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Parameters of Hemodynamic Allostasis in Patients of Various Age Groups with Essential Arterial Hypertension

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We determined the criteria for the diagnosis of hemodynamic allostasis and compared it with the index of allostatic load in patients of different age group with essential arterial hypertension without metabolic syndrome. The study included 87 subjects divided into 3 groups: patients with essential arterial hypertension at the age ⩽60 years (n=31; group 1), patients with essential arterial hypertension above 60 years (n=41; group 2), and healthy volunteers (n=15; age 25-69 years, group 3). The data of 24-h BP monitoring were processed by methods of linear and nonlinear rhythm analysis. Based on the analysis, parameters were identified that allow determining the state of allostatic regulation of the 24-h dynamics of BP, as well as parameters that determine the allostatic hemodynamic load on the cardiovascular system. The data obtained were compared with the index of allostatic load in patients of both groups. Regulation of the hemodynamics in patients with essential hypertension without metabolic syndrome in both age groups remained within the limits of hemodynamic allostasis forming the allostatic load on the body, which does not depend on patient's age.

Key Words: *arterial hypertension; hemodynamic allostasis; allostatic load index*

Essential arterial hypertension (EAH) is considered as a multifactorial disease with a hereditary predisposition [1,2]. At the same time, the number of patients with EAH significantly increases in older age groups [3]. The age dependence of the reactivity of the cardiovascular system affecting the nature and method of its adaptation is largely determined by polymorphic markers of the renin–angiotensin–aldosterone system (RAAS) genes, because activity of proteins of this system leads to stabilization of the BP level in EAH [4]. Thus, RAAS influences the state of hemodynamic allostasis in EAH. Treatment of EAH with ACE inhibitors and ACE receptor blockers in combination with diuretic and β-blockers reduces the risk of complications from the target organs. However, possible dependence of the regulatory effects on the cardiovascular system on patient's age it should be taken into account. The study of the regulation changed in constancy the activity of the functional systems of the body described by the term "allostasis" has now gone beyond the concept of stress [5-8]. The choice of pathogenetic therapy for EAH poses a legitimate question to practitioners and researchers whether it leads to restoration of the homeostatic regulation of the cardiovascular system or it remains within the limits of hemodynamic allostasis? In other words, whether the trend to maintenance of changes in the regulation of the cardiovascular system is typical of EAH patients receiving effective antihypertensive therapy?

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The aim of this study was to develop criteria for the diagnosis of hemodynamic allostasis, as well as its comparison with the allostatic load index (ALI) [5] in EAH patients of different age groups without metabolic syndrome.

MATERIALS AND METHODS

The study included 87 patients undergoing outpatient examination and treatment at the outpatient department of City Clinical Hospital No. 13 of the Moscow City Healthcare Department. Informed consent was obtained from each participant. The study was approved by the Ethics Committee of the Institute of Medicine, Peoples' Friendship University of Russia (RUDN University). Exclusion criteria were concomitant pathology that can change the course of EAH (secondary hypertension, coronary heart disease, and metabolic syndrome).

All patients were diagnosed with the second stage of EAH. Three groups were formed: EAH patients at the age ⩽60 years (n=31; group 1), EAH patients above 60 years (n=41; group 2), and healthy volunteers (n=15; age 25-69 years, reference group). All patients received adequate hypotensive therapy, as a result of which the target BP was achieved. ACE inhibitors or ACE receptor blockers in combination with diuretics and (or) calcium antagonists were most often prescribed.

The following clinical and laboratory parameters were studied in patients of groups 1 and 2: body mass index (BMI), waist circumference, glycated hemoglobin (HbA1c), creatinine and urea concentration in the blood, albumin content in 24-h urine samples (microalbuminuria), and the level of immunoreactive insulin.

