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Аритмогенное действие гипогликемии, регистрируемое при длительном мониторировании ЭКГ у детей и подростков с сахарным диабетом 1 типа

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Цель. *Определить влияния гипогликемии на длительность интервала QT, показатели вариабельности ритма сердца (ВРС) и частоту нарушений ритма, а также установление факторов, связанных с появлением различных нарушений сердечного ритма у детей и подростков с сахарным диабетом 1 типа (СД1).*
Материалы и методы. *В исследование вошли 150 детей и подростков с СД1 в возрасте 6–18 лет. Всем обследованным было проведено параллельное мониторирование ЭКГ и гликемии в течение 24 ч с автоматической оценкой показателей вариабельности ритма сердца (ВРС) (SDNN, RMSSD, CBBP), длительности интервала QTc. Все данные были усреднены за 5 минут. Были выделены пациенты с эпизодами дневных (7:00–23:00) и ночных (23:00–7:00) гипогликемий (уровень глюкозы в крови ≤3,9 ммоль/л). У этих пациентов произведена оценка длительности QT, частоты аритмий и показателей ВРС.*
Результаты. *Всего было зарегистрировано 39 эпизодов ночных гипогликемий у 32 пациентов (21,3%) и 89 эпизодов дневных гипогликемий у 46 пациентов (30,7%). Во время эпизодов гипогликемии в ночное время отмечалось удлинение интервала QTc (гипогликемия и нормогликемия соответственно: 431 и 420 мсек; P<0,05) и снижение показателей ВРС (гипогликемия vs. нормогликемия соответственно: SDNN 68 и 90 мсек; RMSSD 56 и 61 мсек; CBBP 1993 и 2069 мсек; P<0,05). То же самое наблюдалось в дневное время (гипогликемия vs. нормогликемия соответственно: SDNN 58 и 63 мсек; RMSSD 32 и 36 мсек; CBBP 1568 и 1646 мсек; P<0,05). Во время эпизодов гипогликемии по сравнению с нормогликемией как в дневное, так и в ночное время регистрировались различные вентрикулярные и суправентрикулярные нарушения ритма, снижение сегмента ST и амплитуды зубца Т. Наличие различных нарушений ритма было ассоциировано с автономной нейропатией и периферической полинейропатией.*
Заключение. *Во время эпизодов гипогликемии отмечается снижение показателей ВРС, удлинение интервала QT и учащение эпизодов нарушения ритма. Предрасполагающим фактором развития нарушений ритма является наличие в анамнезе автономной нейропатии и периферической полинейропатии.*
Ключевые слова: *сахарный диабет; гипогликемия; аритмия; интервал QTc; автономная нейропатия; вариабельность ритма сердца*

Arrhythmogenic effects of hypoglycemia in children and adolescents with type 1 diabetes mellitus

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Aim. *To determine the effects of hypoglycemia on the duration of QT interval, heart rate variability (HRV) and frequency of arrhythmic events, as well as to closer investigate the factors associated with the development of various heart rhythm disorders in children and adolescents with type 1 diabetes mellitus (T1DM).*
Materials and methods. *The study included 150 children and adolescents with T1DM at the age of 6–18 years. All participants underwent Holter monitoring and continuous glucose monitoring (CGM) for 24 hours. QTc and HRV parameters (SDNN, RMSSD, SVVR) were calculated automatically. Data was averaged for 5'-interval and juxtaposed with CGM. Patients identified with hypoglycemic events (blood glucose <3.5 mmol/L) during the day (7:00–23:00) and nighttime (23:00–7:00) were selected for further study. In these patients length of QTc and RR intervals, HRV parameters and arrhythmic events were analyzed and collated with CGM data.*
Results. *We observed 39 episodes of nocturnal hypoglycaemia in 32 patients (21.3%) and 89 episodes of daytime hypoglycaemia in 46 patients (30.7%). Marked prolongation of QTc (hypo- vs. normoglycemia, respectively: 431 vs. 420 ms; p<0.05) and reduced HRV (hypo- vs. normoglycemia, respectively: SDNN 68 and 90 ms; RMSSD 56 and 61 ms; p <0.05) occurred during episodes of nocturnal hypoglycemia. The same pattern was observed during the day (hypo- vs. normoglycemia, respectively: SDNN 58 and 63 ms; RMSSD 32 and 36 ms; p<0.05). Eleven subjects with nocturnal hypoglycemia demonstrated either ventricular or supraventricular*

