Innov Biosyst Bioeng, 2022, vol. 6, no. 3-4, 148–160
doi: 10.20535/ibb.2022.6.3-4.268504

Original article

INDICATORS OF BIOELECTRICAL ACTIVITY OF THE RAT HEART AFTER PRENATAL HYPOXIA AND PHARMACOLOGICAL CORRECTION

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Received 13 December 2022; Accepted 26 January 2023

Background. Posthypoxic cardiopathy is one of the risk factors for the development of cardiovascular pathology (rhythm disturbances, vascular dystonia, etc.) in subsequent age periods and requires the development of treatment approaches.
Objective. to evaluate the cardioprotective effect of modulators of the NO system by the effect on the ECG of rats after intrauterine hypoxia.
Methods. Modeling of prenatal hypoxia (PH) by daily intraperitoneal administration of sodium nitrite solution to pregnant female white rats weighing 220−240 g, aged 4.5 months, from the 16th to the 21st day of pregnancy at a dose of 50 mg/kg. The offspring were administered daily from the 1st to the 30th day of life – tiazotic acid (morpholinium 3-methyl-1,2,4-triazolyl-5-thioacetic acid), 50 mg/kg, angiolin ([S]-2,6-diaminohexane acid 3-methyl-1,2,4-triazolyl-5-thioacecate), 50 mg/kg, L-arginine, 200 mg/kg, meldonium (2-(2-carboxyethyl)-1,1,1-trimethylhydrazinium), 100 mg/kg. And then after 2 months of life, an ECG was recorded using the ECG TUNNEL system (without anesthesia).
Results. Postponed PG leads to a decrease in heart rate and significant dominance of parasympathetic innervation in regulation of electrical activity of the heart, which can be caused by sinus blockade and may be a reflection of parasympathetic regulation of the heart instead of sympathetic control of electrical activity in the norm. The effectiveness of drugs can be presented in descending order: angiolin > tiazotic acid > meldonium. Angiolin proved to be more effective than tiazotic acidin normalizing the electrical activity of the heart and restoring the neurogenic regulation of the automatism of the function of the sinus node.
Conclusions. The prospects of further study of modulators of the NO system with different mechanisms of action as means of cardioprotection of posthypoxic disorders of the cardiovascular system in newborns are experimentally substantiated.

Keywords: prenatal hypoxia; cardioprotective electrophysiological disorders; myocardium of newborns; pharmacocorrection; angiolin; tiazotic acid; L-arginine; meldonium.

Introduction

In the structure of morbidity in newborns, both full-term and premature, the leading place is occupied by hypoxia. The complex of changes that occur in this case has an adverse effect on the central nervous system (CNS), disrupting the regulatory influence of the subcortical structures of the brain on the functional state of internal organs, in particular on the cardiovascular system (CVS) [1, 2]. The functional changes in the cardiovascular system in the syndrome of posthypoxic circulatory maladaptation are based on a violation of neurohumoral regulation of vascular tone, transient neonatal pulmonary hypertension (PH) and long-term persistence of fetal communications (PFC), as well as a delay in the formation of a mature type of cardiomyocyte metabolism [3]. Disorders of the cardiovascular system are detected already during the initial examination of the newborn – incomplete blockade of the right leg of the His bundle, extrasystole, signs of subendocardial ischemia [4]. Therefore, it is believed that posthypoxic cardiopathy is one of the risk factors for the development of cardiovascular pathology (rhythm disturbances, vascular dystonia, etc.) in subsequent age periods [5]. Therefore, the search for effective and safe methods for correcting posthypoxic CVS changes in newborns is an urgent task of neonatology and pediatrics. Currently, the role of energy metabolism disorders, mitochondrial dysfunction in the formation of posthypoxic cardiomyopathies is known. However, the use of metabolitotropic drugs (L-carnitine, ATP succinic acid salts, etc.) does not always meet the expectations of clinicians. All this stimulates both the study of the subtle mechanisms of the development of posthypoxic cardiomyopathies and the search for new pharmacological targets.

According to modern concepts, endothelial dysfunction and associated disorders in the NO system underlie the development of many cardiovascular diseases [1, 3, 5]. Under the action of hypoxia, the functioning of the nitroxidergic system is disrupted, which, against the background of inhibition of the antioxidant system, leads to aggravation of energy metabolism disorders, disorders in the structure and function of mitochondria, oxidative stress, apoptosis, and the development of the pathology of the cardiovascular system. Unfortunately, publications on the role of the nitroxidergic system in the development of cardylmyopathies after PH and the effectiveness of NO modulators are very few. Our previous studies [6, 7] have obtained data on the presence of anti-ischemic action in pharmacological agents – modulators of NO: L-arginine, tiazotic acid, angiollin and meldonium. L-arginine is a substrate for the formation of NO in vascular endothelial cells, exhibits antioxidant, cytoprotective, antihypoxic, membrane stabilizing properties [8]. Tiazotic acid (morpholinium 3-methyl-1,2,4-triazolyl-5-thioacet) is a specific scavenger of NO and its cytotoxic forms, increases the bioavailability of NO, protecting it from ROS, exhibits hepato-, cardioprotective, anti-ischemic and antioxidant properties. Tiazotic acid (10^{-5}–10^{-7} M) *in vitro* reduced the levels of superoxide radical and peroxynitrite due to the presence of a thiol group in its structure. In rats with modeling isadrin-pituitrin myocardial infarction tiazotic acid (50 mg/kg) stimulated LDH in the direction of the formation of pyruvate from lactate, which eliminated lactic acidosis and normalized intracellular pH and stimulated the Krebs cycle by increasing pyruvate. Angiolin ([S]-2,6-diaminohexaneacid 3-methyl-1,2,4-triazolyl-5-thioacecate) increases the expression of VEGF and the density of proliferating endotheliocytes of the muscular type vessels and microvasculature, increases the bioavailability of NO, and preserves the ultrastructure of mitochondria during ischemia. Increases the expression of eNOS, exhibits endothelial-, cardio-, neuroprotective, antioxidant and anti-ischemic properties. *In vitro* experiments found that angiolin at concentrations of 10^{-3}–10^{-7} M in the reaction of photoinduced oxidation of sodium nitroprusside (accompanied by the formation of NO, judging by the rate of ascorbate oxidation) reduced the level of NO, and angiolin also reduced the level of NO and its conversion into peroxynitrite (measured by nitrotyrosine levels) when incubated with excess iron(II) cysteine complex dinitrosol (DNIC) angiolin introduction in experimentally justified doses of 50–100 mg/kg reduced the progression of necrosis in the zone of ischemia, decreased vascular endothelial cell loss (increased the density of vascular endothelial cells in the capillary network and myocardium), increased the RNA content in the nuclei of endothelial cells, increased the density of proliferating endothelial cells against the background of an increase in the concentration of vascular endothelial growth factor (VEGF) as well as improved myocardial energy metabolism, improved ECG parameters, decreased the levels of molecular and biochemical markers of injury (CPK-MV, ST, D-dimer, myoglobin), and oxidative stress (nitrothiozine, MDA, carbonylated proteins), characterizing the system of production and transport of nitric oxide and thiol-disulfide equilibrium, reducing the formation of endothelial dysfunction in experimental myocardial infarction and heart failure caused by Doxorubicin in rats and rabbits [8, 9]. Meldonium reduces the formation of carnitine from its predecessor – gamma-butyrobetaine, the accumulation of the latter stimulates the synthesis of NO and exhibits anti-ischemic and cardioprotective properties. Meldonium reduces the level of l-carnitine due to the influence on the enzyme synthesis of l-carnitine γ-butyro-beta-hydroxylase and the carnitine/electric cation transporter type 2 (OCTN2), inhibits the oxidation of fatty acids, exhibits a mitoprotective effect, stimulates glucose metabolism and reduces metabolic concentration of l β-carnitines such as long chain acyl carnitines and trimethylamine N-oxide; increases the synthesis of ATP during ischemia [10].

