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Cardioprotective potential of chronopharmacotherapy in patients with arterial hypertension who had a transient ischemic attack

Aim	Analysis of the cardioprotective effectivity of chronopharmacotherapy in patients with arterial hypertension (AH) after transient ischemic attack (TIA).
Material and methods	174 patients with AH and TIA were evaluated. All patients were randomized to three groups based on the dosing schedule of chronopharmacotherapy: group 1 (n=59), patients receiving indapamide retard 1.5 mg and valsartan 160 mg, both in the morning; group 2 (n=58), indapamide retard 1.5 mg in the morning and valsartan 160 mg in the evening; group 3 (n=57), indapamide retard 1.5 mg in the morning and valsartan 80 mg in the morning and evening. Echocardiography (EchoCG) (ALOKA SSD 2500, Japan) was performed for all patients at baseline and at 12 months of the treatment. Statistical analysis of results was performed with the Statistica 12.0 (StatSoftInc, USA) software.
Results	Before the treatment, EchoCG parameters did not significantly differ between the patient groups. After 12 months of the treatment, positive changes in the end-systolic dimension (ESD), interventricular septal thickness (IVST), thickness of the left ventricular posterior wall (TLVPW), LV myocardial mass (LVMM), LVMM index (LVMMI), ejection fraction (EF), ratio of transmitral early peak flow velocity and late filling flow velocity (E/A), and isovolumetric velocity relaxation time (IVRT) were more pronounced in the group of sartan evening dosing (group 2) than in the group of sartan single morning dosing (group 1) ($p<0.05$). In group 3, the changes in ESD, IVST, TLVPW, LVMM, LVMMI, EF, E/A ratio, deceleration time (DT) of LV, and IVRT were significantly greater than those in group 1, whereas the dynamics of ESD, IVST, TLVPW, LVMM, LVMMI, E/A ratio, and DT were better in group 3 than in group 2 ($p<0.05$). In addition, a significantly greater number of patients with normalized LV geometry was registered in group 3 compared to groups 1 and 2 ($p<0.05$). The number of patients with normal LV diastolic function after the treatment was also significantly greater in group 3 than in group 1 ($p<0.05$) and comparable with group 2.
Conclusion	The morning dosing of indapamide retard and the b.i.d. dosing of valsartan provided more pronounced beneficial changes in major EcoCG indexes and improvement of LV geometry and diastolic function than the sartan single dosing only in the morning or evening in combination with the diuretic.

Keywords	Arterial hypertension; transient ischemic attack; chronopharmacotherapy; left ventricular myocardial remodeling; left ventricular diastolic function
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Cerebrovascular accidents, including transient ischemic attack (TIA) and stroke, are multidisciplinary issues requiring the participation of neurologists, cardiologists, and GPs in processes of patient management and rehabilitation. Although TIA is a temporary episode of cerebral ischemia, it has been shown that the risk of ischemic stroke increases by 4–10% within the first 48 hours following such incidents and by 10–20% in the next three months [1–3]. Subsequently, the likelihood of cerebrovascular accident (CVA) increases 13-fold twelve months after TIA and 7-fold in the next few years [2, 4–6]. Arterial hypertension (AH) is known to be the main cause and the key risk factor of various forms of CVA: TIA, ischemic and hemorrhagic strokes [1, 2].

Myocardial remodeling is another important risk factor of CVA (especially TIA and ischemic stroke) [7]. It has been shown that TIA and ischemic stroke result in 30–40% of cases from thromboembolism involving the formation of blood clots in the heart cavities due

to significant morphological and functional changes in the left heart in the long-term AH setting. Moreover, left ventricular (LV) hypertrophy is associated with a three-fold increase in stroke risk [8].

The influence of 24-hour blood pressure (BP) fluctuations on the development of cerebrovascular disorders cannot be ignored [9–11]. For example, the risk of TIA and ischemic stroke increases during insufficient night-time BP lowering and significant/rapid BP increase in the early morning hours [10, 11]. In this connection, the essential role of antihypertensive treatment (AHT) in primary and secondary prevention of CVA, providing both BP control within 24 hours and regression of structural and functional LV changes, has been confirmed by several large clinical trials [12, 13].

