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Melatonin corrective effect on systemic and vascular hemodynamic parameters in patients with the first degree of arterial hypertension suffering from sleep disorders

Efecto corrector de la melatonina sobre parámetros hemodinámicos sistémicos y vasculares en pacientes con primer grado de hipertensión arterial que sufren trastornos del sueño

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SUMMARY

Sleep disturbance is a common reason for seeking primary health care providers` medical attention and maybe the first manifestation of arterial hypertension (AH) at the disease onset. An uncontrolled blood pressure (BP) increase aggravates the course of physiological processes and increases cardiovascular complication (CVC) risk, even with a short AH duration. Additional prescription of substances that increase the body's nonspecific resistance as a physiological regulator of circadian biorhythms in patients with early AH and insomnia stages is justified. The work aims

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are to increase the effectiveness of antihypertensive therapy by including melatonin (MT) in people with sleep disorders, considering the daily blood pressure profile, central blood pressure parameters, and somnological status in patients with newly diagnosed AH. The changes identified indicated a significant activity of the renin-angiotensin-aldosterone system (RAAS), sympathetic tone at night, and desynchronosis caused by MT secretion deficiency. Pharmacotherapy with the synthetic analog of prolonged-release MT included in the treatment regimen for patients with AH and insomnia was accompanied by a significant improvement in the clinical condition. The target BP level was achieved in most patients, as well as positive dynamics of central BP parameters and regression of indicators reflecting peripheral artery rigidity.

Keywords: *Sleep disorders, insomnia, arterial hypertension, central aortic pressure, vascular stiffness, ambulatory blood pressure monitoring, melatonin, ramipril.*

RESUMEN

La alteración del sueño es un motivo común de búsqueda de atención médica por parte de los proveedores de atención primaria de salud puede ser la primera manifestación de hipertensión arterial (HA) al inicio de la enfermedad.
Un aumento descontrolado de la presión arterial (PA) agrava el curso de los procesos fisiológicos y aumenta el riesgo de complicaciones cardiovasculares (CVC), incluso con una duración breve de la HA. Se justifica la prescripción adicional de unas sustancias que aumentan la resistencia inespecífica del cuerpo como regulador fisiológico de los biorritmos circadianos en pacientes con HA temprana e insomnio. El objetivo del trabajo es aumentar la eficacia de la terapia antihipertensiva mediante la inclusión de melatonina en personas con trastornos del sueño, teniendo en cuenta el perfil de presión arterial diaria, los parámetros de presión arterial central y el estado somnológico en pacientes con hipertensión arterial de nuevo diagnóstico. Los cambios identificados indicaron una actividad significativa del sistema renina-angiotensina-aldosterona (SRAA), hipersimpaticotonía nocturna y desincronización causada por la deficiencia en la secreción de melatonina (MT). La inclusión de la farmacoterapia con análogos de MT sintéticos en el régimen de tratamiento para pacientes con HA e trastornos del sueño estuvo acompañada de una mejora significativa en la condición clínica. El nivel de PA objetivo se logró en la mayoría de los pacientes, así como una dinámica positiva de los parámetros de PA central y la regresión de los indicadores que reflejan la rigidez de las arterias periféricas.

Palabras clave: *Trastornos del sueño, insomnio, hipertensión arterial, presión aórtica central, rigidez vascular, monitorización ambulatoria de la presión arterial, melatonina, ramipril.*

INTRODUCTION

More than 20.0 % of people in the world experience general dissatisfaction with the quality of sleep, defined as insomnia (1). Even though sleep disorders have serious consequences for human health, in most cases these disorders are ignored not only by the patient but also by the doctor. The direct relationship between somnological disorders and various somatic diseases emphasizes this pathology`s particular relevance (2-4). According to a number of researchers, 50 % of patients with insomnia have AH, which is often uncontrollable (5-7). Therefore, at present, no one doubts that there is a close functional connection between these two conditions.

Sleep is a highly organized neurochemical process that plays an important role in the body's life, regulation of systemic hemodynamics, and maintaining physical and mental health. The results of the observational study MORGEN, involving more than 20 thousand people aged 20-65 years without cardiovascular disease (CVD), showed that short sleepers, especially those with poor sleep quality, are associated with an increased risk of cardiovascular disease (8).

Undoubtedly, in this pathogenetic process, a change in the secretion rhythm of endogenous MT incretin plays an important role. Disruption of the daily indolamine synthesis cyclicity leads not only to the disruption of physiological rhythms of sleep and wakefulness but is also associated with the risk of developing mental disorders, anxiety and depression, gastrointestinal tract (GIT) pathology, anorexia, oncological pathology, immunological disorders and especially CVD (9). Multilevel neurohumoral restructuring caused by impaired melatonin secretion leads to circadian fluctuations in blood pressure, contributing to the persistent development of AH (10). At the same time, people with constantly high blood pressure have low melatonin levels at night, because of which the duration of sleep is reduced, and its quality characteristics change (11). It has been proven

that sleep disturbances, even in individuals with normal blood pressure levels, contribute to an increase in both systolic blood pressure (SBP) and diastolic blood pressure (DBP), thereby increasing the risk of developing hypertension in healthy people (12). In addition, a high incidence of hypertension and insomnia in the older age group indicates a direct dependence of these conditions on age (13). Considering the great importance of melatonin in the synchronization of biorhythms of the cardiovascular system, the study of the effect of exogenously administered melatonin on systemic hemodynamic parameters in hypertensive patients is currently underway. Some studies show a direct vasodilating effect of melatonin (14,15), in others, it is mediated by pleiotropic, antioxidant action (16,17). Based on the foregoing, the prescription of an MT synthetic analog to patients with AH and insomnia, in addition to standard antihypertensive therapy at the disease onset, seems to be justified and promising. The work aims are to increase the effectiveness of antihypertensive therapy by including MT in people with sleep disorders, considering the daily blood pressure profile, central blood pressure parameters, and somnological status in patients with newly diagnosed AH.