premature complexes. Thirty of subjects with diurnal hypoglycemia also had either ventricular or supraventricular premature complexes. Hypoglycemic episodes vs. normoglycemia were characterized by an increase in ventricular and supraventricular ectopic beats, ST segment and T-wave amplitude depression. Various rhythm abnormalities were associated with cardiovascular autonomic and peripheral neuropathy.

Conclusion. *During episodes of hypoglycemia, HRV parameters decrease, QT elongates and episodes of arrhythmia occur more frequently. History of autonomic and peripheral neuropathy contributes to the development of arrhythmias.*

Keywords: *diabetes mellitus; hypoglycemia; arrhythmia; QTc; autonomic neuropathy; heart rate variability*

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The prevalence of hypoglycemia

In patients with diabetes mellitus (DM) the significance of hypoglycemia is often underestimated, although it is quite common. For example, in adult patients with type 1 diabetes (T1DM) a person has on average 42.9 hypoglycemia episodes per year, and a patient with type 2 diabetes (T2DM) has 16.4 episodes of hypoglycemia per year [1]. Furthermore, the frequency of hypoglycemic episodes requiring extraneous intervention, i.e. severe hypoglycemia, amounts to 1.2-3.2 episodes per patient with type 1 diabetes and 3.5-7 episodes per patient with type 2 diabetes [1, 2].

In children, hypoglycemia is also a widespread problem due to difficulties in the adjustment of insulin dosage, appetite liability, unpredictable physical activity, limited ability of children to feel hypoglycemia and prolonged period of fasting during the night. A particular problem in children are episodes of nocturnal hypoglycemia. This is due to the fact that nocturnal hypoglycemia in children is a frequent phenomenon with many episodes sufficiently severe and prolonged [3]. Most episodes of nocturnal hypoglycemia occur hidden and are recorded only during continuous glucose monitoring (CGM). According to CGM, the frequency of episodes of nocturnal hypoglycemia in children and adolescents reaches 68%, while 77 % of them remain hidden [4]. Hypoglycemia, including asymptomatic, is much more common in younger children. Thus, according to Amin R. et al., the frequency of nocturnal hypoglycemia in children 12 years and younger is 78 %, while 91 % of these occur hidden [5].

The effects of hypoglycemia

Development of various complications is closely associated with episodes of hypoglycemia. Hypoglycemia can lead injuries, accidents and even death [6]. The disturbing fact is that in recent years there is an increasing mortality due to hypoglycemia. Before the 2000s, mortality due to hypoglycemia, according to various authors, was 2 to 4%, while in studies published in 2006-2008 this figure rose to 4-10% [7].

Children are most susceptible to severe consequences of hypoglycemia. The continued maturation of central nervous system puts them in a risk group towards the development of cognitive deficits as a result of hypoglycemia [8]. In children who have suffered from this effect under the age of 5 years, the cognitive function and cerebral structures were affected to a greater extent than those who were exposed hypoglycemia later in life [9]. Hypoglycemia in children is accompanied by problems with memory and learning. Heavy hypoglycemia is associated with decreased verbal function and IQ level [10].