Elements of chronopharmacotherapy in the AH treatment having been used in various international multicenter trials. For example, in the Hope trial, the administration of angiotensin-converting enzyme (ACE) inhibitor ramipril in the evening (21:00) was accompanied by a reduction in the risk of death of repeat CVA and myocardial infarction (MI) in 32% and 20% of cases, respectively [14]. In the Syst-Eur trial, dihydropyridine calcium antagonist nitrendipine was administered in patients over the age of 60 years with isolated systolic AH in the evening (before sleep), along with a decrease in the risk of stroke and fatal and non-fatal cardiovascular complications by 42% and 31%, respectively [15].

However, these trials differed from special chronopharmacotherapy trials due to a lack of comparison groups in which antihypertensive drugs would be administered in the morning. There are separate, including proprietary, data on the effect of administering antihypertensive drugs at different times of day on the 24-hour BP profile, as well as predictors of cardiac and cerebrovascular events such as rate and magnitude of morning rise of systolic and diastolic BP, variability of BP, pulse BP, central aortic pressure, vascular wall stiffness, along with the structural and functional state of the LV myocardium in patients with AH [16–20]. However, the efficacy of the chronopharmacotherapy in AH patients with a history of CVA as important predictors of cerebrovascular complications – specifically TIA and its influence on the structural and functional state and diastolic function of the LV myocardium – have not been widely studied [20]. Thus, our objective in the present study was to analyze the cardioprotective efficacy of chronopharmacotherapy in patients with AH and history of TIA.

Material and Methods

The study included 174 patients with AH and a history of TIA (median age 61 (53.0; 65.5) years). Inclusion criteria: male and female patients over the age of 18 years; confirmed AH [1, 21, 22]; history of TIA of 4 weeks after the acute period (stable neurological status and systemic and cerebral hemodynamics). Exclusion criteria: stroke (ischemic, hemorrhagic); myocardial infarction in the preceding six months exertional angina pectoris of functional class (FC) III–IV; chronic heart failure FC (NYHA) II–IV; heart defects; complex rhythm and conduction disorders; over-dipper 24-hour BP profile; symptomatic AH; concomitant somatic diseases determining adverse short-term prognosis; intolerance of thiazide-like diuretics (TLD); angiotensin II receptor antagonists (ARAs).

The study design was randomized, open-label, prospective, comparative, and parallel. Patients were randomized in three groups depending on the time of administering of antihypertensive drugs during the day: Group 1 (n=59) – patients receiving thiazide-like diuretic indapamide retard 1.5 mg and ARA valsartan 160 mg in the morning; Group 2 (n=58) – patients who took indapamide retard 1.5 mg in the morning and valsartan 160 mg in the evening; Group 3 (n=57) – patients who received indapamide retard 1.5 mg in the morning and valsartan 80 mg in the morning and evening. Treatments including antihypertensive therapy were agreed with neurologists. The rates of administering concomitant medications were comparable in all groups compared. The efficacy of AHT was determined by the results of 24-hour monitoring of BP and office BP [20].

All patients underwent echocardiogram (ALOKA SSD 2500, Japan) at baseline and in 12 months of combined AHT to evaluate LV end-systolic and end-diastolic dimensions (LVESD and LVEDD), LV posterior wall thickness (PWT), and interventricular septal thickness (IVST), LV ejection fraction (LVEF), LV mass, and myocardial index (LVMI). LV diastolic function was also estimated: peak rate of LV early diastolic filling (E); peak rate of LV late diastolic filling (A); E/A ratio, isovolumetric relaxation time (IVRT); deceleration time (DT) of early diastolic blood flow. Three types of diastolic LV dysfunction were distinguished based on the obtained data and according to the current guidelines: hypertrophic, pseudonormal, and restrictive [23].

All patients signed informed consent to be included in the study. The protocol was approved by the local Ethics Committee (Ethics Committee of Krasnodar

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Regional Clinical Hospital No.2, Protocol No. 52 dated November 13, 2013).

The obtained data were processed using STATISTICA 12.0. The quantitative variables are expressed as the median and the lower and upper quartiles (Me [LQ; UQ]). In multiple comparisons, the Bonferroni amendment was used for normal data distribution; the Kruskal-Wallis test was used for non-normal distribution.

