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THE INFLUENCE OF INDIVIDUAL FEATURES OF HEART RATE VEGETATIVE REGULATION ON NEUROHUMORAL AND ELECTROPHYSIOLOGICAL EFFECTS OF PROPRANOLOL

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SUMMARY

The study of the vegetative status influence on neurohumoral and electrophysiological effects of nonselective beta 1,2 – propranolol blocker was the aim of our work. 13 healthy volunteers at the age of 24 ± 4 years participated in the study. A dose of propranolol made up 0.8 mg/kg per os. The HRV study was performed on the basis of 5-min ECG recordings which were made in supine and upright postures before and 90 min after a single propranolol intake. According to the frequency spectral HRV indices that were fixed in supine posture before preparation intake, all the examined volunteers were divided into two groups with prevalence of sympathetic ($LF/HF > 1$, group A) and parasympathetic ($LF/HF < 1$, group B) activity. According to the HRV recordings in supine posture the vagotonic effect of the preparation was observed in group A and sympathotonic in group B. In supine position slow-down of the atrial conductivity caused by propranolol was more acute in group B. The neurohumoral and electrophysiological effects of the preparation were less acute when the volunteers were in upright posture. So the dependence of the propranolol effects on the initial neurohumoral regulation status was shown.

KEY WORDS: heart rate variability, vegetative nervous system, active tilt-test, propranolol, electrophysiology

INTRODUCTION

The adaptation of the sinus node and the cardiovascular system as a whole to variable conditions of the environment and proper organism is mostly provided by the autonomic nervous system (ANS). One of the best noninvasive methods for studying the heart rate autonomic regulation is power spectrum analysis of heart rate variability (HRV) [23]. This method allowed to visualize heterogeneity of the normal subjects population and revealed several types of the heart rate autonomic regulation in resting conditions. Zhemaitite et al. [27] distinguished two extreme types with a maximal sympathetic or parasympathetic activity and three intermediate types. In [14], two types with sympathetic or parasympathetic prevalence were considered.

Taking into account the heterogeneity of the healthy humans population an aspect to be clarified is how one or the other initial state of autonomic regulation modifies the effects of pharmacological substances tropic to ANS. The class of tropic to ANS drugs being widely used worldwide is beta – adrenoblockers. According to [1, 12, 20, 22] at the present time beta – blockers are the drugs to have the ability to diminish the number of sudden death cases and to increase the life quality how the initial state of the heart rate autonomic regulation modifies the propranolol neurohumoral and electrophysiological effects under the orthostatic stress.

in various groups of patients. The mechanisms of this beneficial effect are not clearly understood since beta – blockers in doses used in most clinical trials are only weakly effective against stable ventricular arrhythmias. In [19, 21], the ability of this class of drugs to increase HRV in cardiac insufficiency patients and in healthy subjects was shown other works. [8, 18, 25] revealed the beta – blocker feature to normalize the balance between sympathetic and parasympathetic influences not only by lowering the level of sympathetic cardiac stimulation but also by increasing the level of vagal cardiac inhibition. Thus, beta – blockers alter the outflow of both branches of the heart rate autonomic regulation. Melezhik et al. [14] have examined the effects of a single beta 1, 2 – adrenoblocker propranolol intake on the ANS activity in normal subjects having different initial states of the heart rate autonomic regulation. It was found that in the supine position the drug resulted in a predominant increase of rhythmic activity of the initially depressed branch of ANS. Thus, in subjects with initially prevailing sympathetic activity the drug led to n. vagus activation while in subjects with predominant parasympathetic outflow sympathoexcitation was observed.

