Cardiac repolarization during hypoglycaemia in type 1 diabetes: impact of basal renin–angiotensin system activity

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Aims Hypoglycaemia-induced cardiac arrhythmias may be involved in the pathogenesis of the ‘dead-in-bed syndrome’ in patients with type 1 diabetes. Evidence suggests that the renin–angiotensin system (RAS) influences the occurrence of arrhythmias. The aim of this study was to explore if basal RAS activity affects cardiac repolarization during hypoglycaemia, thereby potentially carrying prognostic information on risk of the ‘dead-in-bed syndrome’.

Methods and results Nine subjects with high RAS activity and nine subjects with low RAS activity were subjected to single-blinded placebo-controlled hypoglycaemia (nadir plasma glucose 2.4 mmol/L). QTc/QTcF and QT dynamics were registered by Holter monitoring. QTc prolonged during [8 (±2.3) ms, P < 0.01] and after [11 (±3) ms, P < 0.001] hypoglycaemia. Dynamic QT parameters reacted ambiguously. Low RAS activity was associated with a slightly more pronounced QT prolongation [6 (±3) ms, P = 0.04]. Adrenaline tended to increase more in the low-RAS group (P = 0.08) and was correlated to QTc (r = 0.67, P < 0.01) and QTcF (r = 0.58, P < 0.05) during hypoglycaemia.

Conclusion Low basal RAS activity may be associated with a slightly more pronounced QT prolongation during hypoglycaemia, when compared with high RAS activity. The impact, however, is modest and the clinical consequence is unclear.

KEYWORDS Type 1 diabetes; Hypoglycaemia; 'Dead-in-bed syndrome'; Cardiac repolarization; QT

Introduction The so-called ‘dead-in-bed syndrome’ refers to the sudden and unexpected overnight death of a young patient with type 1 diabetes, who was seen in good health the day before. Typically, the subjects had no long-term complications and were found dead in an undisturbed bed with circumstantial evidence linking the death to hypoglycaemia. The syndrome constitutes 23–40% of sudden and unexpected deaths among young patients with diabetes¹–³ and may be caused by hypoglycaemia-induced cardiac arrhythmias based on changes in repolarization.⁴ Hypoglycaemia is a frequent adverse effect of insulin therapy and well known potentially to cause QT prolongation and affect QT dynamics.⁴–⁶ The puzzling thing is, why so few type 1 diabetic patients die from the ‘dead-in-bed syndrome’, when hypoglycaemia is so common. Analogously the same phenomenon can be seen in long QT syndrome, where the substrate of arrhythmias is the inherited dysfunction of potassium channels leading to a reduced repolarization reserve. Despite the reduced repolarization reserve, half of all long QT syndrome patients do not have any symptoms, despite the QT prolongation. The substrate has to be combined with a trigger in form of early after-depolarizations to elicit a malignant arrhythmia. The risk for both long QT patients and ‘dead-in-bed syndrome’ in type 1 diabetic patients is therefore low, but significant, due to the demand of multiple factors involved in arrhythmia genesis.

In recent years, the renin–angiotensin system (RAS)—and its activity—has been accepted as an important factor in the pathogenesis of cardiac arrhythmias. A meta-analysis...
showed that angiotensin-converting enzyme (ACE) inhibition after myocardial infarction is associated with a reduced risk of sudden cardiac death—a finding potentially explained by a more or less direct anti-arrhythmic effect of inhibiting the RAS. Moreover, the D (deletion) allele of the ACE-I/D polymorphism (which confers high ACE activity) is related to QTc prolongation, an independent risk marker of ventricular arrhythmia and sudden death.

The RAS activity also influences vulnerability to hypoglycaemia in type 1 diabetes. Thus, patients with high spontaneous ACE activity, high spontaneous angiotensinogen concentration, and the A-allele of the angiotensin II receptor subtype 2 (AT2 receptor) 1675 polymorphism have an increased risk of severe hypoglycaemia, suggesting a general susceptibility to glucose deficiency.

