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The Significance of proANP and NT Pro-BNP Levels Measurement in Patients with Arterial Hypertension.

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Abstract

Introduction: Despite the existence of sufficient information about how to contact progression of AH on the violation of metabolites NP, in particular pro-ANP and NT-pro BNP, the impact of these neuropeptides on the structural- functional state of vessels under the influence of combined anti-hypertensive therapy remains debatable and contradictory.

Aim: The aim of this research is to study the plasma content of pro-ANP and NT pro-BNP and their impact on neuro-humoral auto-regulatory mechanism leading to development of arterial hypertension and stiffness.

Methods and materials: We examined 76 patients with AH I-III stages (43 men and 33 women average age of 46.9 ± 1.5 years and duration of the disease 9.1 ± 1.4 years). Patients were distributed into groups basing on their degree of hypertension: I stage AH- 16 patients, II stage- 43 and 17 patients with III stage AH. The control group consisted of 22 healthy people comparable with the main group. The systolic blood pressure(SBP), pulse pressure(PP), diastolic blood pressure(DBP), pulse wave velocity (PWV) were measure using the dopplerography (phillips "Envisor" frequency 7,5 MHz) on the heart segment of the left radial artery. Statistical processing of the results was carried out using the Statistics 6.0 (StatSoft Inc.).

Results: In the control group, PWV in the BS was 8.14 ± 0.26 m / s, and after muscle work(MW) tended to decrease to 7.68 ± 0.19 m / s ($p > 0.05$), which was 5,7%. Accordingly, on the part of the ABF in the state of rest LLABF was 45.7 ± 3.4 mm Hg, but significantly decreased after MW to 32.3 ± 1.9 mm Hg. Art. ($p < 0.01$), which made up 29,3%. At the same time, ABFR, having formed in the BS was 49.5 ± 3.4 mm Hg and after MW, increased significantly to 58.2 ± 3.0 mm Hg ($p < 0.01$). From the results of proANP and Nt-proBNP metabolites, their plasma content in patients with hypertension was 1598 ± 54 fmol / ml and 445.8 ± 16.9 fmol/ml and 67.9% and 110.7% higher than in the control group (952 ± 51 fmol / ml and 211.6 ± 31.3 fmol / ml, respectively, $p < 0.001$).

Conclusions: In patients with hypertension, an increase in the levels of proANP and NT-pro-BNP in plasma is observed parallel to the increase in arterial hypertension. A close positive correlation was found between the values of proANP, NT-pro-BNP and PWV.

Key Words

Arterial Hypertension; Pulse Wave Velocity; Arterial Stiffness; Natriuretic Peptides.

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Introduction

The generally accepted idea of arterial hypertension (AH) is that, it morphologically restructures (structural remodeling) almost all vessel departments. The important markers of structural damage of the vessels after their remodeling are abnormal thickening in the wall, accompanied by an increase in pulse wave velocity. In addition, structural remodeling of the arterial vessels is closely associated with the mechanism of auto-regulation of blood flow (ABF)^{1, 2}. Arterial hypertension (AH) is accompanied by a violation of the ABF shift range causing the increase in intravascular pressure³. In addition, changes in the

lower limit of the ABF (LLABF) are marked with the smallest size intravascular pressure below which the ABF gets ineffective⁴, increase in which significantly causes the development of hypertensive crisis⁵ and vascular complications¹. on the other hand, an important role in the pathogenesis of AH is played by the neuro-humoral factors. In recent years more attention is paid to the systemic natriuretic peptides (NP)⁶. NP in humans are divided into three peptides – Pro-Atrial Natriuretic peptide (Pro-ANP), Brain Natriuretic Peptide(BNP) and peptide type S. The most significant role in cardiovascular diseases manifestation is played by ANP and BNP levels that are closely correlated with the size, function and

weight of the left ventricle⁷. Anti-hypertensive treatment reduces the structural remodeling of vessels and leads to a lowering of ANP concentration in blood⁸. However, despite the existence of sufficient information about how to contact progression of AH on a violation of metabolites NP, in particular pro-ANP and NT-pro BNP, the impact of these neuropeptides on the structural- functional state of vessels under the influence of combined anti-hypertensive therapy remains debatable and contradictory.