Statistical analysis of the differences in quantitative variables used the Mann–Whitney test (for two independent groups) and the Wilcoxon test (for dependent groups). Qualitative comparison of the groups was carried out using the χ^2 test. The statistical significance of the differences in quantitative variables was tested using a multivariate comparison using the Hotelling t^2 test and discriminant function analysis. The differences between data were statistically significant at $p<0.05$.

Results

Clinical findings were analyzed in patients who reached the target level of BP. With the exception of higher diastolic BP in Group 3 and more male patients in Group 2, no inter-group clinical differences were observed prior to the study (Table 1).

The mean dose of valsartan was 160 mg per day in all groups from the start of the study. The dose was elevated after four weeks of chronopharmacotherapy if target BP was not reached [1, 22]. Eight weeks later, combined AHT was modified in all patients who did not reach the target BP; these patients were excluded from further follow-up [1, 22]. Thus, the median daily dose of valsartan of 160 mg/day following 12 months of treatment was comparable in the three groups. The efficacy of AHT was evaluated in 12 months in 43, 48, and 55 patients of Group 1, Group 2, and Group 3, respectively.

The achievement of target BP was evaluated by measuring office BP after eight weeks of treatment. For example, the target BP was registered in 55 (96.4%) patients who were administered ARA twice a day (morning and evening) and TLD in the morning; this was more frequent than in the groups with a single evening or morning administration of valsartan in combination with indapamide retard: 48 (82.7%) and 43 (72.9%) patients, respectively ($p<0.05$).

Most of the basic parameters of the structural and functional state of the LV myocardium in patients with AH and history of TIA, which did not differ between groups at the time of inclusion, were higher than optimal (Table 2).

Table 1. Clinical characteristics of patients with AH and history of TIA prior to the start of chronopharmacotherapy

Parameter	Group 1 (n=59)	Group 2 (n=58)	Group 3 (n=57)
Age, years	62 [53; 70]	58.5 [54; 69]	59 [55; 64]
Duration of AH, years	5 [4; 7]	5 [3; 6]	5 [4; 6]
Male patients, n (%)	15 (25.4)	31 (53.4)*	20 (35.1)
Female patients, n (%)	44 (74.6)	27 (46.6)*	37 (64.9)
Office SBP, mm Hg	145 [134; 150]	145 [132; 151]	145 [132; 156]
Office DBP, mm Hg	76 [69; 84]	77 [67; 85]	87 [83; 90]**
HR, bpm	68 [63; 72]	66 [60; 71]	68 [60; 72]
BMI, kg/m^2	30.5 [27.5; 33.4]	29.2 [25.6; 32.3]	30.8 [29.4; 32.2]

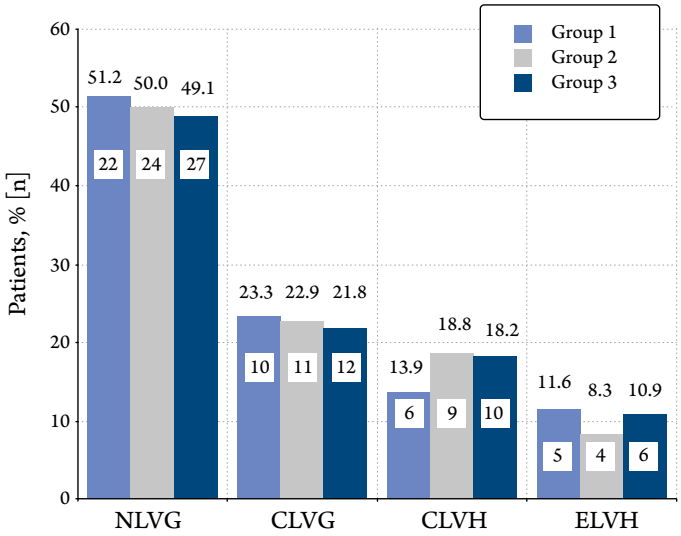
The data are expressed as the median and interquartile range (Me [25th percentile; 75th percentile];
*, $p<0.05$ for the differences in the numbers of male and female patients between Group 1 and Group 2; **, $p<0.05$ for the differences in the DBP levels between Groups 1 and 3 and Groups 2 and 3.
AH – arterial hypertension; SBP – systolic blood pressure; DBP – diastolic blood pressure; HR – heart rate; BMI – body mass index.