To test the hypothesis that RAS activity potentially carries prognostic information about the risk of developing malignant ventricular arrhythmias during a hypoglycaemic episode, we studied if basal RAS activity influences QTc/QTcF and QT dynamics during hypoglycaemia in patients with type 1 diabetes. These parameters are surrogate measures of repolarization known to carry independent prognostic information on risk of sudden cardiac death and development of ventricular tachyarrhythmia.

Methods

Subjects

Eighteen patients with type 1 diabetes, without diagnosed late complications, attending our outpatient clinic were included in the study (Table 1). They were selected from a cohort of 260 patients participating in a larger observational survey concerning the risk of severe hypoglycaemia and ACE activity, and none of the participants received treatment with ACE-inhibitors or angiotensin II antagonists. On the basis of a scoring system that taking into account the three RAS parameters associated with the risk of hypoglycaemia [ACE activity, angiotensinogen concentration, and the AT2 receptor (1675A/G) polymorphism], nine patients with high RAS activity and nine patients with low RAS activity were included (Table 1). One patient in the high-RAS group was later excluded because of Holter recordings of unacceptable quality that could not be repeated. The high-RAS activity group was characterized by ACE activity and angiotensinogen concentration in the highest quartile and the AT2 receptor genotype AA corresponding to low expression (maximum stimulation via the AT1 receptor). The low-RAS activity group was characterized by ACE activity and angiotensinogen concentration in the lowest quartile and the AT2 receptor genotype GG corresponding to high expression (minimum stimulation via the AT1 receptor).

Type 1 diabetes was defined by the insulin treatment from the time of diagnosis and unstimulated C-peptide <300 pmol/L. Data on late complications were extracted from the patients’ medical records and comprised the absence/presence of retinopathy (untreated and laser treated), nephropathy (micro- and macroalbuminuria), peripheral neuropathy (asymptomatic and symptomatic), and autonomic neuropathy (asymptomatic and symptomatic). The study complied with the Declaration of Helsinki. All participants gave written informed consent to participate and the study was approved by the Regional Ethics Committee.

Design

The study was a single-blinded, balanced, controlled, cross-over study. Hypoglycaemia was induced using a standardized intravenous glucose challenge without any exogenous glucose supply during the hypoglycaemic phase of the experiment. This was done to avoid any interference with the natural glucose mobilization and to minimize the insulin dosage, thereby reducing the potential QT prolonging effect of insulin per se. Each subject was studied at two occasions—during hypoglycaemia and during stable glycaemia (designated ‘control’) separated by at least 4 weeks.

Experimental protocol

Subjects were instructed to live and eat as normal as possible and to avoid any rigorous exercise, as well as the use of alcohol or drugs, in the week preceding the experiments.

The day before, a three-channel digital Holter Monitor (DelMar Aria recorder, Delmar Avionics, Irvine, CA, USA) and a continuous glucose sensor (Seni0100, ReliaMed, Ventura, CA, USA) were inserted. The subjects were instructed to eat normal meals and to avoid any rigorous exercise, as well as the use of alcohol or drugs, in the week preceding the experiments.

Table 1 Baseline characteristics of subjects according to basal renin-angiotensin system activity

