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Original article

N-[2-(5-methoxy-1H-indole-3-yl)ethyl]acetamide May Correct Arterial Hypertension in People with Sleep Problems

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SUMMARY

Introduction. Sleep disturbance is a frequent complaint of patients suffering from arterial hypertension (AH) for a long time. A hidden and uncontrolled increase in blood pressure (BP) makes the course of physiological processes more difficult, disrupts the regulation of biological rhythms, and increases the risk of cardiovascular complications even with a short duration of AH. At the same time, chronic sleep disorders contribute to the development of hypertension, defining the role of a new socially significant risk factor. An important role in the pathogenesis of insomnia is played by a deficiency in melatonin (MT) synthesis, which negatively affects the cardiovascular system (CVS).

Aim. The aim of the paper was to study the features of central and vascular hemodynamics in patients with the 1st degree AH and to evaluate the clinical effectiveness of antihypertensive therapy with synthetic analog of prolonged-release MT at the onset of the disease.

Methods. Instrumental examination included registration of an electrocardiogram, office measurement of blood pressure with an automatic tonometer, non-invasive automatic blood pressure monitoring for 24 hours. The severity of insomnia was assessed by somnological questionnaires. Representatives of the 1st group (n = 34) took monotherapy with the ACE inhibitor ramipril, participants of the 2nd group (n = 33) took the ACE inhibitor ramipril in combination with a synthetic analogue of melatonin.

Results. The results of a randomized open prospective study including 78 participants reveal the activity of the renin-angiotensin-aldosterone system (RAAS), hypersympathicotonia at night and desynchronosis due to a possible deficiency in the MT secretion. Pharmacological antihypertensive therapy with the addition of prolonged release MT analog was accompanied by a significant improvement in the clinical condition of hypertensive patients. Positive dynamics of indicators of systemic hemodynamics and functional arterial parameters of stiffness was noted.

Conclusion. The article describes the probable benefits of melatonin as part of combination antihypertensive therapy in patients with early-stage hypertension and insomnia. Additional introduction of MT at the onset of the AH as a physiological regulator of circadian biological rhythms is substantiated.

Key words: **insomnia, sleep disturbance, blood pressure, ambulatory blood pressure monitoring, arterial hypertension, vascular stiffness, melatonin, ramipril**

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INTRODUCTION

Today, more than 20.0% people in the world have somnological disorders and/or experience a general dissatisfaction with the quality of sleep (1). Chronic somnological disorders have serious consequences for a person. However, in most cases, their negative impact is underestimated by both the patient and the doctor. The direct relationship between sleep disturbance and somatic diseases attracts the medical community`s attention and emphasizes particular relevance of this pathology (2- 4).

According to various studies` results, about 50% of patients with complaints of insomnia have hypertension, which is often uncontrollable (5). Therefore, no one doubts the fact of a close functional connection between these two conditions. The results of the MORGEN study demonstrated that the cardiovascular risk in people with sleep disorder without cardiovascular disease (CVD) depends on the duration of sleep and its quality (6). Undoubtedly, in this pathogenetic process, impaired secretion of endogenous neurotransmitter MT plays a primary role. Disturbance of its daily cycle leads to a mismatch of biological rhythms, increases the risk of anxiety and depression, cerebral and eating disorders, anorexia, gastrointestinal tract pathology, oncological pathology, immunological disorders, CVD (7). In addition, a high incidence of hypertension and insomnia in the older age group indicates a direct dependence of these conditions on age (8). However, young people have recently shown a clear tendency towards an increase in both AH and insomnia. In this age group, social and behavioral factors occupy a special place in the early AH onset and voluntary sleep deprivation. These are alcohol consumption, tobacco smoking, intensive work at night, and bright artificial lighting. Long-term exposure to light leads to multilevel neurohumoral restructuring and disruption of circadian biorhythms, contributing to AH persistent development (9). Thus, the role of constant illumination in AH modeling in rats was proved in experimental work (10). Under intense lighting conditions, rodents showed an increase in collagen formation and fibrous aorta restructuring. Under conditions of induced MT deficiency, they led to a BP increase.

The MT regulatory role in the vital activity of all living organisms was identified not long ago, although the history of this unique hormone discovery has been going on for several decades. In 1917, scientists C. P. McCord and F. P. Allen published the results of their observation of Rana pipiens tadpoles` unique discoloration when they were placed in a container with crushed cow epiphyses (11). In 1953, a research group led by prof. Lerner, inspired by this observation, managed to isolate a unique substance from cow epiphyses that could make the frog's skin transparent. However, its main component discovery required studying more than 250 thousand pineal glands. As a result of the five years `s persistent research, it was possible to identify a substance that blocked the secretion of melanocyte-stimulating hormone, which the scientist called «melatonin» (12). Although incretin is secreted mainly by pinealocytes of the pineal gland, MT can be produced by individual cells of GIT, blood, bronchial tree, prostate, ovaries, and retina. This explains its unique properties, which are manifested in various target cells in organs with MT-sensitive receptors.

In addition to systemic management of several physiological processes, MT has a strong antioxidant potential, manifested in oxidative stress reduction and mitochondrial activity regulation (13). On the one hand, this adaptogen can reduce the expression level of inflammatory cytokines (TNF-α, IL-6, and COX-2) and fibrotic markers (PC1 and TGF-β) by inhibiting the NF-κB enzyme. On the other hand, it can initiate antioxidant protection in mononuclear cells (14) by increasing the expression of CAT and

MnSOD, NADPH oxidase (p22 and NOX2)/and other antioxidant enzymes (15). MT activates mitochondrial oxidative phosphorylation (13), preventing the formation of free radicals and depletion of cellular energy reserves (14), thereby exhibiting powerful cardio-, vaso- and neuroprotective properties.

Scientific studies of recent years have shown both the oncoprotective ability of melatonin and its positive role in enhancing the immune response in the treatment of COVID infection (16). In this regard, additional prospects for the use of an angiotensin converting enzyme inhibitor (ACE inhibitor) and melatonin in the treatment of patients with hypertension and somnological disorders are opening, including considering of the ongoing COVID-19 pandemic.

