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Automated detection of hypoglycemia-induced EEG changes recorded by subcutaneous electrodes in subjects with type 1 diabetes—The brain as a biosensor☆

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ABSTRACT

Aims: Hypoglycemia unawareness is a common condition associated with increased risk of severe hypoglycemia. We test the hypothesis that specific changes in the electroencephalogram (EEG) during hypoglycemia can be recorded by subcutaneous electrodes and processed by a general mathematical algorithm, and that hypoglycemia associated EEG changes appear before the development of severe hypoglycemia.

Methods: Fifteen patients with type 1 diabetes were exposed to insulin-induced hypoglycemia and EEG was recorded. The cognitive function was evaluated by repeated cognitive testing. Insulin infusion was terminated when plasma glucose reached 1.8 mmol/l or when the subjects showed obvious signs of cognitive dysfunction. EEG was analyzed by an automated mathematical algorithm with a predefined threshold of hypoglycemia.

Results: Hypoglycemia associated EEG changes were detected by the mathematical algorithm in all subjects. Plasma glucose at the time of EEG changes above the threshold value ranged from 2.0 to 3.4 mmol/l and occurred 29 ± 28 min (range 3–113 min) before termination of insulin infusion.

Conclusions: Hypoglycemia associated EEG changes could be detected by an automated mathematical algorithm in all subjects exposed to insulin-induced hypoglycemia. In 12 of 15 patients, EEG changes occurred before severe hypoglycemia as evaluated by the cognitive testing.

1. Introduction

Hypoglycemia remains a common and potential dangerous complication to tight glycemic control in type 1 diabetes patients and is often a limiting factor for further intensification of insulin treatment [1]. The overall rate of severe hypoglycemia in unselected populations of type 1 diabetic patients is 1.15–1.30 episodes per patient–year [2,3] increasing with the duration of diabetes [4] and with intensified treatment [1]. Some 5% of the patients accounts for more than half of the recorded episodes [2].

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A substantial proportion of patients with type 1 diabetes experience a gradual loss of awareness to hypoglycemia due to attenuated sympathoadrenal, largely sympathetic neuronal response [5,6]. Unawareness, defined as a reduced or abolished ability to sense and respond to hypoglycemia, is a predictor for the risk of severe hypoglycemia [2,7]. Long diabetes duration, tight glycemic control and recent hypoglycemic events all tend to reduce hypoglycemia awareness [6,8].

A continuous measurement of interstitial glucose is possible but, with the current technology, not reliable as a safety alarm for severe hypoglycemia [9]. Twenty years ago it was demonstrated that significant changes in the low frequency range of the electroencephalogram (EEG) appears and disappears within a narrow range of blood glucose concentration [10–13]. Attempts have been made to establish an algorithm which is able to define epochs in the EEG compatible with hypoglycemia [14]. However, to our knowledge, the methodology was not further elaborated to clinical applicability. In pilot studies we have reproduced the EEG-findings during insulin-induced graded hypoglycemia using standard scalp electrodes. These data were used to develop a mathematical algorithm that was able to recognize epochs in the EEG which had the characteristics of hypoglycemia. Permanent use of scalp electrodes is, however, hardly accepted by the patients. We therefore suggest the use of subcutaneously placed electrodes. In addition, for this technology to be clinically applicable as a hypoglycemia alarm, real-time signal processing is mandatory. The aim of the present study is to test the hypothesis that (i) specific changes in EEG can be recorded by use of subcutaneous electrodes, (ii) the signals can be processed by a general mathematical algorithm, and (iii) hypoglycemia associated EEG changes can be detected before the development of severe hypoglycemia with cognitive failure.