<table>
<thead>
<tr>
<th>Basal RAS activity</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (n = 9)</td>
<td>High (n = 9)</td>
</tr>
<tr>
<td>Age (years) 41.2 (10.2)</td>
<td>39.1 (13.3)</td>
</tr>
<tr>
<td>Sex (F/M) 3/6</td>
<td>2/7</td>
</tr>
<tr>
<td>BMI (kg/m²) 25.4 (3.7)</td>
<td>25.6 (1.8)</td>
</tr>
<tr>
<td>Duration of diabetes (years) 16.7 (7.1)</td>
<td>19.7 (9.6)</td>
</tr>
<tr>
<td>Detectable C-peptide (+) 5/4</td>
<td>4/5</td>
</tr>
<tr>
<td>Daily insulin dose (IU) 61.8 (5.2)</td>
<td>57.3 (4.2)</td>
</tr>
<tr>
<td>HbA1c (%) 8.6 (0.8)</td>
<td>8.2 (1.3)</td>
</tr>
<tr>
<td>Insulin dose used to induce hypoglycaemia (IU in total) 18.5 (0.7)</td>
<td>22.9 (3.8)</td>
</tr>
<tr>
<td>Hypoglycaemia awareness (aware/impaired/unaware) 5/2/1</td>
<td>1/7/1</td>
</tr>
<tr>
<td>Renin–angiotensin system characteristics serum ACE activity (U/l) 28.2 (13.0)</td>
<td>59.3 (26.0)</td>
</tr>
<tr>
<td>ACE genotype (II; ID; and DD) 5; 1; 3</td>
<td>0; 4; 5</td>
</tr>
<tr>
<td>AT2 genotype (GG; AG; and AA) 9; 0; 0</td>
<td>0; 9</td>
</tr>
<tr>
<td>Plasma angiotensinogen (nmol/L) 760 (157)</td>
<td>1099 (752)</td>
</tr>
</tbody>
</table>

Baseline characteristics of subjects according to basal RAS activity. Values indicate means. Bracketed values indicate 1 SD; P-values for tests between the two groups.

aUndetectable: <10 pmol/L.

bNormal range: 4.1–6.4%.

cSubjects always recognizing their symptoms of hypoglycaemia were categorized as being ‘aware’, those usually recognizing their symptoms as having ‘impaired awareness’, and those only occasionally or never recognizing their symptoms as being ‘unaware’.
glucose monitoring system (CGMS) device (Medtronic MiniMed; Medtronic Diabetes, Northridge, CA, USA) were mounted in order to monitor heart rhythm and the glycaemic level during the evening and night before the experiment.

On the day of experiment, subjects arrived at 7.30 a.m. in the laboratory after an overnight fast. The data from the CGMS were downloaded and studied. If hypoglycaemia had been present during the preceding night, as indicated by a CGMS value <3.5 mmol/L or a self-monitored plasma glucose concentration <3.5 mmol/L, the experiment was postponed for at least 14 days (in 8 of 36 experiments). Extreme hyperglycaemia (plasma glucose >20 mmol/L) also led to postponement (in 2 of 36 experiments).

Following introduction to the experimental setting and scheme, subjects were equipped with an intravenous cannula in an antecubital vein in both forearms.

An experimental day was characterized by a baseline period lasting 60 min (cycles 1 and 2), a period of variable length where hypoglycaemia was induced, a hypoglycaemic/control period lasting 60 min (cycles 3 and 4), and a recovery period also lasting 60 min (cycles 5 and 6). Venous blood was drawn for measurements of plasma glucose, adrenaline, and electrolytes twice in each period (except for plasma glucose which was measured four times during the hypoglycaemic/control period). The study flow is grossly illustrated in Figure 1. The bedside plasma glucose concentration was measured several times during each period.

Hypoglycaemia

Target nadir plasma glucose was 2.0–2.5 mmol/L, a frequently used hypoglycaemic target level in similar experiments. After a baseline period without intervention, insulin (Actrapid, Novo Nordisk, Bagsvaerd, Denmark) was infused intravenously (500% of the patients morning dose mixed with 500 mL of saline; infusion rate: 100 mL/h) until bedtime plasma glucose was below 5 mmol/L. Thereafter the infusion was stopped. The hypoglycaemic period was considered started when bedtime plasma glucose had fallen below 3.0 mmol/L. The stimulus was terminated by the ingestion of 0.5 L of apple juice.

Control

After the baseline period, a mixture of glucose/insulin was infused intravenously in order to keep a stable blood glucose concentration (500 mL of 10% glucose with human insulin added according to a standardized scheme; infusion rate: 50 mL/h).

![Figure 1](https://academic.oup.com/europace/article-abstract/10/7/860/399575/16396039675/16396039675)

**Figure 1** Plasma glucose profiles during control and hypoglycaemia in the two renin–angiotensin system groups. The study flow is indicated on the X-axis.