The objective of the study was to examine

Determination of concepts

The variations in heart rate can be divided into three main spectral components: very low frequency (VLF), low frequency (LF) and high frequency (HF). A high frequency component (0.15-

0.4 Hz) is generated by modulations in vagal nerve activity. Most investigators agree that the power of the HF band reflects vagal modulations, when expressed both in terms of absolute power and in normalized units [3]. At the same time there are certain disagreement according to physiological interpretation of the low frequency band (0,04 – 0,15). Thus, the LF component is considered by some investigators as a parameter including both sympathetic and vagal influences whereas by other ones only as a marker of sympathetic modulations [13, 23, 26]. Most investigators agree that when expressed in normalized units, the LF power mostly reflects sympathetic outflow [15]. Taking into account the forgoing, in [14] and in the present work the normal subjects under study were divided into groups in terms of the quantitative prevalence of either HF or LF band expressed in normalized units. The group of normal subjects having in the baseline the LF power portion exceeding 50% ($LF/HF > 1$) was referred to as the group with initial prevalence of sympathetic rhythmic activity (group A). The group with HF power portion exceeding 50% ($LF/HF < 1$) was designated as the group with initially predominant parasympathetic rhythmic activity (group B). The groups described should not be identified with sympathotonia and vagotonia, because all LF/HF values in both groups were within the normal range.

MATERIALS AND METHODS

13 volunteers (10 female and 3 male) aged between 20 and 28 years were included in the study. All of the subjects were healthy as determined by their medical history and a brief examination; none received any medications. The subjects gave informed consent, and the study was approved by the local ethical review board. Subjects were instructed to abstain from smoking or coffee and alcohol consumption for 24 h before the study. All recordings were made in a certain time in the morning in quiet surroundings.

The recording protocol:

- 1st stage
 - 5-min rest in supine position
 - 7-min ECG recording in supine position and free breathing
 - Active assuming of an upright posture
 - 7-min ECG recording in upright position and free breathing
 - One-time intake of 0.8 mg/kg per os of nonselective beta 1,2 – adrenoblocker propranolol
 - 90-min break
- 2nd stage

- 5-min rest in supine position
- 7-min ECG recording in supine position and free breathing
- active assuming of an upright posture
- 7-min ECG recording in upright position and free breathing

Heart Rate Variability Analysis

The HRV parameters were obtained with software “CardioLab 2000” using time and frequency domain methods. All HRV parameters were evaluated in compliance with the recommendations of the Task Force of the European Society of Cardiology and North American Society of Pacing and Electrophysiology (1996) [23]. The variables were calculated on the basis of 7 – min ECG recordings. The data obtained on the 1st and 7th min of the recordings were not used for calculation. The first minute was considered as the time for accommodation of the subjects to the new situation and the 7th minute was used for BP measuring, i.e. HRV was obtained on 5-min ECG intervals.

The HRV variables analyzed were the following:

- mRR, ms – mean RR interval
- Total Power, ms^2 – variance of all RR intervals
- VLF, ms^2 – power in the very low frequency range (0,003-0,04)
- LF, ms^2 – power in the low frequency (0,04 – 0,15 Hz)
- LFnorm, % – LF power in normalized units: $LF/(Total\ Power - VLF) \cdot 100$
- HF, ms^2 – power in the high frequency range (0,15 – 0,4 Hz)
- HFnorm, % – HF power in normalized units: $HF/(Total\ Power - VLF) \cdot 100$
- LF/HF – ratio $LF[ms^2]/HF[ms^2]$

The two normalized parameters LFnorm and HFnorm were not analysed because they provide essentially the same information as the ratio LF/HF [23, 7].

Obtaining the Electrical Phase Structure of the Heart Cycle

The parameters of the electrical phase structure of the cardiac cycle calculated were the following: P wave (ms), QT segment, interval QT (ms) and interval TP (ms).

Stratification of the subjects under study

According to the frequency spectral components obtained in the baseline the volunteers were divided into 2 groups:

- Group A ($LF/HF > 1$)
- Group B ($LF/HF < 1$).

The subjects with $LF/HF = 1$ were randomly included into one of the groups. Group A consisted of 6 subjects and group B included 7 individuals.

