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Advantages of individual approach to chronotherapy in Yamal hypertensive shift workers

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Abstract

Objective. To compare efficiency of the chronotherapy based on spectral analysis of blood pressure (BP) with chronotherapy based on the results of 24-hour BP monitoring. **Design and methods.** Ninety-three men, transpolar shift workers, with hypertension (HTN) II stage, 1–2 degree were divided into 2 subgroups: in the 1st group daily BP profile was assessed once («dipper», «non-dipper», «over-dipper», «night-peaker», «Standard treatment» group, n = 57), in the 2nd group BP chronotype was considered (group «Chrono», n = 36). Standard analysis and cosinor-analysis of 24-hour BP monitoring were performed. Lisinopril (LP) 5 mg per day was prescribed for 2 weeks followed by second assessment. **Results.** Chronotherapy based on the chronotype of daily BP and its spectral characteristics is more efficient and allows better BP control. It leads to a better compliance and achievement of the target BP level, normalization of daily dynamics of BP and heart rate. **Conclusions.** In shift workers living in the Far North, chronotherapy of HTN is a promising method used due to the early change of daily BP dynamics. Individual chronotherapy is recommended as a rational approach to treat "northern" HTN and contributes to a better patients' compliance.

Key words: hypertension, chronotherapy, shift work, the Far North

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Преимущества персонализированного подхода к хронотерапии артериальной гипертензии у вахтовиков Ямала

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Резюме

Цель исследования — сравнить эффективность хронотерапии (ХТ) лизиноприлом (ЛП), основанной на персонализированной оценке динамики артериального давления (АД) с учетом амплитудно-фазовых параметров 24-часового ритма и его спектрального состава, с ХТ, назначенной только в соответствии с суточным профилем АД по данным стандартного суточного мониторирования АД (СМАД). **Материалы и методы.** В режиме двухнедельной ХТ ЛП в дозе 5 мг/сутки пролечены 93 мужчины с артериальной гипертензией (АГ) II стадии, 1–2 степени, работники заполярной вахты. Пациенты, принимавшие ЛП, были распределены на 2 подгруппы: 1 — учет суточного профиля АД («dipper», «non-dipper», «over-dipper», «night-peaker», группа — обычное лечение «ОЛ», n = 57) и 2 — учет хронотипа АД и спектрального состава (группа «Хроно», n = 36). Выполнены стандартный анализ и косинор-анализ оценки СМАД. **Результаты.** Двухнедельный курс ХТ ЛП показал, что ХТ, ориентированная на хронотип и спектральный состав суточного ритма АД, более эффективна в достижении целевого уровня АД, сопровождается значимой положительной динамикой основных показателей СМАД с более тонкой коррекцией хроноинфраструктуры АД и частоты сердечных сокращений. **Выводы.** Персонализированный подход к ХТ АГ в условиях вахты на Крайнем Севере представляется перспективным и наиболее оптимальным методом, что обусловлено наличием изначального изменения суточной динамики АД у значительного процента вахтовиков. Персонализированный хронотерапевтический подход в лечении «северной» АГ рекомендован как метод антигипертензивной рациональной терапии и способ увеличения приверженности ей.

Ключевые слова: артериальная гипертензия, хронотерапия, вахта, Крайний Север

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Introduction

The problem is relevant due to high prevalence of arterial hypertension (HTN), poor adherence to anti-hypertensive therapy, and insufficient rate of target blood pressure achievement [1–3], in spite of increasing awareness of HTN and the proportion of people receiving antihypertensive treatment [4], as well as introduction of new drugs into clinical practice. One of the reasons of reduction of anti-hypertensive efficiency is the generalized approach to management, and, in particular, underestimation of blood pressure (BP) biological rhythms, which, in its turn, leads to ignoring time dependence [5]. So attention is drawn to chronotherapy (CT) based on the mutual relationship between antihypertensive therapy and individual circadian rhythms of BP [5–7]. Previously, we showed [8, 9] that, in shift-workers in northern regions, the circadian profile of BP (CPBP) in HTN patients is characterized by low values of circadian indices, high variability, mainly nocturnal hyperbaric overload, high frequency of atypical circadian BP fluctuations, such as "non-dipper" and "night-peaker". Chronopathophysiology of increased BP in northern population is characterized by internal desynchronosis expressed as phase mismatch between BP rhythms and heart rate (HR), decrease in amplitude, percentage contributions and reliability of circadian rhythms of BP in case of of high-frequency and low-differentiated range (noise) of the chronome spectrum [10, 11]. Blockers of the renin-angiotensin-aldosterone system (RAAS), in particular, angiotensin converting enzyme (ACE) inhibitors, are an obligatory component of antihypertensive therapy, which is regulated by the international and national recommendations on HTN management [12, 13].

