университета им.И.И.Мечникова. - 2014.- Том 6, № 2 - С.73-77.

14. Сипливый В. А. Лечение осложненных форм колоректального рака / В.А. Сипливый, А.Г. Гузь, Г.Д. Петренко // Харківська хірургічна школа. 2011. № 3. С.35-37.

15. Матвійчук Б. О. Актуальні проблеми невідкладної хірургії колоректального раку / Б.О. Матвійчук, М.Т. Фецич // Шпитальна хірургія. 2015.- № 2. - С.20-23

16. Перегудов С.И. Диастатические разрывы толстой кишки: диагностика и лечение / С.И. Перегудов, Г.И. Синенченко, А.В. Пирогов, Е.С. Банщиков // Скорая медицинская помощь.- 2004. - Т.5, № 3. - С.116-118.

17. Милица Н. Н. Подходы к проблеме хирургического лечения больных с осложненными формами колоректального рака / Н.Н. Милица, В.Б. Козлов, И.Н. Ангеловский // Харківська хірургічна школа. - 2011. - № 3. - С.32-34.

18. Сажин В.П. Комплексное лечение осложненного колоректального рака/ В.П. Сажин, П.А. Госткин, В.И. Соболева, Д.А. Сяткин // Хирургия.- 2010. -№7.-С.15-19.

19. Севостьянов, В. В., Кутуков В.В. Неотложная онкохирургия рака толстой кишки / В.В. Севостьянов, В.В. Кутуков // Вестник Российской Военно-медицинской академии. Приложение. - 2008. - № 4 (24). - С. 151.

20. Семенцов К.В. Интраоперационная санация толстой кишки в лечении опухолевой толстокишечной непроходимости: Автореф. дис. ... канд. мед. наук. 2010. С.14.

21. Шамолин М.А. Хирургическое лечение больных осложненными формами рака толстой кишки: Автореф. дис. ... д-ра мед. наук.М. 2012. С. 17.

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GENDER SPECIFIC DIFFERENCES IN THE EFFECTS OF ANTIHYPERTENSIVE THERAPY ON ARTERIAL HEMODYNAMIC, ARTERIAL WALL STIFFNESS AND STRUCTURE-FUNCTIONAL CONDITION OF THE HEART IN PATIENTS OVER 65 YEARS OLD WITH UNCOMPLICATED ARTERIAL HYPERTENSION

Abstract. In this research we have investigated in 65 years old non-diabetic patients with uncomplicated arterial hypertension, the influence of two types of antihypertensive treatment based on a renin-angiotensin system inhibitor (RAS) and a dihydropyridine calcium channel blocker (CCB) ± thiazide-like diuretic (indapamide) on central and brachial blood pressure (BP) hemodynamics and in several cardiac and vascular structure-function parameters. We included 174 patients from two centers (83 males and 91 females). After 6 months a total of 158 patients finished the study. We found that amlodipine + indapamide therapy was more effective than RAS inhibitors + indapamide in reducing brachial and central systolic BP, and central pulse pressure in males. In addition, and regardless of gender, the calcium channel blocker therapy achieve a greater reduction on left ventricle

pulsatile load (measured by augmentation markers), on arterial stiffness (measured by carotid-femoral pulse wave velocity) and regression of LV hypertrophy. Therapy with amlodipine plus indapamide was associated with an increase in heart rate.

Summary. Amlodipine plus indapamide is more effective than indapamide with RAS inhibitor to improve several target organ damage in mild-moderate hypertensive patients.

Key Words: arterial pressure, arterial hypertension, arterial wall stiffness, structure-functional condition of the heart

INTRODUCTION

Age is an important determinant in the development of arterial hypertension (AH), which is largely associated with artery consolidation due to age-related changes and other risk factors [5]. There is evidence that in the elderly, the frequency of hypertension in females is greater than that of males [3, 16], which manifests with higher levels of blood pressure (BP) [13]. It is considered a consequence of a rapid increase in arterial wall stiffness [3, 13]. The central systolic (cSBP), pulse pressure (cPP), rigidity markers of the arteries (in particular, the pulse wave velocity (PWV)) is significant markers of target organ damage and independent predictors of cardiovascular morbidity and mortality in patients with AH [14, 24].

There is an evidence that various classes of antihypertensive drugs (AHD), with the same effect on bBP have a different effect on the central BP (cBP) [8, 13, 29], which can explain the differences in the frequency of cardiovascular events [30].

The selection of antihypertensive therapy (AHT) is so important for elderly patients regarding to the cSBP and cPP and arterial wall stiffness which increased with the age. This was the main reason why β- blockers were excluded from the list of first line drugs in these group of patients [11].

There are data on the gender differences in the pulse wave indices and cBP [16, 27], which are consistent with the higher tendency to diastolic dysfunction of the left ventricle (LV) and the development of heart failure in females [7]. This determines the importance of gender specific comparative evaluation in efficacy of various AHD, non β-blockers, and their combined effect on bBP, cBP and rigidity of arteries in elderly patients. Similar studies are almost absent.

The objective of the study: to evaluate 6 month (M6) treatment by renin-angiotensin system inhibitor (RAS) and dihydropyridine calcium channel blocker (CCB) ± indapamide on the variability of brachial and central arterial pressure, elastic properties of the arteries and structure-functional condition of the heart, in patients over 65 years old with mild to moderate non-diabetic uncomplicated arterial hypertension (AH).

MATERIALS AND METHODS.

An open, prospective, randomized, two-centered study with a blinded assessment of endpoints were included 174 patients (83 males and 91 females) aged ≥ 65 years (age 70, 8 ± 0,53 years) with uncomplicated AH 1-2 grades (65.6% and 34.4% respectively).

Data acquisition for the study performed in the Department of Internal Medicine №2 of Bogomolets National Medical University, Kiev, Ukraine and the Hospital Clínico Universitario de Valladolid, Spain in the period of 2012-2019 years.

Inclusion criteria: males and females, 65 to 80 years (on average 70, 7±0, 62 and 70, 4±0, 58, p>0, 05) with AH of 1-2 grades according to the office BP morning measurements; absence of antihypertensive therapy or low adherence for the previous therapy (not taking medications for more than 1 day), withdrawal from therapy in 7 days prior to randomization; absence of exclusion criteria; availability of the written consent.