**QT parameters**

QT intervals were registered by Holter recordings obtained with modified chest leads V2, V3, and V5. Semiautomatic QT analysis was performed in the lead with the best defined T-wave using a modified Laguna algorithm to identify the end of the T-wave. Mean values of all accepted RR intervals and QT parameters were calculated corresponding to baseline, hypoglycaemia/control, and recovery. Correction for differences in heart rate was done according to Bazett’s (QTc = QT/RR) and Fridericia’s (QTcF = QT/RR1/3) formulas. The adaptation of the QT interval to changes in heart rate was assessed as slope, and the intercept of the linear regression line was obtained by analysing pairs of QT interval length and the immediately preceding RR interval. Standard deviations of all accepted RR intervals and all accepted QT intervals were defined as SDNN and SDQT, respectively. The variability ratio (VR) was defined as SDQT/SDNN, and it reflects the variation in QT not explained by heart rate variability.

**Laboratory analyses**

Angiotensinogen was determined as the maximal quantity of angiotensin I generated during incubation of plasma in the presence of excess recombinant human renin as described. Serum ACE activity was determined by a commercial kinetics-based assay (Sigma Diagnostics, St Louis, MO, USA). Using a standard salting-out method, DNA was extracted from peripheral blood leukocytes. The ACE-I/D variant and the AT2 receptor 1675G/A polymorphism were determined by polymerase chain reaction.

Bedside plasma glucose measurements were carried out by a HemoCue Analyser (HemoCue AB, Angelholm, Sweden). Plasma glucose concentrations were measured enzymatically (COBAS INTEGRA, Roche, Basel, Switzerland), and plasma potassium concentrations were measured using a standard ion-selective electrode.

Plasma adrenaline concentrations were measured on blood taken into chilled heparinized tubes containing 12 mg glutathione, centrifuged, drawn off by a pipette, and frozen (−80 °C) within 30 min.

Analyses were done using high performance liquid chromatography (HPLC) with fluorimetric detection.

**Statistics**

Statistical analyses were performed using SPSS (version 13.0). Values are given as mean ± 1 SEM unless otherwise mentioned. Confirmation of normality was done using the Kolmogorov–Smirnov model. To reduce the amount of statistical analyses performed, mean values for the baseline period, the stimulus period, and the recovery period were calculated and included in the statistical models. An independent T-test was used to compare baseline characteristics and the increases in QT during hypoglycaemia in the two groups illustrated in Figure 2. To evaluate both the impact of the RAS group and the intervention (hypoglycaemia vs. control) on the outcome variables, a mixed linear model (ANCOVA) was applied. ‘Renin–angiotensin system group’ and ‘intervention’ were defined as fixed factors and ‘number of participant’ as a random factor. To correct for potential group differences in baseline values, the baseline value of the outcome variable being investigated was included in the model as a covariate. The mixed model was applied on data obtained in the stimulus period and the recovery period, respectively. Correlations were evaluated using Pearson’s correlation coefficient. A P-value < 5% (two-sided) was considered significant.

**Results**

Holter parameters are presented in Tables 2 and 3, which offer absolute values and estimates of the impact of hypoglycaemia and the RAS activity group on Holter parameters,
Table 3
Estimated effect of hypoglycaemia and renin–angiotensin system activity group on Holter parameters