In summary, the appointment of long-acting MT in addition to standard antihypertensive therapy at the hypertension onset may be a justified step. The work aims are to study the features of central and vascular hemodynamics in patients with the 1st degree AH and to evaluate the clinical effectiveness of antihypertensive therapy with ACE inhibitor ramipril in monotherapy and in combination with a chemical analogue of prolonged-release MT at the disease onset.

MATERIAL AND METHODS

Out of 200 patients with identified hypertension in a randomized clinical trial, 78 patients (me-

Table 1. *Parameters of systemic and vascular hemodynamics studied during ABPM and their description*

Parameters		Characteristic, units
Circadian blood pressure profile	SBP24 h	daily mean systolic blood pressure, mm Hg
	DBP24 h	daily mean diastolic blood pressure, mm Hg
	MBP24 h	daily mean blood pressure, mm Hg
	PAP24 h	daily mean pulse aortic pressure, mm Hg
	HR24 h	daily mean heart rate, beats/min
	SBP TI24 h	daily time index systolic blood pressure, %
	DBP TI24 h	daily time index diastolic blood pressure after 12 weeks, %
	SBP AI24 h	daily area index systolic blood pressure, c.u
	SBP HBI24 h	general hyperbaric index systolic blood pressure, %
	DBP HBI24 h	general hyperbaric index diastolic blood pressure, %
	SBP MBPS	morning systolic blood pressure surge value, mm Hg
	DBP MBPS	morning diastolic blood pressure surge, mm Hg
	Var HR24 h	daily variability heart rate, beats/min
	Var SBP24 h	daily variability systolic blood pressure, mm Hg
	Var DBP24 h	daily variability diastolic blood pressure, mm Hg
Central aortic pressure and vascular stiffness	SBPao	systolic blood pressure level in the aorta, mm Hg
	DBPao	diastolic blood pressure level in the aorta, mm Hg
	PAPao	pulse aortic pressure, mm Hg
	Aixao	augmentation index, %
	SEVR	subendocardial viability ratio index, %
	ED	expulsion duration, m/sec
	PPA	pulse pressure amplification, %
	PWVao	pulse wave velocity in the aorta, m/sec
	RWTT	reflected wave time, m/sec
	Aix@75	augmentation index reduced to a heart rate of 75 beats/minute, %
	ASI	stiffness index, mm hg
	AASI	ambulatory arterial stiffness index, c.u.
	dP/dt max	the maximum rate of increase in blood pressure, mm hg

Table 2. *Characteristics of patients with AH included in the study*

Characteristics	Total (n = 67)	Group 1 ACE inhibitor (n = 34)	Group 2 ACE inhibitor +MT (n = 33)	P_{1-2}
Age, year	52.6 (34.6 - 66.2)	51.9 (34.6 - 58.7)	53.2 (40.3 - 66.2)	0.09
SBP office, mm Hg	146.8 (140 – 159)	145.8 (140 – 158)	147.2 (140 – 159)	0.74
DBP office, mm Hg	94.3 (86 – 99)	93.3 (88 – 98)	95.2 (86 – 99)	0.77
Men, %	38.8	42.2	36.4	0.38
Current smoking, %	31.4	38.2	24.2	0.06
Obesity, %	10.5	14.7	6.1	0.04
Body mass index, kg/m^2	26.1 (22.1 - 38.3)	27.4 (23.2 - 38.3)	25.3 (22.1 - 36.7)	0.21
Insomnia, months	7.9 (3.6 - 10.3)	7.8 (5.5 - 8.8)	8.1 (3.6 - 10.3)	0.63
Uric acid, μmol/l	360.3 (283 – 492)	364 (303 – 492)	358.6 (283 – 426)	0.12
Total cholesterol, mmol/l	4.8 (3.3 – 6.9)	4.7 (3.3 – 6.5)	4.9 (4.2 – 6.9)	0.36
Glucose, mmol/l	4.9 (3.8 – 6.3)	5.0 (4.2 – 6.3)	5.0 (3.8 – 6.2)	0.85
Creatinine, μmol/l	70.9 (54.6 - 86.7)	72.1 (69.6 - 85.9)	69.8 (54.6 - 86.7)	0.31
Observation period, days	86.2 (81 – 100)	86.3 (84 – 100)	86.2 (81 – 96)	0.74

Abbreviations: ACE inhibitor - Angiotensin-converting enzyme (ACE) inhibitors; AH - arterial hypertension; DBP - diastolic blood pressure; MT- melatonin; SBP - systolic blood pressure

dian age 52.42 ± 4.67 years) were identified with complaints of various sleep disorders. The study excluded persons with severe CVD (AH of the 2nd and 3rd degree, white coat hypertension, ischemic heart disease, cerebrovascular accidents), as well as those with severe comorbidities requiring ongoing drug therapy, cancer, allergic reactions to the study drug, pregnant women. All participants underwent an extended general clinical examination. Laboratory diagnostics included the obligatory assessment of the glucose level, uric acid, lipid profile, and creatinine. Instrumental examination included registration of an electrocardiogram (Cardiovit AT-1, Schiller), office measurement of blood pressure with an automatic tonometer (M2, OMRON), non-invasive automatic blood pressure monitoring for 24 hours (ABPM) using a complex of software and hardware monitoring «BPLab» (LLC «Petr Telegin»).

ABPM parameters (Table 1) included daytime, nighttime, and average daily values of systolic and diastolic blood pressure (SBP, DBP) and their variability, mean blood pressure (MAP), pulse rate (PR). The degree of nighttime decrease in SBP and DBP (daily index - SI) was calculated to establish the type of daily curves: "non-dipper", "dipper", "over-dipper" and "night-peaker". The value of the total daily BP load was assessed by the area index (AI), time index (TI), and general hyperbaric index (GHI). The AI was taken as a numerical variable of the area of excess blood pressure during the period of automatic monitoring, for the TI - the percentage of blood pressure measurements exceeding the upper limit of normal. The ABPM parameter (%) was taken as the total GHI, reflecting the excess of the upper reference value of the BP fluctuations` permissible range. To assess the parameters of central aortic pressure and stiffness of elastic and elastomuscular vessels, the BPLab complex with Vasotens® technology was used. Blood pressure measurements were made in the period from 06:00 to 23:00 every 30 minutes, and in the period from 23:00 to 06:00 with an interval of 45 minutes.