Table 2. Parameters of the structural and functional LV state prior to the start of chronopharmacotherapy in patients with AH and history of TIA

Parameter	Group 1 (n=43)	Group 2 (n=48)	Group 3 (n=55)
LVESD, mm	35 [29; 40]	36 [34; 37.5]	37 [31; 39]
LVEDD, mm	47 [44; 50]	46 [44; 47.5]	47 [43; 51]
IVST, mm	11 [10; 11]	11 [10; 12]	12 [12; 13]
LVPWR, mm	10 [9; 10]	10 [9; 11]	10 [9; 11]
LV mass, g	175.2 [136.7; 226.8]	181.4 [146.4; 234.3]	193.8 [154.8; 241.4] *
LVMI, g/m^2	100.9 [86.6; 118]	96.3 [73.2; 111.9]	105.8 [98.8; 118.4]
LVEF, %	58 [55; 61]	55 [55; 56]	55 [54; 55]
E/A	1.1 [0.9; 1.3]	1 [0.9; 1.3]	0.9 [0.9; 1.4]
DT, ms	202.4 [199.2; 220.2]	198 [187; 206]	200 [198; 204]
IVRT, ms	100 [74.5; 102.1]	101.3 [80.1; 114.5]	100 [75.7; 111]

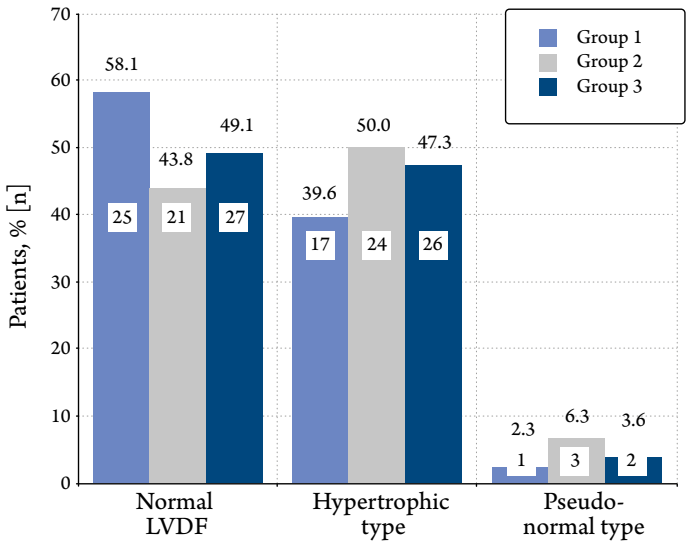
The data are expressed as the median and interquartile range (Me [25th percentile; 75th percentile]).
*, $p<0.05$ for the differences in LV mass in Group 3 compared to Group 1 and Group 2. LVESD – left ventricular end-systolic dimension; LVEDD – left ventricular end-diastolic dimension; IVST – interventricular septal thickness; LVPWT – left ventricular posterior wall thickness – LVMI – left ventricular mass index; LVEF – left ventricular ejection fraction; E/A – the ratio of peak early diastolic filling velocity and late diastolic filling velocity; DT – deceleration time of early diastolic blood flow; IVRT – isovolumetric relaxation time.

Figure 1. Number of patients with different LV geometries prior to chronopharmacotherapy



CLVH – concentric left ventricular hypertrophy;
CLVR – concentric left ventricular remodeling;
NLVG – normal left ventricular geometry;
ELVH – eccentric left ventricular hypertrophy.

Figure 2. Number of patients with different types of LV diastolic functions prior to chronopharmacotherapy



LVDF – left ventricular diastolic function.

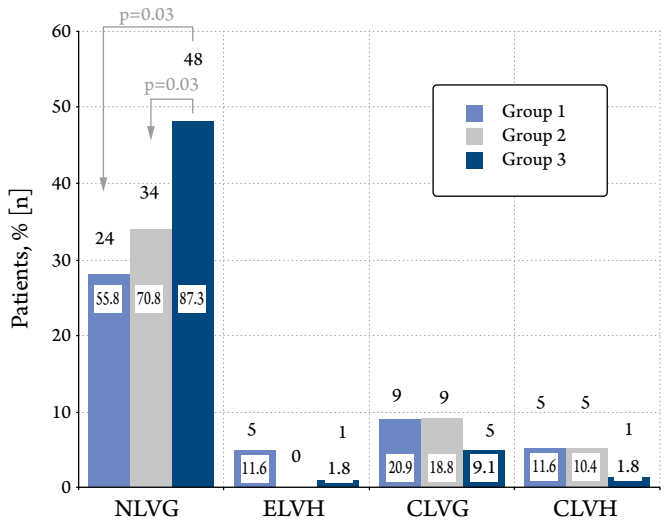
Normal LV myocardial geometry was observed in most patients of all groups at baseline (Figure 1).