<table>
<thead>
<tr>
<th>Hypoglycaemia</th>
<th>Outcome variable</th>
<th>Parameter (fixed)</th>
<th>Stimulus period</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR (ms)</td>
<td></td>
<td>Estimated effect (β)</td>
<td>95% CI</td>
</tr>
<tr>
<td></td>
<td>High RAS</td>
<td></td>
<td>−21 (20)</td>
<td>−63 to 21</td>
</tr>
<tr>
<td></td>
<td>Hypoglycaemia</td>
<td></td>
<td>−31 (14)</td>
<td>−6 to 2</td>
</tr>
<tr>
<td></td>
<td>QTC (ms)</td>
<td></td>
<td>−5 (2)</td>
<td>−10 to 0</td>
</tr>
<tr>
<td></td>
<td>Hypoglycaemia</td>
<td></td>
<td>8 (2)</td>
<td>2 to 12</td>
</tr>
<tr>
<td></td>
<td>QTCF (ms)</td>
<td></td>
<td>−6 (3)</td>
<td>−12 to 0</td>
</tr>
<tr>
<td></td>
<td>High RAS</td>
<td></td>
<td>−5 (3)</td>
<td>−2 to 10</td>
</tr>
<tr>
<td></td>
<td>Hypoglycaemia</td>
<td></td>
<td>−0.005 (0.007)</td>
<td>−0.019 to 0.010</td>
</tr>
<tr>
<td>Slope (no unit)</td>
<td>High RAS</td>
<td></td>
<td>−5.1 (7.3)</td>
<td>−20.8 to 10.6</td>
</tr>
<tr>
<td></td>
<td>Hypoglycaemia</td>
<td></td>
<td>−0.004 (0.004)</td>
<td>−0.012 to 0.005</td>
</tr>
<tr>
<td>Intercept (ms)</td>
<td>High RAS</td>
<td></td>
<td>3.3 (6.1)</td>
<td>−9.7 to 16.4</td>
</tr>
<tr>
<td></td>
<td>Hypoglycaemia</td>
<td></td>
<td>0.36 (0.78)</td>
<td>−1.26 to 1.98</td>
</tr>
<tr>
<td>SDQT (ms)</td>
<td>High RAS</td>
<td></td>
<td>0.42 (0.47)</td>
<td>−0.58 to 1.42</td>
</tr>
<tr>
<td></td>
<td>Hypoglycaemia</td>
<td></td>
<td>−2.20 (5.95)</td>
<td>−14.95 to 10.54</td>
</tr>
<tr>
<td>SDNN (ms)</td>
<td>High RAS</td>
<td></td>
<td>−5.24 (4.33)</td>
<td>−14.46 to 3.98</td>
</tr>
<tr>
<td></td>
<td>Hypoglycaemia</td>
<td></td>
<td>−0.005 (0.012)</td>
<td>−0.031 to 0.022</td>
</tr>
<tr>
<td>VR (no unit)</td>
<td>High RAS</td>
<td></td>
<td>0.032 (0.011)</td>
<td>0.010 to 0.054</td>
</tr>
</tbody>
</table>

Values indicate the estimated effects of (i) belonging to the high renin–angiotensin system activity group (low renin–angiotensin system group serves as a reference point) and (ii) inducing hypoglycaemia (control serves as a reference point). Values are in absolute numbers. Bracketed values indicate 1 SEM.
respectively. None of the investigated Holter variables differed between the RAS groups at baseline (Table 2).

Baseline
At baseline, the RR interval, QTc, QTcF, slope, intercept, SDQT, and VR were all within normal ranges. However, SDNN, which represents an estimate of heart rate variability, showed low baseline values.

Hypoglycaemia
The hypoglycaemic stimulus was similar in both groups [nadir plasma glucose 2.4 (±0.5) mmol/L; mean plasma glucose in the stimulus period 2.6 (±0.3) mmol/L] (Figure 1). The rate whereby glucose fell after insulin administration was 0.10 (±0.02) mmol/L/min vs. 0.8 (±0.02) mmol/L/min (high RAS vs. low RAS, P = 0.10). The plasma insulin concentration was the same in both groups during hypoglycaemia (P = 0.86) and during recovery (P = 0.52).

During hypoglycaemia, the RR interval decreased significantly [−31 (±14) ms, P = 0.04]. QTc prolonged [8 (±2) ms, P < 0.01] and QTcF tended to prolong. The VR increased modestly, P < 0.01, primarily because of an SDNN decrease. In contrast, SDQT was unaffected by hypoglycaemia, in spite of the before mentioned increased heart rate. The slope and the intercept were not affected. Hypoglycaemic symptom scores increased significantly during hypoglycaemia when compared with baseline (P < 0.05) in the low-RAS group, whereas symptom scores in the high-RAS group did not differ from baseline scores during hypoglycaemia. QTc (P = 0.05) (Figure 2) and QTcF (P = 0.06) tended to prolong more in the low-RAS activity group, whereas no other QT variables differed according to the RAS group. Hypoglycaemic symptom scores were higher in the low-RAS activity group than in the high-RAS activity group during hypoglycaemia (P < 0.05).