Purpose of the study – to assess the cardioprotective effect of L-arginine, tiazotic acid, angioline and meldonium by the effect on the ECG of 2-month-old rats after prenatal hypoxia.

Materials and Methods

Characteristics of laboratory animals and the experimental model of pulmonary hypertension

The experimental part of the study was carried out in strict accordance with the national "Joint ethical principles of animal experiments" (Ukraine, 2001), agreed with Council Regulation 2010/63EU of the European Parliament and of the Council of September 22, 2010 on the protection of animals used for scientific purposes, (Council Directive 2010/63EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes). The protocols of experimental studies were approved by the deci-

sion of the Commission on Bioethics of Zaporizhzhia State Medical University (protocol No. 33 of June 26, 2021).

The experiments were conducted on white rats, 50 females and 10 males, weighing 220–240 g, aged 4.5 months, obtained from the vivarium of the Institute of Pharmacology and Toxicology of the National Medical Academy of Ukraine. The rats were kept under standard vivarium conditions at 20–25 °C, humidity 50–55%, natural light, diet recommended for this species of laboratory animals, and water ad libitum. Here, we used the chronic hematic nitrite-induced PH model [11, 12]. For a fixed term of pregnancy, mature male rats were placed with virgin female rats with a ratio of 2 males per 4 females. The Pregnancy period was counted starting from the discovery of spermatozoids in the vaginal smear (day 1 of the pregnancy). Modelling hematic hypoxia was performed in the prenatal period of development by daily intraperitoneal administration of sodium nitrite solution to pregnant female rats from day 16 to day 21 of the pregnancy at 50 mg/kg (the dose causing moderate hypoxia) [11]. Control pregnant rats received physiological solution in the same regime. The progeny was divided into groups:

1. Healthy pups from females with physiologically normal pregnancy which received physiological solution.

2. Control group of pups after PH which received physiological solution daily.

3–6 groups of pups after PH that received drugs daily from postnatal day 1 to day 30.

Justification for the selected drugs and their characteristics

We chose drugs with experimentally proven ability to modulate system of NO:

1. Tiazotic acid preparation (Morpholinium 3-methyl-1,2,4-triazolyl-5-thioacetic acid) (2.5% solution for injections, Arterium, Ukraine), metabolitotropiccardioprotector and antioxidant, 50 mg/kg, i/p [13].

2. Angiolin ([S]-2,6-diaminohexane acid 3-methyl-1,2,4-triazolyl-5-thioacecate) (pharmaceutical substance, RPA "Farmatron", Ukraine), antiischemic, endothelium protective drug, 50 mg/kg, i/p [6, 7].

3. L-arginine (42% solution for injection in vial, Tivortin, Yuria-pharm, Ukraine), an NO precursor; it mitigates disruptions in the nitroxidergic system in ischemia, 200 mg/kg, i/p [14, 15].

4. Meldonium preparation (2-(2-carboxyethyl)-1,1,1-trimethylhydrazinium) (10% solution for injection in ampoules, Grindex, Latvia), metabolitotropic agent, 100 mg/kg, i/p [10].

For the study of ECG, we selected from the offspring 10 animals for each group, that were the most suitable at their age for electrophysiological experiments according to physical data. According to these criteria, male rat pups were more common.

Rats were withdrawn from the experiment on day 30 and 60 under thiopental anesthesia (40 mg/kg). The blood from the celiac artery was harvested for studies.

The study of electrocardiography

Peculiarities of ECG registration in small laboratory animals. Electrocardiography (ECG) in rats is a widely used experimental method in the study of the cardiovascular system. The ECG recording reflects the electrical activity of the heart and can provide important information about the functional and structural characteristics of the myocardium. The ECG recording technique in laboratory animals is quite simple, but the interpretation of electrocardiographic parameters is a difficult task. This is because, unlike humans, rats do not have established ECG benchmark criteria: there are significant differences in ECG parameters between studies in these animals. According to most scientists, this is due to various experimental settings, such as the type of anesthesia, the type of rat strain used, the sex, age of the animals, and heart rate (HR) [16,17].

Preparation of the animal for ECG registration and its implementation. Registration of ECG in rats using the ECG TUNNEL system eliminates most of the problems described above, since the animals are not subjected to anesthesia, but are in an immobilization tunnel (Fig. 1).

Important conditions for the effectiveness of ECG recording are preliminary, for 2-3 days, preparation of the animal for adaptation and exclusion of stress reactions, the creation of maximum noise insulation in an ambient temperature range of 24–26 °C. A great difficulty in recording ECG in rats is created by a high heart rate, exceeding 500 beats per minute, and in some experimental models it reaches 700–800 beats. To solve this problem, the ECG TUNNEL system is equipped with standard filters that reduce noise and electrical artifacts, as well as software-adjustable high- and low-pass band filters. This allows you to highlight certain patterns of electrical activity of the heart. When recording an ECG, simultaneous recording is carried out in six leads: standard (I, II, III) and enhanced (AVR, AVL, AVF).This makes it possible,

in addition to the standard parameters (duration and configuration of intervals and peak of the PQRST complex), using the software to set the average shift of the ST interval, the area of the S wave and its peak amplitude, calculate the efficiency indicator (% ratio of recorded impulses to the total number of signals in one session); calculate the average number of recorded impulses within one session.

