





## Some features of blood pressure variability in patients with arterial hypertension in various modes of antihypertensive therapy

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

### Key words:

arterial hypertension, chronotherapy, blood pressure variability, ambulatory blood pressure monitoring.

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**Aim.** The study objective was to compare different timing modes of hypertension medications dosing in patients with arterial hypertension in relation to blood pressure level and variability.

**Materials and methods.** The study included 103 subjects with previously diagnosed AH in whom 24h ambulatory blood pressure monitoring records of adequate quality were obtained. Participants were stratified to three groups based on timing of hypertension medications dosing – morning dosing (group 1), bedtime dosing (group 2), and as needed (group 3). The last one included patients with low compliance of prescribed medications and irregular antihypertensive drugs intake. The systolic and diastolic blood pressure variability indices – standard deviation (VAR1) and root-mean-square value of the difference between consecutive blood pressure measurements (VAR2) were calculated. The Kruskal-Wallis ANOVA or  $\chi^2$ -test, as appropriate, was used to compare the groups. A two-sided P value  $<0.05$  was considered statistically significant. Analysis of data included corrections for multiple comparisons.

**Results.** Statistically significant differences were found in mean 24-h diastolic blood pressure values between groups 1 and 3, 2 and 3 ( $P = 0.02$ ), awake mean diastolic blood pressure values between groups 1 and 3 ( $P = 0.03$ ) and for VAR1 night-time systolic blood pressure between groups 1 and 3, 2 and 3 ( $P < 0.05$ ). There were no significant differences between any of the studied parameters between the groups with the morning and evening dosing of antihypertensive drugs.

**Conclusions.** Treatment mode does not significantly affect the short-term variability of blood pressure, determined by the standard deviation from the mean blood pressure and the root-mean-square value of the difference between consecutive blood pressure measurements for a given time period.

### Ключові слова:

артеріальна гіпертензія, хронотерапія, варіабельність артеріального тиску, добуве моніторування артеріального тиску.

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## Особенности вариабельности артериального тиску у больных на артериальную гипертензию на тлі різних режимів гіпотензивної терапії

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**Мета роботи** – визначити ступінь впливу різних режимів гіпотензивної терапії на досягнення цільових значень і показники варіабельності артеріального тиску в пацієнтів з артеріальною гіпертензією.

**Матеріали та методи.** У дослідження залучили 103 пацієнти із раніше діагностованою артеріальною гіпертензією. Усім хворим виконали добуве моніторування артеріального тиску. Учасників поділили на групи залежно від часу приймання медикаментів: група 1 – пацієнти, які приймали гіпотензивні препарати 1 раз на день у першій половині дня; група 2 – хворі, які приймали хоча б один гіпотензивний препарат увечері, після 18.00; група 3 – пацієнти, які приймали гіпотензивні препарати епізодично, за потреби. Групи дослідження зіставні за статтю, віком. Варіабельність артеріального тиску оцінювали за допомогою індексів: VAR1 – стандартне відхилення від середнього значення артеріального тиску для конкретного періоду; VAR2 – середньоквадратичне значення різниці між послідовними вимірюваннями артеріального тиску. Групи порівнювали методом дисперсійного аналізу Краскела–Волліса, для якісних ознак розраховували критерій  $\chi^2$  Пірсона з поправкою Сйтса.

**Результати.** Статистично значущі відмінності виявили для середніх значень діастолічного артеріального тиску за 24 год між групами 1 і 3, 2 і 3 ( $p = 0,02$ ) і в період денної активності між групами 1 і 3 ( $p = 0,03$ ), а також для VAR1 систолічного артеріального тиску в нічний період між групами 1 і 3, 2 і 3 ( $p < 0,05$ ). Між групами з ранковим і вечірнім прийманням гіпотензивних препаратів не встановили вірогідні відмінності за жодним із параметрів, що визначали.

**Висновки.** Режим терапії не має вірогідного впливу на короткострокову варіабельність артеріального тиску, яку визначали за допомогою стандартного відхилення від середнього значення артеріального тиску й середньоквадратичного значення різниці між послідовними вимірюваннями артеріального тиску для конкретного часового проміжку.

