REPUBLIC OF AZERBAIJAN

On the rights of the manuscript

ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

CHARACTERISTICS OF HEART RHYTHM VARIABILITY AND ELECTROPHYSIOLOGICAL REMODELING OF THE MYOCARDIUM IN CHILDREN WITH TYPE 1 DIABETES

Spesialty 3220.01 – Pediatrics

Field of science: Medicine

Applicant: **Laman Bakhtiyar Sultanova**

Baku – 2025`

Dissertation work was performed at the Department of Family Medicine and Educational - Therapeutic Clinic of Azerbaijan Medical University.

Scientific Supervisor: doctor of Medical sciences, professor **Ibrahim Isa Isayev**

Scientific advisor: doctor of Medical sciences, professor **Mirzazade Valeh Agasafa**

Official opponents: doctor of Medical sciences **Raksana Yusif Mammadova**

doctor of Medical sciences **Naila Djalil Rahimova**

doctor of Philosophy in Medicine **Zahir Kamil Rahmanov**

Dissertation Council ED 2.27 of Supreme Attestation Commission under the President of the Republic of Azerbaijan operating at Azerbaijan Medical University.

Chairman of the Dissertation council:
doctor of Medical sciences, professor
Vasadat Ali Azizov

Scientific Secretary of the Dissertation council:
doctor of Philosophy in Medicine, associate professor
Tora Akif Sadigova

Chairman of the scientific seminar:
doctor of Medical sciences, associate professor
Fatima Oktay Seyidbeyova

AZƏRBAYCAN RESPUBLİKASI SƏHİYYƏ NAZİRLİYİ AZƏRBAYCAN TİBB UNİVERSİTETİ

İMZANI TƏSDİQ EDİRƏM
Azərbaycan Tibb Universitetinin
ELMİ KATİBİ
Tibb üzrə fəlsəfə doktoru, dosent
Rəşad Şəmsəddin oğlu Talışınskiy
"07" 02 2025 il

GENERAL DESCRIPTION OF THE RESEARCH

Relevance of the topic: Diabetes mellitus (DM), a significant condition within the spectrum of endocrine disorders in children, is marked by a steadily increasing number of cases each year[1]. According to statistics, the global number of diabetes patients has more than doubled in the last decade, exceeding 537 million people by the end of 2021. Forecasts from the International Diabetes Federation (IDF) predict that 643 million people will be living with diabetes by 2030, rising to 783 million by 2045. Additionally, approximately 96,000 children under the age of 15 are diagnosed with type I diabetes (DM type I) annually. Type I diabetes accounts for the majority of diabetes cases in children and adolescents, raising significant concerns among pediatricians and health organizations [2].

As a result of numerous scientific studies, it can be noted that diabetes mellitus causes many serious complications. Cardiovascular system damage is one of the main causes of death during diabetes. According to most clinicians, it is the changes in the cardiovascular system that play a role in increasing the number of deaths in recent years. Thus, from 2000 to 2016, premature deaths related to DM increased by 5%, and in 2019, this pathology was the direct cause of the death of 1.5 million people[3].

---

1. Гарипова, А.Ф., Вагапова, Г.Р., Сайфутдинов, Р.Г. Интервал QT как предиктор внезапной сердечной смерти у больных ишемической болезнью сердца в сочетании с сахарным диабетом 2-го типа // ПМ, -2014. №6 (82), -с. 109-113.
2. Акрамова, Э.Г. Дисперсия интервала QT при холтеровском мониторировании у пациентов с хронической обструктивной болезнью легких и бронхиальной астмой // Клиническая медицина, –2012. Том 90, № 1, - с. 25-28.
3. Darpo, B. Cardiac Safety Research Consortium: Can the Thorough QT/QTc Study Be Replaced by Early QT Assessment in Routine Clinical Pharmacology Studies? Scientific Update and a Research Proposal for a Path Forward / B.Darpo, C. Garnett, C.Benson [and etc.] // American Heart Journal, -2014. №168 (3), -p. 262–272.

Disturbances in the cardiovascular system during DM are called "cardiac autonomic neuropathy" (CAN) by many authors[4]. These pathological processes cause an energetic deficit in cardiomyocytes, and as a result, the metabolic basis of cardiomyopathy is established against the background of functional and ultrastructural changes in the myocardium. One of the most important conditions is to predict the risk of premature death of patients with DM and to determine the markers for preventing these risks. It is known that prolongation of the QT interval is an indicator of electrical instability of the myocardium and can lead to life-threatening fatal ventricular tachyarrhythmia and sudden death[5]. Although several studies have been devoted to the study of changes in the QT interval during DM type 1, there is no complete clarity on this issue: the results are often contradictory, there is no accurate information about the relationship with other symptoms of the disease, duration. Currently, the characteristics of the QT interval, which characterizes the electrical stability of the myocardium during type 1 diabetes in children, depending on age and duration of the disease, have not yet been fully studied, and there are many controversial and unsolved questions in this problem[6]. Assessment of heart rhythm variability (HRV) plays an important role in the detection of CAN[7]. Evaluation of HRV indicators helps to detect early manifestations of pathological changes in the myocardium and allows to prevent complications that may develop in the cardiovascular system during many diseases.

4. Баевский, Р.М., Иванов, Г.Г. Вариабельность сердечного ритма: теоретические аспекты и возможности клинического применения // Ультразвуковая и функциональная диагностика, -2001. № 3, -с. 108-127.
5. Дианов, О.А. Кардиоваскулярные нарушения у детей при СД / О.А.Дианов, С.Ф.Грусаев [и др.] // Сахарный диабет, -2005. №8(4), -с.40-44.
6. Демяненко, А.Н. Эктопическая активность и паузы ритма в ночные часы по данным холтеровского мониторирования у детей с диабетической кардиоваскулярной нейропатией в зависимости от уровня гликемии // Смоленский медицинский альманах, -2018. №4, -с. 45-50.
7. Marek Malik, J Heart rate variability: Standards of measurement, physiological interpretation, and clinical use / J.Marek Malik, B.Thomas Bigger [and etc.] // European Heart Journal, -1996, Vol. 17, Issue 3, -p. 354-381.

Disruptions in myocardial homogeneity that can occur in diabetes mellitus (DM) are associated with an increased risk of developing various arrhythmias. The primary "platform" for the emergence of arrhythmogenic mechanisms is the electrical instability of the myocardium, which is evidenced by the presence of ventricular late potentials[8]. Changes in myocardial homogeneity, in most cases, do not present clinical symptoms but serve as a significant risk factor for sudden ventricular tachyarrhythmias. In the early stages, these changes are primarily characterized by delayed electrical activity.

The increase in the risk of developing complications from the cardiovascular system during DM makes it necessary for clinicians to conduct research in the direction of determining highly informative indicators such as VLPs[9].

Despite this, there are no studies specifically dedicated to examining the characteristics of indicators related to CAN in children with type 1 DM. Additionally, there is a lack of research on the combined analysis of HRV and VLPs in this condition, as well as on identifying diagnostically significant interactions between these parameters.

