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Autonomic cardiac regulation during spontaneous nocturnal hypoglycemia in children with type 1 diabetes

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Abstract

Background: Hypoglycemia is the most common complication in insulin treated diabetes. Though mostly mild, it can be fatal in rare cases: It is hypothesized that hypoglycemia related QTc prolongation contributes to cardiac arrhythmia.

Objective: To evaluate influence of nocturnal hypoglycemia on QTc and heart rate variability (HRV) in children with T1D.

Methods: Children and adolescents with T1D for at least 6 months participated in an observational study using continuous glucose monitoring (CGM) and Holter electrocardiogram for five consecutive nights. Mean QTc was calculated for episodes of nocturnal hypoglycemia (<3.7 mmol/L) and compared to periods of the same duration preceding hypoglycemia. HRV (RMSSD, low and high frequency power LF and HF) was analyzed for different 15 min intervals: before hypoglycemia, onset of hypoglycemia, before/after nadir, end of hypoglycemia and after hypoglycemia.

Results: Mean QTc during hypoglycemia was significantly longer compared to euglycemia (412 ± 15 vs. 405 ± 18 ms, $p = 0.005$). HRV changed significantly: RMSSD (from 88 ± 57 to 73 ± 43 ms) and HF (from 54 ± 17 to 47 ± 17nu) decreased from before hypoglycemia to after nadir, while heart rate (from 69 ± 9 to 72 ± 12 bpm) and LF (from 44 ± 17 to 52 ± 21 nu) increased ($p = 0.04$).

Conclusion: A QTc lengthening effect of nocturnal hypoglycemia in children with T1D was documented. HRV changes occurred even before detection of nocturnal hypoglycemia by CGM, which may be useful for hypoglycemia prediction.

KEYWORDS
diabetes, ECG, heart rate variability, hypoglycemia, QTc

1 | INTRODUCTION

Hypoglycemia is an unavoidable and dreaded acute complication of insulin treated diabetes mellitus. Although most nocturnal hypoglycemic episodes are mild and asymptomatic, they can be fatal in rare cases: Sudden unexpected death in otherwise healthy young people with type 1 diabetes (T1D) has been reported to be up to 10 times higher compared to a population without diabetes.[1,2] It is hypothesized that these overnight deaths (so called "dead in bed phenomenon") are induced by hypoglycemia.[3,4] The precise mechanism by

which hypoglycemia leads to death is still not fully understood. There is some evidence that insulin-induced hypokalemia in combination with sympatho-adrenergic stimulation leads to fatal cardiac ventricular arrhythmia in adults.[5]

Even episodes of mild or moderate hypoglycemia seem to have an impact on cardiac repolarization: In adults with[6–9] and without diabetes[5,10] lengthening of QTc intervals during experimental and spontaneous hypoglycemia has been documented.

In a previous study, we observed frequent nocturnal hypoglycemia in children with T1D, often prolonged for hours.[11] Hence, the question remains, whether alterations of QTc intervals occur during nocturnal hypoglycemia in children with diabetes.

Besides QTc intervals, cardiac regulation is represented by heart rate variability. Heart rate variability measures the beat-to-beat fluctuation of heart rate and represents the interplay of the sympathetic and parasympathetic nervous system.[12] Because hypoglycemia stimulates the sympathetic nervous system, a reaction of heart rate variability during episodes of hypoglycemia can be assumed. In adults, such hypoglycemia-induced changes in heart rate variability have already been reported.[7,9,13] It is hypothesized that these changes may be helpful in the prediction of hypoglycemia.[13,14] However, in children with T1D, the effect of hypoglycemia on heart rate variability has not been studied so far.

Therefore, aims of this study were to investigate if nocturnal hypoglycemia results in QTc prolongation and changes in heart rate variability in children with T1D.

