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CLINICAL TRIAL

Effect of Different Variants of Hypotensive Therapy on Structural Remodeling of The Heart

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Abstract

Background: The remodeling of heart in the light of modern concepts often in essential degree can complicate the course of arterial hypertension, acting not only as a factor that contributes to complications, but also further progression of the disease.

Material and methods: 124 patients (86 men and 38 women) with arterial hypertension of degree I-III with mean age of 55.7±1.0 years were studied. The patients underwent cardiac echocardiography with cardiac remodeling and its type being assessed. After baseline examination, patients received hypotensive therapy with azilsartan medoxomil, losartan, prestans and triplixam for 12 months. Patients with I-II degrees of arterial hypertension were prescribed azilsartan medoxomil or losartan, with II-III degrees – perindopril+amlodipine (prestans) or perindopril+indapamide+amlodipine (triplixam). The studies were repeated after 6 and 12 months.

Results of the study: In terms of the effect on cardiac remodeling, azilsartan medoxomil prevailed over losartan among patients with arterial hypertension degrees I-II. Among patients with II-III degrees of arterial hypertension, triplixam prevailed over prestans. Positive changes were mediated by decreased left ventricular relative wall thickness, myocardial mass, and left ventricular myocardial mass index.

Conclusions: In the aspect of the influence on the cardiac remodeling in patients with I-II degrees of arterial hypertension, azilsartan medoxomil was superior to losartan, and in patients with II-III degrees of arterial hypertension – perindopril+indapamide+amlodipine versus perindopril+amlodipine.

Keywords: arterial hypertension, cardiac remodeling, one-, two- and three-component hypotensive drugs.

Introduction

Cardiac remodeling in the light of modern concepts can often to some extent complicate the course of arterial hypertension (AH), acting not only as a factor contributing to the development of complications, but also further progression of the disease [1]. The main manifestations of cardiac remodeling are increased MM of LV, LV wall hypertrophy (LVH), changes in geometric shape of LV [2].

The dynamics of the indices reflecting cardiac remodeling in the course of long-term hypotensive therapy has been insufficiently studied.

In the present study we investigated a number of indexes reflecting the structural and functional heart state in 124 patients with AH of I-III degree as well as the dynamics of these indexes during 6 and 12 months of therapy with different hypotensive agents.

Material And Methods

The mean age of the patients was 55.7±1.0 years (27 to 81 years). Of the 124 patients studied, 86 were men (mean age 54.7±1.2 years) and 38 women (mean age 57.8±1.7 years). Diagnosis of AH and its degree was performed in accordance with modern recommendations and criteria [3]. The inclusion criteria for the study were patients with AH of I-III degree. The median duration of AH in the whole group was (median, lower and upper quartiles, confidence interval (CI)) 7.5 (5.0;11.0) CI 3.6-4.7 (with variation from 1 to 21 years); in men, 7.0 (6.0;11.0) CI 3.4-4.6; in women, 8.0 (4.0;12.0) CI 3.7-5.9 years.

Inclusion criteria

Patients with AH of I-III degree in different age and sex

Exclusion criteria

Diabetes mellitus type 2, metabolic syndrome, symptomatic AH, acute myocardial infarction, heart rhythm and conduction disorders, blood diseases, cancer, a history of cerebrovascular disease, heart defects, respiratory, renal and hepatic insufficiency.

The study approval was obtained from the Ethics Committee of Clinical Research of Scientific Research

Table 1: Patient futures in the compared groups

The drug	*Azilsartan*	*Per+Inda+Amlo*	*Amlo+Per*	*Losartan*
Daily dose, mg	80	10 + 2.5 + 10	10 + 5	5
Men	26 (21,0%)	17 (13,7%)	18 (14,5%)	25 (20,2%)
Women	6 (4,8%)	9 (7,26%)	10 (8,06%)	13 (10,5%)
Mean age	59,2 ± 1,5	59,9 ± 2,4	54,4 ± 2,3	51,0 ± 1,6
SBP, mm Hg	168,6 ± 2,0	173,1 ± 1,7	174,4 ± 1,8	168,5 ± 2,0
DBP, mm Hg	103,3 ± 1,9	110,6 ± 1,8	111,9 ± 2,1	105,7 ± 1,7
AH I degree	14 (11,3%)	0 (0,0%)	0 (0,0%)	6 (4,8%)
AH II degree	18 (14,5%)	17 (11,29%)	23 (18,55%)	34 (27,42%)
AH III degree	0 (0,0%)	9 (7,26%)	4 (3,2%)	0 (0,0%)
Duration of AH, years	7,7 ± 0,6	9,1 ± 0,7	8,9 ± 0,6	7,0 ± 0,5
Total	32 (25,8%)	26 (21,0%)	28 (22,6%)	40 (32,3%)

Note: SBP – systolic blood pressure; DBP – diastolic blood pressure.

institute of cardiology (date: 22.02.2023 and Decision no: 14/2). The study was performed in accordance with the Declaration of Helsinki.

