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Research Article

Complex assessment of blood pressure regulation system in hypertension patients

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Abstract

Introduction. There are almost no studies characterizing the integrative level of blood pressure (BP) regulation.

Materials and methods. 277 people of both genders aged 58.6±6.4 with stage II hypertension disease were randomized into six groups. The monotherapy of hypertension disease was conducted in five groups, using nebivolol, lisinopril, indapamide, amlodipine, and losartan. The sixth group had a combined therapy (lisinopril/indapamide). The therapy effectiveness was assessed at four levels of blood pressure regulation, using the following methods: 1) laser Doppler flowmetry, determination of the level of tumor necrosis factor-α and interleukin-10; 2) echocardiography and Doppler sonography, ultrasound examination of the renal blood flow, ECG, Holter monitoring of ECG; 3) an examination of the heart rate variability level and a quantitative assessment of beta-adrenoreception of erythrocyte cell membranes; 4) the regulatory and adaptive status was assessed, using the method of cardio-respiratory synchronism.

Results and discussion. A more significant BP decrease was revealed during a combination therapy (by 20.4% of the baseline daily value). At the integrative level, an index of the regulatory and adaptive status (iRAS) increased in the treatment with lisinopril/indapamide combination (by 40.5%), amlodipine (by 40.5%), losartan (by 35.3%), and lisinopril (by 30.2%). Nebivolol administration resulted in a 13.5% decrease in iRAS. Indapamide therapy had no significant effect on iRAS.

Conclusion. A comprehensive assessment of the blood pressure regulation system makes it possible to control the effectiveness of the therapy not only on a target organ or function, but also on the condition of the organism as an integral system.

Keywords

blood pressure, blood pressure regulation, integration of blood pressure regulation levels, assessment of treatment effectiveness for primary hypertension.

Introduction

Previously accumulated data on the mechanisms of blood pressure (BP) regulation in human body made it possible to shape the concepts of the system to maintain (or to stabilize) BP (Coffman 2011, Rahmouni 2016).

It seems that creating a comprehensive evaluation of the BP regulation system at 4 levels (this classification is proposed to be used basing on the theory of a hierarchical system of BP regulation): 1) integrative level; 2) vege-

tative level (through the autonomic nervous system); 3) organ level; and 4) peripheral level (endothelial-microcirculatory) will facilitate the development of new methodological approaches to the understanding of pathogenesis of and to the improvement of treating hypertension.

Currently, the ideas concerning local humoral mechanisms of BP regulation are being successfully developed, and the progress in this direction is quite significant (Burnier and Forni 2012, Mangiafico et al. 2013, Markov 2005, Ruilope et al. 2010, Wood et al. 2013). The role of kidneys and heart in BP maintenance is known and well-researched (Carlström et al. 2015, Esler 2015, Qu et al. 2016, Roman et al. 2016, Wu et al. 2016). The significance of the tonus of sections of autonomic nervous system in BP formation is discussed in (Bakris and Nathan 2014, Bhatt et al. 2014, Mu et al. 2011). In recent years, the genetic component in the regulation of BP has been intensively examined (Ehret et al. 2016, Liu et al. 2016, Surendran et al. 2016).

At the same time, there are almost no studies characterizing the integrative level of regulation, uniting the above levels into a single system and determining the state and targeting of a vegetative (autonomic), organ and peripheral regulation mechanisms. The reason seems to be the absence of methodological approaches providing a quantitative assessment of the integrative regulation level in hypertension (Pokrovskii and Polischuk 2016). This approach is declared in the study (Pokrovskii and Kompaniets 2012), which focuses on the inverse relationship between a hypertension degree and a level of regulatory and adaptive status determined by the method of cardio-respiratory synchronism. At the same time, the integrative level has not been considered in combination with other levels of BP regulation yet.

Objective: this research was conducted for a simultaneous comprehensive assessment of abnormalities of BP regulation in hypertensive disease at four levels, including the integrative level.

Materials and methods

A total of 277 people of both genders, aged 45 to 65 (58.6±6.4 years (M±SD)) with diagnosed hypertension stage II, degrees 1 or 2, moderate or high risk, disease duration from 3 to 14 years (7.2±1.4 years) participated in the study. The study did not include any people with significant comorbidity. *Inclusion criteria:* diagnosed stage II arterial hypertension, 1 or 2 degrees, moderate or high risk.