The following parameters were determined and calculated:

1) correction of the trend of the signal amplitude R_{amp};

2) normalization of the R_{amp} signal relative to the average R_{amp} value of the period:

$$R_{norm}(i) = R(i) - {}_{\Delta}R \cdot i ,$$

where ${}_{\Delta}R = R_n - R_o$, i – serial number of the recording cycle, with subsequent centralization of values, provided that its average value is 1000 mV (the value of the standard calibration signal). Subsequently, R_{norm} was corrected taking into account the position of the iso-line Iso (I);

3) calculation of an additional parameter "± RR" (ms), reflecting the difference in the duration of successive RR cycles (calculated in absolute units of ms);

4) formation of a sample for statistical studies based on continuous recording of 10-second intervals in each individual-episode of the presented ECG.

All data of the source files are presented in tables on the sheets of the book with the name of the series of studies (by the name of the folders). Many recording files contain several episodes of recordings, and if there are any lengthy ones, they are collected in a separate table.

Parameters obtained when recording ECG:

- File – recording file name;
- # – rdinal number of RR cycles;
- period-time, s – recording time RR cycle;
- Ramp, mV – unnormalized R wave amplitude;
- RR, ms – time between two consecutive R waves;
- QRS, ms – duration of ventricular systole;
- Iso, mV – the isoline position;
- STE, mV – the position of the ST segment relative to the isoline;
- Sarea, mV·ms – area under the S wave;
- Sampl, mV – S wave amplitude;
- HR, bpm – heart rate.

ECG parameters obtained by the methods of mathematical calculations:

- normRamp, mV – normalized R-wave amplitude;
- mRR, ms – average statistical deviation of successive RR cycles;
- MoRR, ms – Mode – the most common value of the cardio interval in this dynamic series;
- AMo, % – Mode amplitude – reflects the stabilizing effect of the centralization of heart rate control, which is mainly due to the degree of activation of the sympathetic division of the autonomic nervous system;
- pNN50, % – percentage of consecutive R-R intervals that are greater than 50 ms apart. Indicator of the activity of the parasympathetic link of autonomic regulation;
- normR-Iso, mV – normalized amplitude of the R wave taking into account the position of the isoline Iso.
- pmRR, %RR – percentage of the value of the average statistical deviation of consecutive RR cycles in relation to the duration of RR cycles;
- pQRS, %RR – percentage of the duration of ventricular systole in relation to the duration of RR cycles;
- Rarea, V·ms – Rarea = normR-Iso·QRS – the value characterizing the power of ventricular systole.

In the presented data, the parameters RR and HR are interrelated.

Obviously, it was also valuable to evaluate the effect of drugs on the duration of ventricular **QRS** systole. We also paid attention to the temporal deviation of consecutive RR cycles "**mRR**" (similar to the statistical error of the mean for **RR**). Since, with a "smooth" stable rhythm, the parameter has a minimum value. However, the appearance of episodes of extrasystoles, or conduction blockades, or instability (weakness) of the sinus node, leads to an increase in this parameter.

A preliminary statistical analysis was made for the records:

- Count – sample size;
- max – maximum value in the sample;
- min – minimum value in the sample;
- MEAN – average value;
- sigma – standard deviation;
- S.E.M. – mean error;
- var% – the coefficient of variation;
- $M \pm m$;
- delta – service parameter;
- NORM – distribution normality index;
- Me – median;
- Q1 – 1st quartile;
- Q3 – 3rd quartile.

The data were statistically processed using the standard analysis package of the Microsoft Office Excel 2003 version. Data are presented as sample mean ± standard error of the mean. The distribution was checked for normality using the Shapiro-Wilk test. The significance of differences between the experimental groups was assessed using the Mann – Whitney U-test of the computer program Statistica for Windows 6.0 (StatSoft Inc., № AXXR712D833214FAN5).

Results

Characterization of myocardial automatism parameters

Analysis of the automatism of the appearance of the initial graphic ECG recordings was carried out on the basis of the following parameters (Table 1 and Fig. 1).

Heart rate in all groups of animals was more than 250 beats/min, which suggests the dominance of sinus rhythm in the examined rats. At the same time, the action of the sympathetic division of the NS (Amo = 42.553 ± 3.68) plays a dominant role in the regulation of the electrical activity of the heart of intact animals against the background of the almost complete absence of signs of parasympathetic regulation (pNN50 = 0.425 ± 0.425) (see Fig. 1).

Transferred PH leads to a decrease in heart rate and a significant dominance of parasympathetic innervation in the regulation of the electrical activity of the heart. Due to the lack of graphic ECG recordings, it cannot be ruled out that the decrease in heart rate in pathology could be caused by sinus blockade, which may also be a reflection of parasympathetic regulation of the heart instead of sympathetic control of electrical activity in the norm.

Experimental therapy after PH had a different degree of influence of drugs on the parameters of the electrical activity of the heart. Angiolin and tiazotic acid showed the most pronounced therapeutic effect, which contributed to the almost complete normalization of heart rate, angiolin and the restoration of neurogenic regulation of the automatism of the sinus node function. Changes in the heart rate in the experiment were reflected in the change in the duration of the cardiac cycle (RR interval) and the statistical spread of rhythm stability (mRR parameter). Thus, in case of pathology, HR was characterized by the lowest value in the group of observations and was combined with the longest duration of the cardiac cycle RR and the statistical spread of mRR. Given the different indicators of the duration of the RR cycle, we considered it correct to express the mRR parameter not in absolute terms, but as a percentage of the corresponding duration of the cardiac cycle – the pmRR parameter (Table 2).

Table 1: Parameters of myocardial automatism after prenatal hypoxia and course medication (2 months of life)

Experimental groups	HR, min^{-1}	Amo, %	pNN50, %
Intact (1) (*n* = 10)	**452.365 ± 12.724**	**42.553 ± 3.68**	**0.425 ± 0.425**
PH (control) (2) (*n* = 10)	**341.649 ± 15.01**	**10.826 ± 1.859**	**49.405 ± 4.262**
P(2-1)	2.71642E-07	8.46191E-11	5.50739E-14
PH + arginine (3) (*n* = 10)	**365.374 ± 17.404**	**25.885 ± 3.913**	**35.885 ± 4.993**
P(3-1)	0.000118295	0.002542564	5.81529E-09
P(3-2)	*0.286948401*	0.001137	0.036969604
PH + meldonium(4) (*n* = 10)	**385.897 ± 17.935**	**38.723 ± 4.076**	**27.021 ± 4.808**
P(4-1)	0.002536642	*0.400424198*	7.29728E-07
P(4-2)	*0.065358247*	7.79898E-08	0.000904463
P(4-3)	*0.433885002*	0.035733524	*0.225882523*
PH + tiazotic acid (5) (*n* = 10)	**446.366 ± 9.335**	**29.8 ± 3.73**	**19.4 ± 3.773**
P(5-1)	*0.704754111*	0.016828487	7.43932E-06
P(5-2)	1.28032E-07	2.15454E-05	1.08073E-06
P(5-3)	0.00010663	*0.470797223*	0.009959525
P(5-4)	0.002845163	*0.144898626*	*0.184087745*
PH + angiolin (6) (*n* = 10)	**477.526 ± 4.38**	**35.882 ± 2.209**	**6.617 ± 1.735**
P(6-1)	*0.066679777*	*0.124276365*	0.000879916
P(6-2)	3.78752E-11	6.08384E-14	1.50107E-12
P(6-3)	7.25338E-08	0.029065662	7.6557E-07
P(6-4)	7.98052E-06	*0.541964713*	0.000186665
P(6-5)	0.003501716	*0.164459375*	0.002982466

