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O.A. Senkevich, Z.A. Plotonenko, V.P. Molochny, M.N. Pertsev

SOME CRITERIA FOR DAMAGE TO THE CARDIOVASCULAR SYSTEM OF NEWBORNS DUE TO INTRAUTERINE HYPOXIA

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The results of laboratory and instrumental diagnostic methods in newborns with a history of intrauterine hypoxia were analyzed. Electrocardiographic features were revealed in the form of prolongation of the QT interval; diffuse secondary metabolic-hypoxic changes in the myocardium, such as myocardial hypertrophy, increased myocardial biopotentials from the right and left ventricles; severe overload of both atria. An important role in assessing the state of the cardiovascular system is assigned to the determination of markers for assessing the severity of damage: such as malondialdehyde (MDA) and brain natriuretic peptide (BNP) in the blood serum. As a result of the study, a significantly higher (1.2 times) MDA level was determined in newborns with antenatal hypoxia with NT-proBNP values 4 times higher than the reference laboratory values for the reagent kit. The results obtained suggest the importance of further research into the role of antenatal hypoxia in assessing the state of the cardiovascular system of children.

Keywords: intrauterine hypoxia, electrocardiogram, newborn, malondialdehyde (MDA), natriuretic peptide (BNP), cardiovascular system.

SENKEVICH Olga Aleksandrovna – Professor, Head of the department of pediatrics, neonatology and perinatology with a course of emergency medicine, the Far Eastern State Medical University, e-mail: senkevicholga@ya.ru; **PLOTONENKO Zinaida Anatolyevna** – associate professor, the department of pediatrics, neonatology and perinatology with a course of emergency medicine, the Far Eastern State Medical University, e-mail: basset_2004@mail.ru; **MOLOCHNY Vladimir Petrovich** – Professor, the Department of Outpatient Pediatrics with a course in childhood infectious diseases, the Far Eastern State Medical University, e-mail: molochnyy@yandex.ru; **PERTSEV Mikhail Nikolaevich** – assistant, the department of pediatrics, neonatology and perinatology with a course of emergency medicine, the Far Eastern State Medical University, e-mail: mishanya_percev@mail.ru

Background: The characteristics and effects of intrauterine hypoxia on the cardiovascular system (CVS) of newborns and the consequences it causes continue to be a relevant topic for research, because CVS lesions occur, according to Russian authors, in 40–70% of cases [11], occupying second place in the list of pathological conditions of the perinatal period. It is generally accepted that the main cause of hypoxic heart damage in newborns is a decrease in energy production in the myocardial cell due to perinatal “hypoxic injury” and relative coronary insufficiency caused by the mismatch of the existing coronary blood flow with the functional needs of the heart, resulting from the high hemodynamic load on the ventricular myocardium during the period of postpartum adaptation blood circulation.

The cause of intrauterine hypoxia may be a decrease in oxygen content at the preplacental, placental and postplacental levels. A lack of oxygen supply can develop gradually and be chronic [2], leading to disruption of compensation mechanisms, resulting in activation of anaerobic glycolysis and centralization of blood circulation [6]. Fetal hypoxia leads to dis-

ruption of the mechanisms of automatism and contractility of the myocardium, and at later stages - the processes of repolarization and conduction along the His bundle [9]. With prolonged and pronounced hypoxemia in tissues, the mechanisms of anaerobic glycolysis are activated, acidic metabolic products accumulate [1], and foci of small focal necrosis are formed, located mainly in the subendocardial zone of the ventricular myocardium and papillary muscles [3].

Clinical and experimental research have shown the important role of fat peroxidation (LPO) in the development of oxidative stress, one of the end products of which is malondialdehyde (MDA). MDA is an endogenous aldehyde formed as a result of the metabolism of arachidonic and other polyunsaturated fatty acids. It has been established that the special role of MDA is the prognosis and control of treatment of cardiac pathology; the concentration of MDA correlates with some clinical signs of ischemic heart damage.

In the last decade, the prohormone brain-type natriuretic peptide (BNP), a member of the natriuretic peptide family, and its use as a marker in the diagnosis of heart failure (HF) have been actively studied [3]. There are different types of neurohormones in this family, but the most clinically relevant is brain natriuretic peptide (BNP), which is secreted by cardiomyocytes in response to increased intracardiac volume and pressure overload. Another source of BNP may be the intima of the coronary arteries under the influence of ischemia [14]. Currently, the determination of BNP and the N-terminal fragment of BNP (NT-proBNP) is widely used to diagnose heart failure, assess its severity, prognosis and monitor the effectiveness of therapy. In addition, studies have shown that high levels of BNP/NT-proBNP are an independent risk factor for atrial fibrillation (AF) as well as death in the general population [18]. There are studies [7] that allow the level of NT-pro-BNP in newborns on the first day of life to determine the degree of dysfunction of the cardiovascular system.

