

Effects of the Perindopril/Amlodipine Fixed-Dose Combination Therapy on the Left Ventricular Myocardial Deformation Properties and Arterial Stiffness Parameters in Patients with Arterial Hypertension

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Abstract

Background: Arterial hypertension (AH) is one of the main factors determining the high risk of cardiovascular complications and mortality. Early diagnosis of AH is a key point in its effective control and prevention of severe consequences. In recent years, the deformation properties of the left ventricle have been actively studied in the context of early diagnosis of AH and evaluation of the effectiveness of antihypertensive therapy. Our study aimed to assess effectiveness of the six-month perindopril/amlodipine fixed-dose combination (FDC) therapy on the deformation properties of the left ventricular (LV) myocardium and the elastic properties of arteries in AH patients.

Methods and Results: This study included 55 patients (20 men and 35 women) with AH Grades 1-2 (ESC/ESH, 2018). The mean age of patients was 52.2±10.94 years; the average duration of AH was 7.51±6.77 years. All patients underwent general clinical examination, biochemical blood tests, standard transthoracic two-dimensional echocardiography with ECG synchronization, 2D-speckle tracking echocardiography (STE) with the assessment of global longitudinal strain [GLS] and strain rate (SR). Arterial stiffness was determined using applanation tonometry. All patients received a perindopril/amlodipine FDC. The drug dose, considering the maximum doses, was titrated at 2-week intervals to achieve a target blood pressure. The mean doses of perindopril and amlodipine were 4.4±1.2 mg/day and 7.86±2.5 mg/day, respectively. The final treatment results were determined after 6 months of antihypertensive therapy.

Depending on the types of LV echo-geometry, AH patients were divided into three groups: Group 1 included 25 AH patients with normal LV geometry, Group 2 included 25 AH patients with LV concentric remodeling, and Group 3 included 5 AH patients with concentric LVH. The LV GLS values were -18.0±2.95%, -14.16±2.99%, and -12.4±1.87% in Groups 1, 2, and 3, respectively ($P=0.0000$). Intergroup analysis showed normal GLS value in Group 1, compared with Groups 2 and 3 ($P_{1,2}=0.0001$ and $P_{1,3}=0.0007$, respectively). Correlation analysis between the studied parameters revealed direct correlations of the LV mass index (LVMI) with GLS ($r_s=0.70$, $P=0.000$), SR ($r_s=0.70$, $P=0.000$), and pulse wave velocity (PWV) ($r_s=0.4$, $P=0.000$). In addition, direct correlations were observed between the PWV and GLS ($r_s=0.50$, $P=0.000$) and SR ($r_s=0.50$, $P=0.000$). A direct correlation was also noted between LV ejection fraction (LVEF) and SR ($r_s=0.70$, $P=0.000$).

Before the start of therapy, the average systolic blood pressure (SBP) and diastolic blood pressure (DBP) were 163.05±13.7 mmHg and 96.4±10.7 mmHg, respectively. Analysis of the six-month perindopril/amlodipine FDC therapy in AH patients showed high antihypertensive efficacy. The target levels of SBP and DBP were achieved in 98.2% and 96.4% of patients, respectively. There was a significant positive dynamic in reducing LVMI (from 96.40±25.79 g/m² to 82.3±24.5 g/m², $P=0.000$). The LVEF also improved from 63.08±2.59% to 64.57±1.82% ($P=0.000$). The six-month perindopril/amlodipine FDC therapy positively influenced the LV myocardium deformation properties: GLS increased significantly from -15.0±3.2% to 19.09±2.8%, reaching the normative values ($P<0.001$); SR also increased significantly from 0.84±0.23s⁻¹ to -1.13±0.23s⁻¹ ($P<0.001$). The indicated therapy was effective for central hemodynamics and arterial stiffness.

Conclusion: In AH patients with LV concentric hypertrophy, significant disturbances in the LV deformation properties are formed. The six-month perindopril/amlodipine FDC therapy provides good antihypertensive, cardioprotective, and vasoprotective efficacy, which is expressed in reliable regression of left ventricular hypertrophy, positive effect on the LV deformation properties, and increased elasticity of the arteries. (International Journal of Biomedicine. 2024;14(4):551-557.)

