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Identification of Hypoglycemia and Hyperglycemia in Type 1 Diabetic Patients Using ECG Parameters

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***Abstract*— Hypoglycemia and Hyperglycemia are both serious diseases related to diabetes mellitus. Among Type 1 Diabetic patients, there are who experience both hypoglycemic and hyperglycemic events. The aim of this study was to identify of hypoglycemia and hyperglycemia based on ECG changes in this population. An ECG Acquisition and Analysis System based on LabVIEW software has been developed for collecting ECG signals and extracting features with abnormal changes. ECG parameters included Heart rate (HR), corrected QT interval (QTe_C), PR interval, corrected RT interval (RT_C) and corrected TpTe interval ($TpTe_C$). Blood glucose levels were used to classify glycemic states in subjects as hypoglycemic state (≤ 60 mml/l, Hypo), as normoglycemic state (80 to 110 mmol/l, Normo), and as hyperglycemic state (≥ 150 mml/l, Hyper). The results indicated that hypoglycemic and hyperglycemic states produce significant inverse changes on those ECG parameters.**

I. Introduction

Hypoglycemia is a dangerous and frequent problem in patients with Type 1 diabetes mellitus suffering from too low blood glucose levels. In adults, if not treated properly, severe hypoglycemia may result in coma and irreversible brain damage [1]. Hyperglycemia, in contrast, is a condition characterized by abnormally high blood glucose levels. Hyperglycemia within diabetics can lead to ketoacidocis (i.e. diabetic coma), which can be fatal [2].

Conventionally, to determine whether being hypoglycemia or hyperglycemia, diabetic patients need to frequently monitor blood glucose level. One conventional technique, for example, requires that the patients draw blood, typically by pricking the finger. The drawn blood is then analyzed by a portable device to determine blood glucose levels. The technique can be painful and therefore can significantly discourage the patent from periodically checking blood glucose levels. Obviously, non-invasive techniques would be very desirable.

Non-invasive methods proposed up to date include systems such as: infrared/near-infrared spectroscopy [3], iontophoresis [4], skin conductance [5], etc. However, none of these have proved sufficiently reliable or unobtrusive. Recently, we developed an effective and sensitive system to monitor hypoglycemia non-invasively using physiological parameters such as heart rate, skin impedance and electrocardiogram (ECG) [6, 7]. According to this achievement, ECG offers a quicker, more ubiquitous, non-invasive clinical and research screen for the early detection of hypoglycemia and hyperglycemia than other physiological signals.

It is now known that hypoglycemia can alter results in observable ECG changes, such as prolongation of QT interval [8]. Various methods based on observation of these changes within ECG have been used to detect hypoglycemia, i.e., RR (distance of two nearest R points), RT_C (interval from R point to peak of T wave with Bazett's correction), T wave amplitude, T wave skewness, T wave kurtosis and T wave peak-to-end [9-11]. The relationships of heart rate with hypoglycemia and hyperglycemia were also studied in which hypoglycemia was found to increase heart rate [12], whereas hyperglycemia was associated with reduced heart rate variability [13]. Also, several studies have been reported regarding ECG abnormalities which can possibly be found in cases of acute hyperglycemia in normal subjects such as significant increments of QT_C interval and PR interval [14], and shorter mean RR intervals in hyperglycemic patients [15].

However, the focus of current research has been in hypoglycemia only, or hyperglycemia only diabetic groups. There are very few reports of ECG changes found in the Type 1 diabetic patients with a combination of hypoglycemic and hyperglycemic states. Therefore, we will examine the changes of ECG on a group of diabetic patients with a combination of hypoglycemic and hyperglycemic states by proposing a real-time ECG monitoring and developing technique. This will exploit the alterations of heart rate, PR interval (distance from the onset of P wave to the peak of R wave), corrected QT interval (depicted as interval from the onset of Q wave to the end of T wave with Bazett's formula), corrected TpTe interval (interval from the peak to the end of T wave with Bazett's formula) and corrected RT interval (depicted as interval from the peak of R wave to the peak of T wave with Bazett's formula) to provide important markers for hypo/hyperglycemia detection. In this case, the correlations between glucose levels and important ECG parameters should also be revealed.

The rest of this paper is organized as follow. Section II describes the subjects and method which is based on ECG feature extraction in a LabVIEW system and statistical analysis. Section III presents the results and discussion, and section IV is the conclusion.