Notes. Group 1 – relatively healthy rat pups received saline solution (n = 10); 2 – control group of pups after PH which received saline solution for 30 days (n = 10); 3 – rat pups after PH that received L-arginine in 200 mg/kg, i/p for 30 days (n = 10); 4 – rat pups after PH that received meldonium in 100 mg/kg, i/p for 30 days (n = 10); 5 – rat pups after PH that received tiazotic acid in 50 mg/kg, i/p for 30 days (n = 10); 6 – rat pups after PH that received angiolin in 50 mg/kg, i/p for 30 days (n = 10).

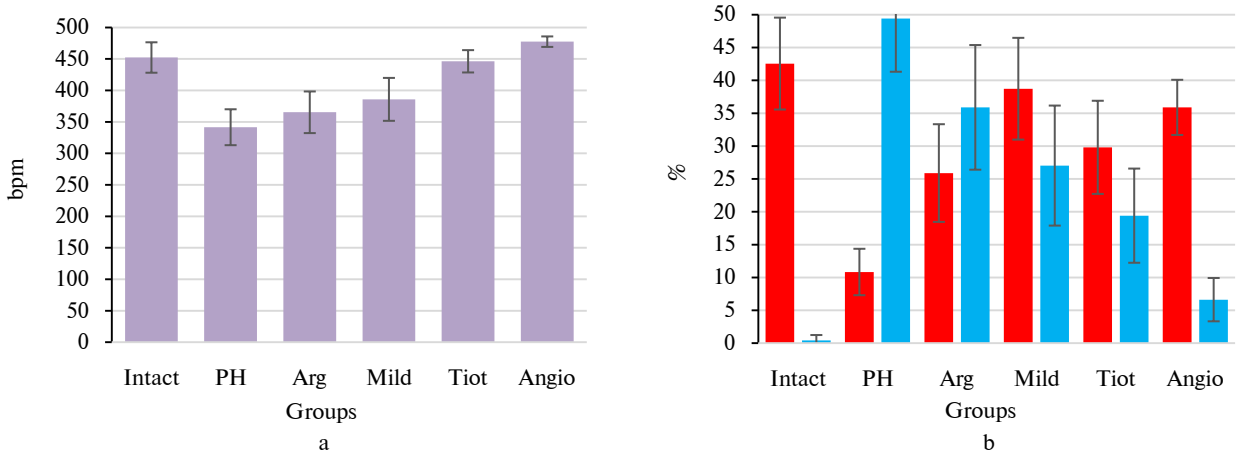

Figure 1: Changes in heart automatism parameters in experimental pathology and its pharmacological correction: heart rate (HR, bpm) (a), which was more than 250 beats/min, which suggests the dominance of sinus rhythm in the examined rats. And second figure is proportion of sympathetic (Amo, %) and parasympathetic (pNN50, %) nervous regulation of the heart (b). Mean values and their confidence intervals are indicated. Intact group – relatively healthy rat pups received saline solution (n = 10); Pato – control group of pups after PH which received saline solution for 30 days (n = 10); Arg – rat pups after PH that received L-arginine in 200 mg/kg, i/p for 30 days (n = 10); Meld – rat pups after PH that received meldonium in 100 mg/kg, i/p for 30 days (n = 10); Tia – rat pups after PH that received tiazotic acid in 50 mg/kg, i/p for 30 days (n = 10); Angio – rat pups after PH that received angiolin in 50 mg/kg, i/p for 30 days (n = 10)

Table 2: Parameters of the cardiac cycle after prenatal hypoxia and course medication (2 months of life)

Experimental groups	RR, ms	mRR, ms	pmRR, %RR
Intact (1)	**138.485 ± 4.031**	**3.687 ± 0.796**	**2.653 ± 0.613**
Pathology (2)	**253.432 ± 30.798**	**120.964 ± 25.01**	**42.738 ± 4.119**
P(2-1)	0.000657788	3.50078E-05	6.24501E-12
Arginine (3)	**201.263 ± 22.792**	**64.646 ± 10.898**	**25.357 ± 2.738**
P(3-1)	0.009141925	1.129E-06	9.57121E-11
P(3-2)	*0.172169031*	0.040473061	0.000789553
Meldonium (4)	**218.002 ± 18.396**	**51.017 ± 9.604**	**16.238 ± 2.394**
P(4-1)	6.09904E-05	6.39447E-06	1.18586E-06
P(4-2)	*0.341782567*	0.012514139	6.00376E-07
P(4-3)	*0.538069821*	*0.369520943*	0.01393969
Tiazotic acid (5)	**159.798 ± 6.926**	**27.974 ± 4.6**	**14.172 ± 1.965**
P(5-1)	0.00949499	3.40084E-06	6.17845E-07
P(5-2)	0.004965243	0.000726762	6.11112E-08
P(5-3)	*0.087272708*	0.002887234	0.001330304
P(5-4)	0.00316411	0.02713264	*0.506571563*
Angiolin (6)	**132.273 ± 1.474**	**12.786 ± 2.085**	**9.372 ± 1.419**
P(6-1)	*0.153224278*	0.000102154	3.65563E-05
P(6-2)	0.000346199	0.000109029	8.09883E-10
P(6-3)	0.004057375	2.23748E-05	1.92459E-06
P(6-4)	2.80236E-05	0.00029474	0.015841722
P(6-5)	0.000282697	0.003682098	*0.050619784*

Notes. Group 1 – relatively healthy rat pups received saline solution (n = 10); 2 – control group of pups after PH which received saline solution for 30 days (n = 10); 3 – rat pups after PH that received L-arginine in 200 mg/kg, i/p for 30 days (n = 10); 4 – rat pups after PH that received meldonium in 100 mg/kg, i/p for 30 days (n = 10); 5 – rat pups after PH that received tiazotic acid in 50 mg/kg, i/p for 30 days (n = 10); 6 – rat pups after PH that received angiolin in 50 mg/kg, i/p for 30 days (n = 10).

The analysis of the pmRR parameter shows that the development of the experimental dependence leads to a 20-fold increase in the statistical interval of RR scatter, which is associated with a violation of the permanent operation of the sinus node. Most likely, this was facilitated by the predominance of parasympathetic regulation of the heart rhythm in experimental pathology, perhaps even elements of sinus blockade, but it is not possible to prove this without a graphic ECG recording. The obtained data on the statistical stability of the heart rate demonstrate the highest therapeutic efficacy of angiolin in restoring the electrical activity of the heart in experimental pathology (Fig. 2).