All examined patients were evaluated for the absence or presence of signs of cardiac remodeling with determination of remodeling type (according to the proposed classification [4]).

After initial examination at baseline, all patients started hypotensive therapy with one of the following drugs (see table 1), which was continued for 12 months (the drugs were taken once a day (in the morning). The study was repeated after 6 and 12 months of receiving therapy.

The distribution of patients with AH who received hypotensive therapy with different drugs is shown in Table 1.

All examined patients underwent cardiac echocardiographic study (EchoCG). Transthoracic EchoCG was performed on Vivid S5 3ScRS (USA) using standard accesses and methods with assessment of LV end-diastolic (EDS) and systolic (ESS) sizes, end-diastolic (EDV) and end-systolic (ESV) volumes, interventricular septal thickness (IVST), LV posterior wall thickness (LV PWT), calculation of LV relative wall thickness (RWT), parameters of cardiac contractile function (stroke volume (SV), ejection fraction (EF), % anteroposterior shortening (ΔS)), LV myocardial mass (MM), MM index (MMI) according to R. Devereux and N. Reicheck (1977) [5], determining the presence and type of cardiac remodeling.

Statistical processing of the obtained data was performed using Statistica 12.6 program. For quantitative characteristics with normal distribution, we determined mean (M)±error of mean (m), for characteristics with non-normal distribution – median (Md), 25th (lower quartile (Lq)) and 75th quartile (upper quartile (Uq)), minimal (min) and maximal (max) values. Student's t-test was used to compare quantitative indicators with normal distribution; Mann-Whitney U-test for independent populations and Wilcoxon's test for related populations were used for non-normal distribution, respectively. The relationship between qualitative variables was examined on the basis of four-field frequency tables according to Chi-square by Pearson with Yates' correction and Fisher's exact two-sided criterion.

Multivariate analyses were performed using One-Way ANOVA/MANOVA with repeated data enumeration and inclusion of all selected variables (age, systolic blood pressure (SBP), diastolic blood pressure (DBP) values, duration of AH, body mass index (BMI) values, myocardial mass (MM), and LV myocardial mass index (MMI) values) as covariates to study the influence of these variables in subgroups of patients with absence of LVH and different variants of LV remodelling separately. General linear models were used in this analysis. Statistica, version 6.12, was the software used for statistical analysis. Statistical significance was defined as $p \leq 0.05$.

Results

According to multivariate analysis (Figures 1-3), there was a significant influence of only AH duration on the type of LV remodelling, while other studied parameters (SBP, DBP, BMI) had no significant influence. Significantly higher indices of LV MM and MMI were in the groups with LV EH and CH in comparison with patients without LVH and with LV CR.

Figures 1-3. The differences in duration of AH, LV MM and LV MMI in subgroups of patients with absence (0) and different types of LV remodelling (1 - eccentric hypertrophy, 2 - concentric hypertrophy and 3 - concentric remodelling).

As shown in Figures 1-3, the duration of AH was the lowest in patients without signs of LV remodelling, and the differences with patients with LV CH and LV CR were statistically significant.

LV MM and MMI were significantly lower in patients without signs of LV remodelling and with LV CR, and they did not differ significantly among themselves.