Physiological background of such a division

laid in M. Pagani's [17] conclusion that instantaneous balance between sympathetic and vagus nerve activities could be captured by means of LF/HF ratio. The groups described should not be identified with sympathotonia and vagotonia, because all LF/HF values in both groups were

within the normal range.

Statistical Analysis

The data obtained were analyzed using parametric and non – parametric methods. All parameters evaluated were expressed as mean and standard deviation. The significance of differences be-

tween baseline vs propranolol was evaluated by Wilcoxon T test. For statistically significant variations 95% confidence interval was provided.

RESULTS AND DISCUSSION

The results obtained suggest that the neurohumoral and electrophysiological effects of propranolol under the orthostatic stress were determined by the initial prevalence of the sympathetic or parasympathetic ANS branch in the subject under study (tab.).

Table
Selected frequency domain measures of HRV and ECG intervals in group A and B on the two stages of the experiment. Values are means \pm SE

Variable	Stage 1			
	Group A		Group B	
	Supine posture	Upright posture	Supine posture	Upright posture
TP (ms ²)	2807 \pm 766	2642 \pm 685	4787 \pm 998	3278 \pm 974
VLF (ms ²)	701 \pm 291	839 \pm 280	1172 \pm 256	973 \pm 226
LF (ms ²)	1044 \pm 388	1209 \pm 320	1084 \pm 330	1168 \pm 183
HF (ms ²)	606 \pm 222	523 \pm 228	2395 \pm 498	849 \pm 393 *
LF/HF	1.75 \pm 0.09	4.38 \pm 0.84	0.49 \pm 0.10	3.35 \pm 0.98 *
mRR (ms)	775 \pm 66	633 \pm 44 *	783 \pm 42	620 \pm 20 *
P wave (ms)	102 \pm 2	92 \pm 5	100 \pm 2	90 \pm 4 *
PQ segment (ms)	44 \pm 8	48 \pm 10	41 \pm 15	49 \pm 10
Interval QT (ms)	354 \pm 7	338 \pm 17	364 \pm 11	333 \pm 17
Interval TP (ms)	214 \pm 7	155 \pm 26 *	218 \pm 11	149 \pm 25 *
	Stage 2			
	Group A		Group B	
	Supine posture	Upright posture	Supine posture	Upright posture
TP (ms ²)	5079 \pm 1457	2828 \pm 511	11994 \pm 3775 †	3448 \pm 726 **
VLF (ms ²)	897 \pm 236	1493 \pm 301	2464 \pm 624 †	1566 \pm 350
LF (ms ²)	1083 \pm 252	1155 \pm 218	3502 \pm 1285 †	1350 \pm 242
HF (ms ²)	2787 \pm 1002 †	233 \pm 40 **	5724 \pm 1969 †	536 \pm 193 **
LF/HF	0.61 \pm 0.13 †	4.88 \pm 0.34 **	0.59 \pm 0.04	3.73 \pm 0.93 **
mRR (ms)	1050 \pm 51 †	852 \pm 16 ‡	974 \pm 39 †	834 \pm 21 ‡ **
P wave (ms)	102 \pm 3	86 \pm 4	110 \pm 6 †	93 \pm 10 **
PQ segment (ms)	55 \pm 6	71 \pm 8 ‡	46 \pm 21	58 \pm 19
Interval QT (ms)	402 \pm 11 †	381 \pm 14	383 \pm 6 †	353 \pm 10 **
Interval TP (ms)	458 \pm 41 †	314 \pm 29 ‡	434 \pm 38 †	332 \pm 14 ‡ **

†, * - the differences vs supine posture before the medication intake are significant (p<0,05)

‡ - the differences vs upright posture before the medication intake are significant (p<0,05)

** - the differences vs supine posture after the medication intake are significant (p<0,05)

Supine position

In response to a single propranolol intake the total power of the neurohumoral regulation (TP) showed a significant increase in group B (p<0,05) and tended to augmentation in group A (Fig. 1).