Keywords: arterial hypertension • left ventricular echo-geometry • global longitudinal strain • strain rate • arterial stiffness • therapy

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Abbreviations

Ao, aortic root diameter; **AH**, arterial hypertension; **AA**, aortic augmentation; **Aix**, augmentation index; **ACEI**, angiotensin-converting enzyme inhibitor; **ARB**, angiotensin receptor blocker; **BP**, blood pressure; **CCB**, calcium channel blocker; **CIMT**, carotid intima-media thickness; **CVR**, cardiovascular risk; **DBP**, diastolic BP; **FDC**, fixed-dose combination; **GLS**, global longitudinal strain; **IVST**, interventricular septal thickness; **LAV**, left atrial volume; **LAVI**, left atrial volume index; **LVDD**, LV diastolic dysfunction; **LVH**, left ventricular hypertrophy; **LVEF**, left ventricular ejection fraction; **LVMM**, left ventricular myocardial mass; **LVMI**, left ventricular mass index; **LVEDV**, left ventricular end-diastolic volume; **LVEDD**, left ventricular end-diastolic dimension; **LVESV**, left ventricular end-systolic volume; **LVESD**, left ventricular end-systolic dimension; **MBP**, mean BP; **PPc**, central pulse pressure; **PWT**, posterior wall thickness; **PWV**, pulse wave velocity; **RAAS**, renin-angiotensin-aldosterone system; **RWT**, relative wall thickness; **SBP**, systolic BP; **SBPc**, central SBP; **SR**, strain rate; **STE**, speckle tracking echocardiography.

Introduction

Arterial hypertension (AH) is a global health problem, as confirmed by numerous scientific studies. This chronic condition is associated with the development of serious complications, such as stroke, myocardial infarction, and chronic kidney disease.¹⁻³ The prevalence of AH depends on various factors, including genetic predisposition, lifestyle, and demographic characteristics.⁴⁻⁶ As is known, AH is a widespread disease affecting millions of people worldwide. The WHO reported that in 2021 more than 1 billion people suffered from AH, and forecast that this number will continue to grow due to changes in lifestyle and population aging.⁷

Early diagnosis of AH is a key point in its effective control and prevention of severe consequences. In recent years, the deformation properties of the left ventricle have been actively studied in the context of early diagnosis of AH and evaluation of the effectiveness of antihypertensive therapy.⁸ As is known, remodeling of the cardiovascular system is an obligatory component of hypertension, as a complication and a factor of progression. The term “remodeling” describes a complex of changes at the molecular and biomechanical levels, including left ventricular hypertrophy (LVH) and vascular wall hypertrophy.^{9,10} The left ventricle plays a key role in pumping blood into the system of large arteries. Deformation properties of the left ventricle, such as global longitudinal strain (GLS) and strain rate (SR), have become the object of research in the context of early diagnosis of AH.¹¹ LV GLS, a measure of myocardial deformation, directly measures the amount of myocardial longitudinal shortening and can detect subclinical myocardial dysfunction.¹² LV SR, which assesses rate of change in strain, is another robust measure of LV systolic function.^{13,14} The reported normal mean values of GLS among the studies varied from -15.80% to -23.40% ;^{4,15-18} normal mean values of SR varied from -1.30 s^{-1} to -2.40 s^{-1} .¹⁹