Exclusion criteria: acute forms of coronary artery disease, cardiac angina, clinically significant arrhythmias and conduction disorders, previous or current disorders of cerebral circulation (hemorrhagic or ischemic stroke, transient ischemic attacks), types 1 and 2 diabetes mellitus or abnormalities of carbohydrate tolerance, chronic heart failure above functional class I, disorders of uric acid metabolism, secondary hypertension forms, obstructive respiratory diseases, renal or hepatic insufficiency, concomitant diseases of inflammatory nature, allergic, oncological, hematological and mental illnesses, patients who had not reached the target BP level and who was taking psychotropic or vegetocorrective drugs, and intolerance to systemic administration of antihypertensive drugs.

The control group consisted of 56 healthy individuals (32 men, 24 women) aged 52.3±4.2 with clinical BP<140/90 mm Hg. The results of the study in the control group were used as a reference range for patients with hypertension. All patients gave their written informed consent to participate in the study.

To determine the disorders of BP regulation system mechanism *at the peripheral level*, the following methods were used:

1. Laser Doppler flowmetry (LDF) on a LAKK-01 device (Lazma Scientific Productive Enterprise Laser Medical Devices, Russia). The probe was located in the area of the posterior surface of the left forearm at the point located 3–4 cm above the base of the ulnar and radial styloids along the median line (tender (Head's) lines). Two hours before the study, the patients were forbidden to eat or drink. The patient had 15–20 minutes to get used to the new environment. The initial LDF-gram was recorded when the patient was lying on his/her back supine position, with the arms along the body, in the absence of external influences. The probe was close to the skin, at the same time without compression of surrounding tissues, and preventing the probe from moving too much. The ambient temperature in the room during the measurements varied within 21–24 degrees. The LDF-gram recording continued for 15 minutes with assessing the following indicators:

I_m	index of microcirculation (Kozlov et al. 2017);
SD	standard deviation of I_m;
C_V	Coefficient of variance (Cv=SD/I_m×100%);
NT	neurogenic tone (frequency range 0.02–0.052 Hz, NT=SD×mean BP/(An×I_m),
An	maximum oscillation amplitude in the neurogenic range;
MT	myogenic tone (frequency range 0.07–0.15Hz, MT=SD×mean BP/(Am×I_m),
Am	maximum oscillation amplitude in the myogenic range;
EDTC	endothelial activity (endothelial-dependent component of the tone) (frequency range 0.0095–0.02 Hz, EDTC=SD×mean BP/(Ae×I_m),
Ae	maximum oscillation amplitude in the endothelial activity range;
CBRF	capillary blood flow reserve.

By the results of the conducted tests, evaluating the ratio I_m at rest and CBRF by occlusive sampling, the following types of microcirculatory bloodstream were distinguished (Makolkin et al. 2002):

- normocirculatory (I_m – 4–6 perfusion units (PU), CBRF – 200–300%);
- hyperemic (I_m > 6 PU, CBRF < 200%);

- spastic (I_m < 4.5 PU, CBRF > 300%);
- stagnant (I_m < 4.5 PU, CBRF < 200%);
- stasic (I_m < 4.5 PU, CBRF < 200%).

2. Determination of proinflammatory cytokine level – tumor necrosis factor-α (TNF-α), anti-inflammatory cytokine – interleukin-10 (IL-10); and balance of pro- and anti-inflammatory cytokines (TNF-α/IL-10 coefficient).

To determine the disorders of BP regulation system mechanisms *at the organ level*, the following steps were made:

1. B- and M-mode echocardiography and a Doppler sonography on a Vingmed System 5 Doppler echocardiographic unit (Israel), with a 3.5-MHz transducer, to determine the structural and functional myocardium condition;
2. examination of the renal blood flow with a Philips HD-11XE ultrasonic scanner (USA), using a triplex Doppler sonography with a 2.5–5-MHz curvilinear transducer and a pulse-wave Doppler color mapping; the quantitative analysis included the determination of peak systolic velocity (PsV), end diastolic velocity (EDV) with a calculation of the resistance index (RI) by formula: RI = (PsV−EDV) / PsV;
3. electrocardiography on a Siemens-Sicard electrocardiograph (Germany), evaluating the Cornell Index, Sokolow-Lyon index and other standard indicators;
4. Holter monitoring of ECG with help of a Schiller MT-100 unit (Switzerland), standard indicators were analyzed to identify cardiac arrhythmias and conduction disorders.