The level of anxiety and depression was assessed using the HADS scale. The somnological disorder severity was assessed according to the questionnaires "Subjective assessment of sleep characteristics" (Vayne A., Levin Y.), "C. Morin Insomnia Severity Index" (ISI), Pittsburgh Sleep Quality Index (PSQI) Questionnaire "Epworth Daytime Sleepiness Scale » (ESS). Based on the results of an extended examination of 78 participants, 11 patients were diagnosed with false isolated systolic hypertension - an increase in peripheral SBP with a normal level of central SBP. These patients were referred for preventive counseling without prescribing antihypertensive

therapy, and therefore they were excluded from the study.

Sixty seven patients were divided into two groups by adaptive randomization (Table 2). Representatives of the 1st group (n = 34) were recommended ACE inhibitor monotherapy with ramipril once a day at 20:00 (average dose 4.6 ± 1.7 mg/day). In patients of the 2nd group (n = 33), a synthetic analog of melatonin with prolonged action at 22:00 in a single dose of 3 mg was added to similar therapy with ramipril. At home, patients monitored blood pressure (diary keeping), adhered to a low-salt and lipid-lowering diet, followed recommendations for sleep hygiene and increased physical activity. For the experiment purity, appointment of other antihypertensive drugs in the two comparison groups was not carried out. All participants were informed about the goals and objectives of the scientific study, signed an informed consent to participate within 12 weeks.

Statistical and mathematical processing of the obtained data was carried out using the SPSS 22.0 for Windows program (SPSS Inc). For quantitative variables, mean values, and standard error of the mean (M ± sd), confidence interval (95% CI) was calculated. Qualitative variables were assessed by the χ^2 criterion. The normality of variables distribution with a sample size of $n < 50$ was assessed by the Shapiro-Wilk test, with a sample size of $n \geq 50$ the Kolmogorov-Smirnov test was used. Intragroup differences were determined using the Wilcoxon rank test for related samples and the Mann-Whitney U-test- for unrelated samples. Differences were considered statistically significant at $p < 0.05$.

RESULTS

An analysis of the results obtained after 12 weeks of observation showed positive dynamics in the condition of patients in both groups during therapy, as indicated by normalization of blood pressure and improvement in the clinical status by the end of the observation period. According to the data from self-monitoring blood pressure diaries at home, 61.76% of patients in group 1 and 69.70% of those in group 2 reached a BP level not exceeding 130/80 mm Hg., and the level of blood pressure was 135/85 mm Hg. - 76.54% and 87.90% respectively. Office SBP in group 1 decreased from 145.8 ± 5.2 to 134.4 ± 3.7 mm Hg (Δ = - 7.8%; $p < 0.0001$), DBP from 93.3 ± 4.6 to 85.7 ± 4.2 mm Hg (Δ = - 8.1%; $p < 0.0001$). In group 2, SBP decreased from 147.1 ± 6.1 to 129.2 ± 9.6 (Δ = - 12.2%; $p < 0.0001$), DBP from 95.3 ± 5.3 to 82.3 ± 6.6 mm Hg (Δ = - 13.7%; $p < 0.0001$).

The ABPM indicator dynamics showed obvious advantages of therapy with the inclusion of a chemical MT analog in the integrated scheme. In representatives of group 1, the average SBP24 h decreased by 8.5% (Table 3), DBP24 h by 7.6%, MBP24 h by 7.5%, PAP24 h by 7.8% ($p < 0.01$). In patients of group 2, average daily values decreased to a greater extent: SBP24 h by 10.9%, DBP24 h by 9.9%, MBP24 h by 10.3%, PAP24 h by 12.4% ($p < 0.001$). Also, a more pronounced decrease was also noted at night in group 2: mean SBP at night (n) decreased on average by 11.8%, PAP (n) by 9.8%. In group 1, these indicators decreased by 6.2% and 6.6%, respectively ($p < 0.05$). A significant decrease in mean SBP values at night was noted, the value of which did not exceed the level of 120 mm Hg: in 61.8% of patients of group 1 ($p = 0.03$) and 84.8% of patients of group 2 ($p = 0.001$).

The SBP TI24 h significantly decreased from 68.7 ± 6.1 to 20.4 ± 4.4 by 65.1% in group 2 ($p < 0.0001$) versus 51.9% (from 69.5 ± 5.8 to 33, 4 ± 4.4 values of patients of group 1). The time index DBP TI24 h decreased by 62.5% (from 55.26 ± 4.73 to 20.71 ± 3.19) versus f53.0% (from 51,27 ± 4.74 to 24.12 ± 4.22 values of patients of group 1). SBP HBI24 h in patients taking the MT analog decreased by 64.2% ($p < 0.00001$), HBI of DBP by 56.3% ($p < 0.00001$). A decrease in hemodynamic pressor load in representatives of the two groups was indicated by a decrease in blood pressure AI: in participants of group 1, the decrease degree in daily SBP AI and DBP AI was 50.7% ($p = 0.01$) and 55.5% ($p = 0.0003$), respectively in patients of group 2 - 71.1% ($p = 0.01$) and 78.4% ($p = 0.05$).

The dynamics of BP and pulse variability indicators was multidirectional. In group 1, Var SBP24 h decreased from 14.7 ± 3.7 to 14.0 ± 3.2 ($p = 0.001$), Var SBP daytime from 14.4 ± 2.6 to 13.8 ± 3.0 ($p = 0.03$), Var SBP nighttime from 13.2 ± 2.7 to 12.7 ± 2.9 ($p = 0.110$), in patients of group 2 this parameter value slightly increased in the daytime (14.6 ± 2.6 to 14.9 ± 4.0; $p = 0.06$), and the diurnal and nocturnal SBP variability tended to decrease (from 14.6 ± 3.6 to 14.9 ± 4.0; $p = 0.127$ and 13.7 ± 3.0 to 12.7 ± 2.5; $p = 0.01$). Indicators of Var DBP24 h decreased in all comparison groups but did not differ rich the criterion of significance.