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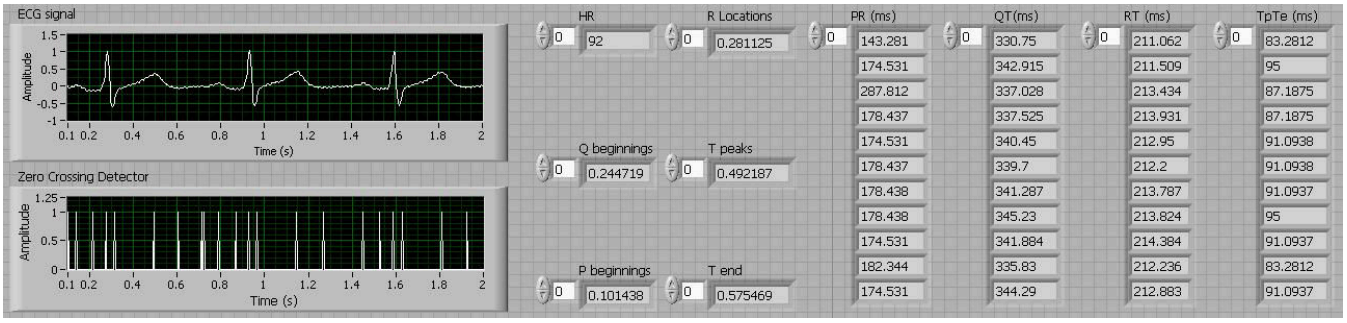

Fig. 1. Pre-processed ECG signals with Zero crossing detector and calculated ECG parameters

II. SUBJECTS AND METHOD

A. *Subjects*

We define diabetic mellitus (DM) patients with a combination of both hypoglycemic and hyperglycemic states during night time studies as those with more than 1 glucose event ≥ 150 mmol/l and more than 1 event ≤ 60 mmol/l. DM patients have been studied for overnight non-invasive blood glucose level (BGL) monitoring at the Princes Margaret Hospital for Children in Perth, Australia. The actual BGLs were routinely collected to be used as reference using Yellow Spring Instruments with the general sampling period of 30 minutes (shown in Fig. 2). Glycemic levels were used to classify glycemic groups, as having hypoglycemic state (BGL ≤ 60 mmol/l), as having normoglycemic state (80 < BGL < 110 mmol/l) and as having hyperglycemic state (BGL ≥ 150 mmol/l). During these encounters, we have found that of 5 Type 1 diabetic patients, 24 hyperglycemic, 43 normoglycemic and 23 hypoglycemic events occurred, corresponding to the 30-minute duration of each blood glucose sampling point from 9 pm to 6 am. During the study, ECG signals were continuously recorded and stored using a medical device called Hypomon®.

B. *Feature extraction*

ECG was processed using an analysis software developed in LabVIEW Professional 2010 (Fig. 1). After collecting data, to effectively remove noise effects on ECG signals (i.e, low frequency noise, baseline wander, power line interference, etc.) a pre-processing procedure was required. The algorithm that was developed uses a digital Butterworth Bandpass filter with high and low cutoff frequencies of 0.5 Hz and 40 Hz respectively. The baseline wandering was reduced in the filtered signal due to the removal of low frequency components, therefore improving signal-to-noise ratio. The electrocardiogram was then passed through a differentiator to enhance the signal. For the purpose of distinguishing hypoglycemic and hyperglycemic states, there are various features extracted from the processed electrocardiogram, including heart rate (HR), QT, PR, RT, and TpTe. We chose the zero crossing method to develop an algorithm for detecting ECG features and related intervals due to it simplicity and high reliability. There are a lot of zero crossing measurement techniques, here below we implement a zero-crossing detection by interpolation to find the number of zero crossings in ECG data. R peaks and T peaks are found using a peak detection VI by setting thresholds. Detection of beginnings/ends, peaks of P waves, Q waves and T waves are carried out by zero crossing method and window threshold. Once R peaks are found, these are taken as reference and the waves are scanned on both sides of the R peaks to get the zero crossing points for obtaining peaks of P waves, beginnings of Q waves, and peak/end of T waves. P peaks are two zero crossings behind R peaks. Q beginnings are one zero crossings behind R peaks. T peaks are two zero crossings ahead of R peaks. T ends are three zero crossings ahead of the R peaks. To detect the beginning/end of P wave, an optimum window width of 100 ms is selected in which 50 ms on either side of P peak. Within the window, if the signal is not crossing isoelectric line, then the minimum values are considered as beginnings and ends.

