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SHORT COMMUNICATION

Cardiac arrhythmia and nocturnal hypoglycaemia in type 1 diabetes—the 'dead in bed' syndrome revisited

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Abstract
Aims/hypothesis Sudden nocturnal death in type 1 diabetes ('dead in bed' syndrome) is thought to be due to ECG QT prolongation with subsequent ventricular tachyarrhythmia in response to nocturnal hypoglycaemia. We investigated this theoretical mechanism using continuous ECG and continuous glucose monitoring in a group of patients with type 1 diabetes.
Methods Twenty-five patients with type 1 diabetes (age 20–50 years) underwent two separate 24 h ECG and continuous glucose monitoring periods. Patients were fully ambulant and carried out normal daily activities.
Results There were 13 episodes (26% of recordings) of nocturnal hypoglycaemia, eight of <2.2 mmol/l and five of 2.2–3.4 mmol/l. Corrected QT interval (QTc) was longer during nocturnal hypoglycaemia compared with normoglycaemic control periods (445±40 vs 415±23 ms; p=0.037). Cardiac rate and rhythm disturbances (excluding sinus tachycardia) were seen in eight of the 13 nocturnal hypoglycaemia episodes (62%). These were sinus bradycardia (<40 beats/min; three episodes), ventricular ectopics (three episodes), atrial ectopics (one) and P wave abnormalities (one).
Conclusions/interpretation This study demonstrates QTc prolongation and cardiac rate/rhythm disturbances in response to episodes of nocturnal hypoglycaemia in ambulant patients with type 1 diabetes. This may support an arrhythmic basis for the 'dead in bed' syndrome.

Keywords Cardiac arrhythmia · Dead in bed syndrome · Nocturnal hypoglycaemia · Type 1 diabetes

Abbreviations

CGM	continuous glucose monitoring
CGMS	continuous glucose monitoring system
QTc	QT interval corrected for heart rate

Introduction

In 1991, Tattersall and Gill [1] defined a newly reported syndrome of sudden nocturnal death in young people with type 1 diabetes, which subsequently became known as the 'dead in bed' syndrome, and was described similarly afterwards in countries outside the UK [2]. Patients were all found dead in undisturbed bedclothes with no sign of sweating or struggle, had been well the previous day, and the autopsy was negative in all cases. Many patients had had recent nocturnal hypoglycaemic attacks, and it became widely postulated that the mode of death was likely to be cardiac arrhythmia precipitated by hypoglycaemia [1, 2].

More recently, it has been demonstrated that hypoglycaemia in type 1 diabetic patients (both induced and spontaneous) is associated with prolongation of the ECG QT interval, which is known to predispose to ventricular tachyarrhythmia [3, 4]. Hypoglycaemia is also associated with raised plasma catecholamine levels and lowering of serum potassium [3, 4], both of which may augment the arrhythmogenic effect of QT prolongation.

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Though the hypoglycaemia/arrhythmia theory is an attractive explanation of the 'dead in bed' syndrome, direct evidence is lacking. We report here a real-life ambulatory observational study of a group of type 1 diabetic patients in whom we recorded simultaneous 24 h ECG and continuous glucose monitoring (CGM), aiming to capture nocturnal hypoglycaemic events and record QT interval and cardiac rhythm simultaneously.

Methods

Recruitment We recruited 25 patients with type 1 diabetes aged 20–50 years and with diabetes duration 5–20 years. We excluded patients with significant retinopathy (more than background), nephropathy, established macrovascular disease, and those on drugs likely to affect cardiac function or rhythm, in particular beta blockers and tricyclic drugs.

Baseline assessment All patients had a baseline 12-lead ECG (M1705B; Hewlett Packard, Palo Alto, CA, USA), and serum potassium, calcium and magnesium were measured. A standard five-point package of cardiovascular autonomic function tests [5] was also performed. This included the response to the Valsalva manoeuvre, deep breathing, standing (heart rate and blood pressure) and hand grip. Patients were instructed to avoid strenuous exercise, drinks containing caffeine, alcohol and cigarettes for 12 h prior to the tests. They were also advised to avoid eating for 2 h before the tests. A capillary glucose level of >4.0 mmol/l was required immediately prior to testing.

Monitoring Each patient then underwent two separate 24 h monitoring sessions (6 weeks apart) during which they were attached to a 24 h ECG monitor with continuous QTc (QT interval corrected for heart rate) measurement (Pathfinder 700 Issue 7.203 continuous QTc analyser; Del Mar Reynolds, Hertford, UK). At the same time they were linked to a simultaneous and time-synchronised continuous glucose monitoring system (CGMS) using MMT-7002 sensors (both supplied by Medtronic MiniMed, Minneapolis, MN, USA). This CGMS has been shown to be clinically accurate, with a correlation coefficient of 0.85 between CGM glucose and separately measured blood glucose levels. The mean absolute difference between sensor and meter glucose values was 18.4% vs 16.1%, and the Bland–Altman analysis showed a median bias of −0.1 (range −1.4 to 1.1) [6]. The system has also been shown to be accurate at hypoglycaemic levels [7]. The CGMS was calibrated in a standard way as recommended by the manufacturer, using four validated self-monitored blood glucose levels during the 24 h monitoring periods. The period of monitoring began at 17:00 hours, and patients returned to have the monitoring equipment detached 24 h later. During this period they undertook normal activities at home and at work, and took their usual dietary and insulin regimens. A total of fifty 24 h electrocardiograph and 49 CGM (one lost due to technical reasons) recordings were completed in the 25 patients.