MATERIAL AND METHODS

200 patients over 18 years of age with AH were examined in an outpatient clinic. Of these, 78 people (32 men, 46 women; average age 52.4 ± 4.7 years) were included in this study. The inclusion criteria were newly diagnosed first-degree arterial hypertension and a somnological status disorder diagnosed at the screening stage (according to questionnaires or complaints), including a reduction in sleep duration, and daytime sleepiness. The average blood pressure in the subjects was 146.8 ± 8.2 / 94.3 ± 5.5 mmHg, and the insomnia duration was - 8.0 ± 2.1 months. The study excluded persons with severe CVD (AH of the 2nd and 3rd degree, white coat hypertension, ischemic heart disease (IHD), heart defects, and a history of cerebrovascular accidents). Participants with severe comorbidities requiring ongoing drug therapy, cancer, allergic reactions to the study drug, pregnant women, and persons driving vehicles were also excluded.

Before the beginning of observation and after 12 weeks, all patients underwent general clinical and instrumental examination: BP measurement with an automatic tonometer (OMRON M2 Basic), ECG registration (Schiller Cardiovit AT-1 electrocardiograph), 24-hour blood pressure monitoring (ABPM) with a complex of software and hardware monitoring of blood pressure BPLab («BPLab», LLC «Petr Telegin»). We recorded daily, nighttime, and daytime values of SBP and DBP, pulse aortic pressure (PAP) and mean aortic pressure (MAP), as well as SBP and DBP variability, morning BP surge value (MBPS), and BP daily index (DI), called the degree of night drop. The following types of daily curves were considered, depending on the DI intensity: «dipper», «non-dipper», «over-dipper» and «night-peaker», according to the approved classification. «Dipper» – with a normal decrease in blood pressure at night (10 %<DI<20 %), «non-dipper» – with an insufficient decrease in blood pressure at night (0<DI<10 %), «over-dipper» – with an excessive decrease in blood pressure at night (20 %<DI), «night-peaker» – hypertension at night (DI<0) (18-20).

The value of the total daily pressure load was carried out separately for SBP and DBP according to the time index (TI), area index (AI), and the general hyperbaric index (HBI). The percentage of measurements in the total number of registrations exceeding the upper limit of the norm was taken as the BP TI. The quantitative characterization of the excess blood pressure area during the entire monitoring period was taken as AI. The BP TI was taken as the measurement's percentage in the total number of registrations exceeding the upper norm limit, for AI - a quantitative characteristic of the BP excess area during the entire monitoring period. HBI is a quantitative ABPM parameter, expressed as a percentage, reflecting the excess of the upper limit of the permissible BP fluctuation range. To determine parameters of arterial stiffness and central aortic pressure, we used a complex of software and hardware blood pressure monitoring BPLab with Vasotens® technology, which makes it possible to study and analyze properties of blood vessels of various calibers. Central (aortic) hemodynamics indicators were

assessed by the SBP level in the aorta (SBPao), the DBP level in the aorta (DBPao), and the pulse aortic pressure (PAP). The main parameters of arterial stiffness were assessed by the reflected wave transit time in the aorta (RWTT), pulse wave velocity in the aorta (PWVao), the expulsion duration (ED), augmentation index aortic AIxao, and its reduced indicator, recalculated for heart rate (HR) equal to 75 beats/min (AIx @ 75). We also assessed the maximum rate of increase in BP (dP / dt max), ambulatory arterial stiffness index (AASI), pulse pressure amplification (PPA), and the subendocardial blood flow efficiency index - subendocardial viability ratio (SEVR) or Buckberg index. The speed characteristics calculation was carried out based on the measured aorta length (upper edge of the sternum - pubic bone), whose value (cm) was entered into the ABPM software during the device initiation. It should be noted that, in accordance with the expert opinion of the American College of Cardiology and the American Heart Association (21), BPao values were taken as the leading prognostic indicator for assessing the left ventricular (LV) afterload, and the pulse wave qualitative assessment was performed according to SBPao, PAP and AIx.data. The HADS scale was used to measure the anxiety and depression levels. The existing sleep disorders' severity was assessed using somnological questionnaires: «Index of the severity of insomnia» (ISI; C. Morin), «Subjective assessment of sleep characteristics» (Wayne A.M., Levin YI), «Epworth Daytime Sleepiness Scale» (ESS), Pittsburgh Sleep Quality Index (PSQI) Questionnaire.

According to the examination results, 11 patients were found to have false isolated systolic hypertension, characterized by an increase in peripheral SBP with a normal value of central SBP. This category of individuals received extended medical advice without prescribing antihypertensive therapy, and therefore they were not included in this study.

