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Modulating effect of target blood pressure achievement on pulse wave velocity in hypertensive patients

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Abstract

Objective. Carotid-femoral pulse wave velocity (PWV) is a strong independent predictor of cardiovascular morbidity and mortality. The aim of the study was to evaluate treatment-induced changes in PWV in hypertensive subjects achieved target clinic blood pressure (BP). **Design and methods.** Patients with grade I–II hypertension were treated to achieve target clinic BP < 140/90 mmHg with combination of RAAS-inhibitors and amlodipine for 1 year. Baseline BP was 163.4 ± 8.1/100.9 ± 4.2 mmHg; achieved BP 123.7 ± 9.7/76.8 ± 6.7mmHg. Central BP and PWV were measured before treatment and after 8 months of target clinic BP was maintained. **Results.** In 47 patients (20 men, age 58.9 ± 9.0 years) target clinic BP was achieved and maintained for 8 months. In 11 (23 %) subjects PWV decreased by ≥ 1 m/s from baseline (G1), in 15 (32 %) patients it remained unchanged (G2), and in 21 (45 %) it increased by ≥ 1 m/s compared to baseline (G3). The groups were comparable by age, risk factors, baseline and achieved clinic BP. PWV differed between the groups at baseline (G1 15.9 ± 2.5 vs. G2 13.6 ± 1.9 vs. G3 10.9 ± 1.7 m/s, $p < 0.05$), but not at the end of the study (13.0 ± 2.1; 13.6 ± 1.9 and 13.4 ± 1.9 m/s, respectively, $p > 0.05$). Also 72.7 % of patients in G1 and 66.7 % in G2 received the highest recommended doses of RAAS-inhibitors and amlodipine 10 mg vs. 28.6 % in G3 (Pearson $\chi^2 = 9.0$; $p < 0.05$). Correlation and multiple regression analysis revealed the association between PWV decrease and doses of RAAS-inhibitors and amlodipine ($r = –0.5$, $\beta = –0.45$, $p < 0.05$). **Conclusions.** There is a modulating effect of target BP achievement on PWV in hypertensive subjects. PWV reduction is associated with higher doses of RAAS inhibitors and amlodipine.

Key words: hypertension, arterial stiffness, pulse wave velocity, combined antihypertensive therapy

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Модулирующий эффект достижения целевого артериального давления в отношении скорости пульсовой волны у пациентов с неосложненной артериальной гипертонией

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Резюме

Цель исследования. Изучить динамику скорости распространения пульсовой волны (СРПВ) при достижении целевого артериального давления (АД) на фоне комбинированной терапии блокатором ренин-ангиотензин-альдостероновой системы (РААС) и антагонистом кальция амлодипином и установить предикторы ее снижения у больных неосложненной артериальной гипертензией (АГ). **Материалы и методы.** У 47 пациентов (20 — мужчины, средний возраст 58,9 ± 9,0 лет) с неосложненной АГ 1–2 степени, получавших комбинированную терапию блокатором РААС и амлодипином с возможным добавлением индапамида-ретард, достигших уровня АД < 140/90 мм рт. ст. не позднее, чем через 6 месяцев лечения, проводилась оценка клинического АД на каждом визите, суточное мониторирование АД (СМАД) и измерение артериальной ригидности методом аппланационной тонометрии исходно и в конце периода наблюдения. **Результаты.** Все пациенты достигли и поддерживали целевой уровень АД в течение 8 месяцев (исходное АД 163,4 ± 8,1/100,9 ± 4,2 мм рт. ст.; конечное — 123,7 ± 9,7/76,8 ± 6,7 мм рт. ст.). На фоне стойкого контроля АД у 11 (23 %) пациентов СРПВ снизилось на 1 м/с и более, у 15 (32 %) — не изменилось, у 21 (45 %) — повысилось. Группы были сопоставимы по основным клинико-демографическим параметрам, исходному и достигнутому АД и показателям СМАД. Выявлены различия по исходной СРПВ (15,9 ± 2,5 м/с; 13,6 ± 1,9 м/с и 10,9 ± 1,7 м/с соответственно, $p < 0,05$). В группе снижения СРПВ или без ее существенного изменения доля пациентов, принимавших максимальные дозы блокаторов РААС и амлодипина, была значительно выше (72,7; 66,7 и 28,6 % соответственно, критерий Пирсона $\chi^2 = 9,0$; $p < 0,05$). Корреляционный и многофакторный регрессионный анализ выявили обратные взаимосвязи между снижением СРПВ и дозами блокатора РААС ($r = –0,5$, $\beta = –0,5$) и амлодипина ($r = –0,5$, $\beta = –0,39$, $p < 0,05$). **Заключение.** Достижение и поддержание целевого АД у пациентов с неосложненной АГ обладает модулирующим эффектом в отноше-

нии артериальной ригидности, оцененной по СРПВ. Предикторами снижения артериальной ригидности являются более высокие дозы блокаторов РААС и амлодипина.

Ключевые слова: артериальная гипертония, артериальная ригидность, скорость распространения пульсовой волны, комбинированная антигипертензивная терапия

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Introduction

Increased arterial stiffness, assessed by pulse wave velocity in the aorta (at the carotid-femoral distance) is considered an important independent predictor of fatal and nonfatal cardiovascular events and mortality in hypertensive patients [1–3]. Control of blood pressure (BP) can help to delay arterial stiffening.