In all participants, one-time daily measurement of BP (office BP) and 24-h BP monitoring using a TM-2430 outpatient BP monitor (A&D) were performed. The interval between the measurements was 15 min during the daytime (from 07.00 to 22.00) and 30 min at night (from 22.00 to 07.00). The data obtained from 24-h BP monitoring were processed using the EZDoctor software (A&D) and subjected to linear and nonlinear analysis using the Chronos-Fit software [9]. Linear analysis was used to determine office systolic and diastolic BP (SBP, DBP), mean daily and mean night values of SBP (SBP_{day}, SBP_{night}), DBP (DBP_{day}, DBP_{night}), and HR (HR_{day}, HR_{night}), as well as the time index for SBP and DBP and the area index for SBP (time and area load) using EZDoctor 2.7software (A&D).

We also studied the parameters that allow evaluating the integrative features of regulation of the cardiovascular system, in particular, circadian indices for SBP, DBP, and HR determined by dividing the mean value of the corresponding parameter during day hours by its mean value during night; the standard point of BP (SPBP) calculated as DBP/SBP; double product (DP) calculated by the formula: HR×SBP/100; coefficient of variation of the studied parameters determined by the formula: standard deviation/mean value×100%. The criteria for DP evaluation: from 76 to 89 arb. units, mean value; ⩾90 arb. units, below mean; ⩽75 arb. units, above mean. The criteria for SPBP evaluation: this value reflects the conditions of tissue perfusion and normally tends to the golden ratio (0.618) [10]. DP is used to assess the metabolic changes, especially in sports medicine (Robinson index).

To assess the rhythmic component, which is also a parameter of the regulation of the cardiovascular system, we used non-linear rhythm analysis that represents a combination of partial Fourier analysis with the step-by-step regression method using the Chronos-Fit software [9]. The following parameters were determined: mesor (the mean level of the studied parameter over 24 h), amplitude (the maximum deviation of the studied parameter from the mesor), oscillation power (% of rhythm, a chronobiological parameter characterizing the proportion of oscillatory processes, or the proportion of values of the studied parameter that has an oscillatory distribution over 24 h).

The type of the 24-h profile of BP was determined on the basis of the diurnal index (DI) reflecting the percentage of nocturnal decrease in BP and calculated by the formula:

$$DI=(SBP_{day}-SBP_{night})/SBP_{day} \times 100\%.$$

Normally, the DI is 10-20%, in this case, the subjects are characterized as "dippers". Patients with DI 0-10% are called "non-dippers" and patients with DI >20% are "over-dippers". Patients with DI< 0% are "night pickers".

The data of nonlinear analysis and integrative parameters (circadian indices, SPBP, coefficients of variation) were used to assess the type of adaptive responses of the cardiovascular system. The possible influence on these age parameters was revealed by pairwise comparison of groups 1 and 2.

To assess the effect of elevated BP on the formation of allostatic load on the body, ALI was calculated and analyzed [5] using biomarkers: SBP, DBP, BMI, blood concentrations of LDL, HDL, triglycerides, glucose, HbA1c, creatinine, albumin, fibrinogen, and immunoreactive insulin. The basis for calculating ALI is an assessment of quartile deviations for each biomarker with the calculation of total score: 0, no load; 1-2, moderate load; 3-4, high load; ⩾5, very high load.

Statistical analysis of the obtained results was carried out using BioStat LE 7.3.0 software (AnalystSoft, Inc.). The data in each group were analyzed based on the calculation of the coefficient of variation, which

allows us to assess the homogeneity of the groups by BP and HR (when coefficient of variation is 33%, the groups are considered homogeneous and are subject to comparative analysis). As the parameters of central hemodynamics are the subject of homeostatic regulation, the mean values (*M*) and the error of the mean (*m*) were calculated for all parameters. The significance of differences between the mean values was assessed using the nonparametric Mann–Whitney *U* test and the Fisher angular transformation for percentages (one-way test). The differences were significant at $p \leqslant 0.05$.