After being examined 67 patients were randomized (adaptive randomization method) into two groups (Table 1). Patients in group 1 (n = 34) were prescribed antihypertensive monotherapy with an angiotensin-converting enzyme inhibitor (ACEI) ramipril, the reception of which was at 8 pm, whose average dose by the end of the observation period was 4.6 ± 1.7 mg/day. In group 2 (n = 33), a chemical analog of prolonged-release MT at a dose of 3 mg 30 minutes before bedtime was added to similar antihypertensive therapy. The main advantage of sustained-release melatonin over rapid-release melatonin is related to the structure of the tablet shell. This allows the body to maintain a constant concentration of melatonin throughout the night and create a physiological structure of sleep (22,23). There was no additional prescription for other antihypertensive medicine classes in the groups. After taking this medicine in the evening, patients were not recommended to be in a brightly lit place, to engage in activities requiring maximum concentration of attention and sports. In addition, all patients were prescribed to keep a diary of BP self-monitoring at home, a lipid-lowering and low-salt diet, more intensive physical activity, and measures for sleep hygiene. Their condition observation lasted 12 weeks. The SPSS 22.0 software (SPSS Inc, USA) for Windows (Microsoft Corporation, USA) was used for statistical analysis. For numeric variables, the mean and standard deviation (M ± S.D.) and the confidence interval (95 % CI) were calculated.

Table 1

Characteristics of patients with AH of groups 1 and 2 depending on the therapy

Patient characteristics	Group 1 (n=34)	Group2 (n=33)
Number of observation days	86.3±2.3	86.2±3.8
Women, number /%	20/58.8	21/63.6
Men, number /%	14/42.2	12/36.4
BMI, kg / m^2	27.4±3.6	25.3 ±4.7
Obesity, number/%	5/14.7	2/6.1
Average age, years	51.9 ±5.4	53.2 ±3.8
SBP office, mmHg	145.8±5.2	147.2±6.0
DBP office, mmHg	93.3±4.7	95.2±5.2
AH degree: 1 st. / 2 nd. / 3d., number of people	34/0/0	33/0/0
Insomnia duration, months	7.8 ±1.8	8.1±2.3
Tobacco smoking, number/ %	13/38.2	8/24.2
Total cholesterol, mmol / L	4.7 ±0.5	4.9 ±0.7
Glucose, mmol / L	5.0 ±0.1	5.0 ±0.2
Creatinine, μmol / L	72.1±2.6	69.8 ±2.9
Uric acid, μmol / L	364.6±15.9	358.6 ±12.0

Abbreviations: BMI - body mass index; SBP - systolic blood pressure; DBP - diastolic blood pressure; AH - arterial hypertension.

To assess the normal distribution of variables, the Kolmogorov-Smirnov test was used. The data distribution normality was assessed using the Kolmogorov-Smirnov criteria (with a sample size of more than 50), or the Shapiro-Wilk one (with a sample size of less than 50). To identify intragroup differences for dependent groups, a nonparametric method was used - the one-sample Wilcoxon test. Correlation analysis was performed using the Spearman method. Intergroup differences were calculated using the U-Mann-Whitney test. The difference was statistically significant at $p < 0.05$.

RESULTS

The obtained results analysis showed positive dynamics of the patients` condition in both groups during the therapy, as evidenced by indicators of the clinical status improvement and blood pressure normalization by the end of the observation period. Thus, according to the data from self-monitoring BP diaries, 76.5 % of patients in the first group and 87.9 % of those in the second group reached a blood pressure level not exceeding 135/85 mmHg. Office SBP in group 1 decreased from 145.75 ± 5.19 to 134.41 ± 3.69 mm Hg (By 7.8 %; $p < 0.0001$), DBP - from 93.26 ± 4.65 to 85.71 ± 4.19 mmHg (By 8.1 %; $p < 0.0001$). In group 2, SBP decreased by 12.2 % (from 147.12 ± 6.11 to 129.24 ± 9.55; $p < 0.0001$), DBP - by 13.7 % (from 95.33 ± 5.29 to 82.28 ± 6.61 mmHg; $p < 0.0001$). The ABPM parameter dynamics indicated clear advantages of therapy with the inclusion of a synthetic MT analog in the scheme (Table 2). In group 1, the average daily SBP decreased by 8.9 %, DBP - by 7.3 % ($p < 0.01$). In patients of group 2, the average daily SBP decreased by 10.8 %, DBP - by 9.9 % ($p<0.001$), which is comparable with the dynamics of BP measured at the brachial artery (BA). There was a more pronounced decrease in the average SBP and PAP indicators in the night period by the end of observation in group 2: SBP (n) decreased on average by 16.2 mm Hg, PAP (n) - by 8.9 mmHg. In patients of group 1, these parameters decreased by 9.6 mmHg and 4.3 mmHg. respectively ($p < 0.05$). A similar pattern was shown by the TI and AI dynamics of BP. The daily SBP TI in group 2 significantly decreased by 65.1 % versus 51.9 % (in group 1). The DBP TI decreased by 62.5 % versus 53.0 %. The maximum degree of decrease in HBI of SBP in patients taking MT was 63.9 % ($p = 0.0003$), in HBI of DBP - 57.6 % ($p = 0.0001$). A decrease in BP AI in patients of two groups during therapy indicated a decrease in pressor load: in representatives 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 parameters of SBP and DBP morning dynamics indicated a statistically significant decrease in the rate of the SBP morning rise and a tendency towards a decrease in MBPS in the group of patients taking MT. No statistical difference was found for DBP. Despite the absence of obvious pathological changes in blood pressure variability in most patients participating in the study, this indicator dynamics had a certain multidirectional character by the end of the observation. While in group 1 the SBP variability decreased at all time intervals (from 4.7 % to 7.3 %), in patients of group 2 this parameter value slightly increased in the daytime (Δ=+2 %; $p = 0,06$), and the diurnal and nocturnal SBP variability tended to decrease (Δ=-2,0 %; $p = 0,127$ и Δ=-7,9 %; $p = 0,01$). Indicators of DBP variability significantly decreased in both groups but did not differ according to the data agreement criterion $\chi 2$.

