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Lizinopril Monotherapy and Sensitivity of the Baroreflex in Patients with Hypertension

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Abstract: *Under supervision, there were 9 female patients with primary arterial hypertension aged 51.6±5.3 years. During the month of observation, all patients took a stable dose of the lisinopril: 7 patients – 10 mg per day (twice daily for 5 mg), 2 patients - 5 mg per day. In the beginning and in the dynamics of treatment (weekly), the sensitivity of the arterial baroreflex (BRS) was recorded.*

In patients with PAH, in comparison with physically healthy persons of the same age, there is a significant decrease in BRS in the low-frequency and high-frequency bands with spontaneous breathing, which, however, responds well to the controlled breathing test. After a week of monotherapy with a lysinopril, there is a significant increase in BRS_{LF} and BRS_{HF} in spontaneous breathing and a significant increase in these parameters with controlled breathing. From the 2nd week of monotherapy, stabilization of BRS_{LF} with spontaneous respiration and reduction of the response to controlled respiration, which reaches a maximum after 3 weeks of treatment, is observed.

Keywords: *hypertension, lisinopril, monotherapy, baroreflex sensitivity*

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I. Introduction

Angiotensin-converting enzyme (ACE inhibitors) is one of the main classes of drugs used to treat cardiovascular disease[1,2]. One of the most commonly used in clinical practice for this group of drugs is Lisinopril[2].

The mechanism of its action of the latter is associated with blocking the effects of circulating angiotensin II and providing rapid system vasodilation and diuretic effect, which contributes to lowering blood pressure, reducing dyspnea and fatigue in CHF[3]. The blockade of tissue activity of angiotensin II, decreased activity of the sympathetic nervous system, inhibition of the action of aldosterone, as well as reversal of inactivation of bradykinin, allow the long-term organoprotective effects of the drug to be realized, but this requires prolonged use[2].

Confirmation of these results is based on data from the ALLHAT (Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial)[4], in which 33357 patients with arterial hypertension participated, and which led to doubt the appropriateness of the use of ACE inhibitors as first-line agents lines in patients with arterial hypertension that are not a high-risk group and not suffering from heart failure.

An important role in maintaining the systemic hemodynamics of the body are mechanisms for providing feedback in the regulation of blood pressure, which provides for the adjustment of the pumping function of the heart to the changing conditions of activity[5,6,7], which has a number of influences mediating by the peripheral and central nervous system[8,9].

A well-known concept is the sensitivity of the baroreflex (BRS), which is the magnitude of the reflex response to the unit of deviation of the parameters of blood pressure from the working point of the baroreflex[10]. It decreases with age[11] when smoking, drinking alcohol, is related to sex, and inversely with body weight[12].

Arterial baroreceptors are extremely sensitive, the afferent impulses from them change with oscillations of the blood vessels of less than 1 mm Hg, that is, they can accept changes in hemodynamics that cannot be measured[13]. With this in mind, relatively recently developed computerized methods for measuring SBP, which are based on the analysis of spontaneous oscillations of blood pressure and heart rate [9,14]. Two basic approaches have been developed for today for the assessment of the BRS: time domain (time domain) and spectral (frequency domain)[15].

Despite a large number of publications in scientific databases on research on the influence of Lisinopril (about 1000), certain mechanisms of its influence remain unclear[16]. The latter led us to investigate changes in baroreceptor sensitivity in patients with PAG due to the effect of a stable dose of Lisinopril rupture during a lunar course of monotherapy.

II. Material And Methods

This prospective comparative study was carried out on patients of Department of Internal Medicine from November 2009 to April 2010. Total 9 adult subjects (females) were for in this study.

Study Design: Prospective open label observational study

Study Location: This was study done in Department of Internal Medicine, at Clinic of Odesa National Medical University.

Study Duration: November 2009 to April 2010.

Sample size: 9 patients.

Subjects & selection method: The study population was consisting hypertensive patients with 2 stage and which were prescribed the lisinopril (10 mg daily to each patients).