Characterization of myocardial excitability parameters

Possible violations of myocardial excitability in pathology are usually manifested by extrasystolic activity, but a graphic recording is necessary to verify this violation. In principle, an extremely high pmRR parameter in animals with experimental pathology may indirectly indicate an "extrasystolic explosion" after episodes of sinus blockade.

Characterization of myocardial excitability parameters

The criteria for myocardial conduction are the parameters of the duration of ventricular systole (QRS interval) and the power of electrical repolarization of the ventricles – the area under the ST interval (Sarea parameter) (Table 3).

The development of violations of the bioelectrical activity of the heart after PG led to a

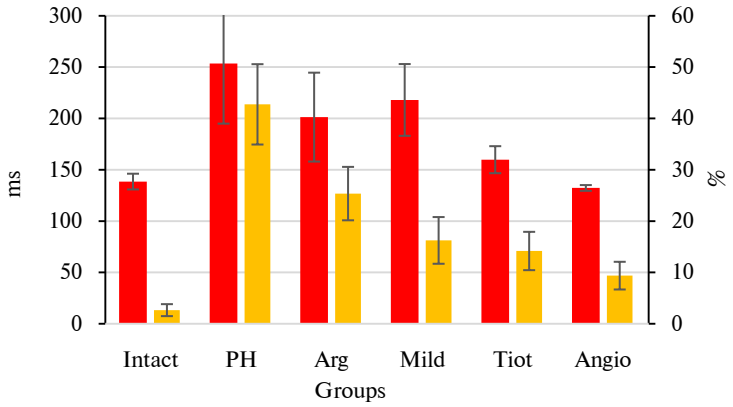

Figure 2: Changes in the parameters of automatism of the sinus node in experimental pathology and its pharmacological correction. The duration of RR intervals, ms (■) is presented on the main scale, and the percentage of the average statistical deviation of consecutive RR cycles pmRR, % (■) – on the auxiliary scale (on the right). Mean values and their confidence intervals are indicated. Intact group – relatively healthy rat pups received saline solution (n = 10); Pato – control group of pups after PH which received saline solution for 30 days (n = 10); Arg – rat pups after PH that received L-arginine in 200 mg/kg, i/p for 30 days (n = 10); Meld – rat pups after PH that received meldonium in 100 mg/kg, i/p for 30 days (n = 10); Tia – rat pups after PH that received tiazotic acid in 50 mg/kg, i/p for 30 days (n = 10); Angio – rat pups after PH that received angiolin in 50 mg/kg, i/p for 30 days (n = 10)

Table 3: Parameters of myocardial excitability after prenatal hypoxia and course medication (2 months of life)

Experimental groups	QRS, ms	pQRS, % RR	Sarea, mV·ms
Intact (1)	**15.263 ± 0.21**	**11.598 ± 0.455**	**4.722 ± 0.867**
PH (control) (2)	**18.584 ± 0.469**	**12.926 ± 2.425**	**22.606 ± 3.46**
P(2-1)	3.46051E-08	*0.593382255*	9.81422E-06
PH + Arginine (3)	**19.221 ± 0.285**	**26.034 ± 3.931**	**16.979 ± 4.632**
P(3-1)	2.02676E-18	0.000647564	0.012186394
P(3-2)	*0.294590287*	0.005821539	*0.289514294*
PH + meldonium (4)	**16.34 ± 0.363**	**9.114 ± 0.46**	**1.9 ± 0.312**
P(4-1)	0.007368916	0.000228865	0.004575077
P(4-2)	0.000525758	*0.13019552*	6.67186E-07
P(4-3)	3.78291E-08	8.95564E-05	0.002269736
PH + tiazotic acid (5)	**17.726 ± 0.26**	**11.753 ± 0.347**	**4.034 ± 0.514**
P(5-1)	7.95188E-11	*0.787897723*	*0.497735058*
P(5-2)	*0.115304012*	*0.634582553*	4.50753E-06
P(5-3)	0.000197918	0.000713036	0.007790156
P(5-4)	0.00485397	1.55854E-05	0.00115104
PH + angiolin (6)	**15.729 ± 0.267**	**11.957 ± 0.217**	**7.348 ± 0.529**
P(6-1)	*0.174366332*	*0.480402933*	0.011651766
P(6-2)	1.70494E-06	*0.692634198*	8.9741E-05
P(6-3)	1.26251E-14	0.00081794	0.044262923
P(6-4)	*0.178895493*	4.71645E-07	2.47219E-14
P(6-5)	4.65807E-07	*0.620234869*	1.73411E-05

Notes. Group 1 – relatively healthy rat pups received saline solution (n = 10); 2 – control group of pups after PH which received saline solution for 30 days (n = 10); 3 – rat pups after PH that received L-arginine in 200 mg/kg, i/p for 30 days (n = 10); 4 – rat pups after PH that received meldonium in 100 mg/kg, i/p for 30 days (n = 10); 5 – rat pups after PH that received tiazotic acid in 50 mg/kg, i/p for 30 days (n = 10); 6 – rat pups after PH that received angiolin in 50 mg/kg, i/p for 30 days (n = 10).

lengthening of the electrical systole of the ventricles, which may be caused by a violation of the conduction of ventricular myocardium. Under these conditions, the power of electrical ventricular repolarization increased by 5.5 times, which indicated significant problems with the restoration of the membrane potential of ventricular cardiomyocytes. Among the pharmacological agents administered to animals after PH, arginine did not show therapeutic efficacy, because the conductivity parameters during its application did not statistically differ from similar indicators in the control group of animals with pathology (Fig. 3).

Characterization of parameters of myocardial contractility

As parameters characterizing myocardial contractility, the amplitude of the R wave normalized relative to the isoline (reflects the strength of the electrical systole of the ventricles) and the area under the QRS curve – R area (reflects the power of the electrical systole), where Rarea = = normR-Iso·QRS/2, are taken as a basis. The formation led to a decrease in the amplitude of the R wave, i.e. the strength of the electrical systole of the ventricles, by 1% in combination with an increase in its power (Rarea parameter) by 20%. We believe that an increase in this value during adequate or enhanced energy supply of the myocardium may indicate an adaptive response of the myocardium to the load. However, if the energy supply of the myocardium decreases, then this may indicate an unfavorable mode of the heart. In the considered case of experimental pathology, such a significant increase in the power of electrical systole may indicate significant energy consumption of myocardium during the period of systolic stress (Table 4 and Fig. 4).

The use of angiolin in the pharmacological correction of experimental pathology showed the best therapeutic effect on the restoration of myocardial contractility. At the same time, Arginine did not have such a therapeutic effect.