Arterial hypertension is often used to study changes associated with various types of LV deformations, such as concentric remodeling and concentric hypertrophy. This is important because deterioration in the fractional contraction of the circular fiber walls may precede a decreased left ventricular ejection fraction (LVEF).^{20,21} Using speckle tracking echocardiography (STE) helps better understand the complex relationships between the various biomechanical properties of the LV in AH. These data suggest that abnormal collagen metabolism and fibrosis may lead to early dysfunction of the LV contractile function, even with normal ejection fraction. The revision of European guidelines for the diagnosis and treatment of hypertension published in 2018 showed the need to initiate antihypertensive therapy with the prescription of a combination of two antihypertensive drugs, preferably in the form of fixed-dose combination (FDC).²² According to modern data, in most clinical situations, the optimal starting FDC should be a combination of an angiotensin receptor blocker (ARB) or angiotensin-converting enzyme inhibitor (ACEI) with calcium channel blocker (CCB) or a diuretic. The combination of two types of antihypertensive drugs significantly increases not only the antihypertensive but also the organ-protective efficacy. Modern scientific advances certainly prove the need for a new approach to the treatment of hypertension. There is no doubt that organ protection, including that of the vascular wall, is an independent goal of therapy. At the same time, resistive arteries and large, elastic vessels should be considered target organs.²³ In this regard, one of the promising areas of further scientific research is the assessment of the therapeutic effect of drugs that affect arterial rigidity by directly influencing the properties of the vascular wall.^{24,25} Thus, new knowledge about the biomechanical properties of the LV myocardium and the elastic properties of arteries is of great importance for developing therapeutic innovations and for research aimed at developing new tools for the quantitative assessment of remodeling processes and monitoring their progression. In this regard, our study aimed to assess effectiveness of the six-month perindopril/amlodipine FDC therapy on the deformation properties of the LV myocardium and the elastic properties of arteries in AH patients.

Materials and Methods

This study included 55 patients (20 men and 35 women) with AH Grades 1-2 (ESC/ESH, 2018). The mean age of patients was 52.2 ± 10.94 years; the average duration of AH was 7.51 ± 6.77 years.

The diagnosis of AH was verified in accordance with the ESC/ESH recommendations (2018).²²

Exclusion criteria were symptomatic hypertension, acute coronary syndrome, chronic heart failure (NYHA FC>III), cardiac arrhythmia, history of myocardial infarction, renal impairment, severe co-morbidities.

All patients underwent the following examinations: assessment of traditional risk factors, physical examination, clinical and biochemical laboratory methods, 12-lead ECG, echocardiography. Office BP was measured using a mercury sphygmomanometer, according to Korotkov's method.

The pulse contour analysis was carried out using the SphygmoCor device (AtCor Medical, Australia), which obtains peripheral arterial pressure waveforms by applying an arterial applanation tonometer to the wrist. Such indicators as the central SBP (SBPc), central DBP (DBPc), central PP (PPc), aortic augmentation (AA), augmentation index (Aix), augmentation index adjusted for heart rate (Aix@HR75), and pulse wave velocity (PWV) were analyzed.

Standard transthoracic, two-dimensional echocardiography with ECG synchronization and 2D-STE with the assessment of GLS and SR were performed using AutoSTRAIN Automated Cardiac Motion Quantification Technology on the Philips Affiniti 70G ultrasound system. Two-dimensional images of four-chamber, three-chamber, and two-chamber apical views and an LV parasternal short-axis view were recorded.

Left ventricular hypertrophy (LVH) was defined as a left ventricular mass index (LVMI) greater than 95 g/m² in women and >115 g/m² (for men).²² The types of left ventricular echo-geometry (concentric remodeling geometry and concentric left ventricular hypertrophy) were assessed according to the ASE recommendations.²⁶ The relative wall thickness (RWT) and LVMI were used to categorize patients as having either normal geometry (normal RWT and LVMI), concentric remodeling geometry (increased RWT and normal LVMI), concentric hypertrophy geometry (increased RWT and LVMI), or eccentric hypertrophy geometry (normal RWT and increased LVMI).^{15,27,28}

Carotid intima-media thickness (CIMT) was assessed for both left and right carotid arteries using a 7.5 MHz linear array transducer (Sonoline Versa Pro system, Siemens, Germany).

All patients received a perindopril/amlodipine FDC. The drug dose, considering the maximum doses, was titrated at 2-week intervals to achieve a target blood pressure. The mean doses of perindopril and amlodipine were 4.4±1.2 mg/day and 7.86±2.5 mg/day, respectively. The final treatment results were determined after 6 months of antihypertensive therapy. The effectiveness of therapy was assessed by achieving the target BP level according to 2018 ESH/ESH Guidelines for the management of AH.²² The primary target level for SBP and DBP was <140 mmHg and <90 mmHg, respectively.

In addition to antihypertensive therapy, patients, if necessary, received antiplatelet (acetylsalicylic acid) and lipid-lowering therapy (rosuvastatin, Rozat, "ADAMED," Poland). The average daily dose of rosuvastatin was 15.5±5.0 mg/day.