Sudden death associated with hypoglycemia

Several mechanisms may be involved in the development of sudden death associated with hypoglycemia. An important pathogenetic link is the development of so-called hypoglycemia-associated autonomic failure (HAAF). HAAF is a form of sympathoadrenal system failure resulting from the recent episodes of iatrogenic hypoglycemia which leads to a decrease in the threshold glucose level in the blood, triggering counter-regulatory response necessary to restore normoglycemia [6]. As a result, patients with frequent episodes of hypoglycemia have no symptoms at lower blood glucose until it reaches the minimum values. HAAF development is associated with more than 25-fold increased risk of severe hypoglycemia against the backdrop of intensified insulin therapy and emergence of repeated episodes of hypoglycemia.

Repeated episodes of hypoglycemia, in turn, can have proarrhythmic action. Clinical studies have shown that episodes of hypoglycemia accompanied by lengthening of the QT interval [11, 12], which may be associated with the development of life-threatening arrhythmias. Recent studies have shown that hypoglycemia is linked with various rhythm disorders in adults with type 1 diabetes [3]. It is believed that the emergence of heavy rhythm disturbances on the background of hypoglycemia is the cause of so-called «dead in bed syndrome », which was described in 1991. There is no doubt that hypoglycemia can lead to death [7], but for a long time it could not be linked to the emergence of sudden death. The death of a young patient with type 1 diabetes against the background of very low levels of blood glucose during CGM glucose was reported in 2010 [13].

Heart rate variability (HRV) is a powerful predictor of sudden cardiac death in patients with cardiovascular disease, as well as in the general population [14]. Furthermore, the HRV reduction is closely associated with deterioration of the functional state of the cardiovascular system [15]. Diagnostics of one of the complications of diabetes – cardiovascular autonomic neuropathy (CAN) is based on the assessment of HRV [16]. The presence of CAN significantly worsens the prognosis in patients with diabetes [3].

The purpose of the study

To determine the effect of hypoglycemia on the duration QT interval, HRV parameters and frequency of rhythm disturbance, as well as to identify factors associated with the appearance of various heart rhythm disorders in children and adolescents with type 1 diabetes.

Materials and methods

The study included 150 children and adolescents with T1DM at the age of 6 to 18 years (mean±SD: 13.8±2.9), with disease duration from 1 month to 16 years (mean±SD: 5.5±3.9) and HbA_{1c} level 9.2% (from 5.3 to 19.6%). All patients or their parents signed informed consent.The main study

All patients were subjected to 12-channel ECG. The following cardiovascular autonomic tests were used to assess the autonomic status: a deep breathing test, Valsalva maneuver, orthostatic test. All samples were carried out in fasted patients in the morning before noon and were performed lying with the upper part of the body raised at 30° while recording ECG continuously. Sample recording began after a 20 minute rest. Interval between samples was not less than 3 minutes. Blood glucose levels before and after the test were at least 4 mmol/l.

Monitoring of blood glucose and ECG

In all patients simultaneous monitoring of glucose and ECG was performed. The duration of a parallel recording in each patient was at least 24 hours. The following systems for CGM were used: CGMS (Medtronic, USA), iPro (Medtronic, USA), Paradigm REAL-Time (Medtronic, USA), Guardian (MiniMed, USA). 24-h ECG was recorded in three modified chest leads MV5, MAVF and MV3 with a sampling frequency of 250 Hz.

The automated measurement of QTc interval, RR, ST segment, T wave was performed in a lead with the maximum amplitude of the T wave using a procedure described previously [10, 11]. HRV assessment was carried out using the parameters recommended by the working group of the European Society of Cardiology: SDNN – standard deviation of normal RR intervals, RMSSD – the root mean square of the differences in successive pairs of RR intervals [17] as well as in terms of the mean weighted variation of rhythmogram (MWVR) developed in Russian Cardiology Research and Production Center [15]. This indicator is validated both in adults and in children with different diseases, and it possesses several advantages compared with other HRV parameters [15].

Holter ECG monitoring and CGM were conducted in parallel. The time of the devices was synchronized. In order to compare the readings of the glucose monitor readings Holter monitor for statistical purposes, we used the values of QTc, heart rate, blood glucose, SDNN, RMSSD, MWVR, and the number of ectopic complexes averaged over 5 minutes. To evaluate the measured values in daytime and night time the daily records were allocated in two timeslots from 7 to 23 hours (DAY) and from 23 to 7 hours (NIGHT).