A detailed analysis of the patients` daily blood pressure profile by the end of the observation period did not reveal statistical differences between the groups. However, in all groups, the number of cases with the pathological profile «non-dipper» decreased and the number of patients with the profile «dipper» increased: up to 70.6 % and 73.5 % for SBP and DBP in the group1 ($p<0.05$), and up to 84.8 % and 81.8 %, respectively, in group 2 ($p<0.05$). Inversion of the 24-hour BP profile at the selection stage in most patients indicated increased sympathetic tone, and therapy`s stronger chronotropic effect by the end of the observation period without taking pulse rate reducing medicines. In patients of group1, the heart rate decreased by 7.1 % (from 78.26 ± 5.98 to 72.67 ± 6.23 beats per minute; $p < 0.05$), in the second group - by 11.9 % (from 78.08 ± 7.62 to 68.83 ± 5.48 beats per minute; p

Table 2

Dynamics of ABPM parameters in patients with AH of groups 1 and 2 during therapy

Characteristics		Group1			Group 2. After treatment			P 1-2
		M	s.d	95% CI	M	s.d	95% CI	
SBP daily, mmHg	initially	146.8	5.2	144.5-148.9	147.1	8.0	143.6-156.3	>0.05
	after 12 weeks	134.4	3,7	133.5-136.7	131.2	9.5	110.0-136.4	0.01
DBP daily, mmHg	initially	91.7	4.7	89.0-93.3	92.3	5.3	86.1-9.3	>0.05
	after 12 weeks	84.7	5.2	80.7-88.8	83.3	6.6	64.6-85.2	0.09
MBP daily, mmHg	initially	107.4	4.9	104.6-108.4	107.6	10.1	103.8-111.4	>0.05
	after 12 weeks	99.3	5.9	97.2-102.8	96.6	6.9	92.9-98.2	0.02
PAP (d), mmHg	initially	54.1	3.8	52.5-56.2	54.8	11.4	50.5-59.1	>0.05
	after 12 weeks	49.9	3.7	46.6-52.5	47.0	6.7	44.6-50.6	0.08
Heart rate, beats / min	initially	78.3	5.9	72.0-83.2	78.1	5.9	76.3-80.5	>0.05
	after 12 weeks	72.7	6.2	63.3-75.4	68.8	5.5	63.0-72.0	0.001
SBP TI daily, %	initially	69.5	5.8	31.4-97.5	68.7	6.2	29.2-100.0	>0.05
	after 12 weeks	33.4	4.4	16.1-54.2	20.4	4.4	12.2-48.5	0.001
DBP TI daily, %	initially	51.3	4.7	26.7-82.4	55.3	5.8	16.3-79.6	>0.05
	after 12 weeks	24.1	4.2	1.4-41.8	20.7	3.2	0.0-34.3	0.001
SBP AI daily, c.u.	initially	140.5	18.5	119.5-179.5	148.2	8.6	122.2-190.4	0.02
	after 12 weeks	69.2	9.1	66.9-101.2	42.9	5.5	20.8-77.5	0.001
DBP TI daily,c.u.	initially	100.7	4.3	97.2-142.8	107.2	15.2	65.6-150.6	0.06
	after 12 weeks	44.8	20.4	2.9-85.3	33.9	6.1	8.8-52.7	0.01
SBP HBI daily, %	initially	163.2	34.6	126.7-213.0	171.5	36.9	128.6-220.2	>0.05
	after 12 weeks	87.3	17.2	76.4-119.7	61.4	16.8	43.5-110.3	0.01
DBP HBI, daily%	initially	107.1	30.5	90.5-152.6	110.4	25.6	86.4-161.1	0.08
	after 12 weeks	51.9	19.4	12.8-95.4	48.3	13.5	12.0-86.3	0.04
Var Heart rate, beats/min	initially	8.8	1.0	8.0-10.8	8.9	0.9	8.0-10.6	>0.05
	after 12 weeks	7.9	0.9	7.3-8.5	6.7	0.6	6.1-7.1	0.001
SBP MBPS, mmHg	initially	40.2	4.9	28.0-58.4	38.7	5.2	32.2-57.8	>0.05
	after 12 weeks	26.8	2.6	14.5-37.6	22.3	3.1	14.6-40.8	0.063
DBP MBPS, mmHg	initially	24.1	3.9	22.8-28.2	25.5	4.6	20.2-34.7	>0.05
	after 12 weeks	17.0	2.8	14.5-22.0	16.2	2.7	12.0-18.3	>0.05
SBP MHR, mmHg	initially	18.9	1.9	12.4-28.5	18.7	2.3	10.4-30.6	>0.05
	after 12 weeks	10.6	1.4	8.9 -12.0	9.2	1.5	8.4 -10.8	0.01
DBP MHR, mmHg	initially	15.0	2.2	10.3-18.5	15.1	2.0	10.2-18.0	>0.05
	after 12 weeks	14.1	2.0	10.0-16.7	13.4	1.8	9.5-15,9	>0.05
Var SBP daily, mmHg	initially	14.7	3.7	12.4-18.0	14.6	3.6	12.5-17.0	>0.05
	after 12 weeks	14.0	3.2	10.2-18.5	14.9	4.0	10.6-18.6	0.04
Var DBP daily, mmHg	initially	13.2	0.6	11.8-14.2	13.3	0.7	10.8-15.0	>0.05
	after 12 weeks	12.2	0.4	9.5-14.0	11.9	0.4	8.5-13.4	0.09

Abbreviations: BP - blood pressure; SBP - systolic blood pressure; DBP - diastolic blood pressure; PAP - pulse aortic pressure; MAP - mean aortic pressure; MBPS - morning BP surge value; DI - BP daily index; Var – the variability; TI - the time index; AI - the area index; HBI - the general hyperbaric index.

