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Risk of Cardiac Arrhythmias During Hypoglycemia in Patients With Type 2 Diabetes and Cardiovascular Risk

Recent trials of intensive glycemic control suggest a possible link between hypoglycemia and excess cardiovascular mortality in patients with type 2 diabetes. Hypoglycemia might cause arrhythmias through effects on cardiac repolarization and changes in cardiac autonomic activity. Our aim was to study the risk of arrhythmias during spontaneous hypoglycemia in type 2 diabetic patients with cardiovascular risk. Twenty-five insulin-treated patients with type 2 diabetes and a history of cardiovascular disease or two or more risk factors underwent simultaneous continuous interstitial glucose and ambulatory electrocardiogram monitoring. Frequency of arrhythmias, heart rate variability, and markers of cardiac repolarization were compared between hypoglycemia and euglycemia and between hyperglycemia and euglycemia matched for time of day. There were 134 h of recording at hypoglycemia, 65 h at hyperglycemia, and 1,258 h at euglycemia. Bradycardia and atrial and ventricular ectopic counts were significantly higher during nocturnal hypoglycemia compared with euglycemia. Arrhythmias were more frequent during nocturnal versus daytime hypoglycemia. Excessive compensatory vagal activation after the counterregulatory phase may account for bradycardia and associated arrhythmias. QT intervals, corrected for heart rate, >500 ms and abnormal T-wave morphology were observed during hypoglycemia in some participants. Hypoglycemia, frequently asymptomatic and prolonged, may increase the risk of arrhythmias in patients with type 2 diabetes and high cardiovascular risk. This is a plausible mechanism that could contribute to increased cardiovascular mortality during intensive glycemic therapy.

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Intensive glycemic control improves microvascular outcomes, but whether the approach reduces macrovascular events is less clear (1). Intensive glycemic control for between 3 and 5 years did not reduce cardiovascular mortality in recent trials (2,3) and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was terminated early owing to increased mortality in patients with type 2 diabetes at high cardiovascular risk (4). It is well-known that intensive glycemic control increases the risk of hypoglycemia. Hypoglycemia was strongly associated with an increased downstream risk of vascular events and death (5), but evidence of a direct causal link is lacking.

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There have been sporadic case reports of supraventricular and ventricular arrhythmias associated with hypoglycemia. Among supraventricular arrhythmias, transient atrial fibrillation is most frequently reported (6). There have also been a number of reports of bradycardia during severe hypoglycemia in diabetic and nondiabetic patients (7). In a study of experimental hypoglycemia in six patients with type 2 diabetes and no cardiac disease, one patient developed a severe bradyarrhythmia and another developed frequent ventricular premature beats (VPBs) (8). Reports of ventricular arrhythmias associated with hypoglycemia are rare, perhaps because events are generally fatal if uncorrected.

Hypoglycemia may be proarrhythmic via a number of mechanisms (9). The direct effect of low glucose on the human Ether-à-go-go Related Gene ion channel (10), hypokalemia, and catecholamine release prolong cardiac repolarization, increasing the risk of early afterdepolarizations and ventricular arrhythmias. We have previously shown that experimental hypoglycemia prolongs the QT interval in individuals with type 1 and type 2 diabetes (11). Since arrhythmias can be triggered by a transient change in sympathovagal balance, it also seems worthwhile exploring the effect of hypoglycemia on autonomic tone. Previous studies have reported inconsistent effects of acute experimental hypoglycemia on cardiac autonomic activity (12,13). We have previously shown that cardiac autonomic neuropathy (CAN) may modify the relationship between hypoglycemia and cardiac repolarization (14).

The aim of this study was to examine the frequency of arrhythmias during spontaneous hypoglycemia and hyperglycemia versus euglycemia in patients with type 2 diabetes and cardiovascular risk. The effect of glucose on cardiac autonomic tone and repolarization were further explored as potential mechanisms.

RESEARCH DESIGN AND METHODS

Twenty-five individuals with type 2 diabetes on insulin treatment for at least 4 years were recruited from Sheffield Teaching Hospitals diabetes outpatient clinics. All had a history of cardiovascular disease (CVD) (ischemic heart disease or peripheral vascular or cerebrovascular disease) and/or two additional cardiovascular risk factors: hypertension, dyslipidemia (both defined as requiring medication), current smoking, and obesity. Those on QT prolonging drugs were excluded. All patients with permanent atrial fibrillation or bundle branch block on baseline electrocardiogram (ECG) were excluded from the study. Written informed consent was obtained from all participants. The study received local ethics approval.

Baseline Assessment

Cardiovascular autonomic reflex tests were performed as previously described (15) in accordance with the latest consensus on diagnosis of CAN (16). Patients were instructed to avoid vigorous exercise, caffeine, and smoking 12 h prior to morning testing. All patients had a capillary glucose test of >4 mmol/L at the time of autonomic function testing. Patient status was classified as definite CAN if two or more cardioreflex tests were below the age-adjusted reference range (16,17). Glycated hemoglobin A_{1c} (HbA_{1c}) was measured using ion-exchange high-performance liquid chromatography.