RESULTS

According to the results of clinical examination and laboratory tests, metabolic syndrome was excluded in all patients of both groups (the level of immunoreactive insulin was within the normal values). There were also slight differences between the groups in the ratio of patients with different types of 24-h BP profile (Table 1). Men prevailed in group 1 and women in group 2. Comparative analysis of the therapy showed that the patients primarily received two groups of drugs; patients above 60 years were more often prescribed diuretics and Ca^{2+} antagonists. The levels of creatinine, urea, and microalbuminuria did not exceed the normal values typical of the corresponding age groups.

We analyzed the data of 24-h BP monitoring according to the standard protocol and independent calculations of the values of DP and SPBP. The development of EAH was accompanied by a decrease in DP in both groups of patients relative to the reference group (Fig. 1). SPBP reflecting the conditions of tissue perfusion approached the "golden section" (0.618) [10] in the reference group (0.620), while in groups 1 and 2, a significant decrease in the parameter (to 0.580 and 0.560, respectively) was observed. These data indicate that, despite the therapy, changed regime of the cardiovascular system control persisted, and this led to changes in SPBP and DP. There is also a significantly higher level of BP load in both groups relative to the reference group (Table 2), as indicated by the SBP time index, the DBP time index, and the SBP area index. This was interpreted by us as the presence of an allostatic load on the cardiovascular system. The presence of hemodynamic allostasis in both groups is also evidenced by the fact that the main significant differences were revealed not between the groups of patients, but between these groups and the reference group. Thus, the patients of groups 1 and 2 differed from the reference group in 9 out of 13 parameters (Fig. 1). Differences between the groups 1 and 2 were revealed only by 2 of 13 parameters analyzed. In group 2, lower values DBP were observed at night,

TABLE 1. Clinical and Laboratory Parameters of Patients of the Studied Groups (*M*±*m*)

Parameter	Patients with EAH under 60 years (*n*=31)	Patients with EAH above 60 years (*n*=41)
Age, years	45.05±2.30	74.5±1.31*
Men, % of patients	62	31
Women, % of patients	38	69
BMI, kg/m^2	25.35±0.32	28.15±0.19
Waist circumference, cm	89.40±1.12	91.50±1.08
Duration of EAH, years	8.8±1.1	15.85±1.12*
HbA1c, %	5.6	6.1
Creatinine, μmol/liter	70.65±2.30	96.2±2.4*
Urea, mmol/liter	3.95±0.29	8.25±0.14*
Microalbuminuria, mg/liter	0.400±0.001	0.700±0.003
Immunoreactive insulin, μU/ml	7.34±0.67	19.39±0.06*
Dipper, % of patients	58	45
Non-dipper, % of patients	23	30
Over-dipper, % of patients	6	9
Night picker, % of patients	13	16
Therapy with ACE inhibitors or ACE receptor blockers, % of patients	80.6	80.5
Therapy with β-blockers, % of patients	12.09	19.5
Diuretic therapy, % of patients	29.0	70.7
Therapy with Ca^{2+} antagonists, % of patients	3.2	39.0

Note. *$p \leq 0.05$.