<0.05). Noteworthy is the statistically significant difference in the number of patients who achieved target values during therapy according to ABPM data. There was a significant change in the mean values of nocturnal SBP (SBPn), whose target values did not exceed 120 mmHg in 84.8 % of patients in group 2 and 61.8 % of patients in group 1 (p = 0.03).

A more detailed analysis of systemic hemodynamics parameters is complemented by central arterial pressure parameters, which in the

compared groups reflected similar data of ABPM values, confirming the advantages of therapy with MT inclusion in the treatment regimen (Table 3). Daytime SBPao in group 1 decreased by 8.9 %, nighttime - by 6.1 %, daily - by 6.9 % (<0.05). In group 2 daytime SBPao decreased by 11.5 %, nighttime - by 9.4 % and daily - by 10.8 % (<0.05). In group 1, central daily DBP decreased by 5.9 % (p <0.05), in group 2 - by 10.9 % (p <0.05). A significant difference in the daily rate of decrease was noted only for SBPao (<0.0001), the DBPao dynamics were unreliable.

Table 3

Dynamics of central aortic pressure indicators and vascular rigidity in patients of groups 1 and 2 with hypertension during therapy

Characteristics	Group 1 (n=34)			Group2 (n=33)			P 1-2
	M	Δ, %	95 % CI	M	Δ,%	95 % CI	
SBPao(d), mmHg initially	133.12	-6.9*	124.2-138.9	134.13	-10.8*	130.9-137.3	<0.001
after 12 weeks	123.85		117.5-130.5	119.6*		110.7-123.5	
SBPao (d/t) mmHg initially	134.58	-8.9*	125.5-142.1	135.83	-11.5*	124.1-144.3	<0.01
after 12 weeks	122.65		118.5-132.9	120.17		110.6-130.4	
SBPao (n/t) mmHg initially	121.60	-6.1*	128.3-136.3	121.22	-9.4*	115.9-129.6	<0.001
after 12 weeks	114.16		111.9-120.0	109.86		107.7-118.8	
DBPao (d), mmHg, initially	83.65	-5.9*	82.45-92.04	83.73	-6.4*	81.3- 93.2	0.09
after 12 weeks	78.69		74.13-85.53	78.35		73.7- 81.9	
PAPao (d), mmHg, initially	45.23	-6.6*	42.95-46.71	46.06	-9.4*	41.0-49.2	<0.01
after 12 weeks	42.76		38.54-45.79	41.73		37.6-44.7	
MAPao (d), mmHg, initially	104.63	-7.3*	102.5-108.2	104.02	-9.9*	100.9-108.3	<0.01
after 12 weeks	96.96		101.7-105.7	93.73		95,8-99.6	
AIxao, % initially	32.42	-7.9*	30.64-34.95	33.12	-10.6*	27.6-40.6	<0.001
after 12 weeks	29.87		22.29-30.39	29.61		18.3-35.16	
SEVR, % initially	118.75	+8.2*	111.8-128.7	118.13	+11.5*	113.2-122.3	<0.01
after 12 weeks	129.42		122.1-135.9	133.54		127.9-146.1	
ED, m/sec initially	329.80	-10.1*	318.5-341.06	331.69	-10.7*	305.4-386.6	0.130
after 12 weeks	296.41		224.4-338.41	296.23		235.4-344.9	
PPA, % initially	135.63	-4.0*	129.94-136.1	134.86	-5.8*	132.1-137.6	0.07
after 12 weeks	130.25		120.84-135.7	127.20		117.3-135.2	
PWVao, m/sec initially	10.80	-5.2*	8.48–12.94	10.79	-9.5*	8.75-13.67	<0.001
after 12 weeks	10.24		7.93-10.97	9.76		7.99-10.42	
RWTT, m/sec initially	141.29	+4.0*	123.7-146.38	142.01	+6.5*	126.6-156.9	<0.01
after 12 weeks	135.63		124.8-142.17	132.73		128.58-154.6	
AIx@75, % initially	-4.95	+8.9*	-9.4-(+5.8)	-4.92	+10.7*	-17.1-(+6.9)	<0.01
after 12 weeks	-5.39		-22.27-(+4)	-5.51		-26.53-(+3)	
ASI mmHg, initially	143.84	-5.9*	120.94-209.7	144.36	-7.1*	127.74-207.5	<0.05
after 12 weeks	135.36		126.14-146.8	134.12		126.54-140.5	
AASI, c.u. initially	0.356	-8.1*	0.209-0.531	0.362	-9.4*	0.225-0.524	0.08
after 12 weeks	0.327		0.163-0.428	0.331		0.167-0.389	
dP/dt max, mmHg, initially	557.14	-7.2*	510.8-616.87	561.60	-9.8*	587.7-624.52	<0,01
after 12 weeks	530.73		518.85-598.6	523.87		509.8-576.87	

Abbreviations: SBPao – systolic blood pressure level in the aorta; DBPao –diastolic blood pressure level in the aorta; PAPao – pulse aortic pressure; MAPao - mean aortic pressure; (d) – daily; (d/t) – daytime; (n/t) – nighttime; AIxao - augmentation index; AIx @ 75 - augmentation index reduced to a heart rate of 75 beats/minute; PPA - pulse pressure amplification; SEVR - index of efficiency of subendocardial blood flow; ASI - stiffness index; AASI - ambulatory stiffness index; RWTT - the value of the pulse wave in the aorta; PWVao - the speed of the pulse wave in the aorta; dP / dt max - the maximum rate of increase in blood pressure.