Monitoring

All patients underwent 5 days of simultaneous 12-lead Holter and continuous interstitial glucose (IG) monitoring (CGM). Patients carried on with their usual daily activities and diabetes treatments. Twelve-lead ambulatory ECGs (Lifecard 12; Spacelabs Healthcare, Hertford, U.K.) were recorded at a sampling rate of 128 Hz with electrodes in a Mason-Likar configuration. Patients also had a time-synchronized CGM attached (FreeStyle Navigator Continuous Glucose Monitoring System; Abbott Diabetes Care, Maidenhead, U.K.). Calibrations were performed at least four times during the study week according to the manufacturer's instructions. Mindful of the limitations of CGM, we selected a system that has been reported to follow the descent in blood glucose to the hypoglycemic nadir (18), with the lowest detection limit of 1.1 mmol/L (20 mg/dL). In published data (19), the mean absolute difference between this CGM system and blood glucose was 0.7 mmol/L (12.7 mg/dL) when CGM glucose was <3.9 mmol/L (70 mg/dL) and the rate of change was between −1 and 1 mg/dL/min. The rate of change of 93% of our hypoglycemic data fell within this limit. Predictive alarms were switched off, and participants were instructed not to view CGM glucose values except during calibrations. Patients were also asked to keep a record of any symptomatic hypoglycemia. An episode of low IG (<3.5 mmol/L) on CGM without simultaneous self-report of symptoms was regarded as asymptomatic.

CGM Analysis

The IG was measured every minute by the CGM, and 10-min averages were reported (CoPilot Health Management; Abbott Diabetes Care). Hypoglycemia was defined as IG ≤3.5 mmol/L in accordance with previously published studies (20,21), and hyperglycemia was defined as IG ≥15 mmol/L. A valid hypoglycemic episode consists of IG below the threshold for ≥20 min (22). The first reading of IG ≤3.5 mmol/L marked the start of the hypoglycemia, and the first reading of IG ≥3.5 mmol/L signified the end of the episode (21). The lowest IG within the hypoglycemic episode was designated the glucose nadir. Each episode was matched with a euglycemic period, equivalent in duration, at the same time of day (within 20 min) on a different day. Similarly, valid hyperglycemic episodes were identified at IG above the 15 mmol/L threshold for >20 min. The highest IG within the episode was designated as the maxima, and matched euglycemic periods on a different day were identified.

Arrhythmia Analysis

The 12-lead ambulatory ECG data were analyzed with the Pathfinder Ambulatory ECG analysis system (version 8.701; Del Mar Reynolds Medical Ltd., Hertford, U.K.). Leads I, II, and V5 were used for analysis, as they represented orthogonal leads. Normal and aberrant beats were labeled by the Pathfinder system with preset sensitivity to optimize the trade-off between preserving useful information versus eliminating artifacts. The ECG was manually screened for gross arrhythmias. The software automatically detected arrhythmic events according to predetermined event definitions (Supplementary Data). These included atrial ectopic beats, bradycardia (defined as ≥4 consecutive beats at <45 bpm), VPBs, and complex VPB (bigeminy, trigeminy, couplet, Salvos, and ventricular tachycardia). All identified arrhythmic events were manually verified for accuracy. Investigators were blinded to glucose values during arrhythmia analysis. Hourly counts for each type of arrhythmia were paired against hourly mean IG, which was categorized into hypoglycemia (IG ≤3.5 mmol/L), hyperglycemia (IG ≥15 mmol/L), and euglycemia (5 mmol/L < IG < 10 mmol/L). Analyses were separated into day and night (2300–0700 h) to take into account diurnal variation.

Heart Rate Variability Analysis

R-R intervals were extracted from annotated normal beats (NN intervals) using the Pathfinder Ambulatory ECG analysis system. A 5-min segment of successive NN intervals was selected around each reported IG value, and spectral analysis was performed on each segment using the Fourier transform. Spectral analysis was performed in accordance with recommendations of the Taskforce on Heart Rate Variability (23). The low-frequency (LF) band was defined as 0.04–0.15 Hz and high-frequency (HF) band as 0.15–0.4 Hz. The ratio between the LF power and total power (LF + HF power) was calculated (LF_{norm}), which was previously suggested to indicate the level of sympathetic modulation in heart rate variability (HRV) (24,25).