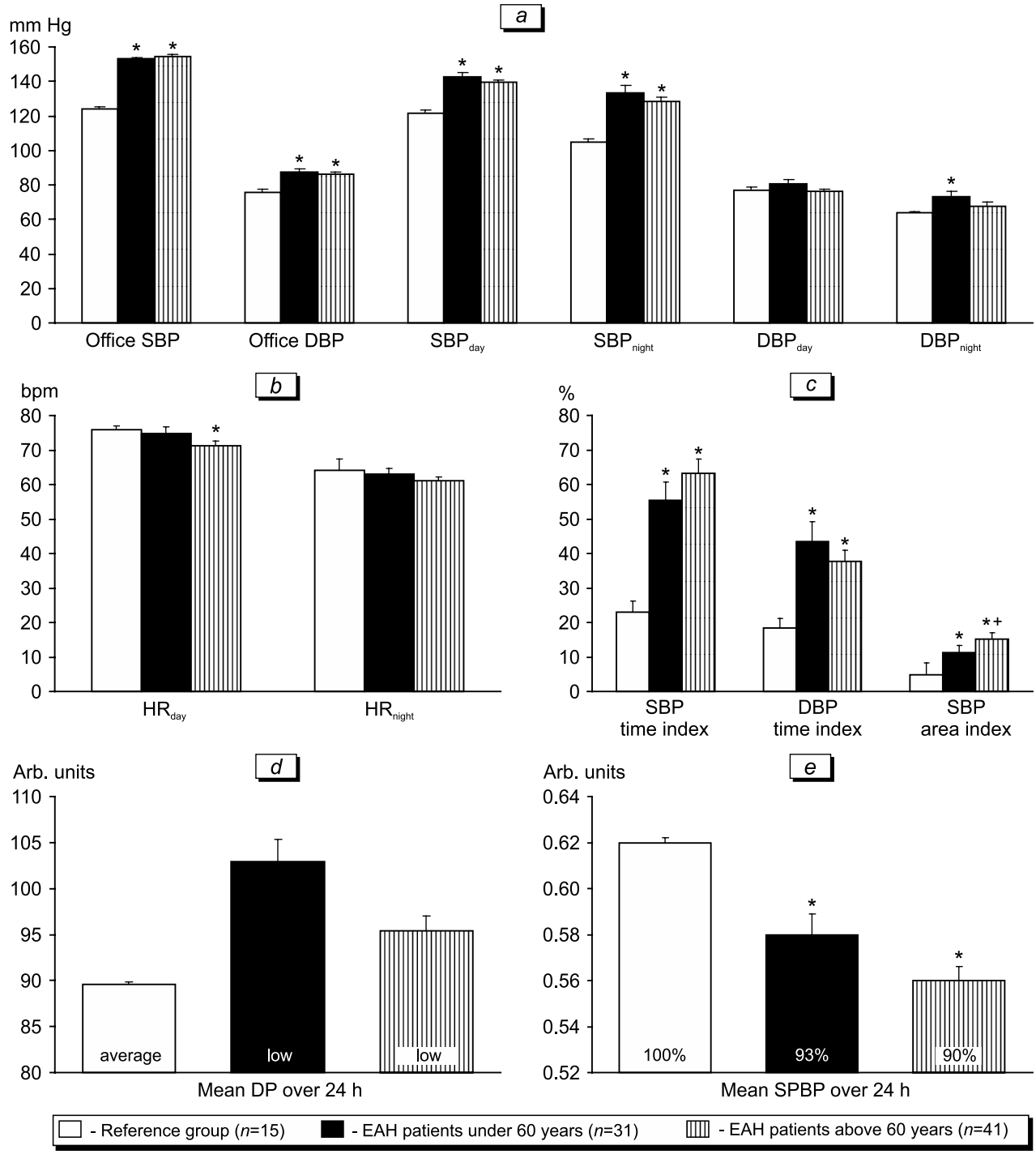

Fig. 1. Comparative analysis of the 24-h dynamics of hemodynamic parameters in the groups. $p \leq 0.05$ in comparison with *the reference group, +patients with EAH under 60 years.

which may be associated with diuretic therapy. Also, a higher SBP area index was registered in this group.

It should be noted that the standard analysis BP using 24-h BP monitoring, in which the measurement of BP is carried out at equal intervals, turns a continuous parameter BP into discrete. Chronos-Fit software allows to restore the continuity of the dynamics of BP and evaluate the features of the chronostructure of the circadian rhythm of BP. In such a comparison, the comparability of the analyzed groups is extremely important. The coefficient of variation allows us to speak about the applicability of this analysis (the value of the parameter is less than 33%) (Table 2). It should be noted that the absence of changes in the dynamics

TABLE 2. Parameters of Chronostructure of 24-h Profile of SBP, DBP, and HR (*M*±*m*)

