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Abstract

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PECULIARITIES OF HEMODYNAMIC AND METABOLIC INDICATORS IN PATIENTS WITH ARTERIAL HYPERTENSION AND CONCOMITANT OBESITY DEPENDING ON PLASMA RENIN ACTIVITY

The aim of the research: to evaluate the effect of plasma renin activity on the state of hemodynamic and neurohumoral parameters in obese hypertensive patients.

Materials and Methods: Anthropometric, biochemical, automated methods of immune analysis, spectrophotometric, instrumental, statistical methods were used to examine 200 hypertensive patients with class I–II obesity aged 45–55 years. Patients were divided into two groups depending on plasma renin activity: the first group included 21 patients with low-renin hypertension, the second – 179 patients with high-renin hypertension.

Results: Patients with HRAH had higher blood pressure BP (DBP, $p = 0.004$, SBP and mean blood pressure, $p<0.001$ for both indicators), higher CIMT bifurcation ($p = 0.003$) and cPWV ($p = 0.023$), larger size of the left ventricle and its MM ($p = 0.039$) compared with patients with LRAH. The HRAH was associated with a more pronounced imbalance of the oxidative stress system – antioxidant protection, higher levels of leptin, total cholesterol and LDL cholesterol. In the absence of differences in glycemic levels, patients with HRAH had significantly higher insulin levels and more pronounced IR, as assessed by the HOMA index. Patients with low plasma renin activity had significantly lower serum aldosterone levels with significantly higher ARR levels than patients with high plasma renin activity.

Conclusions: Features of cardiovascular remodeling and neurohumoral status depending on the phenotype of hypertension in patients with concomitant obesity have been established.

Keywords: arterial hypertension**,** low-renin hypertension, high-renin hypertension, plasma renin activity, obesity.

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Резюме

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ОСОБЛИВОСТІ ГЕМОДИНАМІЧНИХ ТА МЕТАБОЛІЧНИХ ПОКАЗНИКІВ У ХВОРИХ НА АРТЕРІАЛЬНУ ГІПЕРТЕНЗІЮ ІЗ СУПУТНІМ ОЖИРІННЯМ В ЗАЛЕЖНОСТІ ВІД АКТИВНОСТІ РЕНІНУ В ПЛАЗМІ

Мета роботи полягала в оцінюванні впливу активності реніну плазми на стан гемодинамічних параметрів та метаболічних показників у хворих на артеріальну гіпертензією із супутнім ожирінням.

Матеріали і методи: Обстежено 200 пацієнтів із артеріальною гіпертензією (АГ) та ожирінням (ОЖ) I–II ступенів. Пацієнти були поділені на дві групи залежно від активності реніну плазми: до першої групи ввійшов 21 пацієнт з низькореніновою АГ (НРАГ), до другої – 179 пацієнтів з високореніновою АГ (ВРАГ). Антропометричні, біохімічні, автоматизовні методи імунного аналізу, спектрофотометричні, інструментальні та статистичні методи використовували при проведенні дослідження.

Результати. Пацієнти з ВРАГ мали вищі рівні АТ (ДАТ, p = 0,004, САТ і середній АТ, p < 0,001 для обох показників), більші значення показників ТІМ ЗСА на рівні біфуркації (p = 0,003) і ШПХ ЗСА (p = 0,023), більші розміри лівого шлуночка та ММЛШ (p = 0,039) порівняно з пацієнтами із НРАГ. ВРАГ асоціювалася з більш вираженим дисбалансом системи оксидативного стресу – антиоксидантного захисту, вищими рівнями лептину, загального ХС і ХС ЛПНЩ. Пацієнти з ВРАГ мали достовірно вищі рівні інсуліну і більш виражену ІР за відсутності відмінностей щодо рівнів глікемії. Достовірно нижчий рівень сироваткового альдостерону за достовірно більш високого показника АРК установлено в пацієнтів із НРАГ порівняно із групою пацієнтів з ВРАГ.

Висновки. Встановлено особливості серцево-судинного ремоделювання та нейрогуморального статусу залежно від фенотипу АГ у пацієнтів із супутнім ожирінням.

Ключові слова: артеріальна гіпертензія, низькоренінова АГ, високоренінова АГ, активність реніну плазми, ожиріння.