The gold standard for arterial stiffness assessment is the measurement of carotid-femoral pulse wave velocity (PWV) by applanation tonometry [4]. However, in the majority of studies evaluating arterial stiffness (e. g. ASCOT-CAFÉ [5] and EXPLOR [6]), there was a change in indirect arterial stiffness parameters, while the change in PWV were minimal without significant differences between the groups. Since the carotid-femoral PWV is considered to be BP-dependent, the lack of significant changes can be explained by a comparable hypotensive effect of different treatments. However, minor changes of PWV in patients with the significant BP reduction are to be explained.

The potential pleiotropic effects (besides hypotensive action) of antihypertensive drugs [in particular, those of renin-angiotensin-aldosterone system (RAAS) blockers and calcium antagonists (CA)] are of great interest, as well as the ones of statins [7–11].

The aim of the study was to evaluate the dynamics of arterial stiffness in patients with uncomplicated hypertension (HTN), who achieved target BP with combination therapy by RAAS blocker and CA and maintained target BP for 8 months.

Design and methods

Criteria for patients selection

Among 200 outpatients with uncomplicated HTN of 1–2 degrees followed-up in our hospital, we selected 150 patients treated with combination therapy (at least three drugs), and achieved target BP < 140/90 mm Hg within 6 months. The treating physician chose the dose that allowed to start with the minimal doses and to increase them up to the recommended maximum ones. Adherence to treatment was assessed by Morisky Green questionnaire in patients with at least 4 scores [12].

Among enrolled subjects 52 patients with target BP 6 months after initiation of treatment were eligible according to the following critera:

The first two drugs were to be RAAS blocker and amlodipine;

If target BP was not achieved using a maximum dose of RAAS blocker and amlodipine 10 mg, indapamide retard 1.5 mg was added;

Follow-up period was 14 months, and target BP was maintained at the level < 140/90 mm Hg for at least 8 months without changes in therapy.

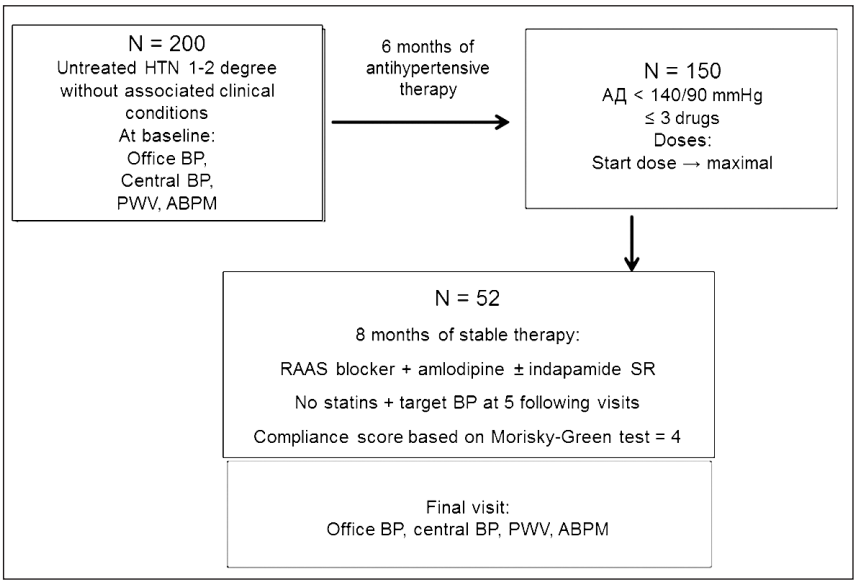
Thus, the total duration of treatment was 14 months; target BP was maintained for at least eight months. Fourteen months after enrollment ambulatory BP monitoring (ABPM) and arterial stiffness assessment were performed again (Fig. 1).

In patients with type 2 diabetes mellitus, disease control was assessed within clinical routine as following: fasting blood glucose level < 7.0 mmol/L, and glycosylated hemoglobin (HbA1c) < 7.0%. All patients received oral hypoglycemic agents, in particular, metformin (85%).

The exclusion criteria were: symptomatic HTN, associated clinical conditions, severe chronic diseases, intolerance to the studied drugs, the use of statins and/or aldosterone antagonists.

Height (auxanometer) and weight (weights SESA 220) were measured at the first visit, and body mass index (BMI) was calculated as following: weight (kg) / height^2 (m^2). At follow-up, weight control was performed.

Figure 1. Design of the study



Note: HTN — hypertension; ACC — associated clinical conditions; BP — blood pressure; PWV — pulse wave velocity; ABPM — ambulatory blood pressure monitoring; RAAS — renin-angiotensin-aldosterone system.