Changes in DBPao, MAP, and PAP were also reflected in the qualitative assessment of the pulse wave and vascular stiffness (Table 3). After 12 weeks, the two comparison groups showed a statistically significant decrease in the PWVao transit speed and the augmentation index AIxao, and an increase in the index of subendocardial blood flow efficiency (SEVR), and RWTT. This, regardless of the blood pressure decrease degree, indicated regression of vascular remodeling and reducing cardiovascular risk in patients with AH. At the same time, the existing intergroup differences in PWVao, AIx75 @, dP / dt max, and SEVR by the end of the observation testified in favor of more effective therapy for patients of group 2. In patients of group 1, PWVao decreased by 5.2 % (from 10.80 ± 1.17 to 10.24 ± 0.94 m / s) and RWTT increased by 4.0 % (from 141.29 ± 13, 28 to 135.63 ± 11.09). 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 group1 - 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 daytime SBP 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 $r = 0.758$).

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 $\chi 2$ reached a statistical difference ($p < 0.001$). Because 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 the group1, and in the group of patients receiving MT -5.51 ± -5.88 (<0.01). Along with the high AIxao predictive value, the importance of a combined assessment of the arterial stiffness index (ASI) and the outpatient/ ambulatory arterial stiffness index (AASI), as predictors of mortality from cardiovascular causes, is shown. Considering 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 %, and in group 1 - by 5.9 % and 8.1 %, respectively. A decrease in the hemodynamic load on the vascular wall as evidenced by a significant decrease in dP / dt max, while the difference between the groups according to the agreement criterion $\chi 2$ indicated the advantage of therapy in the group1 ($p < 0.01$). 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 may indirectly indicate the ACEI significant role in the correction of vascular stiffness pathological changes, which was one of these work`s important conclusions.

With the normalization of systemic hemodynamic parameters many subjective sleep characteristics significantly improved. However, the degree of the positive change in the groups was not the same (Table 4). 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 ± 3.7 to 15.9 ± 2.5; $p = 0.0001$) and the mean PSQI score - by 26.2 % (from 10.7 ± 2.8 to 7.9 ± 1.5), while among representatives of group 1 - by 9.3 % and 7.8 %, respectively. Direct relationship between ISI and the 24-hour SBP ($r = 0.654$; $p = 0.019$), 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 daily SBP ($r = -0.384$; $p = 0.029$) in patients of group 2 by the

Table 4

Dynamics of somnological and psychological indicators of patients with AH of groups 1 and 2 during therapy

Characteristics	Group1 Basic therapy				Group 2 Basic therapy + MT			
	initially (M ± S.D)	95 % CI	After 12 weeks (M ± S.D)	95 % CI	initially (M ± S.D)	95 % CI	After12 weeks (M ± S.D)	95 % CI
HADS Anxiety, score	9.5±3.1	8.2 - 10.8	8.6±1.8	7.9 - 9.4	9.7±2.8	8.6 - 10.7	6.0±1.8*	5.3-6.7
HADS, Depression, score	6.8±2.2	5.9 - 7.8	6.4±2.2	5.5 - 7.3	6.3±2.2	5.5 - 7.2	4.8±1.9*	4.1-5.5
PSQI. score	11.3±1.4	10.7-11.9	10.5±1.6	9.9 - 11.3	10.7±2.8	10.0 - 11.4	7.9±1.5*	5.5-6.7
Duration of sleep. hours	6.2±1.2	5.3- 6.7	6.9±0.9	5.7 - 6.9	6.4±1.2	5.9 - 6.8	7.9±0.9*	7.5-8.2
Number of dreams. score	1.8±0.7	1.5-2.2	2.3±0.7*	1.5-2.8	1.8±0.8	1.3-2.3	2.5±0.7*	1.9-3.0
Number of night awakenings	2.6±1.1	1.9-3.7	3.1±0.9	2.6-3.7	2.6±0.8	2.1-3.4	3.2±1.1	2.6-3.9
Time of falling asleep.score	1.9±0.7	1.3-2.6	2.1±0.9	1.4-2.9	1.9±0.7	1.2-2.5	2.4±0.8*	1.8-3.0
Quality of morning awakening	1.7±0.9	1.2-2.5	2.0±0.9	1.3-2.8	1.7±0.9	1.1-2.4	2.4±0.5*	1.9-2.9
Quality of sleep. Score	2.4±0.9	1.8-3.1	2.7±1.0	1.9-3.5	2.4±0.8	1.7-3.2	3.1±0.8*	2.5-3.9
Epworth scale. score	6.8±2.7	4.3-9.2	6.3±1.9*	4.6-7.2	6.9±2.4	4.7-8.9	6.3±1.7	5.1-7.7
Total score. score	10.3±2.0	8.4-11.9	14.6±2.2*	12.8-16.7	10.4±2.1	8.4-12.1	16.8±1.9*	15.3-18.7
ISI average score	20.4±3.5	17.0-23.3	18.5±2.7*	15.8-21.1	20.3±3.7	16.9-23.5	15.9±2.5*	13.6-18.0

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).

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 were no negative dynamics.