Hypoglycemia

In our study, the decrease of sensor glucose (SG) level according to the CGM to values ≤3,9 mmol/l for over 20 minutes was assumed a hypoglycemia. This value was chosen based on the recommendations by the working group of the American Diabetes Association [6].

Statistical analysis

Statistical processing of the results was performed using the statistical package STATISTISA (StatSoft, Tulsa, OK, USA). The difference between the normally distributed attributes was assessed using t-test. In the case of non-normal distribution the Wilcoxon T test was used. A p value less than 0.05 was considered significant. The following abbreviations were used: M – mean , SD – standard deviation of the sample, p – significance level achieved.

Results

The frequency of hypoglycemia episodes

During the study, at least one episode of nocturnal hypoglycemia was registered in 32 patients (21.3%), and at least one episode in the daytime in 46 patients (30.7%). The total number of episodes of hypoglycemia was 89 and 39 in the daytime and nighttime, respectively. The maximum duration of a hypoglycemia episode with glucose level of ≤3.9 mmol/l was 9 hours 15 minutes, and the maximum duration of a hypoglycemia episode with glucose level of ≤2.5 mmol/l was 7 hours 45 minutes.

Complications of DM

In our study, diabetic peripheral neuropathy (DPN) was diagnosed in 45 patients (30.0%) , diabetic nephropathy at the stage of microalbuminuria in 3 patients (2%), diabetic retinopathy in 11 patients (7.3%). Subclinical CAN was diagnosed when two out of five tests were positive (3 cardiovascular tests, QTc prolongation over 440 ms, a decrease in MWVR to less than 1370 ms in adolescents and to 1170 ms in children). The early signs of CAN were detected in 34 patients (22.7%).

Duration of the QTc interval and HRV during hypoglycemia

The average duration of the QTc interval during hyperglycemia over the total time of the study in all patients was more than during normoglycemia (434±28 and 428±28 ms; $p < 0.05$). Also, in all patients the HRV parameters were reduced during hypoglycemia as compared to normoglycemia (blood glucose ≤3.9 and 5-15 mmol/l: SDNN 66±35 and 75±37 ms; RMSSD 47±34 and 53±35 ms; MWVR 1804±908 and 2008±1187 ms, $p < 0.05$).

In patients with episodes of hypoglycemia we assessed the duration of the QTc interval and HRV parameters separately during the DAY and NIGHT periods (Table 1). Both in the daytime and at night during episodes of hypoglycemia a significant lengthening of the QTc interval and reduced HRV parameters were recorded.

The frequency of rhythm disturbances on the background of hypoglycemia

To assess the arrhythmogenic effect of hypoglycemia the patients with various arrhythmias (ventricular and supraventricular premature beats), and episodes of hypoglycemia were separately analyzed. Rhythm disturbances on the background of nocturnal hypoglycemia were recorded in 11 patients during the NIGHT, and in 30 patients during the DAY (Table 2). During the episodes of hypoglycemia, both in the daytime and at night an increase of ectopic activity, lengthening of the QTc interval, reduction of all HRV parameters , as well as depression of ST-segment and amplitude of the T wave were

observed (Fig. 1).Data are presented as M±SD. SG – sensor glucose, HR – heart rate, bpm – beats per minute, ms – milliseconds, mV – millivolts.

Factors associated with rhythm disturbances

To determine the factors associated with the presence of premature beats, we carried out multiple regression analysis (Table 3). The duration of T1DM (years), age of patients (years), the level of HbA_{1c} (%) and the complications of T1DM were considered predictors; the presence of ectopic complexes in daily ECG (yes/no) was considered a dependent variable. The emergence of various rhythm disturbances on a daily ECG is a result of the presence of the DPN and CAN ($p < 0.05$). The age, duration of the disease, and HbA_{1c} levels did not affect the presence of rhythm disturbances ($p > 0.05$).