Repolarization Analysis

Analysis of QT intervals was performed using custom-built, semiautomatic software based on a selective beat averaging approach (26). Annotated normal ECG beats were identified using the Pathfinder system. On each lead, a 40-Hz high pass filter was implemented to reduce noise. Cubic spline interpolation was then applied to remove LF baseline wander without affecting the higher-frequency ECG components. A composite wave was generated from the orthogonal leads I, II, and V5 to represent global repolarization. Analysis of the composite wave was performed on a 5-min window centered on each IG value. Within this window, beats with stable preceding heart rate were selected to respect restitution properties of ventricular repolarization. Namely, beats with a preceding R-R interval within ±15 ms and a second preceding R-R interval within ±50 ms of the prevailing mean R-R across the 5-min segment were averaged. The composite wave was then calculated from averaged beats derived from leads I, II, and V5. On the composite wave, the onset of the Q wave was marked as the first positive deflection from the isoelectric line >10 microvolts. The end of the T wave was determined using the tangent method, where the tangent to the steepest downslope of the T wave crosses the isoelectric line. All median beats were manually reviewed and fiducial points adjusted if necessary by two independent observers blinded to glucose values. Further, all T waves were manually classified as normal, notched, or fusion according to predetermined criteria (27). QT intervals were corrected for heart rate (QTc) using subject-specific regression formulae generated from QT/R-R values during euglycemia (28).

Statistical Analysis

This was an observational study, and thus no power calculations were performed. The numbers chosen were based upon an assessment of the number of patients it was possible to examine given the constraints on recruitment and projected hypoglycemia rates. Data were inspected for normality. Data that followed an approximate normal distribution were summarized using mean ± SD, while skewed data were summarized using the median (IQR). We compared demographic data between patients who experienced at least one hypoglycemic episode and those who experienced none by the independent *t* test, Mann-Whitney *U* test, or Fisher exact test for effect of insulin regimen and insulin type on hypoglycemia. We used the generalized estimated equations approach to investigate the effect of glycemic status on arrhythmia counts while taking into account correlated measurements from individuals who experienced more than one episode of hypoglycemia or hyperglycemia. The Poisson model, which is usually used in analyzing count data, is not optimal in the current case, as there were many individuals who did not experience arrhythmic events. For this reason, data were fitted with a negative binomial model that takes into account the exposure time and individuals experiencing no arrhythmic events. A first-order autoregressive correlation structure was applied to adjust for within-individual correlation. Exponentiated regression coefficients represent incident rate ratios (IRRs). The IRRs of arrhythmias during hypoglycemia and hyperglycemia compared with euglycemia were calculated. HRV parameters and corrected QT intervals (QTc) were compared at the glucose nadir of the hypoglycemic or glucose maxima of the hyperglycemic episode against an equivalent euglycemic time point on a different day. Where there was more than one matching hypoglycemic-euglycemic episode in an individual participant over the course of the recording period, the mean from all daytime and

nocturnal episodes from that individual was taken. Data were analyzed using a paired *t* test. Statistical analysis was performed with SPSS (version 19.0; IBM, Chicago, IL). A *P* value ≤0.05 was deemed statistically significant.

RESULTS

Participant Characteristics

A total of 2,323 h of valid simultaneous ECG and glucose recordings were obtained from 25 patients. Participants were similar in age, BMI, and prevalence of cardiovascular risk to the population in ACCORD, with a history of CVD in one-third (29) (Table 1). Two of 25 patients were on cardioselective β-blockade. Of 25 patients, 14 experienced at least one episode of hypoglycemia and 12 experienced at least one episode of hyperglycemia. Demographic data, duration of diabetes, and prevalence of CVD were similar between patients who experienced hypoglycemia versus those who did not (Table 1). However, a higher proportion of patients who experienced hypoglycemia were on biphasic and human insulins (Table 1). The duration of insulin therapy and baseline QTc were slightly longer in those who experienced hypoglycemia, but the difference did not reach statistical significance.

Glucose Profiles During Hypoglycemia

In total, there were 134 h of recording at hypoglycemia and 1,258 h at euglycemia, with the remainder outside this range. We analyzed 20 matched day hypoglycemic episodes in 11 participants and 14 matched nocturnal episodes from 10 participants. There were diurnal differences in the duration and depth of hypoglycemia. The mean ± SD duration of daytime episodes was 62 ± 42 min, whereas the mean duration of nocturnal episodes was prolonged at 170 ± 112 min with a lower glucose nadir (1.9 ± 0.7 mmol/L vs. 2.8 ± 0.5 mmol/L). At night, glucose exhibited an undulating profile in contrast to daytime hypoglycemia where there was a single descent to the nadir followed by brisk counterregulation (Fig. 1). Of 34 hypoglycemic episodes that were identified by CGM, 3 were symptomatic.

