Electroencephalogram Reactivity to Hyperglycemia in Patients with Type 1 Diabetes

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***Abstract*— This paper is concerned with a study of hyperglycemia on four patients with type 1 diabetes at night time. We investigated the association between hyperglycemic episodes and electroencephalogram (EEG) signals using data from the central and occipital areas. The power spectral density of the brain waves was estimated to compare the difference between hyperglycemia and euglycemia using the hyperglycemic threshold of 8.3 mmol/L. The statistical results showed that alpha and beta bands were more sensitive to hyperglycemic episodes than delta and theta bands. During hyperglycemia, whereas the alpha power increased significantly in the occipital lobe ($P<0.005$), the power of the beta band increased significantly in all observed channels ($P<0.01$). Using the Pearson correlation, we assessed the relationship between EEG signals and glycemic episodes. The estimated EEG power levels of the alpha band and the beta band produced a significant correlation against blood glucose levels ($P<0.005$). These preliminary results show the potential of using EEG signals as a biomarker to detect hyperglycemia.**

I. Introduction

Patients with type 1 diabetes (T1D) are highly affected by the excursion of blood glucose levels (BGLs), ranging from hypoglycemia to hyperglycemia [1]. Whereas hypoglycemia stands for low blood sugar, hyperglycemia means having high blood glucose levels. Both of these conditions are dangerous complications among T1D patients. Hyperglycemia not only increases the risk of heart diseases [2] but also has effects on the central nervous system [3-5]. This condition of high blood glucose levels disrupts cognitive performance in children with T1D [6]. Hyperglycemia was found associated with the impairment of long-term spatial memory [7]. More seriously, hyperglycemia can progress to ketoacidosis [8].

Hyperglycemia can be detected by frequent monitoring of the blood glucose level. The conventional method uses fingersticks to determine the level of blood sugar. However, this method is painful and inconvenient for continuous monitoring. The introduction of continuous glucose monitoring (CGM) devices helps to estimate blood glucose levels continuously. Although the accuracy of these devices has been improved, there are still limitations. The correct detection rate is defined within 15 minutes of Yellow Springs Instrument sampling [9]. In recent years, the relationship between the hyperglycemic condition and physiological signals has been investigated. The increase in blood glucose levels could be found in electrocardiogram (ECG) signals [10, 11]. There was a significant decrease in heart rate variability during hyperglycemia [12, 13]. The incidence of hyperglycemic episodes in T1D patients can be detected by a combination of ECG parameters and artificial neural networks [14].

Chronic hyperglycemia and glucose variability affected the developing brain in young children in different brain regions [15, 16]. The association between hypoglycemia and EEG signals in T1D has been found in both time and frequency domains [17-19]. EEG is non-invasive, continuous, and provides a direct correlation to the fluctuation of plasma blood glucose. However, little information is known about how hyperglycemic episodes affect brain waves.

The threshold for hyperglycemia was not defined clearly. At blood glucose levels of greater than 8.3 mmol/L, significant changes were found in ECG signals [20]. The association between hyperglycemia and EEG power was established at the threshold of 11 mmol/L [1]. During these nocturnal hyperglycemic episodes, EEG power in high-frequency bands increased significantly.

The aim of this study is to investigate which EEG frequency band is more sensitive to hyperglycemia using the hyperglycemic threshold of 8.3 mmol/L [14, 21, 22]. We observe the changes in power spectral density (PSD) of EEG signals from euglycemia to hyperglycemia. In addition, correlations between EEG spectral features and hyperglycemia will be tested. The rest of this paper is structured as follows. Section II provides information about the methodology: the experiment protocol of hyperglycemia study, estimation of EEG power, and statistical analyses. Section III presents the results of the study population and the correlation between glycemic episodes and EEG signals. Finally, the conclusion is covered in Section IV.