## Особенности вариабельности артериального давления у больных артериальной гипертензией на фоне различных режимов гипотензивной терапии

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**Цель работы** – определить степень влияния различных режимов гипотензивной терапии на достижение целевых значений и показатели вариабельности артериального давления у пациентов с артериальной гипертензией.

**Материалы и методы.** В исследование включили 103 пациентов с ранее диагностированной артериальной гипертензией. Всем пациентам проведено суточное мониторирование артериального давления. Участников поделили на 3 группы в зависимости от времени приема медикаментов: группа 1 – пациенты, принимающие гипотензивные препараты 1 раз в день в первой половине дня; группа 2 – больные, принимающие хотя бы один гипотензивный препарат вечером, после 18.00; группа 3 – пациенты, принимающие гипотензивные препараты эпизодически, по требованию. Изучаемые группы сопоставимы по полу и возрасту пациентов. Вариабельность артериального давления оценивали с помощью индексов: ВАР1 – стандартное отклонение от среднего значения артериального давления для данного временного периода; ВАР2 – среднеквадратичное значение разности между последовательными измерениями артериального давления. Группы сравнивали методом дисперсионного анализа Краскела–Уоллиса, для качественных признаков рассчитывали критерий  $\chi^2$  Пирсона с поправкой Йейтса.

**Результаты.** Статистически значимые различия установлены для средних значений диастолического артериального давления за 24 ч между группами 1 и 3, 2 и 3 ( $p = 0,02$ ) и в период дневной между группами 1 и 3 ( $p = 0,03$ ), а также и для ВАР1 систолического артериального давления в ночной период между группами 1 и 3, 2 и 3 ( $p < 0,05$ ). Между группами с утренним и вечерним приемом гипотензивных препаратов значимые различия ни по одному из изучаемых параметров не обнаружены.

**Выводы.** Режим терапии не оказывает существенного влияния на краткосрочную вариабельность артериального давления, определяемую при помощи стандартного отклонения от среднего значения артериального давления и среднеквадратичного значения разности между последовательными измерениями артериального давления для данного временного периода.

**Ключевые слова:** артериальная гипертензия, хронотерапия, вариабельность артериального давления, суточное мониторирование артериального давления.

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Arterial hypertension (AH) is one of the leading causes of cardiovascular disease (CVD) mortality in the world [1,2]. Despite the advances of modern science and a wide choice of antihypertensive drugs, some questions of effective management of patients with hypertension remain of current interest today in medicine. According to International Society of Hypertension, only in 60 % of treated patients with AH have their blood pressure (BP) controlled [3]. The degree of target organs damage depends not only on the office BP level. It much more closely correlates with the mean night-time BP according to ambulatory BP monitoring (ABPM) data, as well as with the type of daily BP profile [4]. One of the methods for normalizing these indicators is chronotherapy, which in relation to AH is defined as taking at least one antihypertensive drug at bedtime. According to the results of some studies, in patients with hypertension, including those with concomitant pathologies such as diabetes mellitus, chronic kidney disease and obstructive sleep apnea, taking at least one antihypertensive drug at bedtime improves BP control, normalizes daily BP profile and reduces the risk of cardiovascular complications and mortality, compared with patients taking antihypertensive therapy once in the morning [5–7]. Increased blood pressure variability is currently considered as another risk factor for target organ damage and cardiovascular complications in patients with hypertension [8–10].

## Aim

The aim of our study was to determine the various modes of antihypertensive therapy efficiency in terms of hypotensive medications dosing timing in the achievement of target BP levels and short-term BP variability according to the ABPM data in patients with AH

## Materials and methods

Patients with AH were examined on the basis of Kharkiv Out-patient Clinic No. 24. An inclusion criterion was previously diagnosed AH in patients older than 40 years.

103 patients between 41 and 78 years of age, median 61, were enrolled. All the patients signed informed consent.

Exclusion criteria were hemodynamically significant valvular heart disease, cardiomyopathies of any origin, heart failure (HF) III-IV functional class (FC) by NYHA, any acute condition (infection, trauma, surgery) within the previous 3 months, chronic decompensated or acute illness, cancer, as well as any circumstances that could hinder the ambulatory blood pressure monitoring (ABPM) implementation.