Arrhythmias

We compared the incident rate of arrhythmias during hypoglycemia versus euglycemia. The minimum heart rate observed during nocturnal hypoglycemia was 34 bpm, with the longest bradycardic period being 156 consecutive beats. Bradycardia was eightfold higher during nocturnal hypoglycemia compared with euglycemia (IRR 8.42 [95% CI 1.40–51.0]) (Table 2). Bradycardia did not occur during the day under either glycemic

Table 1—Comparison of participant characteristics between those who experienced hypoglycemia and those who did not

	Total	Hypoglycemia	No hypoglycemia	*P*
n	25	14	11	
Age (years)	64 (61–71)	68 (59–74)	64 (60–66)	0.26
Male, *n* (%)	13 (52)	8	5	0.82
Duration of diabetes (years)	17 ± 6	18 (12–21)	17 (15–21)	0.76
Duration on insulin (years)	9 ± 5	10 (7–16)	7 (5–11)	0.14
Insulin regimen				0.12
Twice daily biphasic, *n* (%)	14 (56)	10	4	
Basal-prandial, *n* (%)	11 (44)	4	7	
Insulin type				0.02
Human, *n* (%)	18 (72)	13	5	
Analog, *n* (%)	7 (28)	1	6	
BMI (kg/m^2)	32 ± 5	33 ± 6	32 ± 4	0.49
HbA_{1c}				
%	7.5 ± 1.0	7.4 ± 1.2	8.1 ± 1.0	0.15
mmol/mol	58.0 ± 10.9	57.0 ± 13.1	65.0 ± 10.9	
SBP (mmHg)	142 ± 23	141 ± 26	143 ± 20	0.83
DBP (mmHg)	72 ± 9	72 ± 10	72 ± 9	0.99
HR (bpm)	74 ± 11	76 ± 12	73 ± 11	0.51
Baseline QTc (ms)	434 ± 23	437 ± 25	425 ± 16	0.20
CVD, *n* (%)	8 (32)	5	3	0.65
CAN, *n* (%)	4 (16)	3	1	0.40

Data are means ± SD or median (interquartile range) unless otherwise indicated. *P* value indicates comparison of participant characteristics between hypoglycemia and no hypoglycemia groups via parametric or nonparametric testing. DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.

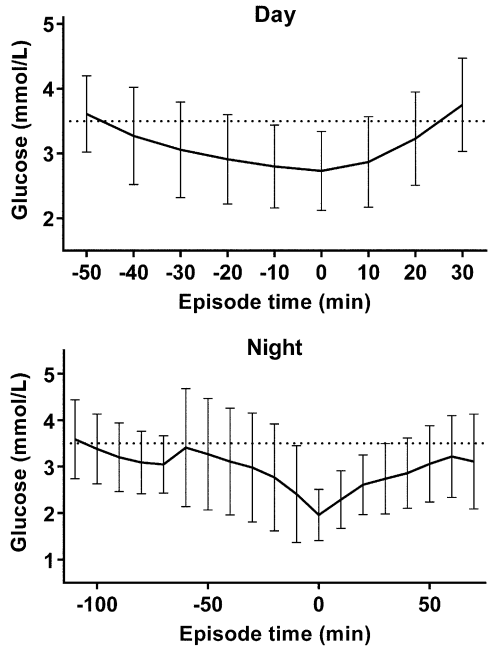

Figure 1—Mean IG values during day versus nocturnal hypoglycemic episodes. Mean IG profiles are shown for 20 daytime episodes from 11 participants and 14 nocturnal episodes from 10 participants. The mean duration of daytime hypoglycemia was 62 ± 42 min with mean IG at the nadir 2.8 ± 0.5 mmol/L. The mean duration of nocturnal hypoglycemia was 170 ± 112 min with mean IG at the nadir 1.9 ± 0.7 mmol/L. The hypoglycemic nadir is shown as episode time 0, with negative time values indicating change from the beginning of the hypoglycemic episode and positive values from the nadir to recovery from hypoglycemia. Data are means ± SD.

condition. Atrial ectopic activity was nearly fourfold higher during nocturnal hypoglycemia (3.98 [1.10–14.4]) but was not significantly different during daytime episodes. VPBs were more frequent during hypoglycemia both day (1.31 [1.10–1.57]) and night (3.06 [2.11–4.44]), but there were no differences in incidence of complex VPBs. Some examples of arrhythmias include sinus bradycardia with ventricular bigeminy at IG 2.7 mmol/L and atrial bigeminy at IG 2.8 mmol/L. We also analyzed our data with the two patients on β-blockers excluded. The risk of bradycardia, atrial ectopics, and VPBs during nocturnal hypoglycemia remained significantly elevated (data not shown).

HRV

We explored changes in HRV during hypoglycemia compared with matched euglycemia. In the day, there was cardioacceleration (decrease in NN interval Δ −66 ± 55 ms, $P = 0.001$) at the glucose nadir accompanied by a decrease in total power (Δ −0.59 ± 0.83, $P = 0.02$) and HF power (Δ −0.62 ± 0.59, $P = 0.003$). Normalized LF was not significantly different (Supplementary Table 1). During the night, analysis of all episodes did not show significant differences in NN interval or any of the HRV indices at the glucose nadir (Supplementary Table 1). However, the glucose response was more heterogeneous (Fig. 1). Closer examination of individual episodes revealed a pattern whereby counterregulatory responses were accompanied by transient vagal withdrawal, with concomitant rise in LF_{norm} reflecting increased sympathetic contribution (Fig. 2). This was followed by a compensatory increase in vagal activity and a relative decrease in normalized LF. Bradycardia was observed in this period of heightened vagal activity. Further examples of this phenomenon are shown in Supplementary Fig. 1.