Table 3. *Dynamics of indicators of systemic and vascular hemodynamics in patients with AH of groups 1 and 2 during therapy*

Parameters	Group 1 ACE inhibitor (n = 34)			Group 2 ACE inhibitor + MT (n = 33)			P_{1-2}
	initially	after	Δ, %	initially	after	Δ, %	
SBP24 h	146.8	134.4	-8.5*	147.1	131.2	-10.9*	< 0.01
DBP24 h	91.7	84.7	-7.6*	92.3	83.3	-09.9*	0.09
MBP24 h	107.4	99.3	-7.5*	107.6	96.6	-10.3*	< 0.05
PAP24 h	54.1	49.9	-7.8*	54.8	47.0	-14.3*	< 0.05
HR24 h	78.3	72.7	-7.2*	78.1	68.8	-11.8*	< 0.01
SBP TI24 h	69.5	33.4	-50.9*	68.7	20.4	-70.3*	< 0.001
DBP TI24 h	51.3	24.1	-53.0*	55.3	20.7	-62.3*	< 0.01
SBP AI24 h	140.5	69.2	-50.7*	148.2	42.9	-71.1*	< 0.001
SBP HBI24 h	163.2	87.3	-46.6*	171.5	61.4	-64.2*	< 0.01
DBP HBI24 h	107.1	51.9	-51.5*	110.4	48.3	-56.3*	< 0.05
SBP MBPS	40.2	26.8	-33.3*	38.7	22.3	-42.4*	0.06
DBP MBPS	24.1	17.0	-29.4*	25.5	16.2	-36.5*	0.186
Var HR24 h	8.8	7.9	-10.2*	8.9	6.7	-24.7*	< 0.001
Var SBP24 h	14.7	14.0	-4.8*	14.6	14.9	+2.1	< 0.05
Var DBP 24 h	13.2	12.2	-7.5*	13.3	11.9	-10.5*	0.09
SBPao	133.12	123.85	-6.9*	134.13	119.6	-10.8*	< 0.001
DBPao	83.65	78.69	-5.9*	83.73	78.35	-6.4*	0.09
PAPao	45.23	42.76	-6.6*	46.06	41.73	-9.4*	< 0.01
Aixao	32.42	29.87	-7.9*	33.12	29.61	-10.6*	< 0.001
SEVR	118.75	129.42	+8.2*	118.13	133.54	+11.2*	< 0.01
ED	329.80	296.41	-10.1*	331.69	296.23	-10.7*	0.130
PPA	135.63	130.25	-4.0*	134.86	127.20	-5.8*	0.07
PWVao	10.80	10.24	-5.2*	10.79	9.76	-9.5*	< 0.001
RWTT	141.29	135.63	+4.0*	142.01	132.73	+6.5*	< 0.01
Aix@75	-4.95	-5.39	+8.9*	-4.92	-5.51	+10.7*	< 0.01
ASI	143.84	135.36	-5.9*	144.36	134.12	-7.1*	< 0.05
AASI	0.356	0.327	-8.1*	0.362	0.331	-9.4*	0.08
dP/dt max	557.14	530.73	-7.2*	561.60	523.87	-9.8*	< 0,01

Comment: decoding of abbreviations in Table 1.

* - The difference is statistically significant

A detailed DBPP analysis by the end of the observation research did not establish statistical differences between the two groups. However, in all groups, the number of patients with the profile «dipper» increased and the number of cases with the profile «non-dipper» decreased: up to 84.8% and 81.8% for SBP and DBP in group 2 ($p < 0,001$), and up to 70.6% and 73.5% in group 1, respectively ($p < 0,05$). The initial change in the DBPP in most patients indicated an increase in sympathicotonia at the onset of the disease and a significant pulse-lowering effect of therapy by the end of the observation without taking drugs that affect the pulse rate, especially in the group of patients taking melatonin. In patients of group 2, the HR24 h decreased from 78.1 ± 7.6 to 68.8 ± 5.5 beats per minute (Δ = - by 11.9%; $p < 0.05$), in the group 1 from 78.3 ± 6.0 to 72.7 ± 6.2 beats per minute (Δ = - 7.1%; $p < 0.05$).

The analysis of systemic hemodynamic parameters is supplemented by indicators of central

arterial pressure (Table 3). In group 1, daytime SBPao decreased by 8.9% (from 134.6 ± 9.7 to 122.7 ± 6.6 mm Hg), nighttime by 6.1% (from 121.6 ± 8.0 to 114.2 ± 6.7 mm Hg), and daily by 6.9% (from 133.2 ± 8.4 to 123.9 ± 7.0 mm Hg). In group 2, daytime SBPao decreased by 11.5% (from 135.83 ± 9.90 to 120.17 ± 10.33 mm Hg,), nighttime by 9.4% (from 121.22 ± 7.44 to 109.86 ± 9.00 mm Hg) and daily by 10.8% (from 134.13 ± 8.24 to 119.60 ± 7.12 mm Hg). In group 1, central daily DBP decreased by 5.9% (to 78.69 ± 6.37 from 83.65 ± 5.44 mm Hg; $p < 0.05$), in group 2 by 10.9% (to 78.35 ± 8.02 from 83.73 ± 6.27 mm Hg; $p < 0.05$). A statistically significant difference in the daily rate of decline was noted only for the central SBPao (< 0.05); the dynamics of the central DBPao was unreliable.

Changes in DBPao, PAP, and MAP were also reflected in the qualitative grade of the pulse wave and parameters of vascular stiffness. After 12 weeks, both comparison groups presented a significant decrease in the augmentation index and PWVao transit rate, as well as an increase in the subendocardial viability ratio index and reflected wave time. However, the established intergroup differences in SEVR, AIx@75, dP/dt max, PWVao showed the benefits of a combination therapy in participants of group 1.