2. Materials and methods

The study was approved by the local ethical committee and was performed in accordance with the Helsinki declarations. Fifteen patients with type 1 diabetes were recruited among the outpatients of the diabetes clinic at the Department of Endocrinology, Odense University Hospital. They received written and oral information about the study procedures and signed informed consent. All patients had a history of symptomatic ($N = 15$) or severe ($N = 12$) hypoglycemia. Exclusion criteria included a medical history of cardiovascular disease, epileptic seizures and the use of antiepileptic drugs for any purpose and the use of beta-blocking agents. Drugs allowed included statins ($N = 7$), ACE-inhibitors ($N = 4$) and ACE-receptor blocking agents ($N = 2$).

The studies were carried out at the Department of Neurophysiology, Odense University Hospital in the morning or during early afternoon. The participants did not fast, and if they had a plasma glucose value less than 3.5 mmol/l, they were asked to consume a small amount of carbohydrates prior to the implantation of the electrodes. Four platinum electrodes, diameter 0.18 mm (Ad-Tech, Racine, WI) approved by the FDA were implanted subcutaneously with sterile technique in local analgesia using lidocain 10% and connected by wires to the EEG recording system (Nervus, Taugagreining, Iceland). EEG was sampled at 200 Hz. The position of the electrodes is shown in Fig. 1A.

During the experiment the patients were sitting in an armchair, and were not allowed to sleep. Hypoglycemia was induced by infusion of actrapid (NovoNordisk, Bagsvaerd, Denmark) with an initial infusion rate of 2–8 iU/h depending on the plasma glucose concentration. Plasma glucose was measured every 5 min by Beckman Glucose Analyzer (Beckman, Palo Alto, CA) and the insulin infusion rate was adjusted to achieve a steady fall in plasma glucose of 4–5 mmol/(l h). When plasma glucose fell to 3 mmol/l, the cognitive function was evaluated by two different tests: the patients were asked to count backwards from a given number between 50 and 100 (correct counting first time: 2 points, correct counting second time: 1 point, unable to complete counting: 0 point) and they were asked to repeatedly subtract seven from a given number between 50 and 100 (five correct subtractions: 5 points; four correct subtractions: 4 points etc.). These tests were repeated every 5 min until insulin infusion was stopped. The patients were under constant observation by a physician who evaluated signs of neuroglycopenia (speech velocity, alertness and ability to concentrate) and signs of adrenergic reactions (shivering and sweating). From the cognitive tests and from these observations, the physician decided to stop the insulin infusion when it was assumed to be too late for the patient to benefit from an alarm. Thus this time-point was not based on a single parameter but rather on a combination of the signs and symptoms observed.

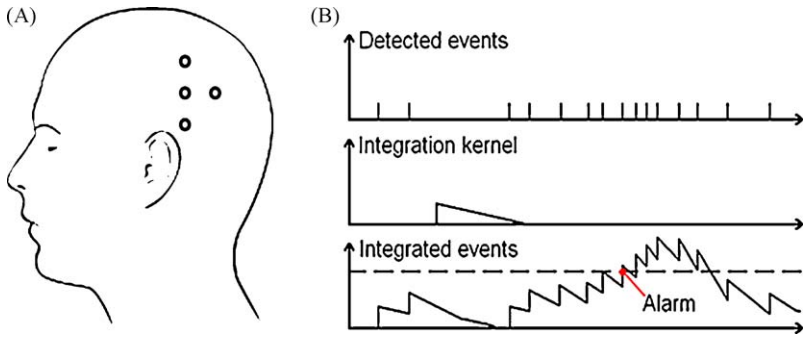

Fig. 1 – Panel A shows where the four platinum electrodes are placed. Panel B illustrates the principle of the algorithm. One second EEG epochs consistent with hypoglycemia give rise to integration kernels summing up over time until the integration curve reaches the predefined threshold of hypoglycemia. For details see Section 2.

At this time glucose (200 g/l) was infused until the patient recovered from all hypoglycemia related symptoms. The patients were allowed to eat and were observed in the clinic until the plasma glucose was stable without glucose infusion. EEG recordings continued 20–30 min after termination of insulin infusion.