Functional efficacy of myocardial ECG (RANKS) after experimental therapy for the consequences of pulmonary hypertension

For a comprehensive assessment of the therapeutic effect of drugs on the parameters of the electrical activity of the heart in the pharmacological correction of experimental pathology, we proposed to rank the measured parameters and conduct a pairwise comparison in the experimental groups according to the non-parametric rank criterion U (Wilcoxon–Mann–Whitney). At the same time, the effectiveness of the therapeutic effect of the drugs was evaluated according to a one-sided criterion, i.e. we were only interested in the maximum approximation to the normal parameters (Table 5 and Fig. 5).

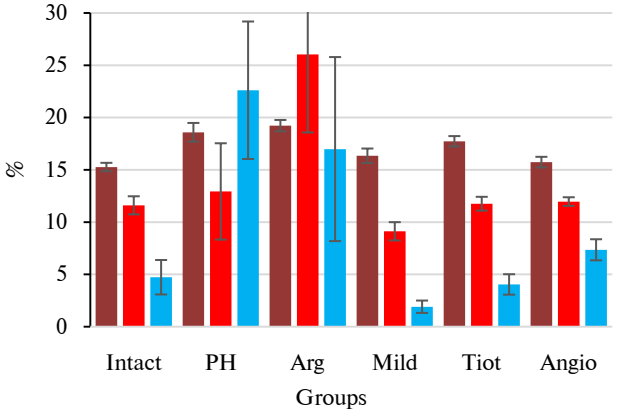

Figure 3: Changes in cardiac conduction parameters in experimental pathology and its pharmacological correction: the duration of the electrical ventricular systole (■ QRS interval, ms), the percentage ratio of the electrical ventricular systole to the duration of the cardiac cycle (■ pQRS, %), the area under the myocardial depolarization wave S (■ Sarea, mV·ms). Mean values and their confidence intervals are indicated

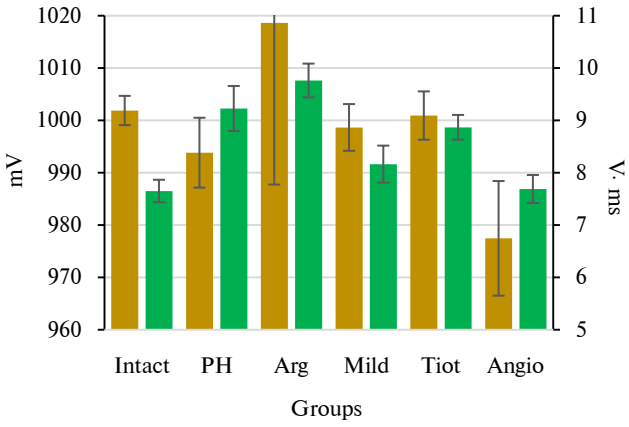

Figure 4: Changes in the parameters of myocardial contractility in experimental pathology and its pharmacological correction. The amplitude duration of the normalized R wave (mV) is presented on the mains cale, and the area under the R wave (Rarea, V·ms) is presented on theauxiliary scale (on the right). Mean values and their confidence intervals are indicated; ■ – normR-Iso, ■ – Rarea

Notes. Intact group – relatively healthy rat pups received saline solution (n = 10); Pato – control group of pups after PH which received saline solution for 30 days (n = 10); Arg – rat pups after PH that received L-arginine in 200 mg/kg, i/p for 30 days (n = 10); Meld – rat pups after PH that received meldonium in 100 mg/kg, i/p for 30 days (n = 10); Tia – rat pups after PH that received tiazotic acid in 50 mg/kg, i/p for 30 days (n = 10); Angio – rat pups after PH that received angiolin in 50 mg/kg, i/p for 30 days (n = 10)

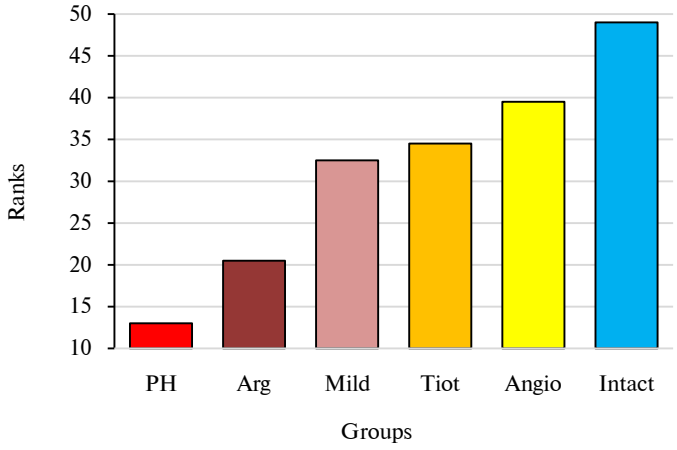

Figure 5: Rank indicators of ECG functional efficiency in experimental pathology and its pharmacological correction. Intact group – relatively healthy rat pups received saline solution (n = 10); Pato – control group of pups after PH which received saline solution for 30 days (n = 10); Arg – rat pups after PH that received L-arginine in 200 mg/kg, i/p for 30 days (n = 10); Meld – rat pups after PH that received meldonium in 100 mg/kg, i/p for 30 days (n = 10); Tia – rat pups after PH that received tiazotic acid in 50 mg/kg, i/p for 30 days (n = 10); Angio – rat pups after PH that received angiolin in 50 mg/kg, i/p for 30 days (n = 10)

Table 4: Parameters of myocardial contractility after prenatal hypoxia and course medication (2 months of life)

Experimental groups	normR-Iso, mV	Rarea, V·ms
Intact (1)	**1001.876 ± 1.47**	**7.65 ± 0.112**
PH + (control) (2)	**993.819 ± 3.514**	**9.226 ± 0.226**
P(2-1)	0.039314832	6.15159E-08
PH + arginine (3)	**1018.617 ± 16.256**	**9.761 ± 0.169**
P(3-1)	*0.310248773*	1.53007E-16
P(3-2)	*0.140916916*	*0.06231457*
PH + meldonium (4)	**998.638 ± 2.349**	**8.163 ± 0.185**
P(4-1)	*0.244768084*	0.020833929
P(4-2)	*0.251504111*	0.00050824
P(4-3)	*0.230394047*	8.09769E-09
PH + tiazotic acid (5)	**1000.914 ± 2.429**	**8.866 ± 0.124**
P(5-1)	*0.7355655*	1.16678E-10
P(5-2)	*0.101227388*	*0.169311886*
P(5-3)	*0.286729867*	5.33509E-05
P(5-4)	*0.505395399*	0.002333149
PH + angiolin (6)	**977.454 ± 5.762**	**7.688 ± 0.14**
P(6-1)	0.000100776	*0.833632383*
P(6-2)	0.017098624	2.16729E-07
P(6-3)	0.020238737	1.90332E-15
P(6-4)	0.00100339	0.044418598
P(6-5)	0.000312717	6.38326E-09