Chronobiological arrangement of the HTN treatment is shown to be the way of individualization and optimization of BP control and cardiovascular risk reduction by many national and internationa l investigators.

Thus, chronobiological optimization of HTN treatment in the Far North is of particular interest.

Objective of the study is to compare the efficiency of CT with lisinopril (LP), based on personalized assessment of BP dynamics considering the amplitude and phase parameters of the 24-hour rhythm and its spectral composition, with the CT based only on CPBP assessment by the standard daily ambulatory BP monitoring (ABPM).

Design and methods

Altogether 538 hypertensive male shift-workers (Yamburg settlement) at the age of 30 to 59 years old were examined during the period from 2002 to 2010. Finally, we selected 93 people comparable by age, shift-work experience, shift mode (one month of work — one month of rest), duration and the degree of BP increase: HTN II stage, 1 to 2 degree of BP increase (systolic BP (SBP) up to

Table 1

COMPARATIVE CHARACTERISTICS OF THE "STANDARD" AND "CHRONO" GROUPS

Characteristics	"Chrono"	"Standard»	p
N, people	57	36	
Age, years	46.3 ± 6.8	47.0 ± 6.5	0.12
Shift work, years	15.4 ± 6.7	17.8 ± 6.8	0.13
HTN, years	6.4 ± 3.7	7.0 ± 3.5	0.45
SBPoff, mm Hg	150.4 ± 15.2	151.2 ± 13.8	0.29
DBPoff, mm Hg	97.2 ± 9.2	98.2 ± 7.3	0.23
LV mass, g	264.4 ± 62.9	272.1 ± 73.5	0.16
LVMI, g/m^2	123.6 ± 26.4	127.6 ± 29.8	0.49
BMI, kg/m^2	28.1 ± 2.9	28.2 ± 2.4	0.22
Total cholesterol, mmol/L	5.95 ± 1.24	5.70 ± 0.89	0.43

Note: HTN — arterial hypertension; SBPoff — office systolic blood pressure; DBPoff — office diastolic blood pressure; LV — left ventricle; LVMI — left ventricular mass index; BMI — body mass index; p — Mann–Whitney tests (U-test). Data are presented as M ± SD.

Table 2

COMPARATIVE CHARACTERISTICS OF THE "STANDARD" AND "CHRONO" GROUPS BY RISK FACTORS

Characteristics	"Chrono"	"Standard"	p
N	57	36	
Smoking	31	20	0.92
Dyslipidaemia	32	19	0.92
Low physical activity	36	24	0.90
Family history of premature CVD	28	18	0.90
Treatment regularity	9	5	0.96

Note: p — χ^2, Yates correction was used to improve the accuracy of the χ^2 test.

165 mm Hg and diastolic BP (DBP) up to 105 mm Hg), cardiovascular risk 3, office SBP and DBP (Table 1). All subjects worked in Tyumen and Ufa (the same time zone).

Groups were also comparable by risk factors (Table 2).

Prior to start of the study all examined patients received ACE inhibitors (LP in a dose of 10 mg/s) as monotherapy, 51 patients with increased level of cholesterol received statins. All examined patients had signs of myocardial left ventricular (LV) hypertrophy at echocardiography. The degree of LV hypertrophy was assessed by calculation of the LV mass (LVM) in accordance with the Penn Convention methodology and indexed to the body surface area (so called LVM index). LV hypertrophy was diagnosed when the LVM index (LVMI) exceeded 115 g/m^2 for men. After the "washout period" lasting at least 3 days, all subjects received treatment with LP in the fixed dose of 5 mg in the CT mode for 5 days. LP was chosen because it is a RAAS blocker, an antihypertensive drug class to be essentially prescribed in HTN. The price, and, as consequence, the affordability of the drug was another reason for the choice. Besides, the active program for cardiovascular prevention, conducted by the medical service of Gazprom Mining Yamburg LLC, provides free antihypertensive drugs, which also include LP as an ACE inhibitor.