To determine the disorders of BP system regulation mechanism *at the vegetative level* (*through the autonomic nervous system*), the following methods were used;

1. The examination of the heart rate variability (HRV) (Lucini et al. 2014, Polupanov et al. 2014, Sala et al. 2017) by a five-minute ECG recording using VNS-Micro software (Neurosoft LLC, Russia) with the assessment of the following indicators:

- RRNN – average of R-R intervals;
- SDNN – standard deviation of normal to normal R-R intervals;
- CV– coefficient of variance of R-R intervals (CV = SDNN/RRNN×100%);
- TP (Total Power) – total capacity of HRV spectrum;
- LF – average of the low-frequency component of HRV spectrum capacity;
- HF – average of the high-frequency component of HRV spectrum capacity;
- VLF – average of the very low-frequency component of HRV spectrum capacity;
- LF norm – the relative capacity of low-frequency waves in normalized units (LF norm = LF/(TP−VLF)×100%);
- HF – relative capacity of high-frequency waves in normalized units (HF norm = HF/(TP−VLF)×100%);
- VLF – average spectrum capacity of an HRV very low frequency component;
- LF% – spectrum capacity of low-frequency variability component as a percentage of the total oscillations power;
- HF% – spectrum capacity of high-frequency variability component, as a percentage of the total oscillations power;
- VLF% – spectrum capacity of very low-frequency variability component, as a percentage of the total oscillations power;
- CI – centralization index (predominance of the activity of the central regulation circuit over the autonomic one);
- LF/HF – vagosympathetic interaction index (Baevskij et al. 2002).

The following vegetative regulation types were distinguished: sympathicotonic (LF/HF > 1.05), parasympathetic (LF/HF < 0.95) and mixed (0.95 < LF/HF < 1.05).

2. A quantitative assessment of beta-adrenoreception of erythrocyte cell membranes (β-ARM) by biochemical method (Striuk et al. 2012) (with an enhanced activity of the sympathoadrenal system resulting in the circulation of its mediators in blood and desensitization of adrenoceptors of red blood cell membranes; β-ARM values increasing).

To determine the disorders of BP system regulation mechanism *at the integrative level*, the regulatory and adaptive status was assessed using the method of cardio-respiratory synchronism.

The sequence of processes through which cardiorespiratory synchronism develops can be represented by some stages. The first stage is perception of a signal from the stimulus that sets the respiratory rate. The second stage includes analyzing this signal and setting the task of arbitrary control of the respiratory rate. The third stage is a conscious formation of the respiratory rate in time with the stimulator and irradiation of excitation from the respiratory to cardiac center. Then the efferent impulses are transmitted along vagus nerves from the medulla oblongata to the rhythmogenic structures of the heart. The fourth stage is an interaction of these pulses with the pace maker. The final result is heart rate generated according to the fixed frequency – development of cardiorespiratory synchronism.

A complex of interacting body systems engaged in implementing the phenomenon of cardiac respiratory synchronization makes it possible to use this method for an integrative assessment of the condition of the body regulatory systems (Pokrovskii and Polischuk 2016).

The possibility of such an assessment for the BP regulation system is discussed in (Pokrovskii and Kompaniets 2012). The examination by using the method of cardiorespiratory synchronism was performed using a software and hardware complex, including a VNS-Micro unit providing a synchronous recording of ECG and pneumogram, and original software for implementing a signal generating algorithm, setting the respiratory rate, recording the onset of cardiorespiratory synchronization and its parameters, and for calculating the index of regulatory and adaptive status (iRAS) by the following formula:

iRAS = (synchronization range / synchronization period at the minimum range) × 100 (Pokrovskii and Polischuk 2016).

Along with the level analysis of regulation mechanisms, BP daily monitoring was performed by using an MnSDP-2 unit (Russia) to establish a daily BP profile.

The patients with hypertension were randomized into groups for a prescribed monotherapy: nebivolol (Nebilet, Berlin Chemie, Germany) at a dose of 7.2±2.8 mg/day – 51 people; lisinopril (Diroton, Gideon Richter, Hungary) at a dose of 15.9±4.1 mg/day – 50 people; losartan (Lorista, KRKA, Slovenia) at a dose of 84.5±15.5 mg/day – 30 people; indapamide (Arifon-retard, Servier, France) at a dose of 1.5 mg/day – 45 people; and amlodipine (Normodipine, Gideon Richter, Hungary) at a dose of 8.4±1.6 mg/day – 44 people. To analyze the sensitivity of the methods used to assess the treatment effectiveness at each level of BP regulation, the study also included a more intensive therapy group of 57 people treaded with a combination of lisinopril and indapamide (at a dose of 8.2±1.8/1.5 mg/day). The mean values of daily systolic and diastolic BP did not vary significantly within the groups.

The studies by means of all the above-described methods were performed at the beginning and then 1, 3 and 6 months after the beginning of the therapy. The article presents the results of the six-month treatment.