In patients of group 1, RWTT increased by 4.0% (from 141.29 ± 13.28 to 135.63 ± 11.09) and PWVao decreased by 5.2% (from 10.80 ± 1.17 to 10.24 ± 0.94 m/s). In group 2, PWVao decreased by 9.5% (from 10.79 ± 1.71 to 9.76 ± 1.42 m/s) and RWTT increased by 6.5% (s 142.01 ± 12.96 to 132.73 ± 10.38). In patients taking MT, the SEVR index significantly increased by 11.5% (from 118.13 ± 9.87 to 133.54 ± 10.55), in group 1 by 8.2% (from 118.75 ± 10.57 to 129.42 ± 11.8). A correlation was found between BP and arterial stiffness parameters in groups 1 and 2 ($p < 0.05$): between SBP24 h and ASI ($r = 0.724$ and $r = 0.671$), daytime SBPao and ASI ($r = 0.548$ and $r = 0.496$), daytime SBPao and RWTT ($r = 0.755$ and $r = 0.698$), daily DBPao and RWTT ($r = 0.424$ and $r = 0.352$), daily SBPao and PWVao ($r = 0.525$ and $r = 0.642$), daytime SBPao and dP/dt max ($r = 0.670$ and $r = 0.758$).

When studying the relationship between cardiovascular risk factors and indicators of arterial stiffness, a significant direct correlation was found in relation to tobacco smoking and PWVao ($r = 0.524$; $p = 0.001$), AASI ($r = 0.618$; $p = 0.0001$), ASI ($r = 0, 0001$). $= 0.436$; $p = 0.03$) and AIx@75 ($r = 0.411$; $p = 0.04$).

A decrease in aortic stiffness during therapy was evidenced by the positive dynamics of AIxao, which in group 1 by the end of observation was 7.9% and 10.6% in group 2, while the data distinction criterion χ^2 reached a statistical difference ($p < 0.001$). Considering the fact that the AIx value is determined by the level of peripheral resistance and heart rate, the degree of change in the corrected HR AIx in PPA by the 12th week decreased and was -5.39 ± -6.69 in group 1, and in the group of patients receiving MT -5.51 ± -5.88 (< 0.01). The importance of a combined assessment of the arterial stiffness index and the outpatient/ambulatory arterial stiffness index, as predictors of mortality from cardiovascular causes, is shown along with the high AIxao predictive value. Reviewing these indicators` reliable dynamics in representatives of the two groups, it was possible to assess the therapeutic efficacy in vascular remodeling processes. At the same time, the difference in the degree of their reduction was greater in patients taking MT. In group 2, ASI decreased by 11 mm Hg (7.1%), AASI - by 9.4%, in group 1 - by 5.9% and 8.1 % respectively. A decrease in the hemodynamic load on the vascular wall was evidenced by a significant decrease in dP/dt max, while the difference between the groups according to the agreement criterion χ^2 indicated the advantage of therapy in group 1 ($p < 0.01$). In addition, in this group, a relationship was established between dP/dt max and SBPao in the night period ($r = 0.714$, $p = < 0.001$), dP/dt max and DBPao in the night period ($r = 0.45$, $p = 0.022$) after 12 weeks of observation. It should be noted that the absence of intergroup statistical differences in AASI, PPA, and ED by the end of the study indicates the ACE inhibitors` significant role in the correction of vascular stiffness pathological changes, which was one of this paper's important conclusions.

With systemic hemodynamic parameter normalization, many subjective sleep characteristics significantly improved. However, the positive change degree in the groups was not the same (Diagram 1). In the group of patients taking MT, a quite expected large positive dynamics was noted: the duration of sleep increased ($\Delta = 23.0\%$; $p = 0.0001$) and the number of dreams, too ($\Delta = 38.8\%$; $p = 0.001$), the time to fall asleep decreased ($\Delta = 26.3\%$; $p = 0.004$) and daytime sleepiness, too %; $p = 0.0001$), the quality of morning awakening improved ($\Delta = 41.2\%$; $p = 0.0001$), which affected the final mark and the quality of sleep. The mean insomnia severity index ISI score in patients of group 2 decreased by 22.3% (from 20.3

