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Assessment of functional reserves of the autonomous control mechanisms on the basis of the heart rate variability analysis under the combined influence of blockers of cardiac activity autonomous control and hypoxia

Oznaczanie rezerwy funkcjonalnej mechanizmów kontroli autonomicznej na podstawie analizy zmienności częstości akcji serca w warunkach jednoczesnego wpływu blokerów kontroli autonomicznej aktywności serca i hipoksji

INTRODUCTION

Under the influence of extreme irritants, including hypoxia, stress-reaction develops as a nonspecific constituent of adaptation. Due to that, energetic, plastic and informative reserves are mobilized for specific adaptation alteration of the organism systems [1,4]. In particular, reserve adaptation possibilities of the cardiorespiratory system play an important role under hypoxia. In general, the functional reserve of control mechanisms consists of specific and nonspecific components. Efficiency of the adaptation reaction is determined by the predominance of one or another component. Therefore, the predominance of specific mechanisms' activity provides a more economical and purposeful use of the organism reserve [1]. It is possible to get the objective information about the organism's functional state on the basis of the assessment of control mechanisms of the blood circulation system by means of the heart rate variability (HRV) analysis [1–5]. Among the tests that are the most frequently used during the HRV research, there are pharmacological tests conducted by means of blockers of the cardiac activity autonomous control. Therefore, we have chosen the introduction of the blocker of M-cholinergic receptors (atropine) and blocker of ß-adrenergic receptor (propranolol) in different doses as a functional loading under hypoxia.

MATERIAL AND METHODS

The tests were carried out on outbred not narcotized white male rats weighing 180–220 gm (n = 140, 7 rats per group). The animals were kept under ordinary conditions of vivarium with standard ration without any restrictions in food and water. The recording of cardiointervalgram was conducted during the period of 5 min., not invasively, using the photoplethysmographic transformer fixed near the base of tail and connected to the fast-acting recording device. For that purpose the rats had been immobilized in the universal plexiglass chamber, the form of which fitted the organization of the body. The chamber was covered with a dark dense velvet fabric to avoid unnecessary irritants, which also caused the "burrow reflex" inherent to the species (the innate propensity to the limited black-out space). The monitoring of the cardiac cycle duration of not narcotized rats was conducted by means of the method introduced by us (Patent of Ukraine № 80520, A61V5/024. The method of non-invasive identification of the cardiac cycle duration of not narcotized rats / M.R.Gzhegotsky, E.V. Storchun, L.V. Panina, O.I. Terletska, S.M. Koval'chuk, R.V.Kmit' /UA/ – № a200702659; It is declared on March 13,2007; published on September 25, 2007. – Bulletin № 15). We carry out the HRV analysis by means of the method introduced by us (Patent of Ukraine № 29596, A61V5/0205, A61V5/024. The functional state estimation method of the experimental animals on the basis of analysis of the heart rate variability / M.R. Gzhegotsky, E.V. Storchun, L.V. Panina, S.M. Koval'chuk, O.V. Kless, O.I. Terletska, Yu.S. Petryshyn, O.G. Mysakovets /UA/ – № u200702660; It is declared on March 13, 2007; published on January 25, 2008. – Bulletin № 2).

The statistical parameters of the cardio intervals dynamic row were analyzed: Successive Deviation of NN-intervals (SDNN); the square root of the sum of differences of successive row of cardio intervals (Root Mean Sum Successive Deviation, RMSSD); the coefficient of variation (CV). The parameters of variation pulsometry are the following: MxDMn, difference between the maximum (Mx) and minimum (Mn) values of the cardio intervals; the mode (Mo); the amplitude of mode (Amo); the stress index (SI) or index of tension of the regulation systems. Using the spectral analysis we characterized such parameters as the total power (TP); the index of centralization (IC). In order to recreate the results received during the tests conducted on the white rats correctly, the HRV analysis was carried out within the following ranges: Low Frequency, LF (0.015 – 0.25) Hz, Mid Frequency, MF (0.25 – 0.75) Hz, High Frequency, HF (0.75 – 3.0) Hz.