Measurement of office blood pressure

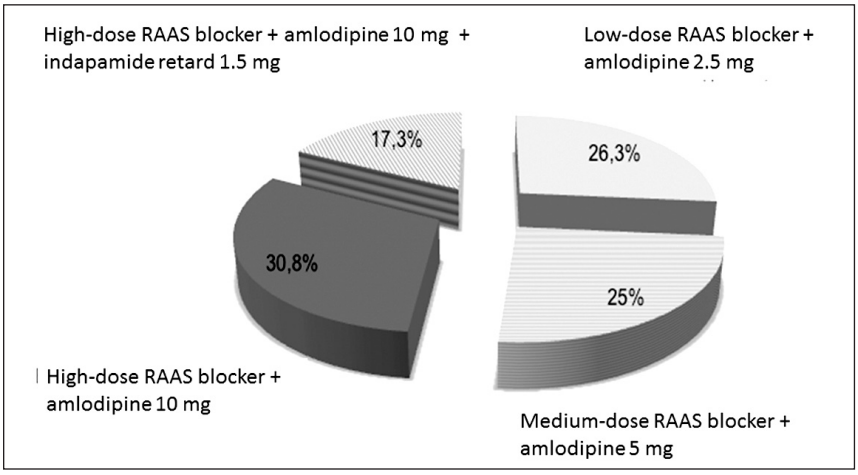
Office BP was measured on brachial artery by a validated full-automatic oscillometric device «OMRON 705CP-II» (Japan). The cuff was adjusted individually: for patients with arm circumference >32 cm a large cuff was used. At the first visit, BP was measured on both arms, at follow-up visits BP measurements were performed on the arm with higher baseline systolic BP. BP and heart rate (HR) measurements were performed in the morning (from 8:00 to 11:00), before the antihypertensive drug intake. BP was measured three times on the same hand in the sitting position, after at least 10 minutes of rest. The mean of three BP measurements was calculated for each visit.

Ambulatory blood pressure monitoring was performed by a standard technique with the use of a validated device "Microlife WATCH BP03". Automatic registration BP was carried out at intervals of 15 minutes during the day (from 7:00 to 23:00 hours) and at intervals of 30 minutes at night (from 23:00 to 7:00). Recordings with at least 85% reliable measurements were considered eligible for the further analysis with the software package. The daytime and nighttime periods were set according to the individual patient diary, so that they corresponded to the periods of wakefulness and sleep. The following parameters were assessed: the average 24-hour, average daytime and nighttime systolic (SBP) and diastolic blood pressure (DBP), and heart rate, as well as variability of daytime, nighttime and diurnal SBP, DBP, HR, and the circadian index of SBP and DBP.

Assessment of central blood pressure and pulse wave velocity

The study was performed in the morning between 8:00 and 11:00 (before the antihypertensive drug intake) by applanation tonometry using the system «Sphygmocor» (AtCor, Australia), in supine position, after at least 10 minutes of rest. Three BP measurements in the supine position were performed, and the mean value was calculated for the procedure. Millar transducer was used to record pulse wave at the radial artery, which was automatically converted into a curve of the central aortic pressure using the transforming function. PWV was measured using the same device, by sequential registration of the pulse wave at the carotid and femoral arteries with the simultaneous ECG recording (three thoracic leads). Carotid-femoral distance was measured as the difference between the distance from the sternal notch to the femoral artery pulsation and the distance from the carotid artery pulsations to the jugular notch (in millimeters). At each visit, at least two measurements were performed, and the mean values were calculated. All measurements were performed by the same specialist.

Figure 2. Distribution of patients according to the dosage regimen (n = 52)



Note: RAAS — renin-angiotensin-aldosterone system.

Laboratory examination

Blood samples were taken from the cubital vein in the morning, after at least 12 hours fasting. At enrollment visit blood count and biochemical analysis [creatinine, total cholesterol (TC), low-density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides (TG), glucose, HbA1c, potassium, sodium, transaminases] were performed. At follow-up visits creatinine, electrolytes, glucose levels were assessed. In patients with uncomplicated HTN, glomerular filtration rate was calculated according to the formula CKD-EPI. Blood samples were analyzed in the laboratory «INVITRO».

According to the criteria of the Russian Society of Cardiology (2009) dyslipidemia was defined as following: total cholesterol > 5.0 mmol/l, or LDL > 3.0 mmol/L, or HDL cholesterol < 1.0 mmol/L for men and < 1.2 mmol/l for women or triglycerides > 1.7 mmol/L [13].

Statistical analysis

Statistical software package Statistica 8 was used for the analysis, and standard algorithms of variation statistics were applied. Based on descriptive statistics, data are presented as M ± SD, where M is the mean value, and SD is standard deviation. For abnormally distributed data non-parametric Mann-Whitney and Wilcoxon tests were used. Categorical variables are presented as absolute (n) vales and rates (%). Pearson chi-square (χ^2) test was used to compare the rates of nominal and categorical values. Spearman rank correlation coefficient was used to assess the relations between variables. Stepwise regression analysis, and logistic regression analysis were performed. Sensitivity and specificity were assessed by ROC-curves (by the software package IBM SPSS Statistics). The differences in variables were considered statistically significant at $p < 0.05$.

Results

Arterial stiffness was assessed in 47 out of 52 patients. In 5 patients, applanation tonometry was not performed due to the anatomical and constitutional features. Clinical and demographic characteristics of 47 included patients are presented in Table 1. The majority (61.5%) were women, mean age 58.9 ± 9.0 years. The mean duration of HTN was 6.5 years, minimal — 3 years, maximal — 18 years. The most common risk factors were abdominal obesity (60%), and dyslipidemia (32.7%).

Figure 2 shows the distribution of patients depending on the drug dose at time when target BP was achieved (drug therapy was continued for 8 months afterwards).

Dynamics of office blood pressure

The baseline BP was 163.4 ± 8.1 / 100.9 ± 4.2 mm Hg (minimal SBP 152 mm Hg, minimal DBP — 91.7 mm Hg; maximal SBP 178 mm Hg, maximal DBP 108.7 mm Hg), after 6 months of therapy it was 126.5 ± 9.8 / 79.2 ± 5.7 mm Hg ($p < 0.05$ compared to baseline). After 14 months, BP was 123.7 ± 9.7 / 76.8 ± 6.7 mm Hg ($p < 0.05$ compared to baseline, $p > 0.05$ compared to the 6-month level).