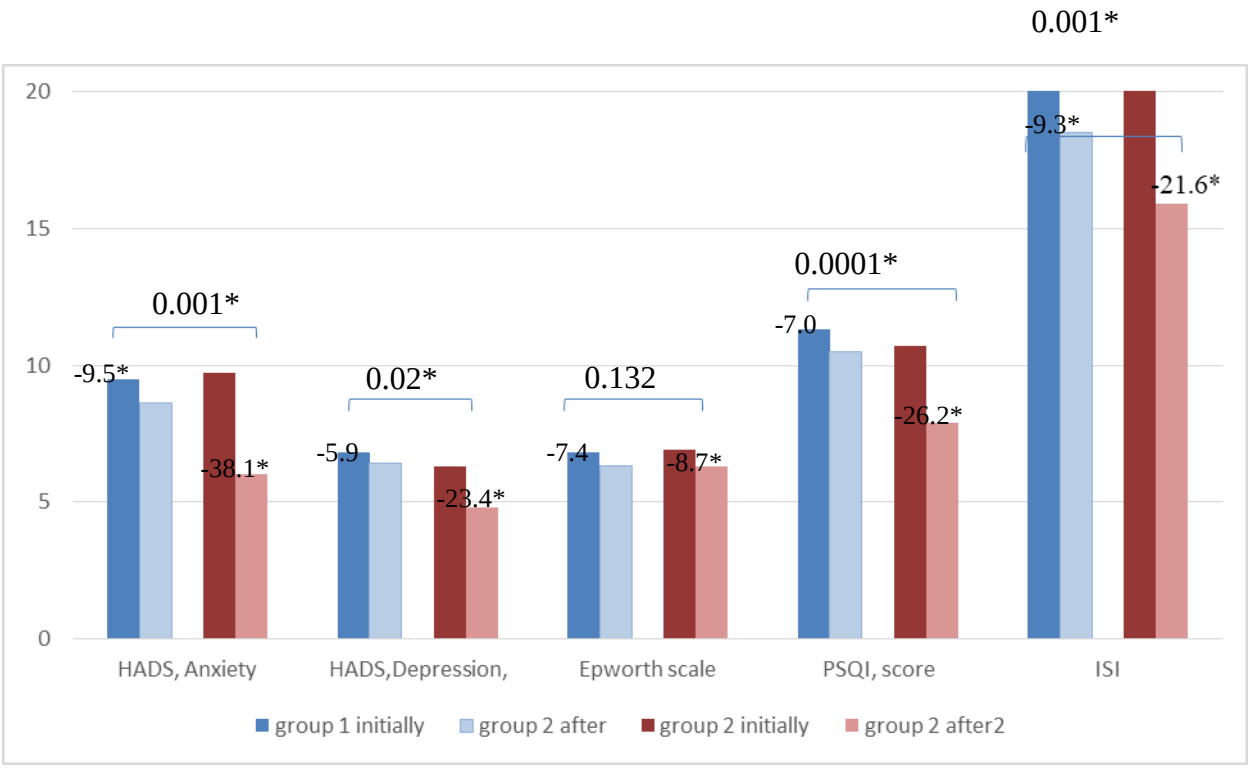

Diagram 1. *Graphical presentation of the dynamics of somnological indicators in patients with AH of groups 1 and 2 during therapy*

Abbreviations: ISI - «Index of the severity of insomnia»; PSQI – «Pittsburgh Sleep Quality Index» HADS - the Hospital Anxiety and Depression Scale (The HADS scale was used to measure the anxiety and depression levels).
* The difference is statistically significant.

± 3.7 to 15.9 ± 2.5; p = 0.0001) and the mean PSQI score decreased by 26.2% (from 10.7 ± 2.8 to 7.9 ± 1.5), while among representatives of group 1 it decreased by 9.3% and 7.8%, respectively. Direct relationship between ISI and SBP24 h (r = 0.654; p = 0.019), PSQI and SBPao in the daytime (r = 0.624; p = 0.039), PSQI and HADS anxiety (r = 0.515; p = 0.044), daytime sleepiness and SBP24 h (r = -0.384; p = 0.029) in patients of group 2 by the end of the observation indicated the importance of adequate antihypertensive therapy for sleep quality and psychological characteristics.

Throughout the observation period, patients participating in the present study showed good tolerance to medicines. On the part of biochemical parameters such as glucose, creatinine, uric acid, and transaminases there was no negative dynamics.

DISCUSSION

Given an increase in mortality in the category of people with low cardiovascular risk, the previous SCORE risk stratification scale has lost its ability to reflect the true probability of developing CVE (17), which determines relevance of development of new scales SCORE2 and SCORE2-OP (18). Therefore, in regions with a very high cardiovascular risk, according to the World Health Organization, it is necessary to carefully and timely assess the impact of modified risk factors, which rightfully include chronic sleep disorders.

The initial results of the examination of patients with sleep disorders and hypertension at the onset of the disease, despite the first degree and short duration, already indicated their cardiovascu-

lar risk (CVR). Violations of the daily blood pressure profile with a predominantly insufficient decrease in blood pressure in the evening and during sleep in patients at the initial stages of AH development indicated an increased activity of the renin-angiotensin-aldosterone system (RAAS), sympathicotonia at night, and desynchronosis of circadian biorhythms due to a probable MT secretion deficiency. An increase in the values of parameters characterizing the CVS state (central and vascular hemodynamics indices), initial excess of ASI ≥ 200, AASI ≥ 0.5 values in most patients with clinical debut of AH indicated development of processes of the cardiovascular system pathological remodeling long before the appearance of subjective complaints and the first symptoms of hypertension.

This underlines the necessity and expediency of early screening of CVD in patients with chronic sleep disorders, considering the possible latent damage to target organs, especially vessels.

The results of recent studies have shown the prognostic role of vascular wall stiffness as an integral predictor of cardiovascular mortality and morbidity (17 - 19). Acceleration of the processes of pathological vascular remodeling is recorded in arterial hypertension, coronary artery disease, insomnia, metabolic syndrome, physical inactivity, obstructive pulmonary diseases, menopause, smoking, etc. (1, 3, 5, 20, 21), which was also reflected in our study.

Variables derived from pressure wave (AIx) and wave separation (RW, reflection magnitude) in patients with insomnia and hypertension expand our understanding of functional arterial stiffness parameters and vascular resistance in the early stages of the disease.

AIxao and HBI in most of the study participants more accurately reflected the LV hemodynamic preload at the onset of AH. Consequently, the change in the SEVR index in patients at the initial stages of AH characterized the physiological shift between the need of cardiomyocytes for oxygen and its consumption, which contributes to the early development of non-atherosclerotic forms of ischemic heart disease. Besides, the detected initial increase in PPA and SBPao in most persons with AH and somnological disorders indicated a latent LV afterload at the early stages of the disease, which did not provide full relaxation of the ventricular myocardium.

It is known that the preclinical stage of hypertension is characterized by an episodic transient increase in blood pressure, with the appearance of subjective complaints in patients in the form of sleep disturbance. It can be argued that during this “silent period” of AH development, the first persistent signs of pathological vascular remodeling develop (arterial hypertrophy, arteriole hyperelastosis) before the development of compensatory LV myocardial hypertrophy (22).

Aggravation of vascular remodeling processes is also associated with hypoxic damage to the vascular endothelium, due to plasma impregnation by various proteins and lipids, closing the "vicious circle" with the formation of vasospasm and early arteriosclerosis (23).

This stage of pathomorphological remodeling of the CVS is manifested by a persistent increase in the level of blood pressure, which, by routine measurement, makes it possible to verify hypertension, as in our study. Most patients had persistent AH at the time of screening, and only 37.2% of patients were unaware of their BP level. However, the predominant complaint for many participants was sleep disturbance (64.2%). A consistently high level of blood pressure enhances desynchronization of circadian physiological rhythms (reducing even more the concentration of endogenous MT), which is reflected in the subjective characteristics of sleep.