The object of the research is the processes occurring in the cardiovascular system in children diagnosed with type 1 diabetes. The characteristics of heart rhythm variability and myocardial electrophysiological remodeling in children belonging to this type are the direct subject of research.

The aim of the study. The purpose of the study is to study the heart rhythm variability and electrophysiological remodeling characteristics of the myocardium in children with type 1 diabetes. For this purpose, the following tasks were carried out.

Objective of the study:

1. Study of the bioelectric stability of the myocardium based on the analysis of the QT interval in children with type 1 DM.

---

8. Олейников, В.Э. Ранние предикторы прогрессирования сердечной недостаточности у больных, перенесших инфаркт миокарда / В.Э.Олейников, Е.В.Душина [и др.] // Кардиология, -2020. №60 (11), -с. 84-93.
9. Fox, L.A. Persistence of abnormalities in white matter in children with type 1 diabetes / L.A.Fox [and etc.] // Diabetologia, -2018. №61(7). –p. 1538-1547.

2. Determining the characteristics of vegetative regulation of the cardiovascular system based on the cycle and spectral analysis of HRV depending on the duration of the disease in children with DM type 1 of different ages;

3. Determining the late potentials of the ventricles by means of high-intensity electrocardiography in school-age children with DM type 1;

4. Study of interactions between indicators characterizing bioelectrical stability of myocardium and variability of heart rhythm during type 1 DM in children;

5. Determining the criteria for remodeling of myocardial bioelectrical activity aimed at early detection of cardiac autonomic neuropathy in school-aged children with DM type 1, depending on the duration of the disease.

Research methods: To conduct the research, fulfill the tasks and achieve the main goal, various research methods and general research methods that are unique to medical science were used. In order to prove the proposed scientific propositions, long-term and short-term observations were made on the patients of the mentioned category, collected facts. comparative analysis, laboratory and instrumental examinations were carried out. In addition, statistical methods were used to clarify various issues.

Key theses to be defended:

1. Myocardial bioelectric activity in school-aged children with type 1 DM is unstable, homogeneity is disturbed, and this manifests itself in early repolarization of the ventricular myocardium accompanied by prolongation of the QT interval, its corrected variant and dispersion.

2. In children with DM type 1, changes in the HRV cycle and spectral indicators are noted from the first years of the disease, and as the duration of DM increases, these disorders deepen.

3. Due to the electrophysiological heterogeneity of the myocardium in children with type 1 DM, VLPs foci exist, the presence of such foci acts as an independent prognostic factor for the

risk of dangerous arrhythmias and creates wide opportunities for reducing the risk of sudden cardiac death in children with diabetes.

Scientific novelty of the study:

- The state of bioelectrical stability of the myocardium in school-age children with type 1 DM was studied depending on the duration of the disease;
- periodical and spectral analysis of the heart rhythm variability in the dynamics of the disease in children with type 1 diabetes mellitus was carried out, and based on the obtained results, the characteristics of the vegetative regulation of the cardiovascular system were determined;
- the frequency of occurrence of late ventricular potentials and the features of their characteristic indicators were studied by means of high-intensity electrocardiography in school-age children, depending on age and duration of diabetes mellitus;
- based on the study of mutual relations between indicators characterizing the bioelectrical stability of the myocardium and heart rhythm variability during type 1 diabetes mellitus in children, the remodeling criteria of the bioelectrical activity of the myocardium aimed at the early detection of cardiac autonomic neuropathy were proposed.

Theoretical and practical significance of the work:

The results of the study allow early detection of myocardial bioelectrical instability based on the analysis of electrocardiographic indicators in children with type I type I diabetes of different ages.

The application of the criteria obtained as a result of the study of the variability of the heart rhythm during DM type 1 in children and determined by high-intensity electrocardiography lays the groundwork for the early detection of cardiac autonomic neuropathy in these patients and the prevention of complications that may develop from the cardiovascular system.

Approbation of dissertation : Reports on the results obtained during the research were made at various local and international

conferences. Among them, "Actual problems of medicine-2020", dedicated to the 90th anniversary of AMU, International scientific-practical congress "Actual problems of medicine-2021" held in connection with the 100th anniversary of prof. Tamerlan Aliyev, The scientific-practical conference (2021) dedicated to the memory of Prof. Kasenkov and the 30th anniversary of the independence of the Republic of Kazakhstan entitled "Demographic transition and issues of aging in biochemical and pathophysiological aspects" should be noted.

Th poster-presentation is presented by author as part of the "Diabetes Technologies Symposium" held in Turkey in May 2021.

The research results were applied in the Department of Children's Health and Diseases of the Educational-Therapeutic Clinic of AMU and in the teaching process of the Department of Family Medicine of AMU.

The initial discussion of the dissertation work was discussed at a joint meeting of the staff of the "Family Medicine", "II Pediatric Diseases" and "II Internal Diseases" departments of the Azerbaijan Medical University on June 16, 2023 (protocol N 11). The dissertation work was discussed at the meeting of the Scientific Seminar under the ED 2.27 Dissertation Council operating under the Azerbaijan Medical University on 4 December 2024.

Application of the research results. The research results were applied in the teaching process of the Department of Children's Health and Diseases of the Teaching-Therapeutic Clinic of AMU and the Department of Family Medicine of AMU.

The name of the organization where the research was performed: Department of Family Medicine of Azerbaijan Medical University, Educational-Therapeutic Clinic.

Scientific publications: the main provisions of the dissertation are reflected in 14 scientific works (8 articles and 6 theses).

Volume and structure of the dissertation: The dissertation consists of 141 computer-written pages, with a total volume of 192,897 characters. It is structured as follows: an introduction (10,349 characters), five chapters (Chapter I – 43,597 characters; Chapter II – 14,371 characters; Chapter III – 19,838 characters; Chapter IV – 36,015 characters; Chapter V – 25,538 characters), a discussion of the obtained results (40,056 characters), conclusions (2,195 characters), practical recommendations (938 characters), a bibliography, and a list of abbreviations. The research work is illustrated with 12 figures and 7 tables. The bibliography includes 148 sources, of which 2 are in Azerbaijani, 44 in Russian, and 102 in English.

MATERIALS AND METHODS OF RESEARCH

120 school-aged children (ages 6-17) were recruited in accordance with the goals and objectives of the research:

Of these, 56 people of junior school age (6-11 years old) formed the I group, and 64 people of senior school age (12-17 years old) formed the II group. 80 of the children included in the examination were patients with DM type 1. Out of 120 schoolchildren, 40 were practically healthy children belonging to the control group, corresponding to sick children by age and gender. According to the duration of diabetes, children were divided into 2 subgroups: subgroup A with a duration of 1-3 years, and subgroup B with a duration of 4 years and more. Thus, 2 subgroups were formed in each age group (1A and 1B; 2A and 2B). In order to form the control group, practically healthy children aged 6-17 years, without a history of endocrine pathology, acute and chronic diseases of the cardiovascular system, who did not have any diseases during the last 6 months, and no pathological changes were detected in the ECG and Ech-ECG examination, were involved. In the research process, the collection of anamnestic data was carried out, the survey was conducted from both children and parents. All children had 12 standard ECGs, HRV assessment, and high-intensity ECG examination.

