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Possibilities of using two treatment regimen for vascular stiffness correction

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Summary

Objective

To find the optimal regimen of antihypertensive therapy with the most evident effect on elastic properties of blood vessels.

Materials and methods

This study involved male patients 20–70 years old with arterial hypertension without severe somatic diseases and compared vasculoprotective activity of two therapeutic regimens based either on long acting metaprolol tartrate or on fixed combination of amlodipine and lisinopril.

Results

Although both treatment regimen had comparable antihypertensive effect, using fixed combination of amlodipine and lisinopril as a basis therapy demonstrated better vasculoprotective activity.

Conclusion

The results of this study allow to recommend fixed drug combination of amlodipine and lisinopril as the preferable one for the treatment of male patients with arterial hypertension and abnormalities of vessel wall elasticity.

Keywords

Arterial hypertension, augmentation index, aortic pulse wave velocity, vessel wall

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Introduction

Slowing down the increase of vascular rigidity and its involution in arterial hypertension (AH) has significant interest in clinical practice. Results of various studies demonstrated positive effect of many non-pharmacological approaches like physical exercises, reducing body weight, low-salt diet, reduced alcohol consumption, addition of garlic, fish oil, α-linoleic acid [1].

Between pharmacological agents angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin receptor type II inhibitors (AR inhibitors), calcium channel blockers (CB), some beta-blockers (β-B), indapamide, nitrates and statins have proved effect on vascular remodeling [2–4]. Reaching the target blood pressure (BP) levels for these drugs is the necessary condition of their effect on elastic properties of blood vessels [3]. The COMPLIOR study for the first time raised the question about additional (pleiotropic) effects of different antihypertensive drug classes on vascular rigidity that are not related to BP reduction [5]. Combined therapy of ACE inhibitors and indapamide reduced aortic pulse wave velocity (PWVVao) by 9 % and there was no correlation between the grade of BP reduction and PWVVao. These data allow to consider some additional factors that influence vascular elasticity besides the grade of BP reduction in patients with AH who receive ACE inhibitors therapy. Another study demonstrated that although the grade of BP reduction was comparable in case of therapy with ACE inhibitors, CB and AR inhibitors only ACE inhibitors therapy allowed to achieve significant reduction of PWVVao [6]. Another study that aimed to prove high vasculoprotective activity of ACE inhibitors compared four classes of antihypertensive drugs (ACE inhibitors, AR inhibitors, β-blockers, CB [7]. Patients who received ACE and AR inhibitors had better characteristics of vascular elasticity after 4 months of antihypertensive therapy comparing with patients who received ß-blockers. Patients with AH who received CB demonstrated intermediate characteristics of vascular elasticity.

Lisinopril is one of the best studied drugs of ACE inhibitors class [8]. Its efficacy is investigated in >50 studies with more than 30000 patients involved. It has been demonstrated that combined therapy with lisinopril and simvastatin has significant positive effect on PWVao and augmentation index (AI) [9]. It necessary to notice that although target levels of BP and lipid characteristics in this patients have been achieved during first 2 month of treatment, PWVao and AI reached normal levels only after 6 and 12 months of treatment. These data prove the necessity of prolonged therapy for slowing down or involution of vascular wall remodeling. Lisinopril administration instead of any other ACE inhibitor in treatment of patients with congestive heart failure (CHF) during 6 months led to significant increase endothelium-dependent vasodilatation and demonstrated positive influence on PWVao and AI [10].

CB have proved its efficacy in reaching target levels of BP and organ protection during AH treatment [11]. Vasculoprotective effect of these drugs is caused by their direct relaxing action on vessels and their ability to regulate collagen metabolism in smooth muscle cells [12]. Amlodipine is the most frequently used dihydropyridine CB. Monotherapy with amlodipine allows to reach target levels of BP in 75–87 % of patients [13]. Major trials demonstrated that amlodipine and ACE inhibitors have the most prominent ability to cause right ventricular hypertrophy (RVH) regression [14]. The PREVENT (Prevention of Recurrent Venous Thromboembolism) study showed the amlodipine ability to reduce the thickness of intima-media complex layer of carotid arteries [15]. Smaller study demonstrated the ability of amlodipine to significantly reduce PWVao during 6-months treatment [16].