The obtained data were normally distributed. To assess the statistical significance of differences in mean values, Student's t-test was used for dependent and independent samples, respectively. The differences were regarded as statistically significant at $p<0.05$.

Results and discussion

The positive BP dynamics was observed within the first month of the treatment, increased towards the third month and remained until the end of the observation period.

The average daily systolic and diastolic BP in the groups 6 months after starting the treatment were the following: when administering nebivolol – 126.6±5.8 and 76.8±5.3 (M±SD), amlodipine – 129.0±5.1 and 76.1±6.0, losartan – 127.3±4.7 and 75.7±5.4, lisinopril – 125.2±4.5 and 75.9±5.6, indapamide – 129.3±5.6 and 76.4±6.2, lisinopril/indapamide – 127.2±5.0 and 76.7±6.1 mm Hg. A more significant BP decrease was revealed when using a combination therapy (by 20.4% of the baseline daily value). The people who had not reached the target BP values within three months of observation were excluded from the study. Influenced by the antihypertensive therapy (AHT), by month 6 the number of patients with "dipper" profile increased, the number of patients with a "non-dipper" profile decreased, and a "night picker" profile was no longer established (Figure 1).

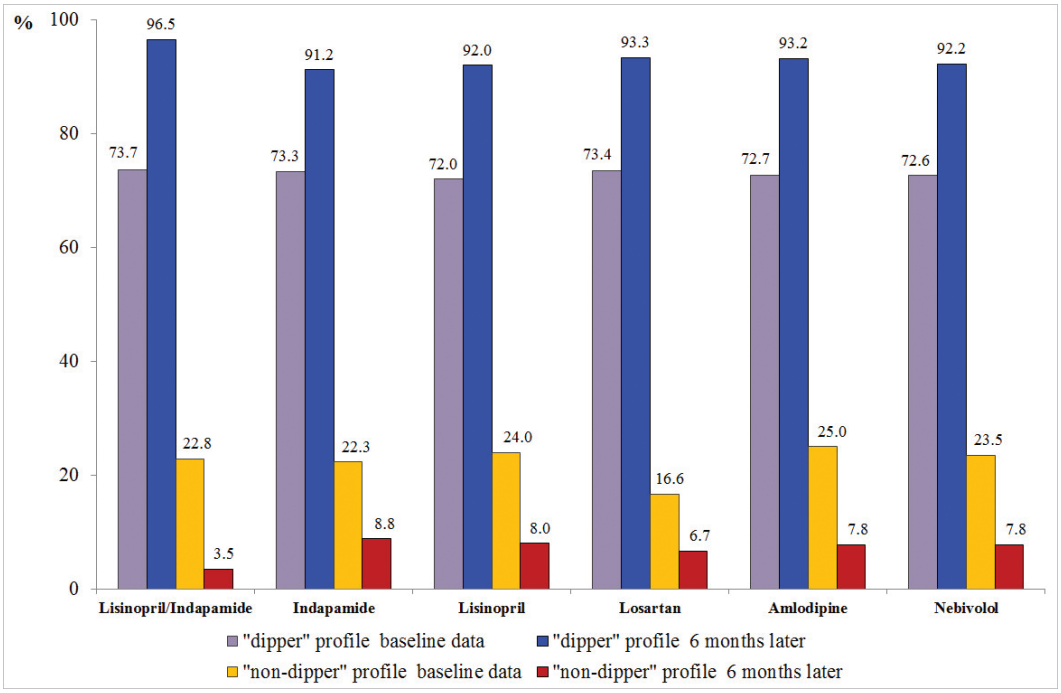

Figure 1. The proportion of patients with "dipper" profile and "non-dipper" profile in the groups at the beginning and after 6 months of treatment.

According to 24-hour BP monitoring data, the initial regular two-phase BP daily rhythm did not change throughout AHT, which suggests a positive physiological effect of the drugs prescribed.

The dynamics of all the parameters (with the statistical significance of the differences) obtained by using the abovementioned methods at 4 selected levels is presented in Tables 1 and 2.

Disorders of BP regulation system mechanisms at the *peripheral level* and their adjustment influenced by antihypertensive therapy

When assessing the peripheral level of BP regulation by LDF method in the patients with hypertension before the treatment, the following types of microcirculation were revealed: normocirculatory (in 42.3% of patients), spastic (in 34.4%), and stasic (in 23.3%). The following changes in microcirculation parameters were observed in the patients with hypertension before the treatment in comparison with the control group: a decrease in I_m (by 14.4%), SD (by 60.2%), C_V (by 54.3%), MT (by 69.7%); an increase in endothelial activity (by 16.6 times); NT values were comparable.