Patients were divided into 2 subgroups: the 1st group (Standard) only considered circadian profile of BP (CPBP) according to the data of ABPM — "dipper", "non-dipper", "over-dipper", "night-peaker" (n = 36); and the 2nd group (Chrono) considered individual BP rhythm spectrum (n = 57 persons). Only standard ABPM analysis with assessment of CPBP was applied in the first group. In case of the "dipper" or "over-dipper" type, the drug was prescribed in the morning (from 8 to 10 a. m.) as usual. In case of "non-dipper" or "night-peaker" circadian profiles, the drug was prescribed in the evening (from 7 to 10 p. m.). In the "Chrono" groups, the drug was prescribed based on the individual values of the main BP rhythm period, namely: period and the validity of the rhythm (T), leading rhythm acrophase (Acph), leading rhythm amplitude (Amp), percentage of the circadian rhythm (PC) impact and the degree of BP and HR rhythm synchronization (to assess desynchronosis). In case of absence of any rhythm (aperiodical HTN), the BP "rhythm forcing" method was applied. Chronobiological parameters were evaluated by the individual chronoanalysis.

The study was performed in accordance with Good Clinical Practice standards and the Declaration of Helsinki principles with obligatory informed consent of patients.

Inclusion criteria were the following: HTN II stage, 1 to 2 degree, cardiovascular risk 3, normal sleep at night, absence of night shifts. Exclusion criteria were the following: cardiovascular risk 4, malignant HTN and symptomatic HTN; any form of chronic coronary heart disease; heart rhythm and conduction disturbances; heart failure II to IV NYHA functional class; severe concomitant diseases (acute and chronic cerebrovascular diseases, endocrinological diseases); cardiomyopathy; congenital and acquired heart diseases, obesity (Quetelet index above 30 kg/m^2). Criteria of early termination of the study were the following: poor tolerability of the drug; adverse events that require discontinuation of the drug; patient's deny from further research.

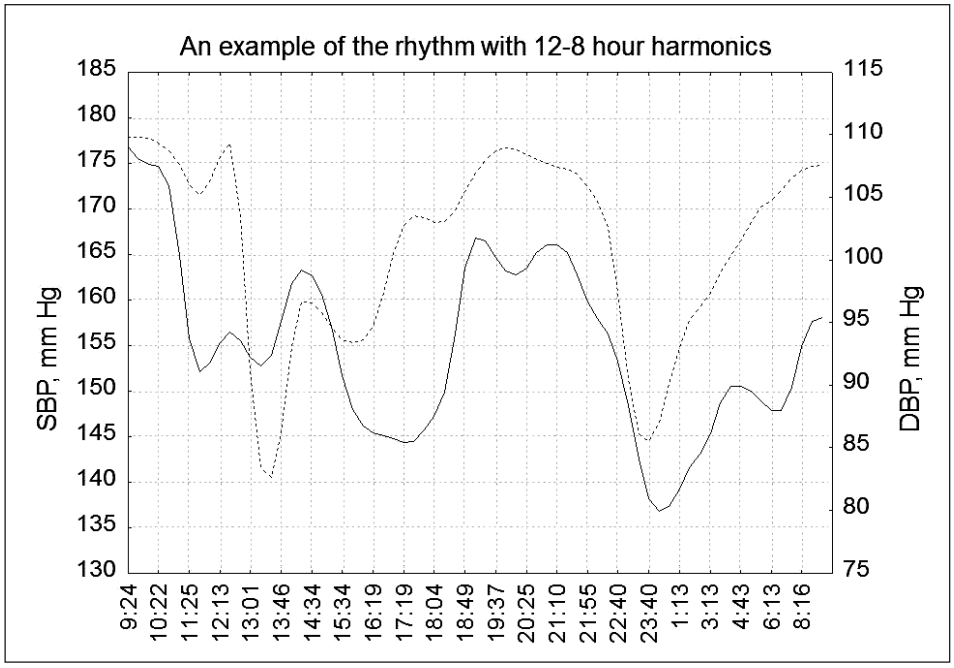
Cosinor-analysis adapted with the help of a program created in the University of Minnesota (Halberg E. et al., 1984) [14] was used in the chronobiological analysis of time series. Analysis algorithm included cosinor-analysis (Nelson W., 1979) with the least-squares method, linearly with the frequency of 1 cycle in 24 hours (expected circadian rhythm) and further fundamental sequential harmonics of ultradian field of the chronome spectrum [15]. Fixed components of the aforementioned spectrum were analyzed regarding the amplitudes and 95 % reliability of fixed ultradian harmonics with periods (T) equal to 24.0; 12.0; 8.0; 6.0; 4.8; and 4.0 hours; T = 3.4 hours. Leading harmonics, i. e., the circadian (T = 24 hours) and circasemidian (T = 12 hours) ones, were additionally analyzed regarding the percentage in the total variability of SBP, DBP, and HR parameters. The following parameters were used for the assessment of BP and HR chronostructure: "Rhythm period", which is the duration of the oscillating cycle of the wave-like process; "Acrophase", which is the time of the maximum value during the period; "Bathyphase", which is the time of the minimum value during the period; "MESOR" (Midline Estimating Statistic of Rhythm), which is the statistical median of the rhythm; "Amplitude", which is the maximum value of the deviation in both directions from the MESOR; "Rhythm phase", which is the maximum value of the oscillating process at a certain moment of time.