Amlodipine and lisinopril combination for treatment of patients with AH allows to increase antihypertensive and pleotropic effects and also to reduce the risk to develop unfavorable reactions. The ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) demonstrated significant reduction of total mortality by 11 %, cardiovascular mortality — by 24 %, the risk of stroke development — by 23 % in patients who received ACE inhibitor/CB comparing with patients who received β-B/thiazide diuretic combination [17]. The CAFÉ (The Conduit Artery Functional Endpoint Study) found out that the reason of this difference is less prominent reduction of central blood pressure in patients who received β-B/thiazide diuretic combination and absence of its influence on elastic properties of vessels [18]. The ACCOMPLISH (Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension) study showed that ACE inhibitor/CB combined therapy has an advantage over ACE inhibitor/thiazide diuretic combination [19]. It was possible to reduce the risk of developing mixed primary endpoint (cardiovascular mortality, acute myocardial infarction, hospital admission with unstable angina, recanalization of coronary arteries procedures) by 19 % in the group of

patients who took ACE inhibitor/CB comparing with ACE inhibitor/thiazide diuretic combination.

Fixed combination of amlodipine and lisinopril allows to reach BP target levels in 77–99 % of patient with AH stage 1–3 according with results of different studies [20–22]. This drug combination also demonstrated good vasculoprotective activity. It was more effective in PWVao reduction after 6-month therapy comparing with enalapril/hydrochlorotiazide combination [23]. Although β-B are the first line therapy of AH, nowadays there is no unambiguous opinion about β-B effect on vascular wall rigidity. Some studies demonstrated lack of this class's influence on parameters of vascular elasticity and central BP and showed even their negative effect — AI increase [24]. Some authors associated with this the certain worsening of prognosis of patients with AH and without comorbid coronary artery disease (CAD) during β-B therapy comparing with other classes of antihypertensive drugs [18, 25]. Nevertheless, therapy with extended release metoprolol demonstrated significant decrease of central BP and PWVao [26].

According with this information, the ACE inhibitor/CB therapeutic regimen is considered to be optimal for vascular "organ protection" but it has to gain further confirmation, particularly to be compared with long acting metaprolol tartrate.

The aim of this study is to estimate vasculoprotective activity of two therapeutic regimen: lisinopril/amlodipine fixed drug combination and long acting metoprolol tartrate as basis therapy.

Materials and methods

This study included male patients with AH who gave their voluntary informed consent to partecipation in this study. Patients with acute diseases or acute conditions of chronic diseases that occurred < 3 months before, acute coronary syndrome, decompensated CHF and acute cardiovascular collapse, acute cerebral circulation disorders (ACCD) that happened < 1 year ago, diabetes mellitus, atrial fibrillation, stable angina of III/IV functional classes (NYHA). Stratified block randomization allowed to distribute the patients who were involved in the study between two groups (n=30 in each one). The first group ("Group 1") received fixed combination of amlodipine and lisinopril as the basis antihypertensive therapy with the starting dose of 5–10 μg Therapeutic regimen in the second group of patients ("Group 2") was based on the long-acting form of metoprolol tartrate with the starting dose of 50μg twice per day.

