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Neural-Network Detection of Hypoglycemic Episodes in Children with Type 1 Diabetes using Physiological Parameters

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***Abstract*—The most common and highly feared adverse effect of intensive insulin therapy in patients with diabetes is the increased risk of hypoglycemia. Symptoms of hypoglycemia arise from the activation of the autonomous central nervous systems and from reduced cerebral glucose consumption. HypoMon is a non-invasive monitor that measures some physiological parameters continuously to provide detection of hypoglycemic episodes in Type 1 diabetes mellitus patients (T1DM). Based on heart rate, corrected QT interval of the ECG signal and skin impedance, a neural network detection algorithm has been developed to recognize the presence of hypoglycemic episodes. From a clinical study of 21 children with T1DM, associated with hypoglycemic episodes, their heart rates increased (1.16±0.16 vs. 1.03±0.11, P<0.0001), their corrected QT intervals increased (1.09±0.09 vs. 1.02±0.07, P<0.0001) and their skin impedances reduced significantly (0.66±0.19 vs. 0.82±0.21, P<0.0001). The overall data were obtained and grouped into a training set, a validation set and a test set, each with 7 patients randomly selected. Using a feed-forward multi-layer neural network with 9 hidden nodes, and an algorithm developed from the training set and the validation set, a sensitivity of 0.9516 and specificity of 0.4142 were achieved for the test set. A more advanced neural network algorithm will be developed to improve the specificity of test sets in the near future.**

I. Introduction

THE Diabetes Control and Complications Trial (DCCT) Research Group in 1993 [1] highlighted significant benefits of improving glycemic control with intensive treatment. However, the most common and highly feared adverse effect of intensive therapy is the increased risk of hypoglycemia (abnormally low blood glucose level). In the DDCT, patients who used intensive therapy experienced a threefold increase incidence of severe hypoglycemic episodes compared to those receiving conventional therapy [1-2]. Hypoglycemic episodes are defined as those in which the patient had blood glucose levels < 60 mg/dl (3.33 mmol/l). Severe hypoglycemic episodes are defined as those in which the patient required assistance to treat the event and had documented blood glucose levels < 50 mg/dl (2.8 mmol/l).

Hypoglycemia develops when rates of glucose entry into the systemic circulation are reduced relative to glucose uptake by tissues. It is usually corrected naturally by the combination of a number of defense mechanisms. Initially, a decrease in insulin secretion in response to declining blood glucose levels occurs. As glucose levels continue to fall, a number of redundant glucose counter-regulatory factors are sequentially activated at specific thresholds to ensure sufficient glucose uptake to the brain and other central nervous system tissue metabolism [3]. These counter-regulatory factors include glucagons, epinephrine, growth hormone, cortisol, and other hormones.

In patients with Type 1 diabetes mellitus (T1DM) undergoing intensive insulin therapy, falling plasma glucose concentrations often do not elicit counter-regulatory responses at normal glycemic thresholds, allowing glucose levels to drop to dangerously low values. After many years of type 1 diabetes, the glucagons secretory response to hypoglycemia could become deficient. Additionally, warning symptoms may be lost in some cases, and the episode may lead to serious acute reactions known as hypoglycemia unawareness. Studies in T1DM patients have demonstrated that as few as two episodes of antecedent hypoglycemia can blunt responses to subsequent hypoglycemia [4].

Symptoms of hypoglycemia arise from the activation of the autonomous central nervous systems (autonomic symptoms) and from reduced cerebral glucose consumption (neuroglycopenic symptoms), some of the latter being potentially life threatening. Autonomic symptoms (e.g., tachycardia, palpitations, shakiness, sweating) are activated before neuroglycopenic symptoms (e.g., reduced concentration, blurred vision, dizziness). Autonomic symptoms may provide the initial indication of the presence of hypoglycemia and allow the patient to recognize this condition early [5].

Nocturnal hypoglycemia is particularly dangerous because sleep reduces and may obscure autonomic counter-regulatory responses, so that an initially mild episode may become severe. The risk of severe hypoglycemia is high at night, with at least 50% of all severe episodes occurring during that time [6]. Deficient glucose counter-regulation may also lead to severe hypoglycemia even with modest insulin elevations. Regulation of nocturnal glycemia is further complicated by the dawn phenomenon. This is a

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consequence of nocturnal changes in insulin sensitivity secondary to growth hormone secretion: a decrease in insulin requirements approximately between midnight and 5am followed by an increase in requirements between 5am and 8am.