Exclusion criteria: the presence of secondary hypertension; previous history of myocardial infarction and/or stroke; heart failure with NYHA above functional class (FC) II; signs of stable angina of the III-IV FC; left ventricular ejection fraction (LVEF) <50% ; diabetes; congenital heart diseases; peripheral vascular disease; heart rhythm disturbances (permanent and persistent form of atrial fibrillation, frequent extrasystolic arrhythmia, ventricular paroxysms or ventricular tachycardia in medical history, persistent sinus tachycardia); violation of atrioventricular conduction or sinus bradycardia (heart rate < 50 bpm) or weakness syndrome of the sinus node; impossibility to withdraw previous AHT; obesity with BMI > 35 kg/m²; chronic kidney disease with GFR for EPI <60 ml/min/1.73 m2 and any other clinically relevant concomitant pathology; hyper- (> 5.5 mmol/L) and hypopotassemia (< 3.5 mmol/L).

At the time of randomization, patients did not take AHD or took it irregularly. Patients were excluded from the study in cases of informed consent withdrawal, loss of contact with hospital (non-attending); the occurrence of adverse events that prohibited further participation in the study, the deterioration of the patient condition not related to the present therapy, with a need for additional examinations or prescription of concomitant drugs not permitted by the protocol.

After the initial examination (see below) randomization was performed by the method of blind envelopes into 2 groups. Each group obtained therapy based on angiotensin-converting enzyme inhibitor (ACE inhibitors) or angiotensin II receptor blocker (ARB) in combination with a diuretic indapamide (called group "A") or dihydropyridine CCB amlodipine + indapamide (Group "B"). At the time of randomization, the male to female ratio was approximately 1:1.

Group «A» was prescribed either perindopril or olmesartan in initial, taking into account office BP, for perindopril 5 mg or 10 mg and for olmesartan 20 mg or 40 mg. The choice of drug and dose were determined by the researcher. Group «B» initiated treatment with a

fixed combination of prolonged release indapamide + amlodipine, 1.5 mg + 5 mg respectively.

The initial appointment at the beginning of the AHT study was carried out directly in the office of the researcher. In the first two months visits for assessment antihypertensive efficacy and tolerability of AHT were carried out once in 2 weeks and subsequently – every 2 to 6 months. The purpose of treatment was to achieve the target office bBP (<140/90 mm Hg). When needed the dose of AHD was increased to full therapeutic, and, if necessary, added indapamide 2.5 mg once per day in group "A". Increase in the dose of indapamide+amlodipine combination to 1.5/10 mg was respectively in group "B".

47 patients (27.0% per protocol) who took β-blockers for possible stable angina I-II FC, tachycardia and extrasystoles before inclusion in the study, continued therapy without changes. In all cases, the dose did not exceed 50% of the total therapeutic. Patients who received statins and aspirin before the inclusion in the study, proceeded, and if this was not the case they were prescribed them at the beginning, in the presence of indications and the absence of contraindications [22].

All of patients were interviewed in each visit for healthy and bad lifestyle habits, nutrition quality.

Before inclusion to the study, patients were examined additionally by general clinical examination, routine laboratory clinical and biochemical studies, measurements of office bBP (brachial systolic, diastolic, pulse, mean BP (bSBP, bDBP, bPP, mean bBP) using a mechanical tonometer Microlife BP AG1-30. The diagnosis of coronary heart disease was established using treadmill-test. In accordance with the purpose of the study and the endpoints (see below) at the beginning of the study (M0) and at the end of 6 months of treatment (M6), applantation tonometry was performed using the SphygmoCor device AtCor Medical (Australia) and Doppler-Echo by the ultrasound diagnostic system of the Hitachi ALOKA Medical.

According to the pulse wave analysis by applanation tonometry [15], we determined central systolic, diastolic, pulse, and mean BP (respectively, cSBP, cDBP, cPP, mean cBP), augmentation pressure (AP), augmentation index (AIx), augmentation index, normalized for a pulse rate of 75 beats/min (AIx75), amplification pressure (PPampl.), and measured carotid-radial (PVWrad.) and carotid-femoral pulse wave velocity (PWVfem). The amplification pressure was was calculated as the ratio between bPP and cPP (%) [2].

Doppler echocardiography was performed according to the recommendations of the American Society of Echocardiographs [20]. The morphologic-functional condition of the heart, left ventricular end-diastolic dimension (LVED) and volume (EDV), end-systolic volume (ESV), cardiac output (CO), LVEF, interventricular septum thickness (IVS), left ventricular posterior wall thickness (LVPW), relative LV wall thickness (RWT), left atrial volume, volumes of LV and left atria were adjusted to the body surface area and expressed as the corresponding indices of (EDI, ESI, stroke volume (SV), LAVI). The total peripheral vascular resistance (TPVR) was calculated as follows TPVR = bSBP/CO.

Left ventricle mass (LVM) was determined by the formula PennConvention [9] and adjusted to the body surface area (LVMI). Left ventricular hypertrophy (LVH) was diagnosed with values of the left ventricular myocardial mass index (LVMI) ≥ 115 g/m2 for males and ≥ 95 g/m2 for females [22].

Evaluation of LV diastolic function were obtained by pulse doppler echocardiography according to the standard method [20]: E - is a peak velocity of early diastolic transmitral flow, A - is peak velocity of late transmitral flow, E/A is the ratio between the amplitudes waves E and A, DT - deceleration time, IVRT - isovolumetric relaxation time. The method of tissue dopplerography measured the transtricuspid velocity (TR velocity), maximum velocity of diastolic waves in the movement of the septal and lateral parts of the mitral valve ring (e` sept. and e` lat.), calculated by the ratio of the maximum velocity of early diastolic filling of LV (E) to the mean value e` sept. and e` lat. movement of the mitral ring (E/e`).

According to the Flachskampf F. A. recommendations (2015) [10] the presence of diastolic dysfunction severity are on the basis of LAVI≥34 ml/m2, e` septal ≤8 cm/s, e`lateral ≤ 10 cm/s. Patients were divided into three stages respectively coefficient E/A < 0,8, DT □ 200 ms, E/e` □9 (grade I); E/A 0.8 - 1.5, DT 160 - 200 ms, E/e ' 9 -12 (grade II); E/A □ 2, DT □ 160 ms, E/e` □ 12 (grade III) [10]. According to recommendations (2016) for the evaluation of LV diastolic function an updated from American Society of Echocardiography and the European Association of Cardiovascular Imaging determined (E/e` >14, e ′septal ≤ 7 cm/s, e ′ lateral ≤ 10 cm/s, TR velocity > 2,8 m/sec, LAVI≥34 ml/m2), <50% change - normal diastolic function, 50% - indeterminate, >50 % - diastolic dysfunction [23].

The rate of glomerular filtration (GFR) was determined by the calculation method according to the CKD - EPI formula, approved by KDIGO 2013 recommendations [17].

The endpoints of the study were office dynamics of bSBP, cSBP, AIx75, PPampl., ΔPWV fem., LVMI, E/e` .