At the same time the mechanisms of TP growth in groups under study were totally different. All subjects from group A showed an augmentation of HF power and the reactions of the LF domain exhibited individual discrepancies (reduction of LF the average by 1.36 times (p<0.05) in group A and by 1.24 times (p<0.05) in group B). It was accompanied by ECG intervals prolongation. The duration of the TP segment appeared to be the most variable interval in both groups (it was lengthened by 2.14 times (p<0.05) in group A and

for 3 subjects and augmentation for 3 ones). In group B the effect was just the opposite, i.e. LF power increased and HF power showed individual changes (excitation of HF for 4 subjects and slight decrease for 3 ones). As a result of the above – described alterations in autonomic activity the LF/HF ratio was brought up to the 0.6 value in both groups (Fig. 2).

The mean duration of the heart cycle (Fig. 3) was prolonged by propranolol in both groups (on by 1.99 times (p<0.05) in group B). The prolongation of the QT interval was less pronounced (by 1.14 times (p<0.05) in group A and by 1.05 (p<0,05) times in group B). Almost no change in the P wave duration was noted in group A, while in group B it was extended on the average by 1.1

($p < 0,05$) times. In five out of seven persons of group B the P wave exceeding the 100 ms value was obtained; in one case the P wave was also

split. PQ segment duration showed a tendency for prolongation in both groups but it was statistically insignificant.

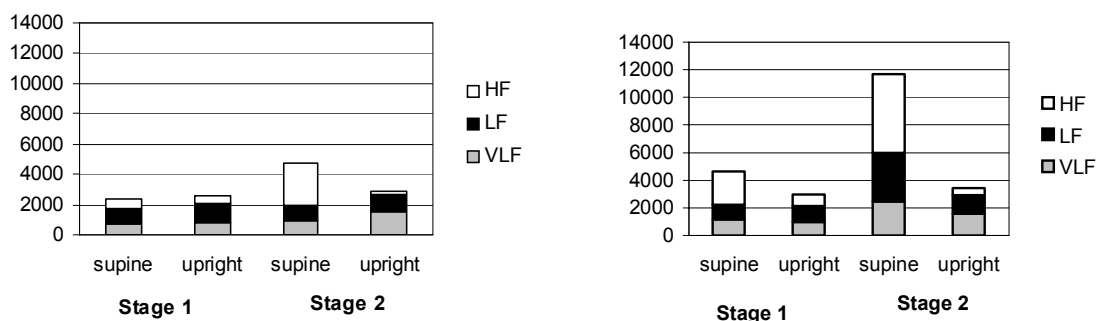


Fig. 1. VLF (ms²), LF (ms²) and HF (ms²) domain powers of spectrum of RR intervals variability at two stages of the experiment in group with initial sympathetic (first graph) and parasympathetic (second graph) prevalence in supine and upright postures.

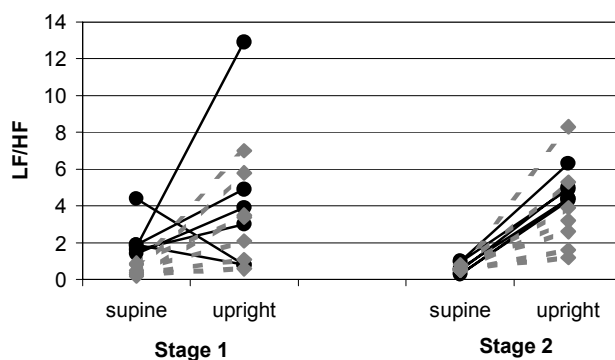


Fig. 2. Changes of LF/HF index in every individual from the group with initial sympathetic (solid black line) and parasympathetic predominance (dash gray line) in supine and upright postures at two stages of the experiment