We similarly analyzed the data with patients on β-blockers excluded. NN interval and HRV indices decreased to a similar extent under hypoglycemic and euglycemic conditions; therefore, this made no material differences to our conclusions (data not shown).

Cardiac Repolarization

We compared QTc between hypoglycemia and euglycemia from 20 matched day episodes in 11 participants and 14 nocturnal episodes in 10 participants. In the day, mean QTc was longer during hypoglycemia (402 ± 49 ms) compared with euglycemia (384 ± 36 ms, mean paired difference 18 ± 27 ms, $P = 0.05$). At night, mean QTc was 440 ± 43 ms during hypoglycemia and 432 ± 16 ms during euglycemia; paired comparison showed no significant difference between the groups (8 ± 44 ms, $P = 0.60$). Two individuals had QTc >500 ms during hypoglycemia. There was maximal prolongation of 100 ms at the glucose nadir, which was accompanied by flattening of the T wave (Fig. 3) and emergence of U waves.

Table 2—IRRs of arrhythmias during hypoglycemia compared with euglycemia in daytime and nocturnal periods

	Day			Night		
	IRR	95% CI	*P*	IRR	95% CI	*P*
Bradycardia	NA	NA	NA	8.42	1.40–51.0	0.02
Atrial ectopic	1.35	0.92–1.98	0.13	3.98	1.10–14.40	0.04
VPB	1.31	1.10–1.57	<0.01	3.06	2.11–4.44	<0.01
Complex VPB	1.13	0.78–1.65	0.52	0.79	0.22–2.86	0.72

IRRs and 95% CI of arrhythmias during hypoglycemia versus euglycemia as analyzed using generalized estimated equations. NA, not applicable.

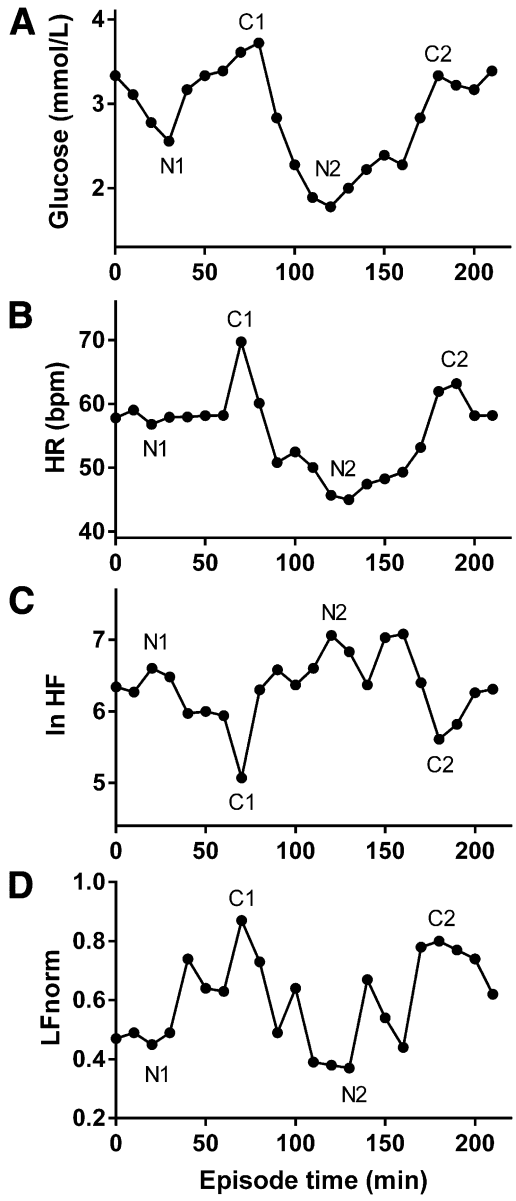

Figure 2—Phasic changes in HRV during a prolonged nocturnal hypoglycemic episode. Glucose, heart rate (HR), HF power, and LF_{norm} across a nocturnal hypoglycemic episode in a single patient are illustrated. The initial fall in glucose to 2.5 mmol/L (N1) was followed by a brief counterregulatory response (C1) (*A*). There was transient cardioacceleration (*B*), withdrawal in HF power (*C*), and increase in LF_{norm} (*D*) at C1. This was followed by a subsequent increase in vagal activity (HF) and relative decrease in LF_{norm}, leading to bradycardia (45 bpm) up to 50 min later. Glucose further decreased to1.8 mmol/L at N2. Glucose counterregulation occurred (C2), which again was accompanied by a transient increase in heart rate and LF_{norm} with HF withdrawal. HF power is expressed as an natural logarithm (ln).