2 | RESEARCH DESIGN AND METHODS

2.1 | Participants

Children and adolescents aged below 18 years with T1D for at least 6 months and followed at our outpatient department were recruited. Participants with pre-existing cardiac disease or medication known to affect cardiac function were excluded. Participants aged 14 years and older and all parents of the participants were asked to provide written informed consent.

The study was approved by the local ethics committee (BASEC 2016-01772).

2.2 | Study design

We performed a prospective observational study in children with T1D in the home setting.

After assessment of baseline data (HbA1c, weight, height, age, diabetes duration, insulin treatment/dosage) participants underwent a 5-day monitoring period: Blinded continuous glucose monitoring (CGM) was performed during five consecutive days and nights and combined with Holter electrocardiogram (ECG) recording during every night. Participants continued with their routine insulin treatment and daily activities and were instructed to perform at least three capillary blood glucose measurements per day for calibration and to record injected insulin doses, consumed carbohydrates, bed- and wake-up time and hypoglycemic symptoms in a logbook. After 5 days, the devices were returned for data download.

2.3 | Baseline assessments

HbA1c, weight, height, insulin treatment and insulin dose (units/kg/day and percentage of basal insulin) were documented at the routine visit preceding the study. All participants were seen by a cardiologist and cardiac disease (such as congenital or acquired structural heart disease, heart insufficiency or clinically relevant arrhythmia) was excluded. At the start of the measurement period, a capillary blood sample was taken for the analysis of serum calcium, potassium and magnesium.

2.4 | Continuous glucose monitoring

Glucose was measured by a blinded CGM system (iPro Transmitter and Enlite sensor, Medtronic Minimed, Northridge, CA). The system has proven accuracy in children with a mean absolute relative difference (MARD) of 10.1%, and in the range of 2.22–4.44 mmol/L a sensor-to blood glucose agreement of 85.5% has been reported.[15] If participants were already using a CGM system (Dexcom or Medtronic), CGM data from these devices were used for analysis. The performance of the Dexcom G4 sensor is comparable to the Enlite sensor (MARD 11%, accuracy in hypoglycemia 80%).[16,17]

2.5 | Electrocardiogram

A three channel Holter ECG (Schiller, FD12plus) was mounted by the participants and parents every evening and worn at nighttime (from bed time to wake up time) for at least five consecutive nights. The participants/their families were educated on the use of the Holter ECG and written and illustrated instructions were handed out.

2.6 | CGM analysis

Hypoglycemia was defined as interstitial glucose below 3.7 mmol/L for at least 15 min. A hypoglycemic event was considered symptomatic, if hypoglycemic symptoms were documented in the logbook.

2.7 | ECG analysis

All ECG recordings were screened by a cardiologist and artifacts were excluded. Excluded beats were not replaced by interpolated beats. ECGs were transferred to MATLAB (MathWorks, Natick, MA) and Labchart (Version 8, AD Instruments, Sidney, AU) for further analysis.

QTc was calculated by the Bazett formula (QT divided by the square root of the RR interval). For every episode of hypoglycemia, mean QTc of the entire episode was calculated and compared to a preceding interval of the same duration. To evaluate the effect of sensor glucose on QTc intervals, all recorded sensor glucose values were correlated to the corresponding QTc intervals (5 min means). To consider a possible time delayed effect of glucose on QTc, glucose level with time shifted QTc intervals (from 15 to 225 min) were compared.

2.8 | Heart rate variability

After exclusion of artifacts, RR intervals were identified automatically by the LabChart software, and heart rate variability parameters according to standards[18] were calculated.

Time domain analysis included standard deviation of the RR interval (SDRR) and square root of the mean standard differences of successive RR intervals (RMSSD). SDRR represents the overall variability and cannot be assigned to a specific part of the autonomous nervous system, whereas RMSSD indicates short-term variability and represents parasympathetic activity.

Frequency domain analysis was performed by fast Fourier transformation to analyze the parameters low frequency power (LF, 0.04–0.15 Hz) and high frequency power (HF, 0.15–0.4 Hz). HF reflects parasympathetic activity, whereas LF is considered to be a marker of sympathetic modulation.