In order to study the changes in the homogeneity of the bioelectrical activity of the myocardium, the average index, maximum and minimum values (QTmax, QT min), dispersion (dQT) of the QT interval were determined. In addition, the corrected index of the QT interval (QTc), along with these indicators, the corrected QT interval indices such as maximum and minimum values (QTcmin, QTcmax), dispersion (dQTc) were determined. The obtained results were compared by groups.

• The calculation of HRV is based on the condition that the regularity of RR intervals of sinusoidal origin is expected for at least 300 seconds, by setting the standard periodic and spectral parameters, the following indicators have been studied:

• RR min (ms) – minimum cycle duration between normal RR intervals (intervals);

• RR max (ms) - maximum cycle duration between normal RR intervals;

• SDNN (ms) – standard deviation from the average duration of normal NN intervals;

• RMSSD (ms) –root mean squared successive RR interval differences;

• pNN50% - % of successive RR intervals that differ by more than 50ms.

In accordance with the goals and tasks set in our work, VLP registration was performed with HI-ECG through the 12-channel "ECGlab" device. In the periodic analysis of VLPs, Simpson's method was used (based on the calculation of the sum of several hundred consecutive cardiac cycles).

Based on the obtained results, the following indicators of EI-ECG were determined:

• TotQRS, ms-filtered QRS complex duration;

• LAS40, ms – low amplitude signal in the terminal lower than 40 mV ;

• RMS40, mV- root mean square voltage of the last 40 ms of the QRS complex

• TotQRS/RMS40 ratio.

Statistical analysis methods. The statistical processing of the results obtained in the research process was carried out in the Microsoft Office Excel 2007 program, using appropriate spreadsheets, using the Statistica 7.0 for Windows special package. The average score coefficient (M) and standard error indicator (m) were determined for each of the groups. . In addition, minimum (min), maximum (max) values are noted. The honesty of intergroup differences and its degree were evaluated by calculating the Student's t-test, when $p<0.05$, the difference was accepted as honest. Correlation between the analyzed indicators was conducted according to the Spearman (Rho) criterion. The values obtained in the research process were processed using the biometric methods adopted in modern statistics and mathematical calculations were performed in terms of comparative analysis. Non-parametric method - Wilcoxon (Manna-Whitney) criterion was used to determine the difference between indicators in groups.

RESEARCH RESULTS AND THEIR DISCUSSION

The analysis of the received data showed that the corrected values of electromechanical systole and the limits of dispersion in children with DM differ from the corresponding parameters of healthy children. It was revealed from the mutual comparison of the data of the studied subgroups that the changes in the QT interval were manifested depending on the duration of diabetes. The indicators characterizing the QT interval of children with DM type 1 are presented in the table below (Table 1).

As can be seen from the table, during the analysis of the results of the patients included in subgroup IA (follow-up period 1-3 years), although the studied indicators of the QT interval differed compared to the control group, the changes were statistically insignificant ($p>0.05$). QTcmax was an exception and was 430.6±5.50 ms in sick children, which honestly differed from the healthy group ($p<0.05$). The average value of the QT interval in the IB subgroup was 3.8±0.73% higher than the control group showed a significant difference ($p<0.001$). This indicator is also honestly different from the IA subgroup ($p<0.05$), giving grounds to evaluate it as a

manifestation of the significant influence of the duration of the disease on the length of the QT interval. Similar changes were noted in other indicators of the QT interval. QTmax and QTmin were statistically significantly longer than the control group by 3.8±0.71% and 4.0±0.83%, respectively ($p<0.001$). During the comparative analysis, a difference was also noted in these indicators with the IA subgroup, but this difference was not honest ($p>0.05$).

Table 1

Characteristics of the QT interval in children aged 6-11 years with diabetes mellitus type 1

Indicators	**Children with DM type 1 subgroup IA (n=22)**	**Children with DM type 1 Subgroup IB (n=14)**	**Control group (n=20)**
Gender (m/f)	9/13 (40,9% / 59,1%)	8/6 (57,1% / 42,9%)	10 / 10 (50% / 50%)
Age (years)	8,0±0,36 (6,0-11,0)	9,1±0,38 (7,0-11,0)	8,7±0,40 (6-11)
Disease average duration of attendance (years)	1,82±0,22 (0-3)	5,3±0,29 (4,0-8,0)	-------
QT (ms)	338,9±3,78 (318,0-376,0)	349,4±3,13 ***^ (331,0-372,0)	334,8±2,41 (316,0-353,0)
QTc (ms)	396,2±2,64 (373,0-422,0)	406,5±2,81 ***^ (384,0-418,0)	390,6±0,57 (388,3-400,2)
QTmax(ms)	364,9±3,42 (341,0-402,0)	373,1±2,70 *** (360,0-390,0)	358,8±1,55 (347,0-368,0)
QTmin(ms)	309,0±3,43 (280,0-346,0)	317,6±2,83 *** (302,0-339,0)	304,4±1,79 (290,0-316,0)
QTcmax(ms)	430,6±5,50 * (389,1-485,5)	444,2±3,67 ***^ (424,8-469,9)	418,8±1,08 (409,0-428,1)
QTcmin(ms)	363,2±6,13 (327,5-430,7)	378,8±3,95 ***^ (358,8-406,0)	355,3±0,74 (349,2-365,7)
dQTc(ms)	67,4±3,18 (44,6-97,3)	65,5±3,23 (44,5-84,5)	63,6±0,85 (56,8-70,1)
dQT(ms)	56,2±0,83 (50,0-64,0)	55,5±1,60 (40,0-64,0)	54,4±0,51 (50,3-57,3)

Note: p- coefficient of integrity* - $p<0.05$ - compared to the control group

***- $p<0.001$ - compared to the control group, ^ - $p<0.05$ - compared to the IA subgroup

Changes of the same nature were found in the QTc index and QTcmax, QTcmin. Thus, the duration of QTc DM was 406.5±2.81 ms in children over 4 years of age, statistically 4.2±0.40% longer than that of the control group ($p<0.001$). Similar changes were observed in QTcmax and QTcmin indicators (respectively, 6.3±0.57%, $p<0.001$ and 6.6±0.61%, $p<0.001$). The above indices were statistically significantly different from the IA subgroup ($p<0.05$). Graphic representation of QT interval characteristics of patients with DM compared to children in the control group, fig. It was given in 1.

