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POSSIBILITY OF USING THE AUGMENTATION INDEx AS A PREDICTOR OF ATHEROSCLEROTIC DISEASE OF CAROTID ARTERIES IN PATIENTS WITH ESSENTIAL HYPERTENSION

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SUMMARY

Objective. Study of the possibility of predicting atherosclerosis of carotid arteries on the basis of the augmentation index in patients with essential hypertension.

Material and methods. A total of 155 patients with EH in the age range 30-70 years. A physical examination, identification of a number of biochemical parameters: glucose and creatinine and blood lipid (LDL, HDL and triglycerides), duplex scanning of carotid arteries, the definition of arterial stiffness by pulse wave contour analysis.

Results. The augmentation index, along with age, was an independent risk factor for atherosclerosis carotid arteries in patients with EH, as well as the severity of its symptoms.

Key words: *essential hypertension, atherosclerosis, vascular stiffness.*

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INTRODUCTION

Arterial hypertension (AH) is the most important risk factor for developing cardiovascular diseases (myocardial infarction, stroke, ischemic heart disease, chronic heart failure) and cerebrovascular (ischemic or hemorrhagic stroke, transient ischemic attack) diseases that make up the majority of diseases of the circulatory system [1].

The combination of hypertension with atherosclerosis (AS), in particular of coronary and carotid arteries, significantly increases the risk of developing cardiovascular diseases (CVD) and their complications. More than 70% of deaths in patients with CVD are associated with AS, which is a vascular wall disease affecting the aorta, carotid, coronary and peripheral arteries, and is a common cause of ischemic stroke, myocardial infarction and acute coronary syndrome [2-4]. In this regard, the identification of patients with atherosclerotic changes in the vascular channel, especially in patients whose atherosclerosis has developed against the arterial hypertension background, is an important task.

No less important indicator characterizing vascular remodeling considered the rigidity of the arterial channel, determined by the speed of distribution of the pulse wave. Data on a high degree of correlation between the likelihood of cardiovascular complications and the speed of pulse wave propagation are given [1, 5, 6]. A number of studies have shown the relationship between increased arterial stiffness and atherosclerosis of carotid artery [7, 8], as well as between the level of the highly sensitive C-reactive protein and the rigidity of large arteries - the marker of the initial stages of atherosclerosis [9, 10].

However, the evaluation of arterial stiffness by the method of determining the speed of distribution of the pulse wave is quite laborious and expensive, requiring special training of personnel and a specialized laboratory [11]. In this regard, the search for alternative methods that allows to assess vascular rigidity and predict the development of complications continue, both in asymptomatic patients and patients with already developed cardiovascular pathology. The study of vascular stiffness based on the contour analysis of the pulse wave is one of such methods [12]. It should be noted that studies on the relationship between the levels of central arterial pressure and other parameters of arterial stiffness (index of amplification, stiffness index, reflection index) with the development of subclinical damage to target organs, in particular atherosclerosis, are few, and their results are quite contradictory [10 , 13-15].

Therefore, the purpose of this study was to study the possibility of predicting atherosclerosis of carotid arteries based on the augmentation index (AIx) in patients with essential hypertension (EH).

MATERIAL AND METHODS

We examined 155 patients with EH at the age of 30-70 years old (average age - 56.1±8.2 y.o.), including 78 men and 77 women. At the time of enrollment, patients did not receive regular antihypertensive therapy. Patients with secondary forms of arterial hypertension, patients with high functional class of heart failure (FC III-IVNYHA), those with hepatic or renal insufficiency, oncological diseases, chronic viral and bacterial infections were excluded from the study.

Clinical and biochemical studies

All the patients underwent the following examinations: measurement of height, weight and waist measurement, measurement of blood pressure and heart rate, and determination of a number of biochemical parameters: blood sugar and blood creatinine and lipid spectrum (LDL, HDL and triglyceride levels).

Blood pressure was measured on both hands using the Korotkov method with the help of an anaeroid sphygmomanometer in the sitting position, following the generally accepted pressure measurement rules (WHO, 1986). To measure excess body weight, the growth measurement using rostomer and weighting on a scale were done. The Quetelet index was calculated: weight (kg)/height (m)2. To identify those with abdominal obesity, the waist circumference was measured at the midpoint of the distance between the costal arch and the iliac crest. Blood for examination was taken from the ulnar vein in a sitting position in the morning on an empty stomach after a 12-hour nighttime meal break. The content of sugar, total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-cholesterol) was determined on a biochemical Sinhron CX4-DELTA auto-analyzer from Beckman (USA). The concentration of low-density lipoprotein cholesterol (LDL) was calculated according to the formula of W.T. Friedewald (1972) [16]: LDL=OX - (TG / 2,2) - HDL.