Adrenaline, noradrenalin and glucagon were measured when plasma glucose was 6, 3 mmol/l and at the end of the insulin infusion period. Adrenalin and noradrenalin were measured by a 2 CAT RIA (Labor Diagnostika Nord GmbH & Co. KG, UK) and glucagon was measured by RIA [15].

To obtain measures of reproducibility, six of the study subjects volunteered to participate in a second study day. The procedures were identical with the first study day and the insulin infusion rate was adjusted to achieve a fall in blood glucose similar to that of the first study day.

2.1. *Algorithm for EEG analysis*

Before initiation of the present protocol, EEG was recorded during insulin-induced hypoglycemia in six type 1 diabetes patients. Data from these experiments were used to develop the automated algorithm applied in the present study. The purpose of the algorithm was to detect parts of the EEG consistent with the presence of hypoglycemia and was based on the Bayesian learning principle. These training examples were not the same as the experimental data presented in this manuscript, which ensured that the algorithm was not over-trained. The EEG from the pilot-experiments was analyzed manually by a neurophysiologist (PS) blinded to the timeline of the experiments. The task for the neurophysiologist was to label 1 s epochs of the EEG as ''EEG consistent or not-consistent with hypoglycemia''. A set of features was extracted from these EEG epochs, and fed into a parametric model alongside with the labels of each EEG epoch. The parametric model used, was a classic two layer neural network that used the hyperbolic tangency function to form a nonlinear response. The features extracted from the EEG were short-term (i.e. 1 s epochs) power estimations that were the outputs of a Fourier transformation and summarized in the four frequency bands (alpha, beta, gamma, and theta). Also noise indicators based on estimates of the maximum peak and the full band power were included. After training, the neural network was modeling the neurophysiologist's ability to determine epochs consistent with impending hypoglycemia. The final model thus includes estimates of frequency, power and amplitude and a noise indicator which rejected epochs with a high noise ratio. The noise detector rejected approximately 5% of the data. Since the mathematical model may occasionally misinterpret epochs of normal EEG as being consistent with hypoglycemia, a single or a few events should not trigger the models detection of impending hypoglycemia. Rather a number of events within a defined time window were assumed to predict hypoglycemia. A window in time that weights past epochs consistent with hypoglycemia was defined by integrating events weighted by a kernel with an initial value of one, a duration of 10 min and a linear decline to zero. This principle is illustrated in Fig. 1B. In the pilot studies the curve of integrated events was found never to exceed 20 during euglycemia while a steep increase above 20 was observed during periods of hypoglycemia. This value was therefore defined as the threshold value for hypoglycemia used in the present study.

After finalizing the present experiments, the EEG recordings were subjected to the automated quantitative analysis, determining the time at which the EEG changes exceed the predefined threshold. The primary variable in the study was defined as the time from the detection of hypoglycemia associated EEG changes above the threshold value by the mathematical algorithm to termination of insulin infusion. Time from EEG changes above the threshold to loss of cognition as judged by the cognitive tests was calculated, and in addition the reproducibility of the results was evaluated in the subgroup of patients participating in the second study day.

3. Results

The characteristics of the patients are given in Table 1. The patients were rather well controlled and all reported occasional hypoglycemia during everyday activity. Two patients were supplied with oral carbohydrate prior to implantation of the electrodes due to asymptomatic, biochemical hypoglycemia (plasma glucose 3.2 and 2.7 mmol/l). These two patients did not diverge from the rest of the study population in any variable. Fig. 2 shows a representative example of EEG during euglycemia (panels A and C) and during an episode of hypoglycemia (panels B and D). Fig. 3 shows the time course of plasma glucose during the study and the mean results of the backward-counting test and the serial-subtraction test. Time 0 define the termination of the insulin infusion. The duration of the insulin infusion ranged from 60 to 197 min. All patients had neuroglycopenia before termination of insulin infusion and all except one experienced autonomic symptoms occurring at a blood glucose of 2.5 mmol/l (range: 2.1–3.3 mmol/l). At termination of insulin infusion plasma glucose ranged from 1.6 to 2.7 mmol/l. Adrenaline and noradrenaline increased during hypoglycemia to values 11 and 2.5 times the basal levels respectively. In seven of the subjects glucagon increment was more than 2×SD from baseline values (mean value at baseline and end of study: 9.1 and 20.0 pmol/l), while the remaining eight subjects are defined as glucagon non-responders (mean value at baseline and end of study: 8.4 and 10.4 pmol/l). By the time at which the EEG changes

Table 1 – Patient characteristics.

