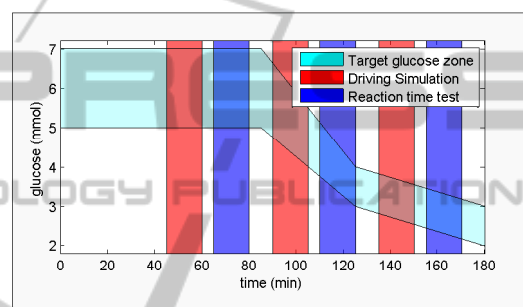


Figure 1: Measurement protocol. Target glucose zone is presented by light blue, driving simulation by red and reaction time tests by dark blue.

Table 1: Ages, sexes and mean duration of diabetes (years) of test subjects in different groups.

	Healthy	T1DM	T1DMc
number	9	6	7
age	43.0 ± 8.9	40.5 ± 9.8	49.4 ± 11.1
sex f/m	2/7	0/6	0/7
diagnosis	-	3.2 ± 2.3	22.7 ± 12.7

Subjects were divided into three groups: 1) 9 nondiabetic healthy subjects (Healthy), 2) 6 diabetics whose diabetes were diagnosed less than 5 years ago (T1DM), 3) 7 chronic diabetics, diagnosed over 5 years ago and who have suffered hypoglycemic events repeatedly (T1DMc). Characteristics of different groups are presented in table 1. Unfortunately T-wave was almost invisible in five subjects ECG and results of repolarization characteristics were not reliable so those measurements were removed from final analysis.

Protocol of the measurement is presented in Figure 1. Firstly, blood glucose value was adjusted range of 5-7 mmol to normoglycemic section. Normoglycemic section lasted approximately 85 minutes and during this period first driving and reaction time