Duplex scanning of carotid arteries

The condition of the carotid arteries was examined on the Sequoia-512 machine of the Acuson firm (USA). The common carotid artery was scanned in a longitudinal section using a linear sensor with a frequency of 7.5 MHz, the image was synchronized with the R wave on the ECG and recorded on videotape using BMSonySVNS. Duplex scanning of the carotid basin examined the bifurcation of the brachiocephalic trunk, the distal, middle and proximal parts of the common carotid artery (CCA), bifurcation of the common carotid artery and the proximal third of the internal carotid artery and the external carotid artery to the right and left.

The thickness of the intima-media complex (TIM) was measured in the middle third of the posterior wall of the common carotid artery in places free from atherosclerotic plaques, as the distance from the internal boundary between the lumen of the artery and intima to the boundary between the media and adventitia.

In the presence of an atherosclerotic lesion, the thickness of the intima-media complex max (TIM max) was the transverse dimension of the atherosclerotic plaque, thickness of the intima-media complex (TIM) and lipid deposits. In the presence of multiple lesions, the size of the plaque, having the largest transverse dimension, was taken into account. The presence of a plaque was indicated by an increase in TIM >1.5 mm or a local increase in thickness by 0.5 mm or by 50% compared to the value of TIM in adjacent parts of carotid artery [17]. The degree of stenosis of the vessel was determined from the ratio of the diameter of the artery in the zone of maximum constriction to the diameter of the "reference" segment of the vessel, which was the expected / proper diameter of the carotid at the level of maximum constriction (ECST, 1991) [18].

Stenosis was determined by degree - small stenosis with stenosis of 0-29%, moderate – 30-59%, expressed – 60-79%, critical – 80-99% and occlusion – 100% (ECST, 1991) [18].

Contour analysis of pulse wave

To evaluate the structural and functional state of the wall of large vessels and parameters of central hemodynamics, the photoplethysmography method was used – the Angioskan-01 machine (Angioskan, Russia). The study was conducted in the morning, strictly on an empty stomach, patients did not smoke and did not drink coffee before the procedure. The analysis was carried out in a quiet, darkened room, at a temperature of 20-22°C. During the study, patients were in a sitting position, their hands with photoplethysmographic sensors were fixed. Sensors of the

device "Angioscan-01" were installed on the terminal phalanges of the index fingers, the manometer cuff was located on the right forearm at the heart level.

In the automatic contour analysis of the pulse wave, the following parameters were evaluated: stiffness index (SI), reflection index (RI), augmentation index (AIx), augmentation index normalized to heart rate=75 beats per minute (AIx75) and central systolic blood pressure (Spa).

Statistical processing of the results of the study

Statistical processing of the data was carried out using the program STATISTICA6.0. The normality of the distribution was determined by the criteria of Shapiro-Wilk and Liljefors. The reliability of differences between groups was determined with the help of the nonparametric Mann-Whitney criteria and Kolmogorov-Smirnov criteria, as well as the Student's parametric t-test. For multiple comparisons, the Kruskal-Wallis criteria and dispersion analysis were used, with the calculation of the coefficient F and the subsequent post-hoc analysis. The relationship between the indicators was studied using correlation analysis with the calculation of the Spearman correlation coefficient (r). To assess the prognostic significance of traditional risk factors for CVD and arterial stiffness indicators in the development of carotid arteriosclerosis, multivariate regression analysis was applied with step-by-step inclusion into the model. Later, for the risk factors identified by this method, the force of their influence on the development of atherosclerosis was estimated with the calculation of the odds ratio 95% or 99% of confidence interval (CI). In addition, an analysis of their sensitivity and specificity was made, as well as the prognostic significance of the positive and negative test results. Differences were considered significant at $p < 0.05$.

RESULTS OF THE STUDY

In general, in the group the systolic blood pressure level was 161.4±23.3 mm Hg, the diastolic blood pressure was 97.9±12.6 mmHg, the body mass index was 30.5±5.0 kg / m^2, waist – 99.2±10.8 cm, total cholesterol – 4.98±1.11 mmol/l, triglycerides – 1.72±0.84 mmol/l, HDL cholesterol 1.16±0.33 mmol/l, LDL cholesterol – 3.01±0.89 mmol/l, creatinine – 92.4±27.5 μmol/l, sugar 5.46±1.2 mmol/l. Diabetes mellitus was diagnosed in 11 (7.1%) patients, obesity – In 80 (51.6%) patients, 38 patients smoked (24.5%). Coronary heart disease was diagnosed in 66 (42%) patients, carotid atherosclerosis in 120 (77.4%) of the examined patients.