Aim

The purpose and the objectives of this research is to study the plasma content of pro-ANP and NT pro-BNP and their impact on neuro-humoral auto-regulatory mechanism leading to development of arterial hypertension and stiffness.

Materials and methods

We examined 76 patients with AH I-III stages (43 men and 33 women with average age of 46.9 ± 1.5 years and duration of the disease being 9.1 ± 1.4 years). Patients were distributed into groups basing on their degree of hypertension: I stage AH-16 patients, II stage- 43 and 17 patients with III stage AH. The control group consisted of 22 healthy people comparable with the main group. The systolic blood pressure(SBP), pulse pressure(PP), diastolic blood pressure(DBP), pulse wave velocity (PWV) were measure using the dopplerography (philips "Envisor" frequency 7,5 MHz) on the heart segment of the left radial artery. The ABF of the forearm was studied by the tetrapolar rheography method with occlusal breakdown and simultaneous registration of pressure in the occlusion cuff using the computer diagnostic complex "Rheocom", VO HAI-Medica, Kharkiv (Patent for Utility Model No. 36087). The recording of the differential rheoplethysmogram (RPG) of the forearm was carried out when the air compressor was injected into the occlusive cuff on the shoulder at a speed of 10 mm Hg for 2-3 cardiac contractions.

With the increase in occlusion, more distal to the imposed occlusive cuff, the blood pressure decreased, in response to the RPG, according to the mechanism of the ABF, recorded an increase in the amplitude of the rheographic complexes. The following indicators of the ABF were studied:

1. The lower limit of the ABF (LLABF) is the smallest intravascular pressure below which the growth of the RPM amplitude ceased. The intravascular pressure was calculated as the difference between the SAT and the pressure in the cuff according to the formula $LLAR = SBP - P_{max}$, (mm Hg), where P_{max} is the pressure in the occlusion cuff with the maximum increase

in the amplitude of the RPG.

2. The ABF range was measured from the beginning of the increase in the amplitude of the RPG to its maximum recovery by the formula: The ABF range (ABFR) were $P_{max} - R_{poc}$, (mm Hg), where R_{poc} is the pressure in the occlusive cuff at the beginning of increasing the amplitude of the RPG complexes. The ABF and PWV study was performed in the basal state (BS) and after the muscle work (MW) of the forearm in the amount of 70% of the maximum.

The content of proANP and Nt-proBNP in blood plasma was determined by immune enzyme method. According to the design of the study, 29 patients with AH 1-2 are. (13 males and 16 females) received combination therapy with amlodipine at a dose of 5 mg / day with losartan at a dose of 50 mg / day once a day. If during a week the target values of blood pressure were not achieved (SBP <140, DBP <90 mm Hg), hydrochlorothiazide 12.5 mg / day was added to the resulted scheme. Duration of treatment was 12 weeks.

Statistical processing of the results was carried out using the Statistics 6.0 (StatSoft Inc.). The significance of the differences between the investigated values was determined by the t-student test, which was considered to be reliable at $p < 0.05$. The degree of interconnection between the pairs of independent signs was evaluated using the P. Spearman rank correlation coefficient.

Results

As the study showed, in the control group, PWV in the BS was 8.14 ± 0.26 m / s, and after MW tended to decrease to 7.68 ± 0.19 m / s ($p > 0.05$), which was 5.7%. Accordingly, on the part of the ABF in the state of rest LLABF was 45.7 ± 3.4 mm Hg, but significantly decreased after MW to 32.3 ± 1.9 mm Hg. Art. ($p < 0.01$), which made up 29.3%. At the same time, ABFR, having formed in the BS was 49.5 ± 3.4 mm Hg and after MW, increased significantly to 58.2 ± 3.0 mm Hg ($p < 0.01$).