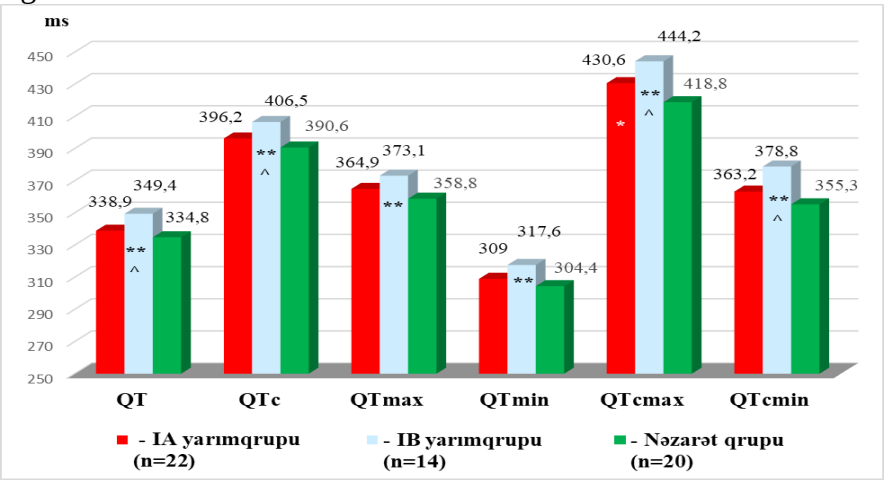


Figure 1. Comparative change of QT interval parameters in 6-11-year-old children with diabetes type 1.

Note: The difference compared to the control group is statistically significant: * – $p<0.05$, ** – $p<0.001$

The difference compared to subgroup IA is statistically significant: ^ – $p<0.05$

Changes in the group of children with DM type 1 with a disease duration of ≥4 years were observed in a larger number of indicators than in children with a duration of 1-3 years and were more pronounced. This also indicates that the deepening of the pathological process during DM type 1 directly affects the bioelectrical stability of the myocardium. In our study, QTc showed an honest difference when the duration of the disease was ≥4 years.

A general trend of prolongation of QT interval was observed in patients from subgroup IIA, which was reflected in the increase of values of all indices of QT interval in sick children compared to the control group.

These differences were more pronounced in the IIB subgroup, which can be considered an indirect confirmation of the above. The mean value of QT was significantly higher than the control group (3.5 ± 1.08% higher, $p < 0.05$).

QTmax ($p<0.01$) and QTmin ($p<0.05$) were statistically significantly different from the corresponding indicators of practically healthy children. A statistically significant difference was found in those indicators compared to the IIA group ($p <0.05$).

Changes in the same direction were also observed in indicators such as QTc, QTcmax and QTcmin. It was found that QTc in patients with DM duration ≤4 was significantly different from the control group (3.6±0.76 % higher, $p <0.001$).

Similar differences were determined in indices such as QTcmax and QTcmin (respectively, 4.5±0.67 %, $p <0.001$ and 4.5±0.82 %, $p <0.001$). It should be noted that these indicators also differed from the indicators of the IIA group, but the integrity of the changes was not observed ($p> 0.05$).

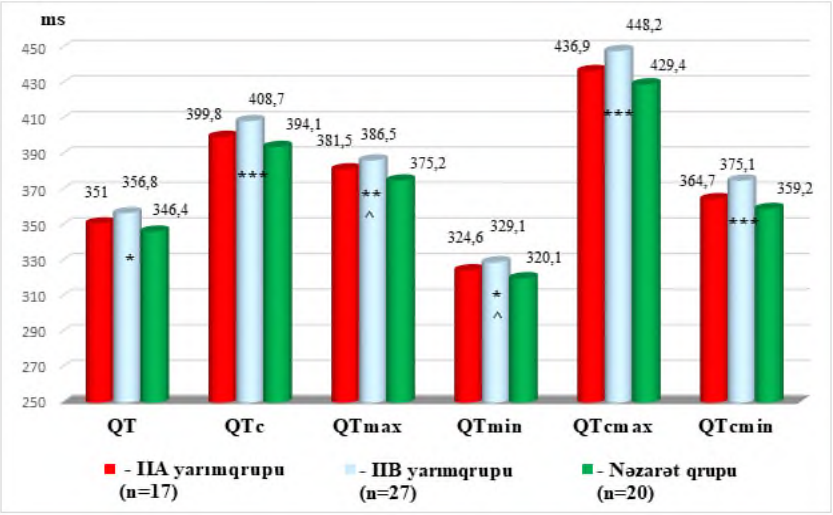


Figure 2. Comparative change of QT interval parameters in 12-17-year-old children with diabetes mellitus type 1.

Note: The difference compared to the control group is statistically significant:

* – $p<0.05$, ** – $p<0.01$, *** – $p<0.001$,

The difference compared to subgroup IA is statistically significant: ^ – $p<0.05$.

During the evaluation of the dispersion of the QT interval, it was found that dQT and dQTc were longer in DM patients with duration of 4 years compared to healthy children. (4.0±0.85% and 4.2±0.87% more, respectively). Even if these changes are not statistically honest ($p>0.05$), they reflect the general trend and speak of gradually developing disorders in the myocardium. It can be assumed that in the near future, such disturbances may lead to CAN deepening and more serious cardiovascular complications and fatal arrhythmias in children with DM.

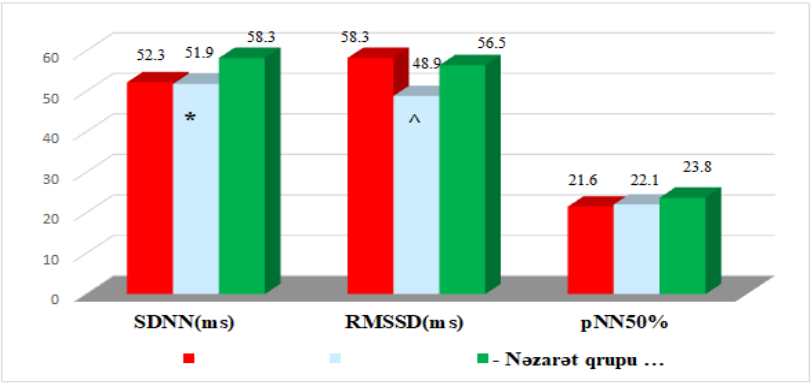
The period (SDNN, RMSSD, pNN50%) and spectral (HF, LF, VLF, LF/HF index (sympatho-vagal index)) parameters of HRV were studied in both DM patients and children from the control group.

SDNN duration was 5.5±1.79%, and pNN50% was 6.0±0.73% lower than the control group in 1-3 year olds ($p>0.05$).

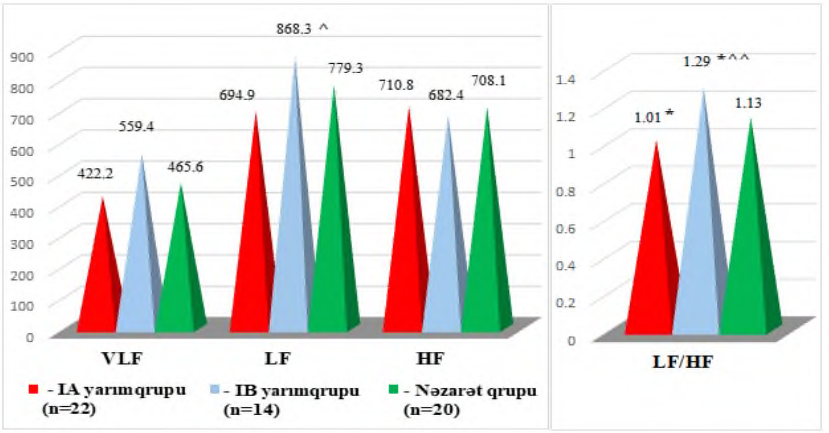
More clear changes were recorded in the spectral indicators of HRV. HF, which characterizes the parasympathetic regulation of the heart rhythm, characterizing the power of the spectrum of variability in the high frequency range, was 11.9±0.70% higher in the IA group than in the medically healthy subjects ($p>0.05$). The mentioned point is an indicator that despite the short duration of the disease, vegetative disorders have started.