LV myocardial remodeling, such as concentric LV remodeling (CLVR), concentric LV hypertrophy (CLVH), and eccentric LV hypertrophy (ELVH), were found in all groups with the same frequency ($p>0.05$).

The numbers of patients with normal diastolic function and a number of diastolic LV dysfunction variants were comparable in the study groups. Moreover, hypertrophic diastolic dysfunction was registered significantly more often than pseudonormal variant (Figure 2).

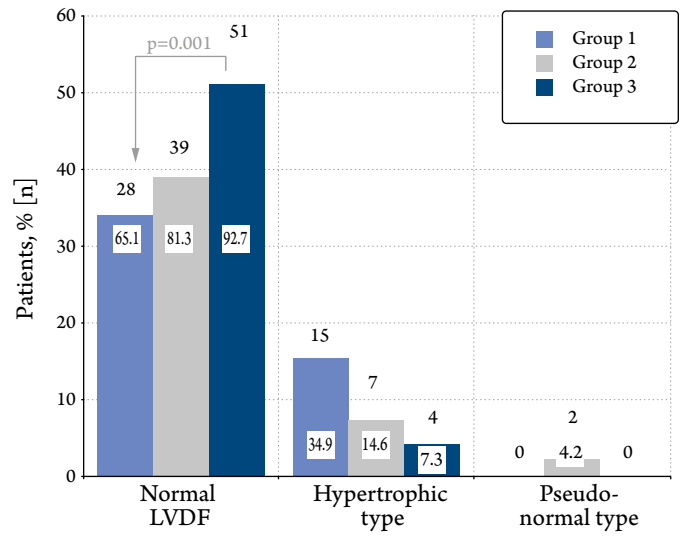
Although positive statistically significant changes in the echocardiographic indicators were observed in all groups after 12 months, a comparison of the rates of changes in the main structural and functio-

Figure 3. Number of patients with AH and history of TIA, with different LV geometries after 12 months of chronopharmacotherapy



NLVG – normal left ventricular geometry;
CLVH – concentric left ventricular hypertrophy;
CLVR – concentric left ventricular remodeling;
ELVH – eccentric left ventricular hypertrophy.

Figure 4. Number of patients with AH and history of TIA, with different types of LV diastolic function after 12 months of chronopharmacotherapy



LVDF – left ventricular diastolic function.

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Table 3. Comparative analysis of changes in the main echocardiographic parameters during chronopharmacotherapy in Group 1 and Group 2

Parameter	Group 1 (n=43), priot to treatment	Group 1, (n=43), after 12 months of treatment	Δ%1	Group 2 (n=48), priot to treatment	Group 2, (n=48), after 12 months of treatment	Δ%2	p Δ%1–2
LVESD, mm	35 [29; 40]	33 [25; 37]	-3.4*	36 [34; 37.5]	33 [32; 35]	-6.9*	0.01
LVEDD, mm	47 [44; 50]	42 [41; 45]	-5*	46 [44; 47.5]	43 [40; 44]	-6.5*	ns
IVST, mm	11 [10; 11]	10 [9; 11]	-7.6*	11 [10; 12]	9 [9; 10]	-11.1*	0.01
LVPWR, mm	10 [9; 10]	9 [9; 10]	-5.5*	10 [9; 11]	9 [8; 10]	-11.1*	0.01
LV mass, g	175.2 [136.7; 226.8]	140.3 [126; 202.3]	-7*	181.4 [146.4; 234.3]	170.3 [137.2; 190.7]	-10.2*	0.01
LVMI, g/m^2	100.9 [86.6; 118]	90.3 [75.1; 105.4]	-4.6*	96.3 [73.2; 111.9]	87.8 [69.6; 96.6]	-10.2*	0.01
LVEF, %	58 [55; 61]	59 [55; 62]	1.8*	55 [55; 56]	60 [56; 60]	8.1*	0.01
E/A	1.1 [0.9; 1.3]	1.3 [1; 1.4]	1.9*	1 [0.9; 1.3]	1.2 [1.1; 1.4]	1.8*	ns
DT, ms	202.4 [199.2; 220.2]	199 [187; 200.2]	-5.2*	198 [187; 206]	189 [165; 97]	-4.6*	ns
IVRT, ms	100 [74.5; 102]	98 [74; 101]	-2*	101.3 [80.1; 114.5]	98 [78.6; 98.5]	-7.4*	0.01