Heart rate variability (HRV) parameters were calculated in 15 min windows before the onset of hypoglycemia, at the start of hypoglycemia, before nadir, after nadir, at the end of hypoglycemia and for the first 15 min after a hypoglycemic episode.

2.9 | Statistical analysis

Baseline data and hypoglycemic episodes were described using frequencies (%), means (±SD) or medians (range) as appropriate. Differences between average QTc intervals before and during hypoglycemic episodes were compared by random-intercepts regression analysis (using patient as a random variable). Possible moderation by variables such as sex, age, diabetes duration, HbA1c, duration and nadir of hypoglycemia and serum level of calcium, potassium and magnesium was examined by testing interaction effects between the candidate moderator and the episode (hypoglycemic episode yes/no).

To estimate the effect of glucose values on concurrent and subsequent QT intervals, we employed the same analysis method (i.e., random-intercepts regression analysis with patient as a random variable).

Heart rate variability parameters over time were estimated by random-intercepts regression analysis, using episodes as random variable. For each parameter, two separate models were tested: a first from before hypoglycemia to after nadir; and a second from before nadir to after hypoglycemia. Analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

3 | RESULTS

3.1 | Participant characteristics

Twenty-five children (44% female) aged 8.1–17.6 years (mean age 13.5 years, SD 2.5 years) were included in the study. Diabetes duration ranged from 0.5 to 13.3 years. Fourteen participants (56%) used continuous subcutaneous insulin infusion, HbA1c ranged from 6.3 to 12.9% (mean 7.8%, SD 1.4%).

See Table 1 for an overview of baseline characteristics.

3.2 | Recordings

Complete simultaneous CGM and Holter ECG recordings for five nights were available in 13 patients (=65 nights), 4 complete nights in another 8 patients (=32 nights). In four children, more than one night of glucose or ECG was missing. A total of 106 nights with complete simultaneous recordings were available for analyses. Twelve participants used their own CGM (10 Medtronic, 2 Dexcom), 13 used the iPro system.

3.3 | Hypoglycemia

During 32 nights 42 episodes of nocturnal hypoglycemia occurred in 19 patients. Fourteen patients had repeated nocturnal hypoglycemia. Simultaneous ECG recordings were available for 34 hypoglycemic episodes in 17 patients, in 11 patients two or more episode were integrated in the analysis. In 16 (47%) of those episodes nadir sensor glucose level was below 3.0 mmol/L, in 18 episodes between 3.0 and 3.6 mmol/L.

The duration of analyzed hypoglycemia events ranged from 15 to 365 min (mean 101 min, SD 78 min). Only five events of nocturnal hypoglycemia (all with ECG recording) were stated as symptomatic (sweating, trembling).

TABLE 1 Baseline and laboratory participant characteristics

	Mean (SD)	Median (range)
N = 25		
Age, years	13.5 (2.5)	13.9 (8.1–17.6)
Male, n/%	14/56%	
HbA1c, %	7.8 (1.4)	7.5 (6.3–12.9)
HbA1c, mmol/mmol	62.1 (14.8)	58.5 (45.4–117.5)
Insulin regimen: CSII, n/%	14/56%	
Insulin, U/kg/d	0.9 (0.2)	0.9 (0.5–1.4)
Pre-study potassium, mmol/l	4.7 (0.5)	4.6 (3.8–5.9)
Pre-study calcium, mmol/l	2.4 (0.1)	2.4 (2.2–2.6)
Pre-study magnesium, mmol/l	0.8 (0.05)	0.8 (0.7–0.9)

3.4 | Arrhythmia

No cardiac arrhythmias were observed.

