

Review

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CHRONOTHERAPY OF HYPERTENSION: LITERATURE REVIEW

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Review devoted to chronotherapy of hypertension. The questions of chronomedicine and chronobiology, biological rhythms, especially circadian regulation of blood pressure, types of daily blood pressure profile violations, the role of de-synchronization of biological rhythms in the development and course hypertension, opportunities to optimize antihypertensive therapy with the method of chronotherapy using alpha- and beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, diuretics, calcium channel blockers and melatonin are contemplated.

KEY WORDS: hypertension, circadian rhythms, chronotherapy, ambulatory blood pressure monitoring

ХРОНОТЕРАПІЯ ГІПЕРТОНІЧНОЇ ХВОРОБИ: ОГЛЯД ЛІТЕРАТУРИ

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Огляд присвячений хронотерапії гіпертонічної хвороби. Розглядаються питання хронобіології і хрономедицини, біологічних ритмів, насамперед, циркадної регуляції артеріального тиску, типів порушень добового профілю артеріального тиску, роль десинхронізації біологічних ритмів в розвитку і перебігу гіпертонічної хвороби, можливості оптимізації антигіпертензивної терапії методом хронотерапії з використанням альфа- і бета-блокаторів, інгібіторів ангіотензинперетворюючого ферменту, блокаторів рецепторів ангіотензину II, діуретиків, блокаторів кальцієвих каналів та мелатоніну. Робиться висновок про актуальність проблеми і недостатність її розробленості.

КЛЮЧОВІ СЛОВА: гіпертонічна хвороба, циркадні ритми, хронотерапія, добуве моніторування артеріального тиску

ХРОНОТЕРАПИЯ ГИПЕРТОНИЧЕСКОЙ БОЛЕЗНИ: ОБЗОР

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Обзор посвящён хронотерапии гипертонической болезни. Рассматриваются вопросы хронобиологии и хрономедицины, биологических ритмов, прежде всего, циркадной регуляции артериального давления, типов нарушений суточного профиля артериального давления, роль десинхронизации биологических ритмов в развитии и течении гипертонической болезни, возможности оптимизации антигипертензивной терапии методом хронотерапии с использованием альфа- и бета-блокаторов, ингибиторов ангиотензинпревращающего фермента, блокаторов рецепторов ангиотензина II, диуретиков и блокаторов кальциевых каналов и мелатонина. Делается вывод об актуальности и малой разработанности проблемы.

КЛЮЧЕВЫЕ СЛОВА: гипертоническая болезнь, циркадные ритмы, хронотерапия, суточное мониторирование артериального давления

Arterial hypertension (AH) is one of the most worldwide pathologies. Its prevalence in Europe is about 45 % of the general population, and characterized by dramatic increase with aging [1, 2]. Experts from the World Health Organization consider

hypertension as a scaled non-infectious pandemic [3]. AH is the most important risk factor for acute myocardial infarction and cerebrovascular events, considerable cause of mortality [3, 4]. In the Seventh report of the Joint National Committee of USA on

prevention, detection, evaluation and treatment of high blood pressure (BP) stated that with BP increase on each 20/10 mmHg, starting from the level of 115/75 mm Hg, the risk of cardiovascular diseases (CVD) is doubled [5].

Despite the advances of modern science and a wide variety of antihypertensive drugs, the management of patients with AH remains one of the most actual problems in medicine [6, 7]. According to the American Heart Association, only in 64 % of patients, who take antihypertensive medications, succeed to achieve adequate BP control. [8].

Traditional treatment regimens of AH based on the concept of homeostasis, and do not take into account the biological rhythms and their influence on physiological and pathological processes in the human body. This approach often does not provide sufficient efficacy of antihypertensive therapy [9, 10] and is accompanied by the development of a number of side effects, such as internal organs hypoperfusion, humoral profile and electrolyte balance disorders [11-14].

In accordance with the definition of Society for Research on Biological Rhythms, chronobiology is the science that objective studies the biological mechanisms of temporary structures on a quantitative basis, including the rhythmic manifestation of life [15].

Chronomedicine is a separate area of chronobiology, the purpose of which is to improve the existing and develop new methods of prevention, diagnosis and effectiveness of treatment of various diseases on the basis of the human body biorhythms data. One of the objectives of chronomedicine is to identify general and specific patterns of biorhythms violation as a result of pathological processes and develop ways of their correction.