Diagnosis of heart damage is significantly difficult in the first days of life, which is due to the peculiarities of adaptation of the newborn's cardiovascular system. The search for a universal, reliable, reproducible method for diagnosing hypoxic heart damage determined the relevance of the study [10, 12].

Objective: To assess the significance of electrocardiographic parameters, the level of malondialdehyde (MDA) and B-type brain natriuretic peptide (NT-proBNP) in the blood serum as additional criteria for hypoxic damage to the cardiovascular system (CVS) in newborns.

Methods: In accordance with the inclusion and exclusion criteria, a random sampling method was used to analyze the clinical and laboratory data of 30 newborns whose prenatal period occurred against the background of antenatal fetal hypoxia.

The level of malondialdehyde (MDA) in blood taken at the time of birth from the umbilical cord artery was determined using the standardized thiobarbituric method.

On days 4-5 of life, an electrocardiographic study (ECG) was performed using a standard 12-lead technique and the concentration of the N-terminal fragment of the precursor of brain natriuretic peptide (NTproBNP) in the blood serum was determined using an ELISA kit of reagents for a one-step enzyme immunoassay determination of the concentration in the blood serum. The solid-phase sandwich ELISA method, "NT-pro BNP-ELISA-Best cat No. A-9102" was used. Laboratory equipment: ELISA analyzer "Alisei Q S".

The source of information was the developmental history of newborns (form No. 097-1/u-97), the results of the analysis of electrocardiograms and laboratory data.

The study did not include children with premature birth, manifestations of asphyxia at birth, infectious diseases, or severe condition at birth caused by any reasons.

Inclusion criteria for the study: gestational age 37 (0/7) – 41 (6/7) weeks of pregnancy, urgent vaginal delivery, diagnosis of "chronic fetal hypoxia" established during pregnancy, voluntary informed consent of the parents or legal representatives of the child for the procedure. examinations.

The ECG data obtained were compared with the results obtained in 30 apparently healthy newborns born without antenatal hypoxia.

Statistical analysis of the obtained data was carried out using standard statistical processing methods using Microsoft Office Excel 2013 and Statistica 6.0. The level of statistical significance when testing the null hypothesis was considered to be $p < 0.05$.

The study was approved by the local ethics committee at the Far Eastern State Medical University of the Russian Ministry of Health (protocol No. 10 of September 10, 2022), conducted in accordance with the ethical principles of medical research involving human subjects (Helsinki, 1964; revision - Scotland, October 2000).

Results: All children included in our study were relatively healthy at the time of the study, had no clinical manifestations of pathology of the cardiovascular system, and were born with average indicators of physical development corresponding to the gestational age. The Apgar score was 7.8±1.0 points in the first minute of life and 8.4±0.9 points in the fifth minute of life. All children were put to the mother's breast in the delivery room, stayed with their mother and were discharged from the maternity hospital in a timely manner.

When analyzing the MDA indicator, it was found that the results obtained (5.71±3.7) of all examined children did not correspond to the normal laboratory values specified in the method for the reagent kit; the MDA level exceeded the reference values 1.2 times ($p = 0.01$). Exceeding the MDA level is typical for intense physical activity in newborns and pregnant women, therefore, the indicators of activation of peroxide processes we obtained can be considered a reaction of the newborn's body to the intense effects of birth oxidative stress. The detected levels of MDA in newborns indicate oxidative stress, which makes this indicator a marker of the unfavorable course of the adaptation period in a newborn child.

The level of NTproBNP, determined on days 4-5 of life in the blood serum, turned out to be 813.39 ± 549.61 pg/ml with variability from 133.64 to 2117.92 pg/ml with the reference laboratory values specified in the method for the reagent kit, from 0.0 to 200.0 pg/ml. The indicators obtained in our study are in the range of normal values for the first day of life [7], but significantly, 4 times higher than the reference laboratory values for the set of reagents. The obtained data with a pronounced variability of the indicator (max 2117.92 pg/ml), a different age of the children during the study (4-5 days, the end of the period of acute adaptation) do not allow for an unambiguous assessment and suggest further research to clarify the diagnostic role of the NT-proBNP indicator in assessment of CVS damage during hypoxia.