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Introduction

Hypertension remains one of the few nosologies without a common etiological basis. In most publications on hypertension, you can find formulated with varying degrees of categorical, but unchanging in essence, the statement that the etiology of hypertension (essential arterial hypertension) still remains undisclosed. At the very best, information is given about the multifactorial origin of the disease, followed by a more or less complete list of these factors: genetic predisposition, overweight and obesity, sedentary lifestyle, smoking, diabetes, kidney disease, diet rich in fats and salt. Probably, the list can be extended, but it does not clarify the etiology of hypertension, it is very difficult to assess the causal role of each of these factors in the origin of the disease in a particular patient with subsequent cardiovascular complications [1–4].

The discovery of forms of arterial hypertension with known mechanisms allows for targeted effective therapy and in some cases to achieve a complete cure. However, the contingent of patients with LRAH belongs to the group of patients with unclear etiology, as its development is associated with polygenic systems and with a significant influence of environmental factors, ethnicity, age, blood pressure, the presence of comorbid pathologies: kidney disease, diabetes, metabolic syndrome [3, 5, 6].

Attempting to understand the essence of this form, attention was paid to aldosterone as one of the most effective factors in the suppression of renin, on the one hand, and the formation of hypertensive

status – on the other hand [4, 7]. As the mechanisms of aldosterone involvement in the pathogenesis of low-renin hypertension deepened, the main genetic and physiological links in the development of various forms and syndromes of LRAG were established. The study of genetic and physiological mechanisms of the low-renin form of arterial hypertension provides an illustrative example of how penetration into the intimate mechanisms of blood pressure regulation in each case allows identifying individual-specific syndromes and establishing the original causes of the disease [8–12]. Progress has obviously been done in revealing the causes and mechanisms of essential hypertension.

Analysis of the forms and manifestations of LRAH gives an example of how you can expand the pool of hypertensive conditions of known etiology and gradually move towards the disclosure of multiple and diverse, but still largely unclear causes of the origin of the essential hypertension [13, 14].

Thus, the study of the activity of such components of RAAS as renin and aldosterone, their evaluation in hypertensive patients depending on the presence and absence of obesity, IR, is an urgent problem that requires detailed study.

The aim of the research: to evaluate the effect of plasma renin activity on the state of hemodynamic and neurohumoral parameters in hypertension patients with concomitant obesity.

Clinical characteristics of patients and research methods. We examined 200 hypertensive patients with class I–II obesity aged 45–55 years. Patients were divided into two groups depending on plasma renin activity: the first group included 21 patients with low-renin hypertension, the second – 179 patients with high-renin hypertension.

Measurements of height, body weight, and BMI calculation formed physical examination of patients. The waist-to-hip ratio was determined due to patients' waist circumference (WC) and hip circumference (HC). Office BP was measured in accordance with the 2018 ESC/ESH Guidelines for the management of AH [15]. Difference between SBP and DBP evaluated as pulse BP. Average BP was calculated by the formula:

$$Average\ BP = 0.42 \times (SBP - DBP) + DBP$$

Morphofunctional properties of the myocardium were evaluated during ultrasound examination of the heart in one-dimensional, two-dimensional and Doppler modes by conventional methods. The volumes of left and right atria (LAV and RAV, respectively), end-systolic and end-diastolic diameters (LVESD and LVEDD, respectively) of the left ventricle (LV), diameters of LA and aorta (LAD and AD, respectively) were evaluated. The ejection fraction (EF) was calculated by the formula:

$$EF = (EDV - ESV) / EDV,$$

where ESV and EDV are the end-systolic and end-diastolic LV volumes, respectively.

The thickness of the posterior wall of the LV and the thickness of the interventricular septum in the systole (TPWs and TIVSs, respectively) and diastole (TPWd and TIVSd, respectively) were measured. The relative wall thickness of the LV (RWT) was calculated by the formula:

$$RWT = (TPWd + TIVSd) / LVEDD$$

The LV myocardial mass index (LVMI) was calculated as the ratio of the LV myocardial mass (LVM) to the surface area of the body (S):