Under supervision, there were 9 female patients with stage II hypertension, 51.6 ± 5.3 years old, who underwent inpatient and outpatient treatment at the clinical center of the Odessa National Medical University. During the month of observation, all patients took a stable dose of Lisinopril: 7 patients - 10 mg per day (twice daily for 5 mg), 2 patients - 5 mg per day (one in two and one in one in the morning hours). Before receiving Lisinopril, all patients did not receive treatment.

Procedure methodology

At the beginning of the treatment, a comprehensive clinical examination of patients was carried out, which included the use of anthropometric, biochemical and instrumental studies, and allowed verifying the diagnosis. In the beginning and in the dynamics of treatment (weekly), in the morning, in the state of relative muscular and mental rest, the parameters of the cardiorespiratory system were measured. For this purpose it was used the special device – spiroarteriocardiorhythmography (SACR), which in a simultaneous mode register defines the parameters of HR, systolic blood pressure (SBP) and diastolic blood pressure (DBP) for each heart reduction[17]. According to the data measuring sequences of cardiac rhythm (CR), systolic (SBP) and diastolic blood pressure (DBP) and data respiratory ventilation conducted Fourier's spectral analysis, which determines the capacity of regulatory influences in different frequency ranges that are measured in the absolute values of power (ms^2 – for CR, $mmHg^2$ – for SBP and DBP, $(l/min)^2$ – for spontaneous breathing). By the date of a lot modern authors very-low-frequency (VLF, 0-0.04 Hz) – characterizes activity of over-segmental structures on the CR, low-frequency (LF, 0.04-0.15 Hz) – activity in that range connecting with regulation of sympathetic branches of autonomic nervous system (ANS), high-frequency (HF, 0.15-0.4 Hz) – activity in that range connecting with regulation of parasympathetic branches of ANS, TP (ms^2) – characterizes the total power of HRV and reflect of the general state of the ANS[9].

The study of women was conducted in the morning with an empty stomach in sitting position. Duration of the registration was 2 minutes for spontaneous and 2 minutes for controlled respiration.

Additionally using the spectral method we determined the index of arterial baroreflex sensitivity (SBR, ms/mmHg) – α-coefficient, what was calculated in high (BRS_{HF}) and low (BRS_{LF}) frequencies ranges[7,11,18].

$$BRS_{LF} = \sqrt{LF_{HRV}/LF_{SBPV}} \quad (1)$$

$$BRS_{HF} = \sqrt{HF_{HRV}/HF_{SBPV}} \quad (2)$$

In previous studies, changes in the parameters of central hemodynamics, cardiac activity, blood pressure, as well as vegetative maintenance of the heart rate, blood pressure and spontaneous respiration with different pathological processes and states of the body[19-21] have been analyzed, including this group of patients[22-24]. This report analyzes the changes in the indicators of the BRS. To process the data, a package of statistical nonparametric methods of analysis using the Wilcoxon criterion was used.

III. Result and Discussion

In tabl. 1-3 shows the analysis of the morphometric parameters and data of the activity of the cardiovascular system at the beginning of treatment, which indicate a certain increase in anthropometric indices and overweight in the group of patients (Table no1), which are significantly higher than in practically healthy women of this age [25,26], as well as the hemodynamic stress of the organism, which is characterized by a significant increase in the parameters of the SBP and a certain increase in DBP (Table no2), as well as the parameters of central hemodynamics (Table no3) and the cardiorespiratory synchronization – Index Hildebrandt (IH) and cardiac output related to minute breathing volume (CO/MBV)[27], which, along with other criteria determine the presence of PAG. The information on the course of PAG was quite informative in terms of the Kerdo index (Table no2), which showed a significant predominance of vagotonic influences.

Table no 1: Anthropometric parameters of patients in the study group at the beginning of treatment, M (Q1; Q3)

Parameter	Value
Body length, cm	168 (165; 172)
Body mass, kg	78 (76; 79)
BMI, kg/m^2	27.2 (27.0; 28.6)
Coverage of the chest, cm	85 (84; 92)
Waist coverage, cm	92 (90; 95)

Table no 2: Parameters of heart rate (HR) and blood pressure (BP) of patients in the study group at the beginning of treatment, obtained from the data of SACR, M (Q1; Q3)

Parameter	Norm	Value
HR, min.$^{-1}$	60-90	65.3 (63.8; 70.7)
SBP, mmHg	110-130	144.6 (137.7; 154.3)
DBP, mmHg	65-89	86.7 (80.1; 100.5)
Kerdo index	-0.15-0.15	-0.41 (-0.42; -0.39)

The data of the indicators of central hemodynamics indicate a significant increase in the shock volume of the heart (SVH), cardiac output (CO) and the cardiac index, which characterize the development of PAG. Particular attention deserves the indicator of volumetric cardio-pulmonary synchronization, a significant increase of which above the normative values may indicate a certain strain of mechanisms of regulation of peripheral hemodynamics.