The data are expressed as the median and interquartile range (Me [25th percentile; 75th percentile]);
*, p<0.05 for the differences in the parameters prior to and after 12 months of treatment; Δ%, differences in percentages prior to and after 12 months of treatment; p Δ%1–2, for the differences between Group 1 and Group 2 after 12 months of treatment; ns, nonsignificant (p>0.05). LVESD – left ventricular end-systolic dimension; LVEDD – left ventricular end-diastolic dimension; IVST – interventricular septal thickness; LVPWT – left ventricular posterior wall thickness – LVMI – left ventricular mass index; LVEF – left ventricular ejection fraction; E/A – the ratio of peak early diastolic filling velocity and late diastolic filling velocity; DT – deceleration time of early diastolic blood flow; IVRT – isovolumetric relaxation time.

Table 4. Comparative analysis of changes in the main echocardiographic parameters during chronopharmacotherapy in Group 1 and Group 3

Parameter	Group 1 (n=43), priot to treatment	Group 1, (n=43), after 12 months of treatment	Δ%1	Group 3 (n=55), priot to treatment	Group 3, (n=55), after 12 months of treatment	Δ%3	p Δ%1–3
LVESD, mm	35 [29; 40]	33 [25; 37]	-3.4*	37 [31; 39]	33 [30; 37]	-7.9*	0.01
LVEDD, mm	47 [44; 50]	42 [41; 45]	-5*	47 [43; 51]	41 [39; 45]	-11.8*	0.01
IVST, mm	11 [10; 11]	10 [9; 11]	-7.6*	12 [12; 13]	8 [7; 10]	-32.1*	0.0001
LVPWR, mm	10 [9; 10]	9 [9; 10]	-5.5*	10 [9; 11]	8 [7; 9]	-22.2*	0.0001
LV mass, g	175.2 [136.7; 226.8]	140.3 [126; 202.3]	-7*	193.8 [154.8; 241.4]	145.6 [135; 178.9]	-20.1*	0.0001
LVMI, g/m^2	100.9 [86.6; 118]	90.3 [75.1; 105.4]	-4.6*	105.8 [98.8; 118.4]	84.2 [73.8; 94.9]	-20.1*	0.0001
LVEF, %	58 [55; 61]	59 [55; 62]	1.8*	55 [54; 55]	60 [58; 62]	7.6*	0.001
E/A	1.1 [0.9; 1.3]	1.3 [1; 1.4]	1.9*	0.9 [0.9; 1.4]	1.3 [1.2; 1.4]	33.3*	0.0001
DT, ms	202.4 [199.2; 220.2]	199 [187; 200.2]	-5.2*	200 [198; 204]	179 [173; 189]	-8.3*	0.01
IVRT, ms	100 [74.5; 102]	98 [74; 101]	-2*	100 [75.7; 111]	89 [74; 95]	-7.6*	0.01

The data are expressed as the median and interquartile range (Me [25th percentile; 75th percentile]);
*, p<0.05 for the differences in the parameters prior to and after 12 months of treatment; Δ%, differences in percentages prior to and after 12 months of treatment; p Δ%1–3, for the differences between Group 1 and Group 3 after 12 months of treatment. ns – nonsignificant (p>0.05); LVESD – left ventricular end-systolic dimension; LVEDD – left ventricular end-diastolic dimension; IVST – interventricular septal thickness; LVPWT – left ventricular posterior wall thickness – LVMI – left ventricular mass index; LVEF – left ventricular ejection fraction; E/A – the ratio of peak early diastolic filling velocity and late diastolic filling velocity; DT – deceleration time of early diastolic blood flow; IVRT – isovolumetric relaxation time.