Statistical analysis was performed using the statistical software «Statistica» (v10.0, StatSoft, USA). Baseline characteristics were summarized as frequencies and percentages for categorical variables and as mean±standard deviation (SD) for continuous variables. A paired t-test was used to compare two groups. Multiple comparisons were performed with one-way ANOVA. Spearman's rank correlation coefficient (r_s) was calculated to measure the strength and direction of the relationship between two variables. A probability value of $P<0.05$ was considered statistically significant.

Results

The clinical characteristics of the patients are presented in Table 1. Before the start of therapy, the average SBP

and DBP were 163.05±13.7 mmHg and 96.4±10.7 mmHg, respectively. Obesity (BMI ≥30 kg/m²) was found in 50.9% of patients, and 34.5% of patients were overweight. LVH was detected in 23.6% of patients, dyslipidemia in 74.5%, and increased arterial stiffness in 29.1%. Thus, according to the risk stratification of patients with AH, more than half had high or very high cardiovascular risk (CVR).

Depending on the types of LV echo-geometry, AH patients were divided into three groups: Group 1 included 25 AH patients with normal LV geometry, Group 2 included 25 AH patients with LV concentric remodeling, and Group 3 included 5 AH patients with concentric LVH. The LV GLS values were -18.0±2.95%, -14.16±2.99%, and -12.4±1.87% in Groups 1, 2, and 3, respectively ($P=0.0000$). Intergroup analysis showed normal GLS value in Group 1, compared with Groups 2 and 3 ($P_{1,2}=0.0001$ and $P_{1,3}=0.0007$, respectively). The worst GLS value was found in Group 3, which may depend on many factors, including hypertrophy, myocardial fibrosis, and LV diastolic dysfunction.

Table 1.

Clinical characteristics of the study patients (n=55)

Variable	M ± SD / n (%)	
Age, years	52.21 ± 10.94	
AH duration, years	7.51 ± 6.77	
SBP, mmHg	163.05 ± 13.69	
DBP, mmHg	96.4 ± 10.67	
MBP, mmHg	118.61 ± 9.05	
BMI, kg/m ²	30.15 ± 4.92	
BMI ≥30 kg/m ² , n/%	28	50.9%
BMI of 25 to 29.9 kg/m ²	19	34.5%
LVH, n/%	13	23.6%
LVDD, n/%	31	56.4%
PWV >10 m/sec, n/%	16	29.1%
CIMT ≥0.9 mm, n/%	13	23.6%
Dyslipidemia, n/%	41	74.5%
Men, n/%	20	36.4%
Women, n/%	35	62.6%

Correlation analysis between the studied parameters revealed direct correlations of the LVMI with GLS ($r_s=0.70$, $P=0.000$), SR ($r_s=0.70$, $P=0.000$) (Table 2), and PWV ($r_s=0.4$, $P=0.000$). In addition, direct correlations were observed between the PWV and GLS ($r_s=0.50$, $P=0.000$) and SR ($r_s=0.50$, $P=0.000$). A direct correlation was also noted between LVEF and SR ($r_s=0.70$, $P=0.000$).

Analysis of the six-month perindopril/amlodipine FDC therapy in AH patients showed high antihypertensive efficacy with a significant decrease in SBP, DBP, and MBP by 23.78±6.24%, 22.44±10.56%, and 22.58±6.93%, respectively. The target levels of SBP, DBP, and MBP were achieved in

98.2%, 96.4%, and 94.5% of patients, respectively (Table 3). Achieving the target BP levels in patients ensured the high organo-protective efficacy of the therapy (Table 4). Analysis of the dynamics of the LV morpho-functional parameters against the background of the therapy showed a significant regression in LVH, mainly due to a decrease in the LV wall thickness. Thus, there was a significant positive dynamic in reducing LVMM (from 191.58±58.8g to 161.89±53.45g, $P=0.002$). We found a significant reduction in LAVI from 20.41±5.15 mL/m² to 18.0±3.90 mL/m² after six-months of therapy ($P=0.007$). The degree of decrease in LVMI and LAVI was 16.3% and 11.8%, respectively. The LVEF also improved from 63.08±2.59% to 64.57±1.82% ($P=0.000$). The six-month perindopril/amlodipine FDC therapy positively influenced the LV myocardium deformation properties. In particular, GLS increased significantly from -15.0±3.2% to 19.09±2.8%, reaching the normative values ($P<0.001$); SR also increased significantly from 0.84±0.23s⁻¹ to -1.13±0.23s⁻¹ ($P<0.001$). The indicated therapy was effective for central hemodynamics and arterial stiffness. In particular, the SBPc, DBPc, PPc, AA, and PWV significantly decreased.