Table no 3: Parameters of central hemodynamics of patients in the study group at the beginning of treatment, obtained from the data of SACR, M (Q1; Q3)

Parameter	Norm	Value
SVH, cm^3	47.2-71.8	89.8 (82.7; 93.3)
CO, l	4.2-5.7	5.8 (5.6; 6.2)
CI, l/(min×m^2)	2.24-3.14	3.13 (2.62; 3.35)
SI, cm^3/m^2	39.5-54.5	48.0 (43.2; 49.5)
IH	3.98-6.20	4.65 (4.52; 4.99)
CO/MBV	0.48-0.75	0.78 (0.55; 0.99)

Follow up after 4 weeks

Table no 4: Shows the changes in the clinical and biochemical parameters of the group of patients with PAG at the beginning and at the end of treatment, from which it can be stated that during the month of monotherapy with a stable dose of lisinopril there are significant changes in the lipid profile of patients. First and foremost, they relate to a significant reduction in triglyceride levels and an increase in HDL, which may indicate a reduction in atherosclerosis. On the other hand, there is a significant increase in liver enzymes, which, in our opinion, characterizes the tension of the liver function.

Table no4: Indicators of clinical and biochemical study of patients at the beginning and at the end of treatment, M (Q1; Q3)

Parameter	At beginning	After 4 weeks treatment
Hemoglobin, g/L	137 (129; 152)	138 (132; 142)
Leukocytes, 10^9/L	6.3 (5.8; 6.7)	6.5 (5.7; 6.8)
RES, mm/h	6 (5; 7)	5 (5; 6)
Total protein, g/L	79.0 (75.7; 81.6)	78.2 (77.1; 79.8)
Creatinine, mkmol/L	54 (50; 61)	55 (54; 57)
Total cholesterol, mmol/L	6.16 (5.38; 6.38)	6.20 (4.94; 6.39)
Triglycerides, mmol/L	1.40 (1.16; 2.20)	1.00 (0.92; 1.68)*
LDL, mmol/L	4.14 (3.64; 4.44)	3.90 (3.38; 4.80)
HDL, mmol/L	0.96 (0.80; 1.19)	1.12 (0.68; 1.20)*
ALT, un./L	26 (20; 29)	32 (25; 38)*
AST, un./L	33 (29; 40)	35 (34; 44)*
Blood glucose is onset, mmol/L	5.0 (4.5; 5.6)	4.8 (4.6; 5.2)

* - $p<0.05$ - differences between current and previous measurements

Table no 5: Shows the changes in the basic parameters of the cardiovascular system, which are used in monitoring the progress of PAG. In this case, their registration was carried out using SACR. After a week of taking the Lisinopril, there was a significant decrease SBP ($p <0.05$), and also according to the Kerdo index, the reduction of vagotonic effects ($p<0.01$). At the same time, the heart rate and DBP remained unchanged. Their change occurred after 2 weeks of treatment and was characterized by a significant increase ($p<0.01$ and $p <0.05$, respectively), which was accompanied by an even greater decrease in vagotonics ($p<0.01$) and optimization of vegetative effects by the Kerdo index at the ithonian level. The achieved effect was preserved after 3 weeks of

monotherapy with the use of a stable dose of a Lisinopril. However, after a month of treatment, a reverse effect was observed, which was accompanied by a significant decrease in heart rate ($p<0.05$), an increase in SBP ($p<0.05$) and DBP ($p<0.01$), as well as a change in the Kerdo index toward marked vagotonia ($p<0.01$). At the same time, the value of SBP did not differ from those at the beginning of therapy, and the values of DBP significantly exceeded. The latter suggests that taking a stable dose of a Lisinopril has a sufficient antihypertensive effect only during the first week of therapy, in the future it stabilizes at the level of certain optimization of vegetative effects, which is achieved through increased chronotropic function of the heart and increased vascular resistance maintained for the next 2 weeks of therapy. After a month of treatment, one can assume a decrease in the sensitivity of the body to a stable dose of Lisinopril.