3.5 | Cardiac repolarization/QTc

3.5.1 | QTcintervals and nocturnal hypoglycemia

Mean QTc during nocturnal hypoglycemia (412 ± 15 ms) was longer compared to euglycemia (405 ± 18 ms, $p = 0.005$), Figure 1. This
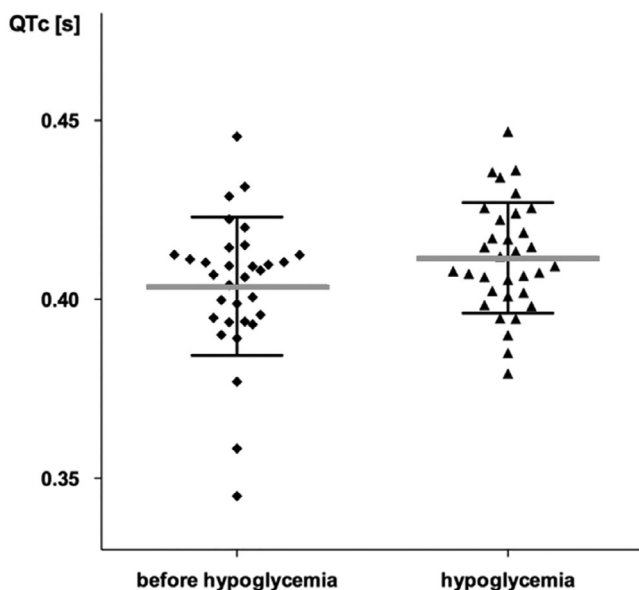

FIGURE 1 QTc(s) during hypoglycemic episodes, compared to preceding intervals of the same duration (thick gray line represents mean, black bars represent ±1 SD)

change was not dependent on age ($p = 0.99$), sex ($p = 0.06$), HbA1c ($p = 0.76$) or duration of diabetes disease ($p = 0.31$). No significant impact on QTc lengthening was observed for the duration or severity (nadir) of the hypoglycemic episode ($p = 0.90$ and 0.38, respectively). However, QTc prolongation was more pronounced with lower magnesium levels ($p = 0.045$).

3.5.2 | Overall correlation of QTc intervals and glucose levels

QTc duration and interstitial glucose were inversely correlated: QTc intervals were longer with lower glucose levels (p-values between <0.001 and 0.02 depending on lag times; Figure 2). This effect was not observed when QTc intervals were correlated to simultaneously recorded glucose values, but only detectable from a time delay of 15 min on. The strongest effect of glucose level on QTc intervals was seen after 105 min: per every 1 mmol/L fall in glucose, QTc increased by 0.96 ms ($p = <0.001$, Figure S1), after which the association faded again.

3.6 | Heart rate variability

Changes in heart rate and HRV parameters are displayed in Table 2 and Figure 3.

Heart rate increased from the 15 min interval before hypoglycemia (mean 69 ± 9 bpm) to the 15 min interval after nadir (mean 72 ± 12 bpm, $p = 0.040$, Figure 3A).

Similarly, several HRV parameters changed during hypoglycemia, that is, from 15 min before hypoglycemia to the interval after nadir of the hypoglycemic event. RMSSD decreased from 88 ± 57 ms to 73 ± 43 ms ($p = 0.039$, Figure 3B), as well as HF power (given in normalized units): from 54 ± 17 to 47 ± 19 ($p = 0.041$, Figure 3D).
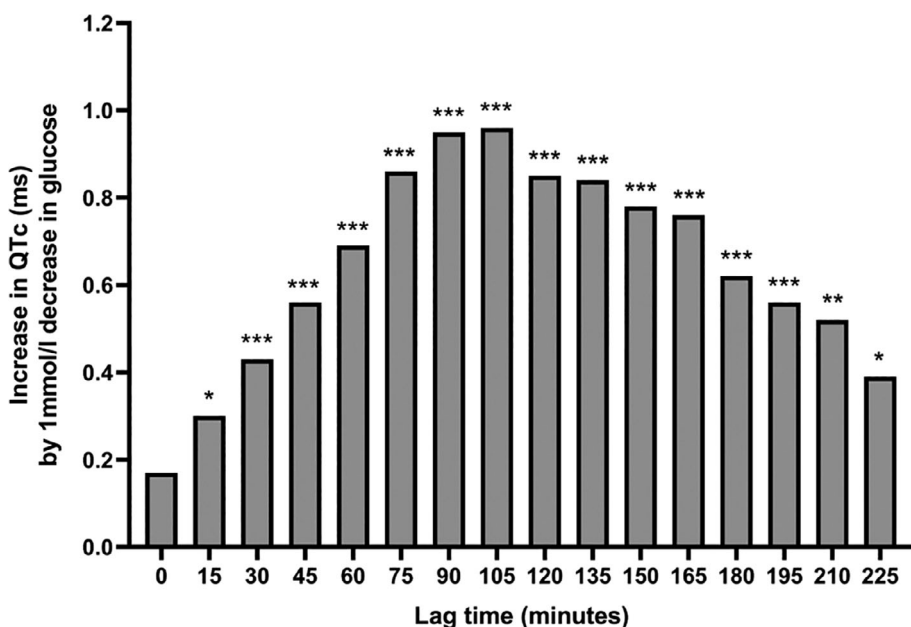

