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Hypoglycemia detection based on cardiac repolarization features.

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Abstract— **Hypoglycemia is known to affect repolarization characteristics of the heart. These changes are shown from ECG by prolonged QT-time and T-wave flattening. In this study we constructed a classifier based on these ECG parameters. By using the classifier we tried to detect hypoglycemic events from measurements of 22 test subjects. Hypoglycemic state was achieved using glucose clamp technique. Used test protocol consisted of three stages: normoglycemic period, transition period (blood glucose concentration decreasing) and hypoglycemic period. Subjects were divided into three groups: 9 healthy controls (Healthy), 6 otherwise healthy type 1 diabetics (T1DM) and 7 type 1 diabetics with disease complications (T1DMc). Detection of hypoglycemic event could be made passably from 15/22 measurements. In addition, we found that detection process is easier for healthy and T1DM groups than T1DMc group diabetics because in T1DMc group subjects' have lower autonomic response to hypoglycemic events. Also we noticed that changes in ECG occurs few minutes after blood glucose is decreased below 3.5mmol/l.**

I. INTRODUCTION

Earlier studies have shown that hypoglycemia affects somehow on the autonomic nervous system and cardiac repolarization. Thus cardiac repolarization characteristics have been studied and QT time prolongation and T-wave flattening during hypoglycemia have been reported [1], [2]. In addition a connection between hypoglycemia and vector electrocardiogram parameters such as QRS-T-angle has been found [3].

In a short term, hypoglycemia may result in seizure or unawareness, and can thus be fatal e.g. in driving conditions [4]. In the long term, hypoglycemic events can cause complications such as neuropathy and cardiovascular disease. Thus, good blood glucose control is crucial for diabetics. Since hypoglycemia seems to affect ECG, there have been some studies which try to predict hypoglycemic events using these ECG changes [5], [6]. However, in almost all studies normoglycemic and hypoglycemic clamps are analyzed separately, and thus, temporal information on correlation between hypoglycemia and ECG changes has not been assessed. Earlier studies have also analyzed only healthy and/or diabetic subjects. However it is known that diabetics who have suffered from chronic diabetes for a long time have lower autonomic response than subjects with shorter history of diabetes. For this reason our dataset contains three groups: 1) healthy subjects, 2) otherwise healthy type 1 diabetic patients diagnosed less than five years ago 3) type 1 diabetic patients diagnosed over five years ago who had history of reduced hypoglycemia awareness.

The aim of this study was to develop a classifier using principal component analysis (PCA) for a detection of hypoglycemic events. As an input of classifier, ECG parameters which have been found to change during hypoglycemia were used. These parameters were estimated using principal component regression based method [7]. By using this method we can analyze ECG parameters beat-by-beat which enables the compararison of repolarization characteristics parameters and blood glucose values in any given time instants. After parameters were extracted PCA classification was used for detection of hypoglycemic time points from each measurement. We wanted to test how fast hypoglycemic events could be detected and how duration of diabetes and hence lower response for hypoglycemic events affects detection of these events.

II. MATERIALS

ECG measurements were recorded in Turku University Hospital and 27 subjects participated the test sessions. The study protocol was approved by the Ethics Committee of the Hospital District of Southwest Finland, and each patient gave written informed consent. 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 which was recorded using a modified chest lead V5 with a sample rate of 128 Hz.

Subjects participating the study were divided into three groups: 9 healthy control subjects (Healthy group), 6 diabetics diagnosed less than 5 years ago (T1DM group), and 7 diabetics diagnosed over 5 years ago and who have suffered from hypoglycemic events repeatedly (T1DMc group). Characteristics of different groups are presented in Table I. None of the participants had a previous history of heart or cardiovascula diseases. Five subjects were excluded from analyses because extremely low amplitude T-waves or anomalies in ECG such as inverted T-waves, and thus, reliable T-wave detection would have been impossible.