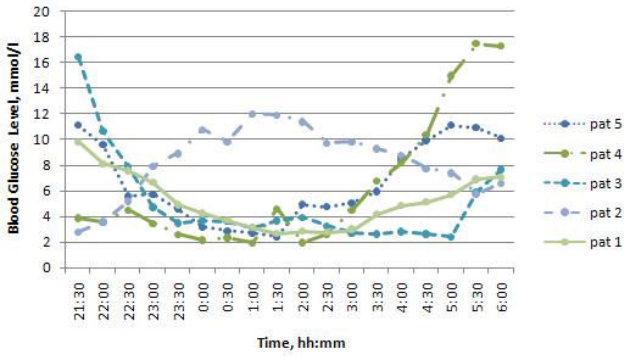

Fig. 2. Overnight measurement of Blood glucose level profiles of five DM patients

C. *Calculations and statistical analysis*

After feature extraction, ECG parameters are corrected in Bazett's formula, including QT_C (defined as $QT/\sqrt{RR}$), PR, RT_C (defined as $RT/\sqrt{RR}$) and $TpTe_C$ (defined as $TpTe/\sqrt{RR}$). The overall data are separated into two glycemic groups (Hypoglycemia - Normoglycemia; Hyperglycemia - Normoglycemia) regarding to glycemic levels defined previously. Two independent *t*-tests were then applied to every feature to estimate the significant difference between pairs of glycemic groups. Moreover, in this study, Pearson's correlation analysis was used to evaluate the relations between ECG parameters (HR, PR, QT_C, RT_C, $TpTe_C$) and BGLs both overall and in each glycemic group. All statistical analyses were conducted with IBM SPSS version 19 (SPSS Inc, Chicago, IL, USA). Significance value (*p*-value) less than 0.05 is considered to be significant. Results are presented as mean ± standard errors.

III. RESULTS AND DISCUSSION

The changes in measured ECG parameters in each glycemic group are summarized in Table I-II. Statistical results revealed that the hypoglycemic state had significant increases in heart rate, QT_C, RT_C and $TpTe_C$ (all with $p < 0.0001$) but no significant change in PR ($p > 0.05$). In this study, we confirmed that Type 1 diabetic patients have important QT_C prolongation following by lengthening of RT_C and $TpTe_C$. These outcomes concur with other reports that describe an abnormal ventricular repolarization during both experimental and spontaneous clinical nocturnal hypoglycemia [16-18].

TABLE I. CHANGES IN ECG PARAMETERS UNDER HYPOGLYCEMIA CONDITION

Parameters	**Hypoglycemic State** *(Mean ± SD)*	**Normoglycemic State** *(Mean ± SD)*	***p* value**
HR (bpm)	79.09 ± 8.878	68.85 ± 7.663	< 0.0001
QT_C (ms)	463.44 ± 24.15	395.20 ± 16.743	< 0.0001
PR (ms)	119.46 ± 7.246	122.40 ± 11.963	0.23
RT_C (ms)	298.12 ± 16.396	269.20 ± 8.703	< 0.0001
$TpTe_C$ (ms)	119.23 ± 17.411	104.87 ± 12.287	< 0.0001

HR = Heart rate

TABLE II. CHANGES IN ECG PARAMETERS UNDER HYPERGLYCEMIA CONDITION

Parameters	**Hyperglycemic State** *(Mean ± SD)*	**Normoglycemic State** *(Mean ± SD)*	***p* value**
HR (bpm)[a]	64.82 ± 7.818	68.85 ± 7.663	0.066
QT_C (ms)[b]	380 ± 20.042	395.20 ± 16.743	0.001
PR (ms)[a]	145.42 ± 8.490	122.40 ± 11.963	< 0.0001
RT_C (ms)[b]	253.42 ± 14.119	269.20 ± 8.703	0.003
$TpTe_C$ (ms)[b]	95.08 ± 9.356	104.87 ± 12.287	0.004

HR = Heart rate

TABLE III. CORRELATIONS BETWEEN ECG PARAMETERS AND BLOOD GLUCOSE LEVELS ON GLYCEMIC GROUPS

Relations	**Hypoglycemia**		**Hyperglycemia**	
	Coef. r	***p value***	***Coef. r***	***p value***
BGL-HR	-0.608	< 0.0001	0.174	0.440
BGL-QT_C	-0.795	< 0.0001	-0.678	0.001
BGL-PR	0.145	0.384	0.806	< 0.0001
BGL-RT_C	-0.583	0.002	-0.584	0.004
BGL-$TpTe_C$	-0.705	0.003	-0.449	0.036

HR = heart rate
BGL = blood glucose level

The study also showed that under the hyperglycemic state there were significant increases in PR ($p < 0.0001$), decreases in QT_C ($p < 0.0001$), RT_C ($p = 0.001$), $TpTe_C$ ($p = 0.004$) but no change in HR ($p > 0.05$). These findings are different from previous research in response to the increment of QT_C during hyperglycemia [14, 19, 20]. We found that QT_C was significantly different at hyperglycemia as compared to normoglycemia and hypoglycemia.