Table 5. Comparative analysis of changes in the main echocardiographic parameters during chronopharmacotherapy in Group 2 and Group 3

Parameter	Group 2 (n=48), priot to treatment	Group 2, (n=48), after 12 months of treatment	Δ%2	Group 3 (n=55), priot to treatment	Group 3, (n=55), after 12 months of treatment	Δ%3	p Δ%2–3
LVESD, mm	36 [4; 37.5]	33 [32; 35]	-6.9*	37 [31; 39]	33 [30; 37]	-7.9*	ns
LVEDD, mm	46 [44; 47.5]	43 [40; 44]	-6.5*	47 [43; 51]	41 [39; 45]	-11.8*	0.01
IVST, mm	11 [10; 12]	9 [9; 10]	-11.1*	12 [12; 13]	8 [7; 10]	-32.1*	0.0001
LVPWR, mm	10 [9; 11]	9 [8; 10]	-11.1*	10 [9; 11]	8 [7; 9]	-22.2*	0.0001
LV mass, g	181.4 [146.4; 234.3]	170.3 [137.2; 190.7]	-10.2*	193.8 [154.8; 241.4]	145.6 [135; 178.9]	-20.1*	0.0001
LVMI, g/m^2	96.3 [73.2; 111.9]	87.8 [69.6; 96.6]	-10.2*	105.8 [98.8; 118.4]	84.2 [73.8; 94.9]	-20.1*	0.0001
LVEF, %	55 [55; 56]	60 [56; 60]	8.1*	55 [54; 55]	60 [58; 62]	7.6*	ns
E/A	1 [0.9; 1.3]	1.2 [1.1; 1.4]	1.8*	0.9 [0.9; 1.4]	1.3 [1.2; 1.4]	33.3*	0.0001
DT, ms	198 [187; 206]	189 [165; 197]	-4.6*	200 [198; 204]	179 [173; 189]	-8.3*	0.01
IVRT, ms	101.3 [80.1; 114.5]	98 [78.6; 98.5]	-7.4*	100 [75.7; 111]	89 [74; 95]	-7.6*	ns

The data are expressed as the median and interquartile range (Me [25th percentile; 75th percentile]);
*, p<0.05 for the differences in the parameters prior to and after 12 months of treatment; Δ%, differences in percentages prior to and after 12 months of treatment; p Δ%2–3, for the differences between Group 2 and Group 3 after 12 months of treatment; ns – nonsignificant (p>0.05); LVESD – left ventricular end-systolic dimension; LVEDD – left ventricular end-diastolic dimension; IVST – interventricular septal thickness; LVPWT – left ventricular posterior wall thickness – LVMI – left ventricular mass index; LVEF – left ventricular ejection fraction; E/A – the ratio of peak early diastolic filling velocity and late diastolic filling velocity; DT – deceleration time of early diastolic blood flow; IVRT – isovolumetric relaxation time.

nal parameters of the LV myocardium showed more pronounced positive changes of the main echocardiographic parameters in Group 2 versus Group 1 (p<0.05) (Table 3). At the same time, IVRT reduced statistically more significantly in the group of the evening administration of ARA (Group 2) than in Group 1 (Table 3). By comparing the rates of changes in the echocardiographic parameters of the structural and functional state of the LV myocardium between Group 1 and Group 3, it was shown that the best positive changes were observed in patients who took sartans twice a day in combination with TLD in the morning (Group 3; Table 4).

E/A, DT, IVRT were statistically significantly higher in Group 3 than Group 1 (Table 4). Moreover, the comparisons of echocardiograms revealed that LVEDD, IVST, LVPWT, LV mass, LVMI, E/A, and DT changed more in Group 3 than in Group 2 (Table 5).

The discriminant analysis used to compare the groups in pairs prior to chronopharmacotherapy showed statistically significant discrimination: Group 1 and Group 2 (Wilks's λ=0.48934, F=5.6651, p<0.00001), Group 1 and Group 3 (Wilks's λ=0.46397, F=6.8494, p<0.00001) and Group 2 and Group 3 (Wilks's λ=0.48293, F=6.7301, p<0.00001). While the parameters of interest differed between the groups as a whole, the quality of discrimination can be considered average. The highest quality of discrimination during chronopharmacotherapy was found between Group 1 and Group 3 (Wilks's λ=0.33093, F=1.697, p<0.00001). Group 1 and Group 2 (Wilks's λ=0.48349, F=4.0442, p<0.00001) and Group 2 and Group 3 (Wilks's λ=0.56198, F=3.6187, p<0.00001) differed statistically significantly reliably; however, here the quality of discrimination was average.