The increased concentrations of proinflammatory cytokine TNF-α and anti-inflammatory cytokine Interleukin-10 were found in the patients with hypertension in comparison with the control group.

Influenced by AHT, by month 6 an increase in proportion of people with normocellular and spastic hemodynamic microcirculation types was detected; there was a decrease in the share of people with the stasic type.

In course of the treatment, a significant decrease in TNF-α (11.6%) and IL-10 level (5%) was observed in comparison with the baseline data only in the combined therapy group (Tables 1, 2).

When administering nebivolol, indapamide, amlodipine, losartan as well as lisinopril/indapamide combination, a significant increase in the SD amplitude of blood flow deviations from the arithmetic mean value of microcirculation index was observed.

Besides, when administering nebivolol, indapamide, amlodipine, losartan and the lisinopril/indapamide combination, C_V significantly increased.

In course of the treatment with lisinopril and losartan, NT and MT significantly decreased.

Only administering nebivolol and a combination therapy (lisinopril/indapamide) led to an increase in the initially low MT (MT increased by 54% and 118%, respectively). Therapy with nebivolol, indapamide, amlodipine, and a lisinopril/indapamide combination significantly decreased the endothelial activity.

Disorders of BP regulation system mechanisms at the *organ level* and their adjustment influenced by antihypertensive therapy

The following types of left ventricular myocardial remodeling were revealed in the patients with hypertension: concentric hypertrophy (in 86% of patients), and concentric remodeling (in 14%).

There was a decrease in left ventricular mass index (LVMI) (by 7.4% in the treatment with nebivolol and by 6.9% in the combination therapy) due to the decrease in thickness of the posterior wall of the left ventricle and interventricular septum; an increase in the ratio of the early (E) to late (A) diastolic transmitral flow velocity (E/A) (in treatment with nebivolol by 13.6% and with amlodipine – by 9.5%).

Besides, the following observations were made in all the groups: the decrease in thickness of the posterior wall of the left ventricle and interventricular septum, a decreased final diastolic size of the left ventricle, and a decreased isovolumetric relaxation time (IVRT). The size of the left atrium did not change significantly. The differences between the groups in all these parameters were insignificant.

The comparative analysis of the changes in renal blood flow showed minor changes influenced by AHT 6 months later.

Disorders of BP regulation system mechanisms at the *vegetative level* (through the autonomic nervous system) and their adjustment influenced by antihypertensive therapy

According to the results of HRV examination, the following types of vegetative regulation were revealed in patients with hypertension: sympathicotonic – in 49.1% of patients, parasympathetic – in 22.4%, and mixed – in 28.5%. In comparison with the control group, there was a decrease in TP (by 34.3%), HF (by 2.0 times), and an increase in VLF% (by 2.5 times), CI (by 3.0 times). β-ARM was initially increased in all the patients with hypertension in comparison with the control group (by 6.8 times).

In the treatment with nebivolol, there was an increase in: SDNN – by 39.5%, CV – by 39.2%, TP – by 50.2%, and a decrease in: LF/HF (by 48.3%), CI (by 64.4%), and β-ARM (by 37.2%).

As a result of the therapy with lisinopril, SDNN increased by 23.8% and TP decreased by 11.5%. At the same time, the vagosympathetic interaction index did not change significantly, but there was a 45.3%decrease in β-ARM.

In the treatment with indapamide and amlodipine, an increase was recorded in: TP (by 33.4% and 34.0% for indapamide and amlodipine, respectively), LF/HF (by 21.1% and 22.2%), CI (by 35.6% and 35.7%), β-ARM (by 32.1% and 22.6%) (Tables 1, 2).

When administering losartan, SDNN increased by 24.9%, the vagosympathetic interaction index did not change significantly, but there was a 38.5%.decrease in β-ARM

In the combined therapy group, there was an increase in SDNN by 44%, CV – by 43.9%, TP – by 50.1% and a decrease in CI by 62.2%. LF/HF ratio did not change significantly, but β-ARM decreased by 42.9%.

Table 1. Evaluation of hypertension treatment efficiency at blood pressure (BP) regulation levels with drugs used in mono- and combined therapy.