The dynamics of central blood pressure and arterial stiffness

The changes in central pulse wave and arterial stiffness are shown in Table 2.

The treatment was associated with a significant decrease in SBP, DBP and pulse pressure (PP) in the aorta. The characteristics of the reflected wave (pressure increase, augmentation index, duration of the reflected wave) did not change. There were no significant changes in the mean values of carotid-femoral PWV.

Thus, despite the achievement and maintenance of target BP and the reduction of office central BP, arterial stiffness remained unchanged.

According to the European guidelines on HTN (2013) [2], carotid-femoral PWV > 10 m/s is a sign of target organ damage. At baseline, such values were registered in seven patients, and therefore the comparative analysis in subgroups was not carried out. Further analysis was performed depending on individual reference values considering age and baseline BP [12]. According to these

Table 1

CLINICAL AND DEMOGRAPHIC CHARACTERISTICS OF PATIENTS WITH UNCOMPLICATED HYPERTENSION

Index	Value (n = 52)
Age, years	58.9 ± 9.0
Sex, m/f, n (%)	20/32 (38.5/61.5)
Mean duration of HTN, years	6.5 ± 3.3
BMI, kg/m^2	26.9 ± 2.5
Smoking, n (%)	10 (19.2)
Dyslipidemia**, n (%)	17 (32.7)
Diabetes mellitus, n (%)	6 (11.5)
Total cholesterol, mmol/l	5.6 ± 1.1
Fasting plasma glucose, mmol/l	5.2 ± 1.6
HbA1c, %	5.8 ± 2.5
Serum creatinine, mmol/l	73.7 ± 12.2
GFR (EPI), mL/min/1.73 m^2	93.7 ± 19.4

Note: HTN — hypertension; BMI — body mass index; TC — total cholesterol; HbA1c — glycated hemoglobin; GFR — glomerular filtration rate; * — According to the criteria of the Russian Society of Cardiology in 2011 and the European Society of Cardiology / European Society of Hypertension 2013 (waist circumference in women ≥ 80 cm in men ≥ 94 cm); ** — According to the criteria of the Russian Society of Cardiology 2011 (low-density lipoprotein cholesterol > 3.0 mmol/l, HDL cholesterol < 1.0 mmol/l for men and < 1.2 mmol/l for women, triglycerides > 1.7 mmol/l).

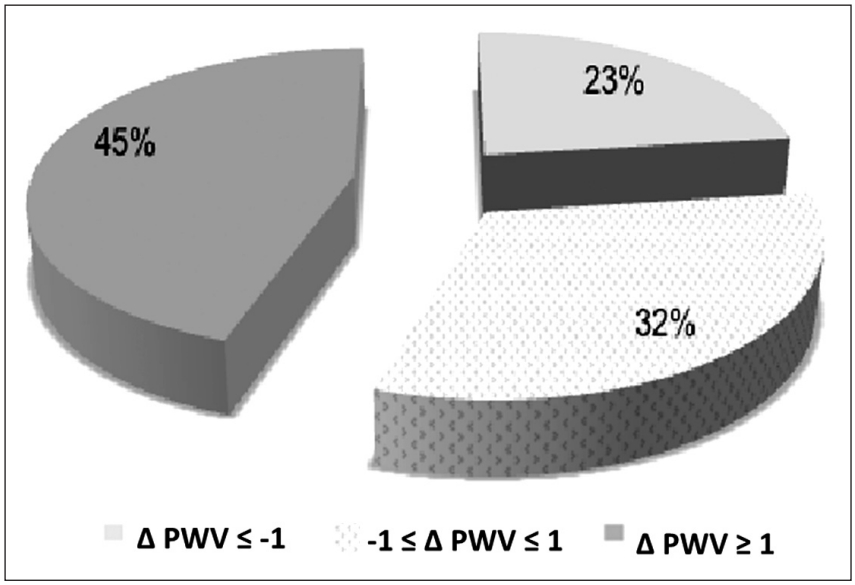
Table 2

DYNAMICS OF CENTRAL BLOOD PRESSURE AND ARTERIAL STIFFNESS

Index	Value	
	Baseline	After 14 months
SBPao, mm Hg	137.8 ± 17.3	125.2 ± 13.5*
DBPao, mm Hg	86.6 ± 12.0	80.3 ± 6.6*
PPao, mm Hg	51.4 ± 11.4	44.9 ± 11.5*
PP augmentation, mm Hg	124.5 ± 4.0	124.5 ± 11.2
Augmentation pressure ao, mm Hg	15.9 ± 7.3	13.9 ± 6.3
Augmentation index — augmentation pressure / PP@HR 75, %	25.2 ± 9.6	25.2 ± 9.0
Tr, ms	137.6 ± 11.8	137.7 ± 19.1
PWV, m/s	12.9 ± 2.7	13.4 ± 1.9

Note: the garden — central systolic blood pressure; DBPao — central diastolic blood pressure; PPao — central pulse pressure; HR — heart rate; Tr — time of the reflected wave; PWV — pulse wave velocity; * — $p < 0.05$ compared to baseline (Wilcoxon test).