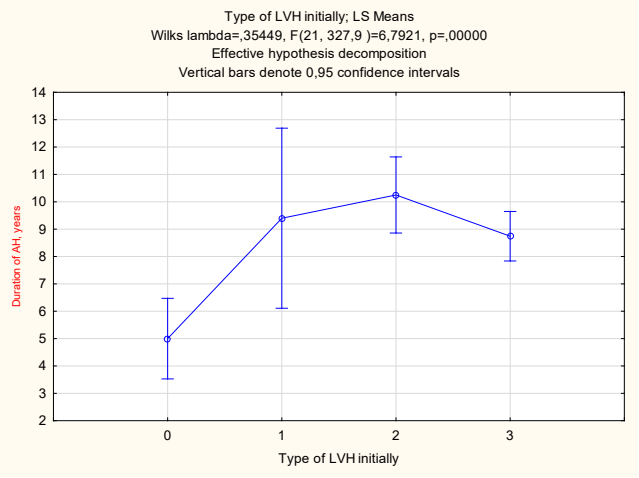

Figure 1: Type of LVH initially

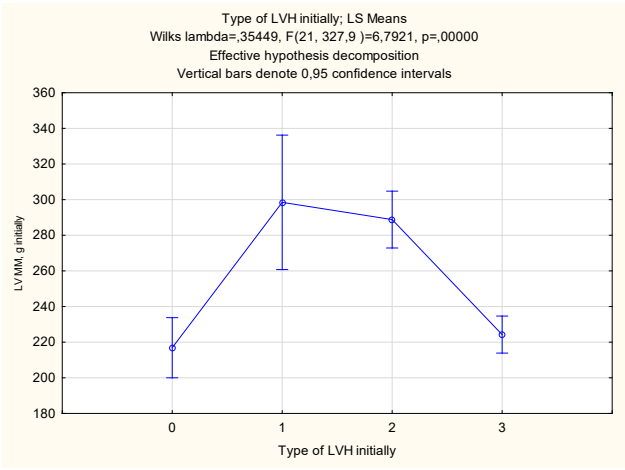

Figure 2: Type of LVH initially

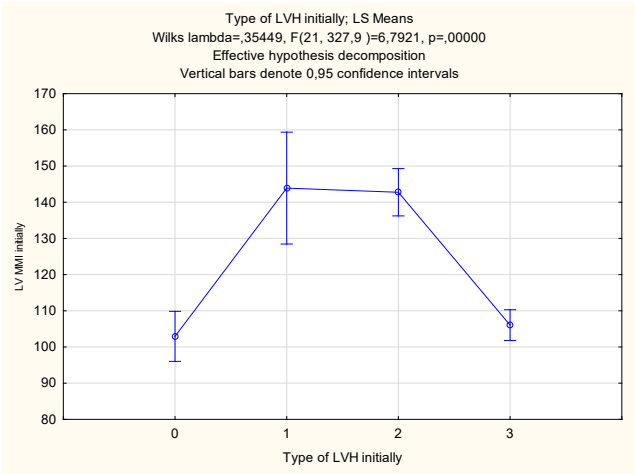

Figure 3: Type of LVH initially

After 6 and 12 months of therapy, both SBP and DBP significantly decreased from baseline values in all compared patient subgroups. To a comparatively greater extent in the subgroups taking azilsartan medoxomil (AZS) (SBP by 28.2/32.4%, p<0.01, p<0.01; DBP by 21.3/30.5%, p<0.01, p<0.001) and perindopril+indapamide+amlodipine (Per+Inda+Amlo) (SBP by 30.7/34.4%, p<0.001, p<0.001; DBP by 21.8/30.9%, p<0.01, p<0.001) compared with subgroups taking prestans perindopril+amlodipine (Amlo+Per) (SBP by 25.1/27.4%, p<0.01; p<0.001; DBP by 12.0/16.6%, p<0.05, p<0.01) and losartan (LOS) (SBP by 25.1/27.4%, p<0.01, p<0.01; DBP by 12.0/21.3%, p<0.05, p<0.01), respectively.

MM of LV in some patients receiving AZS and Per+Inda+Amlo decreased relatively more: by 15.4% (p<0.001) and 16.8% (p<0.001) after 6 months, and by 25.3% (p<0.001) and 15.4% (p<0.001) after 12 months of therapy. In the subgroups of patients receiving Amlo+Per and LOS, there was also a decrease in MM, but to a comparatively lesser extent: by 5.2% and 3.6% after 6 months, and by 7.3% (p<0.05) and 5.7% after 12 months of therapy. MMI of LV in some patients receiving AZS and Per+Inda+Amlo also decreased relatively more: by 11.9% (p<0.05) and 15.4% (p<0.01) after 6 months, and by 24.3% (p<0.001) and 27.5% (p<0.001) after 12 months of therapy. In the subgroups of patients receiving Amlo+Per and LOS, there was also a decrease in MMI, but to a comparatively lesser extent: by 3.8% and 5.6% after 6 months, and by 5.6% and 6.7% after 12 months of therapy.

Figures 4-5 show the types of LV remodeling before and during hypotensive therapy with different drugs. After AZS therapy, the number of patients without LVH increased by 1 patient after 6 months due to 1 case of concentric remodeling (CR) of LV. At the same time, the number of patients with prognostically dangerous concentric hypertrophy (CH) of LV decreased by 3 due to conversion to CR, whose number increased by 2 (after 6 months) and 6 patients (after 12 months of therapy). In 1 patient with eccentric hypertrophy (EH) of LV there were no dynamics. The described changes were caused by a parallel simultaneous decrease both in LV wall thickness, and correspondingly, in RWT, as well as in MM and MMI of the LV in several patients.