During the measurement blood glucose concentration was changed using glucose clamp technique [8]. Steady rate of insulin infusion (1.5 mU/kg/min) was given to subjects

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and desired blood glucose level was adjusted by changing the glucose infusion rate. Firstly, blood glucose value was adjusted into a range of 5-7 mmol/l for normoglycemic period. After the normoglycemic period, glucose infusion rate was decreased and blood glucose concentration started to decrease. During this transition period, blood glucose value was 5 - 3.5 mmol/l. After the transition period, blood glucose values were kept in hypoglycemic range (the target blood glucose concentration was below 3.0 mmol/l) approximately 55 minutes, after which glucose infusion rate was increased and blood glucose was restored to normoglycemic range.

TABLE I

THE NUMBER OF SUBJECTS (N), AGE (YEARS, MEAN±SD), GENDER (FEMALE/MALE), BODY MASS INDEX (BMI, MEAN±SD) AND DURATION OF DIABETES (YEARS, MEAN±SD) OF TEST SUBJECTS IN THE THREE GROUPS.

	Healthy	T1DM	T1DMc
N	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
BMI	26.2 ± 2.8	26.7 ± 5.6	24.3 ± 3.0
Duration of diabetes	-	3.2 ± 2.3	22.7 ± 12.7

III. METHODS

For a classification of hypoglycemic and normoglycemic states ECG parameters such as QTc and RT-amplitude ratio were used and estimation of these ECG parameters was done by using advanced principal component regression method. Detailed description of the method is presented in [7] and only short description is shown here. First of all QRS-detection algorithm was used to detect R-waves and using R-wave time-points QRS-complexes and T-wave segments were extracted from ECG. In the method signal to noise ratio of T-wave and QRS-complexes is improved by modeling them using two optimal basis vectors which are calculated using principal component regression from large dataset (1000 waves) of previously detected T-wave and QRS-complex segments. After modeling T-waves and QRS-complexes individually, Q-wave onset and T-wave onset, apex and end points are detected using traditionally used methods, similar as [7]. Heart rate corrected QTc was calculated by using Friedricia's method

After the parameters were calculated, PCA classification algorithm was used for hypoglycemic event detection. Firstly, mean values of 5 minutes section of each parameter was calculated corresponding to each glucose measurement and secondly five dimensional feature vector was constructed. Feature vectors z constructed for PCA classification were

$$z = (\mathrm{QTc}, \mathrm{RT}_{\mathrm{amp}}, \mathrm{T}_{\mathrm{slope}}, \mathrm{T}_{\mathrm{d}}, \mathrm{RR})\,. \qquad (1)$$

definitions of these parameters are presented in figure 1. Baseline value of each parameter were excluded by either dividing with (RT-amp and $\mathrm{T}_{\mathrm{slope}}$) or substracting (QTc, T_{d} and RR) the mean value from the normoglycemic period. Dimensionality of these feature vectors was then reduced using principal component approach and then classification into normoglycemic/hypoglycemic states were made based on the first and second principal component (PC). The classification result were computed by using the leave one out method.

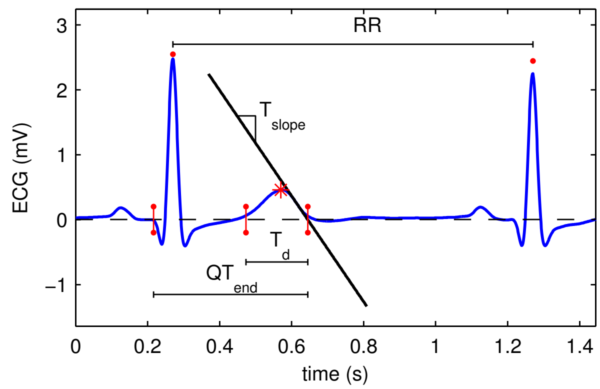

Fig. 1. Parameters used for classification. QTc-time is calculated from Q-wave onset to T-wave end and corrected with the heart rate duration, T-duration (T_{d}) is time between T-wave onset to T-wave end, $\mathrm{T}_{\mathrm{slope}}$ is minimum slope of T-wave end, $\mathrm{RT}_{\mathrm{amp}}$ is defined as a ratio of R-wave and T-wave amplitudes and RR is time between successive R-waves.