FIGURE 2 Associations of QTc and interstitial glucose for different lag times, from concurrently measured (0 min) to glucose preceding QTc (up to 225 min). Bars represent the increase in QTc (ms) for each 1 mmol/L decrease in glucose. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

TABLE 2　Heart rate and selected HRV parameter changes during hypoglycemia

| Variable	Before hypoglycemia mean (SD)	Hypoglycemia start mean (SD)	Before nadir mean (SD)	After nadir mean (SD)	p-Value[a]	Hypoglycemia end mean (SD)	After hypoglycemia mean (SD)	p-Value[b]
Heart rate, bpm	69 (9)	68 (8)	69 (10)	72 (12)	0.040	73 (12)	69 (17)	0.112
RMSSD, ms	88 (57)	80 (45)	79 (42)	73 (43)	0.040	77 (47)	85 (45)	0.080
SDRR, ms	97 (39)	98 (36)	95 (32)	99 (33)	0.99	102 (34)	99 (39)	0.768
pRR50, %	38 (23)	38 (21)	38 (21)	33 (23)	0.14	33 (22)	37 (21)	0.184
LF, nu	44 (17)	48 (19)	48 (18)	52 (21)	0.048	51 (20)	48 (14)	0.394
HF, nu	54 (17)	50 (17)	51 (17)	47 (19)	0.041	47 (17)	49 (14)	0.538
LF/HF	1.0 (0.7)	1.2 (0.8)	1.2 (0.7)	1.6 (1.3)	0.024	1.5 (1.3)	1.2 (0.7)	0.116
Total, ms^2	4150 (3163)	2930 (1854)	3359 (2487)	4572 (2765)	0.17	4896 (8980)	3720 (2488)	0.182

Note: Parameters calculated for different intervals of 15 min. Values given in mean and SD.

Abbreviations: HF, high frequency power, given in normalized units; HRV, heart rate variability; LF, low frequency power, given in normalized units; pRR50, percentage of subsequent RR intervals that differ more than 50 ms; RMSSD, square root of the mean standard differences of successive RR intervals; SDRR, standard deviation of the RR interval.

[a]Represents linearly tested change from before hypoglycemia to after nadir.

[b]Represents linearly tested change from after nadir to after hypoglycemia.