$$LVMI = LVM / S$$

Left ventricular diastolic function was evaluated by pulmonary artery blood flow and transmitral diastolic blood flow in pulsed Doppler with the determination of the following parameters: maximum early LV filling rate in spectral mode (E), maximum late (atrial) filling speed (A), ratio of maximal rates of early and late filling of LV at spectral mode (E/A), time of isovolumic relaxation of LV (IVRT), time of deceleration early diastolic flow rate (DT), maximum early LV filling rate at tissue mode (e´), mean pulmonary artery pressure (AP) by Kitabatake, ratio of E and e´ (E/e´). For studying endothelial function, the degree of endothelium-dependent vasodilation (EDVD) in reactive hyperemia was determined in all patients. Investigations were carried out using a broadband linear transducer 5–12 MHz Doppler color mapping with three readings being taken arteries at 15-min intervals between samples on the left and right brachial arteries, according to the method of Celermajer D. S. (in the modification of the method by Ivanova O. V.) [16, 17]. Normally, the maximum vasodilation of the brachial artery should exceed 10% of the original diameter. Simultaneously, we measured the intima media thickness (CIMT) of the carotid artery (CA, 2 cm proximal to the bifurcation of the common CA). The pulse wave velocity (PWV) in the carotid artery (cPWV) was determined by the W-Track method; determination of the PWV in the abdominal aorta (aPWV) was performed using a phased sensor.

In this study we defined venous blood glucose concentration and insulin levels with standard biochemical methods. The patients were also tested for glucose tolerance. Insulin resistance (IR) was determined using the homeostasis model assessment

index (HOMA-IR). The activity of the renin–angiotensin–aldosterone system (RAAS) was evaluated by the levels of aldosterone and plasma renin activity (PRA), as well as by the aldosterone-renin ratio (ARR). Low-renin hypertension was set at < 0.65 ng/ml/h, and high-renin hypertension was set at ≥ 0.65 ng/ml/h. The inflammatory activity was evaluated by the levels of interleukin 6 (IL-6) and C-reactive protein (CRP). The functional state of adipose tissue was assessed by blood levels of leptin and adiponectin. The intensity of peroxide oxidation of lipids was assessed for indicators of prooxidant activity – the levels of malonic dialdehyde (MDA) and diene conjugates (DC), and the state of the antioxidant protection system – by the total antioxidant activity. Lipid metabolism was assessed by total cholesterol, triglycerides, LDL and HDL cholesterol.

The statistical processing of the obtained data was carried out using the package of statistical software "SPSS 17" (IBM), Microsoft Office Exel-2003. The data are presented as mean values ± standard deviation. Significance was set at a p value of < 0.05 in all cases.

The study protocol was approved by the Ethics Committee. All participants were informed about the aim of the study and signed a written consent form.

Results and Discussion. Among patients with hypertension and concomitant obesity 89.5% have HRAH, and 10.5%, respectively, LRAH. It was found that BMI in patients with HRAH was higher than in patients with LRAH (p = 0.000). In the absence of differences in glycemic levels, patients with HRAH had significantly (p = 0.000) higher insulin levels and more pronounced IR, as assessed by the HOMA index (Table 1).

Table 1 – Anthropometric indicators and neurohumoral parameters of obese hypertensive patients with LRAH and HRAH

Indicators	**AH + obesity**		
	LRAH	**HRAH**	**p**
	n = 21	n = 179	
Weight [kg]	92,00 ± 8,56	101,91 ± 10,61	0,000
BMI [kg/m2]	31,46 ± 1,09	35,20 ± 2,65	0,000
Waist [cm]	108,71 ± 7,13	107,51 ± 7,58	0,491
Hip [cm]	115,43 ± 10,87	115,96 ± 8,07	0,786
Waist-to-hip ratio	0,95 ± 0,11	0,93 ± 0,11	0,514
Total cholesterol [mmol/L]	5,84 ± 0,46	6,11 ± 0,47	0,016
Triglycerides [mmol/L]	1,89 ± 0,32	2,01 ± 0,39	0,189
LDL cholesterol [mmol/L]	4,05 ± 0,56	4,89 ± 0,54	0,000
HDL cholesterol, [mmol/L]	0,99 ± 0,04	1,00 ± 0,10	0,556
Blood glucose [mmol/L]	4,93 ± 0,27	5,07 ± 0,50	0,206
Insulin [μU/mL]	8,67 ± 0,66	15,78 ± 5,06	0,000
HOMA-IR	1,90 ± 0,12	3,58 ± 1,28	0,000
HbA1c (%)	5,19 ± 0,24	5,29 ± 0,52	0,357
Overall antioxidant protection [mmol/L]	1,13 ± 0,06	1,05 ± 0,06	0,000
MDA [nmol/mL]	32,52 ± 3,59	36,01 ± 3,28	0,000
DC [nmol/mL]	30,06 ± 1,88	32,12 ± 3,42	0,008
IL-6 [pg/mL]	137,57 ± 8,73	138,58 ± 8,19	0,596
CRP [mg/L]	7,50 ± 1,07	7,51 ± 1,18	0,991
Aldosteron [ng/dl]	11,94 ± 1,98	17,49 ± 2,11	0,000
PRA , ng/ml/hour	0,55 ± 0,06	2,63 ± 0,48	0,000
ARR	21,83 ± 3,65	6,92 ± 1,79	0,000
Adiponectin [ng/mL]	6,44 ± 0,11	6,49 ± 0,47	0,086
Leptin [ng/mL]	12,22 ± 1,06	15,40 ± 2,43	0,000