Symptomatic Versus Asymptomatic Hypoglycemia

There were only three symptomatic episodes in three participants out of a total of 34 matched episodes identified, 2 of which occurred in the day. No arrhythmias were observed during the symptomatic episodes. We also compared the mean HRV indices at the glucose nadir between symptomatic and asymptomatic episodes. There was a trend toward higher heart rates during symptomatic episodes, as shown by decrease in NN interval (ΔNN −32 ± 37 ms vs. 1 ± 87 ms). There was also a trend toward greater vagal withdrawal during symptomatic episodes (ΔlnHF −0.53 ± 0.79 vs. −0.19 ± 0.79 and Δln[total power] −0.64 ± 0.67 vs. −0.27 ± 0.77), although owing to the small numbers the uncertainty is large.

Effect of Depth and Duration of Hypoglycemia

We explored the role of depth and duration of hypoglycemia by analyzing HRV and QT changes in *1*) episodes with glucose nadirs <2.5 mmol/L vs. ≥2.5 mmol/L and *2*) episodes <120 min vs. ≥120 min. Episodes with glucose nadir ≥2.5 mmol/L were associated with a greater degree of QT prolongation compared with episodes with a lower glucose nadir (42 ± 69 ms vs. 2 ± 14 ms, $P = 0.04$). Prolonged episodes were associated with a smaller degree of QT change, although this did not reach statistical significance (16 ± 42 ms vs. 30 ± 62 ms, $P = 0.51$). It is of note that prolonged episodes also had lower glucose nadirs. Similarly, longer and deeper episodes tended to be associated with a trend of slowing of heart rate (increase in NN) and decreased sympathetic contribution manifested as decreased ΔLF_{norm} (data not shown).

Hyperglycemia Versus Euglycemia

Hyperglycemic episodes were observed predominantly during the day. There was a total of 22 daytime and 3 nocturnal hyperglycemic events in 12 patients, 5 of whom were in the no hypoglycemia group. We did not observe any significant arrhythmias during nocturnal hyperglycemic episodes, which were very few. Daytime hyperglycemia was associated with lower rates of atrial ectopics (IRR = 0.41, $P < 0.01$) and complex VPB (0.28, $P < 0.01$) compared with euglycemia, although there appeared to be a higher risk of VPB (1.44, $P < 0.01$) (Table 3). There were no significant differences in HRV parameters during hyperglycemia compared with matched euglycemia (data not shown). Similarly, there were no significant differences in QTc between hyperglycemia and euglycemia (paired difference 0.65 ± 21.0 ms, $P = 0.92$, two tailed paired *t* test).

DISCUSSION

This study demonstrates that hypoglycemia is associated with an increased risk of cardiac arrhythmia in patients with type 2 diabetes and history of CVD or at high cardiovascular risk. There has been debate from post hoc analyses of trials of intensive glycemic therapy as to whether the association between hypoglycemia and cardiovascular mortality is causal or due to confounding factors (5). In this study, participant characteristics and CVD status were similar between patients who experienced hypoglycemia versus none. Yet, our observational data showed an increase in bradycardia and atrial and

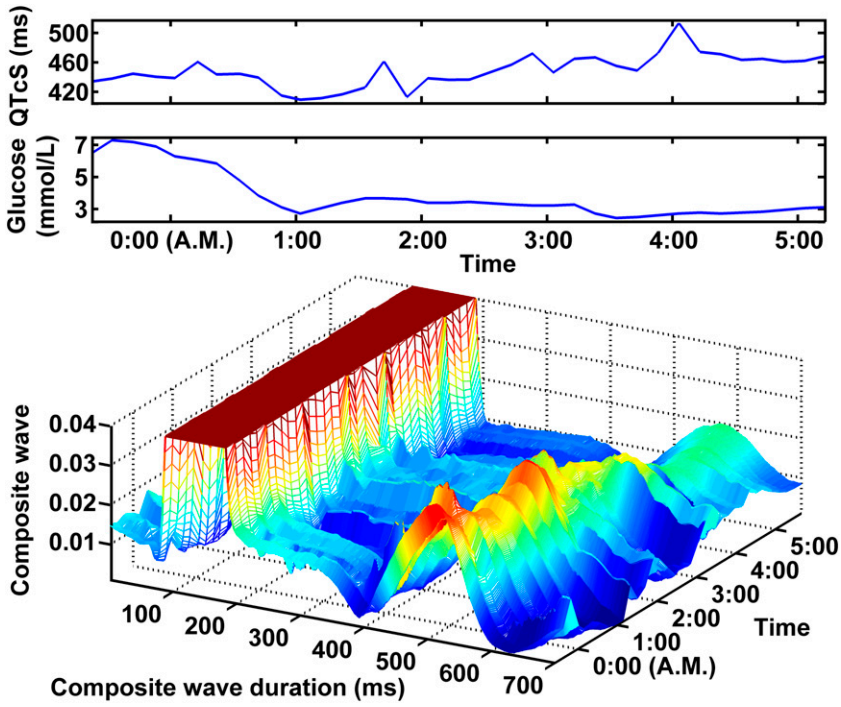

Figure 3—Abnormal QT prolongation and T-wave morphology during hypoglycemia in a single patient. Glucose and QTc change over the course of a hypoglycemic episode are shown in the two *top* panels. In this participant, QTc prolonged from 456 ms at euglycemia to 547 ms at the glucose nadir 2.51 mmol/L. The change in complex morphology with absolute time is shown in the *bottom* panel. There is progressive flattening of the T wave with fall in glucose. QTcS, QT interval corrected for heart rate using a subject-specific method.

ventricular ectopic activity that was coincident with hypoglycemic periods. The patterns of arrhythmia were consistent with those from anecdotal case reports (7), previous studies of experimental hypoglycemia in type 2 diabetes (8), and ambulatory data in type 1 diabetes (20).