Figure 3. Distribution of patients depending on the dynamics of carotid-femoral pulse wave velocity



Note: PWV — pulse wave velocity.

reference values, normal carotid-femoral PWV was detected in 12 (25.5%) patients (mean PWV 10.0 ± 1.5 m/s), and elevated — in 35 (74.5%) patients (mean PWV 13.8 ± 2.4 m/s). The groups were matching regarding the main demographic, clinical, and hemodynamic parameters. In the group with increased PWV, a less pronounced decrease in nocturnal BP and HR was registered at the last visit (circadian index (CI) SBP 9.9% vs 15.6% in the group with normal PWV; DBP CI 14.8% vs 20.7%, HR CI 11.7% vs 21.7%, $p < 0.05$). Univariate analysis demonstrated an inverse relationship between baseline PWV and SBP, DBP, and HR CI ($r = –0.4, –0.4$ and $–0.5$, respectively). However, multivariate regression analysis showed no significant predictors of PWV increase above individual reference value.

Individual analysis of carotid-femoral pulse wave velocity

Given the absence of PWV changes and its high variability (baseline PWV ranged from 7.6 to 19.2 m/s, with the median of 12.2 m/s, achieved PWV varied from 9.9 to 17.4 m/s, median — 13.4 m/s) in patients with stable normal BP, analysis of individual patient data was performed. It showed 3 variants of PWV dynamics with the treatment: 1) a reduction of PWV ≥ 1 m/s observed in 11 (23%) patients; 2) no change in PWV (difference between baseline and follow-up PWV

Table 3

CLINICAL AND DEMOGRAPHIC CHARACTERISTICS OF PATIENTS ACCORDING TO THE CHANGES IN CAROTID-FEMORAL PULSE WAVE VELOCITY DURING TREATMENT

Index	ΔPWV ≤ -1 (n = 11)	-1 ≤ ΔPWV ≤ 1 (n = 15)	ΔPWV ≥ 1 (n = 21)
Sex, m/f, n (%)	4 (36)/7 (64)	5 (33)/10 (67)	10 (48)/11 (52)
Age, years	59.8 ± 7.18	62.1 ± 8.1	56.3 ± 10
BMI, kg/m^2	25.6 ± 2.62	27.5 ± 2.2	26.6 ± 2.4
HTN duration, years	7.1 ± 3.8	5.3 ± 2.6	6.6 ± 2.9
Diabetes mellitus, n (%)	2 (18)	2 (13)	2 (10)
Dyslipidemia, n (%)	7 (64)	9 (60)	10 (58)
Smoking, n (%)	1 (9)	4 (27)	3 (15)
Abdominal obesity, n (%)	5 (45)	10 (67)	11 (55)

Note: BMI — body mass index; HTN — hypertension.

< 1 m/s) in 15 (32 %) patients, and 3) an increase in PWV ≥ 1 m/s in 21 subjects (45 %) (Fig. 3).

Groups allocated depending on the PWV change were comparable by the main clinical and demographic characteristics. Interestingly, in the group with the decrease of PWV there was only one smoker (Table 3).

There were no significant differences in the baseline and achieved office BP, as well as by the degree of its decline. In the group with reduced PWV office BP decreased from 154.8 ± 7.3 / 91.7 ± 10.2 to 128.4 ± 7.26/80.1±4.55 mm Hg, HR — from 76.2±8.9 to 67.8± 8.9 beats/min; in the group without any change in PWV, BP decreased from 152.7 ± 12.1 / 92.3 ± 8.3 to 125.6 ± 11.4 / 79.2 ± 6.5 mm Hg, and HR — from 78.3 ± 13.2 to 71.7 ± 10.6 beats/min; in the group with an increase in PWV, BP decreased from 149.3 ± 8.1 / 91.7 ± 6.04 to 126.6 ± 8.4 / 78.5 ± 5.97 mm Hg, and HR — from 75.8 ± 10.9 to 73.3 ± 9.3 beats/min ($p < 0.05$ for all values).

The frequency of achieving the target BP within a month of treatment at an increased PWV was highest, although the differences were not statistically significant (Pearson $\chi^2 = 3.5$, $p = 0.06$).

The groups were matched for baseline and achieved mean daitime and nocturnal and the mean 24-hour BP by ABPM. In each group, there was a significant decrease in these parameters with therapy (Table 4). The frequency of latent uncontrolled HTN (mean daytime BP by ABPM at the final visit > 135/85 mm Hg) was 27.3 % in the group with the reduction of PWV, 33.3 % in the group without any change in PWV, and 57.1 % in the group with the increase in PWV. However, the differences were not significant.

Thus, there was no difference in main clinical characteristics (age, sex, concomitant risk factors), brachial office BP and BP values by ABPM between the groups allocated based on the changes in carotid-femoral PWV. In the group with PWV increase, the rate latent uncontrolled HTN was higher, although the differences were not significant.

However, there were differences in the dynamics of central pulse wave. In patients with decreased PWV and those without PWV changes, there was a significant decrease in central SBP, DBP and PP, whereas in the group with the increase in PWV, central BP values remained unchanged. Patients