IV. RESULTS

In figure 2 parameter changes from the baseline are presented. Each group is presented by different colors (Healty by red, T1DM by green and T1DMc by blue). For every group, group mean value ± standard deviation is presented in normoglycemic (glucose >3.5 mmol/l) and hypoglycemic (glucose <3.5 mmol/l) sections. As can be seen changes between hypoglycemic state and normoglycemic state are not large but some changes are visible at least in parameters QTc and $\mathrm{T}_{\mathrm{slope}}$.

In figure 3, there is presented two most significant PCs θ_1 and θ_2. Color of each point correspond measured glucose value. Area were points are classified to hypoglycemic is visualized as light gray and area were points are classified as normoglycemic is marked as dark gray.

In figure 4, result of classification for each subject are presented. Solid blue line represents measured glucose value and red stars are the time points were PCs shown in figure 3 are in hypoglycemic area i.e, measured parameters indicate that blood glucose is lower than normal value. In Healthy group, classification results are quite good, for 7/9 of test subjects hypoglycemic events are detected more or less correctly. In T1DM group 4/6 subjects' hypoglycemic sections are detected passably. However, as can be seen in figure 3 parameter changes in T1DMc group are much smaller than in the other two groups. Because of that, detection of hypoglycemic events is much harder in T1DMc group. Results in figure 4 show that hypoglycemia can be detected passably for three subjects and for one subject glucose values never go below 3.5 mmol/l so detection is basically successful. For one subject hypoglycemia was not detected and one subject had clear false positive detections.

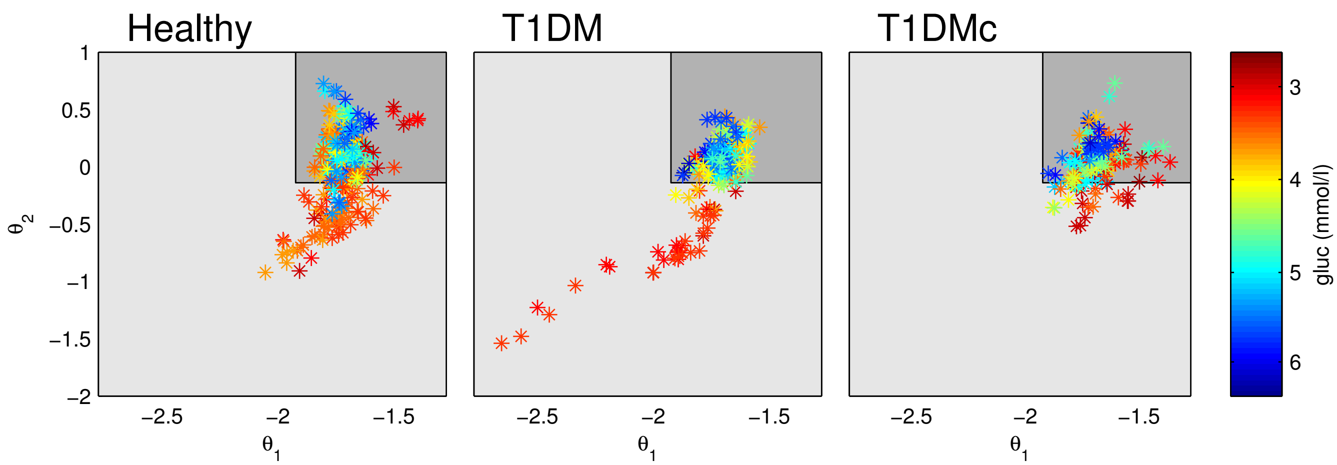

Fig. 3. Two most significant PCA components. Area where points are classified as hypoglycemic is marked light gray and normoglycemic area is marked as dark gray.