FIGURE 3　Changes of heart rate and HRV during hypoglycemia. (A) Heart rate (bpm). (B) RMSSD (ms; square root of the mean standard differences of successive RR Intervals) (C) LF (normalized units, nu), low frequency power. (D) HF (nu) high frequency power. HR and LF increase from before hypoglycemia to after nadir with no further change thereafter. RMSSD and HF decrease in the same time intervals. HF, high frequency power; HRV, heart rate variability; LF, low frequency power
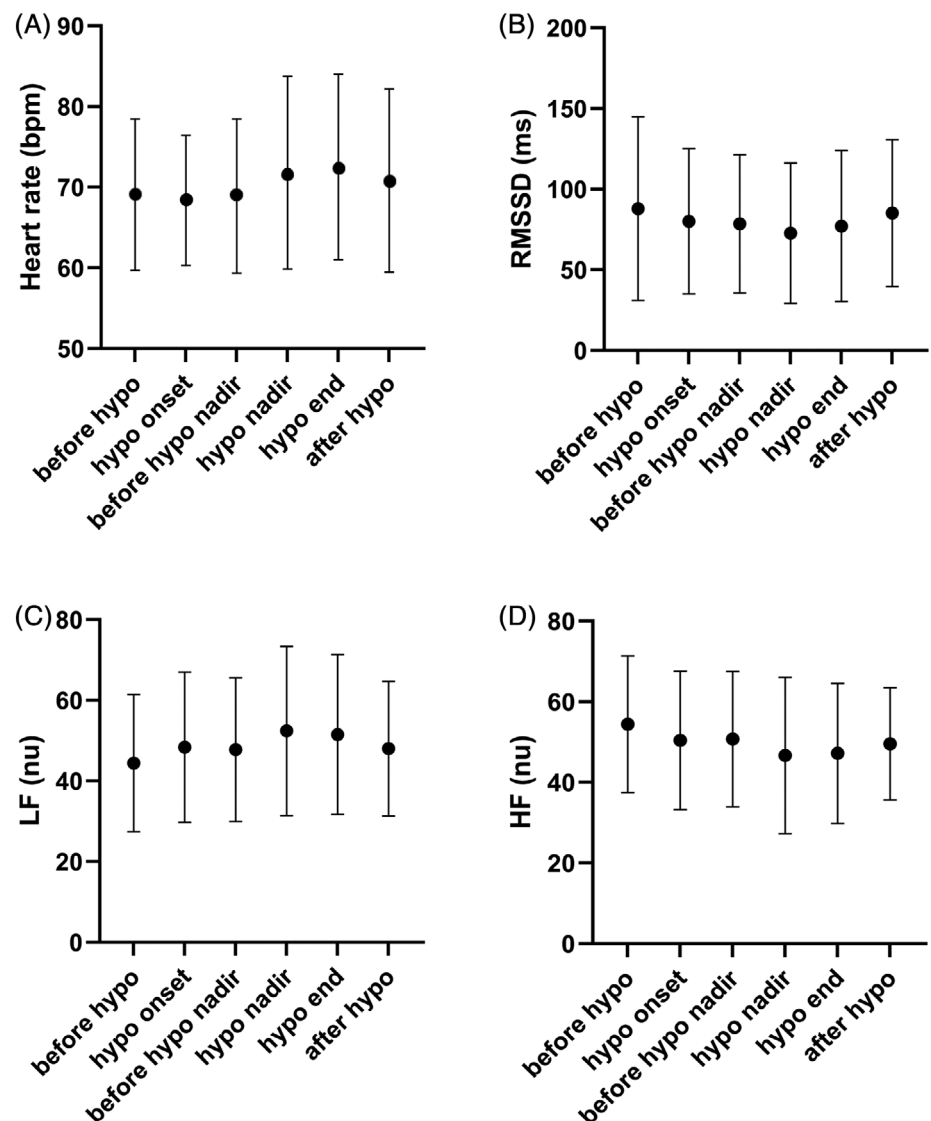
LF power (given in normalized units) increased from 44 ± 17 to 52 ± 21 ($p = 0.048$ s. Figure 3C), as did the relation LF/HF (from 1.0 ± 0.7 to 1.6 ± 1.3, $p = 0.024$).

These changes in HRV variables were not dependent on age, sex, HbA1c, diabetes duration, the duration or nadir of hypoglycemia.

No significant changes in the intervals after nadir to end of hypoglycemia and after hypoglycemia were observed. Furthermore, no significant changes during hypoglycemia were observed for SDRR, pRR50 or total power.