BP regulation level	Indicators	Reference Group (n=56) M±SD	Drugs used in mono- and combined therapy					
			lisinopril (n=50) M±SD		indapamide (n=45) M±SD		lisinopril / indapamide (n=55) M±SD	
			Baseline	6 months	Baseline	6 months	Baseline	6 months
Peripheral	I_m, perf.units	4.52±0.81	4.02±0.3§	4.0±0.5	3.67±0.6§	3.85±0.5	**3.53±0.4§**	**4.1±0.6†**
	SD, perf.units	0.71±0.42	0.25±0.01§	0.3±0.06	**0.32±0.01§**	**0.46±0.02†**	**0.28±0.01§**	**0.71±0.04†**
	Cv %	16.51±7.3	6.2±0.9§	7.5±0.7	**8.7±0.03§**	**11.9±0.5†**	**7.9±0.7§**	**17.3±2.6†**
	NT	0.71±0.2	**0.7±0.02**	**0.48±0.02†**	0.73±0.03	0.71±0.02	0.68±0.02	0.68±0.04
	MT	24.4±1.2	**8.5±1.1§**	**6.8±0.7†**	6.13±0.6§	6.3±0.7	**6.8±0.8§**	**14.8±1.6†**
	EDTC	0.45±0.04	6.1±0.8§	6.2±0.6	**8.9±1.3§**	**3.7±0.5‡**	**8.9±1.4§**	**3.7±0.6†**
	TNF -α, pg/ml	15.9±6.8	18.5±6.4§	17.8±4.3	18.0±6.5	17.1±5.3	**19.0±8.3§**	**16.8±5.4†**
	IL-10, pg/ml	40.8±21.8	42.7±19.0	41.3±22.4	43.0±21.2	42.1±18.2	**42.2±17.2**	**40.1±18.0†**
	TNF-α /IL-10	0.37±0.3	0.43±0.3	0.41±0.1	0.40±0.5	0.39±0.4	**0.45±0.2**	**0.42±0.1†**
Organ	LVMI, g/m²	79.2±8.9	126.8±12.4§	119.8±11.2	121.3±18.2§	118.1±13.2	**126.9±10.6§**	**118.1±12.3†**
	E/A, units	0.97±0.03	0.88±0.002§	1.0±0.05	0.82±0.001§	0.93±0.02	0.84±0.002§	1.0±0.05
Vegetative support	SDNN, ms	34.1±3.3	**34.9±3.6**	**43.2±3.1†**	34.8±2.6	35.3±2.9	**34.8±3.2**	**50.1±13.2†**
	Cv, %	4.0±0.4	4.2±0.1§	4.6±0.1	3.95±0.02	4.5±0.04	**3.96±0.04**	**5.7±0.01†**
	TP, mc²	2678.5±21.8	**3103.4±48.0§**	**2746.3±32.2†**	**1743.5±35.2§**	**2326±36.4†**	**1744.7±15.2§**	**2619.7±26.4†**
	LF/HF	0.54±0.06	1.2±0.1§	0.98±0.01	**1.9±0.05§**	**2.3±0.05†**	1.9±0.04§	0.98±0.04
	CI	0.86±0.09	2.2±0.03§	1.7±0.01	**4.5±0.02§**	**6.1±0.4†**	**4.5±0.04§**	**1.7±0.04†**
	β-ARM, cond.units	7.6±0.8	**47.5±0.3§**	**21.5±0.4‡**	**54.2±0.2§**	**71.6±0.6†**	**54.1±4.0§**	**23.2±0.5†**
Integrative	iRAS	75.2±3.4	**36.4±0.6§**	**47.4±3.4†**	39.1±1.5§	37.1±1.6	**29.4±1.2§**	**41.3±2.2†**

Note: †,‡ − significant changes (in bold) in comparison before and after treatment, p<0.01; <0.001 respectively; § − significant differences from the control group, p<0.05; I_m − microcirculation rate; SD − standard deviation of I_m; Cv − coefficient of variance; NT − neurogenic tone of the microvascular wall; MT − myogenic tone; EDTC − endothelial activity (endothelial-dependent tone component); TNF-α − tumor necrosis factoralpha; IL-10 − interleukin-10; HR − heart rate; LVMI − left ventricular mass index; E/A − the ratio of the early (E) to late (A) diastolic transmitral flow velocity; SDNN – standard deviation of normal to normal R-R intervals; TP − total spectral power; LF − capacity of low frequency waves; HF − capacity of high frequency waves; LF/HF − vagosympathetic interaction index; CI − centralization index; β-ARM − β-adrenoreception of erythrocyte membranes; iRAS − index of the regulatory and adaptive status.

Table 2. Evaluation of hypertension treatment efficiency at blood pressure (BP) regulation levels with drugs used in monotherapy.