When analyzing the parameters of arterial stiffness and central hemodynamics in patients with essential hypertension with or without atherosclerosis of carotid arteries, we obtained the following results. It turned out that the index of amplification normalized with a heart rate of 75 beats per minute (AIx75) in patients with atherosclerosis of the carotid arteries, was 16.6±10.7%, which is significantly higher than in patients with essential hypertension without carotid atherosclerosis (9.2±11.7%, $p<0.005$). Similarly, Aix index in the group of patients with atherosclerosis reached a level of 20.9±13.3% and was significantly higher than in patients without atherosclerosis of the carotid arteries (11,1±13,7%, $p<0,01$). By levels of central systolic blood pressure (Spa), stiffness index (SI) and index of amplification (RI), groups of patients with essential hypertension with or without carotid atherosclerosis did not significantly differ ($p>0.05$) (table 1).

Table 1. Indicators of arterial stiffness and central hemodynamics in patients with EH with or without atherosclerosis of carotid arteries

Indicators	1st group (atherosclerosis –), n=35	2nd group (atherosclerosis +), n=120	p
AIx 75, %	9,2±11,7	16,6±10,7	<0,005
AIx, %	11,1±13,7	20,9±13,3	<0,01
Spa, mmHg	137±19	145±22	нд
SI, m/s	7,5±1,3	7,5±1,2	нд
RI, %	38,8±15,6	42,3±19,4	нд

Note: AIx75 – augmentation index normalized to heart rate=75 beats / min; AIx – augmentation index; Spa – central systolic blood pressure; SI – stiffness index; RI – reflection index; p – reliability of differences between groups; nd – differences between groups are unreliable; AC – atherosclerosis.

It should be noted that we did not find a correlation relationship between the parameters of arterial stiffness and the thickness of the CMPSA among the examined patients ($p>0.05$).

To assess the prognostic significance of the traditional risk

Table 2. The influence of traditional risk factors for cardiovascular diseases and arterial stiffness indicators on the presence and severity of carotid atherosclerosis in patients with essential hypertension

Indicators	atherosclerosis +/-		Number of affected vessels		% of stenosis	
	β	p	β	p	β	p
	F = 5,149; p<0,0001		F = 5,149; p<0,0001		F = 7,147; p<0,0001	
Age, y.o.	0,39	<0,0001	0,47	<0,0001	0,31	<0,0001
Office systolic blood pressure ,mmHg	0,14	= 0,04	-	-	-	-
Sugar, mmol/l	-	-	-	-	0,12	=0,09
AIx, %	0,15	=0,04	0,24	<0,05	0,39	<0,004
AIx 75, %	-	-	-0,14	=0,25	-	-
Spa, mmHg	0,07	=0,31	0,14	<0,03	0,13	=0,09
OT, cm	-	-	-	-	-0,08	=0,24
SI, m/s	-0,10	=0,15	-	-	-0,08	=0,27

Note: SBP – systolic blood pressure; AIx75 – augmentation index normalized to heart rate=75 beats / min; AIx – augmentation index; Spa – central systolic blood pressure; SI – stiffness index; OT – waist volume; β – index of multiple regression; F – criterion of Fisher ; p – reliability of the multiple regression coefficient.

factors for cardiovascular diseases and arterial stiffness indicators in the development of carotid arteriosclerosis, multivariate regression analysis was performed (table 4). At the same time, three models were formed in which dependent variables were: the presence of atherosclerosis of carotid arteries (model 1), the number of affected vessels (model 2) and the severity of carotid atherosclerosis (in%) (model 3). As dependent variables we used: the traditional risk factors for cardiovascular diseases (age, systolic and diastolic blood pressure levels, total cholesterol, blood sugar, waist size, body mass index and smoking status), as well as arterial stiffness parameters (Alx75, Alx, Spa , SI, RI). The results of the analysis are presented in table 2.

When analyzing the obtained results, it was found that the independent risk factors for the presence of carotid atherosclerosis in patients with essential hypertension were: age (β=0.39; p <0.0001); SBP level (β=0.14; p <0.05); and Alx (β=0.15, p <0.05). The number of affected carotid arteries was independently associated with age (β=0.47, p <0.0001), Alx (β=0.24, p <0.05) and Spa level (β=0.14, p <0, 03). Predictors of carotid arteriosclerosis are: age (β=0,31; p<0,0001) and Alx (β=0,39; p<0,004) (table 2).

Thus, in all models, in addition to age, the index of amplification (Alx) was an independent predictor of the presence of carotid atherosclerosis. The median of this indicator for the group was 25%. Therefore, as the cutting point for predicting the presence of atherosclerosis of the carotid arteries, the value of AI >25% was taken. In addition, it is known that this indicator varies with ages, that suggests the need to assess its prognostic significance separately for patients of middle and old age.