Therefore, the results of our work allowed us to draw an important conclusion about the need for timely detection and treatment of patients at the AH initial stage (including patients with complaints of insomnia at the disease onset) by prescribing pathogenetically justified medicines to curb processes of pathological systemic remodeling. That is why the authors` particular interest was associated with the assessment of the ACE inhibitor efficacy, both in monotherapy and in combination with MT at the early onset of AH pathogenesis, and especially in the parameters of systemic and vascular hemodynamics.

This emphasizes feasibility of conducting extended medical consultations for patients with complaints of insomnia. At the same time, appointment of pathogenetically substantiated drugs at the onset of the disease will slow down the processes of the cardiovascular system pathological remodeling. Thus, the scientists` interest in studying the therapeutic efficacy of both ACE inhibitors and MT on the parameters of systemic and vascular hemodynam-

ics has not been lost recently.

The increased tone of arterioles, forming arterial rigidity and local oxidative stress contributed to the early generation of pulse waves (the formation of reflected waves in the aorta), as evidenced by increased values of BPao and PPA. Accordingly, a decrease in PWVao and dP/dt max indicated improvement in the damping properties of the vascular wall in all observation groups, which ultimately led to a decrease in SBPao, DBPao, and PAP.

With improvement of functional arterial parameters stiffness and decrease in the speed of the pulse wave passage, there occurred isometric relaxation of the ventricles and improvement of the diastolic function of the left ventricle. This was evidenced by the increase in the SEVR index and RWTT, in the duration of the ED period in patients of the two comparison groups, regardless of the treatment regimen. The decrease in hemodynamic load contributed to the compensatory abilities of the myocardium contractile drive, and therefore, revealed the cardioprotective effect of the initial therapy, especially among the representatives of group 2.

In addition, a particularly important proof of MT protective properties was normalization of central arterial pressure, a statistically significant regression of indicators, functional arterial parameters stiffness and resistance in patients of group 2 (Table 3).

The augmentation index of aortic dynamics, a parameter characterizing the functional state of the vascular bed, indicated improvement in damping properties of the great vessels in the group taking synthetic analog of melatonin (19, 24). Its more pronounced decrease in representatives of group 2 was evidenced as a significant reduction in central blood pressure, rigidity of the arterial wall, diastolic function improvement, and, consequently, the vasoprotective action of therapy with melatonin (adaptation to hypoxia in reperfusion injury). In this regard, the decision to prescribe a synthetic analogue of MT in complex antihypertensive therapy at the onset of the disease as a physiological regulator of circadian biological rhythms seems justified.

An increase in MT concentration at night, especially in patients with subjective complaints of insomnia, contributes not only to a qualitative improvement in the sleep process, but also to neutralization of the RAAS negative effects and cumulation of the antihypertensive drugs effect. This explains a more pronounced increase in the daytime SBP variability and a significant decrease in mean SBP and PAP at night and before awakening by the end of observation in group 2.

The MT-mediated hypotensive effect is realized not only due to normalization of the sleep phase. The main antihypertensive action is associated with the mediated vasodilating properties of melatonin: by stimulating the GABA-ergic repressive effects of the hypothalamus paraventricular nucleus, melatonin can increase bioavailability of nitric oxide (25). This proves its vasodilating and, therefore, antihypertensive effect.

In addition, the hypotensive property of MT can be explained by its sedative effect (the ability of protective relaxation), which manifests itself in a decrease in the level of emotional excitation, the speed and intensity of a person's reaction to external stimuli (26). This was reflected in reduction of anxiety and depression after 12 weeks of treatment.

An association between MT antioxidant and antihypertensive effects was identified during the COVID pandemic. The antioxidant effect of melatonin is combined with its anti-inflammatory action. This determined a new therapeutic target for melatonin – acute respiratory infectious diseases, including Coronavirus disease 2019 (SARS-CoV-2).

Melatonin shows its antioxidative and anti-inflammatory effects against SARS-CoV-2 through stimulation of antioxidant enzymes (superoxide dismutase, glutathione peroxidase, catalase), inhibition of pro-oxidant mediators (cyclooxygenase-2, interleukins, inducible nitric oxide synthase, nuclear factor kappa B, Toll-Like receptor, tumor necrosis factor et all.) and direct removal of free radicals (16, 27, 28). Melatonin attenuates the cytokine storm caused by SARS-CoV-2, neutralizes reactive oxygen species, while activating cellular immunity produced by T-helpers type 2 (29, 30).

The protective actions of MT on the effects of SARS-CoV-2 are associated not only with the aforecited, but also with inhibiting angiotensin II and facilitating angiotensin I (16). This association once again proves an important aspect of MT involvement in hemodynamics regulation.

The central MT hypotensive effect may be associated with normalization of daily fluctuations in MT secretion and improvement in cerebral blood flow. Besides, the hypotensive effect is partially realized through the uptake of reactive oxygen species, antioxidant enzymes overexpression, and efficiency increase in the mitochondrial transport chain (13, 27).

It is known that each decrease in SBP by 1 mm Hg can lead to a decrease in heart rate up to 10 beats/min. Accordingly, a greater reduction in corrected AIx@ 75 without taking heart rate slowing drugs in patients, taking melatonin, could be a consequence of BPDP normalization, and increased sleep duration, which was another benefit of combination therapy with MT. The results of several studies have shown a persistent negative chronotropic effect of melatonin due to binding melatonin MT1 and MT2 receptors of endothelial cells to G-proteins and its direct central action (14).

Normalization of systemic hemodynamics regulation also contributed to a favorable effect on sleep physiology in patients with hypertension in its debut. However, MT addition to the basic hypotensive therapy (ramipril) led to an additional positive effect on somnological characteristics. In the group of persons receiving MT, the duration of night sleep increased, the time to fall asleep and daytime sleepiness decreased, the quality of awakening improved, which was reflected in the dynamics of the circadian index CI, PSQI, ISI. It is important to note that the main advantage of MT exogenous substance is associated with its ability to maintain the neurophysiological structure of sleep (7).