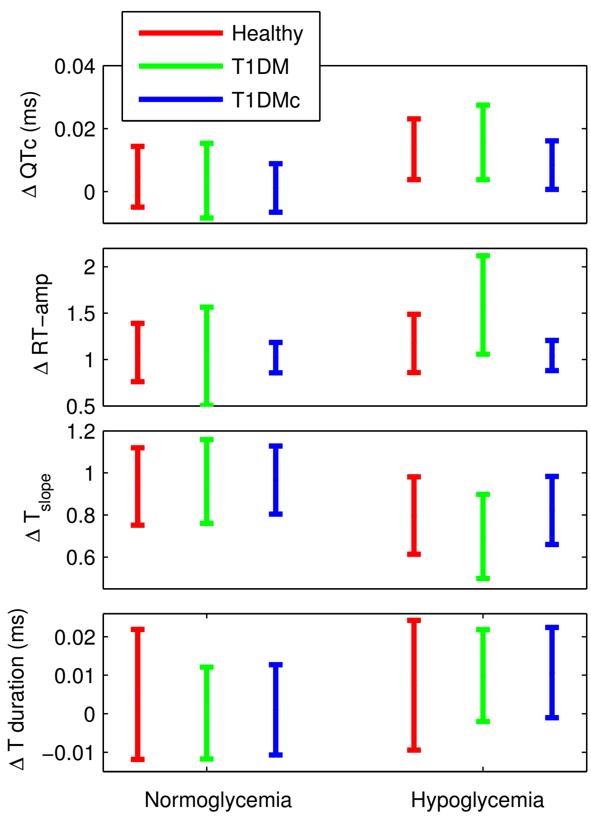

Fig. 2. Mean ± standard deviation of parameters used in classification. Group mean values of parameters are calculated separately from normoglycemic section (glucose >3.5mmol/l) and hypoglycemic section. Groups are marked in different colors Healthy group as red, T1DM group as green and T1DMc as blue.

V. Discussion

ECG parameter classifier for detection of hypoglycemic events has been presented. Results shows that detection of hypoglycemic event could be made passably from 15/22 measurements. For two measurements where hypoglycemia could not be detected, measurement time was clearly shorter. The shorter measurement period could explain the inability to detect hypoglycemia, because ECG changes had not taken place yet.

The biggest limitation of this study is lack of handling anomalies in ECG waveforms such as significant changes in T-wave morphology (e.g. flat, partly inverted or fully inverted T-wave). Before a hypoglycemia detector could be used in real life situations such anomalies should also be detected and treated appropriately. Because of such ECG anomalies, five subjects were excluded from final analysis.

As shown by the results, detection of hypoglycemic events by using ECG parameters is quite challenging because there are rather high individual differences in the hypoglycemia related ECG changes and changes are strongest in healthy group and lower in diabetic groups were blood glucose prediction is mostly needed. However better results could be obtained if individual reactions for hypoglycemic events could be taken into account in the detection procedure, i.e. the classifier could be trained with individual data.

One disadvantage for prediction of hypoglycemic events is the delay between the decrease in blood glucose (<3.5 mmol) and ECG changes. As can be seen from Figure 4, in almost all subjects blood glucose value has been below 3.5 mmol/l more than 15 minutes before changes are detectable and classification to hypoglycemia can be done. However in real life situations blood glucose fluctuations are slow and thus this 15 min delay of detection is not crucial

Results of this study show that detection of hypoglycemic events can be done with a quite good success rate (15/22 subjects) from ECG parameters. Results show that ECG based hypoglycemia detector is feasible at least for diabetics in the early phase of the disease together with traditional glucose measurements to improve their glycemic control.