DISCUSSION

In an extended examination beyond the standard one by a primary care physician, the baseline data of patients with AH and sleep disorders indicated a significant cardiovascular risk despite the initial AH stage, its first degree, and its short duration. The revealed impaired blood pressure daily profile (BPDP), insufficient lowering of blood pressure during sleep, and insomnia in patients with an initial degree of hypertension indicated not only significant activity of the renin-angiotensin-aldosterone system (RAAS) but also desynchronosis of biological rhythms and probable deficiency of MT secretion (due to increased stimulation of the sympathetic nervous system at night - «non-dipper» and «night-peaker» profiles).

Considering the fact that in recent years there has been an increase in mortality in groups with a low cardiovascular risk, the standard risk assessment system does not allow reflecting the true probability of CVC with persistent morpho-functional changes in the cardiovascular system (CVS), including the vascular bed (24).

Recent studies have proven the vascular stiffness prognostic role as an independent integral predictor of cardiovascular morbidity and mortality development (21,24,25). The vascular wall`s impaired elasticity is recorded in the process

of aging, smoking, physical inactivity, insomnia, metabolic syndrome, AH, IHD, bronchial asthma, and menopause (1,3,5,26). When studying the relationship between cardiovascular risk factors and vascular stiffness indicators, a significant relationship was found only in relation to tobacco smoking between PWVao ($r = 0.524$; $p = 0.001$), AASI ($r = 0.618$; $p = 0.0001$), ASI ($r = 0.436$; $p = 0.03$) and AIx @ 75 ($r = 0.411$; $p = 0.04$). This allows us to confirm the existence of a vicious circle of the relationship between smoking and hypertension, possibly disturbed by the rhythm of melatonin production with tobacco smoking (possibly with tobacco smoking before bedtime). This fact should be considered by the attending physician when selecting therapy for smoking patients to ensure effective treatment (increasing the dose of ACEI / increasing the course of melatonin therapy).

High central and vascular hemodynamics indices indicated the development of CVS pathological vascular remodeling long before the first AH symptoms onset, which emphasizes a special value of earlier CVD risk factor screening in patients with insomnia and the need to accurately identify high cardiovascular risk groups, considering the possible latent asymptomatic lesion of target organs. The initial excess of the values ASI≥200, AASI≥0.5 c.u., PWVao> 8.0 m / s, corrected by Aix from -10 to ≤10 % and higher, determining a high risk of CVC, was observed in 35.8 % of patients with clinical AH onset, which does not fit into the SCORE risk stratification (taking into account the true pressure load) and requires a special approach in therapy selection. HBI and AIxao increase in patients with AH of the first degree more accurately reflected the LV hemodynamic preload (i.e., the degree of LV wall tension at the end of diastole) at the initial stages of myocardial hypertrophy. Consequently, the SEVR index exceeding reference values in patients with AH of the first degree and insomnia already characterized a physiological shift in the relationship between myocardial oxygen demand and consumption, contributing to cardiomyocyte hypertrophy and, possibly, the early development of non-atherosclerotic IHD forms. In addition, it should be noted that the Reflected Wave return to the aorta occurs at the beginning of the diastole phase. This promotes modulation of the vascular bed propulsive properties and adequate coronary blood flow (24). Therefore, the detected initial increase in SBPao and PPA in persons with AH and insomnia indicated an already increasing and latent LV afterload (i.e., the resistance that the LV must overcome during systole) at the early stages of the disease, which did not provide full relaxation of the ventricular myocardium.

It is known that the AH preclinical stage is manifested by transient hypertension with short-term episodes of increased blood pressure. It is during this "mute" stage that persistent morphological signs of pathological vascular remodeling develop, characterized by hypertrophy of the arteries and arterioles muscular layer, by their hyperelastosis and spasm before the development of compensatory LV myocardial hypertrophy (27). Arteriole remodeling is the most characteristic feature of AH initial stages. Hypoxic damage to the endothelium contributes to its persistent dysfunction, aggravated by plasma impregnation of various proteins and lipids, which subsequently leads to vasospasm and arteriosclerosis (28). It is this stage of common pathomorphological changes in blood vessels that characterizes the period of persistent increase in blood pressure, which can be randomly measured routinely, as most patients in this study did. In the predominant number of cases, the AH «unsteadily persistent» nature (52.2 %) and/or complaints of sleep disturbance (64.2 %) were the main reasons for referring to primary health care physicians. Not previously diagnosed AH aggravated the course of physiological processes (desynchronosis) and determined a pathogenetic decrease in the concentration of circulating endogenous MT, which was indirectly evidenced by sleep subjective characteristics and the MBPS, the exceeded level of which (more than 55 mm Hg) was initially detected in 15 (22.4 %) of 67 patients who participated in the study.

Thus, 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 ACEI efficacy, both in monotherapy and in combination with MT in the early onset of AH

pathogenesis, and especially in the parameters of systemic and vascular hemodynamics.

The initially increased tone of arterioles, under conditions of their rigidity and oxidative stress, accelerated reflected wave formation in the aorta and led to pulse waves early generation, as evidenced by increased BPao and PPA values. Consequently, in the course of therapy in all observation groups, a decrease in PWVao indicated improvement in damping properties of blood vessels and a decrease in their rigidity. This eventually manifested itself in a decrease in SBPao and DBPao, and, accordingly, in a decrease in PAP.