The study involved 32 men (31 %) and 71 women (69 %). HF was diagnosed in the 77 cases (75 %): HF I FC was determined in 31 patients (30 %), II FC – 42 (41 %); coronary heart disease (CHD) – 81 cases (79 %): stable angina (I–III FC) – 15 (15 %), postinfarction cardiosclerosis (PICS) – 5 (5 %), focal atherosclerotic cardiosclerosis (ACS) – 64 (62 %). Acute cerebrovascular events in anamnesis had 6 (6 %) patients.

The study participants were divided into 3 groups, depending on the mode of antihypertensive therapy: group 1 – patients who received antihypertensive drugs once daily, in the morning; group 2 – patients who received at least one antihypertensive drug at bedtime; group 3 – patients with low antihypertensive treatment compliance. Studied groups were comparable by sex and age.

All the patients were under standard antihypertensive therapy, in form of mono- or combined therapy, recommended by Ukrainian Association of Cardiologists 2016: angiotensin converting enzyme inhibitors – enalapril (5–20 mg/day), lisinopril (5–30 mg/day), perindopril (2–5 mg/day); angiotensin receptors blockers – valsartan (80–320 mg/day), losartan (50–100 mg/day); diuretics – hydrochlorothiazide (6.25–25.00 mg/day), indapamide (1.25–2.50 mg/day); calcium channels blockers – amlodipine (5–10 mg/day), lecardinipine (10 mg/day); beta-blockers – bisoprolol (2.5–10.0 mg/day), nebivolol (2.5–7.5 mg/day). Combined therapy prevailed over monotherapy in all groups and amounted to 57 % in group 1, 70 % in group 2, 71 % in group 3. Studied groups were comparable by a percentage of mono- and combined therapy.

All the patients underwent ABPM using the computer system "Cardiosens" (KhAI Medica, Ukraine) with an oscillometric method of BP measurement. The mean values of systolic BP (SBP) and diastolic BP (DBP) were estimated at different periods of monitoring. The periods of day and night

**Table 1.** Levels of blood pressure, M, Me, [min–max] (mmHg)

Groups	Group 1, n = 46	Group 2, n = 43	Group 3, n = 14	P
<b>Office BP</b>				
<b>SBP</b>				0.564
M	142	140	147	
Me	140	140	148	
[min–max]	[105–220]	[110–185]	[125–180]	
<b>DBP</b>				0.053
M	87	86	94	
Me	83	90	98	
[min–max]	[65–120]	[60–120]	[70–110]	
<b>ABPM, 24-hours</b>				
<b>SBP</b>				0.10
M	132	133	139	
Me	129	129	140	
[min–max]	[101–190]	[104–163]	[125–155]	
<b>DBP</b>				0.02
M	78	78	85	
Me	77	78	86	
[min–max]	[57–100]	[60–105]	[74–94]	
<b>ABPM, awake BP</b>				
<b>SBP</b>				0.09
M	135	136	142	
Me	132	132	142	
[min–max]	[104–193]	[107–166]	[130–155]	
<b>DBP</b>				0.03
M	80	81	88	
Me	80	82	89	
[min–max]	[60–101]	[62–107]	[75–99]	
<b>ABPM, nighttime BP</b>				
<b>SBP</b>				0.45
M	122	123	128	
Me	121	123	125	
[min–max]	[89–184]	[89–158]	[105–166]	
<b>DBP</b>				0.30
M	69	69	73	
Me	69	68	73	
[min–max]	[48–94]	[50–97]	[58–88]	
<b>ABPM, morning BP</b>				
<b>SBP</b>				0.34
M	133	135	138	
Me	132	133	142	
[min–max]	[101–181]	[102–173]	[110–154]	
<b>DBP</b>				0.23
M	80	82	86	
Me	80	82	87	
[min–max]	[58–104]	[58–114]	[64–105]	

were determined by a patient's diary. The degree of sleep-time relative BP decline was calculated using the formula:

$$(100 \times [\text{mean awake BP} - \text{mean asleep BP}] / \text{mean awake BP}).$$

Depending on the value of this ratio, the following types of daily BP profile were defined:

“dipper” – physiological decrease in BP during the night – sleep-time relative BP decline more than 10 %;

“nondipper” – the lack of BP reduction at night, sleep-time relative BP decline <10 % [11].

The presence of night and morning hypertension, as well as SBP and DBP variability indices were estimated. BP variability was assessed using the following indices: VAR1 – the standard deviation from the mean

BP value for a given time period; VAR2 – the root-mean-square value of the difference between consecutive BP measurements.

