A Knowledge-Based Electrocardiogram-Monitoring System for Detection of the Onset of Nocturnal Hypoglycaemia in Type 1 Diabetic Patients

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Abstract

Nocturnal hypoglycaemia has been implicated in the sudden deaths of young people with diabetes. Experimental hypoglycaemia has been found to prolong the ventricular repolarisation and to affect the T wave morphology. It is postulated that abnormally low blood glucose could in certain circumstances, be responsible for the development of a fatal cardiac arrhythmia.

We have designed a monitoring and alarm system for detection of the onset of spontaneous nocturnal hypoglycaemia through monitoring of the electrocardiogram. The system incorporates expert-knowledge in the form of a rule-base. It performs monitoring of two ECG features and raises alarms if abnormalities are detected corresponding to hypoglycaemia. The top performance of the system is 100% and 91.30% for sensitivity and specificity respectively. This study supports the hypothesis proposing a relationship between cardiac function and abnormally low blood glucose.

1. Introduction & background

The aim of this work is to detect the onset of nocturnal hypoglycaemia indirectly through analysis of the electrocardiogram (ECG) of Type 1 diabetic patients. In order to achieve this, ECG feature extraction is performed and the features produced are monitored over time for detection of abnormal changes related to hypoglycaemia.

Nocturnal hypoglycaemia has been implicated in the sudden deaths of individuals with Type 1 diabetes, particularly those between the ages of 15 to 40 years old, a syndrome known as "Dead in Bed" [1]. The mechanism and cause of such deaths remains unclear. Those affected were well the night before and were found dead in an undisturbed bed the following morning. There was no brain damage, a symptom of profound hypoglycaemia, hence the deaths were caused by a different mechanism. One possibility is that the deaths were due to a fatal cardiac arrhythmia. It has been shown that experimental hypoglycaemia prolongs ventricular repolarisation (VR), a situation associated with ventricular arrhythmias [2].

A single lead from the 3-lead orthogonal ECG was used for the purposes of this research. An illustration of an ECG cycle is presented in figure 1. The T wave corresponds to the ventricular repolarization of the myocardium. During hypoglycaemia, the counter-regulatory responses cause the release of adrenaline and a fall in potassium, which delays repolarisation. These changes may be reflected on the ECG by changes in T wave morphology. If these changes can be automatically identified it may provide a warning of hypoglycaemia or of a potentially pro-arrhythmogenic condition.

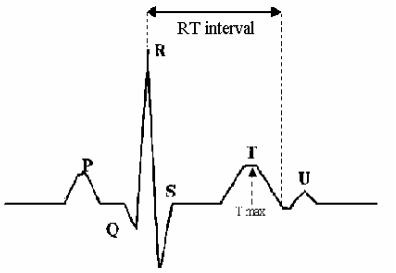

Fig 1: an ECG cycle

2. Methods

2.1. Data acquisition

The data used in this study consisted of both the ECG traces and their corresponding blood glucose levels. They were obtained from 19 Type 1 diabetic patients over 32 nights, with mean (sd) age 36.4 (14.56), recruited from secondary care diabetic clinics in Sheffield. The ECG

data were recorded in the patient's own environment by a custom-built system that captures data from the YY' orthogonal lead [3]. One-minute recordings were captured every 15 minutes. Blood glucose was recorded by an implantable glucose sensor (CGMS, MiniMed Inc.) [4] that measures glucose in the subcutaneous tissue every 5 minutes. The above acquisition was carried out for two successive nights and produced a data-set of paired ECG-glucose readings.

2.2. ECG features

Two ECG features were used: the T wave amplitude (T-ampl) and a time interval feature (RTc), describing the VR duration. RT is the time interval from the R peak up to the T-end. This was corrected for heart rate using Bazett's formula (RTc = RT/√RR) [5] to produce the RTc feature where the suffix "c" stands for "corrected". The end of the T wave was detected using the tangent method [6].

The RT interval was chosen for this study, instead of the QT, since R point detection is more straight-forward than Q point detection, especially in the presence of noise. Moreover the RT interval still describes the process of ventricular repolarisation satisfactorily. The RT has been used before [7] but to a lesser extent than the QT.

2.3. Hypoglycaemic threshold

A glucose concentration threshold of 2.5 mmol/l was used to define hypoglycaemia. ECG traces corresponding to glucose equal or below 2.5 mmol/l were classed as arrhythmic (hypoglycaemic) while those corresponding to glucose values greater than 2.5 mmol/l were classed as normal (euglycaemic).

2.4. Knowledge-based classifier

We have developed the software engine for a prototype system used for ECG interpretation. The system is designed to raise alarms if abnormal cardiac events, related to hypoglycaemia are detected. It comprises an ECG pre-processor, a feature extractor and a knowledge-based system (KBS). The monitoring system is depicted in figure 2.