Analysis Nocturnal hypoglycaemia was defined as a glucose level below 3.5 mmol/l during sleeping (between 23:00 and 08:00 hours). QTc was analysed throughout the entire hypoglycaemic period, and expressed as mean QTc. A control period was analysed for QTc similarly; this was a normoglycaemic period (glucose >5.0 mmol/l) of identical duration to the hypoglycaemic episode, immediately prior to hypoglycaemia. Statistical analysis was performed using StatsDirect Biomedical Software (StatsDirect, Sale, UK). Mean QTc (±1 SD) was compared for the hypoglycaemic and non-hypoglycaemic periods using Student's paired *t* test.

All patients gave informed consent to participation in the study. Ethical approval was obtained from the Liverpool Local Research Ethics Committee.

Results

Patient details The 25 patients all had type 1 diabetes; 13 (52%) were female, age (mean±SD) was 36±7 years and diabetes duration 13±6 years. HbA_{1c} was 8.3±1.2%. There were 21 (84%) on four times daily and four (16%) on twice daily insulin regimens. Twenty (80%) were on analogue insulin (including 16 [64%] on long-acting analogues).

Baseline assessment Twelve-lead ECG and measurements of serum potassium, calcium and magnesium were normal in all patients. The standard five-point autonomic function tests were normal in 23 of the 25 patients. Two showed early autonomic damage (two out of the five autonomic tests were abnormal). Interestingly, both patients experienced episodes of nocturnal hypoglycaemia.

Nocturnal hypoglycaemia Eight patients experienced nocturnal (23:00–08:00 hours) hypoglycaemia with a CGM level <2.2 mmol, and a further five had levels <3.5 but >2.2 mmol/l. The episodes occurred between 23:25 and 07:50 hours, and the duration of hypoglycaemia ranged from 30 to 150 min (mean 68 min). Overall therefore, 13 (52%) patients had nocturnal hypoglycaemia, and the rate for the 50 recordings was 13/50 or 26%.

QT interval During the 13 episodes of nocturnal hypoglycaemia, QTc (mean±SD) was 445±40 ms vs 415±23 ms

Table 1 Abnormalities of cardiac rate or rhythm observed during 13 nocturnal hypoglycaemia episodes

Abnormality	Number of episodes (*n*)
Ventricular ectopics[a]	3
Sinus bradycardia (<40 beats/min)[b]	3
Atrial ectopics	1
P wave abnormalities[c]	1

[a] Including one couplet of ectopics (see Fig. 1)
[b] A further two patients had variable bradycardia/tachycardia during hypoglycaemia, including rates <60 but more than 40 beats/min
[c] See Fig. 1

for the normoglycaemic (>5.0 mmol/l) control period of similar duration prior to the hypoglycaemic episode. The QTc prolongation during hypoglycaemia was statistically significant (12 *df*, t=2.350, p=0.037).

Rate and rhythm disturbances One patient had sustained ventricular bigeminy on both recordings, with no hypoglycaemia. The patient underwent full cardiological assessment, and the bigeminy was felt to be benign, but the patient was excluded from further analysis (leaving 48 recordings). Abnormalities of rate and/or rhythm (not seen during normoglycaemia) were observed in eight of the 13 episodes of nocturnal hypoglycaemia (62%) (sinus tachycardia during hypoglycaemia was considered a normal response) (Table 1). These abnormalities included ventricular ectopics (three patients), sinus bradycardia <40 beats/min (three patients), atrial ectopics (one patient) and P wave abnormalities (one patient). Examples are shown in Fig. 1, and include a patient with a couplet of multifocal ventricular ectopic beats during hypoglycaemia, following a QTc interval of 560 ms. None of these abnormalities were seen during normoglycaemia with the exception of the patient with P wave abnormalities. These occurred consistently during nocturnal hypoglycaemia, but a short run was seen in one normoglycaemic period.