Table 2.

Correlations between the LV parameters and PWV.

Variable	r _s	P-value
LVMI and GLS	0.7	0.000
LVMI and SR	0.7	0.000
LVMI and PWV	0.4	0.000
PWV and GLS	0.5	0.000
PWV and SR	0.5	0.000
LVEF and SR	0.7	0.000

Table 3.

Antihypertensive efficacy of the six-month perindopril/amlodipine FDC therapy (n= 55).

Variable	Initial data	After six-month therapy	P-value
	M±SD	M±SD	
SBP, mmHg	163.05 ± 13.69	122.58 ± 8.34	0.0000
DBP, mmHg	96.4 ± 10.67	75.89 ± 6.82	0.0000
MBP, mmHg	118.61 ± 9.05	91.45 ± 6.65	0.0000
Δ% SBP	-23.78 ± 6.24		
Δ% DBP	-22.44 ± 10.56		
Δ% MBP	-22.58 ± 6.93		
Achievement of target BP levels after the six-month perindopril/amlodipine FDC therapy			
Variable			
SBP, %	54 (98.2%)		
DBP, %	53 (96.4%)		
MBP, %	52 (94.5%)		

Table 4.

LV morpho-functional parameters against the background of the therapy (n=55).

Variable	Initial data	After six-month therapy	P-value
	M ± SD	M ± SD	
Ao, cm	2.91 ± 0.35	2.8 ± 0.2	0.0003
IVST, cm	1.09 ± 0.18	0.95 ± 0.15	0.0000
PWT, cm	1.00 ± 0.14	0.90 ± 0.14	0.0002
LVEDD, cm	4.66 ± 0.39	4.53 ± 0.38	0.09
LVESD, cm	3.0 ± 0.49	2.85 ± 0.42	0.29
E/A	1.01 ± 0.41	1.07 ± 0.42	0.43
LAV, mL	39.14 ± 12.63	34.49 ± 9.38	0.05
LAVI, mL/m ²	20.41 ± 5.15	18.0 ± 3.90	0.007
LVMM, g	191.58 ± 58.80	161.89 ± 53.45	0.002
LVMI, g/m ²	96.40 ± 25.79	82.3 ± 24.5	0.000
LVEDV, mL	87.49 ± 21.68	84.31 ± 21.15	0.44
LVESD, mL	32.74 ± 9.11	30.27 ± 7.96	0.13
LVEF, %	63.08 ± 2.59	64.57 ± 1.82	0.000
Δ% LVMI	- 16.3 ± 9.9%		

Table 5.

Central hemodynamics and arterial stiffness parameters against the background of the therapy (n=55).

Variable	Initial data	After six-month therapy	P-value
	M±SD	M±SD	
SBPc, mmHg	152.66 ± 20.03	124.92 ± 9.48	0.000
DBPc, mmHg	89.37 ± 10.29	77.41 ± 5.49	0.000
PPc, mmHg	64.49 ± 17.06	47.96 ± 8.59	0.000
AA, mmHg	14.43 ± 7.78	11.47 ± 5.39	0.022
Aix, %	30.18 ± 11.33	28.18 ± 12.24	0.376
AIx@HR75, %	28.60 ± 9.54	26.12 ± 10.70	0.202
PWV, m/sec	9.32 ± 3.30	7.15 ± 1.66	0.000

Discussion

Recent studies have shown that LV deformation properties are highly sensitive to changes in the functioning of the cardiovascular system, making them a valuable indicator for detecting even small changes associated with hypertension in the early stages. This is especially important since other diagnostic methods may be less effective in the early detection of such changes.²⁹⁻³¹ Previous studies have shown that the LV deformation properties correlate with the BP levels.³² Determination of the LV deformation properties

can be successfully used to assess remodeling processes, non-invasively monitor their progression, and assess the effectiveness of therapeutic interventions.