Examination and treatment of patients has been done according with the guidelines of The Russian Medical Society on Arterial Hypertension [27]. All patients underwent 24-hours BP monitoring (24h-BPM) and parameters of vascular rigidity were assessed by oscillometric technique with 24-h BP monitor "MiSDP-2" and Vasotens software (BPLab company,

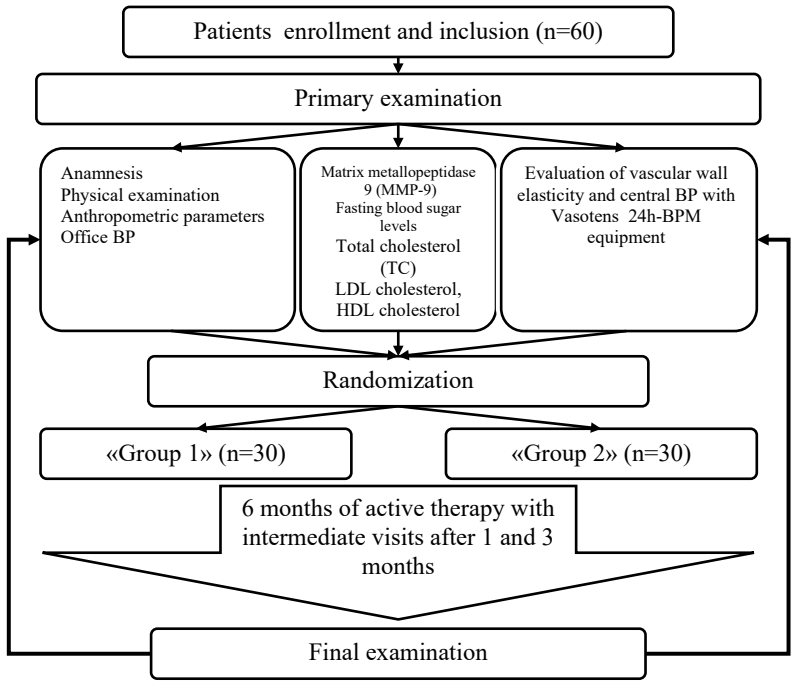

Figure 1. Study design

Nizhny Novgorod) [28]. Study program included investigation of matrix metalloproteinase-9 (MMP-9), the enzyme that participates in collagen and elastic fibers [29].

We used nonparametric methods of statistical analysis. Quantitative data are represented as median with demonstration of 25th and 75th quantiles (M [25, 75]). Qualitative and ordinal data are present as percentage. Mann-Whitney test was used to evaluate significance of differences between two independent groups of quantitative characters. To estimate the differences between three and more groups Kruskal-Wallis was used. χ^2 test was used for evaluation of differences between the groups of qualitative and ordinal characters. Significance of differences in the same group of patients before and after treatment was estimated with McNemar test in case of quantitative characters, and in case of qualitative characters. χ^2 test was used. Multiple comparisons adjustments were performed if it was necessary. Correlation analysis was done with Spearman's rank correlation test.H0 was rejected if p-value was less than 0.05. All statistical analysis was done using IBM SPSS Statistics 22 software.

Results and discussion

A comparative characteristic of two groups of patients before the start of active therapy is demonstrated in Table 1. Studied groups were comparable in age of patients, AH duration, waist circumference. body mass index, systolic blood pressure (SBP) and pulse rate, number of smokers and the number of pack years, occurrence of alcohol consumption and sedentary life, and also the frequency LVH, CAD and ACCD in anamnesis. Diastolic blood pressure (DBP) "Group 2" was 98 [90; 102] mm Hg (here and further data are presented as median, 25th and 75th quantiles), and in "Group 1" it was 100 [93; 104] mm Hg (p=0.037). Groups of patients were comparable in all blood test characteristics: total cholesterol levels (TC), low density lipids cholesterol (LDL cholesterol), high density lipids cholesterol (HDL cholesterol), triglycerides (TG), creatinine, glomerular filtration rate (GFR), MMP-9 concentration. Initial 24h monitoring of peripheral and central BP and of parameters of vascular rigidity didn't show the differences between the groups of patients.

It is worth to mention that in past all patients didn't receive CB regularly, although high antihypertensive activity and a lot of evidences of this class of drugs is well known. In general, previous antihypertensive therapy didn't differ in the groups of patients.