Parameter	Reference group (*n*=15)	Patients with EAH under 60 years (*n*=31)	Patients with EAH above 60 years (*n*=41)
Mesor			
SBP, mm Hg	114.36±1.00	137.95±1.52*	136.20±3.04*
DBP, mm Hg	71.15±1.52	78.9±1.13*	77.05±1.02*
HR, bpm	72.16±1.05	74.15±1.30	75.25±1.73
Amplitude			
SBP, mm Hg	18.06 ±1.60	25.05±1.52*	23.25±2.22
DBP, mm Hg	15.5±0.95	16.90±1.98	17.30±2.90
HR, bpm	16.31±0.90	18.37±1.64	19.20±2.22
Power of oscillation (% rhythm)			
SBP, %	57.38±3.76	44.95±1.73*	33.70±3.74*+
DBP, %	51.07±2.27	38.40±2.26*	31.95±1.02*
HR, %	53.95±5.53	51.40±0.14	44.05±2.72
Coefficient of variance			
SBP, %	1	9	6
DBP, %	1.2	12	10
HR, %	10	10	10
Circadian index			
SBP, mm Hg	1.18±0.01	1.19±0.02	1.16±0.01
DBP, mm Hg	1.18±0.04	1.07±0.07	1.08±0.02
HR, bpm	1.20±0.02	1.10±0.03*	1.12±0.03*
DP, arb. units	1.35±0.006	1.27±0.043	1.27±0.03

Note. $p \le 0.05$ in comparison with *the reference group, +the group of patients with EAH under 60 years.

of the studied parameters for HR, their "non-involvement", in our opinion, is also related to the methodology of the study: analysis of HR variability using Holter ECG monitoring is more adequate approach for assessment of changes in HR in hemodynamic allostasis in EAH patients.

Analyzing the dynamics of parameters (Table 2) for SBP and DBP by the method of nonlinear analysis, we can note the same pattern that was revealed when analyzing the 24-h BP monitoring data in linear analysis: both groups significantly differed from the reference group by mesor, which reflects the presence of a pathological process. The amplitude of SBP was significantly higher relative to the reference group in the group of patients younger than 60 years, and for the group of patients older than 60 years, there was a tendency to increase this parameter.

Extremely important is significant decrease in the power of oscillations (% of the rhythm) in the 24-h dynamics of SBP and DBP. At the same time, in the group of patients over 60 years, this decrease was deeper than in younger patients. In fact, the decrease in the percentage of the 24-h rhythm is due to an increase in the number of ultradian rhythms in the 24-h dynamics of BP, which are associated with fluctuations in the level of electrolytes [11], which determined the need for a separate study of mean values of BP during the day and at night and their comparison based on the assessment of circadian indices (Table 2). The analysis of this parameter for SBP, DBP, and DP has showed unidirectional changes in the circadian DBP index in the form of a significant decrease in both study groups relative to the reference group.

Thus, the presence of hemodynamic allostasis in patients of both groups is confirmed by the fact of significant differences in most analyzed parameters not between the studied groups, but relative to the reference group. The differences concerned not only the values of BP as a reflection of the pathological process, but also such integral parameters as SPBP, DP, circadian indices of BP and DP, mesor and magnitude of BP, and the power of oscillation (% of rhythm) for BP. At the same time, these parameters did not depend on the age of patients and were determined by the main pathology – EAH.

Taking into account the fact that the BP level is the leading variable in terms of its contribution to the definition of ALI [5], we calculated the value of this

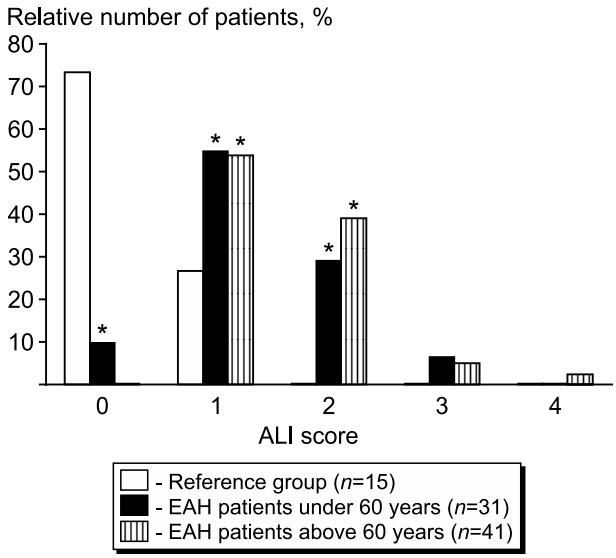

Fig. 2. Evaluation of ALI. *$p \leq 0.05$ in comparison with the reference group.