However, it is difficult to understand what led to a significant positive effect of combined antihypertensive therapy with MT. Could this be a direct effect of MT on somnological characteristics, or the synergistic cumulative antihypertensive effect of the combination of ramipril and MT? Could this be an indirect effect of an ACE inhibitor on the quality of sleep due to normalization of the daily blood pressure profile? To find an answer it is necessary to expand the scope of study. In recent years there have been studies confirming the corrective role of RAAS blockers in somnological features and circadian rhythms in patients with cardiac pathology (24, 30 - 32). An imbalance between the sympathetic and parasympathetic nervous systems, impaired BPDP, increased arterial parameters stiffness and a tendency to tachycardia are important constituent pathophysiological components in the AH onset, and therefore a therapeutic target for many clinical MT effects. This probably explains the more pronounced positive influence of MT therapy on the course of AH.

CONCLUSION

1. For a timely assessment of cardiovascular risk, all persons with sleep disorders in the early onset of hypertension require an in-depth medical examination.

2. Careful assessment of functional arterial parameters of stiffness and resistance is a necessary and important method of examination of hypertensive patients to identify preclinical lesions of target organs.

3. All patients with insomnia and arterial hypertension need a personalized and pathogenetic choice of drug therapy, taking into account changes in systemic hemodynamics.

4. The use of MT as a cardioprotective, antioxidant effect in addition to basic antihypertensive therapy will open up new horizons for its use in the treatment of patients at cardiovascular risk.

5. Antihypertensive therapy for hypertension with inclusion of the ACE inhibitor ramipril and extended-release MT is characterized by greater regression of the processes of cardiovascular system pathological remodeling, a significant decrease in the level of systolic, diastolic, and central blood pressure, a decrease in adverse sympathetic effects, circadian normalization of biorhythms and improved sleep quality.

Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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List of abbreviations

AH – arterial hypertension
BP – blood pressure
MAP – mean arterial pressure
MBPS – value - morning blood pressure surge value
HBI – hyperbaric index
DBP – diastolic blood pressure
ACE – inhibitor -inhibitor of angiotensin converting enzyme
IHD – ischemic heart disease
TI – time index
AI – area index
GIT – gastrointestinal tract
MT - melatonin
BA – brachial artery
PAP – pulse pressure
RAAS – renin-angiotensin-aldosterone system
SBP – systolic blood pressure
ABPM – ambulatory (24-hour) blood pressure monitoring
nocturnal BP – decrease (NBP dip)
CVD – cardiovascular diseases
CVC – cardiovascular complications
MHR – morning hypertension rate
HR – heart rate
AASI – ambulatory (outpatient) arterial stiffness index
AIxao – augmentation index aortic
ASI – arterial stiffness index
dP/dt max – maximum rate in blood pressure increase
ED – expulsion duration
PPA - pulse pressure amplification
PWVao – pulse wave velocity aortic
RWTT – reflected wave transit time
SEVR – subendocardial viability ratio

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N-[2-(5-metoksi-1*H*-indol-3-il)]acetamid može da koriguje arterijsku hipertenziju kod ljudi koji imaju problema sa spavanjem

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SAŽETAK

Uvod. Poremećaj sna je česta tegoba kod bolesnika koji već duže vreme pate od arterijske hipertenzije. Skriveno i nekontrolisano povećanje krvnog pritiska otežava fiziološke procese, remeti regulaciju bioloških ritmova i povećava rizik od kardiovaskularnih komplikacija, čak i sa arterijskom hipertenzijom kraćeg toka. U isto vreme, hronični poremećaji sna doprinose razvoju hipertenzije, definišući ulogu novog, društveno važnog faktora rizika. Važnu ulogu u patogenezi nesanice igra deficijencija sinteze melatonina, što negativno utiče na kardiovaskularni sistem.

Cilj. Cilj rada bio je ispitivanje karakteristika centralne i vaskulrne hemodinamike kod bolesnika sa prvim stepenom arterijske hipertenzije i procena kliničke efikasnosti antihipertenzivne terapije sa sintetičkim analogom melatonina produženog oslobađanja na početku bolesti.

Metode. Instrumentalni pregled uključio je rađenje elektrokardiograma, ambulantno merenje krvnog pritiska pomoću automatskog tonometra, kao i neinvazivni automatski monitoring krvnog pritiska u trajanju od 24 sata. Ozbiljnost nesanice procenjivana je primenom somnološkog upitnika. Predstavnici prve grupe (n = 34) uzimali su mononoterapiju koja je uključila ACE inhibitor ramipril, dok su ispitanici druge grupe (n = 33) uzimali ACE inhibitor ramipril u kombinaciji sa sintetičkim analogom melatonina.

Rezultati. Rezultati randomizovane otvorene prospektivne studije sa 78 učesnika otkrili su aktivnost renin-angiotenzin-aldosteron sistema, hipersimpatikotoniju u toku noći, kao i desinhronozu usled mogućeg smanjenog lučenja melatonina. Farmakološka antihipertenzivna terapija, uz dodatak analoga melatonina produženog oslobađanja, bila je praćena značajnim poboljšanjem kliničkog stanja pacijenata sa hipertenzijom. Zabeležena je pozitivna dinamika indikatora sistemske hemodinamike i funkcionalnih parametara krutosti arterija.

Zaključak. Rad opisuje moguće benefite melatonina kao dela kombinacione antihipertenzivne terapije kod pacijenata sa hipertenzijom u ranoj fazi i nesanicom. Potvrđeno je dodatno uvođenje melatonina na početku arterijske hipertenzije kao fiziološkog regulatora cirkadijalnog biološkog ritma.

Ključne reči: **nesanica, poremećaj spavanja, krvni pritisak, ambulatorno praćenje krvnog pritiska, arterijska hipertenzija, krutost krvnih sudova, melatonin, ramipril**