Table 1. **Comparison of main parameters before the beginning of therapy in the groups of patients (men with AH)**

Parameter	«Group 1» (n=30)	«Group 2» (n=30)	p
Age (years)	50 [42; 59]	50 [39; 58]	0,359
AH duration (years)	8 [5; 10]	5 [3; 15]	0,386
Waist circumference (cm)	105 [100;118]	106 [96; 119]	0,882
Body mass index	29,4 [28,4; 34,7]	29,7 [26,3; 34,5]	0,515
SBP (mm Hg.)	154 [148; 170]	152 [146; 158]	0,358
DBP (mm Hg.)	100 [93; 104]	98 [90; 102]	0,037
Pulse (beats per minute)	72 [62; 75]	70 [65; 78]	1,000
Frequency of smoking	6 (20%)	10 (33%)*	0,191
Number of pack-years	22 [5; 38,3]	30 [18,5; 38,8]	0,408
Frequency of alcohol consumption	24 (80%)	20 (67%)	0,191
Frequency of regular physical activity	0 (0%)	2 (7%)	0,246
Frequency of LVH registration	22 (73%)	16 (53%)	0,090
Frequency of CAD registration	12 (40%)	14 (47%)	0,397
Frequency of регистрации of ACCD	0 (0%)	0 (0%)	1,000
Glucose (mmol/L)	5,1 [3,8; 5,5]	4,9 [4,4; 5,4]	0,614
TC (mmol/L)	5,8 [4,9; 6,7]	5,1 [3,9; 6,3]	0,123
HDL (mmol/L)	1 [0,9; 1,3]	1,04 [0,9; 1,4]	0,572
LDL (mmol/L)	3,2 [2,2; 3,6]	2,8 [2,2; 4,2]	0,836
TG (mmol/L)	2,2 [1,6; 3,2]	1,8 [1,47; 2,6]	0,328
Creatinine (umol/L)	92 [76; 105]	85 [68; 100]	0,076
GFR (mmol/L)	77,5 [64,4; 101,5]	89,7 [65; 112,9]	0,391
MMP-9 (ng/mL)	93,2 [65,1; 125,4]	64 [42,4; 100]	0,051
SBP_{24} (mm Hg.)	139 [132; 156]	138 [128; 145]	0,700
DBP_{24} (mm Hg.)	92 [80; 104]	87 [83; 100]	0,745
PP_{24} (mm Hg)	52 [46; 63]	51 [44; 57]	0,574
Pulse $rate_{24}$ (beats per.)	67 [64; 73]	72 [66; 73]	0,389
AI_{24} (%)	–13 [–20; 7]	–16 [–37; –4]	0,110
$SBPao_{24}$ (mm Hg.)	131 [124; 146]	128 [119; 134]	0,359
$DBPao_{24}$ (mm Hg	94 [80; 105]	88 [85; 102]	0,813
$PPao_{24}$ (mm Hg.)	41 [35; 47]	39 [32; 45]	0,359
$Alao_{24}$ (%)	22 [14; 35]	25 [10; 33]	0,407
$PWVao_{24}$ (m/sec)	9,44 [9,1; 9,9]	9,34 [8,7; 10,7]	0,953

* Here there is relative number of patients in %, in relation to the total number of patients together with the absolute number.

Patients from the "Group 1" received 5+10 mg starting dose of amlodipine and lisinopril with possible increase of dosage up to 10+20 mg respectively. Therapeutic regimen of the "Group 2" considered administration of 50 mg starting dose of extended-release metaprolol tartrate twice per day with further increase of dosage up to 200 mg and higher. During the first week of therapy (during hospital treatment) correction of dosage and, if necessary, addition of other antihypertensive drugs was performed. Characteristic of prescribed therapy is present in

Table 2. **Therapy of patients with AH involved in this study**

Parameter	«Group 1» (n=30), abs.	«Group 2» (n=30), abs.	p
CB	30	0	0,000
β-B	0	30	0,000
Diuretics	6	8	0,753
ACE inhibitors	30	0	0,016
Statins	30	26	0,112
Central-acting agents	1	2	0,862

Table 2. It demonstrates that significant differences between groups exist only in basis therapy provided with the study protocol.