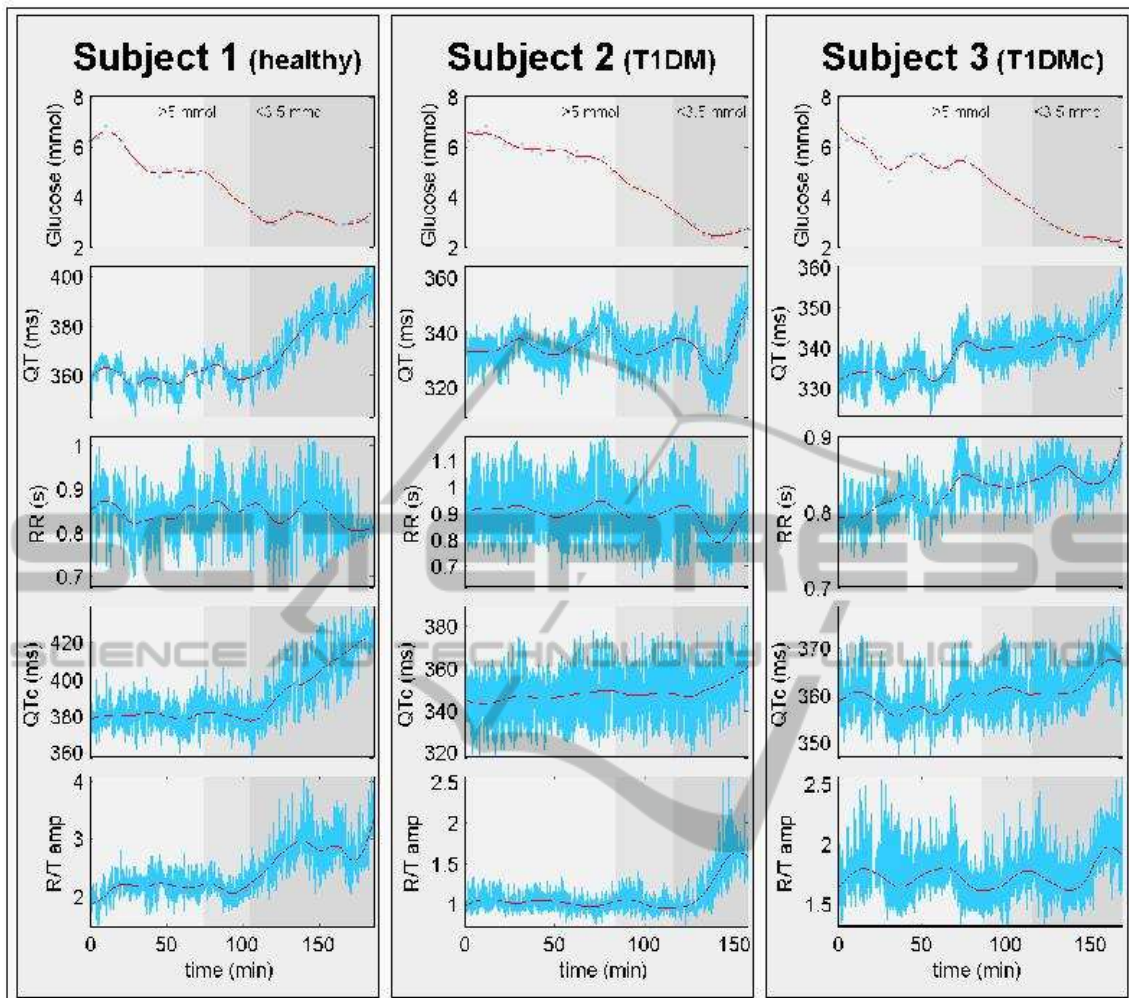


Figure 2: Representative time series of three different subjects. Subject 1 is from healthy group, subject 2 is from T1DM group and subject 3 is from T1DMc group. In uppermost axes there are glucose values and timeseries are presented in four lower axes. Original timeseries are presented by blue line and trend is as red line. Time series from top to bottom are QT-interval, RR-interval, heart rate corrected QT-time (QTc) and R/T amplitude ratio (R/T amp).

tests were done. Secondly insulin infusion was increased and blood glucose concentration started to decrease (decreasing state), are the period second driving and reaction time tests were made. During the decreasing state blood glucose value was 5 - 3.5 mmol and it lasted approximately 40 minutes. However, reactions to insulin infusion differ between individuals, and thus, this section time differs between individuals. After the decreasing state blood glucose was in hypoglycemic state and third driving and reaction time tests were made. Third stage lasted approximately 55 minutes and target blood glucose concentration was below 3.0 mmol.

4 RESULTS

In Figure 2, representative time series from each group are shown. First subject is from healthy group, second subject is from T1DM group and third subject is from T1DMc group. In uppermost axes there are subject's glucose values and different time series are presented in lower axes. Time series are QT-interval, RR-interval, heart rate corrected QT-interval and R/T amplitude ratio. In addition also the trends of each timeseries are presented by red solid line. Trend was calculated by using a smoothing parameter $\alpha = 10^6$ which means a cutoff frequency 0.001 Hz.