As follows from the data presented in table 3, in patients with essential hypertension of middle age, an increase of Aix >25% increased the probability of detecting carotid atherosclerosis in 2.2 times (odds ratio-2.17, 95% confidence interval 1.00-6.58) with high sensitivity (85.7%). The prognostic significance of the positive test result was 76.4%. At the same time, in the elderly group, an increase in Aix >25% was associated with an unreliable increase in the probability of detection of AS of carotid arteries (OR-2.94, 95% CI 0.47-18.4).

Table 3. Predictive ability of the Alx index >25% for the presence of carotid atherosclerosis in patients with essential hypertension

Indicator	Average age (n=77)	Elderly age (n=78)
Alx,%	>25%	>25%
OR	2,17	2,94
95% CI	1,00-6,58	0,47-18,4
Se	26,5%	40,2%
Sp	85,7%	85,7%
PV (+)	76,4%	96,6%

Note: as a reference group we consider a group of patients with Aix <25%; OR – odds ratio; CI – confidence interval; Se – sensitivity; Sp – specificity; PV (+) – prognostic significance of positive test result.

DISCUSSION

The purpose of our study was to study the relationship between the stiffness of the arteries and the wave equivalent of stiffness – Alx with the presence of carotid atherosclerosis in patients with essential hypertension. We have shown that Alx is, along with age, an independent risk factor for the development of atherosclerosis of the carotid arteries, as well as its severity. At the same time, Alx values above 25% with high specificity (>85%) were associated with atherosclerotic lesions of the carotid arteries.

The last decade in cardiology has been marked by a number of studies to assess the clinical and prognostic value of indicators of central hemodynamics and the characteristics of the elastic properties of arteries. Thus, according to the results of recent studies, central arterial pressure, arterial stiffness, Alx are sensitive indicators of damage of target organs and the risk factor of cardiovascular disease not only in individuals with atherosclerosis [19], but also in healthy individuals [14]. It was demonstrated that the stiffness of the aorta maintained its independent prognostic significance after correction for classical risk factors, including pulsatile arterial pressure in the brachial artery [6]. Moreover, the stiffness of the arteries retains its importance as a predictor of coronary heart disease after correction according to the Framingham scale of risk, which suggests that it carries an additional value in relation to a combination of risk factors [20].

Vascular stiffness, estimated by the speed of the pulse wave propagation, closely correlates with the level of Spa and Alx [21]. In this case, the central arterial pressure (systolic, pulse) is associated with the degree of hypertrophy of the vascular wall, the severity of atherosclerosis in the carotid artery [22]. A number of studies have shown that the level of the Spa can be an independent prognostic factor not only for the development of structural changes in the cardiovascular system [23], but also for unfavorable clinical outcomes [13, 24]. At the same time, as indicated above, the prognostic value of Alx is not so unambiguous, and the data about its effect on the prognosis and development of complications are contradictory [22, 13].

In our study, a direct relationship between the presence and severity of atherosclerosis of the carotid arteries and Alx was demonstrated. At the same time, almost linear growth of Alx was observed with increasing degree of carotid stenosis. The multivariate regression analysis showed that Alx, along with age, was an independent risk factor for identifying carotid atherosclerosis in patients with essential hypertension. An important result of the study is the proven possibility of predicting the presence of atherosclerosis depending on Alx magnitude. According to our data, the Alx value of more than 25% with high specificity (85%) allows to predict the presence of carotid atherosclerosis in middle-aged patients: the frequency of detection of atherosclerosis increased in 2.2 times. At the same time, the prognostic significance of the positive test result reaches 77%. In the older age, such a pattern is not observed, probably due to the high prevalence of atherosclerosis (90%) among this category of patients.

It should be noted one more circumstance. In our study, a photoplethysmographic method was used for the contour analysis of the pulse wave, and not the method of applanation tonometry, as in previous studies [23]. The method used by us is valid, validated [25], well reproducible and at the same time, in comparison with other methods it doesn't require special training of personnel, which determines its advantages in mass population surveys as a screening test.

CONCLUSIONS

1. *The index Alx, determined by finger photoplethysmography based on the contour analysis of the pulse wave, is associated with the presence and severity of carotid atherosclerosis.*
2. *In patients with essential hypertension of middle age, the Alx value of more than 25% with high specificity (85%) allows to predict the presence of atherosclerosis of the carotid arteries.*

In this case, the prognostic significance of the positive test result reaches 77%.

3. *The presented results convincingly substantiate the necessity of using this method in the framework of population and screening studies, as well as to determine the indications for conducting duplex scanning of carotid arteries in patients with essential hypertension of middle age at the out-patient-policlinic level of healthcare.*

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