After 6 months of treatment the level of office SBP in the "Group 2" reduced significantly from 152 [145; 158] mm Hg. to138 [128; 144] mm Hg. (p=0.08). DBP levels reduced from 98 [90; 102] mm Hg. to 82 [80; 90] mm Hg. At the same time significant pulse rate reduction from 70 [65; 78] beats per minute to 64 [63; 74] beats per minute existed only during the first months of therapy. The most prominent antihypertensive effect was present after 1 month after the start of active therapy. And some reduction of antihypertensive effect was reported between the third and fourth visits: SBP increased from 128 [120; 138] mm Hg to 138 [128; 144] mm Hg, but nobody had SBP higher than 140 mm Hg.

In the "Group 1" during 6 months of therapy SBP levels reduced from 154 [148; 170] mm Hg to 138 [126; 154] mm Hg, and DBP levels reduced from 100 [93; 10] mm Hg to 82 [80; 96] mm Hg. There was no significant difference in pulse rate. As in the "Group 2", that used extended release metoprolol tartrate, maximal SBP reduction occurred between the first and the second visit. And also there was some "loss" of antihypertensive activity between the third and the fourth visits. During this period of time SBP increased from 120 [118; 136] mm Hg to 38 [126; 154] mm Hg. DBP levels in this group reduced significantly between the first and the second visits and further remained stable in the borders of normal blood pressure.

Partial "loss" of antihypertensive effect on SBP between 3 and 4 visits in both groups can be related to the violation of treatment regimen and not precise following other medical adivices.

It is necessary to mention that there were no significant differences in the grade of BP reduction between visits in both groups (Table 3); it allows to consider that the use of both extended release metoprolol tartrate and amlodipine/lisinopril combination as basic pharmacological agents has comparable efficacy in influencing office BP during 6 months of active therapy. as basic pharmacological agents.

Table 3. **Comparison of antihypertensive effect dynamics in the groups of patients involved in the study**

Parameter	«Group1» (n=30) (mm Hg.)	«Group2» (n=30) (mm Hg.)	p
SBP reduction between 1 and 2 visits	27 [16; 40]	28 [10; 42]	0,554
SBP reduction between 2 and 3 visits	0 [–4; 10]	4 [0; 8]	0,744
SBP reduction between 3 and 4 visits	–12 [–28; –4]	–6 [–16; 0]	0,103
SBP reduction between 1 and 4 visits	16 [–4; 38]	18 [4; 24]	0,882
DBP reduction between 1 and 2 visits	18 [14; 24]	18 [12; 24]	0,406
DBP reduction between 2 and 3 visits	0 [–2; 8]	2 [-8; 10]	0,882
DBP reduction between 3 and 4 visits	–4 [–17; 0]	–4 [–10; 4]	0,744
DBP reduction between 1 and 4 visits	18 [10; 23]	12 [8; 20]	0,172

The results of 6-months treatment with chosen therapeutic regimen influence on 24h-BPM, BP, condition of vascular wall, central BP and some laboratory parameters in the "Group 2" are presented in the Table 4. It was possible to reduce average daily value of SBP and DBP both in brachial artery and aorta. The levels of peripheral average daily BP reduced significantly from 138 [128; 145] / 87 [83; 100] mm Hg. to 129 [125; 136]/ 82 [79; 93] mm Hg. (p<0.05). The levels of average daily central BP reduced sig-

Table 4. **Influence of 6-month therapy in the "Group 1" on 24-hour blood pressure monitoring and some laboratory tests characteristics (n=30)**