Table 4

CHANGES IN INDICATORS OF AMBULATORY BLOOD PRESSURE MONITORING DEPENDING ON PULSE WAVE VELOCITY DYNAMICS

Parameter	ΔPWV ≤ -1 (n = 11)		-1 ≤ ΔPWV ≤ 1 (n = 15)		ΔPWV ≥ 1 (n = 21)	
	Baseline	After 14 months	Baseline	After 14 months	Baseline	After 14 months
SBP_{24}, mm Hg	138.6 ± 14.9	124.8 ± 12.1*	133.8 ± 15.9	121.9 ± 12.3*	132.0 ± 8.4	126.9 ± 9.4*
DBP_{24}, mm Hg	83.5 ± 8.2	74.9 ± 5.2*	78.8 ± 10.0	72.5 ± 6.5*	80.9 ± 6.1	76.8 ± 6.3*
HR_{24}, beats/min	71.3 ± 7.5	68.9 ± 10.0	67.8 ± 7.2	68.7 ± 10.1	68.9 ± 8.1	67.9 ± 7.5
SBPday, mm Hg	146.2 ± 15.1	130.3 ± 11.6*	141.1 ± 17.2	128.3 ± 12.7*	139.6 ± 9.2	136.0 ± 9.7*
DBPday, mm Hg	89.6 ± 9.0	80.2 ± 5.6*	85.7 ± 10.8	79.0 ± 7.0*	88.5 ± 8.1	84.7 ± 7.8*
HRday, beats/min	77.2 ± 8.3	73.5 ± 12.8	73.4 ± 7.4	73.8 ± 10.0	75.4 ± 9.3	73.9 ± 9.2
SBPnight, mm Hg	131.0 ± 15.5	119.3 ± 14.0*	126.5 ± 15.3	115.5 ± 13.0*	124.4 ± 11.1	117.8 ± 11.5*
DBPnight mm Hg	77.4 ± 8.3	69.6 ± 6.4*	71.8 ± 9.6	65.9 ± 7.3*	73.3 ± 7.5	69.0 ± 6.8*
HRnight, beats/min	65.5 ± 7.0	64.4 ± 8.2	62.2 ± 8.3	63.6 ± 11.1	62.3 ± 8.7	61.8 ± 7.6
SBP CI, %	10.7 ± 4.6	8.7 ± 6.4	10.6 ± 4.3	9.8 ± 5.7	10.5 ± 7.8	13.8 ± 6.7
DBP CI, %	13.8 ± 6.4	12.9 ± 7.4	15.7 ± 5.1	16.1 ± 6.8	15.7 ± 9.3	18.2 ± 7.9
HR CI, %	14.1 ± 4.7	11.5 ± 7.8	15.1 ± 8.0	13.9 ± 8.8	15.0 ± 8.3	16 ± 8.9

Note: PWV — pulse wave velocity; SBP24 — mean 24-hour systolic blood pressure; DBP24 — mean 24-hour diastolic blood pressure; HR24 — mean 24-hour heart rate; SBPday — mean daytime systolic blood pressure; DBPday — mean daytime diastolic blood pressure; HRday — mean daytime heart rate; SBPnight — mean nocturnal systolic blood pressure; DBPnight — mean nocturnal diastolic blood pressure; HR night — mean nocturnal heart rate; CI — circadian index; * — $p < 0,05$ compared to baselines values (Wilcoxon test).

Table 5

DYNAMICS OF CENTRAL BLOOD PRESSURE AND ARTERIAL STIFFNESS IN STUDIED GROUPS

Parameter	ΔPWV ≤ –1 (n = 11)		–1 ≤ ΔPWV ≤ 1 (n = 15)		ΔPWV ≥ 1 (n = 21)	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
SBPao, mm Hg	147.5 ± 12.0	125.1 ± 20.3^{xx}	141.7 ± 17.6	121.1 ± 10.3^{xx}	129.9 ± 16.1**$^{<}$	127.8 ± 10.5
DBPao, mm Hg	91.8 ± 9.2	79.9 ± 6.9^{xx}	86.3 ± 13.1	77.5 ± 7.3^{xx}	84.1 ± 11.3	83.0 ± 5.3
PPao, mm Hg	55.8 ± 10.8	45,2 ± 15.9^{xx}	55.5 ± 9.1	43.6 ± 7.8^{xx}	46.0 ± 11.6**$^{<}$	44.9 ± 10.9
AI@HR75, %	27.4 ± 8.0	26.5 ± 10.5	27.3 ± 7.9	26.6 ± 8.0	22.7 ± 11.0	24.4 ± 9.3
Augmentation PP, mm Hg	123.4 ± 16.3	122.5 ± 8.8	123.0 ± 11.7	125.5 ± 9.3	126.1 ± 15.4	124.3 ± 14.0
Augmentation pressure, mm Hg	18.0 ± 7.7	14.9 ± 8.2	17.5 ± 5.7	13.4 ± 4.6^{xx}	13.9 ± 7.9	13.8 ± 6.6
Tr, msec	137.2 ± 7.2	134.4 ± 19.4	132.9 ± 8.3	134.9 ± 19.9	139.8 ± 12.9	141.0 ± 19.5
PWV, m/s	15.9 ± 2.5	13,0 ± 2.1^{xx}	13.6 ± 1.9**	13.6 ± 1.9	10.9 ± 1.7**$^{<}$	13.4 ± 1.9^{xx}

Note: SBPao — central systolic blood pressure; DBPao — central diastolic blood pressure; PPao — central pulse pressure; AI@HR75 — augmentation index normalized to heart rate of 75 beats/min; Tr — return time of the reflected wave; PWV — pulse wave velocity; xx — $p < 0.05$ compared to baseline values (Wilcoxon test); ** — $p < 0.05$ compared to ΔPWV ≤ –1 m/s; < — $p < 0.05$ compared to — 1 ≤ ΔPWV ≤ 1 m/s (Mann-Whitney test).

with the decreased PWV and without changes in PWV showed higher baseline SBP and PP in the aorta, as well as higher baseline PWV compared to the group with increased PWV.