At the same time, the fact that LF is 6.4±1.35% lower than that of the control group is considered as an indication of reduced sympathetic effects. These changes lead to an honest change of the LF/HF ratio (15.4±0.60% lower than the indicator in healthy children, $p<0.05$), which can be evaluated as the initial signs of the appearance of vegetative imbalance.

Fig. 3 shows the changes of heart rhythm variability period and spectral parameters depending on the duration of the disease in small school-aged children against the background of DM.



a)



b)

Figure 3. HRC/HRV period (a) and spectral (b) indicators depending on the duration of the disease in schoolchildren with type 1 diabetes (6-11 years old)

Note: The difference compared to the control group is statistically significant: * – $p<0.05$,

The difference compared to subgroup IA is statistically significant: ^ – $p<0.01$, ^^ – 0.001.

Thus, SDNN was 10.7±0.74% ($p<0.05$), RMSSD was 13.9±1.20% ($p>0.05$), and pNN50% was 9.1±1.55% of the control group. was lower ($p>0.05$).

In the presented indicators, HF in the IB group was 5.7±1.68% less relative to healthy children ($p>0.05$). This point can be considered as an indicator of the weakening of the parasympathetic system.

At the same time, LF in the patients belonging to the mentioned group was 7.2±1.94% higher than in the control group. As a result, an honest increase in the LF/HF ratio was noted (13.4±1.09% higher than the control group, $p<0.05$), which indicates a change in the vegetative imbalance in the opposite direction.

In support of this opinion, a statistically significant ($p<0.01$) reduction of RMSSD, which characterizes parasympathetic activity, can be shown in this group of patients.

The changes of the VLF index were also not different from the IA group. The value of this parameter was 559.4±64.9 and 6.5±1.58% higher compared to healthy children. Although the difference was not statistically significant, changes occurred in the opposite direction with the IA group.

RMSSD was statistically significantly lower ($p<0.001$) by 18.7±2.99% in patients included in group IB compared to children included in group IA. LF was higher ($p<0.01$) at 17.0±1.11%, and LF/HF ratio was higher ($p<0.001$) at 34.7±1.19%.

Complaints related to the cardiovascular system were recorded in only 19.4% of the children with DM involved in the study. Shortness of breath during physical exertion, orthostatic hypotonia, pain in the heart area, a feeling of "stopping" of the heart, syncopal states, dizziness, etc. is intended. Clinical symptoms were observed in 11.1% of patients. These symptoms include tachy- and bradyarrhythmias, changes in heart tones, and other heart rhythm disorders. Most of these symptoms were recorded in patients with duration of diabetes 4 or more.

The prolongation of the duration of DM occurs in the opposite direction of the changes of LF, HF and LF/HF characterizing HRC, that is, it becomes deeper. Such disorders can be considered as a

feature of the early stages of CAN in children. Clinical signs are observed in children from this category, and changes in the electrocardiogram are recorded.

In order to study the characteristics of HRV in the age group of 12-17 years, evaluation of HRV was carried out in 64 children (44 with DM type 1, and the remaining 20 practically healthy of the corresponding age). SDNN in patients lasting 1-3 years was honestly lower than the control group by 10.2±2.59% ($p<0.05$). The same changes apply to pNN50% and RMSSD (22.0±1.05% ($p<0.05$) and 14.0±1.34% ($p<0.05$), respectively), indicating sympathetic autonomic effects. gives information about the increase.

At the same time, LF was 11.1±1.84% higher than the control group, which can be considered a sign of activation of the sympathetic nervous system. The aforementioned causes a statistically significant difference in the LF/HF index (15.2±1.47% higher than the control group, $p<0.05$), which is an early sign of autonomic nervous system dysregulation despite the duration of DM not exceeding 3 years. can be evaluated.

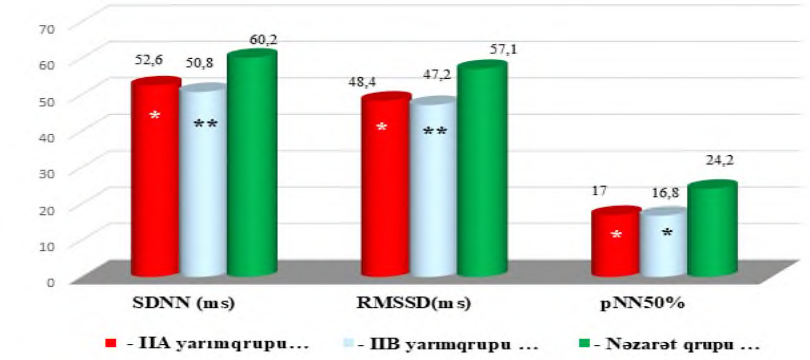
In children with DM with disease duration of 1-3 years (subgroup II A), VLF was 1026.9±187.3 and increased by 6.2±1.14% ($p>0.05$).

Changes in the characteristics of HRC were noted in patients included in subgroup IIB. Thus, SDNN was significantly lower than the control group by 14.4±2.32% ($p<0.01$), similar results were obtained for RMSSD and pNN50% (respectively, 17.5±0.23% ($p<0$ .01) and 29.6±1.80% ($p<0.05$) was lower). There were noticeable differences in the parameters related to the spectral domain of heart rhythm variability. has been done. As can be seen from the table, HF was 11.7±1.71% lower in children of subgroup B compared to healthy children ($p<0.05$). This result can be considered as a manifestation of the weakening of the effects of the parasympathetic system.

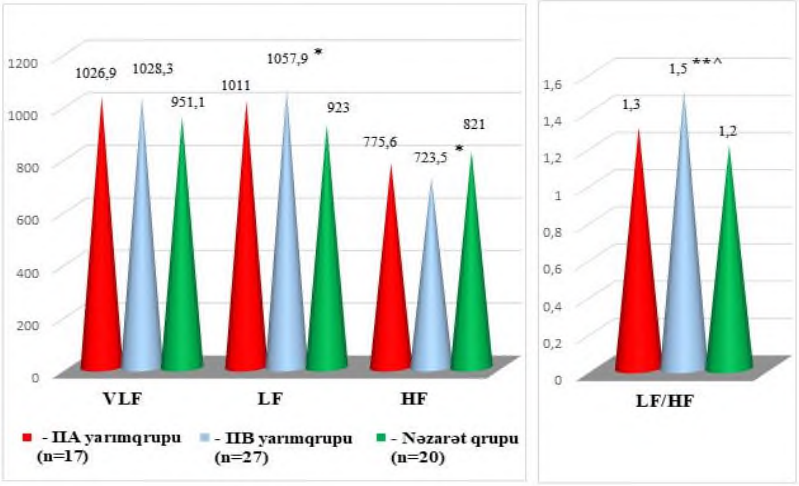
In children diagnosed with DM more than 4 years, LF increased significantly and was 16.2±1.21% ($p<0.05$) higher than the control group. A significant increase in the LF/HF ratio was also observed (31.7±1.64% higher than the control group, $p<0.001$), which indicates a deepening of the autonomic imbalance underlying CAN.