Parameter	1st visit	4st visit	p
SBP_{24} (mm Hg)	138 [128; 145]	129 [125; 136]	0,000
DBP_{4} (mm Hg.)	87 [83; 100]	82 [79; 93]	0,003
PP_{24} (mm Hg.)	51 [44; 57]	47 [44; 54]	0,243
$Pulse_{24}$ (beats per minute)	72 [66; 73]	68 [64; 74]	0,041
AI_{24} (%)	–16 [–37; –4]	–21 [–38; –6]	0,194
$SBPao_{24}$ (mm Hg.)	128 [119; 134]	119 [116; 128]	0,000
$DBPao_{24}$ (mm Hg.)	88 [85; 102]	84 [81; 94]	0,005
$PPao_{24}$ (mm Hg.)	39 [32; 45]	36 [33;40]	0,135
$PWVao_{24}$ (m/s)	9,34 [8,7; 10,7]	11,02 [9,7; 11,4]	0,003
$Alao_{24}$ (%)	25 [10; 33]	21 [10; 28]	0,105
Glucose (mmol/L)	4,9 [4,4; 5,4]	4,8 [4,5; 5,4]	0,403
TC (mmol/L)	5,1 [3,9; 6,3]	4,8 [4,3; 5,6]	0,873
TG (mmol/L)	1,8 [1,5; 2,6]	1,4 [1; 2,3]	0,000
HDL (mmol/L)	1,04 [0,9; 1,4]	1,2 [1; 1,9]	0,016
LDL (mmol/L)	2,8 [2,2; 4,2]	2,7 [2; 3]	0,005
Creatinine (μmol/L)	87 [70; 100]	98 [90; 106]	0,096
GFR (ml/min/m^2)	89,7 [65; 112,9]	76,5 [67,5; 88,6]	0,289
MMP-9 (ng/mL)	64 [42,4; 100]	72,76 [42,5; 132,5]	0,232

Note: Negative IA24 value indicates more favorable condition of vessel wall

nificantly from 128 [119; 134]/ 88 [85; 102] mm Hg. to 119 [116; 128]/ 84 [81; 94] mm Hg. ($p<0.05$). Average daily pulse rate also decreased significantly from 72 [66; 73] beats per minute to 68 [64; 74] beats per minute ($p=0.041$). At the same time it was impossible to affect such parameters of vascular rigidity like pulse pressure (PP_{24}), AI24, $AIao_{24}$. More than that, $PWVao_{24}$ significantly increased ($p=0.03$) from 9.34 [8.7; 10.7] m/sec to 11,02 [9,7; 11,4] m/sec (normal value ⩽10 m/sec). Thus, although the antihypertensive effect of extended release metoprolol tatrate 6-months therapy is sufficient, in this study suc h treatment didn't have positive effect on vascular wall properties. The results of other studies prove that metoprolol tartrate is not enough effective for correction of arterial rigidity comparing with other classes of antihypertensive drugs including β-blockers with additional vasodilating properties [24, 25, 30].

In the "Group 1" 6-month therapy reached significant reduction of peripheral and central BP (Table 5). The level of average daily peripheral BP significantly decreased from 139 [132; 156]/ 92 [80; 104] mm Hg to 133 [123; 141]/ 81 [79; 89] mm Hg ($p<0.05$). The level of average daily central BP reduced from 131 [124; 146]/ 94 [80; 105] mm Hg to 126 [115; 127]/83 [80; 90] mm Hg ($p<0.05$). Combined therapy with lisinopril/amlodipine had no significant influence on pulse rate. In this group the parameters of vascular wall properties changed positively: PP24 reduced from 52 [46; 63] mm Hg to 47 [40; 64] mm Hg ($p=0.038$). $PPao_{24}$ reduced from 41 [35; 47] mm Hg to 37 [31; 46] mm Hg ($p=0.042$).