Chronotherapy is one of the main and most developed parts of chronomedicine, and its main task is the development of methods to influence the disease process, taking into account the individual chronobiological characteristics of the patient.

A man's life from birth to death is subordinated to biological rhythms. All processes in the body, starting with the cell cycle, are oscillatory in nature with regular repetition of the same event at regular intervals of approximately equal size. [16].

Of particular interest are the circadian rhythms, which are dominant in mans life [17]. They are close in duration to the 24-hour solar day. For the first time the term «circadian rhythm» («circa» - about, «diem» - day) was first proposed by Halberg and Stephens in 1959 [18].

Many biological processes are synchronized in accordance with the periods of sleep and wakefulness, the change of day and night, the length of day photoperiod [17].

Complex self-regulating human body from birth operates on individual circadian program, the main pacemaker and synchronizer of which are suprachiasmatic nuclei (SCN) cells of the hypothalamus [19]. Exactly SCN contributes to organism adaptation to changing environmental conditions [20].

With the help of light information, coming directly from the retina, and melatonin, produced by the pineal gland, the main pacemaker monitors and synchronizes the rhythms of peripheral organs and tissues. [21].

The pineal hormone melatonin is a major endogenous regulator of biological rhythms, acting on the central circadian clock via specific melatonin receptors located in the cells of the SCN [22]. The characteristic feature is the rhythm of its secretion - melatonin is produced mainly at night, and during the day there is a decrease of its secretion [21, 22].

The role of melatonin in the regulation of diurnal BP variations is proven [23]. Melatonin stimulates the production of nitric oxide and reduces its breakup, thereby rendering a vasodilating and hypotensive action. Melatonin affects the autonomic nervous system, ensuring the dominance of its cholinergic departments on adrenergic ones. Finally, melatonin may influence BP level through their specific melatonin receptors located in the peripheral vessels and central nervous system [24].

As well as other organs and tissues, cardiovascular system has its own internal biological rhythm. Nonaka H, Takeda N, Durgan DJ, Leibetseder V proved the presence of the peripheral biological clock in the vascular endothelial cells [25], cardiomyocytes [26], vascular smooth muscle cells [27] in animals and in humans [28].

Cardiovascular system is most dynamic and its activity varies throughout the day, the seasons and years. BP, heart rate and their variability are synchronized in accordance with the periods of sleep and wakefulness [29]. The daily fluctuations in BP have a biphasic rhythm and determined by a number of internal and external factors. [30].

The internal factors include the activity of the autonomic nervous system and humoral mediators such as melatonin, cortisol, renin, vasoactive intestinal peptide, atrial natriuretic peptide, etc. [31].

External factors that determine the daily variability of BP include physical and mental activity, emotional status, food intake, state of the sleep / wake (behavioral cycle) [32].

In most healthy people there is a decrease in BP during the night and increase in daytime. In the early morning BP starts to rise, reaching a peak around 10.00 a.m. In the evening, after 19.00, it gradually decreases, reaching minimum values between 2.00 and 5.00 a.m. At night, BP in the vast majority of people is reduced by 10-20 % compared with day-time values, which is defined as the physiological degree of nocturnal decline in BP (BP ND) or dipping-pattern of circadian BP profile [33].

Circadian rhythms are quite sensitive to the action of external factors (stress, night work, change of time zone, and so on.), and their violations may be the first signs of incipient deviation in the vital activity of the organism. Desynchronization of biological rhythms leads to the violation of basic functions and the development of pathological conditions in the body [15, 34].

Desynchronizes can be defined as a pathological condition characterized by disruption of biological rhythms in the body. Desynchronizes make a significant contribution to the development of cardiovascular diseases, particularly hypertension. The presence of chronobiological disorders in hypertensive patients was noted by Pickering TG, Takeda N., Machado RM [30, 35, 36].

According to the current guidelines, the measurement of BP by Korotkoffs method remains the primary in AH diagnosis and monitoring. [2]. However, conventional single or multiple office BP measurements do not provide complete information about the daily profile of BP, as well as it is not

sufficiently informative for the AH diagnosis, for the treatment effectiveness monitoring and prognosis of cardiovascular complications [37,38].