ABPM was performed according to the standard protocol (in accordance with the NBREP requirements, USA, 1990) with the Tonoport IV equipment (Hellige, USA). In accordance with the protocol (Joint National Committee on Detection, Evolution and Treatment of High Blood Pressure, 1993), standard ABPM parameters were calculated.

Statistics

Methods of parametric and nonparametric dispersion analysis with variance criteria for independent and dependent populations were used. The t-test for independent populations was applied in case of normal distribution. The Mann–Whitney test (U-test) was applied as the non-parametric alternative. In order to assess differences between dependent groups, t-test for dependent variables was used (in case of normal distribution). The sign test and Wilcoxon test were used as alternative non-parametric tests. McNemar chi-square test was used for category variables.

Figure. Example of circadian rhythms of daily blood pressure and diastolic blood pressure of a patient from the North with arterial hypertension and leading periods of 8-hour and 12-hour harmonics



Note: SBP — systolic blood pressure; DBP — diastolic blood pressure.

Table 3

EFFICIENCY OF THE 14-DAY CHRONOTHERAPY WITH LISINOPRIL, DEPENDING ON THE METHOD OF DRUG PRESCRIPTION

The results of chronotherapy after 14 days	Groups		
	"Chrono" (n = 57)	"Standard" (n = 36)	χ^2/p
Target BP level, N	50	26	1.82/0.17
Normalization of 24h index of BP, N	56	17	4.48/0.03
Normalization of circadian rhythm BP, N	55	18	3.68/0.06

Note: BP — blood pressure; χ^2/p — Fisher's exact test.

Standard statistics and corresponding criteria for cross tables were used to assess the associations between category variables: χ^2, Yates correction was used to improve the accuracy of the χ^2 test.

Results

In the northern group with desynchronosis and low reliability of 24-hour rhythms, ultradian periodics played a significant role for the drug prescription. The figure illustrates a typical example of circadian BP curve of a HTN patient at shift-work. The prevalence of 8-and 12-hour harmonics are clearly seen in the spectrum.

After 14-day CT, there were significant differences between the 1st and 2nd groups (see Table 3) regarding normalization of circadian BP indices and BP circadian rhythm. At the same time target level of BP was achieved similarly in both groups.

According to the ABPM data, after two-week CT with LP 5 mg/day, there was a significant reduction of SBP in the "Chrono" group from 145.8 ± 8.5 down to 127.8 ± 6.2 mm Hg (p = 0.0001), while in the "Standard" group it reduced from 149.0 ± 10.7 only to 132.6 ± 10.5 mm Hg (p = 0.0241).

As compared to the standard CT in the "Chrono" group, the circadian variability of the SBP was significantly lower (12.0±2.7 vs. 13.6 ± 3.1, p = 0.0041), which indirectly evidences stabilization of SBP rhythms. This was also confirmed by significant increase in the SBP circadian index (7.0 ± 6.6 % to 11.7 ± 4.2 %, p = 0.0001) from the "non-dipper" to the "dipper" range. In the "Standard" group, the changes in the SBP circadian index were less significant (from 7.1 ± 6.1 % up to 10.2 ± 5.7 %, p = 0.0011).