Table 5. **Influence of 6-month therapy in the "Group 1" on 24-hour blood pressure monitoring and some laboratory tests characteristics (n=30)**

Parameter	1st visit	4th visit	p
SBP_{24} (mm Hg)	139 [132; 156]	133 [123; 141]	0,000
DBP_{4} (mm Hg.)	92 [80; 104]	81 [79; 89]	0,001
PP_{24} (mm Hg.)	52 [46; 63]	47 [40; 64]	0,038
$Pulse_{24}$ (beats per minute)	67 [64; 73]	63 [58; 68]	0,212
AI_{24} (%)	–13 [–20; 7]	–16 [–20; –7]	0,006
$SBPao_{24}$ (mm Hg.)	131 [124; 146]	126 [115; 127]	0,001
$DBPao_{24}$ (mm Hg.)	94 [80; 105]	83 [80; 90]	0,001
$PPao_{24}$ (mm Hg.)	41 [35; 47]	37 [31; 46]	0,042
$PWVao_{24}$ (m/s)	9,44 [9,1; 9,9]	9,69 [9,3; 10,6]	0,094
$AIao_{24}$ (%)	22 [14; 35]	20 [7; 32]	0,001
Glucose (mmol/L)	5,1 [3,8; 5,5]	5,4 [4,7; 5,7]	0,101
TC (mmol/L)	5,8 [4,9; 6,7]	5,5 [4,7; 6]	0,314
TG (mmol/L)	2,2 [1,6; 3,2]	2,2 [1,1; 3,4]	0,584
HDL (mmol/L)	1 [0,9; 1,25]	1,6 [1,31; 1,95]	0,000
LDL (mmol/L)	3,2 [2,2; 3,6]	2,9 [2,6; 3,2]	0,112
Creatinine (**μmol/L**)	92 [76; 105]	106 [91; 122]	0,102
GFR (ml/min/m2)	77,5 [64,4; 101,5]	68,5 [58,1; 78,1]	0,110
MMP-9 (ng/mL)	93,2 [65,1; 125,4]	54,79 [43,2; 100,9]	0,015

Note: Negative IA24 value indicates more favorable condition of vessel wall

Average daily AI in aorta also decreased significantly from 22 [14; 35]% to 20 [7; 32]% ($p=0.001$). Average daily AI in brachial artery reduced significantly from $_{(minus)}$ –13 [–20; 7]% to $_{(minus)}$ –16 [–20; –7]% ($p=0.006$). Nevertheless, it was impossible to reach significant PWVao reduction that can be related to short duration of active therapy (6 months). Thereby, fixed combination of amlodipine and lisinopril can lead to significant decrease of average daily peripheral and central BP and melioration of some average daily values of vascular wall properties like PP and AI during 6-month therapy.

Comparison of 6-month treatment with both therapeutic regimens of antihypertensive therapy and its influence on 24-h BPM and characteristics of vascular rigidity is presented at Figure 2.

Characteristics of lipid spectrum improved significantly during treatment (Table 4 and 5). It is worth