Minor variations in the augmentation index, the tendency to an increase in the duration of the reflected wave and reduction of augmentation pressure were found in all groups (Table 5).

The univariate analysis showed a direct correlation between achieved PWV and age (r = 0.5), HTN duration (r = 0.3), diabetes mellitus (r = 0.3), nocturnal SBP at follow-up (r = 0.4), and inverse correlations with SBP CI at baseline and at follow-up, DBP CI at follow-up (r = –0.3 in all cases, $p < 0.05$ in all cases).

There were direct correlations between achieved central PP and age (r = 0.4), HTN duration (r = 0.4), achieved mean 24-hour SBP (r = 0.3). It correlated negatively with baseline mean 24-hour DBP (r = –0.5), baseline average daytime DBP (r = –0.4), baseline SBP and DBP CI (r = –0.3 and r = –0.4, respectively, $p < 0.05$ for all parameters). Multivariate analysis demonstrated the relation only for the achieved mean 24-hour SBP ($\beta = 0.34 \pm 0.13$, $p = 0.01$).

ROC-analysis showed that the achieved mean 24-hour SBP > 137.5 mm Hg might indicate central PP elevation for more than 40 mm Hg, the sensitivity was 31%, and the specificity was 82%. However, the results were not statistically significant (area under the curve AUC = 0.51 ± 0.09, 95% CI 0.32–0.69, p = 0.96).

Thus, in spite of the achievement and maintenance of target office BP, the varied change in carotid-femoral PWV was found: 11 (23%) patients demonstrated its decrease, 15 (32%) had no change of PWV, while 21 (45%) developed an increase in PWV. The groups were matched by major clinical and demographic characteristics, baseline and achieved office and ABPM BP parameters. The group with increased PWV was characterized by greater rate of latent uncontrolled HTN ($p > 0.05$). BP lowering is important for the reduction of increased arterial stiffness, and it is confirmed by at least three findings. First, patients with decreased PWV show higher baseline values of PWV and central SBP, and PP, confirming a more severe arterial stiffening in this subgroup. Secondly, these patients had simultaneous decrease in office BP, PWV and central SBP and PP during treatment. Third, when target BP was achieved (office BP and mean ABPM values), the values of central PP more than 40 mm Hg were associated with the daytime SBP higher than 137.5 mm Hg.

Analysis of therapeutic schemes

Taking into account the changes in arterial stiffness in patients with controlled HTN and a variety of dosage schemes, we have analyzed the role of the therapeutic factors. As mentioned above, by the 6th month of treatment, patients were divided into four groups based on dose regimens: low-dose RAAS blocker / amlodipine 2.5 mg (26.9 %), medium-dose RAAS blocker / amlodipine 5 mg (25 %), maximum-dose RAAS blocker / amlodipine 10 mg (30.8 %) and maximum-dose RAAS blocker / amlodipine 10 mg / indapamide SR 1.5 mg (17.3 %). The proportion of patients treated with indapamide retard 1.5 mg was equal in all subgroups, so we analyzed the frequency of various dose combinations of RAAS blocker and calcium antagonists. The group with reduced PWV or without any significant change in PWV, the rate of patients treated with the maximum doses of RAAS blockers and amlodipine was significantly higher (Table 6).

Spearman correlation analysis showed a significant inverse correlation between the decrease in PWV and RAAS blocker doses ($r = –0.5$) and amlodipine ($r = –0.5$, $p < 0.05$). Multivariate regression analysis (including additional factors such as age, sex, presence of diabetes mellitus, smoking, and baseline office SBP) confirmed significant associations only with doses of RAAS blockers ($\beta = –0.5$, $p = 0.01$) and amlodipine ($\beta = –0.39$, $p = 0.01$).

Thus, our data suggest that higher doses of RAAS blockers and amlodipine may have a BP-independent effect on PWV changes.

Discussion

Increased arterial stiffness is an important independent predictor of fatal and nonfatal cardiovascular morbidity and mortality in hypertensive patients [3].

BP reduction and HTN control are considered the main approach to delay the progression of arterial stiffening. Carotid-femoral PWV measurement by applanation tonometry is the gold standard for arterial stiffness assessment [4]. There is no consensus about the role of carotid-femoral PWV in HTN: is it a marker of treatment efficiency or a cardiovascular risk factor? Approaches to reduce arterial stiffness remain relevant, since PWV is one of the main potentially modifiable factors associated with survival in hypertensive patients.

We assessed arterial stiffness in relation to ABPM parameters in patients with uncomplicated HTN, achieved target BP with the therapy by different doses of RAAS blockers and amlodipine and possible additional diuretic (indapamide retard) that is the choice therapy for arterial stiffness reduction, based on the recent data [4, 7, 15, 16].

Altogether we included 47 patients with uncomplicated HTN of 1–2 degrees, and achieved target BP < 140/90 mm Hg at 6 months of therapy. An advantage of our study is a detailed analysis of changes in carotid-femoral PWV and subgroup analysis depending on its dynamics (increase, decrease and no change). To our knowledge, there have been no similar studies published yet, so we can consider it a pilot analysis.