Compared between groups IIA and IIB, SDNN 4.6±1.42%, RMSSD 4.0±1.40%, pNN50% 9.8±1.45% were lower ($p>0.05$) in group IIB, which It led to statistically significantly higher ($p<0.05$) LF/HF ratio (14.4±0.80%).

The period and spectral parameters of heart rhythm variability in older school-aged children are shown in figure 4.



a)



b)

Figure 4. HRV cycle (a) and spectral (b) parameters depending on the duration of the disease in older school-age children with DM type 1

Our results in groups IIA and IIB confirm that the LF/HF ratio is a more sensitive indicator in the early diagnosis of CAN.

The increase in the duration of DM is characterized by the deepening of LF, HF and LF/HF changes characterizing HRC. Such violations are considered as indicators and signs of the initial stages of CAN in those children.

In school-age children with DM type 1, the indicators characterizing VLPs were evaluated. In subgroup IA, TotQRS was higher by 6.0±0.99%, LAS40 by 19.6±1.27% ($p<0.01$). At the same time, RMS40 showed a lower value of 9.5±0.86% ($p<0.001$) compared to healthy children, which led to an honest increase of TotQRS/RMS40 (respectively, 1.16±0.01 and 0.99± 0.01 ($p<0.001$)).

TotQRS was higher than the control group by 12.8±1.49% ($p<0.001$), and LAS40 was higher by 38.7±1.94% ($p<0.001$). RMS40 value was 25.6±1.46% lower than healthy children ($p<0.001$).

Statistical analysis showed that all indicators in subgroup IB were significantly different ($p<0.001$) not only from healthy children, but also from children with DM with a disease duration of 1-3 years (subgroup IA) (Fig. 5).

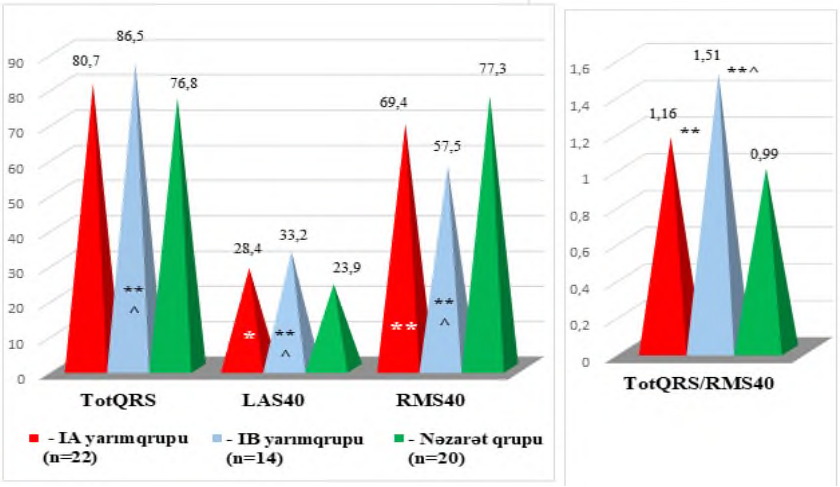


Figure 5. Indicators characterizing the late potentials of the ventricles in children of primary school age (6-11 years old) with DM type 1

Note: The difference compared to the control group is statistically significant: * – p<0.01, ** – p<0.001,

The difference compared to subgroup IA is statistically significant: ^ – p<0.001.

As the duration of endocrine pathology increased in high school-aged children with DM, the changes were more profound. (Figure 6).

Thus, in subgroup IIB, TotQRS 15.9±0.93%, LAS40 27.8±0.76%, TotQRS/RMS40 ratio 59.0±1.90% higher, and RMS40 27.0±0.43% , has been low. It should also be noted that all differences were highly statistically significant.

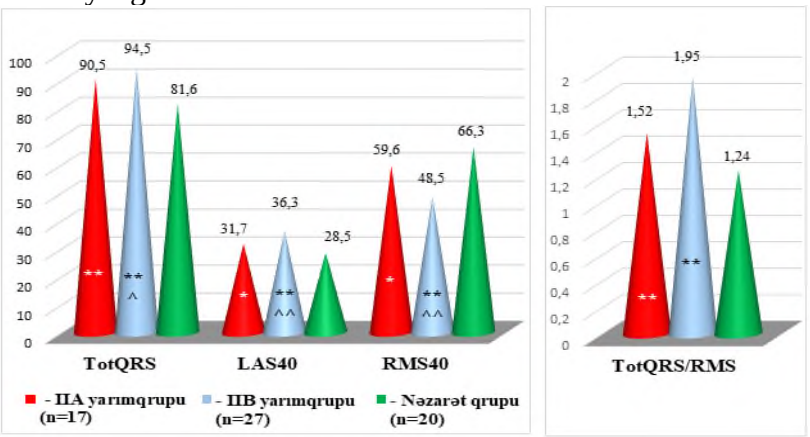


Figure 6. Indicators characterizing the late potentials of the ventricles in older school-aged children (12-17 years old) with DM type 1

Note: The difference compared to the control group is statistically significant: * – p<0.01, ** – p<0.001,

Compared to subgroup IA, the difference is statistically significant: ^ – p<0.05, ^^ – p<0.001.

In order to more deeply assess the electrical instability of the myocardium in children with DM, the interactions between the indicators characterizing the late potentials of the ventricles and the parameters of the LVH were also studied. For this purpose, correlational relationships between indicators were determined using Pearson's correlation criterion.

In subgroup IA, among the indicators characterizing HRV in children with disease duration up to 3 years, a number of indicators of VLPs and TotQRS (r= 0.025; p=0.912), LAS40 (r=0.076; 0.738), TotQRS/RMS40 (r =0.146; p=0.516) and inverse correlation with RMS40 (r=-0.076; p=0.735). Also, inverse correlations were determined between RMSSD and most indicators of VLPs: TotQRS (r=-0.304; p=0.169), LAS40 (r=-0.162; p=0.472), RMS40 (r=-0.427; p=0.048) . Negative correlations of pNN50% indicator with several indicators characterizing VLPs in patients (TotQRS (r=-0.072; p=0.750), LAS40 (r=-0.219; p=0.328), RMS40 (r=-0.307; p=0.165)) has been done.