In our study, the LV deformation properties were studied in association with arterial stiffness parameters. The results showed that in AH patients with concentric LVH, significant disturbances are formed in the deformation properties of the LV myocardium. Direct correlations were found between LVMI and the GLS and SR, and the PWV, characterizing the elastic properties of the arteries, and GLS and SR. A direct correlation was observed between LVMI and PWV, indicating a relationship between LVH and arterial stiffness. Considering the features of the antihypertensive drug effects in the context of the potential benefits of their combined use, we should again turn to the results of the largest multicenter Anglo-Scandinavian study ASCOT, which demonstrated a completely new approach to the strategy of modern antihypertensive therapy.^{33,34} The ASCOT study, which included more than 19,000 patients, allowed us to take a new look at CCB and ACEI in preventing CVR. The ASCOT-BPLA study³⁵ convincingly demonstrated that the combination of amlodipine with perindopril is significantly more effective in reducing CVR than the combination of atenolol with bendroflumethiazide, a thiazide diuretic. There was a significant reduction in the risk of coronary endpoints by 13%, fatal and nonfatal stroke by 23%, cardiovascular death by 24%, new cases of renal dysfunction by 15%, and new cases of diabetes mellitus by 30%. The results of the ACCOMPLISH study demonstrated a clear advantage of the combination of CCB and ACEI over the combination of ACEI with a diuretic in the correction of high CVR, mainly in patients with obesity and hypertension.³⁶

The high efficiency of the CCB and ACEI combination is achieved, on the one hand, due to the pronounced arteriodilating action of CCB, and on the other hand, due to the leveling of the effects of RAAS. The combined use of CCB and RAAS inhibitors neutralizes the counter-regulatory mechanisms that reduce the effectiveness of drugs. Thus, ACEI suppresses the activity of RAAS and SAS, the activation of which reduces the effectiveness of CCB. In turn, the negative sodium balance caused by the latter is eliminated by ACEI. In addition, the combined use of drugs of these classes can significantly reduce the number of side effects. It has been shown that such an undesirable side effect of CCB as ankle edema disappears or is significantly reduced with the parallel use of ACEI. CCB reduces the incidence of dry cough, one of the most common side effects of ACEI.³⁶⁻⁴²

It should be noted that RAAS inhibitors and CCB are metabolically neutral antihypertensive drugs, which makes this combination attractive for patients with impaired lipid, carbohydrate, and purine metabolism. In our previous study, the combined use of azilsartan, an angiotensin II receptor blocker, with nitrendipine, we found the metabolic neutrality of the presented therapy regimen and a decrease in the level of blood uric acid.⁴³ In the current study, the combined use of ACEI with CCB is characterized by high antihypertensive efficacy, organo-protective effects, and good tolerability, which generally characterizes this combination as the most

optimal and effective in reducing the risk of cardiovascular complications in AH patients.

Thus, the six-month perindopril/amlodipine FDC therapy contributed to achieving target levels of SBP and DBP in 98.2% and 96.4% of patients, respectively. A decrease in LVMI and LAVI by 14.6% and 11.8%, respectively, was accompanied by an improvement in LVEF and LV deformation properties assessed by GLS and SR. Parameters of central hemodynamics and arterial stiffness (cSBP, cDBP, cPP, AA, and PWV) also demonstrated improvement against the background of the therapy.

In conclusion, in AH patients with LV concentric hypertrophy, significant disturbances in the LV deformation properties are formed. The six-month perindopril/amlodipine FDC therapy provides good antihypertensive, cardioprotective, and vasoprotective efficacy, which is expressed in reliable regression of LVH, improvement of LV diastolic function, positive effect on the LV deformation properties and increased elasticity of the arteries.

Ethical Considerations

This study was conducted within the framework of the project PZ 202007075 with the support of the Ministry of Innovative Development of the Republic of Uzbekistan. The study protocol was reviewed and approved by the Ethics Committee of the Republican Specialized Centre of Cardiology. All participants provided written informed consent.

Competing Interests

The authors declare that they have no competing interests.

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