Thus, the received data testify that PWV is not a constant value, which essentially influences the functional state of vessels. In healthy people, it was found that there is a decrease in PWV by 5.7% after MW. Along with the expansion of ABFR due to the reduction of LLABF, it says about the decrease of tone (stiffness) of vessels, as a manifestation of adaptation to muscular work.

In the main group (patients with hypertension) the index of PWV in the BS with hypertension was equal to 8.45 ± 0.31 m/s and did not differ from such in healthy people, but in groups AH 2 stage

and 3 stage, it has probably increased to 9.08 ± 0.42 ($p < 0.05$) and 10.33 ± 0.50 ($p < 0.02$) m / s, respectively. Similarly LLABF in the BS with AH stage 1 and 2 was 43.4 ± 6.2 and 53.0 ± 5.9 mm Hg respectively, that did not differ significantly from such in healthy people ($p > 0.05$). But in the group AH 3 stage it has risen to 55.3 ± 4.4 mmHg ($p < 0.05$). More significant changes in these indicators were observed after MW.

So, the value of PWV with AH 1 stage was equal to 8.58 ± 0.40 m/s and practically did not differ from the resting state ($p > 0.05$), whereas in the case of AH stage 2, there has been a tendency towards its growth to 9.45 ± 0.42 (an increase of + 4.1%, $p > 0.05$), which exceeded the probabilities for AH 3 stage reaching 11.16 ± 0.50 m/s with an increase of + 8.0%, ($p < 0.05$). Similarly, after MW in groups with AH stage 2 and 3, parameters of LLABF increased significantly to 63.3 ± 7.4 mm Hg and 86.8 ± 9.2 mm Hg ($p < 0.001$), which was an increase of + 18.4% and + 62.7%, respectively. In this case, the absolute value of ABFR in patients with AH stage 1, 2 and 3 remained without probable changes 57.1 ± 4.0 , 62.4 ± 5.0 and 58.5 ± 4.9 mm Hg respectively.

However, comparing the ABFR with the resting index showed a 19.7% reduction compared to an increase of 47.3% in healthy people. Thus, in contrast to the control group, in the group of patients with AH, the progression of hypertension is accompanied by an increase in PWV, in patients with AH stage 1 and 2. Even more significant changes were observed after MW with an increase in the rate (up to 8.0% with AH stage 3). From the results of ABF in the main group, there was a shift of LLABF toward a higher level of blood pressure with a decrease in the ABF range and the restriction of regulatory adaptive vascular mechanisms, which manifested as much as possible in muscle load.

From the results of proANP and Nt-proBNP metabolites, their plasma content in patients with hypertension was 1598 ± 54 fmol / ml and 445.8 ± 16.9 fmol/ml and 67.9% and 110.7% higher than in the control group (952 ± 51 fmol / ml and 211.6 ± 31.3 fmol / ml, respectively, $p < 0.001$). An analysis of proANP and NT-pro-BNP values in patients with AH depending on the degree of hypertension, showed a significant increase in the level of peptides in parallel with the growth of arterial pressure. Thus, the difference between the indicators in the control group and the groups with AH stage 1, 2 and 3 for proANP 22.0%, 69.2% and 98.6% respectively, and for NT-pro-BNP were 39.4%, 118.2% and 158.0% respectively. The obtained data indicate a significant activation of the NP system with an increase in the content of proANP and NT-

pro-BNP in blood plasma parallel to the increase in hypertension.