BP regulation level	Indicators	Reference Group (n=56) M±SD	Drugs used in monotherapy					
			nebivolol (n=51) M±SD		amlodipine (n=44) M±SD		losartan (n=30) M±SD	
			Baseline	6 months	Baseline	6 months	Baseline	6 months
Peripheral	I_m, perf.units	4.52±0.81	3.9±0.6§	3.6±0.4	3.64±0.3§	3.82±0.2	4.05±0.7§	4.1±0.2
	SD, perf.units	0.71±0.42	**0.34±0.02§**	**0.46±0.01†**	**0.30±0.04§**	**0.45±0.03†**	**0.24±0.05§**	**0.32±0.04†**
	Cv %	16.51±7.3	**8.7±0.06§**	**12.8±0.02†**	**8.2±0.02§**	**11.8±0.3†**	**5.9±0.6§**	**7.8±0.9†**
	NT	0.71±0.2	0.68±0.01§	0.63±0.008	0.72±0.01	0.70±0.04	**0.71±0.02**	**0.49±0.05†**
	MT	24.4±1.2	**7.9±0.8§**	**12.2±0.8†**	6.15±0.4§	6.6±0.8	**8.3±1.2§**	**6.5±0.4†**
	EDTC	0.45±0.04	**7.6±0.5§**	**4.6±0.5†**	**8.7±1.2§**	**3.8±0.4‡**	6.0±0.4§	6.1±0.3
	TNF -α, pg/ml	15.9±6.8	17.2±4.1	16.0±5.2	16.9±3.2	15.9±4.0	18.2±5.3	17.4±6.3
	IL-10, pg/ml	40.8±21.8	42.1±19.4	41.3±20.5	42.8±17.8	41.4±16.9	43.4±20.1	42.1±22.4
	TNF-α / IL-10	0.37±0.3	0.41±0.5	0.40±0.2	0.42±0.3	0.41±0.7	0.39±0.8	0.38±0.6
Organ	LVMI, g/m²	79.2±8.9	**128.4±7.1§**	**118.9±8.6†**	122.3±18.0§	119.0±11.2	118.9±11.2§	116.0±11.2
	E/A, units	0.97±0.03	**0.81±0.02§**	**0.92±0.01†**	**0.84±0.005§**	**0.92±0.07†**	0.86±0.04§	0.96±0.03
Vegetative support	SDNN, ms	34.1±3.3	**32.4±3.0§**	**45.2±1.8†**	34.6±2.1	34.2±2.2	**34.2±3.1**	**42.7±3.0†**
	Cv, %	4.0±0.4	**3.95±0.07**	**5.5±0.02†**	4.1±0.05	4.3±0.07	4.1±0.1	4.7±0.1
	TP, mc²	2678.5±21.8	**1743.5±1.9§**	**2618.8±9.6†**	**1739.6±31.8§**	**2330.4±31.8†**	3101.2±42.3§	2740.5±30.8
	LF/HF	0.54±0.06	**1.8±0.5§**	**0.93±0.05†**	**1.8±0.05§**	**2.2±0.05†**	1.2±0.1§	0.97±0.01
	CI	0.86±0.09	**4.5±0.04§**	**1.6±0.04†**	**4.2±0.02§**	**5.7±0.4†**	2.2±0.03§	1.5±0.01
	β-ARM, cond.units	7.6±0.8	**51.9±4.2§**	**32.6±0.1†**	**52.6±0.3§**	**64.5±0.1†**	**50.7±0.8§**	**31.2±0.5†**
Integrative	iRAS	75.2±3.4	**37.1±1.6§**	**32.1±2.1†**	**36.8±1.4§**	**51.7±2.2†**	**35.4±0.4§**	**47.9±2.3†**

Note: †,‡ − significant changes (in bold) in comparison before and after treatment, p<0.01; <0.001 respectively; § − significant differences from the control group, p <0.05; I_m − microcirculation rate; SD − standard deviation of I_m; Cv − coefficient of variance; NT − neurogenic tone of the microvascular wall; MT − myogenic tone; EDTC − endothelial activity (endothelial-dependent tone component); TNF-α − tumor necrosis factor alpha; IL-10 − interleukin-10; HR − heart rate; LVMI − left ventricular mass index; E/A − the ratio of the early (E) to late (A) diastolic transmitral flow velocity; SDNN – standard deviation of normal to normal R-R intervals; TP − total spectral power; LF − capacity of low frequency waves; HF − capacity of high frequency waves; LF/HF − vagosympathetic interaction index; CI − centralization index; β-ARM − β-adrenoreception of erythrocyte membranes; iRAS − index of the regulatory and adaptive status.