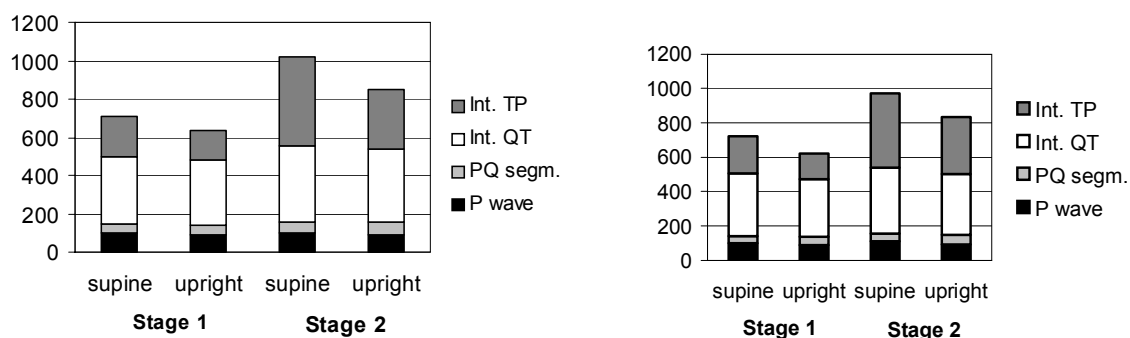


Fig.3. Electrical phase structure of the heart cycle (P wave (ms), PQ segment (ms), QT interval (ms), TP interval (ms)) at two stages of the experiment in group with initial sympathetic (first graph) and parasympathetic (second graph) prevalence in supine and upright postures

Active tilt – test

Active tilt – test at both stages of the experiment led to a reduction of TP in both groups (fig. 1). It should be noted that the TP lowering in both groups was more expressed under propranolol (stage 2) than at stage 1. The TP reduction in

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group B at both stages of the experiment exceeded the TP drop in group A.

At stage 1 the TP fall in both groups was provided by a significant lowering of the HF – power, which was accompanied by a slight increase in LF band. The rates of changes in sympathetic and

parasympathetic activity in group A appeared to be almost equal (LF power was increased by 1.16 times and HF was decreased by 1.16 times). In group B the HF power reduction was more pronounced than the LF band growth (LF power was increased by 1.08 times and HF was reduced by 2.8 times ($p < 0.05$)).

Under propranolol the regulative systems response to the orthostatic stress was modified in both groups. LF power in group A was augmented only by 1.07 times while a well pronounced decrease in HF – power was observed (on the average by 11.96 times ($p < 0.05$)). In group B both LF and HF power were reduced in the upright position (by 2.59 and 10.68 ($p < 0.05$) times respectively). According to our findings, at both stages of the experiment the supine posture in group A and B was characterized by a wide dispersion of VLF, LF and HF values. After assuming the upright posture the powers in all the domains in the two groups tended to the same values. In both groups orthostatic LF and HF power values at stage 1 appeared to be close to those obtained at stage 2. At the same time orthostatic VLF power values at stage 2 exceeded those obtained at stage 1.

Active tilt test at both stages of the experiment was accompanied by shortening of the heart cycle duration (Fig 3). Orthostatic mRR values in group A and B were close to each other. The mRR duration in the upright posture at stage 2 exceeded the orthostatic mRR value at stage 1 in both groups, which was due to the negative chronotropic action of propranolol. At both stages of the experiment in both groups standing up was accompanied by shortening of most of ECG intervals. In all cases a most pronounced decrease was observed in the TP segment duration (segment TP was reduced by 1.38 times ($p < 0.05$) in group A and by 1.46 times ($p < 0.05$) in group B at stage 1 and by 1.46 times in group A and 1.31 times ($p < 0.05$) in group B at stage 2). The shortening of interval QT was less pronounced. The P wave duration was reduced by 1.11 times in both groups at stage 1 (in group A $p < 0.05$) and by 1.19 times in group A and 1.1 times ($p < 0.05$) in group B at stage 2. The elements of the intra - atrial blockade observed in group B under propranolol in supine posture completely disappeared after assuming the upright posture. 2 to the one observed under active tilt at stage 1. The above reasoning may indicate that in upright posture both the sympathetic and parasympathetic outflow were not affected by propranolol influences.