II. Methods

A. Study Protocol

This study is part of an overnight glycemic study under natural occurrence conditions. Data were collected from four T1D adolescents during sleep at the Princess Margaret Hospital for Children in Perth (Perth Children's Hospital), Australia. EEG signals were acquired continuously using a Compumedics System device. In parallel, we measured participants' blood glucose levels every 5 to 30 minutes using a Yellow Springs Instrument (YSI) device. The YSI sampling

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values were used as a reference for the study. Eight EEG channels (F3, F4, C3, C4, P3, P4, O1, and O2) were reported at the sampling rate of 512 Hz according to the international 10/20 system. A1 and A2 were used as the reference probes. The study protocol was approved with informed consent from all participants.

B. *Analysis of EEG Data*

EEG analysis was performed on the central (channels C3 and C4) and occipital (channels O1 and O2) areas. At each blood sampling point, we extracted a 20-second EEG epoch. The epochs were labeled as hyperglycemia (BGL $\geq$ 8.3 mmol/L) and euglycemia (3.9 $\leq$ BGL $<$ 8.3 mmol/L). 20-second EEG epochs of a representative participant during euglycemia and hyperglycemia are shown in Fig. 1. This figure shows an increase in high-frequency components when the patient experienced the hyperglycemic episode.

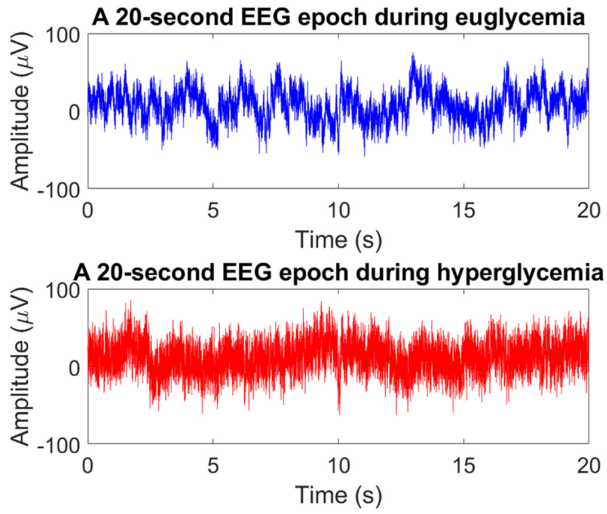

Figure 1. 20-second EEG epochs during euglycemia and hyperglycemia in channel O1 of a representative patient.

The power spectral density of the selected EEG epochs was estimated using Welch's technique. The spectral resolution is 0.25 Hz. The relationship between hyperglycemia and EEG signals was investigated on four frequency bands: delta (0.25 – 3.75 Hz), theta (4 – 7.75 Hz), alpha (8 –12.75 Hz), and beta (13 – 29.75 Hz). The power of each frequency band was then computed using the trapezoidal rule.

C. *Statistical Analysis*

The differences between hyperglycemia and euglycemia of all spectral features were examined using the Wilcoxon rank-sum test. Pearson correlation was conducted to evaluate the correlation between power spectra and blood glucose levels. All tests are considered statistically significant if having P-values of less than 0.05.

III. Results

A. *Study profiles*

The final dataset of the hyperglycemia study from four T1D patients is composed of 10 hyperglycemic and 17 euglycemic blood sampling measures. Table I provides information about blood glucose levels of the participants in hyperglycemia and euglycemia conditions. The average blood glucose level of the patients during hyperglycemia is 10.41 mmol/L, whereas their normal blood sugar has an average of 5.40 mmol/L.

20-second EEG segments corresponding to each blood sampling point were extracted. In this paper, we only analyzed EEG signals from the central and occipital areas since significant changes were found in these areas in the previous study [1]. The power spectral density was estimated from EEG signals of the four channels. Consequently, the power level of each frequency band was computed.

TABLE I. Blood Glucose Characteristics of Four Participants

Condition	Number of Measures	BGL (mmol/L)
Hyperglycemia	10	10.41 ± 2.09
Euglycemia	17	5.40 ± 1.34

B. *Statistical Results*

The EEG power levels of four patients during hyperglycemia and euglycemia are shown in Fig. 2 – Fig. 5. Mostly, the figures show an increase in the power of the four frequency bands when patients' blood glucose levels are in hyperglycemic states. The difference in the power between hyperglycemia and euglycemia becomes prominent at higher frequency bands.