Disorders of BP regulation system mechanisms at the *integrative level* and their adjustment influenced by antihypertensive therapy

The patients with hypertension had a lower level of regulatory and adaptive status before the treatment in comparison with the control group (iRAS was by 46.5% lower), which is consistent with the previous data (Pokrovskii and Kompaniets 2012).

As a result of the six-month therapy against the background of achieving the target BP values, the integrative indicator iRAS increased in the treatment with the lisinopril/indapamide combination (by 40.5%), amlodipine (by 40.5%), losartan (by 35.3%), and lisinopril (by 30.2%). Administration of nebivolol resulted in an iRAS decrease by 13.5%. Indapamide therapy had no significant effect on iRAS.

The most important task in the treatment of patients with hypertension is the achievement of the BP target level using five main classes of antihypertensive drugs as first-line drugs, but, as shown by the results of meta-analyses of recent years, none of them have an advantage in reducing BP (Emdin et al. 2015, Ettehad et al. 2016, Mancia et al. 2013, Thomopoulos et al. 2015).

Because of the large amount of earlier data on the effect of these drugs on BP, this study looked at the other parameters that can reflect the condition of BP regulation mechanisms at the main levels and proposed the comprehensive assessment system described above.

The disorders of BP regulation mechanisms at the *peripheral* level in 57.7% of patients with hypertension were represented by pathological types of microcirculation. The increased concentrations of proinflammatory cytokine TNF-α and anti-inflammatory cytokine interleukin-10 reflect the immune component of the disease pathogenesis (Jastrzebski et al. 2006, Stumpf et al. 2005).

An increase in the SD of the amplitude of blood flow deviations from the arithmetic mean of the microcirculation index characterizes a temporal perfusion variability and reflects an increase in the average blood flow modulation within all frequency ranges (Fedorovich 2010) under the administration of nebivolol, indapamide, amlodipine, losartan as well as lisinopril/indapamide combination. The increase in C_V when taking nebivolol, indapamide, amlodipine, losartan and the lisinopril/indapamide combination reflects the improvement of microcirculation condition since it is connected with an increase in SD resulting from a more efficient functioning of the active mechanisms regulatingtissue blood flow, with practically unchanged arithmetic mean of I_m.

At the *organ* level, the results of dynamics analysis of morphometric parameters influenced by AHT are consistent with the data from (Borzova and Gorbachenkov 2008), describing the changes when taking the drugs included in the study. The changes observesd confirm the improvements in structural and functional myocardium condition influenced by AHT, especially when taking nebivolol.

At the *vegetative* level (through *the autonomic nervous system*), a decrease in the activity of sympathetic effects was observed in people taking nebivolol, and an increase – in those taking indapamide and amlodipine; the therapy with lisinopril, losartan and a combination of lisinopril with indapamide did not have a significant effect on the type of vegetative regulation of the patients according to HRV data, but led to a decrease in β-ARM, which approached the normal values in people taking lisinopril as a monotherapy, as well as combined with indapamide.

At the *integrative* level, an increase of iRAS in the treatment with lisinopril/indapamide combination, amlodipine, losartan, and lisinopril reflected the positive dynamics, but iRAS values remained lower than in the control group. Further prospective studies are needed to reveal the mechanisms of regulatory and adaptive status recovery in hypertension patients. The open question remains what comes first: deadaptation or hypertension.

The decrease in the level of the regulatory and adaptive status during the treatment with a drug from the beta-blocker group (nebivolol) is consistent with the data in (Eremina et al. 2016). Bisoprolol, carvedilol, and nebivolol were shown to improve the outcomes in randomized controlled trials (RCTs) in heart failure (Ponikowski et al. 2016); however, there are no RCTs reporting on the outcomes of treating hypertensive patients with these beta-blockers (Williams et al. 2018). According to (Whelton et al. 2018), beta blockers are not recommended as first-line agents unless the patient has ischemic heart disease or heart failure.

Due to a high sensitivity of the iRAS used for the description of the integrative level, it is advisable in further studies to assess its potential as an indicator of a risk of developing complications.

Conclusion

The proposed approach to the complex assessment of BP regulation at 4 levels: 1) integrative level; 2) vegetative level (through the autonomic nervous system); 3) organ level; and 4) peripheral level (endothelial-microcirculatory) makes it possible to analyze the role of each level in the primary hypertension development in patients and to monitor the treatment efficiency. The quantitative evaluation of treatment efficiency at the integrative level is a universal indicator of a therapy impact based on detecting the effect of the treatment not only on a target organ or function, but also on the condition of the organism as an integral system.

Conflict of interests

The authors state no conflict of interest concerning with the present submitted manuscript.

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