Table 5: Functional efficiency of myocardial ECG (RANKS) after prenatal hypoxia and course medication (2 months of life)

Experimental groups	HR	AMo	pNN50	RR	pmRR	QRS	Sarea	normR-Iso	Rarea	Ranks
Intact (1)	5.5	6	6	5.5	6	5.5	4.5	4.5	5.5	49.0
PH (control) (2)	1.5	1	1	2	1	2	1	2	1.5	13.0
PH + arginine (3)	1.5	2.5	2.5	2	2	2	2	4.5	1.5	20.5
PH + meldonium (4)	3	4.5	2.5	2	4	4	6	4.5	4	34.5
PH + tiazotic acid (5)	4	2.5	4	4	4	2	4.5	4.5	3	32.5
PH + angiolin (6)	5.5	4.5	5	5.5	4	5.5	3	1	5.5	39.5

Notes. Group 1 – relatively healthy rat pups received saline solution (n = 10); 2 – control group of pups after PH which received saline solution for 30 days (n = 10); 3 – rat pups after PH that received L-arginine in 200 mg/kg, i/p for 30 days (n = 10); 4 – rat pups after PH that received meldonium in 100 mg/kg, i/p for 30 days (n = 10); 5 – rat pups after PH that received tiazotic acid in 50 mg/kg, i/p for 30 days (n = 10); 6 – rat pups after PH that received angiolin in 50 mg/kg, i/p for 30 days (n = 10).

Table 6: Comparison of the effectiveness of drugs in normalizing the ECG after prenatal hypoxia and a course of medication (2 months of life) (according to the non-parametric rank criterion U)

Experimental groups	Intact	PH (control)	PH + angiolin	PH + arginine	PH + meldonium
PH (control) (2)	<0.05				
PH + arginine (3)	<0.05	**>0.05**	–	–	–
PH + meldonium (4)	<0.05	<0.05	<0.05	–	–
PH + tiazotic acid (5)	<0.05	<0.05	<0.05	**>0.05**	–
PH + angiolin (6)	<0.05	<0.05	<0.05	**>0.05**	<0.05

Notes. 2 – control group of pups after PH which received saline solution for 30 days (n = 10); 3 – rat pups after PH that received L-arginine in 200 mg/kg, i/p for 30 days (n = 10); 4 – rat pups after PH that received meldonium in 100 mg/kg, i/p for 30 days (n = 10); 5 – rat pups after PH that received tiazotic acid in 50 mg/kg, i/p for 30 days (n = 10); 6 – rat pups after PH that received angiolin in 50 mg/kg, i/p for 30 days (n = 10).

The results obtained made it possible to rank the therapeutic efficacy of the drugs used in descending order: angiolin > tiazotic acid > meldonium. Despite the fact that angiolin proved to be more effective than tiazotic acid in normalizing the electrical activity of the heart in pathology, and in the compared pairs angiolin–tiazotic acid and tiazotic acid–meldonium, the drugs have approximately equal (statistically unreliable differences) therapeutic effect. The drug Arginine did not show effectiveness in eliminating disturbances in the electrical activity of the heart in experimental pathology (Table 6).

Discussion

There is no doubt that the origins of many chronic, disabling or fatal pathological conditions in adults, including diseases of the cardiovascular system, originate in the peri- and neonatal period, and some diseases of the neonatal, infancy and older age represent a prolonged pathology of embryo and fetus [18]. Fetal hypoxia leads to disruption of the autonomic regulation of the coronary vessels, deterioration of energy metabolism – deficiency of ATP, ADP and creatine phosphate, discoordination in the Krebs cycle, activation of anaerobic glycolysis, it also leads to disruption of the ultrastructure of mitochondria, both in cardiomyocytes and in the cells of the conducting system. Metabolic acidosis, transmitter autocoidosis, hypoglycemia, oxidative stress, deterioration of the rheological properties of blood are decisive in the pathogenesis of hypoxic damage to the cardiovascular system in a newborn and cause a decrease in myocardial contractile function and disruption of the normal functioning of the sinus node [9]. In the contractile myocardium and the conduction system, cells with signs of apoptosis and dystrophy are found with a certain relationship between the severity of morphological changes and bioelectrical rhythm and conduction disturbances. The end result of hypoxic heart damage can be focal dystrophy, leading to focal cardiosclerosis with insufficient therapy [19]. Our previous studies have obtained data indicating the role of the NO system in the formation of post hypoxic cardiomyopathy. So, in children who underwent intrauterine hypoxia, a deficiency of stable NO metabolites was found in blood against the background of eNOS inhibition [12].

The introduction of drugs that positively affect the NO system had a positive effect on the bioelectrical activity of the heart of rat pups after PH.

The revealed primary cardio-protective effect of angiolin when it is prescribed after intrauterine hypoxia, with the preservation of the effect even after a monthly withdrawal, is explained by its following properties. Angiolin in conditions of acute myocardial ischemia increases the expression of eNOS, increases the production of NO, has the property of a NO scavenger, which increases its "life" [20]. Normalization of the nitroxidergic system under the action of angiolin can have a beneficial effect not only on the function of myocardial excitability and contractility, be the basis of the endothelioprotective action, but also positively affect the function of myocardial mitochondria. NO limits mitochondrial Ca^{2+} overload, normalizes mitochondrial potential ($\Delta\Psi m$) during ischemia. Angiolin is able, together with vitamin C, to form L-carnitine and normalize the work of mitochondria [21]. In our work, it was found that angiolin normalized the amplitudes of the ventricular R wave and the amplitude of the repolarization T wave under conditions of myocardial ischemia, which is associated with an improvement in the energy supply of the myocardium and a more rational use of macroergs to ensure the contractile function of the heart [12]. Angiolin increases the expression of HSP_{70}, which "prolongs" the action of HIF-1a, and also independently maintains the expression of