Ambulatory BP monitoring (ABPM) is the methods which make it possible to perform the most comprehensive chronobiological analysis of the BP profile in an ordinary everyday activity of the patient.

Since the development of portable devices for ABPM at the end of the 1980s, the ABPM method was used not only in clinical studies, but clinical practice also [38]. In Canada and the UK it is recommended as the preferred method for the diagnosis of AH [39].

In patients with AH data, obtained by ABPM, most accurately reflect the severity of the disease and risk of cardiovascular events [40]. Several independent prospective studies have shown that the level of BP during sleep is the best predictor of CVD risk and target organ damage than the daily or 24-hours means of BP levels [41].

ABPM provides not only static, but also dynamic information about the level of BP. It allows, first of all, to assess the biphasic BP pattern according to the degree of its night-time reduction, the so-called «sleep-time relative BP decline», which is defined as the percent decrease in mean BP during nighttime sleep relative to the mean BP during daytime activity, and calculated as $(100 \times [\text{awake BP mean} - \text{asleep BP mean}] / \text{awake BP mean})$ [42].

Depending on the value of this present ration the following types of daily BP pattern are distinguished [42, 43]: «dippers» - physiological decrease in BP during the night - sleep-time relative BP decline 10-20 % ; «overdippers» - an excessive fall in BP at night, sleep-time relative BP decline > 20 %; «nondippers» - the lack of BP reduction at night, sleep-time relative BP decline < 10 %; «night-peakers» - night-time BP more than during daily activity, sleep-time relative BP decline < 0.

Sleep-time relative BP decline can be calculated for systolic (SBP), diastolic (DBP), pulse pressure and mean (MAP) arterial pressure. MAP is an integral indicator of the pressure throughout the cardiac cycle, and is calculated as the sum of one-third of SBP and two-thirds of DBP:

$$\text{MAP} = \frac{1}{3} \text{SBP} + \frac{2}{3} \text{DBP}$$

Which index - SBP, DBP or MAP – should be used to determine the circadian BP profile, still remains debated. Some authors have used sleep-time relative SBP decline to determine the BP pattern, in other works BP pattern was referred to a particular group if both SPB and DBP fit with the established criteria for the definite pattern. In such cases the authors did not specify to which group they included patients whose sleep-time relative decline for SBP and DBP were referred to different daily profiles, and whether such patients were excluded from the analysis. In some cases, the authors do not mention at all what index was chosen to determine dipping-status of the patient. Considering that in clinical practice there are common situations when one patient has different diurnal patterns of SBP and DBP, some researchers suggest to use the MAP to determine the circadian BP pattern [44].

Patients with insufficient and excessive sleep-time relative BP decline or persistent increased BP at night are referred to a group with impaired circadian rhythm of BP, which is a risk factor for a number of cardiovascular and cerebrovascular diseases [45].

Lack of BP decline at night is associated with a faster (compared to hypertensive with an adequate sleep-time relative BP decline) progression of target-organ damage. In nondippers left ventricular hypertrophy, myocardial infarction, heart failure, microalbuminuria, chronic renal failure, insulin resistance, and cerebrovascular disease are more frequent. [46].

ABPM method also allows to identify patients with early morning hypertension and morning BP surge (MBPS). Early morning hypertension is defined as elevated BP during the first two hours after awakening [47]. There is no consensus on the MBPS definition, most researchers use the method proposed by Kario et al. [48]. The authors suggest to calculate MBPS in two ways: the rise in BP during sleep, so called «sleep-trough MBPS», defined as the difference between the morning BP (average BP during the first 2 hours after awakening) and the lowest nocturnal BP (average BP of 3 readings - the lowest night-time reading plus the readings immediately before and after); and the rise of BP before awakening - prewaking MBPS, defined as the difference between the morning and preawakening BP

(average BP 2 hours before awakening) [48]. The pronounced MBPS and morning hypertension is closely correlated with target organ damage and the onset of cardiovascular events [49, 50].