The statistical analysis was conducted using the IBM SPSS Statistics 19 program. All values are given in the form M ± m, where «M» is the average value of the indicator, «m» is the standard error of the average. During the statistical analysis, the criteria of the Student and the nonparametric criteria for independent samples and the Spirman`s correlation analysis were used. To compare categorical variables, the $\chi 2$ test was used. Statistically significant differences were considered at $p < 0,05$.

RESULTS. A total of 158 patients (90.8%) completed the study follow up and the specific evaluation, including 69 in group A (33 males and 36 females) and 89 in group B (39 males and 50 females). During the study course 16 (9, 2%) of patients were excluded, 9 (5, 2%) due to the lost contact with researcher, 7 (4, 0%) due to the

development of side effects. Specific side effect were following – cough in 2 patients in the group A; lower limbs edema in 3 patients and reddening of the face in 2 patients in group B. 7 patients from group B manifested with small peripheral edema that did not require withdrawal of the drug.

Table 1 shows the clinical characteristics of patients in 4 groups (data per protocol) at the time of inclusion in the study, according to which the groups were comparable (p 0,05), with factors potentially affecting the level of cBP such as age, BMI, smoking, glucose and cholesterol levels, bSBP, and heart rates (HR) [15, 37]. Additionally same gender patients in group A and B had comparable height (p>0,05).

Most common previous AHD among patients (Table 2), were the treatment with ACE inhibitors. Treatment of 4 groups patients during the study are presented in Table 2. Males and females in group A were comparable in the distribution of RAS inhibitor type (ACEi or ARB in the ratio of 1: 1) and the dose level (mainly in full therapeutic), and the comparability of all 4 groups in the frequency of continuation of previous therapy with β-blockers in doses ≤50% of the total amount, as well as statins and aspirin (p>0,05).

Table 1.

CLINICAL CHARACTERISTICS AND CARDIOVASCULAR RISK FACTORS IN PATIENTS OF FOUR GROUPS

Indicator	Group A (n = 69)		Group B (n = 89)	
	Male (n = 33)	Female (n = 36)	Male (n = 39)	Female (n = 50)
Age, years	71,1±0,93	70,5±0,88	70,3±0,93	70,3±0,72
Newly diagnosed AH	15 (45,5%)	13 (36,1%)	12 (30,8%)	19 (38,0%)
Duration of AH, years	17,8±1,53	18,6±1,81	17,6±1,77	18,6±1,57
Grade of AH: 1st 2nd	21 (63,6%) 12 (36,4%)	22 (61,1%) 14 (38,8%)	26 (66,7%) 13 (33,3%)	32 (64,0%) 18 (36,0%)
Stable angina of I-II FC	10 (30,3%)	12 (33,3%)	17 (43,6%)	20 (40,0%)
Smoking, n	5 (15,2%)	4 (11,1%)	10 (25,6%)	9 (18,0%)
BMI, kg/m²	30,6±0,74	31,9±1,19	28,8±0,69	29,7±0,81
BMI >25, n	24 (72,7%)	26 (72,2%)	28 (71,8%)	38 (76,0%)
Height, sm	173,9±1,58	163,4±0,88 °°°	171,6±1,34	163,7±0,82 °°°
bSBP, mm hg	152,0±1,56	153,7±2,01	157,0±2,18	154,6±1,38
HR, bpm	65,3±1,35	66,8±1,16	65,0±1,35	66,1±0,94
TCh, mmol/L	5,6±0,24	6,03±0,23	5,4±0,24	6,2±0.19
LDL cholesterol,mmol/L	3,33±0,16	3,36±0,18	3,27±0,16	3,79±0,17
Glucose, mmol/L	4,93±0,10	5,29±0,13	5,06±0,11	5.16±0,10
GFR, ml/min/1.73m2	86,4±1,19	69,3±1,17 °°°	83,2±1,11	69,4±1,09 °°°

Note**:** p<0,05; p<0,01; p<0,01 in comparison with the markers of different gender patients M0

Table 2.

TREATMENT OF PATIENTS IN FOUR GROUPS

Indicator	Group A (n = 69)		Group B (n = 89)	
	Male (n = 33)	Female (n = 36)	Male (n = 39)	Female (n = 50)
Initial inclusion: -ACE inh./ARB -CCB -thiazides -β-blockers	14(42,4%) 5 (15,2%) 4 (12,1%) 8 (24,2%)	11 (30,5%) 7 (19,4%) 5 (13,9%) 5 (13,9%)	13 (33,3%) 8 (20,5%) 6 (15,4%) 8 (20,5%)	19 (38,0%) 6 (12,0%) 5 (10,0%) 7 (14,0%)
Study ending (M6):				
- perindopril including a dose of 10mg	17 (51,5%) 14 (42,4%)	19 (52,8%) 17 (47,2%)	0 0	0 0
-olmesartan including a dose of 20mg including a dose of 40mg	16 (48,5%) 5 (15,2%) 14 (42,4%)	17 (47,2%) 5 (13,8%) 14 (38,9%)	0 0 0	0 0 0
-amlodipine * including a dose of 10mg	0 0	0 0	39 (100%)	50(100%)
-indapamide	28(84,8%)##	32(90,0%)##	39 (100%)#	50 100%)#
β-blockers * *	9 (27,3%)	8 (22,2%)	9 (23,1%)	8 (16,0%)
statins , n (%)	33 (100%)	36 (100%)	39 (100%)	50 (100%)
aspirin , n (%)	13 (39,4%)	13 (36,1%)	19 (48,7%)	24 (48,0%)

Note: * - as part of the combination drug, # - prolonged release indapamide 1.5 mg in the combination drug, # # - indapamide in 2.5 mg dose,** - β-blockers in the dose ≤ 50% of the total

As can be observed from the data in Table 3, males and females from groups A and B were comparable at baseline (M0) of all indicators of office bBP, as well as cBP, TPVR and HR (all p>0,05). After six months of treatment in males and females in both groups values of bSBP, bDBP, bPP, mean bBP were accompanied by a decrease in cSBP, cDBP, cPP, mean cBP, TPVR (Table 3, p□0,01, p□0,001). The magnitude of BP decrease in males and females in the group of RAS inhibitors was not significantly different. In the CCB group, the absolute reduction in cSBP in females was lower than in males (–21,8±1,81 mm Hg, -26,4±2,19 mm Hg, p <0,05).

Table 3.