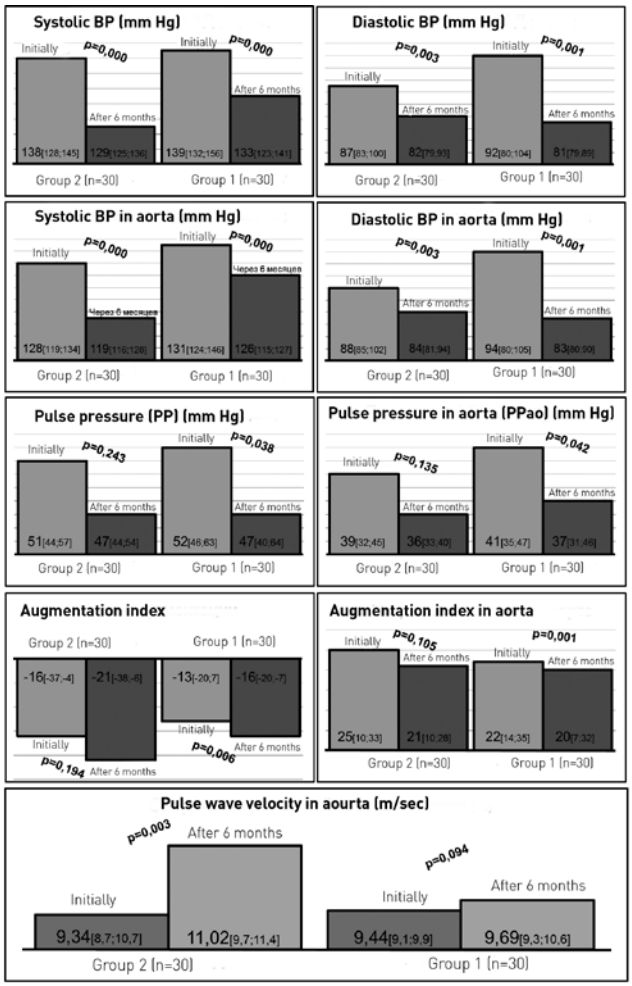

Figure 2. Influence of 6-month therapy on parameters of 24-h monitoring of peripheral and central BP and characteristics of vascular rigidity in both groups of patients with AH

to mention that part of patients received statins if it was indicated. It was not forbidden according with the study protocol and it corresponds clinical guidelines [27].

In addition it is necessary to mention that MMP-9 concentration didn't change significantly during active therapy in the group of patients who received extended release metoprolol tartrate ("Group 2"), whereas the decrease of MMP-9 (from 93.2 [65.1; 125.4] to 54.79 [43.2; 100.9] (p=0.015)) concentration was achieved in the "Group 1" (amlodipine/lisinopril). This correlates with the results of positive influence of fixed drug combination on vascular wall condition (Table 5, Figure 2).

It is important that negative metabolic effects were not registered in both groups during 6-month therapy of AH with chosen drugs. Particularly, starving levels of glucose, creatinine concentration and GFR didn't change negatively (Table 4 and 5).

Quantitative comparison of registered clinically significant adverse reactions that had developed during therapy revealed that they appeared more often in the "Group 1" than in the "Group 2". Particularly, two patients from the "Group 1" developed shin edema during increase of dosage of fixed combination amlodipine/lisinopril (up to 10+20 mg/day) that aimed to reach target BP levels. This adverse reaction required dose reduction up to initial one (5+10 mg/day). One patient of this group had complaints of palpitation that disappeared without assistance after two weeks of therapy without changing the drug dosage. Another patient felt discomfort in epigastrium after drug intake, these adverse reactions didn't require the cancellation of treatment and disappeared without assistance. At the same time no clinically significant adverse reactions were registered in the group of extended release metoprolol tartrate during 6 months of therapy.

There were no fatal outcomes in both groups. At the same time 16 surrogate endpoints were registered. According with the study protocol, these endpoints included: admission to hospital with cardiovascular diseases, death for cardiovascular causes, development of acute coronary syndrome, including AMI, ACCD, atrial fibrillation. 15 cases were related to previously scheduled admission to hospital with cardiovascular diseases and one case was connected with atrial fibrillation paroxysm (In the "Group 2"). In the second group 12 endpoints were registered during six months, whereas in the first one only 4 endpoints were registered (p=0.020).

Conclusion

This study allows to consider more prominent efficacy of hypertensive therapy based on fixed combination of lisinopril and amlodipine comparing with extended-release metoprolol tartrate therapy as a basis antihypertensive medicine. Although both therapeutic regimen were led to reaching similar levels of target BP, the advantage of combined therapy was characterized with positive influence on vascular elasticity and more rare development of "surrogate" endpoints. Particularly, the group that had been treated with fixed combination of amlodipine and lisinopril demonstrated upregulation of MMP-9 linked with AI reduction. The results of our study together with literature analysis allow to recommend fixed combination of lisinopril and amlodipine as the preferable one in treatment of male patients with AH and impaired vascular wall elasticity.

Conflict of interest: None declared.

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