Another important parameter determined by ABPM, is the so-called short-term BP variability from measurement to measurement. This parameter reflects the adaptive capabilities of neuro-humoral mechanisms of BP regulation under the influence of various external factors, such as emotional stress, exercise, and so on. Increased short-term BP variability reflects the violation of these regulatory mechanisms [51]. Prognostic value of short-term BP variability still remains not fully clarified. However, studies carried out both with hypertensive patients and in general population have shown a close relationship between short-term BP variability and the incidence of cardiovascular events. An analysis of 11 population-based studies involving 8938 patients showed that short-term BP variability from measurement to measurement is an independent factor of cardiovascular risk [52].

As circadian rhythms play an important role in the regulation of BP, AH can be defined as circadian disorder, when chronotherapeutic approach is required. Nevertheless, the data reflecting the incidence of cardiovascular disease and other complications in patients with hypertension, depending on BP pattern, in the literature is extremely small.

With the introduction of ABPM in clinical practice the ability and quality of care of patients with hypertension is increased.

Along with the maintenance of BP during the 24 hours at target level, the need to control its morning surge and to save daily BP pattern with the physiological sleep-time decline is proven [40, 53, 54]. The approach to antihypertensive therapy should be individualized according to the patient chronotype. Excessive reduction of BP with medications can lead to negative consequences such as hypoperfusion of the internal organs, pronounced MBPS, impaired physiological circadian rhythm of BP with increased risk of cardiovascular events [55, 56].

A wide range of endogenous circadian rhythms in combination with various

exogenous factors influence not only on the BP variability and its circadian pattern, but also on the pharmacokinetics and pharmacodynamics of antihypertensive drugs [57].

Studies that have examined the benefits of chronotherapy in AH, revealed clinically significant differences in the efficacy and safety of antihypertensive drugs, depending on the time of their admission - in the morning or in the evening.

Thus, in non-dippers physiological degree of sleep-time relative BP decline can be achieved through the taking antihypertensive drugs in the evening, at bedtime [58].

The effectiveness of AH treatment with beta-blockers (BB) is directly dependent on the activity of the sympathetic nervous system (SNS) [59]. BB are mostly reduced daytime BP and have little influence on his daily profile. They are more pronounced effect on the daytime BP than the nighttime reflects the circadian rhythm of the sympathetic nervous system [60].

Data on AH chronotherapy with BB are extremely small. In a study with participation 82 hypertensive patients with AH of 1-2 stage, who took nebivolol, the degree of daily BP reduction did not differ between the groups of the evening and morning ingestion of the drug [61], though a more marked reduction in the daily readings compared with the nighttime were noted, the most pronounced in the group of morning ingestion. At the same time, use of the nebivolol in the morning, along with a decrease in daily BP average, resulted in a twofold increase in the number of non-dippers, while an evening ingestion didn't have a significant influence on circadian BP profile and didn't lead to increase number of non-dippers. According to the authors' opinion, the ingestion of nebivolol in the evening is the most optimal, compared with the morning regime of drug intake, because this provides the control of BP within 24 hours, and prevents distortion of circadian BP pattern.

M.C. Acelajado et al. [62] carried out a study with participation of 38 patients with AH. 13 of them were dippers and 6 - night-pickers, all patients were randomized to groups of morning and evening nebivolol ingestion. After 3 weeks of treatment, it was found clinically significant and equivalent reduction in daytime, nighttime and 24-hours

BP means in both groups, as well as the prevalence of dipping-status in the group of patients taking the drug in the morning. In both groups there was a clinically significant effect of nebivolol on the MBPS, more pronounced in the group of the evening ingestion. The conclusion was that the effectiveness of nebivolol in reducing daytime, nighttime and 24-hours BP regardless of the time of it ingestion.

The level of BP at night is more dependent on the activity of the renin-angiotensin-aldosterone system (RAAS), so drugs that have influence on it, consider being more effective when taken at bedtime [63]. Also it should be noted that most angiotensin-converting enzyme (ACE) inhibitors are activated in the liver by process of deesterification, wherein the flow velocity during sleep is reduced, which may lead to delayed activation.

In recent decades, a number of studies on the comparative effectiveness of drugs from the group of ACE inhibitors, depending on the time of drug taking, were performed [64]. Most of them showed a more pronounced effect of the evening ingestion on nighttime BP than on daytime, with subsequent modification of the circadian BP profile to dipping-pattern [63]. It was also noted a statistically significant reduction of MBPS in the group of evening ingestion of ACE inhibitors, compared with the morning group [65].