To confirm the relationship of hypoglycemic and hyperglycemic groups with indicated ECG parameters, Pearson's correlation coefficients were calculated to examine the associations between five ECG parameters and glycemic groups through blood glucose levels. In overall three groups, HR (r = -0.466) was moderately related to BGLs, while QT_C, PR, RT_C, $TpTe_C$ had strong relations with BGLs (r = -0.712, 0.783, -0.781, -0.586, respectively, all with $p < 0.0001$).

When the correlations between ECG parameters and BGLs were examined in hypoglycemic and hyperglycemic groups, HR was significant related to BGL only in Hypo (r = -0.608, $p < 0.0001$), but not in Hyper (r = 0.174, p = 0.440). Conversely, PR was significantly related to BGL only in Hyper (r = 0.806, $p < 0.0001$), but not in Hypo (r = 0.145, p = 0.384). QT_C, RT_C, $TpTe_C$ were significantly associated with BGLs in both Hypo and Hyper groups (data as shown in Table III). The results demonstrated that the significant features to identify hypoglycemia and hyperglycemia are QT_C, PR, and HR.

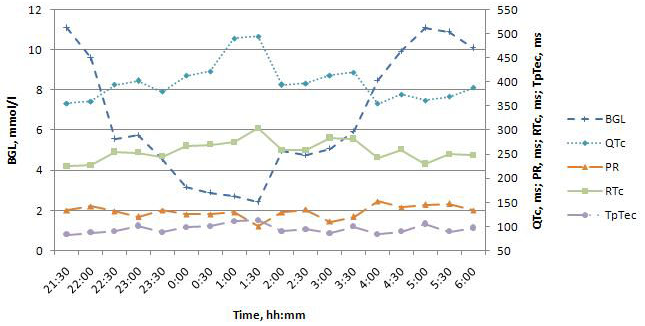

Fig. 3. Overnight measurement of Blood glucose level and ECG parameters of patient 5

In this study, a lower blood glucose level was related to increased QT_C, RT_C, $TpTe_C$ and had no relation with PR. Interestingly, a higher blood glucose level was associated with decreased QT_C, RT_C, $TpTe_C$ and increased PR. Indeed, while hypoglycemia was widely proved to alter ventricular repolarization in lengthen of QT_C interval [17, 21, 22], the role of hyperglycemia in causing abnormal cardiac repolarization in people with diabetes is not yet clear. Gordin et al. [19] reported that hyperglycemic glucose clamp induces QT_C interval prolongation in diabetic patients and in healthy control subjects. Marfella *et al.* [20] has proposed that hyperglycemia may produce ventricular instability by increased sympathetic activity, increased cytosolic calcium content in myocytes or both. Inversely, in a recent study [23] where simultaneously recorded QT_C values and glucose levels were analyzed in patients with Type 1 Diabetes, QT_C prolongation was associated only with hypoglycemia, not with hyperglycemia. In Type 1 diabetic patients with both hypo and hyper states, we found

the same results that the highest QT_C values ($\geq$ 460 ms) were seen at night when blood glucose values were low (i.e., patient 5 in Fig. 3). Moreover, prolongation of QT_C led to the lengthening of RT_C, $TpTe_C$ and vice versa. This prolonged repolarization could be explained by a physiologically longer cardiac repolarization at night and thus an electrically instable myocardium worsened by the hypoglycemia induced adrenergic stimulation [24]. Results from clinical studies are less consistent, then in order to establish the clinical relevance of the findings of Gordin and Marfella *et al.*, further studies are needed.

Increased PR in hyperglycemia have been discussed in the research of Marfella *et al.* [14] with acute hyperglycemia in healthy males. This effect is due to PR intervals commonly associated with atrial fibrillation [25, 26], and chronic hyperglycemia but not hypoglycemia may contribute to atrial fibrillation burden in several ways [27, 28]. Therefore hyperglycemic state in type 1 diabetic patients with both hypoglycemic and hyperglycemic states can result in changes of PR interval. However our ECG assessments of diabetic patients did not indicate atrial dysfunction.

IV. Conclusion

In this paper, we explore the changes of ECG parameters associated with hypoglycemic and hyperglycemic states in Type 1 diabetic patients. An ECG acquisition and feature extraction based on LabVIEW has been developed to detect these alterations. Several statistical analyses have been done to evaluate the effect of ECG parameters on hypoglycemia and hyperglycemia. This study also shows the different findings of decreased ventricular repolarization in Type 1 diabetic patients with combination of hypoglycemic and hyperglycemic states. Further work in a larger population is absolutely necessary to investigate a mechanism that possibly causes inverse effects on ventricular repolarization in diabetics between hypoglycemic and hyperglycemic states.

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