Hypoxic hypoxia with a 10 minutes' period was simulated by means of the pressure chamber "raising" (with the speed of 180 m/s) of rats from separate groups on conditional "heights" of 6000 m and 9000 m above the sea level. The recordings of cardiointervalgram were conducted before that effect (initial level) and 15 min after it.

The introduction of atropine (blocker of M-cholinergic receptors) was carried out with a 0.4 mg/kg dose subcutaneously and 2 mg/kg dose intravenously. Propranolol (blocker of ß-adrenergic receptor) was introduced with the doses of 2 mg/kg intraperitoneally and 5 mg/kg intravenously. The control introduction of NaCl was carried out, and the way of introduction and the solution volume (did not exceed 0.5 ml) was the same as during introduction of atropine and propranolol. The analysis of the HRV indexes after the injections of NaCl, conducted in a number of different ways, found out their difference. In the sequel, increasing the dosage of the medicine stipulated the choice of the intravenous way of introduction. The recording of the cardiointervalgram was conducted before the introduction of the correspondent medicine (initial level) and 30 min after it.

30 min after the introduction of atropine and propranolol with the dosage noted before the rats of separate groups were subjected to 10 minutes' influence of extreme hypoxia (9000 m). The recordings of the cardiointervalgram were conducted before the introduction of the correspondent medicine (initial level) and 15 min after hypoxia.

The paired comparison of the means was conducted according to Student t-criterion. The differences were considered to be reliable at the significance level P <0.05.

RESULTS

Having conducted the hypoxia tests on the “heights” of 6000 m and 9000 m above the sea level no significant changes of the cardiac rhythm of the intact animals and of the animals with the previous use of the higher doses of blockers were revealed (Fig. 1). It is possible to describe the regulatory influence which determined the (Heart Rate) HR under those conditions by means of the HRV analysis. Moreover, the intact animals gained the increase of statistical parameters induced by hypoxia (SDNN, RMSSD, CV). However, such changes on the “height” of 6000 m had tendentious character (Fig. 1). During the analysis of spectral power we revealed the increase of the integrative index of TP by 2.3 and 3.7 times, which depends upon the degree of the hypoxic influence, in comparison with the initial level. Changes of that value were characterized by the brightly expressed growth of all investigated spectral constituents which depended upon the intensity of the hypoxic influence. In particular, as the “height” grew, the absolute values of HF grew 2.9 and 4.7 times, MF 1.9 and 3.6 times, LF 1.9 and 2.5 times, in comparison with the initial level. The indexes, calculated on the basis of the relative values of spectral constituents which characterize the entry of each of them to the general power, changed reversely (Fig. 1). In particular, the index of MF/HF tended to decrease on the “height” of 6000 m, but activated on the “height” of 9000 m. Similar changes were observed in IC. On the contrary, the index of LF/HF increased only on the “height” of 6000 m, in comparison with the initial level.

As a result of hypoxic stimulus on the background use of atropine we registered a decline of statistical parameters in comparison with the parameters for the intact animals under the terms of hypoxia (9000 m).

Conducting the spectral analysis at these conditions enabled to find out the increase of Total Power (TP) and all spectral constituents; moreover, it was considerable with the previous introduction of atropine in a lower dose. Under those conditions all absolute indexes of the spectral analysis were significantly lower than analogical parameters of the intact animals under the conditions of hypoxia (9000 m). The increase of atropine dose under hypoxia resulted in the growth of indexes: MF/HF and LF/HF; however, it was before the decline of IC, in comparison with the values during the introduction of atropine in the proper dose.