At stage 1 active tilt test in both groups was accompanied by an increase of sympathetic and decrease of parasympathetic activity as it was

PQ segment tended to be prolonged under active tilt test in both groups, but this prolongation was in all cases statistically insignificant.

Our study indicated that the heart rate regulatory systems response to pharmacological beta 1,2 – adrenoreceptor blockade is basically determined by initial prevalence of sympathetic or parasympathetic activity. The increase of the total power of the neurohumoral regulation under propranolol in supine posture described in [5, 9, 18, 21], in our experiment was accompanied by redistribution of the autonomic activity with a predominant activation of the initially depressed ANS branch. Thus, in group A we observed a vagotonic effect of propranolol which was also described in [21, 25] and revealed the ability of the drug to increase sympathetic rhythmic activity in group B.

The TP growth under propranolol was accompanied by an extension of RR – intervals shown in many previous works [9, 25]. In both groups the bradycardial effect was chiefly provided by the electrical diastole prolongation. The bradycardial effect was more pronounced in group A, which could be accounted for as a result of the predominant n. vagus activation observed in this group. More pronounced bradycardial beta – blocker effect in conditions of initially high sympathetic tone was also described in previous works [18].

Alterations in the P wave duration exhibited some discrepancies between groups A and B. Thus, an expressed P wave lengthening described in [4], was observed only in group B while in group A almost no change in the P wave duration was noted.

The active tilt – test at both stages of the experiment was accompanied by reducing the total power of regulation. Similar findings were reported by [10]. The active tilt – test in the present study also gave rise to pronounced alterations in all branches of regulation, which resulted in VLF, LF and HF power values becoming close in the two groups. This finding indicates that in upright posture a level of activity, which is common for all healthy individuals, exists for every regulatory system. Another important finding, which is worthy of notice is attempt to bring up the LF and HF power values obtained in upright posture at stage

shown in [16, 24]. In group A as in [11] the changes in LF and HF power occurred in opposite directions but they were almost equal while in group B a predominant decrease in HF power with LF remaining unchanged as in [2] was observed. Nonselective blockade of beta 1,2 – adrenoreceptors as in [6], eliminated low frequency increases with standing in both groups and while the HF

power decrease became more pronounced.

According to the forgoing in upright posture LF and HF power observed at stage 1 and 2 were almost equal in groups A and B. At the same time in all subjects under study the mean value of RR duration and VLF power in upright position at stage 2 significantly exceeded those obtained at stage 1. This finding indicates that under orthostatic stress the new level of neurohumoral regulation that was induced by propranolol and initially provided by reactions of the autonomic nervous system was maintained mostly by humoral regulatory systems.

Tachicardial orthostatic reactions similar to the above – described bradycardial propranolol effect was mainly provided by corresponding changes in the electrical diastole duration. All other ECG intervals except PQ segment duration were also shortened under orthostatic stress. Both in supine and upright postures propranolol brought about an augmentation of discrepancies in interval QT duration between the two groups under study.

CONCLUSION

Our findings show that the reactions of the neurohumoral regulatory systems are largely deter-

mined by initial predominance of one of the ANS branches. In supine posture under propranolol the vagotonic effect of the drug can be observed in group with initial sympathetic prevalence and sympathotonic in group with initial parasympathetic predominance. The final point of the neurohumoral regulation alteration caused by propranolol in supine posture is bringing the LF/HF ratio up to the common for all healthy individuals level of values. Active tilt test at both stages of the experiment is characterized by the VLF, LF and HF power values becoming close in the two groups under study. In upright posture propranolol action is mostly maintained by the humoral regulatory systems while the autonomic activity appears to be free from the drug influences. Most changes in the electrical phase structure of the heart cycle under propranolol are similar in all healthy individuals. However, in supine position propranolol induces a more pronounced slow – down of the atrial conductivity in subjects with initial parasympathetic predominance.