Discussion

As in other studies, we have shown that episodes of hypoglycemia are quite a common occurrence, and many of the episodes are prolonged and serious. We have previously described in detail the prolongation of the QTc interval recorded during hypoglycemia as well as the mechanisms leading to this [11, 12, 18]. Reduction in HRV parameters on the background of hypoglycemia in T1DM patients has also been previously described, although only in adult patients [19]. QT prolongation and reduced HRV parameters in patients with DM are the signs of autonomic neuropathy and are used as diagnostic criteria for this complication [16]. Change repolarization combined with deterioration of HRV reflects the impairment of vascular dynamics and of the regulation of cardiac rhythm. Impairment of heart rate regulation during autonomic neuropathy is associated with decreased vagal tonus, leading to the relative sympathicotonia. In our work, we have shown a decrease of HRV parameters during spontaneous episodes of hypoglycemia, which can also be explained by the increased sympathetic activity, because during hypoglycemia on the background of secretion of contra-insular hormones, the sympathoadrenal system is activated. The difference between these states is that in patients with autonomic neuropathy the changes are persistent and associate with damage to the autonomic nerve fibers.

We found that episodes of hypoglycemia were accompanied by the increase in the frequency of premature beats. Arrhythmias or ECG changes in patients with diabetes have been described during spontaneous and induced hypoglycemia. Among them are ventricular ectopic complexes and ST

Table 1

ECG parameters depending on the SG level

	SG ≤3.9 mmol/l	SG 5–15 mmol/l	p value
	NIGHT (23:00-7:00) n=32		
SG, mmol/l	3.2±0.5	7.7±2.1	<0.05
HR, bpm	68±10	69±18	0.03
SDNN, ms	68±38	90±37	<0.05
RMSSD, ms	56±34	61±37	<0.05
AWV, ms	1993±883	2069±922	<0.05
QTc, ms	431±27	420±24	<0.05
	DAY (7:00-23:00) n=46		
BG, mmol/l	3.3±0.5	8.6±2.6	<0.05
HR, bpm	92±18	89±16	<0.05
SDNN, ms	58±28	63±31	<0.05
RMSSD, ms	32±26	36±38	<0.05
AWV, ms	1516±596	1655±785	<0.05
QTc, ms	436±22	430±25	<0.05

Data are presented as M ± SD. SG - sensor glucose, HR – heart rate, bpm – beats per minute, ms - milliseconds, mV – millivolts.

Table 2

Frequency of supra- and ventricular premature beats and other ECG parameters depending on the SG level

	SG ≤ 3.9 mmol/l	SG 5-15 mmol/l	p value
	NIGHT (23:00-7:00) n=11		
Average amount of ectopic episodes, premature beats/5 min	0.09	0.046	<0.05
HR, bpm	70±10	74±18	<0.05
SDNN, ms	69±36	81±41	<0.05
RMSSD, ms	54±33	60±41	<0.05
MWVR, ms	1873±895	2117±1091	<0.05
QTc, ms	449±28	422±28	<0.05
Displacement of ST segment, mV	0.006±0.15	0.081±0.07	<0.05
T wave amplitude, mV	0.41±0.31	0.66±0.21	<0.05
	DAY (7:00-23:00) n=30		
Average amount of ectopic episodes, premature beats/5 min	0.576	0.069	<0.05
HR, bpm	95±18	90±16	<0.05
SDNN, ms	58±29	61±30	<0.05
RMSSD, ms	33±29	34±30	0.3
MWVR, ms	1567±799	1646±978	<0.05
QTc, ms	444±22	439±25	<0.05
Displacement of ST segment, mV	0.046±0.09	0.016±0.09	<0.05
T wave amplitude, mV	0.422±0.27	0.376±0.26	<0.05