Table 6

DOSE SCHEMED DEPENDNG ON THE CHANGES IS PULSE WAVE VELOCITY

Drug doses, mg	ΔPWV ≤ –1 (n = 11)		–1 ≤ ΔPWV ≤ 1 (n = 15)		ΔPWV ≥ 1 (n = 21)	
	n	%	n	%	n	%
Low-dose RAAS blocker/ amlodipine 2.5 mg	1	9.1	4	26.7	9	42.9**<<
Medium-dose RAAS blocker/ amlodipine 5 mg	2	18.2	1	6.7	6	28.6**<<
High-dose RAAS blocker/ amlodipine 10 mg	8	72.7	10	66.7	6	28.6**<<
Indapamide retard 1.5 mg	4	36.4	3	20	2	9.5

Note: PWV — pulse wave velocity; RAAS — renin-angiotensin-aldosterone system; ** — compared to the group with decreased PWV (Pearson test $\chi^2 = 9.0$, $p < 0.05$); << — compared to the group without PWV changes (Pearson test $\chi^2 = 5.8$, $p < 0.05$).

Despite BP control in all patients, the changes in carotid-femoral PWV were variable, and in most cases it tended to increase. At the same time indirect signs of the decrease in arterial stiffness were observed: a significant reduction in central BP and PP and a tendency to the augmentation pressure reduction and increase of the return time of the reflected wave.

One of the possible causes of PWV increase could be a relatively short follow-up period (8 months of therapy). Moreover, similar results were found in the studies ASCOT-CAFE and EXPLOR, which showed that carotid-femoral PWV, being a cardiovascular risk marker, is not always a criterion for therapy efficiency assessment at short-term follow-up. In these studies, mainly indirect arterial stiffness characteristics were observed, while PWV changed minimally, and almost no significant differences were found between groups with different modes of therapy. In ASCOT-CAFE study, there was no difference in the degree of office BP and PWV reduction in the two treatment groups, although therapy with amlodipine / thiazide diuretic was associated with the lower central PP and augmentation index (43.4 vs. 46.4 mm Hg; 25.3 and 31.9%, respectively, $p < 0.0001$), indicating reduction of arterial stiffness [5]. Similar results were shown in the study EXPLOR: there was a significant decrease in central PP (for 5.51 ± 0.65 mm Hg in the group of amlodipine / valsartan and for 1.77 ± 0.63 mm Hg in the group of amlodipine / atenolol) and augmentation index (for 5.65 ± 0.84 and 2.81 ± 0.84%, respectively), while PWV remained unchanged (0.98 ± 0.18 and 0.95 ± 0.17 m/s, respectively, $p = 0.92$) [6]. Since the carotid-femoral PWV is a BP-dependent parameter, the lack of differences is due to a partly comparable antihypertensive effect.

Traditionally, arterial stiffness is a direct function of BP: since arterial stiffness increases with increasing BP, any antihypertensive intervention should reduce arterial stiffness. In practice, as shown by our study, passive BP-dependent reduction of arterial stiffness, and changes in the arterial wall are difficult to distinguish. The latter include both the immediate effects associated with relaxation of smooth muscles of the vascular wall and remote effects related to the arterial wall remodeling including changes in the ratio and structure of collagen and elastin, and reduction in intima-media thickness [17]. Several variants of carotid-femoral PWV and BP changes during treatment are described. The most common types are their unidirectional reduction, reduction of PWV and small BP changes, and BP reduction in the absence of PWV changes [18–20]. PWV changes should be discussed together with other hemodynamic parameters (BP, HR and peripheral resistance) [21]. We conducted an appropriate analysis of changes in BP and HR and found no differences between the groups: target BP was achieved in all patients, and there were no significant changes in HR during treatment.

Increased carotid-femoral PWV in a significant proportion of our patients probably does not reflect changes in the vascular wall, and is associated with the so-called "modulatory effect" of target BP achievement. It assumes that the carotid-femoral PWV tends to reach the same value (in our study it is 13 m/s). This effect may play an important role for evaluating the treatment efficacy regarding arterial stiffness, and possibly for the definition of "target PWV".

Another possible cause for controversial changes in carotid-femoral PWV and BP found in our study might be a BP-independent effect of antihypertensive therapy. Different groups of antihypertensive drugs are known to affect arterial stiffness in a different way: besides pharmacological properties, it depends on the duration of treatment, methods of arterial stiffness assessment, and the degree of BP reduction [20]. Frequently, changes in arterial stiffness cannot be completely explained by BP reduction. These are BP-independent effects of the drug. In general, RAAS blockers in combination with thiazide diuretics and calcium antagonists (as in our study) can cause such effects, which is confirmed by several studies, including CAFE [5, 9, 22, 23].

Our study showed dose-dependent changes in carotid-femoral PWV: high-dose amlodipine and RAAS blocker were the main predictors of PWV reduction. These effects are described for angiotensin converting enzyme inhibitors. The effects on vascular wall are observed with higher doses than antihypertensive ones [21]. P. Boutouyrie confirmed this having showed that BP-independent decrease in arterial stiffness is dose-dependent and determined by the dose of perindopril [23].

Based on our results, routine assessment of arterial stiffness should be recommended in all patients with uncomplicated controlled HTN, and in case of elevated carotid-femoral PWV (compared to the individual reference values) further titration of RAAS blocker and/or amlodipine should be considered.

A small sample size and a short follow-up period are the main limitations of our study.

Conclusions

In patients with uncomplicated HTN target BP achievement has a modulating effect on arterial stiffness assessed by carotid-femoral PWV. Predictor of the reduction in carotid-femoral PWV is therapy with the high-dose RAAS blocker and calcium antagonist. This is an indirect evidence of their BP-independent effects on vascular wall.

Conflict of interest

The authors declare no conflict of interest.

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