	Mean	Median	Range
Age (years)	49	52	27–64
Weight (kg)	75	76	60–87
Height (m)	1.75	1.76	1.60–1.88
Sex (M/F)	9/6		
Duration of diabetes (years)	26.5	23	6–53
HbA1c (%)	7.2	7.2	5.6–8.3
Awareness status (1/2/3)[a]	5/8/2		

[a] Awareness status—1: always able to feel hypoglycemia, 2: usually or sometimes able to feel hypoglycemia, 3: never able to feel hypoglycemia.

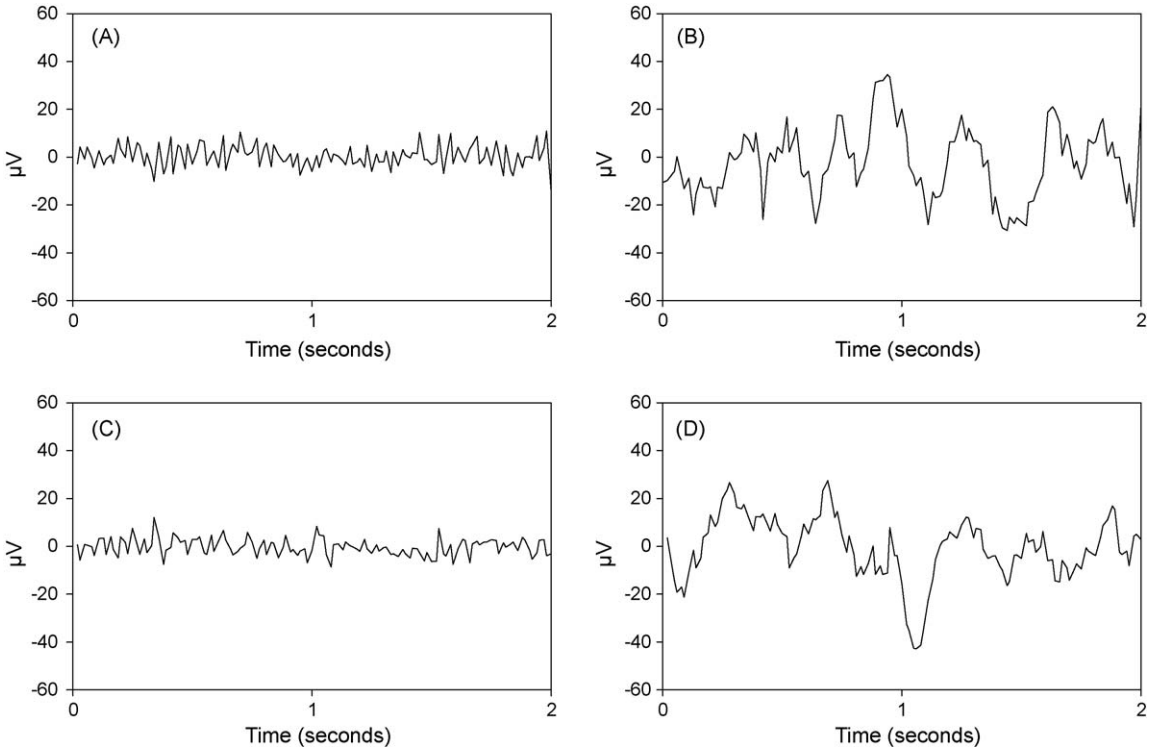

Fig. 2 – This figure shows representative examples of EEG recording during euglycemia (A and C) and during hypoglycemia (B and D). The panels A and B are from the same patient as are panels C and D. Mean values from the four inserted electrodes are shown. During hypoglycemia the appearance of slow frequency waves with larger amplitude are seen. Both amplitude and frequency measures are integrated in the mathematical algorithm.