As a result of personalized CT, in the northern group of patients changes in chronobiological parameters of circadian SBP rhythms were more significant than in the "Standard" group. In both groups, there was an increase in the percentage of the 24-hour rhythm, but it was more evident in the "Chrono" group: from 18.7 ± 15.2 % up to 30.1 ± 16.4 % (p = 0.0032), while patients of the "Standard" group demonstrated only 9 % rise, having achieved 26.1 ± 17.3 % (p = 0.0432). More significant positive dynamics of amplitudes of circadian BP rhythms was found in the "Chrono" group as compared to the "Standard" group (from 8.4 ± 4.4 up to 11.8 ± 5.2 mm Hg and from 8.9 ± 5.4 up to 9.5 ± 4.1 mm Hg, respectively, p = 0.0070). Personalized CT, as a result of significant reduction of daily SBP, led to a reduction the morning SBP surge (from 53.0 ± 18.8 down to 44.3 ± 15.7 mm Hg, p = 0.0025), while in the "Standard" group it reduced only from 52.3 ± 13.2 down to 47.6 ± 12.3 mm Hg (p = 0.0131). No significant dynamics of morning velocity SBP increase in both groups.

After 14-day CT with LP, the 24-hour rhythm structure became more consistent in the "Chrono" group as compared to the "Standard" group, 8-hour and 12-hour spectrum harmonics and DBP chaotic fluctuations almost disappeared. These changes resulted from the more evident reduction of nocturnal parameters and reduction in DBP variability. Mean reduction of the nocturnal DBP in both groups was similar (8 to 10 mm Hg), but the patients of the "Chrono" group demonstrated lower nocturnal DBP than patients from the "Standard" group (69.4 ± 8.1 vs. 75.2 ± 5.5 mm Hg, p = 0.0009). Patients from the "Chrono" group demonstrated more evident (as compared

to the "Standard" group) reduction in variability of nocturnal DBP (from 15.4 ± 2.2 down to 8.9 ± 2.7 mm Hg, p = 0.0001) and variability of daytime DBP (from 14.9±2.7 down to 7.5 ± 3.0 mm Hg, p = 0.0001), and reduction by almost 6.5 mm Hg. In the "Standard" group the difference comprised only 4 mm Hg (from 15.0 ± 2.2 down to 10.8 ± 2.8 mm Hg, p = 0.0001).

The nocturnal DBP reduction in the "Chrono" group is improved as confirmed by evident increase of the DBP circadian index from 8.3 ± 8.0 up to 17.8 ± 7.4 % (p = 0.0001). In the "Standard" group, this parameter also changed significantly but was less evident (from 8.4 ± 6.2 up to 12.1 ± 5.3 %, p = 0.0001). Due to quite evident increase of the amplitude of the circadian rhythm of the DBP, values of these parameters were comparable in both groups by the 14th day of treatment. One of the positive aspects of personalized CT was reduction of the morning DBP surge (28.9 ± 8.9 vs. 36.9 ± 12.2 mm Hg, p = 0.0099).

CPBP changed in 14 days depending on the mode of treatment. In the "Chrono" group, the "dipper" CPBP value increased significantly (from 39.8 up to 71.9 %, p = 0.0002) after CT with LP. This was accompanied with significant reduction of the "non-dipper" CPBP frequency (from 46.2 down to 22.8 %, p = 0.0046) and the "night-peaker" CPBP frequency (from 11.8 down to 1.8 %, p = 0.0300). The distribution of CPBP types after CT was also found in the "Standard" group, but it was less evident ("dipper" — from 36.4 up to 61.9 %, p = 0.0014; "non-dipper" — from 47.0 down to 32.8 %, p = 0.0146, and "night-peaker" — from 10.2 down to 3.8 %, p = 0.0411).

The CT led to normalization of daily rhythms of the SBP and DBP almost in each patient of the "Chrono" group (93.2 %) and of every other patient of the "Standard" group (66.3 %, p = 0.0417). As a result, the rate of patients with normal SBP rhythm was higher in both groups after the treatment than before the treatment, irrespectively of the CT mode.