As a result of hypoxia on the background introduction of propranolol with the increase of dose we registered the increase of the statistical indexes (SDNN, RMSSD, CV), in accordance with the doses in comparison with propranolol in the proper dose. We observed an increase of spectral indexes, which attained unexpectedly high values with the increase of the dose of medicine. At the same time, while using the blocker at a lower dose those indexes remained low in comparison with the analogous ones for the intact animals under the terms of hypoxia (Fig. 1). It is characteristic that the changes of indexes were opposite, comparing to such at previous application of atropine.

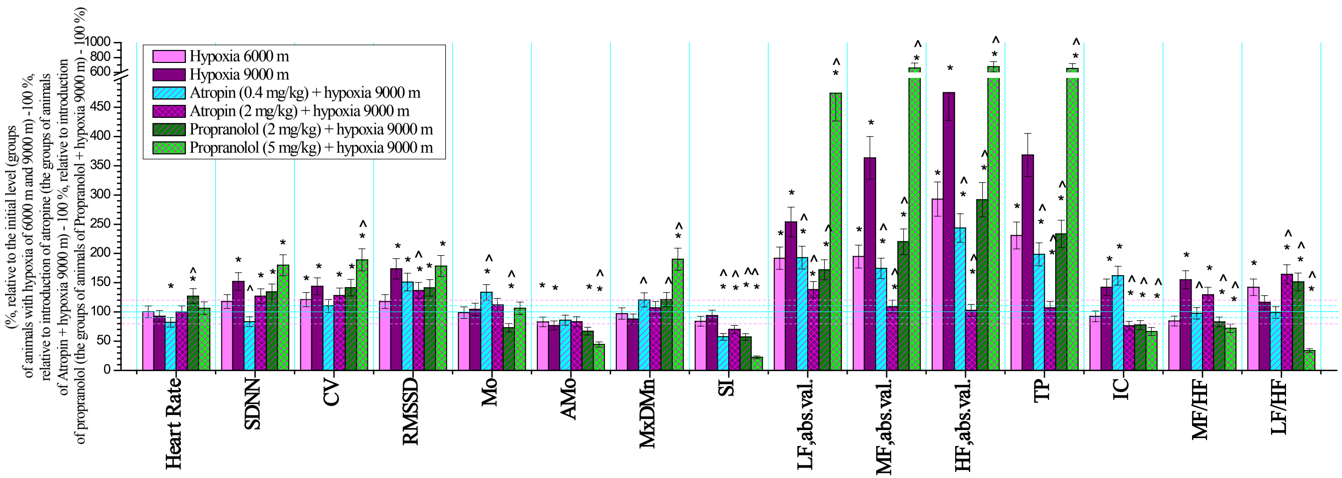

Fig. 1. HRV under hypobaric hypoxia (10 min., 6000 m or 9000 m) and application of atropine and propranolol, accordingly, relative to the initial level (groups of animals with hypoxia of 6000 m and 9000 m) – 100 %, relative to introduction of atropine (the groups of animals of Atropin + hypoxia 9000 m) – 100 %, relative to introduction of propranolol (the groups of animals of Propranolol + hypoxia 9000 m) – 100 %, (HRV under the introduction of atropine and propranolol, relative to the solution introduction) *P < 0.05, compared with every quantity before the hypoxic influence ^P < 0.05, compared with every quantity under extreme hypoxia (9000 m)

DISCUSSION

Hypoxic influence was marked by the absence of significant changes of the HR both in the intact animals and during previous blocker introductions in higher doses. Among the reasons for the cardiac rhythm character under a few minutes' hypoxic hypoxia, we consider short-term hypokinesis, as during the test the rats were placed into a pressure chamber for 10 minutes; and during the cardio rhythm registration after the 15 minute normoxia they were placed into a plexiglass universal chamber for 5 minutes. Obviously, under these conditions we registered a resultant which was determined by the presence of 15 minutes' normoxia and by the periods of short-term forced hypokinesis.