Table no 5. Dynamics of the main parameters of the activity of the cardiovascular system according to SACR in patients of the study group in the course of treatment, M (Q1; Q3)

Parameter	At begin treatment	After week treatment	After 2 weeks treatment	After 3 weeks treatment	After 4 weeks treatment
HR, $min.^{-1}$	65.3 (63.8; 70.7)	65.1 (62.6; 71.4)	73.5 (72.4; 78.1)**	74.7 (70.3; 78.9)	71.5 (66.8; 72.7)*
SBP, mmHg	144.6 (137.7; 154.3)	140.7 (124.6; 143.7)*	136.6 (126.8; 148.6)	132.8 (131.1; 141.3)	142.5 (138.8; 151.6)*
DBP, mmHg	86.7 (80.1; 100.5)	87.0 (83.8; 97.9)	96.5 (77.3; 108.0)*	93.5 (89.9; 97.7)	104.6 (99.6; 106.8)**
Kerdo index	-0.41 (-0.42; -0.39)	-0.23 (-0.29; -0.13)**	-0.06 (-0.13; -0.02)**	-0.05 (-0.18; 0.00)	-0.21 (-0.26; -0.20)**

* - $p<0.05$, ** - $p<0.01$ – differences between current and previous measurements

The results confirm the expediency of increasing of the dose starting from the second week of treatment, and reaching the target dosage of the lisinopril, which reaches 30-35 mg per day, by the end of the second - the beginning of the third week of treatment of PAG.

In order to achieve the goal of this study, the analysis of the indices of BRS_{LF} and BRS_{HF}, which characterize the possibility of substitution of central hemodynamics, was performed. In this case, we used a controlled breathing test (CB_6), which usually characterizes the reactivity of the cardiovascular and autonomic nervous system[28] (Table no6). In our previous studies, normative values of these indices were worked out in practically healthy persons of male and female of different age, as well as their changes in different nosologies and performance of controlled breathing tests were shown [19,26,29]. Thus, the normative limits of the BRS_{LF} index for arbitrary respiration in 50-year-old individuals vary in the range from 4.0 to 10.7 ms/mmHg, and BRS_{HF} from 5.6 to 14.3 ms/mmHg. When performing a test on CB_6, the values of these indicators, as a rule, significantly increase.

Significant decrease in BRS_{LF} and BRS_{HF} indices during spontaneous breathing at the beginning of treatment characterizes the mechanism of systemic blood flow modulation in PAG patients[30]. However, their reactivity is evidenced by the presence of a certain reserve, which more closely relates to sympathetic effects, which is reflected by a more significant increase in BRS_{LF} ($p<0.01$) than BRS_{HF} ($p<0.01$) when performing the CB_6 test. At the same time, monotherapy with a stable dose of a Lisinopril in a week leads to a significant increase in the BRS_{LF} ($p<0.001$) and BRS_{HF} ($p<0.05$) rates at arbitrary breathing, while the CB_6 test is even more significant and significant ($p<0.01$ and $p<0.05$, respectively) increase of the BRS. In this case, the results obtained, both in spontaneous breathing and in control, are the most significant of all points of control. The latter is consistent with the data that characterized the change in the absolute values (Table no5) in a week of treatment.

In the future, there is a certain stabilization of the BRS_{LF} indicator (Table no6) with spontaneous breathing, although it varies significantly and a certain amount of observations has a significant tendency to decrease, especially after 3 weeks of monotherapy with a Lisinopril, and its reactivity in response to CB_6 is significantly reduced, especially due to 3 weeks of treatment. The latter can characterize a number of mechanisms associated with the habituation of a stable dose of a Lisinopril. At the same time, one month after receiving the preparation of BRS_{LF}, remaining at the level reached with spontaneous respiration, at CB_6 shows a significant increase in reactivity. It should be reminded that according to the main parameters of control (Table no5) there is a significant expressed tendency to return the values of SBP, heart rate and Kerdo index to the initial level, and DBP even higher than the initial. Such changes can characterize an increase in rigidity of vessels, which is reflected by an increase in the reactivity of BRS_{LF} at CB_6.