The heart rate (HR) in the control group in most cases (93.3%) corresponded to the age norm and averaged 146-156 beats per minute (Table 1). In the group of children with intrauterine hypoxia, normal heart rate parameters were less common than in the control group (63.3% - $p=0.03$ OR=1.66). In every third case (36.6%), sinus tachycardia was di-

Some characteristics of the ECG of newborns (min-max, average value)

Groups	Heart rate (bpm)	EOS	P wave (ms)	PQ interval	QTs	QRS interval (V5) (ms)	R (V1) (mm)
Experimental group	156-190 (164)	-40/-80 (-65)	60-80	70-100 (85)	400-430 (425)	50-70 (60)	0-10
Control group	146-156 (150)	+78 /+180 (130)	60-70	100	400-410 (405)	50-60 (55)	0-17

agnosed with a heart rate averaging 175-190 beats per minute at rest [13]. The average duration of the P wave in children with antenatal hypoxia was 60-80 ms (56.6% - p=0.03 OR=1.4). In cases where sinus tachycardia was recorded, the P wave length was 40-60 ms (43.3% - p=0.02 OR=0.6). In the control group, the duration of the P wave averaged 60-70 ms (93.3% - p=0.01 OR=1.73), which is normal [16].

The duration of the PQ interval in children with intrauterine hypoxia averaged 90-100 ms (63.3% p=0.02 OR=1.83) with a norm of 70-140 ms [16]. A shortening of the length of the PQ interval in some children (36.6% - p=0.03 OR=1.56) was associated with an increase in heart rate and averaged 70-80 ms, which also corresponds to the conventional norm. In the control group, the length of the PQ interval averaged 100 ms (96.6% - p=0.04 OR=1.43) and was within the reference values [16]. The width of the QRS complex in all children we examined did not exceed 70 ms, with average values in children with intrauterine hypoxia in the group 50-60 ms (90% - p=0.04 OR=1.93), in the control group 50-70 ms (93.3% - p=0.03 OR=1.85), which is the age norm [15].

The T wave in the main (83.3% - p=0.03 OR=1.87) and control (90% - p=0.03 OR=1.75) groups had a low amplitude in the limb leads. In the right chest leads, the T wave was negative, in the left - positive, which is the norm for children in the first week of life [5].

It is known that the duration of the QT interval varies depending on the heart rate [4]; accordingly, to assess it, it is necessary to carry out a correction for a given heart rate - calculate the corrected QTc interval. In our study, the calculation was carried out using the Bazett's formula: QTc (c) = QT (c)/√RR (c) [17]. The average QTc duration in children with a history of antenatal hypoxia was 420-430 ms (60% - p=0.01 OR=1.83), with sinus tachycardia the QTc duration was 400-410 ms (40% - p=0.02 OR=1.56). In the control group, QTc duration was 380-400 ms (93.3% - p=0.05 OR=1.80). Newborns older than 4 days with a prolonged QT interval of more than 440 ms have a significantly higher risk of sudden death [17]. The values established during the study did not exceed 440 ms, however, some children with a history of intrauterine hypoxia were in the border zone in terms of QT level.

A feature of the electrical axis of the heart (ECA) in newborns is the right axis with an average value of 130° and variability from 55° to 200° [8]. In the control group, a shift of the EOS to the right was most often noted (86.6% - 26/30). In children with intrauterine hypoxia, a "levogram" was most often observed (76.6% - p=0.03 OR=1.06), in some cases (23.3% - p=0.02 OR=1.26) a shift of the EOS to the right.

Every second child with a history of antenatal hypoxia had diffuse secondary metabolic-hypoxic changes in the myocardium (56.6% - p=0.01 OR=1.73); myocardial hypertrophy (53.3% - p=0.04 OR=1.39); enhanced myocardial biopotentials from the right and left ventricles (46.6% - p=0.01 OR=1.21); severe overload of both atria (33.3% - p=0.02 OR=1.41).

Conclusion: Intrauterine fetal hypoxia causes disturbances in the state of the cardiovascular system, while the clinical picture may be absent, as in our study, or may be erased. The diagnostic significance of markers of CVS damage during hypoxia is different and requires the search for a universal and accessible test to assess the state of the CVS with minimally expressed clinical symptoms. In children with a history of intrauterine hypoxia, the electrocardiogram has a number of features in the form of a shift of the electrical axis of the heart to the left and hypertrophy of the myocardium of the left ventricle and left atrium (76.6%), an increase in the duration of the QTc interval (60% of cases), diffuse secondary metabolic-hypoxic changes in myocardium (56.6%), increased myocardial biopotentials from the right and left ventricles (46.6%), increased heart rate (36.6%), which can be regarded as a consequence of a lack of energy supply in the myocardial cell and a risk factor for the development of sudden death in children with a history of hypoxia.

Determining the level of MDA in the blood of newborns allows not only to assess the intensity of lipid peroxidation in tissues, but also to use this indicator to diagnose the severity of intrauterine hypoxia.

The determination of MDA and NT-proBNP is of particular interest for use in clinical practice as markers of intrauterine hypoxia with the possibility of predicting critical neonatal conditions. It is necessary to study the dynamics of indicators in the process of adaptation of newborns to extrauterine life under various pathological conditions.