DYNAMICS OF BP AND PULSE WAVE INDICES IN FOUR GROUPS OF PATIENTS

Indicator	Group A (n = 69)				Group B (n = 89)			
	Men n = 33	Women n = 36	Men	Women	Men n = 39	Women n = 50	Men	Women
	M0	M0	M6	M6	M0	M0	M6	M6
bSBP, mm Hg	152,0±1,56	153,7±2,01	131,6±1,76***	132,5±1,89***	157,0±2,18	154,6±1,38	128,1±1,51***	127,4±1,12*** °°
ΔbSBP, mm Hg	-	-	-20,8±2,53	-21,3±2,61	-	-	-29,3±2,65##	-27,1±1,76°
bDBP, mmHg	89,1±1,68	93,2±1,89	80,2±1,17***	80,8±1,40***	91,89±1,65	89,4±1,48	78,4±1,0***	78,0±0,76*** °°
bPP, mmHg	62,2±2,0	60,1±2,03	52,1±1,78***	52,3±1,38***	65,1±1,95	62,2±1,50	49,6±1,27***	49,5±1,11***
ΔbPP, mm Hg	-	-	-13,9±2,71	-11,4±2,71			-18,8±2,14#	-15,8±1,67
cSBP, mm Hg.	138,4±1,48	141,7±2,04	122,6±1,90***	125,0±1,82***	145,1±1,69	139,2±1,49	118,7±1,53***	117,1±1,09***°°
ΔcSBP, mm Hg	-	-	-15,8±2,83	-16,0±2,4	-	-	-26,4±2,19##	-21,8±1,81°
cDBP, mmHg	87,8±1,54	91,5±1,74	80,6±1,07***	83,2±1,54***	91,0±1,56	88,4±1,34	80,5±0,81***	78,2±0,75***°°
cPP, mmHg	50,6±1,89	49,6±2,09	42,0±1,54***	41,8±1,33***	54,2±1,52	51,0±1,57	38,1±1,25***	38,3±1,05***
ΔcPP, mm Hg	-	-	-8,9±2,61	-7,6±2,73			-15,4±1,85#	-12,4±1,83
Mean bBP, mm Hg	110,1±1,39	113,3±1,64	97,0±1,13***	100,0±1,43***	113,6±1,60	110,1±1,25	95,4±1,03***	94,5±0,73***
Mean cBP, mmHg	104,7±1,23	108,3±1,57	96,0±1,10***	97,9±1,51***	109,0±1,44	105,4±1,21	92,7±0,93***	91,7±0,73***
TPVR, mm Hg/ml	2,06±0,10	2,19±0,10	1,89±0,08**	2,06±0,10*	2,18±0,09	2,16±0,06	1,84±0,07**	1,90±0,05**
HR, bpm	65,3±1,35	66,8±1,16	64,6±1,16	67,3±1,11	65,0±1,35	66,1±0,94	70,5±0,85***###	70,1±0,69**°
AP, mm Hg	15,5±1,17	17,3±0,96	13,9±0,92	15,3±1,13	17,2±1,02	15,8±0,78	12,3±0,85**	11,9±0,60***°°
AIx, %	31,1±1,63	34,5±1,29	28,7±1,50	30,5±1,49	32,8±1,29	34,06±1,03	27,5±1,17**	28,6±0,84***
AIx75, %	27,4±1,52	30,7±1,21	26,1±1,39	27,2±1,17*	28,0±1,14	30,0±1,03	23,6±1,01**	24,6±0,78***°
ΔAIx75, %	-	-	-1,5±2,29	-4,42±2,09	-	-	-4,43±1,44	-5,36±1,35#
PPampl., %	122,3±2,40	119,0±1,60	125,2±1,91	124,2±1,87*	120,0±1,58	119,2±1,24	130,4±1,46***#	129,6±1,21***°
PWVrad, m/s	9,3±0,33	10,3±0,36	8,8±0,24	9,4±0,24	10,4±0,32	10,3±0,32	8,9±0,18***	8,8±0,17***°°
ΔPWVrad, m/s			-0,61±0,37	-0,53±0,35			-1,46±0,39	-1,44±0,35
PWV fem , m/s	11,5±0,29	11,6±0,38	10,3±0,28**	10,6±0,31*	12,3±0,38	12,6±0,31	10,0±0,25***	10,4±0,18***
ΔPWVfem, m/s			-1,21±0,38	-1,10±0,37			-2,35±0,46#	-2,24±0,37°

Note 1:
Statistically relevant difference in scores after the treatment * p <0.05; ** p <0.01; *** p <0.001.
Statistically relevant difference in scores in females after the treatment° p < 0,05; °° p < 0,01; °°° p <0,001.
Statisitcally relevant difference of scores in males after the treatment # p <0.05; ## p <0.01; ### p <0.001.

Note 2: bSBP, bDBP, bPP, mean bBP - brachial systolic, diastolic, pulse, mean blood presure; cSBP, cDBP, cPP, mean cBP - central systolic, diastolic, pulse, and mean BP; AP-augmentation pressure; AIx-augmentation index; AIx75 - augmentation index, normalized for a pulse rate of 75 beats/min; PPampl.- amplification pressure ; PVWrad., PWVfem - carotid-radial and carotid-femoral pulse wave velocity; TPVR - total peripheral vascular resistance.

As a result of treatment, office bBP □ 140/90 mmHg, as a "minimal" therapeutic target was achieved in group "A" in 47 (68,1 %) patients, and in group "B" in 73 (82,0 %) (p□0,05).

Comparing gender-specific effects of two types of treatment, the CCB - based combination had an advantage over such a RAS inhibitor in males with an absolute decrease in cSBP (-15.8 ± 2.83 mm Hg, -26.4 ± 2, 19 mm Hg, p <0.01), and in females in bSBP, cSBP (p <0.01, Table 3).

We found no significant gender differences in the initial values of the augmentation parameters and pulse wave amplification in patients with AH (all p <0.05) (Table 3). Antihypertensive therapy for males and females based on CCB was more effective with positive dynamics of these indicators than treatment based on RAS inhibitors. In males, treatment with RAS inhibitor and indapamide were not followed by a pulsatile load on the LV, whereas combination therapy with CCB+indapamide concluded by a decrease in AP 28.5%, AIx75 to 15,7 %, and PPampl. increasing by 7.7 % (p □0.01 - 0.001) and became 4% higher than its level in group A (p□0,05). Six months later, in women assigned to therapy with CCB+indapamide, compared to patients in group A, AP and AIx75 became 24.7% and 18% lower than PPampl. by 8,1% higher (all p□0,001, Table 3) and increased by 4,2% compared with women of group A (p□0,05). It should be noted that the initial level of PVWfem was slightly lower, however, these differences were not statistically significant.