Changes of the heart rhythm are, as known, a universal operative reaction of a single organism in reply to any influence of factors of external or internal environment [1]. An equal HR frequency can relate to different combinations of the system rate activity, which is proved by the vegetative homeostasis. Average HR represents only the final effect of numerous regulator influences on the blood circulation system and it characterizes the features of the homeostatic mechanism. According to R.M. Bayevskiy (2000, 2009), one of the most important tasks of this mechanism is to provide balance between the sympathetic and parasympathetic parts of the nervous system, i.e. vegetative homeostasis. It is necessary to mark that the cardiac rhythm power of spectrum changes were the most significant under hypoxia, as well as under the condition when its action was combined with the action of blockers. Hence, as a result of the hypoxic stimulus, we could observe an increase of the TP index and all constituents of spectrum that depend upon its intensity. Previous atropine introduction, compared with the hypoxia of intact animals, resulted in a decline of these parameters. It is characteristic that the diminishing of spectral fluctuations occurred, which was a result of application of this blocker (Fig. 1). During hypoxia the previous introduction of a lower dose of the propranolol was accompanied by a spectrum power decline, compared with the hypoxia of intact animals. However, the increase of the propranolol dose under these conditions appeared to be a compensator increase of all spectral constituents. Obviously, it can have its explanation from the point of view of the accented antagonism in the autonomous regulation of the organism physiology functions [1, 2, 4].

The organism's functional state is determined by its adaptation possibilities, i.e. by the ability to adapt to the terms of existence, and also by the homeostasis stability, i.e. by the ability to preserve the homeostasis under the changing living conditions. The assessment of the functional reserve under the effect of blockers of the vegetative heart work control can be informative of the diagnostics of the organism adaptation possibilities. At the same time, research of the homeostasis stability can be conducted under hypoxia influence. Thus, conducting the HRV analysis under the introduction of the cardiac rhythm autonomous control blocker enabled to reveal activating of both sympathetic and parasympathetic regulation links with the prevailing effect of the latter, which depends upon the degree of the hypoxic influence. Such changes of the autonomous control quality under extreme hypoxia are considered to be a state of overstrain of the functional activity of the regulator systems [1, 4]. The complex of the obtained results favours understanding of the autonomous control mechanisms of the cardiac rhythm under hypoxia, they also favour understanding the nature of separate indexes of the HRV analysis within the frequency ranges.

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SUMMARY

We have chosen the introduction of the blocker of M-cholinergic receptors (atropine) and blocker of ß-adrenergic receptor (propranolol) in different doses as a functional loading under hypoxia. During the analysis of spectral power we revealed an increase of the absolute values of HF, MF and LF in comparison with the initial level. As a result of hypoxia on the background introduction of propranolol with the increase of the dose we registered an increase of the statistical indexes. We observed an increase of spectral indexes, which attained unexpectedly high values with the increase of the dose of medicine. It is characteristic that the changes were opposite, comparing to the ones with previous application of atropine.

Key words: heart rate variability, atropine, propranolol, hypoxia, white rats

STRESZCZENIE

W przeprowadzonych badaniach jako funkcjonalnego obciążenia w warunkach hipoksji użyto w różnych dawkach blokera receptorów M-cholinergicznych i blokera receptorów β-adrenergicznych (propranolol). Podczas analizy siły spektralnej stwierdzono wzrost wartości bezwzględnej HF, MF i LF w porównaniu z wartościami wyjściowymi. W wyniku hipoksji i podania propranololu we wzrastających dawkach odnotowano wzrost wskaźników statystycznych. Zaobserwowano wzrost wskaźników spektralnych, które uzyskiwały nieoczekiwanie wysokie wartości wraz ze wzrostem dawki leku. Charakterystyczne, że zmiany były przeciwne w odniesieniu do wcześniejszych po podaniu atropiny.

Słowa kluczowe: zmienność częstości akcji serca, atropina, propranolol, hipoksja, białe szczury