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D.Yu. Avedova, Yu.L. Osipova, L.A. Zyulkina, A.V. Yurkevich, I.D. Ushnitsky

EFFICIENCY OF USING AUTOGENIC BONE IN COMBINATION WITH A XENOGENIC BONE MATERIAL FOR GUIDED BONE TISSUE REGENERATIONIN AN EXPERIMENT

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Currently, the search for effective methods of reconstructive interventions aimed at increasing alveolar ridge height and thickness remains a pressing issue in dentistry. However, the results of studies on the comparative assessment of the effectiveness of the use of autogenic bone from various donor sites are extremely small and ambiguous. **Aim.** Substantiate the effectiveness of using the optimal composition of autogenic bone chips (ABC) and xenogenic bone material (XBM) taking into account the anatomical localization of the donor zone in guided bone regeneration (GBR) according to the data of microhemodynamics of the experiment. **Research materials and methods.** The object of the study in the research was 84 sexually mature male rabbits of the chinchilla breed weighing 2500-3200 g. The materials of Cardioplant LLC (Penza) with registration certificates: Xenogenous bone material (XBM) "Xenograft Mineral" (medical device registration certificate No. RZN 2015/3086 dated 16.09.2015) and bioresorbable membrane "BioPLATE Barrier" (medical device registration certificate No. RZN 2016/4808 dated 26.01.2021). A defect in the mandible area was formed in the animals under study, which was then filled with osteoplastic material. Laser Doppler flowmetry (LDF) was used to monitor the state of microhemodynamics of gingival tissues in the area of surgery using a laser analyzer of capillary blood flow "LAKK-02," (NPP "Lazma," Moscow). Results and discussion. It was established that within the first two weeks after the intervention, optimal rates of microcirculation recovery in the surgical area are characteristic of osteoplasty using a mixture of XBM (75%) and ABC (25%) from the oral donor zone. On the 14th day after the operation, capillary blood flow was stabilized, which was manifested by a decrease in the studied parameters in all observation groups. However, the normalization of microvessel functioning was not the same in the study groups. At the same time, the normalization of capillary blood flow was optimal in animals of subgroup 3 in group II, with the microcirculation indicator at the level of 20,59±1,18 perf. units, and its intensity at the level of 2,31±0,12 perf. units by the 14th day. Starting from the 30th day of observation, microcirculation recovery proceeded at the same pace in all groups of animals, with the exception of a slight lag in animals of subgroup 3 in group III, however, by the 90th day and by the end of the observation period, significant differences in capillary blood flow levels could not be found.
Conclusion. The obtained results should be taken into account in outpatient dental practice when performing manipulations related to the use of the GBR technique.
Keywords: autogenic bone, donor zone, guided bone regeneration, microcirculation.

AVEDOVA Diana Yurievna – postgraduate student of the department of Therapeutic Dentistry of the Federal State Budgetary Educational Institution of Higher Education V.I. Razumovsky Saratov State Medical University, Ministry of Health of Russia, sto-kafedra@yandex.ru, ORCID 0009-00090201-1129; **OSIPOVA Yulia Lvovna** – MD, Professor of the Department of Therapeutic Dentistry, V.I. Razumovsky Saratov State Medical University, Ministry of Health of Russia, osipova-sgmu@mail.ru ORCID 0000-0002-0669-2867; **ZYULKINA Larisa Alekseevna** – MD, Head of the Department of Dentistry, Penza State University, Ministry of Education and Science, larisastom@yandex.ru, ORCID 0000-0002-2938-3063; **YURKEVICH Alexander Vladimirovich** – Dean of the Faculty of Dentistry, Head of the Department of Orthopedic Dentistry of the Far Eastern State Medical University of the Ministry of Health of Russia, Doctor of Medical Sciences, Associate Professor, Corresponding Member of the Russian Academy of Natural Sciences. dokdent@mail.ru, orcid.org/0000-0003-1746-5878; **USHNITSKY Innokenty Dmitrievich** – MD, Professor, Head of the Department of Therapeutic, Surgical, Orthopedic Dentistry and Pediatric Dentistry of the Medical Institute of M.K. Ammosov North-Eastern Federal University, incadim@mail.ru, orcid.org/0000-0002-4044-3004

Introduction. Currently, the search for effective methods of reconstructive interventions that contribute to an increase in the height and thickness of the alveolar ridge remains an urgent problem [5, 11, 12, 14, 15]. The need for such dental operations arises when there is insufficient bone level for the installation of implants, or incorrect ratio between the length of the implant and the height of the orthopedic structure, or in case of indications for such interventions in an aesthetically significant area [4, 8, 10, 13]. The predictability and successful outcome of surgical intervention largely depends on the material for augmentation of the alveolar ridges. Autogenic bone in combination with a membrane, not without reason, has the status of the "gold standard" during guided bone regeneration (GBR), however,