In conditions of improving vascular wall damping properties and decreasing the pulse wave transit speed during the therapy, there occurred isometric relaxation of the ventricles and sufficient filling of the coronary arteries. This was evidenced by the established increase in RWTT, the SEVR index, and the duration of the ED period in patients of both groups. This provided an initial decrease in the LV hemodynamic load and showed an increase in coronary circulation options, and therefore, the cardioprotective effect of initial therapy.

In addition, a decrease in the maximum rate of BP growth (dP / dt max) indicated not only a decrease in the dynamic load on the vascular wall during the pulse wave passage but also indicated an improvement in the compensatory capabilities of the myocardium contractile function. At the same time, its decrease level was greater in patients in group 2.

Indeed, important evidence of the MT protective properties were more significant changes in central blood pressure parameters, an increase in the coronary circulation, greater indicators` regression, the pulse wave qualitative characteristics, and peripheral al arteries` rigidity in patients of group 2 (Table 3). The AIxao dynamics, an indicator characterizing the structural and functional state of the entire vascular bed up to the microcirculatory state, spoke especially clearly about improvement in damping properties of the main blood vessels in the group taking MT (24,27,29). Its more significant decrease in representatives of group 2 was direct evidence of a significant decrease in central BP, arterial stiffness, and diastolic dysfunction, and, hence, of the vasoprotective therapy effect with MT inclusion into the regimen. In this regard, the prescription of an adaptogen as part of complex therapy, as a physiological regulator of circadian biorhythms is justified.

An increased MT level concentration at night helps to neutralize the RAAS effects, to lengthen the sleep phase, and to cumulate the antihypertensive properties of medications. This explains the more pronounced nighttime decrease in mean SBP and PAP by the end of observation in group 2 and an increase in the daytime SBP variability.

The MT antihypertensive effect is realized not only through its beneficial influence on the sleep process. The main hypotensive effect is associated with the MT vasodilating effect due to its ability to enhance the nitric oxide bioavailability, which stimulates GABA-ergic inhibitory effects in neurons of the hypothalamus paraventricular nucleus (30). This determines its direct vasodilatory and, consequently, its hypotensive effect. Also, MT can exert its antihypertensive effect due to a moderate sedative effect (31), manifested in a decrease in a person's response to external stimuli, protective relaxation, and a mild hypnotic effect, which was reflected in a decrease in anxiety and depression level by the end of the observation period. 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 (16,32). The central MT hypotensive effect may be associated with the normalization of daily fluctuations in MT secretion and improvement in cerebral blood flow.

It is known that each increase in SBP by 1 mmHg. can lead to an increase in heart rate up to 10 beats/min. Accordingly, a greater decrease in heart rate and intergroup difference in corrected AIx @ 75 to heart rate, without taking anti-arrhythmic medications in patients of group 2 could be a consequence of BPDP, normalization, and a sleep duration increase, which was another advantage of combination therapy with an MT analog. Experimental results have shown a persistent negative chronotropic effect of exogenous melatonin due to binding melatonin MT1 and MT2 endothelial cell receptors to G-proteins and its direct central action (17).

Changes in systemic hemodynamics contributed to a beneficial effect on sleep physiology in patients of two groups. However, the addition of a medication containing exogenous MT to antihypertensive therapy led to an additional positive effect on somnological characteristics. In addition to improvement in the total sleep score in patients receiving MT, the quality of morning awakening significantly improved, the duration of sleep increased, the time to fall asleep and anxiety decreased, and positive dynamics of the circadian index (CI), ISI, PSQI testified to the MT synchronizing role in circadian biorhythms regulation. It is especially important to note that the significant advantage of exogenous MT over many hypnotics is associated with its ability to maintain the neurobiological basis and physiological structure of sleep (9). It is difficult to understand what led to a greater positive effect of the proposed combination therapy in the first place - the direct MT effect on somnological characteristics, the ACEI indirect effect on sleep quality due to normalization of the daily blood pressure profile, or the synergistic antihypertensive effect of a combination of an ACEI and MT. Moreover, in recent years there have been works confirming RAAS blockers` corrective role in somnological characteristics and circadian biorhythms in patients with cardiac pathology (33,34,35). An imbalance between the parasympathetic and sympathetic autonomic nervous systems, impaired BPDP, increased vascular resistance and a tendency to tachycardia are important pathophysiological components in the AH onset, and therefore a therapeutic target for many MT effects. This probably explains the more pronounced positive influence of exogenous MT therapy on the AH clinical course.

CONCLUSIONS

The results of this study emphasize the need for an extended examination of patients with sleep disorders in the early AH onset for a timely cardiovascular complications (CVC) risk assessment.

Establishing vascular stiffness parameters in outpatient-polyclinic patients is a necessary and important method of examining hypertensive patients to identify preclinical lesions of target organs.

An important aspect of managing patients at the initial AH stage from a prognostic point of view is a pathogenetically justified choice of medication therapy considering BPDP, and changes in systemic and vascular hemodynamics.

Combined AH therapy with the inclusion of an ACEI and a synthetic MT analog is characterized by a more significant decrease in the level of systolic, diastolic, and central BP, regression of CVC pathological remodeling processes, and a decrease in hyper sympathetic influences, circadian biorhythms normalization and sleep quality improvement. This will enhance the management of cardiovascular risk factors and reduce doses of standard antihypertensive medicines. However further confirmatory data including larger patient groups is necessary.

The use of MT to enhance the cardioprotective, antioxidant effect of therapy may prove to be a very effective pharmacotherapeutic strategy in the treatment of cardiovascular risk patients.

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
ACEI – angiotensin II converting enzyme inhibitor
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
BPDP- blood pressure daily profile