Combined therapy with amlodipine+indapamide resulted in HR increase in both genders at 5,5 ± 0,53 bpm (7.8%) in males (p<0,01) and 4,1 ± 0,62 bpm (5.7%) in females (p<0,01). This effect was absent in group «A».

The presence of statistically significant correlations in males of group B of the values of AP , PPampl. with a HR at baseline (r = -0,511, r = 0,566, all p<0,01) and 6 months (r = -0,521, r = 0,514, all p<0,01) and absolute changes in AP and PPampl. (ΔAP i ΔPPampl.) with ΔHR (r = -0,581, r = 0,532, all p<0,01) suggests the positive effect of this AHT. Due to an increase in HR we considered to the augmentation wave, which corresponds to the literature data [7, 8]. Although, in females receiving amlodipine+indapamide therapy, such correlation rates of HR with AP were absent in M0 (r = -0,181, p>0,05), PPampl. (r = ,358, p<0,01) and M6 (r = -0,009, r = 0,23, all p>0,05), as well as ΔHR with ΔAP i ΔPPampl. (r = -0,037, r = 0,268, all p>0,05). That is, a decrease in aortic pressure that forms a retrograde pulse wave in females during diuretic with CCB treatment did not increase HR significantly. It is established that in addition to HR, the retrograde pulse wave can be influenced by bSBP [24, 27]. However, significant correlations ΔbSBP with ΔAP, ΔAIx75 and ΔPPampl. were absent in males (r = 0,023, r = -0,164, r = 0,161, r = 0,258, all p>0,05), and in females (r = 0,243, r = 0,135, r = -0,145, r = 0,265, all p>0,05).

Initial measurements of PWVfem and PWVrad in males and females with AH did not differ significantly (Table 3., p>0,05).

In the absence of significant changes in the rigidity of the muscular type arteries in the RAS inhibitors group, PWVrad decreased significantly in both genders receiving CCB and diuretic therapy (Table 3., all p<0,001).

The indicator of arteries elastic type rigidity is PWVfem. It was decreased in both type of treatment on the RAS inhibitors and CCB, and almost identically in both males and females of both groups (p<0,05-0,001, Table 3). However, with the mean absolute drop in ΔPWVfem CCB+ indapamide had little benefit before using a combination of RAS inhibitors±diuretic in males (-2,35±0,46 m/s vs. -1,21±0,38 m/s, p<0,05) and women (-2,24±0,37 m/s vs. -1,10±0,37, p<0,05). This significant correlation ΔPWVfem with ΔHR in both men and women were missing, as in group A (men r = -0,143, women r = 0,1 33 all r>0,05) , and in group B (r = -0,011, r = 0,12 respectively, all p>0,05). We also did not find significant correlation between ΔPWV with ΔbSBP and ΔcSBP, regardless of the type of treatment and gender (Table 4.).

Table 4

CORRELATION BETWEEN CHANGES IN BP AND PULSE WAVE VALUES, ARTERIAL STIFFNESS AND LV HYPERTROPHY, DEPENDING ON THE TYPE OF AHT AND GENDER

	ΔAP		**ΔAIx75**		**ΔPPampl.**		**ΔPWVfem**		**Δ LV MI**	
	men	**woman**	**men**	**woman**	**men**	**woman**	**men**	**woman**	**men**	**woman**
Group A										
ΔbSBP	0.027	0.219	0.036	0,236	-0.244	-0.166	0,208	0.249	0.282	0.154
ΔcSBP	0,256	0.23	0.128	0,215	-0.295	-0.28	0.034	0.26	0,209	0.24
Δmid.bBP	-0.113	-0.104	-0.036	0.078	-0.132	0.008	0.112	0,139	0,299	-0.2
Δmid.cBP	-0.058	-0.156	0,028	0.09	-0.116	0.015	0.002	0.169	0,266	-0.055
Group B										
ΔbSBP	0.023	0.243	-0.164	0.135	0.161	-0.145	0.258	0.265	0.32	0.095
ΔcSBP	0.251	, 283 *	0.024	0,118	-0,006	-0.142	0,266	0.271	0,296	0,097
Δmid.bBP	-0.171	-0.043	-0.252	0.044	0,242	0.025	-0.018	0.048	0.293	0,097
Δmid.cBP	-0.119	0.066	-0.181	0.092	0.195	-0.041	-0.05	0.115	, 335 *	0.065

Note: * - the correlation is significant at the level of 0.05; ** - the correlation is significant at the level of 0.01

In the start of the study we identified moderate increase the LV PW and IVS thickness (Table 5.) with the formation of LV hypertrophy. According to the LV MI was observed it in 28 (70,0 %) females and 24 (60, 0 %) males that were randomized to group A and 42 females (80, 7%) and 22 (62, 5 %) males that were randomized to group B (p>0,05). In the absence of gender differences in the mean values of LV MI (p>0,05), signs of LV diastolic dysfunction was noted in a small number of patients – 8 (4,6%): I stage in 5 (2,8%) patients, II stage in 3 (1,7%). According to the recommendations none of the patients had signs of increase the pressure in the left atrium (III stage) [10, 23].

After 6 months of treatment, patients receiving the combination of diuretic+CCB therapy had a significant decrease in EDI and SV(p<0,05, Table 5), which was probably related to increase in HR (p<0,05). There was decrease LV MI dynamics a in both genders in group «B» (by 14.6% and 11.2%, p<0.05-0.01) with the absence of changes in group «A» (p>0,05). Absolute values reduction of the LV MI (ΔLV MI) did not correlate either with ΔbSBP nor with ΔcSBP in patients of both genders (p <0.05, Table 4), but correlated in males with ΔHR (r = ,375, p<0,05) and with Δmid.bBP (r = ,363, p<0,05) in the absence of such data in females. Decrease in the LV MI in group «B» at the end of the study (M6) correlated with a reduction in bSBP and cSBP in males (r = ,412, r = ,432, p<0,05-0,01) in the absence of this markers in females of this group (r = ,073, r = ,179, p>0,05).