Subsequently, in order to determine the relationship between proANP and NT-pro-BNP values with violations of ABF and stiffness of the muscular type arteries, in the group of patients with hypertensive disease in general, the rank correlations of P. Spearman were studied. In patients with AH in the BS, a weak positive relationship was observed between proANP and NT-pro-BNP with SFX ($r = + 0.34$ and $r = + 0.34$, respectively, $p < 0.05$), the degree of which after MW increased significantly ($r = + 0.56$ and $r = + 0.61$ respectively, $p < 0.02$). Similarly, in the resting state, there was no relationship between the values of proANP and NT-pro-BNP from LLABF and ABFR, but after MW there was a close relationship between these indices. In LLABF difference between proANP and NT-pro-BNP was $r = + 0.47$ and $r = + 0.54$ ($p < 0.05$) respectively, and ABFR proANP and Nt-pro-BNP was $r = + 0.53$ and $r = + 0.58$ respectively ($p < 0.01$).

Discussions

The results of 12 weeks study of treatment with the combination of amlodipine and losartan showed that in patients with hypertension, a significant decline in SBP from 157.8 ± 4.2 mmHg to 134.9 ± 2.3 mmHg was noted. (by-16.2%, $p < 0.01$), DBP 95.2 ± 2.3 mm to 83.8 ± 1.8 mm Hg (-11.9%; $p < 0.05$) and PP 63.6 ± 1.6 mmHg to 49.1 ± 1.4 mmHg. (-22.8%; $p < 0.001$). At the same time, LLABF with a respectable decrease of 91.4 ± 2.0 mm Hg was found to 71.4 ± 1.4 mm Hg (-21.9%; $p < 0.001$), which occurred in parallel to positive changes in the structural and functional state of vessels. Thus, PWVin the BS tended to decrease from 9.45 ± 0.61 m / s to 8.54 ± 0.45 m / s (-9.6%, $p > 0.05$), but after the MW, PWV decreased (by -2.4%; $p > 0.05$). Also, the levels of proANP and NT-pro-BNP were reduced by 43% and 76%, respectively, $p < 0.01$.

Therefore, the study has shown that the progression of hypertensive disease is accompanied by a disruption of the metabolites pro-ANP and NT-pro-BNP, whose content increased parallelly with the increase of hypertension. At the same time, a close positive correlation was found between the values of proANP and NT-pro-BNP with PWV and ABF indicators, which was substantially influenced by a functional test with physical activity. It should be recalled that representatives of natriuretic peptides, which include proANP and NT-pro-BNP metabolites, are referred as the depressors of the regulatory system of arterial pressure. It is found that the increase in the magnitude of NT-pro-BNP in patients with AH,

in fact, is a marker of structural and functional changes not only from the heart, but also from the peripheral arteries of the muscular type. Significantly, the positive relationship between NT-pro-BNP and ABF and its growth after muscular work has been revealed. This proves the prognostic role of the peptides studied in the sense of possible functional vascular disorders in the unfavorable course of AH.

Conclusion

1. The PWV index is a constant value, and it is substantially affected by the functional state of the vessels. The progression of hypertension is accompanied by an increase in it and is effected by a shift in the range of auto regulation causing higher levels of intravascular pressure and a decrease in range of auto-regulation, which manifests itself as much as possible after muscle load.
2. In patients with hypertension, an increase in the levels of proANP and NT-pro-BNP in plasma plasma is observed parallel to the increase in arterial hypertension. A close positive correlation was found between the values of proANP, NT-pro-BNP and PWV and the violation of the forearm blood flow auto regulation, which increased after muscular loading, makes it possible to talk about the high sensitivity of the peptide as a marker of lesions of the muscular type arteries.
3. A 12-week hypertensive treatment with amlodipine 5 mg/day and losartan 50 mg/day in patients with arterial hypertension significantly improved the mechanisms of auto-regulation and elastic properties of muscular vessels while reducing the levels of proANP and NT-pro-BNP in plasma.
4. The application of functional tests with muscle loading and determination of the level of metabolites of natriuretic peptides proANP and NT-pro-BNP allows a more accurate assessment of the degree of structural and functional lesions of muscular arteries against hypertension.

Conflicts of Interest: None declared by the authors.

Informed consent and ethical committee approval: An informed consent was taken from the patients for their participation in this study and a local ethics committee permission was also obtained.

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