BMI – body mass index; ARR – aldosterone-renin ratio; CRP – C-reactive protein; DC – diene conjugates; MDA – malonic dialdehyde; HbA1c – glycated hemoglobin; HDL – high density lipoprotein; LDL – low-density lipoprotein; IL-6 – interleukin 6; HOMA-IR – Homeostatic Model Assessment for Insulin Resistance

Table 2 – Hemodynamic parameters of obese hypertensive patients with LRAH and HRAH

Indicators	AH + obesity		
	LRAH	HRAH	p
	n = 21	n = 179	
SBP [mm Hg]	171.44 ± 4.48	175.24 ± 2.98	0.000
DBP [mm Hg]	101.25 ± 3.00	103.24 ± 2.98	0.004
Heart rate [bpm]	72.60 ± 1.92	72.71 ± 1.52	0.511
Pulse BP [mm Hg]	70.20 ± 4.00	72.00 ± 4.14	0.053
Average BP [mm Hg]	130.73 ± 3.12	133.48 ± 2.17	0.000
CIMT [mm]	0.90 ± 0.07	0.91 ± 0.09	0.401
CIMT bifurcation [mm]	1.27 ± 0.13	1.37 ± 0.15	0.003
cPWV [m/s]	8.06 ± 1.32	8.62 ± 1.04	0.023
aPWV [m/s]	8.28 ± 0.86	8.51 ± 1.07	0.362
EDVD (%)	7.14 ± 0.96	6.88 ± 1.18	0.340
TIVSd [cm]	1.12 ± 0.14	1.18 ± 0.11	0.050
TIVSs [cm]	1.40 ± 0.18	1.47 ± 0.15	0.045
TPWd [cm]	1.13 ± 0.14	1.19 ± 0.14	0.106
TPWs [cm]	1.49 ± 0.17	1.62 ± 0.36	0.086
LVEDD[cm]	4.74 ± 0.31	4.91 ± 0.34	0.029
LVESD[cm]	3.18 ± 0.11	3.22 ± 0.28	0.503
EDV [mL]	104.95 ± 17.06	114.09 ± 19.11	0.037
ESV [mL]	40.46 ± 3.34	42.17 ± 9.38	0.408
EF (%)	62.85 ± 4.95	63.24 ± 3.00	0.072
LVM [g]	235.60 ± 55.83	267.57 ± 67.79	0.039
LVMI [g/m^2]	115.45 ± 25.98	126.32 ± 31.75	0.133
RWT	0.47 ± 0.06	0.48 ± 0.04	0.500
LAD [mm]	38.60 ± 2.25	38.24 ± 3.32	0.627
AD [mm]	34.30 ± 2.07	32.90 ± 1.34	0.000
Mean pulmonary AP [mm Hg] by Kitabatake	16.10 ± 2.90	16.31 ± 3.26	0.774
RAV [mL]	41.55 ± 4.75	39.16 ± 4.74	0.030
LAV [mL]	49.05 ± 2.93	52.36 ± 5.03	0.004
e´[cm/s]	12.10 ± 2.18	11.42 ± 2.23	0.187
E [cm/s]	71.72 ± 13.18	66.43 ± 9.70	0.024
A [cm/s]	85.54 ± 10.08	77.87 ± 10.65	0.002
E/A	0.83 ± 0.07	0.87 ± 0.16	0.347
DT [s]	0.15 ± 0.08	0.15 ± 0.10	0.931
IVRT [s]	0.14 ± 0.02	0.12 ± 0.02	0.000
E/e´	6.06 ± 1.26	5.96 ± 2.88	0.695