We explored potential mechanisms by studying the effect of hypoglycemia on *1*) heart rate, which is linked to cardiac autonomic activity, and *2*) repolarization, which determines the propensity for nondriven cardiac action potentials and arrhythmogenesis. We further separated our analysis into day and night owing to diurnal differences in glucose counterregulation. We found transient cardioacceleration at the glucose nadir and vagal withdrawal during daytime episodes, consistent with studies of experimental hypoglycemia in patients with type 1 diabetes (12,30). However, what is striking is the difference in heart rate response and eightfold higher incidence of bradycardia during nocturnal hypoglycemia. Defective counterregulation during nocturnal hypoglycemia is well-known, characterized by blunted and delayed epinephrine responses (31). Nocturnal hypoglycemia is usually prolonged, with an undulating glucose profile with multiple nadirs that may occur as a result of repeated counterregulatory attempts to resist the glucose-lowering effects of injected insulin.

During nocturnal episodes, we observed a pattern of transient cardioacceleration with each glucose nadir, followed by a phase of heightened vagal counteraction up to 40–50 min later that was associated with bradycardia. We hypothesize that the occurrence of bradycardia may be linked to increased vagal counteraction after sympathetic neural activation. This view is supported by studies of experimental hypoglycemia with autonomic blockade (32,33). When hypoglycemia was induced with concomitant β-blockade, a late bradycardia was observed 45 min after the acute sympathetic reaction at the glucose nadir (32), with heart rates below that on propranolol alone. This decrease in heart rate was abolished by atropine, confirming the role of heightened vagal tone (33). The dampened sympathoadrenal response during nocturnal hours may be analogous to the effect of adrenergic blockade in these experimental studies, such that while heart rate may be restored to the normal range during

Table 3—IRRs of arrhythmias during daytime hyperglycemia compared with matched euglycemia

	IRR	95% CI	*P*
Bradycardia	NA	NA	NA
Atrial ectopic	0.41	0.33–0.50	<0.01
VPB	1.44	1.15–1.80	<0.01
Complex VPB	0.28	0.17–0.46	<0.01

IRRs and 95% CI of arrhythmias during hyperglycemia versus euglycemia as analyzed using generalized estimated equations. NA, not applicable.

the day, the rate-slowing effects would be more profound at night where sympathetic responses are weakened and circadian vagal tone is high (34). Furthermore, nocturnal hypoglycemia is likely to be driven by basal insulin, where the relatively slow decline in glucose may be linked with a weaker sympathetic response in contrast with a faster decline secondary to rapid-acting insulins in the day. There may also be an additional contribution due to impaired sympathetic responses in those who experience repeated episodes of hypoglycemia (8 of 14 patients in our study).

We explored the effect of hypoglycemia on cardiac repolarization with QT as a marker of action potential duration prolongation. The degree of QT prolongation was smaller than that reported in previous experimental studies and ambulatory studies in type 1 diabetes, only achieving significance in the day (11,35,36). This may reflect attenuated sympathoadrenal responses in this advanced type 2 diabetes group who were older and had a relatively long duration of disease (37). In our study, QTc was prolonged to >500 ms with abnormal T-wave morphology in two individuals during hypoglycemia, a level that can strongly predispose to Torsade de pointe and ventricular tachyarrhythmias. These two individuals also had the longest baseline QTc in the group (456 ms in a male patient, 484 ms in a female patient). It is possible that individuals with decreased repolarization reserve, related to coronary heart disease or structural abnormalities, may be particularly predisposed to arrhythmias during a hypoglycemic challenge.

It has been suggested that abnormal repolarization associated with hypoglycemia may be mediated by catecholamines, hypokalemia (11), or low glucose (10). In the absence of simultaneous biochemical measurements, we can only speculate on the mechanism involved. We observed that hypoglycemic episodes that reached a higher glucose nadir (>2.5 mmol/L) were associated with greater QT prolongation in contrast to episodes with nadirs <2.5 mmol/L. We interpret this to suggest that the degree of QT prolongation may be linked to the sympathoadrenal response rather than absolute glucose per se. During clinical episodes of spontaneous hypoglycemia (in contrast to hypoglycemia induced experimentally), episodes of hypoglycemia with a higher glucose nadir might generally reflect a stronger sympathoadrenal response. Conversely, in individuals with impaired counterregulation, glucose may fall to a lower nadir due to reduced sympathoadrenal activation. Thus, one explanation of our data is that greater QT prolongation occurred in episodes that are less deep owing to greater sympathoadrenal activation. Figure 3 illustrates a hypoglycemic episode with a higher glucose nadir (>2.5 mmol/L) where it was possible that the combination of sympathoadrenal activation and inherent repolarization abnormalities resulted in significant QT lengthening. We acknowledge that such speculation requires confirmation in the laboratory. Similarly, we also cannot exclude an additional role for hypokalemia, as this is also linked to epinephrine release.