Data were expressed as percentages (P), mean (M), median (Me), minimum (min) and maximum (max). Analysis of the variables was carried out using Kruskal–Wallis ANOVA or  $\chi^2$ -test, as appropriate, with corrections for multiple comparisons. A two-sided P value <0.05 was considered statistically significant.

## Results

The office means of SBP in all 3 groups exceeded the recommended threshold [12]. Office DBP means in groups 1 and 2 corresponded to the category of high normal blood pressure, and in group 3 was higher than 90 mmHg. According to the ABPM data, the mean 24-h, daytime and nighttime SBP values in all studied groups exceeded the recommended target levels and only in the morning period – two hours after awakening – corresponded to the allowable values [13]. The mean DBP values in groups 1 and 2 did not exceed the normative values during all periods. In group 3, the mean DBP value was higher than the recommended one during the entire monitoring period (Table 1).

Statistically significant differences were found for mean 24-h DBP values between groups 1 and 3, 2 and 3 (P = 0.02) and awake mean DBP values between groups 1 and 3 (P = 0.03) (Table 1).

Table 2 presents the ratios of patients in the studied groups, depending on the grade of hypertension, established according to office BP measurements [12] and ABPM data [13] and the percentage of controlled, night and morning AH.

Based on office BP measurements, the largest percentage was formed by patients with controlled AH in groups 1 and 2, in group 3 – by patients of grade 2 and 3 AH. In groups 1 and 2, the proportions of patients with controlled hypertension were almost equal and three times higher than in group 3. According to the ABPM, in groups 1 and 3, the largest percentage was formed by patients of 1 grade hypertension, in group 2 – with controlled hypertension. According to ABPM, patients with controlled hypertension were absent in group 3. In all the studied groups, patients with night and morning hypertension accounted for more than the half, with the highest rates in group 3. Statistically significant differences were found for controlled AH, confirmed by ABPM method, between groups 1 and 3, 2 and 3 (P < 0.05) (Table 2).

The means of sleep-time relative SBP decline in all groups corresponded to nondipper type and ranged from 9.1 to 9.9, and the means of sleep-time relative DBP decline – to dipper type, ranged from 13.5 to 16.8. Thus, dippers in all the groups constituted a smaller part than nondippers, with the smallest proportion in group 3. No statistically significant differences were found between the groups.

Table 3 presents the mean values of BP variability indices – VAR1 and VAR2. Statistically significant differences were found for VAR1 SBP<sub>night</sub> between groups 1 and 3, 2 and 3. The p values are presented in the table.

In groups 1 and 2, patients with increased variability accounted for 54 % and 53 %, respectively, in group 3 – exactly half of all cases.

## Discussion

The highest values of SBP and DBP, both according to the office measurements and ABPM, during various monitoring periods, as expected, were observed in the group of patients with low compliance and in most cases exceeded the recommended target BP values. In group 3, the lowest percentage of controlled AH according office measurements was observed, and controlled AH was completely absent according to ABPM in this group. In general, there were no discrepancies between the values of BP obtained by different measurement methods.

It is noteworthy that the percentage of controlled and grade 3 AH according to ABPM was lower in all the groups, compared with the proportion of the same category of patients according to the office BP measurement results. Regarding the grade 1 AH, the opposite situation was observed – according to the ABPM, there were more such patients than according to the office measurements. Additional analysis showed that according to the office measurements in ¼ of all patients, included in the study, the grade of AH was overestimated, and the same proportion of patients had an underestimated grade of AH, when compared with the ABPM data.

Our data correspond to the results of other researchers. The estimates from current studies suggest that office BP measurements misdiagnose AH, when the readings are sufficiently above the hypertension threshold of 140/90 mm Hg in a clinic but below outside the clinic. This phenomenon was described by Pickering and colleagues as white coat hypertension (WCH), which is thought to occur because of the stress of the occasion [14]. Thus, Gorostidi et al. report that the prevalence of WCH ranged from 15.5–29.2 % in untreated patients and the prevalence of false-resistant hypertension due to the white-coat effect ranged from 24.2 % in treated males to 37.5 % in hypertensives resistant to three or more drugs [15].