exceeded the defined threshold, the plasma glucose ranged from 2.0 to 3.4 mmol/l and all patients were still able to do the backward-counting test with a full score. Ten patients scored 4 or 5 points in the serial-subtraction test, three patients did a score of one, one patient was unable to do the test while the test was not performed in the last patient since plasma glucose was above 3 mmol/l. From the time when EEG changes exceeded the threshold value to termination of insulin infusion, there was a marked fall in the performance in the serial-subtraction test from (mean) 3.3 to 0.8. The primary end point defined as the lead-time from EEG changes above the threshold value to termination of insulin infusion ranged from 3 to 113 min (mean ± SD = 29 ± 28 min). The time from EEG changes above the threshold value to a score less than two in the backward-counting test likewise ranged from 3 to 113 min (27 ± 29 min) while the time from EEG changes to a score less than three in the serial-subtraction test ranged from −4 to 73 min (16 ± 22 min). Thus three patients scored less than three before or at the time of EEG changes above the threshold value.

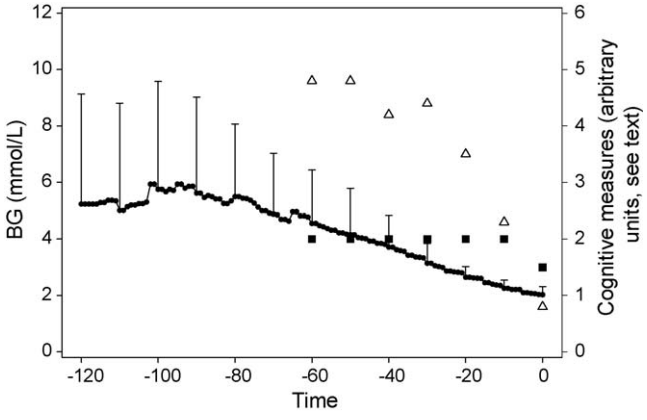

Fig. 3 – The figure shows the time course of plasma glucose (+SD) during the graded hypoglycemia as a mean value of all patients demonstrating a steady fall in blood glucose. Time 0 is defined as the time of glucose infusion. The figure also shows the results from the repeated cognitive testing (backward-counting test (■), serial-subtraction test (Δ)).

The curve of integrated events rapidly decreased after initiation of glucose infusion in all subjects and was normalized (under the threshold of 20) after (mean) 10.3 min in 14 of the 15 subjects (the last subject had a value of 24 when the EEG recording was ceased).

Representative examples of the experiment showing the integration curve, concomitant plasma glucose values and the time of EEG changes above the threshold value are shown in Fig. 4. Most of the experiments resembled the pattern in Fig. 4A with a prominent peak before the onset of severe hypoglycemia. Fig. 4B shows the patient with the shortest interval (3 min) between the time of EEG changes above the threshold value and termination of insulin infusion. This patient experienced a smaller peak approximately 30 min before but this peek did not meet the predefined threshold. Fig. 4C shows a patient with a peak of cumulated events occurring at a plasma glucose as high as 5.9 mmol/l. By this time the patient