At each sampling instant the ECG is fed to the pre-processing stage where a number of filtering steps (notch filtering, baseline wandering removal, signal averaging etc) are carried out. Next, the filtered ECG is passed to the feature extraction stage where the ECG features are extracted. The ECG features are then fed to the KBS that infers, using the rule-base, whether they correspond to a normal or abnormal ECG cycle. The system uses ECG features from the current, as well as previous ECG cycles to make a decision on whether to raise an alarm or not.

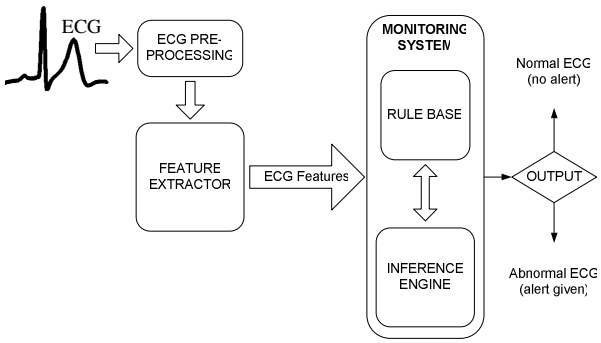

Fig 2: ECG monitoring system

The time-series of the two ECG features described previously (RTc and T-ampl) were the inputs to the monitoring system. The data used were offline but the monitoring approach simulated an online patient monitoring scenario. The approach reflected a situation where a patient would be monitored online by the bedside.

2.5. KBS adaptivity

During the monitoring process, abnormal changes in feature value as time elapsed were detected by comparison to an adaptive threshold. This threshold was based on a moving average (MA) value. A moving window was used containing a few samples prior to the current time instant. This was combined with a moving value of the standard deviation (MSD), calculated from the same moving window, to define an accepted range of feature values. The equation of the MA filter used is given below in its generic form for nth order:

$$\bar{x}(k)=\begin{cases}\dfrac{\sum_{i=1}^{n}x(k-i)}{n},\ for\ n<k \quad n,k\in\aleph^{+} & eq^{n}\ 1a\\ \dfrac{\sum_{i=1}^{k-1}x(k-i)}{k-1},\ for\ n\geq k \quad n\in\aleph^{+},k\in\aleph^{+}\wedge k>1 & eq^{n}\ 1b\\ 0,\ for\ k=1 & eq^{n}\ 1c\end{cases}$$

x(k) is the raw feature value at sample *k*, and $\bar{x}(k)$ is the MA filtered version. The equation for the calculation of MSD is given below in its generic form for nth order:

$$y(k)=\begin{cases}\dfrac{\sum_{i=1}^{n}(x(k-i)-\bar{x}(k))^{2}}{n-1},\ for\ n<k \quad n,k\in\aleph^{+} & eq^{n}\ 2a\\ \dfrac{\sum_{i=1}^{k-1}(x(k-i)-\bar{x}(k))^{2}}{(k-1)-1},\ for\ n\geq k \quad n\in\aleph^{+},k\in\aleph^{+}\wedge k>2 & eq^{n}\ 2b\\ 0,\ for\ k\in\{1,2\} & eq^{n}\ 2c\end{cases}$$

x(k) is the raw feature value at sample *k* and $\bar{x}(k)$ is the MA value at sample *k* calculated from the moving window that spans up to *x*(*k*-1). *y(k)* is the standard

deviation of the feature values that lie in the moving window. This standard deviation is not the deviation from a static mean but the deviation from the moving average.

2.6. Rule-base

The knowledge-base for the KBS is a set of rules generated from observations of ECG changes under hypoglycaemia, within guidelines provided by clinical experts. The rule-base consisted of eight rules. The two principal rules used for monitoring are presented below:

1. **IF** (T-ampl is flattened) **and** (T-ampl_prev is flattened) **and** (RTc is prolonged) **and** (RTc_prev is prolonged) **THEN** (DiabeticState is hypoglycaemic)
2. **IF** (T-ampl is normal) **or** (T-ampl_prev is normal) **or** (RTc is normal) **or** (RTc_prev is normal) **THEN** (DiabeticState is euglycaemic)

The suffix "_prev" stands for previous sample before the current one. The above rules summarize the knowledge of the rule-base and are given for illustration only. The actual rules were formulated differently but convey the same information as the above two.

2.7. Assessment of performance

Two definitions of true-positives (TP) were used to assess the performance of the system:

i. Each hypoglycaemic night monitored, was assessed as TP if hypoglycaemia was detected at the exact time it occurred during the night.
ii. Each hypoglycaemic night monitored, was assessed as TP if hypoglycaemia was detected within an hour from the time it occurred during the night. (One hour is equivalent to 4 samples since data was sampled every 15 minutes.)