NAD-MDH-mx, thereby maintaining the activity of the compensatory mechanism of ATP production – the malate-aspartate shuttle mechanism for a long time. Our work has shown that angiolin can activate the malate-aspartate shuttle mechanism in the myocardium during ischemia [22]. Tiazotic acid exhibits the properties of a scavenger of cytotoxic forms of NO, has a protective effect on NO transport, due to a positive effect on the thiol-disulfide balance and an increase in the level of reduced thiols. In addition, we assume that tiazotic acid itself can be a carrier of NO, forming stable S-nitrosyl complexes with it [4]. Tiazotic acid exhibits a cardioprotective effect, positively affecting energy metabolism in ischemic myocardium – increases ATP during ischemia and hypoxia due to the normalization of the Krebs cycle, increases the utilization of glucose, free fatty acids, activates the conversion of lactate to pyruvate. Due to the antioxidant action, tiazotic acid maintains the threshold sensitivity of receptors, maintains membrane fluidity, and protects phospholipids from oxidation [15]. L-Arginine is a substrate for the formation of NO in vascular endothelial cells, a peripheral vascular dilatation factor. It is formed from arginine NO, reduces the total peripheral vascular resistance and blood pressure, reduces oxygen starvation, especially in the tissues of the heart [18]. NO production by tiazotic acid increases proangiogenic VEGF-A and PGF in cultured human trophoblasts, while inhibition of NO synthesis leads to increased SFLT-1 levels and hypertensive responses in pregnant rats [8]. Tiazotic acid in experimental myocardial infarction normalized heart rate, reduced the total deviation of the ST segment. Tiazotic acid in acute non-ST segment elevation coronary syndrome, increased left ventricular ejection fraction, reduced end-systolic and end-diastolic heart volumes, reduced the total duration of myocardial ischemia episodes and the number of ventricular and supraventricular arrhythmias [2]. Meldonium is an inhibitor of the biosynthesis, transport and reabsorption of L-carnitine, prevents the accumulation of toxic acylcarnitines in ischemic tissue and shifts cell metabolism towards increased glucose consumption, which is beneficial in ischemic conditions. Meldonium compensatory increases the activity of acyl-CoA synthetase and carnitine palmitoyl transferase I in mitochondria and increases peroxisomal fatty acid oxidation. Treatment with meldonium is accompanied by a compensatory increase in the expression in the myocardium of a number of genes encoding lipid metabolism enzymes – lipoprotein lipase, fatty acid translocase, carnitine palmitoyltransferase I and triacylglycerol synthesis enzymes [10, 20]. Meldonium is able to improve myocardial contractility, hexokinase activity, as well as the ratio of ATP/ADP/AMP due to the activation of AMP-activated protein kinase, which restores the level of ATP [3, 9]. Meldonium can increase NO production in the ischemic myocardium and brain by modifying stores of esters of γ-butyrobetaine [20]. The introduction of meldonium inhibits the hydroxylation of GBB and increases the intracellular store of γ-butyrobetaine, which exhibits cholinomimetic properties during esterification. Esters of γ-butyrobetaine through acetylcholine receptors on endothelial cells can activate eNOS. The introduction of meldonium inhibits the hydroxylation of GBB and increases the intracellular store of γ-butyrobetaine, which exhibits cholinomimetic properties during esterification. Esters of γ-butyrobetaine through acetylcholine receptors on endothelial cells can activate eNOS. However, in a number of studies, the effect of meldonium on NO production was not confirmed [10]. L-arginine, a precursor of NO synthesis, exhibits cardioprotective, anti-ischemic, endothelial protective properties associated with an increase in NO [23]. There is evidence of some effect of L-arginine in PH. The insignificant effect of L-arginine on the bioelectrical activity of the heart revealed by us can be explained by the fact that part of the formed NO can lose its properties under the action of ROS. In addition, it is possible that in maintaining myocardial activity after PH, their properties are also necessary, in particular antioxidant, energy modulating, etc.

Conclusions

The experimental PH was postponed to reduce the heart rate to a decrease in the heart rate and the exact dominance of the parasympathetic innervation in the regulation of the electrical activity of the heart, which may be caused by sinus blockade and may be irritated by the parasympathetic regulation of the heart and the activity in the electrical control of the heart.

Efficacy of drugs in terms of the degree of influence on ECG parameters can be represented in the order of change: angiolin > tiazotic acid > meldonium. Moreover, angiolin proved to be more effective than tiazotic acid in normalizing the electrical activity of the heart and inspiring neurogenic regulation of the automatism of the function of the sinus node. Arginine did not show the effectiveness

of the destruction of electrical activity of the heart after PH.

Thus, the search and development of approaches to the pharmacotherapy of prenatal myocardial damage based on the modulation of the NO system is an urgent task of modern pharmacology.

The prospect of studying modulators of the NO system with different mechanisms of action – L-arginine, tiazotic acid, angiolin and meldonium as a means of cardioprotection of posthypoxic disorders of the cardiovascular system in newborns is theoretically substantiated.

Interests disclosure

The authors have no conflicts of interest to declare.

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ПОКАЗНИКИ БІОЕЛЕКТРИЧНОЇ АКТИВНОСТІ СЕРЦЯ ЩУРІВ ПІСЛЯ ПРЕНАТАЛЬНОЇ ГІПОКСІЇ ТА ФАРМАКОЛОГІЧНОЇ КОРЕКЦІЇ

Проблематика. Постгіпоксична кардіопатія є одним із факторів ризику розвитку серцево-судинної патології (порушення ритму, вегетосудинна дистонія тощо) у подальші вікові періоди та потребує розробки підходів до лікування.
Мета. Оцінити кардіопротекторну дію модуляторів системи NO за впливом на ЕКГ щурів після внутрішньоутробної гіпоксії.
Методика реалізації. Моделювання пренатальної гіпоксії (ПГ) шляхом щоденного внутрішньоочеревинного введення розчину нітриту натрію вагітним самкам білих щурів масою 220–240 г віком 4,5 місяця з 16-ї по 21-шу добу вагітності в дозі 50 мг/кг. Потомству щодня з 1-ї по 30-ту добу життя вводили тіазотну кислоту (морфоліній 3-метил-1,2,4-триазоліл-5-тіооцтова кислота) – 50 мг/кг, ангіолін ([S]-2,6-діаміногексанова кислота, 3-метил-1,2,4-триазоліл-5-тіоацетат) – 50 мг/кг, L-аргінін – 200 мг/кг, мелдоніум (2-(2-карбоксиетил)-1,1,1-триметилгідразиній) – 100 мг/кг. Потім на 2-му місяці життя проводили запис ЕКГ за допомогою системи ECG TUNNEL (без наркозу).
Результати. Перенесена ПГ приводить до зниження частоти серцевих скорочень і значного домінування парасимпатичної іннервації в регуляції електричної активності серця, що може бути викликано блокадою синусового вузла, а також бути відображенням парасимпатичної регуляції серця замість симпатичного контролю електричної активності в нормі. Ефективність препаратів можна подати в порядку спадання: ангіолін > тіазотна кислота > мелдоніум. Ангіолін виявився більш ефективним, ніж тіазотна кислота, у нормалізації електричної активності серця та відновленні нейрогенної регуляції автоматизму функції синусового вузла.
Висновки. Експериментально обґрунтовано перспективи подальшого вивчення модуляторів системи NO з різними механізмами дії як засобів кардіопротекції постгіпоксичних розладів серцево-судинної системи у новонароджених.

Ключові слова: внутрішньоутробна гіпоксія; кардіопротекторні електрофізіологічні порушення; міокард новонароджених; фармакокорекція; ангіолін; тіазотна кислота; L-аргінін; мелдоніум.