In Figure 3 mean glucose values and mean QTc-

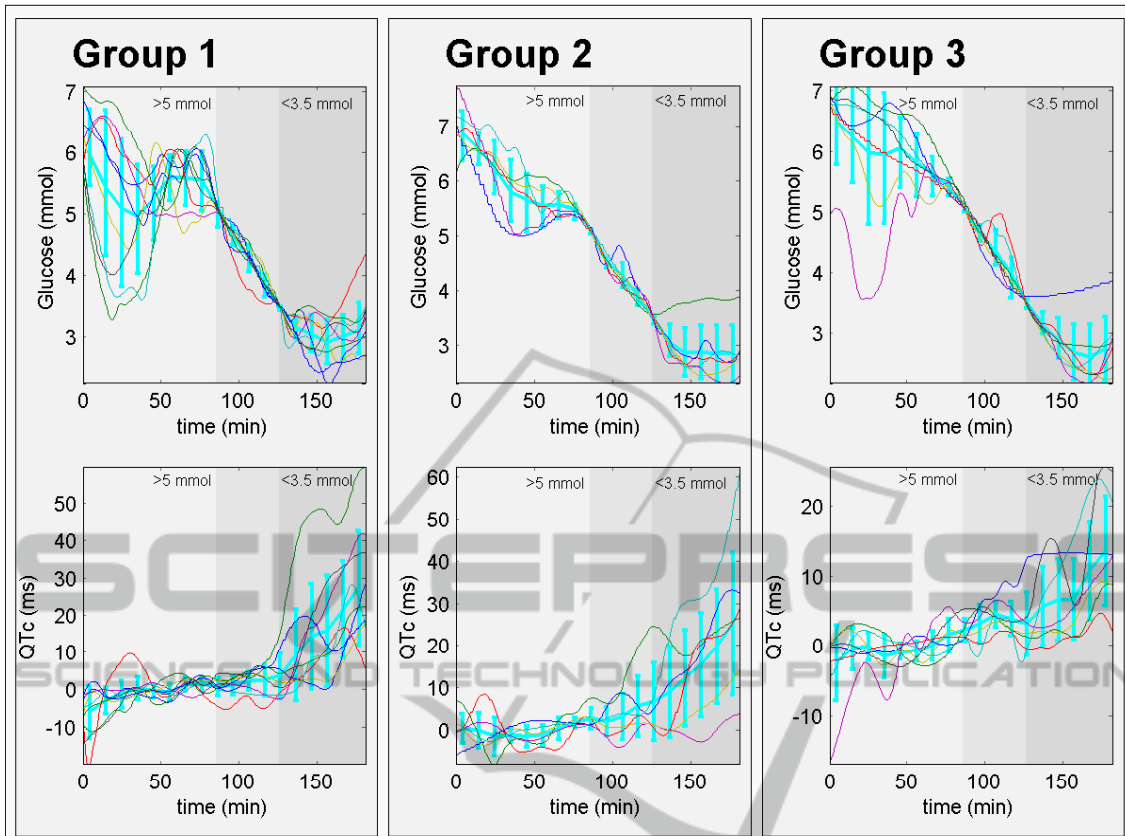


Figure 3: Glucose values and change of QTc-times during the measurement, for the three groups. Upper axes there are each individual subjects glucose values by thin line and group mean and standard deviations of thick blue line. Lower axes there are trends of QTc-times from each subjects by thin line and group mean values and standard deviations by thick blue line.

times for each group are presented as thick blue line. Each subject's glucose values and trend of the QTc-times are presented as thin lines. QTc times are presented as changes from baseline, where the mean of the normoglycemic section was taken as the baseline value. Reaction to insulin infusion is highly variable between individuals and thus QTc time series are timescaled using measured glucose values and mean section lengths. That is, time when blood glucose was last time more than 5 mmol was set to end of the section 1 (i.e. 85 minutes), time when blood glucose was first time lower than 3.5 mmol was set to end of the second section (i.e. 125 minutes) and rest of the data is scaled to section 3 which lasts 55 minutes.

5 DISCUSSION

Time series analysis of repolarization characteristics have been presented. As can be seen in Figure 2 normal variation of QTc and R/T amplitude ratio time series is quite large and thus changes affected by glu-

ucose concentration might be hard to find without beat-to-beat analysis. Especially diabetic groups changes are only visible in low frequency trend component and normal variation is much bigger than changes affected by hypoglycemia. In Figure 3 group analyses of QTc time series are shown. Although measurements were made by using scripted protocol, glucose variation between individuals, is so large, that in group analysis we have to scale time series using glucose values. Time scaling was done so that the end of the section one glucose was 5 mmol and end of the section 2 glucose value was 3.5 mmol in all subjects. Without the time scaling time series between the subjects cannot be compared in time domain.

In healthy normal group QTc time increased over 10 ms during hypoglycemia when comparing to normoglycemic section. In diabetic groups (T1DM, T1DMc) QTc time was not increasing by one subject/group. However, in both groups mean value was clearly higher than baseline value which can be clearly seen in Figure 3. When comparing differences between the three groups it can be seen that largest re-

sponses were in healthy group and lowest in T1DMc group. Subjects in T1DMc group have suffered from diabetes for a long time and they might be habituated to hypoglycemic events and thus autonomic response are lower than other in groups.

Prediction of hypoglycemic events by using ECG parameters seem to be quite challenging, because changes originating from glucose are delayed so that they occur normally more than 10 minutes after the glucose value has decreased below 3.5 mmol, which can be seen in Figure 3. Furthermore, changes are most intensive in healthy group and lower in diabetic groups were glucose prediction is needed. However changes are visible and thus some intelligent algorithms might recognize hypoglycemic events early enough to prevent some dangerous situations.

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