BP – blood pressure; DBP – diastolic blood pressure; SBP – systolic blood pressure; A – maximum late (atrial) filling speed; AP – artery pressure; DT – time of deceleration early diastolic flow rate; E – filling rate in spectral mode; e – maximum early LV filling rate at tissue mode; E/A – ratio of maximal rates of early and late filling of LV at spectral mode; E/e – ratio of E and e; IVRT – time of isovolumic relaxation of LV; EDVD – endothelium-dependent vasodilatation; EF – ejection fraction; CA – carotid artery; IMT – intima-media thickness; LVM – left ventricular mass; LVMI – left ventricular mass index; PWV – pulse wave velocity (cPWV – carotid artery, aPWV – abdominal aorta); RAV – right atrial volume; LAV – left atrial volume; TIVSd – thickness of the interventricular septum (diastole); TIVSs – thickness of the interventricular septum (systole); TPWd – thickness of the posterior wall of the left ventricle in diastole; TPWs – the thickness of the posterior wall of the left ventricle in systole; LVEDD – end-diastolic diameters; LVESD – end-systolic diameters; EDV – end-diastolic volume; ESD – end-systolic volume; RWT – relative wall thickness; LAD – left atrial diameter; AD – aortic diameter.

A negative cross-link between RAAS activity and insulin signal may be responsible for impaired regulation of carbohydrate metabolism and increased risk of cardiovascular events and mortality. More pronounced IR in HRAH was accompanied by significantly (p = 0.000) higher levels of leptin at the specified phenotype of AH, that confirms the association of IR with leptin resistance. At the same time, in the group of hypertensive patients with low renin activity, a lower level of serum aldosterone (p = 0.000) was observed at a higher ARR (p = 0.000) than in the group with a high PRA (Table 1). These features can be explained by the fact that LRAH in population-based studies shows a bimodal distribution of aldosterone levels, which confirms the existence of two broad categories of LRAH: people with low aldosterone levels and people with normal or high aldosterone, whereas the presence of high levels of renin increases the level of angiotensin II (AT II) and aldosterone, which is one of the main mechanisms of regulation of RAAS activity [1, 18, 19].

In the absence of differences in HDL cholesterol and triglycerides, patients with HRAH had higher levels of total cholesterol (p = 0.016) and LDL cholesterol (p = 0.000) compared with patients with LRAH (Table 1). The results can be explained by the directed interaction between RAAS and LDL cholesterol activity: on the one hand, increased RAAS activity is confirmed in unstable atherosclerotic plaques, and on the other hand, increased LDL cholesterol can stimulate RAAS [20]. It is known that blood pressure II stimulates the synthesis and incorporation of cholesterol into the vascular wall, as well as the oxidation of LDL. Moreover, population-based studies suggest that in patients with AH AT II has a stimulating effect on LDL oxidation and their degradation by macrophages [20–22].

Patients with HRAH had higher BP levels than patients with LRAH: the significance of the difference in DBP levels was p = 0.004, the significance of the differences between SBP and mean BP p <0.001 for both indicators (Table 1).

The severity of cardiovascular remodeling in obese hypertensive patients was significantly higher in the HRAH presence. Thus, patients with HRAH had significantly higher CIMT bifurcation (p = 0.003) and cPWV (p = 0.023) compared with patients with LRAH. In addition, in the presence of HRAH, significantly larger sizes of LV and its LVM were noted (Table 2).

More pronounced cardiovascular remodeling in the presence of HRAH was accompanied by a greater imbalance of the oxidative stress system – antioxidant protection in this phenotype AH: the significance of the difference in overall antioxidant protection was p = 0.000, and the significance of differences MDA and DC – p = 0.000 and p = 0.008, respectively (Table 1).

Conclusions

Features of cardiovascular remodeling and neurohumoral status depending on the phenotype of hypertension in patients with concomitant obesity have been established.

Prospects for future research

Further study of the forms and manifestations of different phenotypes of hypertension and, above all, low-renin hypertension will provide an opportunity to expand the pool of hypertensive conditions with known etiology, a similar picture of the disease and biochemical and molecular genetic traits and markers. This will expand the possibilities of disclosing multiple and various, completely incomprehensible causes of the origin of essential hypertension.

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Conflict of interest

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