Correlative relations with the indicators of VLPs were found. Thus, between HF, TotQRS (r=0.129; p=0.568), LAS40 (r=0.124; p=0.584), TotQRS/RMS40 (r=0.299; p=0.177) were positively correlated, and a negative correlation was found with RMS40 indicator (r=-0.059; p=0.796).

Determination of the correlation between indicators in the IB subgroup also revealed certain relationships. In this group, statistically honest inverse correlations between SDNN and a number of indicators of VLPs are noted: TotQRS (r= -0.553; p=0.040), TotQRS/RMS40 (r=-0.731; p=0.003). A direct correlative relationship was found with other indicators RMS40 (r= 0.618; p=0.018). LAS40 (r=0.229; p=0.431), of which the correlation with RMS40 showed statistical integrity ($p<0.05$). A negative correlation was found with TotQRS (r= -0.180; p=0.538), TotQRS/RMS40 (r= -0.512; p=0.061), and a positive correlation with other indicators.

In this subgroup, direct correlative relations between HF and some indicators of VLPs were determined. The characteristics of the correlations found between LF and VLPs parameters were as follows: negative with TotQRS (r=-0.248; p=0.393) and TotQRS/RMS40 (r=-0.552; p=0.041), LAS40 (r=0.074 ; p=0.801) and positive correlation with RMS40 (r=0.597; p=0.024) has shown. The correlation of the LF parameter with indicators such as TotQRS/RMS40 and RMS40 showed statistical integrity. According to the above, certain interactions of the LF/HF index with the VLPs indicators were determined. This index is directly correlated with

TotQRS (r=0.144; p=0.622) and TotQRS/RMS40 (r=0.273; p=0.344), LAS40 (r=-0.282; p=0.329) and RMS40 (r=-0.247; p= 0.394) showed an opposite correlation.

Negative correlative relationships of pNN50% indicator with VLPs characterizing indicators - LAS40 (r=-0.271; p=0.292), RMS40 (r=-0.370; p=0.144) were determined in patients with 1-3 years duration of DM. Besides, a positive correlation was found with TotQRS (r=0.136; p=0.602) and logically with TotQRS/RMS40 (r=0.480; p=0.051). In this subgroup, certain interrelationships of the spectral parameters of the HRV with the indicators of the VLPs have been determined. Direct correlative relations with indicators of HF VLPs were determined: TotQRS (r=0.261; p=0.311), RMS40 (r=0.064; p=0.807), TotQRS/RMS40 (r=0.155; p=0.553). LAS40 indicator showed a negative relationship with HF (r=-0.031; p=0.907). Correlative relationships between LF and VLPs parameters are characterized by their own characteristics. LF with TotQRS (r=0.329; p=0.197) and TotQRS/RMS40 (r=0.304; p=0.236) positive, LAS40 (r=-0.040; p=0.879) and RMS40 (r=-0.028; p=0.917) showed a negative correlation. In children included in subgroup IIB, straight correlations of several parameters of SDNN and VLPs among the periodic indicators characterizing HRV were determined: TotQRS (r=0.110; p=0.587), TotQRS/RMS40 (r=0.160; p=0.426), LAS40 (r=0.022; p=0.915). The correlation with RMS40 was negative (r= -0.077; p=0.704). The interaction with TotQRS (r=0.488; p=0.010) was evaluated as statistically significant. pNN50% VLPs in elderly patients in subgroup IB with some parameters (TotQRS (r=-0.266; p=0.180), LAS40 (r=-0.363; p=0.063), TotQRS/RMS40 (r= -0.273; p=0.169) negative, Positive correlative relations were determined with RMS40: (r= 0.081; p=0.688). In this subgroup, direct correlations were established between some indicators of HF and VLPs: TotQRS (r=0.081; p=0.688), LAS40 (r=0.021; p=0.918), RMS40(r=-0.438; p=0.022) Of these, the correlation with RMS40 was statistically significant ($p<0.05$). Some of the correlations found between LF and VLPs parameters were negative: LAS40 (r=-0.130; p=0.517), TotQRS/RMS40 (r=-0.336; p=0.087).

Thus, the analysis of our obtained results shows that there are foci of electrophysiological heterogeneity of the myocardium in children with DM type 1. The presence of such changes leads to the development of CAN. Early detection of CAN symptoms should be widely used in order to reduce the risk of fatal arrhythmias and sudden cardiac death in children with diabetes.

CONCLUSIONS

1. In school-aged children with type 1 diabetes mellitus DM, the bioelectric homogeneity of the myocardium is impaired. This manifests as the onset of early myocardial repolarization, accompanied by prolonged QT, QTc, QTcmax, and QTcmin intervals ($p<0.001$) and their dispersion in children aged 6–11 years. Among children aged 12–17 years, when the disease duration is ≥4 years, changes in the state of bioelectric stability are statistically significant. Compared to healthy children, these changes are characterized by elevated QT ($p<0.05$), QTc ($p<0.001$), and QTmax ($p<0.01$). Furthermore, compared to subgroups with a disease duration of 1–3 years, QTmax ($p<0.05$) and QTmin ($p<0.05$) are notably higher, indicating signs of myocardial remodeling [2, 3, 4, 8].
2. In children aged 6–11 years with type 1 DM, a disease duration of ≥4 years leads to a 10.7±0.74% decrease in SDNN ($p<0.05$) compared to the control group, while the LF/HF ratio shows a statistically significant increase of 13.4±1.09% ($p<0.05$), indicating heart rate variability (HRV) impairment. In children aged 12–17 years with a disease duration of 1–3 years, reductions in HRV parameters such as SDNN, pNN50%, and RMSSD are observed ($p<0.05$), along with a statistically significant increase in the LF/HF ratio ($p<0.05$). In older school-aged children with a disease duration of ≥4 years, an increase in the LF/HF index is more pronounced than other parameters ($p<0.001$), reflecting the progressive deepening of autonomic imbalance underlying

cardiac autonomic neuropathy and the development of more severe changes [6, 7].

3. In children with type 1 DM across both age groups, there is a significant increase in LAS40 and TotQRS/RMS40 ($p<0.001$), along with a decrease in RMS40 ($p<0.001$). These findings indicate the presence of heterogeneous foci in the myocardium and the onset of electrophysiological remodeling [10, 11].
4. In children with type 1 DM of different ages, correlations are noted between QTc and its indices, the periodic and spectral parameters of HRV, and MPG indicators. The direction and degree of these correlations are directly dependent on the duration of the disease [10, 11].
5. In school-aged children with type 1 DM, prolonged QT, QTc, QTmax, and QTmin intervals, along with reductions in periodic HRV parameters such as SDNN, pNN50%, and RMSSD, and increases in spectral indicators such as the LF/HF ratio and MPG indicators such as LAS40 and TotQRS/RMS40, are early predictors of myocardial bioelectric activity remodeling. Detecting these changes, considering the duration of the disease, allows for the earlier diagnosis of cardiac autonomic neuropathy in type 1 DM [10, 11].

PRACTICAL RECOMMENDATIONS

1. During the dispensation of children with type 1 diabetes mellitus, QT, QTc and their maximum and minimum values, dispersion index should be determined, which allows early detection of myocardial bioelectric instability and timely preventive measures in children at risk of developing cardiovascular pathology.