After AZS therapy, already after 6 months the number of patients without LVH increased by 1 patient at the expense of 1 case with CR. At the same time, the number of patients with prognostically dangerous CH decreased by 3 due to conversion to CR, whose number increased by 2 (after 6 months) and 6 patients (after 12 months of therapy). In 1 patient with EH, no dynamics were observed. The described changes were mediated by the decrease of both LV wall thickness, RWT, as well as MM and MMI of LV in several patients.

After 6 months of Per+Inda+Amlo therapy, the number of patients without LVH increased by 2 patients after 6 months and by 4 patients after 12 months of therapy due to the conversion of 2 patients with LV CR and 5 with LV CH to the normal LV shape. At the same time, the number of patients with CH decreased by 2 (after 6 months) and by 5

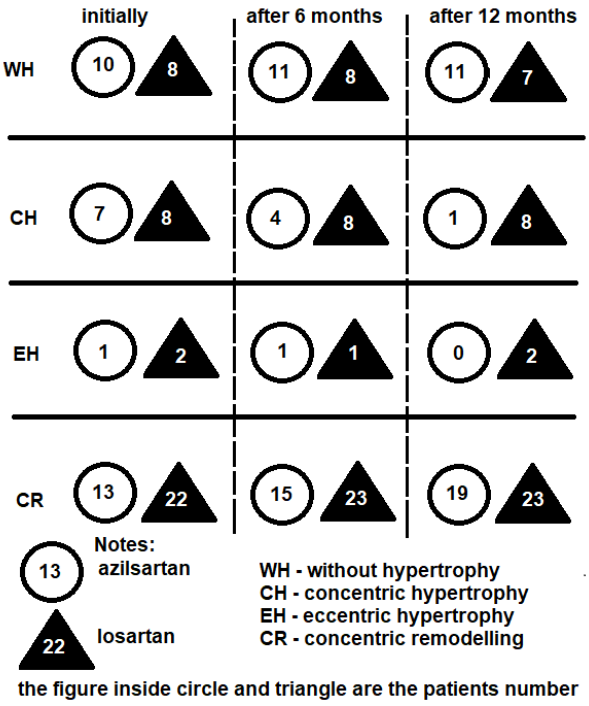

Figure 4: The dynamics of AH patient number with absence and different types of LV remodeling during antihypertensive therapy

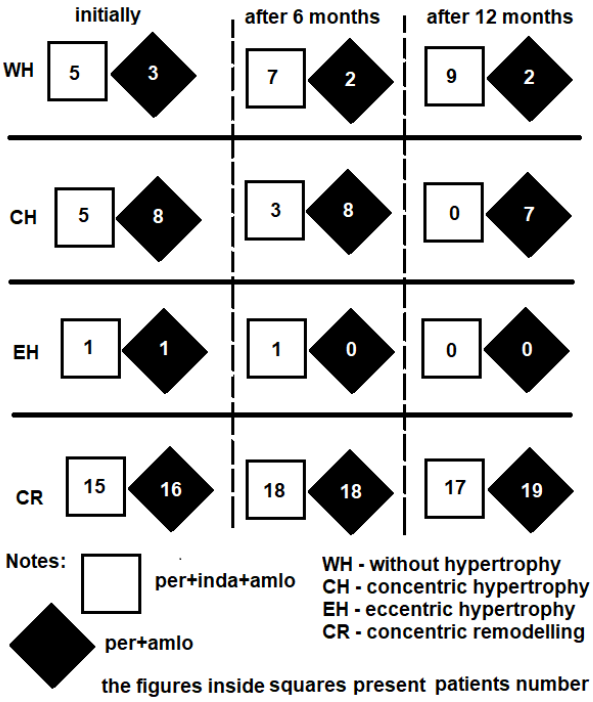

Figure 5: The dynamics of AH patient number with absence and different types of LV remodeling during antihypertensive therapy

(after 12 months). The number of patients with CR increased by 2 after 12 months of therapy due to the conversion of CH and its transition to LV CR. In 1 patient with initially existing EH there was a transition to normal geometric shape of LV, that was apparently caused by the reduction of volumetric overload. The number of patients with LV CR increased by 2 patients after 12 months of therapy due to transition from LV CH due to decrease both in LV wall thickness and MMI.