In this paper, we develop a neural network algorithm for the detection of hypoglycemia episodes in T1DM children using physiological parameters such as heart rate, corrected QT interval and skin impedance. Section II provides an overview of the method used for non-invasive and continuous detection of hypoglycaemia. Section III presents the development and results of an optimized neural network used for the identification of hypoglycaemic episodes in T1DM children. Section IV provides a conclusion for this study.

II. METHODS

A. Non-Invasive Hypoglycemia Monitor

Current technologies used in the diabetes diagnostic testing and self-monitoring market have already been improved to the extent that any additional improvements would be minimal. For example, glucose meter manufacturers have modified their instruments to use as little as 2 μl of blood and produce results in under a minute. Technological advancement in this market is expected to occur using novel design concepts. An example of such technology is the non-invasive glucose meter.

There is a limited number of non-invasive blood glucose monitoring systems currently available but each has specific drawbacks in terms of functioning, cost, reliability and obtrusiveness. GlucoWatch G2 Biographer from Cygnus Inc is designed to measure glucose levels up to 3 times per hour for 12 hours. The AutoSensor (the disposable component) which is attached to the back of the GlucoWatch monitor and adheres to the skin will provide 12 hours of measurement. The product uses reverse iontophoresis to extract and measure glucose levels non-invasively using interstitial fluid. It has to be calibrated before each measurement period and requires a two-hour warm-up period. It requires costly disposable components, the gel pads must be replaced after each use, sweating may cause skipped readings, and the measurement has a time delay of about 10-15 minutes.

Intensive research has been devoted to the development of hypoglycemia alarms, exploiting principles that range from detecting changes in the electroencephalogram (EEG) or skin conductance (due to sweating) to measurements of subcutaneous tissue glucose concentrations by glucose sensors [7-8]. However, none of these have proved sufficiently reliable or unobtrusive.

We have developed a continuous non-invasive hypoglycemia monitor which uses physiological responses. During hypoglycemia, the most profound physiological changes are caused by activation of the sympathetic nervous system. Among the strongest responses are sweating and increased cardiac output [9-11]. Sweating is mediated through sympathetic cholinergic fibres, while the change in cardiac output is due to an increase in heart rate and increase in stroke volume [11]. Tattersall and Gill [12] raised the possibility of hypoglycemia induced arrhythmias, and experimental hypoglycemia has been shown to prolong QT intervals and dispersion in both non-diabetic subjects and in those with type 1 and type 2 diabetes [13].

HypoMon® from AIMedics Pty Ltd is a non-invasive monitor that measures physiological parameters continuously to provide detection of hypoglycemic episodes in Type 1 diabetes mellitus patients (T1DM). The system consists of a battery-powered chest belt worn that houses a set of four skin-surface bio-sensor electrodes for the measurement of physiological parameters and a hand-held receiver computer.

The sensors are composed of a conductive polymer-based material such as polypyrrole which has low impedance and low noise characteristics. These characteristics enable the sensors to measure both skin impedance and quality ECG signals.

The chest belt digitizes, encrypts and transmits the measured parameters to the receiver computer which analyzes and identifies hypoglycemic episodes. An alarm system is available for warning various stages of hypoglycemia.

B. Study

Twenty-one children with T1DM (14.4±1.6 years) volunteered for the 4-hour glucose clamp study at the Princess Margaret Hospital for Children in Perth, Australia. Data were collected with approval from Women's and Children's Health Service, Department of Health, Government of Western Australia, and with informed consent.

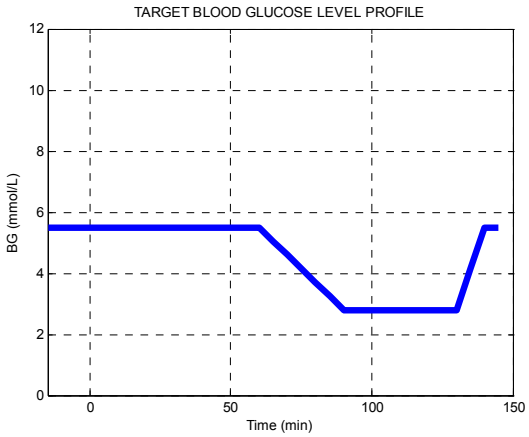

Fig. 1. Target blood glucose levels profile.