In the current study, only 3 of 34 hypoglycemic episodes were accompanied by symptoms, and no arrhythmias were observed during these episodes. The high prevalence of asymptomatic hypoglycemia is striking and probably reflects diminished counterregulatory responses associated with long disease duration and with nocturnal episodes where hypoglycemia occurred during sleep in a supine posture. Asymptomatic hypoglycemia can contribute to an excess of arrhythmic risk, and these episodes may be frequent and go unnoticed. Our data indicate a trend to a lower heart rate and greater vagal tone during asymptomatic compared with symptomatic hypoglycemia; we cannot draw any firm conclusions from such small numbers.

Our study suggests that hypoglycemia is a proarrhythmic condition with a risk higher than during euglycemia or hyperglycemia. The electrophysiological conditions during hypoglycemia could contribute to the initiation of ventricular tachyarrhythmias in a number of ways. In the day, QT prolongation may lead to increased triggered activity in the form of early afterdepolarizations. Sympathetic activation and increase in cytosolic calcium can similarly lead to delayed afterdepolarization and premature beats (9). Both mechanisms can contribute to increased ventricular ectopic activity, which we observed in daytime hypoglycemia. However, rates of arrhythmia were even higher at night, where sympathoadrenal responses are attenuated. Arrhythmias during spontaneous nocturnal hypoglycemia may be explained by alternate mechanisms, in contrast to strong sympathoadrenal activation and QT prolongation that is typically observed in experimental hypoglycemia. During a state of vagal dominance, a slow sinus rate may reveal latent pacemakers, particularly under conditions of enhanced automaticity. This may explain the excess atrial and ventricular ectopic activity that we observed during nocturnal hypoglycemia. Ventricular bigeminy during bradycardia occurred at low glucose levels in our study, and the consequent long-short activation intervals are a common trigger for Torsade de pointe (38). QT prolongation during bradycardia can also increase the frequency or risk of long-short intervals (39). Although this combination did not occur in patients during this study, it has previously been reported in a patient with type 2 diabetes during hypoglycemic coma (7,38). Thus, hypoglycemia has the potential to trigger a fatal arrhythmic event by more than one mechanism during spontaneous hypoglycemia in patients at high cardiovascular risk.

Most of the arrhythmias that we observed in our study may be well tolerated by young healthy individuals but could be clinically relevant in those with type 2 diabetes. A previous study has examined symptoms of ischemic heart disease in adults with type 2 diabetes undergoing CGM and reported a higher frequency of

chest pain during hypoglycemic episodes (40). The authors did not separate their periods of recording into night and day, but it is conceivable that if their patients were generally reporting symptoms during the day (as is most likely), this might reflect the transient cardioacceleration during hypoglycemia (causing subsequent angina) that we observed in our study. Ischemia may further enhance hypoglycemia-associated repolarization abnormalities.

There are limitations to CGM in its accuracy at low glucose values and time lag due to diffusion of glucose between blood and interstitial compartments. Although there are reports that CGM glucose may be falsely low during hypoglycemia in type 1 diabetes (41), in type 2 diabetes CGM glucose has been reported to be falsely high owing to differences in glucose distribution in the interstitial space (42). Therefore, we are reasonably confident that IG $\leq$3.5 mmol/L as detected by CGM in this study represents true biochemical hypoglycemia. Since it would be unethical to perform experimental hypoglycemia studies in these patients at high cardiovascular risk, CGM remains, at the moment, the best available tool to study clinical hypoglycemia in an ambulatory setting.

In conclusion, we have shown that hypoglycemia is associated with increased susceptibility to cardiac arrhythmias in patients with type 2 diabetes at cardiovascular risk. Changes in cardiac autonomic tone and abnormal repolarization are potential contributory mechanisms. Our findings may also be relevant to the "dead-in-bed" syndrome in type 1 diabetes, which also occurs at night, typically in individuals with recurrent asymptomatic hypoglycemia, where an arrhythmic mode of death has been suggested (43). Our study confirms that hypoglycemia is common and frequently unrecognized in patients with advanced type 2 diabetes, even where glycemic control is not as aggressive as that in recent interventional trials (29). Hypoglycemia should be minimized in this group of patients who may be particularly vulnerable to cardiac arrhythmias, as it may contribute toward increased cardiovascular mortality.

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