2. Determination of SDNN, RMSSD, pNN50, LF/HF, VLF from the periodic and spectral indicators of heart rhythm variability is recommended for the purpose of early detection of cardiac autonomic neuropathy in children with type 1 diabetes and prevention of complications that may develop from the cardiovascular system .

3. Determination of indicators characterizing the late potentials of the myocardium - TotQRS, LAS40, RMS40, TotQRS/RMS40 index in school-age children with type 1 DM should be applied as a factor enabling the detection of electrophysiological heterogeneity and the planning of appropriate therapeutic and preventive measures.

LIST OF SCIENTIFIC WORKS PUBLISHED ON THE SUBJECT OF THE DISSERTATION

1. Uşaqlarda şəkərli diabet zamanı kardiovaskulyar avtonom neyropatiyanın inkişafının müasir aspektləri // Azərbaycan təbabətinin müasir nailiyyətləri, 2017, №2, səh.74-80/
2. 1-ci tip şəkərli diabeti olan uşaqlarda QT intervalının təhlilinə əsasən miokardın bioelektrik sabitliyinin vəziyyəti // Azərbaycan kardiologiya jurnalı, 2019, №2 (16), səh.36-41.
3. Şəkərli diabet tip 1 olan müxtəlif yaşlı uşaqlarda miokardın bioelektrik sabitliyinin xüsusiyyətləri // Metabolizm jurnalı, 2020, №4 (17), səh.14-23 (həmmüəlliflər: V.A.Mirzəzadə, İ.İ.İsayev, M.M.Fətəliyeva).
4. Анализ интервала QT в оценке электрической стабильности миокарда у детей с сахарным диабетом I типа // Медицинские новости .2020, №12 (315), стр.68-70.
5. Uşaqlarda I tip şəkərli diabet zamanı ürək əzələsinin elektrik sabitliyinin vəziyyətinin öyrənilməsi / Azərbaycan Tibb Universitetinin 90 illik yubileyinə həsr olunmuş "Təbabətin aktual problemləri-2020" mövzusunda beynəlxalq elmi-praktik konqresin materialları, 19-20 dekabr 2020-ci il. səh.179-180.
6. Şəkərli diabet tip 1 olan kiçik məktəb yaşlı uşaqlarda ürək ritminin dövrü və spektral parametrlərinin vəziyyəti // Azərbaycan perinatologiya və pediatriya jurnalı, 2021 №1. cild 7, səh.36-41 (həmmüəlliflər: İsayev İ.İ., Mirzəzadə V.A., Məmmədova R.R.).
7. Böyük məktəbyaşlı uşaqlarda I tip şəkərli diabet fonunda ürək ritminin variabelliyinin dövri və spektral parametrlərinin vəziyyəti // Azərbaycan Tibb Jurnalı, 2021 №3, səh.57-62 (həmmüəlliflər: İsayev İ.İ., Mirzəzadə V.A., Mustafayeva A.İ., Rəfiyeva S.K.).
8. Tip I Diyabet tanılı 6-17 yaş aralığındakı çocuklarda miyokard durumunun QT intervalı analizine göre değerlendirilmesi / 3.Diyabet Teknolojileri Sempozyumu (e-sempozyum),27-29 Mayıs 2021

9. Məktəb yaşlı uşaqlada şəkərli diabet tip 1 fonunda ürək ritminin variabelliyinin dövrü və spektral parametrlərinin vəziyyəti / Professor Tamerlan Əliyevin anadan olmasının 100 illiyinə həsr olunan "Təbabətin Aktual Problemləri" Beynəlxalq Konqresin materialları, səh. 166 (həmmüəlliflər: İsayev İ.İ., Mustafayeva A.İ., Fətəliyeva M.M.)/ 6-8 Oktyabr 2021
10. Поздние потенциалы желудочков у детей школьного возраста с сахарным диабетом I типа // Современная Педиатрия, Украина 8(120), 2021, стр.42-46 (həmmüəlliflər: Мирзазаде В.А., Исаев И.И., Новрузов И.Г).
11. Şəkərli diabet tip 1 olan kiçik məktəb yaşlı uşaqlarda mədəciklərin gec potensialının qiymətləndirilməsi // Azərbaycan Təbabətinin Müasir Nailiyyətləri 2022, №2, səh. 63-67 (həmmüəlliflər: İsayev İ.İ., Novruzov İ.H., Mustafayeva A.İ., Fətəliyeva M.F.).
12. Uşaqlarda şəkərli diabet tip 1 zamanı yüksək informativli EKQ vasitəsilə miokardın bioelektrik fəallığının öyrənilməsi // I Türk Dövlətləri Kardioloji Qurultayı, 19-21 aprel 2024, səh.100-101 (həmmüəlliflər: Mustafayeva A.İ.).
13. Поздние потенциалы желудочков у детей старшего школьного возраста с сахарным диабетом 1 типа // Professor Sabir Əliyevin anadan olmasının 80 illiyinə həsr olunmuş elmi-praktik konfransın materialları,2024,səh.203-204 (həmmüəlliflər: Мустафаева А.И.).
14. Study of the electrical stability of the heart mescle in children with type 1 diabetes mellitus // 62nd Annual Meeting of the European Society for Paediatric Endocrinology (ESPE) Liverpool, United Kingdom, November 16–18, 2024, p.554

ABBREVIATIONS

CAN	Cardiac autonomic neuropathy
DM	Diabetes Mellitus
ECG	Electrocardiography
HF	(high frequency) – the strength of rhythms in the high frequency range
HI -ECG	High intensity electrocardiography
HVR or HRC	Heart rhythm variability or heart rhythm changes
LAS40	At the end of the QRS complex, the duration of filtered electric waves with a frequency below 40 mV
LF	(low frequency) – the power of the spectrum in the low frequency range
LF/HF	Sympatho-vagal index
pNN50%	Percentage of RR intervals whose durations differ by more than 50ms
RMS40	An index characterizing the mean square amplitude of the filtered QRS complex during the last 40 ms
RMSSD	Mean squared difference in duration of normal RR intervals
SDNN	Standard deviation from the mean duration of normal NN intervals
TotQRS	The duration of the filtered QRS complex
VLF	(very low frequency) – the power of the spectrum in the very low frequency range
VLPs	Ventricular late potentials

The defense will be held on "12" March 2025 at "16^{00}" at the meeting of the Dissertation council ED 2.27 of Supreme Attestation Commission under the President of the Republic of Azerbaijan operating at Azerbaijan Medical University

Address: AZ 1022, Baku, A.Gasimzade st, 14

Dissertation is accessible at the Library of the Azerbaijan Medical University.

Electronic versions of dissertation and the abstract are available on the official website of the Azerbaijan Medical University (www.amu.edu.az)

Abstract was sent to the required addresses on "7" February 2025.

Signed for print: _._.2025
Paper format: 60 x 84 $^{1}/_{16}$
Volume: 37 142 characters
Number of hard copies: 30