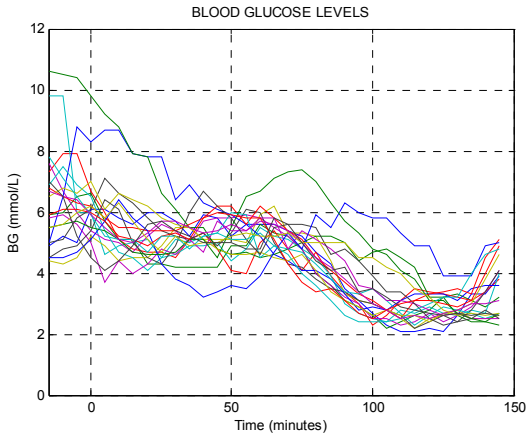

Fig. 2. Actual blood glucose levels profiles in 21 T1DM children.

Fig. 3. HypoMon from AIMedics Pty Ltd

Each study consists of five phases: baseline (30 min), euglycemia (60 min), ramp phase (30 min), hypoglycemia (40 min) and euglycemia (30 min) as shown in Figure 1. HypoMon was used to measure the required physiological parameters, while the actual blood glucose (BG) levels were collected as reference using Yellow Spring Instruments. The main parameters used for the detection of hypoglycemia are the heart rate, corrected QT interval and skin impedance. The actual blood glucose level profiles for 21 T1DM children are shown in Fig. 2.

III. RESULTS

The HypoMon (Hypoglycemia Monitor) as shown in Fig. 3 was used to measure the relevant physiological responses (heart rate, corrected QT interval of the ECG signal, skin impedance), while the actual blood glucose (BG) measurements were collected as reference. The four skin-surface bio-sensor electrodes are multiplexed and shared to measure both skin impedance and ECG signals.

The responses from 21 T1DM children exhibit significant changes during the hypoglycemia phase against the non-hypoglycemia phase. Normalization was used to reduce patient-to-patient variability and to enable group comparison by dividing the patient's heart rate, corrected QT interval and skin impedance by his/her corresponding values at time zero. The study shows that associated with hypoglycemic episodes in 21 T1DM children, using normalized values, their heart rates increase significantly (1.16±0.16 vs. 1.03±0.11, P<0.0001), their corrected QT intervals increase significantly (1.09±0.09 vs. 1.02±0.07, P<0.0001), and their skin impedances reduce significantly (0.66±0.19 vs. 0.82±0.21, P<0.0001).

The detection of hypoglycemic episodes (BG<=60 mg/dl or 3.33 mmol/l) using these three variables is based on an advanced neural network algorithm developed from the obtained clinical data. This neural network has a multilayer feed-forward neural network structure with one input layer, one hidden layer and one output layer.

The overall data set consisted of a training set, a validation set and a test set, each with 7 patients randomly selected. For these, the whole data set which included both hypoglycemia data part and non-hypoglycemia data part were used. The final feed-forward multi-layer neural network had heart rate, corrected QT interval and skin impedance as inputs, 9 hidden nodes and 1 output node (estimated blood glucose level). From this neural network which was derived from the training set with a stopping procedure determined by the validation set, the estimated BG profiles produced a significant correlation (P<0.0001) against measured values.

The corresponding ROC Curve area for the combined training/validation dataset was 0.79 with 95% CI of (0.74, 0.85). This ROC plot is shown in Fig. 4. The optimal cut-off point selected in this study was -0.55.

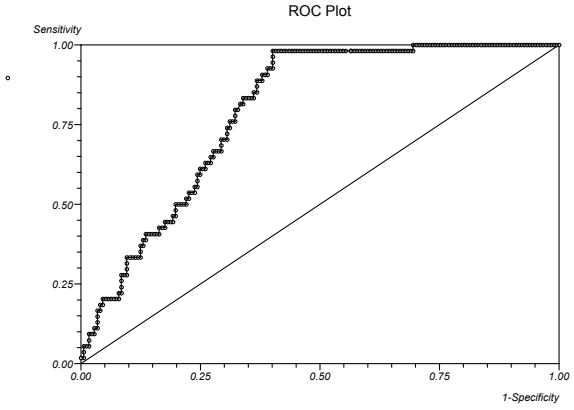

Fig. 4. ROC Plot.

The selected neural network algorithm was then applied to the test set which consists of physiological responses from 7 T1DM children randomly selected. It produced a sensitivity of 0.9516 (true positive) and a specificity (true negative) of 0.4142.

IV. Conclusion

The above result indicates that hypoglycemic episodes in T1DM children can be detected effectively from the real-time physiological responses measured by HypoMon. In this study, the sensitivity obtained by the hypoglycemia detection neural network is excellent but its specificity could be improved. A more advanced neural network algorithm will be developed to improve the specificity of test sets in the near future.

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