Table no6. Weekly dynamics of changes in the indicator BRS_{LF} and BRS_{HF} (ms/mmHg) in spontaneous (SB) and controlled breathing (CB_6) in the treatment process, M (Q1; Q3)

Parameter		At begin treatment	After week treatment	After 2 weeks treatment	After 3 weeks treatment	After 4 weeks treatment
BRS_{LF}	SB	4.4 (4.1; 4.5)	7.1 (5.8; 7.6)**	6.4 (4.0; 7.7)	5.8 (2.9; 8.7)	6.3 (4.6; 7.4)
	CB_6	7.9 (5.9; 14.4)$^{\#\#}$	11.7 (6.1; 16.8)$^{\#}$	8.8 (4.3; 12.1)$^{\#}$	7.4 (3.5; 11.0)	10.5 (7.0; 12.5)$^{\#}$
BRS_{HF}	SB	5.1 (3.7; 5.8)	6.9 (4.6; 9.0)*	4.1 (3.1; 4.7)*	3.9 (2.2; 6.3)	4.4 (3.8; 4.7)
	CB_6	6.9 (4.3; 9.1)$^{\#}$	9.1 (4.7; 10.3)$^{\#}$	6.3 (2.8; 14.7)$^{\#}$	7.8 (1.9; 8.9)$^{\#}$	7.1 (4.1; 10.5)$^{\#}$

* - $p<0.05$, ** - $p<0.01$ – differences between current and previous measurements;
$^{\#}$ - $p<0.05$, $^{\#\#}$ - $p<0.01$ – differences between SB and CB_6.

At the same time, since 2 weeks of treatment, the BRS_{HF} score varies significantly with spontaneous breathing and is significantly reduced after 3 weeks and a month of treatment compared with baseline. At the same time, the reactivity of this indicator at CB_6 has a significant individual variation, which in a number of individuals is characterized by even a decrease compared with spontaneous breathing. Although the group as a whole has a significant ($p<0.05$) increase in response to CB_6.

In general, analyzing the index of BRS_{HF} can be noted that starting from 2 weeks of monotherapy with a stable dose of Lisinopril, there is deterioration in the sensitivity of vagotonic baroreceptors in spontaneous breathing while maintaining their reactivity to CB_6, which is, by extension, purely individual.

So, summing up the results obtained in this study, we can draw some conclusions regarding the changes in baroreceptor sensitivity in patients with PAG in the use of monotherapy using the standard dose of a Lisinopril.

IV. Conclusion

First, given the evidence of changes in the basic parameters of the cardiovascular system, it is possible to state that the administration of a stable dose of a Lisinopril has sufficient hypotensive effect only during the first week of therapy, which after 2 weeks of treatment is characterized by an increase in chronotropic function of the heart and increased vascular resistance, which is maintained during the next 2 weeks of therapy, and one month later returns to the baseline level.

Second, according to the analysis of changes in the sensitivity of arterial baroreflex in spontaneous and controlled respiration, it can be stated that in patients with PAG, in comparison with physically healthy persons of the same age, there is a significant decrease in BRS in the low-frequency and high-frequency bands, which, however, is good responds to a guided breath test. Accepting a stable dose of Lisinopril (10 mg/day) a week after monotherapy leads to a significant increase in BRS_{LF} and BRS_{HF} in spontaneous breathing and a significant increase in these parameters in controlled respiration. Starting from 2 weeks of receiving a stable dose of Lisinopril, the stabilization of BRS_{LF} with spontaneous respiration and reduction of the response to controlled respiration, which reaches a maximum after 3 weeks of treatment, is observed. On the other hand, starting from the 2nd week, the BRS_{HF} index, this up to 4 weeks of monotherapy with a Lisinopril, decreases significantly with spontaneous breathing below the baseline values, and with controlled breathing has a very individual variation.

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