Each hypoglycaemic night monitored was assessed as false-negative (FN) if hypoglycaemia was not detected, that is no alarm raised. Each euglycaemic (i.e. normal) night monitored correctly was a true-negative (TN) and each euglycaemic night where a false-alarm was raised was a false-positive (FP). After performing monitoring on all nights the accuracy, sensitivity and specificity, over all nights, were calculated by the formulas:

- accuracy = TP + TN / (TP+TN+FP+FN) (eq^n 3)
- sensitivity = TP / (TP + FN) (eq^n 4)
- specificity = TN / (TN + FP) (eq^n 5)

Using the two different definitions for TP yields two pairs of results for the above metrics.

3. Results

Monitoring results are presented in table 1. The first column of the table contains the patient code and corresponding night. The second column describes the ECG record at which glucose fell below 2.5 mmol/l. The third column contains the record at which the alarm was raised, with zero denoting no alarm raised. Finally the fourth column provides an assessment of the performance. The number in brackets denotes the deviation of the alarm from the actual onset, i.e. TP(3) denotes an alarm raised 3 samples away from the hypoglycaemic onset. Such cases are marked in bold.

Table 1: monitoring results

patient	gl<2.5	alarm@rec	perf
p201Anght1	0	0	TN
p201Anght2	0	0	TN
p202A	24	**27**	**TP(3)**
p202	41	**37**	**TP(4)**
p203nght1	11	**15**	**TP(4)**
p203nght2	0	0	TN
p204	18	18	TP
p205nght1	0	0	TN
p205nght2	0	0	TN
p207nght1	0	0	TN
p207nght2	0	0	TN
p208nght2	0	0	TN
p209nght1	0	0	TN
p209nght2	55	**53**	**TP(2)**
p210	0	0	TN
p212nght1	0	0	TN
p212nght2	59	**58**	**TP(1)**
p215nght1	0	0	TN
p215nght2	0	0	TN
p218Anght1	0	0	TN
p218Anght2	0	0	TN
p221	0	0	TN
p222	0	0	TN
p227nght1	22	**21**	**TP(1)**
p227nght2	39	39	TP
p230nght1	0	6	FP
p231nght1	0	0	TN
p231nght2	0	0	TN
p232nght1	0	0	TN
p232nght2	0	0	TN
p244nght1	18	**21**	**TP(3)**
p244nght2	0	41	FP

There were 9 hypoglycaemic and 23 euglycaemic nights available. This non-uniformity between the two classes is because the hypoglycaemic events were spontaneous, i.e. naturally occurring, and hence their frequency was less than that of euglycaemic nights.

When alarms were classed as correct only if they were raised on the exact record of hypoglycaemic onset then

the accuracy, sensitivity and specificity of the system were: 78.13%, 44.44%, 91.30% respectively. However if alarms raised within 4 samples were classed as acceptable then the above metrics reached 93.75%, 100% and 91.30%.

4. Discussion

The current dataset consisted of ECG-glucose data points captured every 15 minutes. A deviation of 1 hour between the alarm raised and the actual hypoglycaemic onset was in fact a deviation of just 4 sample points. This means that the monitoring system was inaccurate by only 4 samples. Recording ECG more frequently during the night could have improved the performance yielding shorter deviations of alarms from actual hypoglycaemic onset.

Previous work focused on static pattern classification of ECG features using multi-layer perceptron (MLP) neural networks (NN) and statistical classifiers [8]. The performance of these classifiers was inferior to the knowledge-based system. A factor that boosted the performance of the KBS was the inclusion of the temporal dimension. The system was monitoring the time-series of the ECG features instead of performing static classification like the neural and statistical classifiers. Inclusion of temporal information was not possible in the case of NN because the datasets were not long enough to be used in the training of a NN.

Using a knowledge-based approach introduced some advantages. The incorporation of human-expert knowledge allowed the system to focus on the significant ECG changes and ignore the unrelated ones. MLPs were confused by unrelated ECG changes and overcoming this would require very long datasets that were not available. Regardless of the above, the KBS made better use of the dataset since all the data could be used to assess performance. In the case of MLP, a portion of the data had to be set aside for training and only the remaining data could be used for assessment of performance.

Furthermore, the transparency of a KBS allows the rules and related process to be understood by clinicians. In contrast, a black box approach such as a trained MLP obscures easy investigation of its internal structure and inference scheme. A drawback of using a KBS however is that it requires human expert knowledge and this knowledge must be effectively coded into the system.

5. Conclusions

This study has demonstrated the success of a knowledge-based ECG-monitoring system in detecting the onset of spontaneous nocturnal hypoglycaemia. The system achieved satisfactory performance on the existing dataset. Such a result supports and strengthens the hypothesis proposing a relationship between cardiac function and hypoglycaemia. Future acquisition of more data will be important for further testing of the system.

Extension of the rule-base and inclusion of more inputs to the KBS, in particular ECG features that describe the ST segment, T morphology and the occurrence of U waves, could considerably improve performance.

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