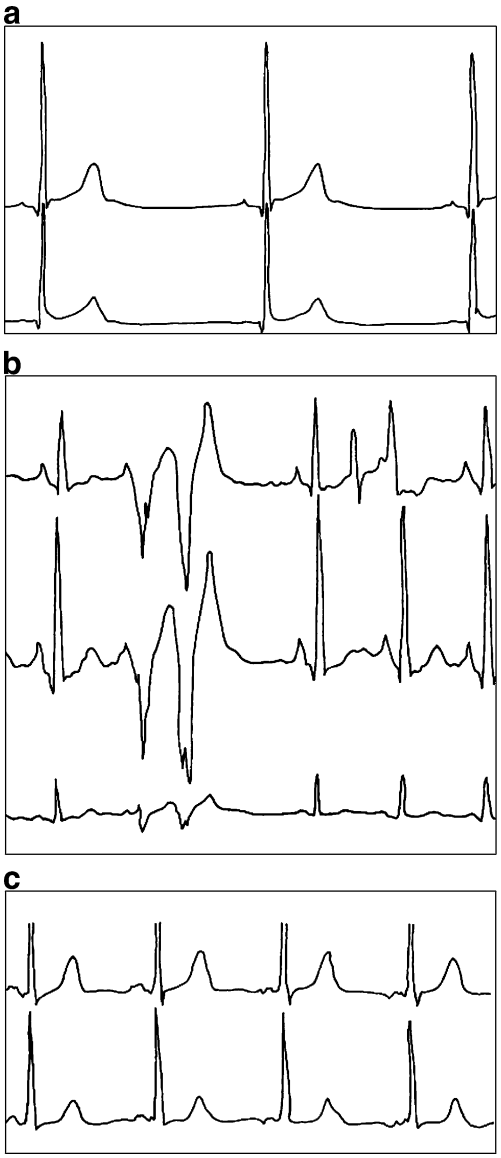

Fig. 1 Examples of hypoglycaemia-related ECG abnormalities. **a** Sinus bradycardia (31 beats/min) recorded at 06:10 hours with a CGM of 3.1 mmol/l, having been <2.2 mmol/l from 04:40 to 05:15 hours. **b** Couplet of multifocal ventricular ectopic beats recorded at 01:20 hours, and preceded by a QTc interval of 560 ms. The CGM level at the time was 3.4 mmol/l, but this had varied between 2.9 and 3.2 mmol/l for some time before. **c** Variable P wave structure, recorded at 04:30 hours with a CGM of 2.3 mmol/l. The patient continued at or below this level for a further 90 min

Discussion

We believe that this study has, for the first time, demonstrated ECG abnormalities during nocturnal hypoglycaemia in patients with type 1 diabetes in a real-life ambulant situation. As with other studies, we found nocturnal hypoglycaemia to be common [8], and many episodes were severe and prolonged. Arrhythmias and/or ECG abnormalities have been recorded during hypoglycaemia in patients with diabetes, either accidentally observed or during induced hypoglycaemia. These include ventricular ectopics and S–T depression [9], though this study involved only participants with type 2 diabetes and occult coronary artery disease is difficult to exclude.

In our patients, eight out of the 13 episodes of nocturnal hypoglycaemia recorded were associated with ECG abnormalities—mostly ventricular or atrial ectopics, and (perhaps surprisingly) profound sinus bradycardia. Interestingly, one patient in the study referred to above (induced hypoglycaemia in patients with type 2 diabetes) developed severe bradycardia during hypoglycaemia. Three of our patients

developed rates below 40 beats/min during hypoglycaemia, and one (Fig. 1a) had a rate as low as 30 beats/min. A recent review of QT prolongation and torsades de pointes in patients who did not have diabetes has shown bradycardia to be a risk factor [10]. Three of our patients had ventricular ectopics, and perhaps the most concerning was the patient shown in Fig. 1b, in whom a multifocal couplet occurred after a much widened QTc interval of 560 ms. Interestingly, this occurred during the recovery phase (CGM 3.4 mmol/l) of a more severe hypoglycaemic event. The significance of the unusual changes in P wave morphology (Fig. 1c) is uncertain.

Though we used only standard autonomic function tests, it is of interest that both patients with early abnormalities experienced nocturnal hypoglycaemia, though of course the numbers were very small and this could be coincidental. Our patients may have had minor or earlier degrees of autonomic neuropathy that were not detected by our standard cardiovascular tests. Autonomic neuropathy itself can be associated with QTc lengthening and possibly sudden death [2], and a recent study has found QTc prolongation to be common in adolescent patients with type 1 diabetes with early autonomic dysfunction [11]. Autonomic neuropathy has also been proposed as a factor predisposing to the ‘dead in bed’ syndrome [2].

We accept that our study has limitations. Patient numbers were relatively small; ideally, larger confirmatory trials should be performed. Though we tried to select a group of type 1 diabetic patients who were relatively free of complications, it is possible that some of the older participants and those with a longer disease duration could have had occult or undiagnosed coronary artery disease. CGM systems may be less accurate than direct measurement of glucose, though the CGMS we used has been validated at low glucose levels [7].

Nevertheless, our research has confirmed that QTc lengthening and ECG abnormalities occur during naturally occurring nocturnal hypoglycaemia in patients with type 1 diabetes. This appears to lend support to a cardiac basis of the ‘dead in bed’ syndrome and indicates the need for replication in a larger-scale trial.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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