Table 5

VARIABILITY OF DOPPLER-ECHOCARDIOGRAPHIC PARAMETERS OF THE STRUCTURE-FUNCTIONAL CONDITION OF THE HEART IN PATIENTS OF FOUR GROUPS

Indicator	Group A (n = 69)				Group B (n = 89)			
	Men n = 33	Women n = 36	Men	Women	Men n = 39	Women n = 50	Men	Women
	M0	M0	M6	M6	M0	M0	M6	M6
EDI, ml/m2	56,4±2,78	55,6±1,82	55,4±2,46	53,4±2,15	57,6±2,14	57,5±1,65	52,1±1,88*	52,4±1,67*
ESI, ml/m2	22,3±1,37	21,4±1,0	22,7±1,30	21,1±1,18	23,3±1,25	22,9±1,04	21,2±1,14	20,6±1,02
SV, ml/m2	34,1±1,63	34,1±1,10	32,6±1,38	32,3±1,23	34,4±1,13	34,6±0,76	31,0±1,10*	31,8±0,85*
EF,%	59,7±0,91	60,0±0,88	59,4±0,83	60,2±0,91	58,7±0,79	60,1±0,74	60,7±0,63*	61,7±0,74
IVS, sm	1,27±0,03	1,21±0,02	1,25±0,03	1,18±0,02	1,26±0,03	1,2±0,02	1,19±0,02*	1,11±0,03*
LVPW, sm	1,16±0,02	1,15±0,02	1,16±0,02	1,13±0,02	1,17±0,02	1,14±0,01	1,11±0,02*	1,08±0,02**
LVMI, g/m2	113,8±5,42	118,5±4,26	112,4±4,89	115,8±4,52	121,5±5,91	122,6±2,93	103,8±4,0*	108,9±2,77**
ΔLVMI, g/m2	-	-	-1,7±6,59	-3,18±5,46	-	-	-17,6±1,01##	-13,65±4,12°
RWT, units	0,48±0,02	0,48±0,01	0,49±0,02	0,47±0,01	0,48±0,01	0,46±0,01	0,47±0,01	0,46±0,02
LAVI, ml/m2	31,4±1,71	34,6±1,56	29,9±1,54	32,2±1,46	30,75±1,98	29,4±1,76	27,1±1,25	28,01±0,86
E/A , units	0,92±0,04	0,83±0,04	1,14±0,21	0,82±0,03	0,77±0,03	0,86±0,05	0,78±0,02	0,83±0,02
DT, ms	233,2±12,7	235,2±12,7	221,3±11,0	232,7±12,73	238,4±12,4	226,7±9,25	227,2±10,3	229,1±7,65
IVRT, ms	104,0±2,82	102,5±2,17	104,5±2,52	104,3±2,34	109,0±3,01	107,2±2,09	108,7±2,81	106,1±2,10
TR velocity, cm/sec	260,4±8,03	271,0±9,27	247,6±8,58	254,5±8,92	256,0±7,73	247,5±7,75	224,6±6,07**	224,4±6,83*
e sept., cm/s	7,5±0,35	7,73±0,23	7,4±0,32	7,59±0,22	6,8±0,23	7,4±0,23	6,6±0,18	7,3±0,18
e lat., cm/s	9,1±0,29	8,89±0,26	8,5±0,23	8,63±0,20	8,4±0,32	8,4±0,23	8,3±0,28	8,3±0,20
E/e	8,5±0,47	8,65±0,45	7,8±0,29	8,38±0,37	8,7±0,41	8,6±0,36	8,0±0,28	7,71±0,20*

Note 1:
Statistically relevant difference in scores after the treatment * p <0.05; ** p <0.01; *** p <0.001.
Statistically relevant difference in scores in females after the treatment° p < 0,05; °° p < 0,01; °°° p <0,001.
Statisitcally relevant difference of scores in males after the treatment # p <0.05; ## p <0.01; ### p <0.001.

Note 2: EDI - left ventricular end-diastolic index, ESI - end-systolic index, SV - stroke volume, EF - left ventricular ejection fraction, IVS - interventricular septum thickness, LVPW - left ventricular posterior wall thickness, LAVI - left atrial volume index, RWT -coefficient of the relative LV wall thickness, LVMI - left ventricle mass index, E - peak velocity of early diastolic transmitral flow, A - peak velocity of late transmitral flow , E/A- ratio between the amplitudes waves E and A, DT - deceleration time, IVRT - isovolumetric relaxation time, TR velocity - transtricuspid velocity, e` sept. and e` lat. - maximum velocity of diastolic waves in the movement of the septal and lateral parts of the mitral valve ring, E/e`- calculated by the ratio of the peak velocity of early diastolic transmitral flow of LV (E) to the mean value e` sept. and e` lat. movement of the mitral ring.

CCB therapy with indapamide was accompanied by an increase in HR (an average of 4.8 ± 0.57 bpm.) and a reliable correlation between PWVfem with bSBP and cSBP at the end of the study in males (r = ,382, r =

,416, p<0,05) and in females (r = ,299, r = ,315, p<0,05). In group A, the same correlation was noted only in males (r = ,380, r = ,404, p<0,05), but not in females (r = 0,25, r = 0,181, p>0,05).

Among the markers of diastolic LV function, reduction dynamics by 11.4% (p<0,05, Table 5) was observed in E/e` only in females who received CCB-based therapy. E/e` reduction in females can be attributed to regression of LV hypertrophy, verified by the correlation between the absolute values of reduction of LVM with E/e` (r = ,357, p<0,05) that was absent in males (r =0,146, p >0,05). The absence of changes in other markers of diastolic function, including e`, LAVI, E/A, DT, IVRT, point that those changes may be random.

DISCUSSION.

Definition of gender differences in the effect of various types of AHT in patients with AH on the pulse wave index is so actually. This is due to available data on the increase of cSBP, AIx75 and PWVfem. in females, compared to males [3, 25, 26]. Gender differences in the central hemodynamic and arterial wall stiffness have been partly explained by hormonal causes, endothelial function, height, aortic size, HR [12, 15]. Although according to research results of Russo et al. differences in height and HR do not fully explain gender differences in parameters of arterial wall stiffness [27].

Evaluation of gender differences was not the aim of our study, and absence of these differences may be due to the relatively small number of examined patients and inclusion criteria, for instance, the limitation on the degree of AH (1st and 2nd grades) and NYHA FC (not more than II FC). Although received results of our treatment, demonstrated a significant decrease in the office BP in the both genders. The magnitude in achievement of the BP<140/90 recommended by the European Society of Cardiology as target by September 2018 [11] was suboptimal and worse in treatment based on RAS inhibitors (68,1%) than on the CCB basis (82.0%, p <0.05).