4 | DISCUSSION

This study shows that nocturnal hypoglycemia causes mild but significant prolongation of corrected QT intervals in children with T1D, and that QTc intervals correlate directly with glucose levels most pronounced toward the end of the hypoglycemic episode. Furthermore, HRV parameters changed significantly during hypoglycemia reflecting autonomic modulation. To our knowledge, this is the first study that evaluates cardiac repolarization and heart rate variability during episodes of spontaneous nocturnal hypoglycemia in children with T1D in the home setting.

The prolongation of QTc intervals was significant, however, no abnormal QTc values (i.e., longer than 460 ms) were seen. The changes in QTc intervals seen in our study were rather small. This could be associated to the fact that ECG was only measured through the night. It is known, that sympatho-adrenergic response is reduced by sleep and horizontal position.[19]

The extent of QTc lengthening in our study is comparable to an earlier study in children with diabetes,[20] where glucose was measured in serial venous and not CGM overnight samplings.

Several studies in adults reported a lengthening of QTc intervals during spontaneous nocturnal hypoglycemia, however with variable extent and different methods,[6,8,9] Table S1.

A recent study differentiating between hypoglycemia at daytime and nighttime in 37 adults with diabetes mellitus showed a moderate change in QTc interval during the day and an even smaller change at nighttime.[9]

Gill et al used a setting comparable to our study and found a more distinct prolongation of QTc during hypoglycemia compared to euglycemia in 25 adults with type 1 diabetes.[8]

One single study group documented even shorter QTc intervals during nocturnal hypoglycemia compared to euglycemia.[21] This study however, included only 10 hypoglycemic episodes in six adult patients, and they chose a very short period of 10 heartbeats around the nadir of hypoglycemia for QTc analysis.

The QTc lengthening in our patients was neither dependent of the duration nor the severity of the hypoglycemic episode. This may be explained by the small number of hypoglycemic episodes that were available with concomitant ECG recording.

Because changes in cardiac repolarization are induced by sympatho-adrenergic stimulation due to hypoglycemia, we could have expected a smaller change in QTc in children with longer diabetes

duration or history of severe hypoglycemia. However, this was not observed, which could be attributed to the rather short disease duration in children and the small number of participants that experienced severe hypoglycemia in the past. The only moderating factor that influenced QTc prolongation in the context of hypoglycemia was the serum magnesium level. In participants with lower magnesium levels, the increase in QTc was more pronounced. This is of relevance, as serum magnesium levels are easy to measure and substitution is uncomplicated, not expensive and with few side effects. The effect of magnesium on the hypoglycemia induced QTc lengthening is even more significant given that children with type 1 diabetes were found to have lower magnesium levels than healthy controls.[22]

In addition to a lengthening of QTc intervals during nocturnal hypoglycemia in children, QTc intervals were correlated to glucose levels. The strongest effect could be seen with a delay of 105 min. This temporal association could support the hypothesis that hypoglycemia counter regulation by sympatho-adrenergic activation is responsible for the QTc lengthening. Further inpatient studies with the possibility to measure adrenal hormones and ECG during nocturnal hypoglycemia would be necessary to prove this hypothesis.

Furthermore, the study found significant changes in HRV parameters reflecting autonomic modulation during hypoglycemia.

Of note, a significant change in HRV parameters occurred already 15 min before low sensor glucose levels were detected. This is in accordance with results of a study in adults with diabetes that combined HRV measures from Holter ECGs with CGM and showed that hypoglycemia could be predicted earlier and with a higher sensitivity than by CGM alone.[14,23] Two other studies in adults report hypoglycemia induced changes in HRV parameters.[9,24] In contrast to our results, they reported lower values for LF in hypoglycemia. However, their approach was not comparable to our study: HRV changes were not analyzed before the onset and throughout hypoglycemia, but they compared a 5 min period in hypoglycemia with an euglycemic period in another night.