index for both groups. The following biomarkers were used: SBP, DBP, BMI, blood concentrations of LDL, HDL, triglycerides, glucose, HbA1c, creatinine, albumin, fibrinogen, and immunoreactive insulin. The majority of patients in both groups (54.8 and 53.7%, respectively) had a significantly higher level of ALI (1.0) relative to the reference group (Fig. 2). An increase in the proportion of patients in group 2 (patients with EAH above 60 years) with ALI by 2 points compared with group 1 (patients with EAH under 60 years) we are associated with the age-dependent increase in the main biochemical parameters, primarily immunoreactive insulin (Table 1). At the same time, the values of the parameters did not exceed the limits of the physiological norm. This fact, as well as the absence of metabolic syndrome in patients, suggest that the increase in the level of ALI in both groups is associated with hemodynamic allostasis, which persists despite ongoing therapy. Thus, it can be concluded that hemodynamic allostasis in patients with adequate therapy of hypertension contributes to ALI regardless of the age of the patients. Based on the data obtained, evaluation criteria were developed to verify hemodynamic allostasis and allostatic load in patients with hypertension (Table 3). Analysis of the main parameters obtained by linear and nonlinear analysis of the daily dynamics of BP using integral parameters (DP, SPBP, and circadian indices) (Table 3) allows us to assert that the regulation of the activity of the

TABLE 3. Parameters Characterizing Hemodynamic Allostasis and Allostatic Load on Hemodynamics in Patients with EAH

Parameter	Hemodynamic allostasis	Diagnostics methods	Allostatic load
SBP_{day} SBP_{night} DBP_{day} DBP_{night}	Reflects the dynamics of the pathological process	Analysis of 24-h BP monitoring data with EZDoctor (individual values) and Chronos-Fit (individual+group) software	—
CI for BP, STBP, and DP	Reflects abnormalities (reduction) of regulatory influences day—night	Analysis of 24-h BP monitoring data using EZDoctor software and Excel application	Circadian index for BP ≤1: reflects allostatic load formation
DP	Reflects features of tissue metabolism	Analysis of 24-h BP monitoring data using EZDoctor software and Excel application	—
STBP	Reflects features of tissue perfusion	Analysis of 24-h BP monitoring data using EZDoctor software and Excel application	—
Coefficient of variance of BP	Reflects the adaptive capacity of the cardiovascular system for individual parameters and the homogeneity of the group for the group parameters	Excel application	—
Power of oscillation (% rhythm) for BP with 24-h rhythm	Reflects the appearance of the ultradian rhythms in EAH	Analysis of 24-h BP monitoring data using Chronos-Fit software	—
Area and time index	—	Analysis of 24-h BP monitoring data using EZDoctor software and Excel application	The main cause of target organ failure
Power of oscillation (% rhythm) with 12-, 4-, 6-, and 8-h rhythms	—	Analysis of 24-h BP monitoring data using Chronos-Fit software	Reflects changes in ultradian rhythms with water-salt exchange disturbance against the background of EAH

cardiovascular system in patients with hypertension is characterized by the retention of the changed parameters, *i.e.* the development of the state of hemodynamic allostasis. The latter in hypertension does not depend on age, participates in the formation of an allostatic load on the body and is not stopped by hypotensive therapy that has reached the target values. This conclusion is made in connection with the available data on accelerated aging of the body in the presence of signs of allostasis [12].

Thus, the results of the study allow us to recommend the use of integral indicators reflecting hemodynamic allostasis in patients with hypertension, as well as the evaluation of ALI for drug correction of allostasis parameters in EAH.

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