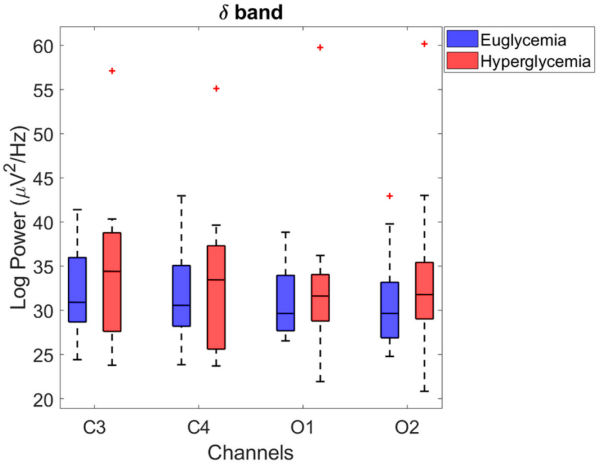

Figure 2. Power levels of the delta band during euglycemia and hyperglycemia. No significant differences were found in this band.

The response of EEG power to hyperglycemia is non-linear. Fig. 2 presents an increase in the power of the delta band during hyperglycemia. However, no significance was found in this band. For the theta band, as shown in Fig. 3, only the change in channel C4 is significant ($P<0.05$). The alpha power of this channel also increased significantly ($P<0.05$). Fig. 4 reveals the significant changes in the

occipital lobe in which channel O1 is more sensitive to hyperglycemic episodes than channel O2 ($P<0.005$ vs. $P<0.01$).

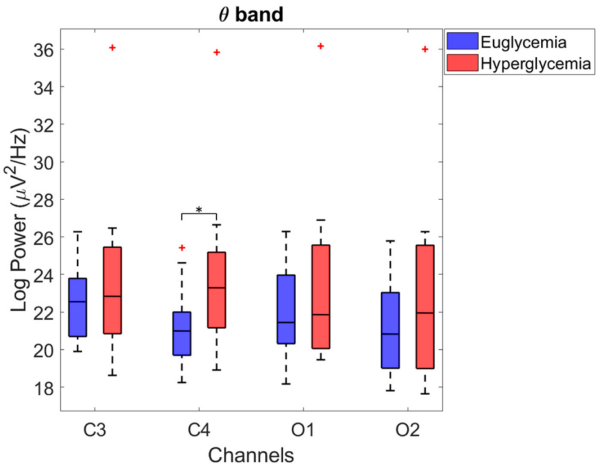

Figure 3. Power levels of the theta band during euglycemia and hyperglycemia. The level of significance is represented by asterisks (* means $P<0.05$).

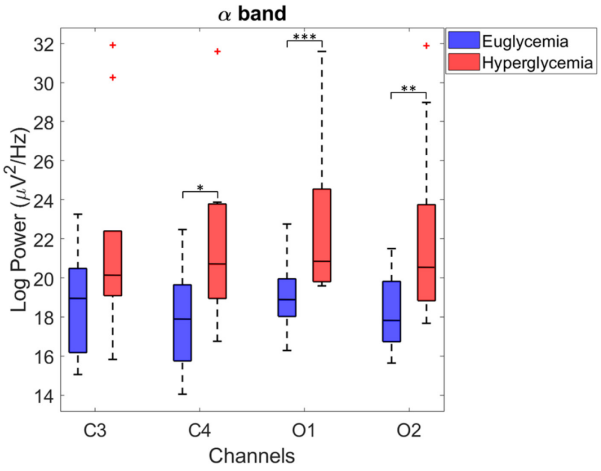

Figure 4. Power levels of the alpha band during euglycemia and hyperglycemia. The level of significance is represented by asterisks (*** means $P<0.005$, ** means $P<0.01$, and * means $P<0.05$).

As shown in Fig. 5, changes in the power of the beta band were found to be significant in both central and occipital areas. Associated with hyperglycemic episodes, the power in the central increased significantly ($P<0.05$). However, the most significant increase in the power of this band came from channel O2 ($P<0.01$). The significant results from the alpha and the beta bands suggest that the higher frequency bands of EEG signals are more responsive to hyperglycemic episodes.