Plasma adrenaline tended to increase more in the low-RAS activity group, P = 0.08 (Figure 3), an increase positively correlated to QTc prolongation (r = 0.67, P < 0.01) (Figure 4) and QTcF prolongation (r = 0.58, P < 0.05).

Recovery
Heart rate was still significantly increased during this period (P < 0.05), just as the QTc and QTcF prolongation was still present when compared with baseline [QTc: 11 (±3) ms, P < 0.001; QTcF: 9 (±3) ms, P < 0.005]. The RAS group had a significant impact on QTcF prolongation, with the low RAS activity being associated with a longer QTcF [6 (±3) ms, P = 0.04]. Except for QTcF, no outcome variables were significantly influenced by the RAS group. Plasma adrenaline returned to baseline levels in this period, just as plasma potassium tended to.

Discussion
Hypoglycaemia and QT
In the present study, the QT interval prolonged during hypoglycaemia in type 1 diabetic patients without known neuropathy. The prolongation, however, was only 8–10 ms and neither QTc nor QTcF prolonged beyond the upper normal limit (reference range: QTc: 361–457 ms and QTcF: 359–445 ms²). In contrast, a similar study found QTc to prolong 25 ms during hypoglycaemia in patients without autonomic neuropathy and up to 60 ms in patients with autonomic neuropathy. The shorter QT prolongation in the present experiment is probably explained by the use of continuous Holter recordings and the applied beat-to-beat analysis, which included the entire hypoglycaemic period (30 min). In contrast, Lee et al. used 1 min electrocardiogram...
recordings at the end of each hypoglycaemic plateau. Furthermore, different ways of inducing hypoglycaemia may also have affected the result, as Lee et al. used a hyperinsulinaemic–hypoglycaemic clamp, whereas we used intravenous insulin to improve standardization and minimize the exogenous glucose supply. The clamping method is associated with larger doses of insulin, which is known to affect membrane potential and myocardial calcium channels in rats.

Dynamic QT parameters describe changes in QT over time and have, to the best of our knowledge, only been investigated in relation to hypoglycaemia in healthy subjects. The VR, which reflects variation in QT in not explained by heart rate variability, increased during hypoglycaemia. As the VR is a new risk marker of sudden death in patients with myocardial infarction, the hypoglycaemia-induced rise may support an association between hypoglycaemia and arrhythmia in the pathogenesis of the 'dead-in-bed syndrome'. The QT/RR slope was unaffected by hypoglycaemia in the present study.

Impact of renin–angiotensin system activity on QT parameters

QTc (and QTcF) prolonged more in the low-RAS activity group than in the high-RAS activity group. This finding is unanticipated, as there are parallels between low RAS activity (according to our definition) and ACE inhibitor treatment, which shortens the QT interval on a long-term basis. In addition, high basal RAS activity is associated with an increased vulnerability to hypoglycaemia, which might have been reflected in a more pronounced QT prolongation. The present result may of course be explained by the uncertainty of QT measurements, as the difference between RAS groups only amounted to 6 ms. This is probably the most plausible explanation and indicates that the RAS group has no impact on QT prolongation during hypoglycaemia. Alternatively, and very hypothetically, the slightly larger QT prolongation in the low-RAS group represents an anti-arrhythmic response that mimics the effect of class III anti-arrhythmic drugs. Basal RAS activity had no impact on QT prolongation in healthy subjects.