Studies with angiotensin II receptor blockers valsartan, telmisartan, olmesartan showed the similar results. In Hermida R.C. study in 75 % of patients, who took valsartan at bedtime, were achieved physiological degree of night BP reduction, as well as a significant increase in the number of patients with adequate control of BP during the day [66]. Similarly, the ingestion of telmisartan and olmesartan in the evening was more effective than in the morning, and showed normalization of daily BP profile with maintaining its adequate control during 24 hours [67, 68].

In chronotherapeutic studies with calcium channel blockers (CCB) the effects of morning versus evening regimen of amlodipine, cilnidipine, diltiazem, isradipine, nifedipine, nisoldipine and nitrendipine ingestion were examined [69]. Both regimens showed similar efficacy in

reducing the 24-hours BP means, but evening regimen reduced it to a greater extent, resulting in a normalization of diurnal BP pattern with a substantial leveling of MBPS. In addition, taking CCB in the evening versus the morning time was associated with better tolerability and a reduction in the incidence of edema as a side effect of CCB [70].

Limited data were found comparing administration time differences for diuretics. Ingestion of torasemide (5 mg / day) before going to bed, compared with taking the same dose on awakening, demonstrated significantly greater efficacy in reducing the average daily values of SBP and DBP, while the taking after awakening did not lead to adequate reduction of nighttime BP [69].

Chronotherapy with hydrochlorothiazide was studied in a randomized controlled trial involving 181 black patients with hypertension of 1-2 degrees. In the group of patients with an evening administration versus morning had greater reductions in SBP and DBP, but the difference was not reliable enough to confirm the benefits of the evening ingestion of hydrochlorothiazide compared with the morning. The achievement of adequate 24-hours BP control in both groups of patients also failed; although in the evening group a faster decline in left ventricular mass was noted [71].

Despite the positive obtained results, the administration of diuretics at bedtime remains debated. None of the studies looked at troublesome nocturnal diuresis and quality of sleep among the night-time group.

Some researchers believe that diuretics administration at bedtime reduces the likelihood of a physiological BP pattern achievement, as the patient throughout the night will be forced to go to the toilet [72].

On the other hand, an average dose of diuretics for AH treatment, in recalculation on hydrochlorothiazide, does not exceed 50 mg / day, and in this case hypotensive action is not achieved by diuresis but through indirect and direct vasodilatory effects of diuretics [73].

The effectiveness of alpha- blockers, as well as beta-blockers, depends of the circadian rhythm of the SNS and is characterized by a marked decrease in

peripheral resistance when taken in the early morning hours [74]. Evening dosing of alpha-blocker doxazosin reduces SBP and DBP during the day and night, but the greatest effect was observed when the drug was taken early in the morning [75].

In clinical studies of Hermida at al. in patients with AH of 1-2 stage the effects of the long-acting formulation of the α -antagonist, doxazosin, depending on the time of administration was studied. A significant decrease in asleep-BP was observed with bedtime versus morning administration. Awake- and asleep-BP were also lowered from baseline, whereas morning administration did not significantly affect these values [76].

Since melatonin plays an important role in the regulation of circadian rhythms, including BP ones, and is an important endogenous hypotensive factor [22, 23], studies on the use of exogenous melatonin in hyperensive patients with impaired circadian rhythm are of interest.

Some trials showed that administration of melatonin in addition to hypotensive agents significantly reduced nocturnal systolic and diastolic blood pressure [77]. Moreover, melatonin was demonstrated to exert meteoprotective action and thereby reduce the dependence of patients with AH on the adverse environmental factors [78].

CONCLUSION

Biological rhythms play an important role in the regulation of BP, which causes the development of chronobiological approach in the treatment of AH. ABPM is an important method in patients with hypertension for diagnosis and for monitoring the disease, although this practice is still not widespread. Therapeutic interventions based on individual BP chronostructure allow to optimize treatment and to reduce the incidence of side effects of antihypertensive drugs. The hypotensive effect of all groups of antihypertensive drugs recommended for the AH treatment, is most pronounced when taken at bedtime.

Publications, however, are fragmentary and incomplete. The widespread introduction of chronotherapeutic approach into clinical practice requires further serious scientific clinical studies.

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