Of note, the normal LV geometry was registered more often in patients who received TLD in the morning and ARA twice a day (morning and evening before sleep; Group 3) than in Group 1 and Group 2 (48 (87.3%) patients versus 24 (55.8%) and 34 (70.8%) patients, respectively) after 12 months of treatment. The number of patients with ELVH, CLVR, and CLVH decreased equally in all groups during the course of the treatment (Figure 3).

Moreover, there were more patients with normal LV diastolic function (92.7%) among those who took valsartan twice a day in combination with indapamide retard in the morning (Group 3) than in Group 1

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(65.1%) and was comparable to that in Group 2 after 12 months of treatment (Figure 4). LVDDs such as hypertrophic and pseudonormal diastolic dysfunction were registered in all groups with the same frequency during chronopharmacotherapy (Figure 4).

Discussion

Chronopharmacotherapy with the administration of indapamide retard in the morning and valsartan twice a day in patients with AH and history of TIA was associated with more significant positive changes of the main parameters of the structural and functional LV state, as well as more frequent normalization of LV geometry and diastolic function, than the administration of ARAs (in the morning or evening) in combination with morning TLD. The anti-remodeling effect of sartans in the evening in combination with diuretics in the morning fell in between the other treatment option: while it was superior to the morning administration of drugs, it was inferior to the use of ARA twice a day and TLD only in the morning.

In our previous paper, it was shown that the majority of patients with AH and a history of TIA had a pathological 24-hour BP profile of non-dipper type [20]. There is evidence of excessive activity of the sympathetic nervous system (SNS) in an insufficient decrease in BP at the night hours, which in turn is associated with night-time hyperactivity of the renin-angiotensin-aldosterone system (RAAS) [20, 24–26]. The administration of sartans only in the evening or twice a day (morning and evening) might have led to the suppression of RAAS and SNS hyperactivity during the daytime and night hours, resulting in the optimized 24-hour BP profile. That may partly explain the improvement of the structural and functional LV state, the regression of LV hypertrophy, and the normalization of LV diastolic function.

Since valsartan has a relatively short half-life of 6–9 hours, the twice-a-day administration of valsartan provided more stable antihypertensive and anti-remodeling effects compared to the once-a-day administration, which may be due to heterogeneous suppression of the RAAS activity during the day [27].

Moreover, circadian rhythms are disturbed with age due to a progressive decrease in secretory activity of the epiphysis [17, 28]. Given the median age of patients in our study (61 (53–65.5) years) and the prevalence of patients with pathological non-dipper 24-hour BP profile, an impairment of 24-hour sleep-wakefulness rhythm due to possible insufficient melatonin production by the pineal gland at night cannot be excluded [17, 20, 28]. Several trials showed the significant role of melatonin in the biological rhythm regulation of endocrine and immune functions. As well as its antioxidant and stress-protective effects, melatonin improves the 24-hour BP profile due to vasodilatation by directly influencing vascular smooth muscle cells; this provides regression of the structural and functional changes in the LV myocardium [28, 29]. Thus, the improved cerebral microcirculation (including in the epithalamic region) in the night and early morning hours might be due to the twice-a-day administration of valsartan or taking it before sleep [27, 30]. The suggestion that the cerebroprotective effects of valsartan help to optimize the night-time secretion of melatonin by the pineal gland can partly explain the positive changes in the 24-hour BP profile, LV geometry in patients with AH, and history of TIA. However, this suggestion clearly requires further study.

Limitations

This study was restricted by its design that lacked an evaluation of the correlation between the use of valsartan and changes in the melatonin secretion during the day. This correlation should be studied and discussed further.

Conclusion

As compared to the use of sartans only in the morning or evening hours in combination with diuretics, the administration of indapamide retard in the morning and valsartan twice a day provided more pronounced positive changes in the main echocardiographic parameters, including improved LV geometry and diastolic function. Thus, chronopharmacotherapy provides a certain cardioprotective effect in patients with AH and a history of TIA and can be used in real-world clinical practice.

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