Adrenaline and potassium

The adrenaline response tended to be larger in the low-RAS activity group than in the high-RAS activity group. The finding corresponds well with the higher hypoglycaemic symptom scores observed in the low-RAS group, as hormonal counter-regulation and symptoms of hypoglycaemia are known to co-segregate. The reason for the different adrenaline responses in the two RAS groups is unclear. Duration of diabetes, which is known to affect the counter-regulatory response to hypoglycaemia, did not differ significantly between the groups. The rate whereby plasma glucose fell did not differ significantly in the RAS groups and does not explain the different adrenaline responses. Information on antecedent hypoglycaemia was limited to 20 h before the start of the study, and hypoglycaemic episodes in the preceding week might have differed between the groups. In addition, basal RAS activity in itself may have affected hormonal counter-regulation by an unknown mechanism. The fact that low basal RAS activity was also associated with a longer QT interval suggests that the counter-regulatory adrenaline response may prolong QT and thereby constitute a potential trigger of arrhythmia. The possible importance of adrenaline is underlined by the significant correlation between QTc and QTcF prolongation and adrenaline increase in the present study. In accordance, β antagonist treatment (atenolol) blunts hypoglycaemia-induced QTc prolongation, and adrenaline infusion prolongs QTc in spite of potassium clamping. Action potential duration may increase because adrenaline stimulates the depolarizing L-type calcium channels and inhibits the repolarizing transient outward potassium current (Ito). These effects are important as they potentially increase the risk of early afterdepolarisations, as L-type calcium channels escape inactivation and become excitable again. Adrenaline also increases Tpeak – Tend, which is thought to provide an index of transmural dispersion of repolarization (TDR). Tpeak – Tend may therefore constitute a window of arrhythmogenic vulnerability, and increases in TDR seem to facilitate the propagation of early after-depolarizations, which may trigger the development of Torsade de Pointes. However, recently this perception was challenged and Tpeak – Tend may alternatively be an index of global dispersion of ventricular repolarization.

In the present study, the potassium fall was significantly larger in the high-RAS activity group, which presented the smallest QT prolongation. In addition, the potassium concentration did not correlate to the QT prolongation. This is unexpected, as hypokalaemia seems to inhibit the human ether-a-go-go related gene (HERG) potassium channel. It thereby reduces the rapid delayed rectifier potassium current (Ikr), which reduces Tpeak, Ikr and Tend. In correspondence with this, hypokalaemia is known to be associated with early after-depolarizations, which is important as they potentially increase the risk of early after-depolarisations, as L-type calcium channels escape inactivation and become excitable again. Adrenaline also increases Tpeak – Tend, which is thought to provide an index of transmural dispersion of repolarization (TDR). Tpeak – Tend may therefore constitute a window of arrhythmogenic vulnerability, and increases in TDR seem to facilitate the propagation of early after-depolarizations, which may trigger the development of Torsade de Pointes. However, recently this perception was challenged and Tpeak – Tend may alternatively be an index of global dispersion of ventricular repolarization.

In the present study, the potassium fall was significantly larger in the high-RAS activity group, which presented the smallest QT prolongation. In addition, the potassium concentration did not correlate to the QT prolongation. This is unexpected, as hypokalaemia seems to inhibit the human ether-a-go-go related gene (HERG) potassium channel. It thereby reduces the rapid delayed rectifier potassium current (Ikr), an important repolarizing current, and potentially causes QT prolongation. In correspondence with this, hypokalaemia is a known risk factor for arrhythmogenesis in congenital and acquired long QT syndromes. The reason for the apparently peripheral role of potassium in the QT prolonging process in the present study is unclear, but probably has to do with the relatively modest potassium fall observed.

In conclusion, the ‘dead-in-bed syndrome’ seen among patients with type 1 diabetes may be caused by lethal cardiac arrhythmias induced by hypoglycaemia-induced hormonal counter-regulation. In the present study, QTc, QTcF,
and the VR, a dynamic QT parameter, increased during moderate hypoglycaemia, tentatively supporting this theory.

Low RAS activity was associated with a slightly more pronounced QT prolongation, which may have been caused by a larger unexplained adrenaline response in this group. The clinical importance of this is unclear. The dynamic QT parameters were unaffected by RAS.

We conclude that the basal RAS activity per se is probably not a significant risk marker of the ‘dead-in-bed syndrome’. Instead, the magnitude of the adrenaline response to hypoglycaemia may be the principal determinant of hypoglycaemia-induced QT alterations and potentially associated arrhythmias.

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