Data are presented as M ± SD. SG - sensor glucose, HR – heart rate, bpm – beats per minute, ms - milliseconds, mV – millivolts

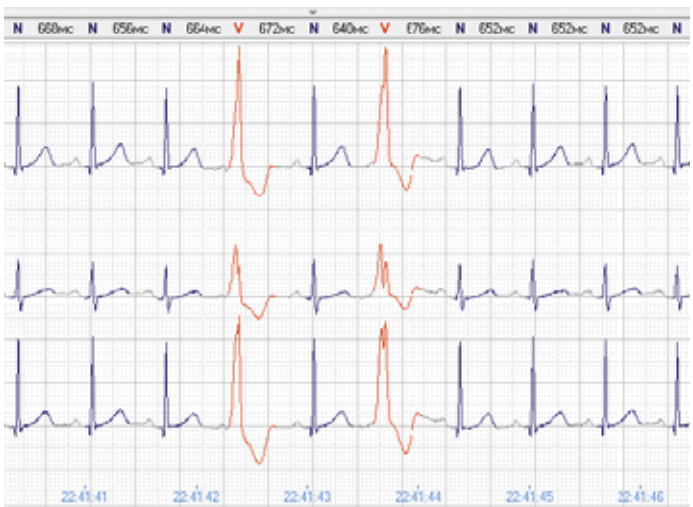

Figure 1. Ventricular premature complexes registered during an episode of hypoglycemia in patients 15 years of age. Blood glucose: 3.3 mmol/l. Duration of the QTc interval: 495 ms.

Table 3

Factors associated with the presence of rhythm disturbances. The results of multiple regression

n=150	β	SE	B	SE	p value
Age at the moment of study	0.19	0.10	0.03	0.02	0.06
Duration of T1DM	-0.18	0.11	-0.02	0.01	0.11
HbA_{1c}	0.00	0.10	0.00	0.03	0.97
DAN	0.25	0.11	0.27	0.11	<0.05
Microalbuminuria	0.00	0.09	0.07	0.29	0.80
Retinopathy	0.08	0.10	0.14	0.19	0.45
CAN	0.20	0.10	0.24	0.11	<0.05

SE - standard error of the mean.

segment depression [20]. However, only T2DM patients were included in that study, which leads to the possible presence of coronary artery disease (CAD). In another study [3] in adult T1DM patients various ECG abnormalities (prolongation of the QT interval, sinus bradycardia less than 40 beats/min, ventricular and supraventricular ectopic rhythms, and changes of the P wave) were registered during nocturnal hypoglycemia. In our study, only the increase in the frequency of supra- and ventricular premature beats, and depression of the ST-segment and the T-wave amplitude were detected on the background of hypoglycemia. A smaller range of different rhythm disturbances in our study is likely associated with lesser age and T1DM duration of the patients.

In our study, arrhythmias were associated with the presence of DPN and CAN. Autonomic neuropathy may itself be connected with lengthening of the QTc interval, and possibly sudden death [21]. Lengthening of the QTc interval occurs frequently in children and adolescents with T1DM [18], especially when there are early signs of autonomic neuropathy [22]. It is believed that autonomic neuropathy is a predisposing factor to the sudden death syndrome – «dead in bed syndrome» [21], which is a consequence of fatal rhythm disturbances.

The main limitation of our study is the possibility of low frequency of the rhythm disturbances in the surveyed population, which is related to the age and not particularly prolonged disease. Rhythm disturbances in combination with hypoglycemia were registered only in 11 patients at night and in 30 during the day time. In addition, the CGM systems may be less accurate than the direct measurement of blood glucose, although they are validated in the hypoglycemic range [23].

Despite the potential limitations, our study shows that hypoglycemia may lead to the lengthening of the QTc interval, reduced HRV parameters, reduced amplitude of the T wave and ST segment and, importantly, has an arrhythmogenic effect in children and adolescents with DM1.

The authors declare no conflict of interest associated with the data presented in this paper.

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