The same dynamics was found for desynchronosis symptoms regarding the BP and HR rhythms. In the "Chrono" group, the frequency of desynchronosis reduced from 54.4 down to 8.6 % (p = 0.0001), in the "Standard" group — from 53.1 down to 9.8 % (p = 0.0011).

In the personalized CT mode, the frequency of aperiodic HTN reduced significantly from 12.9 down to 3.5 % (p = 0.0506). Similar effect was found in the "Standard" group, but was less evident — from 13.1 down to 6.5 % (p = 0.0633).

Discussion

Interaction between biological rhythms in periodically varying environment generates temporal organization of biological systems, which forms the basis for the adaptation process [5].

There is close relationship between BP control mechanisms and the circadian system. Recently, the angiotensin system was shown to coordinate biological rhythms on the central and peripheral levels. For instance, there is an antagonistic relationship between daily angiotensin production and melatonin in the brain neurons [16]. The latter one has a hypotensive effect [17] particularly evident at night [9, 18]. In smooth muscle cells, angiotensin acts as a chemical factor that directly coordinates biological clock genes [19, 20]. Thus, the RAAS internal rhythm plays an important role in formation of the circadian BP and HR rhythm for keeping the optimal conditions of vital activities. In conditions of modified daily photoperiodics and desynchronosis, the role of RAAS circadian rhythm disorders in HTN development in the Far North require further investigation and look promising.

Recent studies including our works prove that CT of HTN with drugs of various groups (calcium channel blockers, ACE inhibitors, β-adrenoblockers) helps to reach stable clinical effect earlier, at lower drug doses, and is better tolerated compared to traditional prescription without consideration of the circadian rhythm [21, 22].

ACE inhibitors are an obligatory component of antihypertensive therapy with an extensive evidence regarding cardio- and nephroprotection, as well as atherosclerosis-associated cardiovascular risk reduction [23, 24].

We used mono-CT with LP (ACE inhibitor) 5 mg/day. ACE inhibitor, in particular LP, prescribed at the right time, eliminated RAAS imbalance even at a small dose (5 mg), leading to the synchronous functioning of the HR and BP rhythms. And we demonstrated it quite clearly based on individual parameters of circadian fluctuations spectrum of BP and HR when the time of drug prescription is

associated with the acrophase (bathyphase) of the leading rhythm.

The "northern" HTN has few peculiarities. Despite relatively low BP, target organs damage (in particular, LV hypertrophy) occurs at early stages, thus, the II stage of the disease is diagnosed. Lack of symptoms also plays an important role, as it leads to late referral to the doctor and poor adherence to treatment, which is a threat to life and health of a patient who needs BP correction and normalization.

Our study showed that individualized CT is quite effective as compared to the usual therapy in Far North. The explanation is that BP reduction is not the only goal, it is mostly aimed at normalization of BP circadian rhythms, elimination of desynchronosis signs, particularly in the aperiodic forms of HTN, which is especially important in shift-workers in polar regions, in violated circadian photoperiodics, hard working and living conditions.

Desynchronosis is a classical manifestation of stress in the rhythmic structure of various parameters. That is why elimination of desynchronosis is deemed to be the most important part of CT. We achieved persistent reduction of office BP and average daily BP values due to reduction of the daytime and nocturnal parameters (particularly nocturnal ones) in both groups, but still a more accurate (individual) approach led to more evident BP changes.

Reduction of BP variability (particularly at nighttime) and stabilization of morning BP surge were of high importance in individual CT.

Conclusions

Thus, ACE inhibitors, in particular, LP prescribed at the correct time, eliminated RAAS imbalance even at a small dose (5 mg), resulting in the synchronous functioning of the HR and BP rhythm. Individualized CT as compared to the usual therapy is efficient regarding normalization of circadian BP rhythms, elimination of desynchronosis, particularly in persons with aperiodic form of HTN upon violated daily photoperiodics, hard working and living conditions in the North. Individual CT leads to a more stable reduction of office BP and average daily BP, particularly by reducing nighttime BP and its variability, stabilization of morning BP surge, reduction of the maintenance dose of the antihypertensive drug. Personalized CT of HTN seems to be a prospective and optimal method in shift-workers that is justified by the initially disturbed circadian BP profile. Our data confirm that chronotherapeutic approach can be recommended as a method of antihypertensive therapy in the "northern" H.

Conflict of interest
The authors declare no conflict of interest.

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