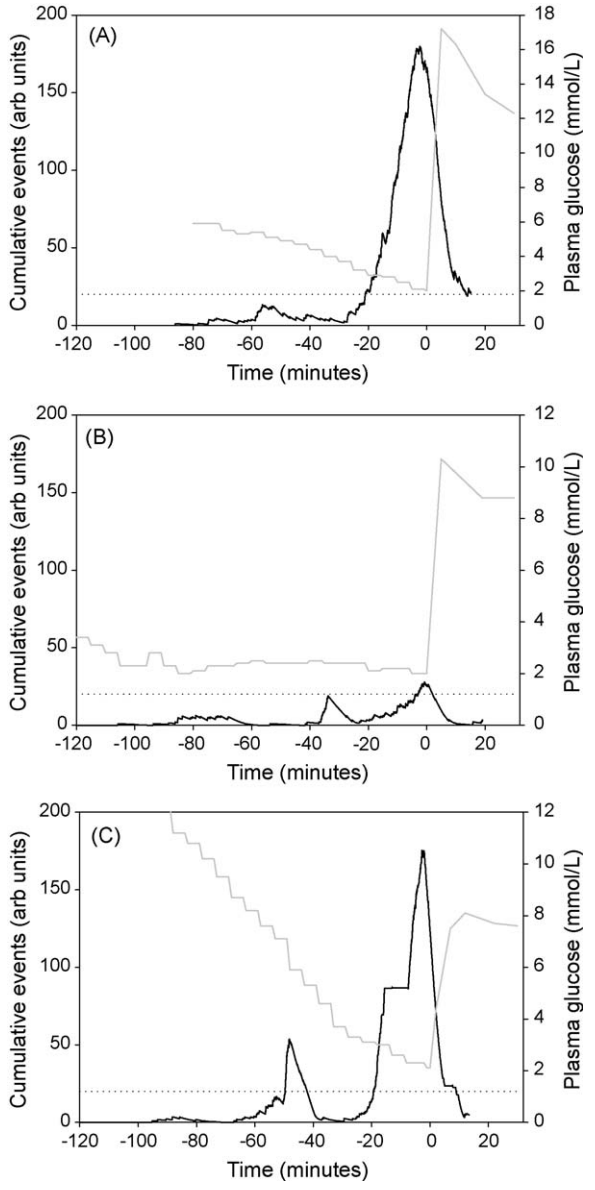

Fig. 4 – The figure shows three representative examples of experiments. Plasma glucose (gray line), the curve of cumulated events (black line) and the predefined threshold of EEG changes indicating hypoglycemia (dotted line) are shown. Time 0 denotes the start of glucose infusion. Note the immediate fall in integrated events following initiation of glucose infusion. For further details see Section 3. The horizontal part of the line in panel C represents linear interpolation in a period of data loss.

felt uncomfortable and experienced symptoms consistent with hypoglycemia. The patient, however, recovered from the episode despite further reduction in plasma glucose and developed symptoms of hypoglycemia and EEG changes above the threshold value when plasma glucose was 2 mmol/l.

Also in the subjects participating in the second study day all had EEG changes above the threshold value. The difference in plasma glucose at the time of EEG changes between the two experiments were (mean) 0.25 mmol/l (range 0.0–0.5 mmol/l) and the mean intra-individual coefficient of variation (CV) was 8% compared to a mean interindividual CV in the whole group of 14%. The blood glucose at EEG changes above the threshold value at the two study days correlated significantly ($r^2 = 0.82$, $p = 0.046$ (Spearmanns correlation test)).

There was no correlation between the primary variable and the age of the patient, the diabetes duration, the overall diabetes regulation as measured by the HbA1c or the rate of glucose fall during the last 15 min of insulin infusion (all $p > 0.1$). Also there was no difference in the primary variable between the glucagon responders and the non-responders ($p > 0.5$).

4. Discussion

This is the first study to demonstrate that hypoglycemia associated EEG changes recorded by subcutaneous electrodes and processed by an automated algorithm precede development of severe cognitive dysfunction in type 1 diabetic patients. Hypoglycemia associated EEG changes exceeded a predefined threshold between 3 and 113 min before the patients were severely cognitive impaired as assessed by simple cognitive testing and a general clinical evaluation. In 14 out of 15 patients this time interval was 9 min or more. These observations parallels the findings by Howorka et al. [16] demonstrating increased occurrence of slow wave activity before worsening of cognitive performance. If an alarm was given at the time of EEG changes above the threshold value, this would, in most cases, allow the patients to ingest carbohydrates and thus potentially avoid an episode of severe hypoglycemia. The participants in the study were well controlled with a mean HbA1c of 7.2%. They all had a history of recurrent or severe hypoglycemia and many of the patients suffered from unawareness. Thus they represent the group of patients being candidates for a permanent hypoglycemia alarm.