Comparative studies of the effect of various AHD combinations that would not include β-blockers, on the markers of central aortic pressure and PWV in individuals over 65 years, are almost absent. Only one study [13] compared the effect of the combination of sartans and amlodipine with diuretic in females after menopause, but they were significantly younger (mean age 61 years), and hydrochlorothiazide was used as a diuretic, which is not an optimal choice, because it is less effective than indapamide[1, 13]. Obtained results by these authors regarding the comparative efficacy of the two regimens of AHT on brachial and central BP and the reduction of PWVfem differ from the results of our study in females ≥65 years, which revealed a significant advantage of the combination based on CCB therapy. Although in our study, unlike Hayoz D. (2012), combination CCB+diuretic was accompanied by an increase in HR in patients of both genders, with absolute values in females, 4.1 ± 0.62 bpm, 5.5 ± 0.53 bpm in males. The HR at 6 months and its absolute increase did not correlate with cSBP, ΔcSBP and PWVfem, Δ PWVfem in either females or males, which indicates the significance of the HR increase. As can be observed in a number of studies [8, 29], the decrease in HR during AHT using β-blockers, was associated with an increase in AIx and cSBP, as well as PWVfem. However, the literature lacks research on the effects of AHT on BP, reflection of pulse wave and its velocity in conditions of increase of HR from the initial level.

Both the changes in HR and the magnitude of the reduction in bSBP and cSBP did not correlate with the decrease of PWVfem. in our patients treated with CCB and diuretic, regardless of gender. This suggests that this AHT may have an BP - independent positive effect on arterial stiffness. Similar data have been obtained by other authors on ACEi, ARB and CCB, but not thiazide diuretics [8, 18, 26, 29, 30]. At the same time, Mackenzie Isla S. with co-authors (2009), who compared the effect of monotherapy lercanidipine, perindopril, and thiazide diuretics on pulse wave indeces in patients of both genders ≥60 years, on average 69 years old, with a marked decrease in bBP and cBP did not reveal significant changes in PWVfem. and PPampl. [21].

First time we observed the positive effect of CCB-based therapy on the arterial wall stiffness according to the data of PWVrad in patients of both genders. These effects that were absent in therapy based on RAS inhibitors. It can be explained by the dilation of the small the resistance arteries, which is inherent to the blockage of Ca2+ channels, with the possible additional effect of indapamide, which has the properties of myotropic vasodilator [6]. Further research is important because of observed data in gender differences of absolute reduction in cSBP during CCB+indapamide therapy mostly in males with the same absolute reduction of bSBP and PWVfem. Absence of this data in literature cannot exclude coincidental character of observation.

Taking into account the prognostic significance of cardiovascular events independent of the level of BP in patients with AH, hypertrophy of LV [4, 7, 13], it is important that we obtained the data on the reduction of LV MI in the treatment of the combination of amlodipine+ indapamide in patients of both genders, which did not happen in the comparison group. This can be explained by a more marked decrease in the pulsating load on the LV according to the data of AIx75, AP and ΔcSBP in the basis treatment of CCB compared with RAS inhibitors (p<0,05-0,001,, Table 3), as well as a decrease in EDI (p <0,05, tab. 5). Some authors point out that a more tight coupling of the pulsatile load with hypertrophy of LV, in comparison with bSBP and average hemodynamic pressure, in TPVR [4, 26]. According to one of the meta-analyzes, which included 7684 patients, a statistically significant reduction in the LV MI occurred only in patients receiving CCB compared with other AHD (p<0,02) [28]. Left ventricle mass index decreased from 135 ± 15 g/m 2 to 114 ± 14 g / m2 (p <0,001), which was also accompanied by a decrease e`sept., e` lat. and E/e` (all p<0,001) in patient after 6 months of treatment with valsartan [19].

The absence of significant changes in LV diastolic dysfunction after treatment can be explained by its preservation at the time of inclusion in the study in 8 (4.6%) patients, which corresponds to the selected inclusion criteria. However, there are reasons to think that control of the cSBP level with the preservation of the achievement of the CCB and indapamide by reducing the pulsatile load on the LV according to the indicators of pulse wave augmentation and PWVfem will lead to prevention of further myocardial damage, in particular, its diastolic function.

The clinical value of our study is to establish the ability of a relatively new combination of dihydropyridine CCB with indapamide to contribute to a more marked reduction in arterial wall stiffness than the "traditional" combination of a RAS inhibitor with diuretic, with the most effective representative of this group - indapamide. This advantage was observed in both male and female patients, who are more likely to have complication of "hypertensive heart", and development of preserved EF heart failure [6]. However, due to the predisposition of elderly patients to resistant AH, the use of amlodipine combination with indapamide in most of them will be inadequate, and achievement of the therapeutic goal will require the addition of the RAS inhibitors.

CONCLUSIONS.

1. In patients with AH of 1-2 grades without diabetes, the 6-month combination therapy of amlodipine+ indapamide was more effective over the combination of indapamide with an ACE inhibitor/ARB with magnitude of reduction of bSBP, cSBP, cPP in males, and regardless of gender, on the pulsatile load of LV by augmentation markers, reduction of arterial wall stiffness according to PWVfem. and regression of LV hypertrophy.

2. Therapy with amlodipine+indapamide was accompanied by increase in the heart rate (an average of 4.8 ± 0.57 beats/min.). The heart contraction rate did not correlate with the values of cSBP and arterial wall rigidity (PWVfem.). The decrease in PWVfem. in patients of both genders did not correlate with the values of reduction in bSBP, cSBP, LVMI, in the presence of such a correlation at the end of the treatment.

REFERENCES

1. Agnoletti Dl, Zhang Y, Borghi C, Blacher J, Safar ME. Effects of antihypertensive drugs on central blood pressure in humans: a preliminary observation. American Journal of Hypertension. 2013;26(8):1045-52 doi: 10.1093/ajh/hpt081

2. Avolio AP, van Bortel LM, Boutouyrie P, Cockcroft JR, McEniery CM, Protogerou AD, et al. Role of pulse pressure amplification in arterial hypertension: experts' opinion and review of the data. Hypertension. 2009; 54(2):375-83. doi: 10.1161/HYPERTENSIONAHA.109.134379.

3. Bordin PB, Filho SRF. Comparison between Central and Brachial Blood Pressure in Hypertensive Elderly Women and Men. Int J Hypertens. 2017(3):1-5 - ID 6265823. doi: 10.1155/2017/6265823.

4. Caballero-Gonzalez FJ. Calcium channel blockers in the management of hypertension in the elderly. Cardiovasc Hematol Agents Med Chem. 2015;12(3):160-5.
DOI: 10.2174/1871525713666150310111554

5. Chen Y, Shen F, Liu J, Yang GY. Arterial stiffness and stroke: de-stiffening strategy, a therapeutic target for stroke. Stroke Vasc Neurol. 2017;2(2):65-72. doi: 10.1136/svn-2016-000045.

6. Christopher JB, Ruth P, Jan AS, et al. Fracture risk and the use of a diuretic (indapamide SR) ± perindopril: a substudy of the Hypertension in the Very Elderly Trial (HYVET). Trials journal.2006;7: 33 doi:10.1186/1745-6215-7-33

7. Coutinho T, Borlaug B, Pellikka P, et al. Sex differences in arterial stiffness and ventricular–arterial interactions. J. Am. Coll. Cardiol. 2013;61:96–103. doi: 10.1016/j.jacc.2012.08.997.