VI. Acknowledgments

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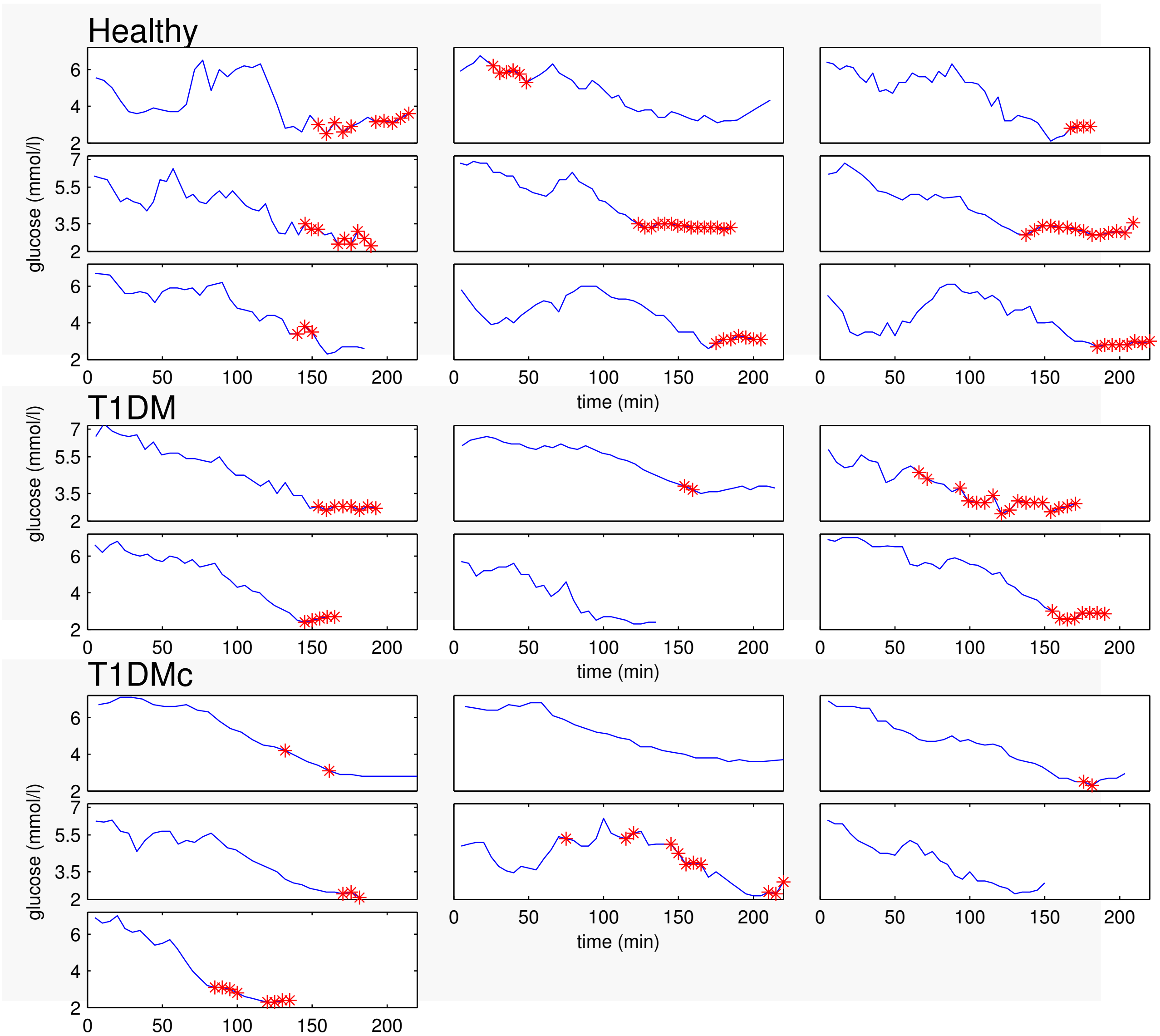

Fig. 4. Results of classification. Measured blood glucose value is marked as blue line and time points which are classified as hypoglycemic are marked as red stars.

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