EEG changes in the parieto-occipital and temporal area with reduced alpha activity and increased slow wave activity during hypoglycemia have previously been demonstrated using scalp electrodes [12,13]. These changes appear at a median blood glucose concentration of 2.3 mmol/l [12]. In agreement with these observations, we found that EEG changes above the threshold value occurred at a plasma glucose ranging from 2.0 to 3.4 mmol/l. A history of severe and repeated hypoglycemia is associated with permanent occurrence of slower frequencies in the EEG which may interfere with the interpretation of the signals and potentially give rise to false positive alarms or reduced sensitivity of the algorithm [17,18]. False positive alarms would not be harmful per se but will certainly be annoying to the patients and may, in addition, cause a reduced alertness to the alarm. Increased delta-activity seen in diabetes patients during normoglycemia is, however, primarily located in the frontal regions thus being distant away from the location of the electrodes used in our study [19]. We recorded more than 24 h of EEG before clinical hypoglycemia occurred and recorded only one episode consistent with a false positive alarm. As described above, this occurred during a period of discomfort for the patient. The present study was, however, not designed to address this issue of specificity.

The primary variable in our study was defined as the time from EEG changes exceeding a predefined threshold value to termination of insulin infusion. Insulin infusion was terminated when the patient was obviously affected by the hypoglycemia. We defined this time-point by a combination of the cognitive tests and a general evaluation of the patients including alertness, speech velocity and concentration and without knowledge of the time of EEG changes, which was analyzed post hoc. To our best judgment we stopped the insulin infusion and started glucose infusion when it would have been "just too late" to receive an alarm. We acknowledge that the definition of this time-point is crucial to the sensitivity of the experiment and that it is somewhat arbitrary. In 14 out of the 15 patients, however, the time from EEG changes above the threshold value to termination of insulin infusion was 9 min or more. In one patient this interval was only 3 min, and it can be questioned if this study subject would have been able to react adequately at the time of EEG changes. Whether the patients will in fact be able take appropriate action at the time of EEG changes above the threshold value, will be a subject for future studies.

To assess reproducibility of the results, a subgroup of the subjects was subjected to an additional study day with identical study procedures. These results indicate an individual set point of EEG changes. Thus the mean intra-individual CV of blood glucose at the time of EEG changes above the threshold value was as low as 8%.

It has been implicated that nocturnal hypoglycemia-induced EEG changes are only present in patients with impaired glucagon response [11]. In our study eight of 15 patients had reduced or absent glucagon response during hypoglycemia using the same definition. These patients did not differ from the responders with respect to the primary variable and EEG changes were detected in all subjects. This discrepancy may be due to the fact that we studied hypoglycemia during daytime and not nocturnal events or, alternatively, to a different signal processing. Nocturnal events are obviously of highest clinical relevance and will be the subject of further studies.

In conclusion the study presents the first steps in the development of an alarm which can be used by type 1 diabetes patients suffering from recurrent hypoglycemia and unawareness. The lead-time from EEG changes above the threshold value to severe cognitive dysfunction is, in most cases, presumably long enough for the patient to correct hypoglycemia. The use of subcutaneous electrodes provides an alternative to surface electrodes which makes promises for the development of a device that can be carried during everyday activities.

Conflicts of interests

The authors have a competing interest to declare. Rasmus Elsborg is fulltime employed in Hyposafe A/S. Henning Beck-Nielsen is chairman of the board and holds stock in Hyposafe A/S. Claus B. Juhl, Kurt Højlund, Mikael Kjær Poulsen and Peter Selmar receive consultant fees from Hyposafe A/S. Claus Christiansen is CEO in Nordic Bioscience, an investor in Hyposafe A/S.

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