8. Dahlof B, Sever PS, Poulter NR, et al. ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet. 2005;366: 895–906 DOI:10.1016/S0140-6736(05)67185-1

9. Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findigs. Amer. J. Cardiology. 1986;57: 450-458

10. Flachskampf FA, Biering-Sørensen T, Solomon SD et al. Cardiac Imaging to Evaluate Left Ventricular Diastolic Function. JACC Cardiovascular Imaging. 2015;8(9):1071-1093 doi: 10.1016/j.jcmg.2015.07.004.

11. Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults // ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA – 2017 - HYP.0000000000000065

12. Harvey A. et al. Vascular Fibrosis in Aging and Hypertension: Molecular Mechanisms and Clinical Implications. Canadian Journal of Cardiology.2016;32:659-668 DOI: 10.1016/j.cjca.2016.02.070

13. Hayoz D, Zappe D, Meyer M. Changes in Aortic Pulse Wave Velocity in Hypertensive Postmenopausal Women: Comparison Between a Calcium Channel Blocker vs Angiotensin Receptor Blocker Regimen. The Journal of Clinical Hypertension.2012;14(11):773 –778 https://doi.org/10.1111/jch.12004

14. Hodson B, Norton GR, Ballim I, et al. Impact of aortic rather than brachial pulsatile haemodynamics on variations in end-organ measures across the full adult blood pressure range. Journal of Hypertension. 2017;35(12):2443–2453 doi: 10.1097/HJH.0000000000001471

15. Jayesh DS, Hemant BM, Chinmay JS. Aortic

pulse wave velocity and augmentation index@75 measured by oscillometric pulse wave analysis in Gujarati nonhypertensives. Vascular Investigation and Therapy.2018;2(1):50-55

16. Joyner M., Barnes J., Hart E, et al. Neural Control of the Circulation: How Sex and Age Differences Interactin Humans. Comprehensive Physiology. 2015;5(1):193-215. doi: 10.1002/cphy.c140005.

17. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD). Kidney Int. 2017; 7(1):1-59

18. Kim SY, Joo SJ, Shin MS, Kim C. Clinic and Home Blood Pressure Lowering Effect of an Angiotensin Receptor Blocker, Fimasartan, in Postmenopausal Women with Hypertension. Medicine (Baltimore). 2016; 95(22) - e3764. doi: 10.1097/MD.0000000000003764.

19. Kucukler N, Kurt IH, Topaloglu C, Gurbuz S, Yalcin F. The effect of valsartan on left ventricular myocardial functions in hypertensive patients with leftventricular hypertrophy. J Cardiovasc Med (Hagerstown).2012;13(3): 181-6. doi: 10.2459/JCM.0b013e3283511f00

20. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J. Am. Soc. Echocardiogr. 2005;18: 1440-1463.

21. Mackenzie IS, McEniery CM., Dhakam Z, et al. Comparison of the Effects of Antihypertensive Agents on Central Blood Pressure and Arterial Stiffness in Isolated Systolic Hypertension. Hypertension. 2009;54:409-413. DOI: 10.1161/HYPERTENSIONAHA.109.133801

22. Mancia G., Fagard R., Narkiewicz K. et al . 2013 ESH/ESC guidelines for the management of arterial hypertension.Hypertension. 2013;31:1281 – 1357 doi: 10.1097/01.hjh.0000431740.32696.cc

23. Nagueh S, Smiseth OA., Appleton CP, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr.2016;29: 277–314.

24. Narayan O, Davies JE., Hughes AD. Central Aortic Reservoir-Wave Analysis Improves Prediction of Cardiovascular Events in Elderly Hypertensives. Hypertension.2015;65:629-635. DOI: 10.1161/ HYPERTENSIONAHA.114.04824.

25. Panagiota A, Areti T, Stella D. Hemodynamic and Arterial Stiffness Parameters in Ambulatory Blood Pressure Phenotypes and the Clinical Scenario of Polypharmacy and Comorbidities. The Journal of Clinical Hypertension 2015;17(8):655 doi.org/10.1111/jch.12544

26. Ruilope LM. Fixed-Combination Olmesartan/Amlodipine Was Superior to Perindopril + Amlodipine in Reducing Central Systolic Blood Pressure in Hypertensive Patients With Diabetes. J Clin Hypertens (Greenwich). 2016;18(6):528-35 doi: 10.1111/jch.12673.

27. Russo C, Jin Z, Palmieri V, et al. Arterial stiffness andwave reflection: sex differences and relationship with left ventricular diastolic function. Hypertension.2012;60:362–368 doi:10.1161/HYPERTENSIONAHA.112.191148

28. Salvetti M, Paini A, Bertacchini F, et al Changes in left ventricular geometry during antihypertensive treatment.Pharmacol Res. 2018;134:193-199. doi: 10.1016/j.phrs.2018.06.026.

29. Sohn SI, Kim CJ. Modulation of renin-angiotensin system and arterial stiffness: evidence from clinical trials. Curr Hypertens Rev.2014;.10(1):37-40. DOI : 10.2174/1573402110011411111603l1

30. Xiaoming Z, Cheng J, Yeqiang LD. Arterial Stiffness as a Predictor of Clinical Hypertension.The Journal of Clinical Hypertension. 2015;17(8): 582- 591 https://doi.org/10.1111/jch.12556

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DYNAMICS OF IL-6 AND CK-18 CONCENTRATION IN BLOOD PLASMA IN PATIENTS WITH FAMILIAL HYPERCHOLESTERINEMIA WITH NON-ALCOHOLIC STEATOHEPATITIS AGAINST THE BACKGROUND OF STATIN THERAPY AND HEPATOPROTECTOR

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Materials and methods. There was made a comprehensive examination of 71 patients with FHC and NASH and formed groups of patients: I - n = 35 with FHC and NASH receiving rosuvastatin 20 mg / day; II - n = 36 of FHC and NASH who received rosuvastatin and hepatoprotector "Hepadif" 2 capsules three times a day for 90 days. The results were evaluated on the 45th and 90th day of treatment.

Results. With rosuvastatin monotherapy, a decrease in the level of LDL (p = 0.001) and an increase in HDL (p = 0.01) were detected. Transaminase activity and IL-6, CK-18 concentrations tended to decrease but were not statistically reliable. In group II the LDL level reached the target value, transaminase activity was lower (p = 0.001). IL-6 concentration decreased significantly by 28% (p = 0.01), CK-18 - by 36.8% (p = 0.003).