At the same time, the number of patients with normal LV shape did not change after Amlo+Per therapy. The number of patients with CH decreased by 1 person due to conversion to LV CR, the number of patients with the latter variant increased by 1 after 6 months of therapy and by 2 after 12 months of therapy due to conversion of 1 patient with CH and 1 patient with EH to LV CR variant.

After LOS therapy, however, the number of patients without LVH decreased by 1 patient after 12 months of therapy due to transition of LV form into CR, the number of patients with which increased by 1 patient after 12 months of receiving therapy. The number of patients with CH remained unchanged. The number of patients with EH decreased by 1 patient after 6 months, but increased again by 1 patient after 12 months of therapy.

Discussion

In patients with AH occurred both normal heart geometry and different variants of its remodeling – LV concentric remodeling, LV concentric hypertrophy and LV eccentric hypertrophy [6-8]. Cardiac remodeling observed in AH has a significant prognostic value and represents one of the most significant risk factors of life-threatening cardiovascular complications (primarily, increased risk of sudden death due to asystole or life-threatening paroxysmal arrhythmias) [9].

LV concentric hypertrophy in the majority of cases develops as a result of pressure overload due to overcoming the increased blood flow resistance [10]. LV dilatation, apparently, represents the late stage of transition from LV concentric hypertrophy to myocardial insufficiency. Although all types of LV remodeling in AH patients lead to the increase in the incidence of CVCs, but LV concentric hypertrophy is associated with the highest risk [11]. In general, it is known that decreased LV EF and disorders of local LV contractility in AH patients are associated with a 2.4-3.5-fold increase in the incidence of cardiovascular complications and lethal outcomes [12], [13]. There was noted a great importance of participation of various genetic determinants in the process of cardiac remodeling, determining significant differences of the whole process of cardiac remodeling in separate populations [14].

In this regard, one of the most important tasks of AH treatment is the prevention of LV remodeling. The issue of prognostic significance of each of different variants of myocardial remodeling in clinical course of AH is still not fully studied. A number of studies have shown that both in eccentric hypertrophy (more frequent), and in concentric hypertrophy, LV diastolic dysfunction type II develops, which also causes a high risk of cardiovascular events [15-18].

From another hand, it has been shown in a number of studies that positive treatment results of patients were largely associated with positive dynamics of cardiac remodeling parameters and restoration of myocardial segment contractility [19], [20].

To date, the effect of hypotensive drugs of new classes on the initially altered structural and functional state of the heart has been insufficiently studied, which makes further research in this direction urgent due to the emergence of both new groups of drugs and new hypotensive agents. There were indications that optimal pharmacotherapy of AH should be aimed not only at normalization of elevated BP level, but also at correction of structural disorders in the heart. This goal can be achieved partly by leveling (reducing) the mechanical load on the heart muscle (due to the normalization of elevated BP), as well as by influencing the chemical mediators of remodeling processes, primarily on angiotensin II [21]. In experimental [22] and clinical conditions [23]; [24] it was demonstrated that the effect of new generation drugs from the sartan group prevails over the old ones both in the aspect of achieving the target BP level [25], and improvement of LV diastolic function [26]. Though greater ability of LOS in comparison with aliskiren to reverse the developed LV cardiac remodeling has been described [27], however the comparative analysis in this aspect with other sartans was not carried out. According to our data, AZS was superior to the effect of LOS in this respect. Combined hypotensive agents with different mechanisms of action are increasingly used in AH therapy at the present stage [28], which include per+amlo and per+ind+amlo used in the presented study. The effectiveness of combined therapy in reversing cardiac remodeling has been demonstrated [29], but there has been no comparison of their effectiveness in this aspect. According to our data, per+ind+amlo was superior to per+amlo in its ability to improve the geometric shape of the heart, which may be due to the presence of an additional diuretic in the drug.

From these positions, the comparative assessment of the action of various hypotensive agents in terms of their ability to reverse manifestations of cardiac remodeling is of undoubted scientific and practical interest, dictating the need to continue research in this direction with the assessment of potential advantages of using various hypotensive drugs, taking into account the prognostic significance of the effect of reversal of cardiac remodeling manifestations in patients with AH.

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Conclusion

Concentric remodelling is a more favorable variant of LV remodelling in comparison with other types - concentric and eccentric LV hypertrophy, which is confirmed by significantly lower values of LV MM and LV MMI, slightly differing from the values obtained in patients without echocardiographic signs of LVH.

In the aspect of the influence on the left ventricular remodeling in patients with I-II degrees of AH, AZS was superior to LOS, and in patients with II-III degrees of AH better reverse remodelling effect in perindopril+indapamide+amlodipine versus perindopril+amlodipine was observed.

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