It is noticeable that outliers appear in the results of the delta, theta, and alpha bands. The reason could be a significant difference in power levels among patients. A normalization algorithm could be developed as in [23, 24] to reduce the variability of power. However, the selection of the time origin for the normalization will affect the results. In the current study, by using the original power values, that selection for the normalization was not required.

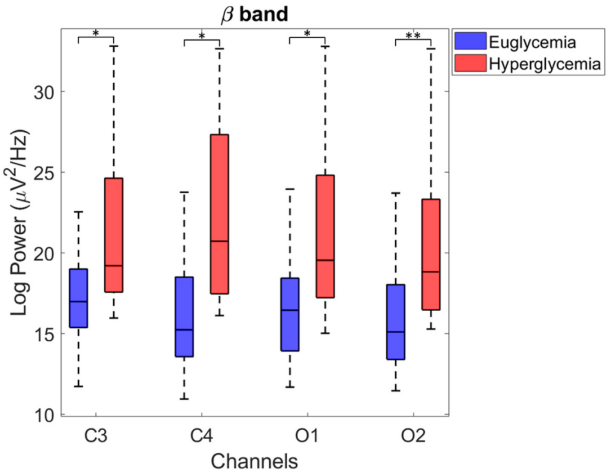

Figure 5. Power levels of the beta band during euglycemia and hyperglycemia. The level of significance is represented by asterisks (** means $P<0.01$ and * means $P<0.05$).

TABLE II. CORRELATION BETWEEN EEG POWER AND BLOOD GLUCOSE LEVELS

Bands	Channels	Correlation Coefficients (r)	P-values
Delta	*C3*	0.22	0.28
	C4	0.17	0.39
	O1	0.17	0.38
	O2	0.19	0.33
Theta	*C3*	0.21	0.30
	C4	**0.41**	**<0.05**
	O1	0.21	0.28
	O2	0.23	0.26
Alpha	*C3*	0.37	0.06
	C4	**0.50**	**<0.01**
	O1	**0.55**	**<0.005**
	O2	**0.54**	**<0.005**
Beta	***C3***	**0.47**	**<0.05**
	C4	**0.55**	**<0.005**
	O1	**0.48**	**<0.05**
	O2	**0.49**	**<0.01**

Table II reports the correlation between the power of different frequency bands with blood glucose levels. The delta band had no significant correlation with glycemic episodes. Looking at the theta band, channel C4 produced a correlation of 0.41 ($P<0.05$). The highest correlation of the alpha band came from channel O1 ($r=0.55$, $P<0.005$). For the beta band, the significant correlation was found in all channels, in which the best correlation was 0.55 (at channel C4, $P<0.005$).

Results of the Wilcoxon rank-sum test and Pearson correlation showed that high frequencies of EEG signals were

more sensitive to hyperglycemia. This finding is consistent with the previous study in which the threshold for hyperglycemia was of 11 mmol/L [1]. In the current study, changes in EEG signals can be seen at the hyperglycemic threshold of 8.3 mmol/L. In addition, the data established that the occipital lobe was highly affected by the incidence of hyperglycemic episodes, and the changes were more significant in the right hemisphere than the left hemisphere.

IV. Conclusion

In this paper, we investigated the association between hyperglycemic episodes and EEG signals in the central and occipital areas. Changes in the alpha and beta bands were more significant than the lower bands. During high blood sugar episodes, the EEG power levels of the two high-frequency bands changed significantly. It is noticeable that the occipital lobe is more sensitive to high blood glucose conditions, compared to the central area. Although the present study had a limited number of participants, the significant correlation established that the incidence of hyperglycemic episodes could be non-invasively found using the brain waves.

Future developments will be related to the investigation of the association between hyperglycemic episodes and other spectral features and the collection of data of more T1D patients for a robust conclusion. A real-time system could be developed to detect the presence of nocturnal hyperglycemia by adding classification algorithms.

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