A recent publication presented data of HRV changes (LF/HF and RMSSD) before the onset of hypoglycemia measured by a Health-Patch in 23 adults. Similar to our study, LF/HF increased significantly, whereas RMSSD decreased.[13]

So far, HRV during nocturnal hypoglycemia has not been studied in children. However, one recent study reported a change in heart rate before nocturnal hypoglycemia compared to euglycemia.[25]

Strengths of this study are the continuous recording of high-quality long-term ECG, the gold standard for HRV analysis combined with glucose monitoring for five consecutive nights. A second strength is the real-life setting of the study. Furthermore, young patients from school age were included.

Limitations are the small sample size of 25 participants. However, other studies in this field report data of a similar sample size. As the study was performed in the home setting, and ECG recording was initiated by the participants/parents every night, technical problems occurred in some participants resulting in incomplete recordings. Confirmation of low sensor glucose levels by capillary blood glucose

measurements would have been desirable. However, we mostly used blinded CGM and only analyzed nighttime glucose profiles, thus hypoglycemia was not noticed by the patients in most cases. As the measurements were not carried out in the hospital, Magnesium levels could not be measured at the moment of hypoglycemia, but at the first day, before the start of the measurement period. Therefore, some variations in Magnesium levels during the study cannot be ruled out. However, a rather low intraindividual variation in serum Magnesium levels has been reported in different studies (1.93 and 3.2%).[26,27]

In conclusion, this study documents that nocturnal hypoglycemia has a QTc prolonging effect in children with diabetes. This QTc alteration was not clinically relevant in our patient group. However, one can assume that in predisposed subjects (i.e., intrinsic QT prolongation due to genetic polymorphisms in ion channel genes, electrolyte imbalances and/or co-medications which prolong QT intervals), QTc prolongation aggravated due to hypoglycemia might become clinically significant. Such patients should be identified and risk constellations avoided.

This is particularly important, as there is evidence, that children with T1D have longer QTc intervals than healthy controls.[28-30] A recent study even found prolonged QTc intervals (>450 ms) in one-third of children with T1D.[25] A superimposed additional QTc prolonging effect of hypoglycemia could be critical in those children. Remarkably, not only hypoglycemia but also diabetic ketoacidosis (DKA) seems to have an impact on QTc intervals: several studies report mean QTc intervals during DKA between 447 and 458 ms with prolonged QTc in 31 up to 53% of patients.[31-34]

It may therefore be advisable to perform occasional ECG recordings in children with diabetes, as treatment with beta-blockers could reduce the risk of cardiac arrhythmia.[35] In these patients at risk, hypoglycemia should be avoided even more aggressively. Avoidance of hypoglycemia is however more difficult in children, because they may not be able to recognize or communicate symptoms of hypoglycemia due to their age.[36] In addition, eating behavior and physical activity are mostly unforeseeable. Children with T1D would therefore particularly benefit from the possibility to earlier detect hypoglycemic events.

The findings of this study suggest that HRV measurements could help to detect hypoglycemia in advance. We could show for the first time in children that HRV parameters change during hypoglycemia and even before hypoglycemia was detected by CGM. Larger studies would be needed to further evaluate the association of HRV and glucose and to confirm these findings.

The recording by Holter ECG used in this study would not be suitable for everyday use and was only performed at nighttime. Comfortable wearable devices measuring heart rate variability are however available, and it may thereby be promising to include measurements of HRV into treatment algorithms for children with diabetes.

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AUTHOR CONTRIBUTIONS

Sara Bachmann and Birgit Donner designed and performed the study. Gabor Szinnai, Melanie Hess and Urs Zumsteg recruited patients and reviewed the manuscript. Marie-Anne Burckhardt reviewed and edited the manuscript. Anne Auderset contributed to the analysis as part of her medical master thesis. Kris Denhaerynck analyzed the data and reviewed the manuscript. Sara Bachmann and Birgit Donner wrote the paper.

PEER REVIEW

DATA AVAILABILITY STATEMENT

Research data are not shared.

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