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ВПЛИВ ІНДИВІДУАЛЬНИХ ОСОБЛИВОСТЕЙ ВЕГЕТАТИВНОЇ РЕГУЛЯЦІЇ СЕРЦЕВОГО РИТМУ НА НЕЙРОГУМОРАЛЬНІ І ЕЛЕКТРОФІЗІОЛОГІЧНІ ЕФЕКТИ ПРОПРАНОЛОЛУ

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РЕЗЮМЕ

Метою дослідження було вивчення впливу початкового вегетативного статусу на нейрогуморальні та електрофізіологічні ефекти неселективного бета_{1,2} – блокатора пропранолола. У дослідженні приймали участь 13 здорових добровольців у віці 24±4 років. Вивчення варіабельності серцевого ритму (ВСР) проводилося на основі 5 – хвилинних ЕКГ фрагментів, записаних в горизонтальному положенні та в умовах активної ортостатичної проби до та через 90 хв. після одноразового прийому пропранолола. Доза препарату складала 0.8 мг/кг per os. На основі спектральних показників ВСР, зафіксованих у горизонтальному положенні до прийому препарату, усі досліджувані були розділені на 2 групи з переважанням симпатичної (LF/HF>1, група А) та парасимпатичної (LF/HF<1, група Б) активності. Під час запису ВСР у горизонтальному положенні у групі А був зафіксований ваготонічний, а в групі Б – симпатотонічний ефект препарату. У групі Б збільшення тривалості зубця Р було більш вираженим. Під час ортостатичної проби як нейрогуморальні, так і електрофізіологічні ефекти препарату були менш вираженими. Таким чином, була показана залежність ефектів пропранолола від початкового стану нейрогуморальної регуляції.

КЛЮЧОВІ СЛОВА: варіабельність серцевого ритму, вегетативна нервова система, активна ортостатична проба, пропранолол, електрофізіологія

ВЛИЯНИЕ ИНДИВИДУАЛЬНЫХ ОСОБЕННОСТЕЙ ВЕГЕТАТИВНОЙ РЕГУЛЯЦИИ СЕРДЕЧНОГО РИТМА НА НЕЙРОГУМОРАЛЬНЫЕ И ЭЛЕКТРОФИЗИОЛОГИЧЕСКИЕ ЭФФЕКТЫ ПРОПРАНОЛОЛА

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РЕЗЮМЕ

Целью данной работы было изучение влияния исходного вегетативного статуса на нейрогуморальные и электрофизиологические эффекты неселективного бета_{1,2} – блокатора пропранолола. В исследовании принимали участие 13 здоровых добровольцев в возрасте 24±4 лет. Изучение variability сердечного ритма (ВСР) проводилось на основе 5-минутных ЭКГ фрагментов, записанных в горизонтальном положении и в условиях активной ортостатической пробы до и через 90 мин после однократного приема пропранолола. Доза препарата составляла 0.8 мг/кг per os. На основании спектральных показателей ВСР, зафиксированных в горизонтальном положении до приема препарата, все обследованные были разделены на 2 группы с преобладанием симпатической (LF/HF>1, группа А) и парасимпатической (LF/HF<1, группа Б) активности. При записи ВСР в горизонтальном положении в группе А был отмечен ваготонический эффект препарата, а в группе Б – симпатотонический. В группе Б увеличение продолжительности зубца Р было более выраженным. При переходе обследуемых в вертикальное положение как нейрогуморальные, так и электрофизиологические эффекты препарата были менее выраженными. Таким образом, была показана зависимость эффектов пропранолола от исходного состояния нейрогуморальной регуляции.

КЛЮЧЕВЫЕ СЛОВА: variability сердечного ритма, вегетативная нервная система, активная ортостатическая проба, пропранолол, электрофизиология