The other less commonly than WCH recognized phenomenon is masked hypertension (MH), where the patient's office BP levels are below the hypertension threshold of 140/90 mm Hg but are above outside the clinic [16]. Bane-gas and colleagues report MH prevalence of 30 % among treated hypertensive patients [17].

Thus, taken together, misdiagnosis of AH grade can occur in 20 % to 30 % of patients if classified with office BP measurements, which corresponds to our data.

All this confirms the need for widespread use of ABPM in clinical practice for the management of AH patients, since the percentage of patients with over – or undervalued degree of AH is quite large.

Despite the growing evidence that the evening taking of antihypertensive drugs helps to normalize the daily BP profile [18,19], our study did not confirm this hypothesis.

In our study, nondippers prevailed in all the groups, regardless of the time of antihypertensive drugs intake. Although among patients, who received treatment regularly, this percentage was slightly lower than in patients with low compliance.

BP is a dynamic index; its fluctuations are a physiological phenomenon determined by the influence of different external and internal factors. Nowadays there is an increasing number of clinical and observational studies data indicating that increased BP variability increases the risk of cardiovascular complications and death, regardless

**Table 2.** Grade of arterial hypertension, controlled, night and morning arterial hypertension, %

	group 1, n = 46	group 2, n = 43	group 3, n = 14
<b>Office BP measurements</b>			
AH grade 1	24	28	36
AH grade 2	22	19	36
AH grade 3	13	12	14
Controlled AH	41	42	14
<b>ABPM</b>			
AH grade 1	48	33	64
AH grade 2	11	30	29
AH grade 3	4	2	7
Controlled AH *	37	35	0
Night AH	57	56	79
Morning AH	52	56	64

\*: P < 0.05 between groups 1 and 3, 2 and 3.

**Table 3.** Blood pressure variability according to ambulatory blood pressure monitoring, M, Me, [min–max] (mmHg)

Group	group 1, n = 46	group 2, n = 43	group 3, n = 14	P
<b>VAR 1 Day</b>				
<b>SBP</b>				0.79
M	14	14	15	
Me	14	14	15	
[min–max]	[6–25]	[9–22]	[11–18]	
<b>DBP</b>				0.93
M	11	11	11	
Me	11	10	11	
[min–max]	[4–19]	[6–24]	[7–16]	
<b>VAR 1 Night</b>				
<b>SBP</b>				0.01
M	13	13	10	
Me	12	13	9	
[min–max]	[6–23]	[5–19]	[5–16]	
<b>DBP</b>				0.10
M	10	10	8	
Me	9	10	8	
[min–max]	[5–20]	[4–17]	[6–12]	
<b>VAR 2 Day</b>				
<b>SBP</b>				0.60
M	15	16	16	
Me	15	16	16	
[min–max]	[7–27]	[10–26]	[13–22]	
<b>DBP</b>				0.90
M	12	13	12	
Me	11	12	12	
[min–max]	[5–22]	[7–35]	[8–20]	
<b>VAR 2 Night</b>				
<b>SBP</b>				0.27
M	16	16	14	
Me	14	16	13	
[min–max]	[6–29]	[8–26]	[9–20]	
<b>DBP</b>				0.67
M	eleven	12	eleven	
Me	eleven	eleven	eleven	
[min–max]	[5–18]	[7–25]	[6–14]	

of BP level [20]. Gosmanova [21] and Mehlum [22] with their colleagues showed that in patients with and without AH, higher BP variability was associated with increased risks of all-cause mortality, ischemic heart disease, stroke, and end-stage renal disease. Stevens et al. presented

the meta-analysis where the short-term BP variability was associated with cardiovascular and mortality outcomes [23]. Increased BP variability can also indicate the lack of antihypertensive therapy benefit, and therefore the optimization of antihypertensive treatment from the standpoint of pronounced BP fluctuations correction is seems to be important. The results of our study showed that the mode of antihypertensive therapy does not affect the short-term variability of BP. The mean values of the variability indices were equal or slightly differed between the groups, and the differences revealed were statistically significant only when comparing the group of low compliance with the groups using antihypertensive drugs regularly. There were no significant differences between any of the studied parameters between the groups with the morning and evening dosing of antihypertensive drugs.

## Conclusions

1. Regular intake of antihypertensive drugs helps to reduce the level of blood pressure and normalize its variability, regardless of the time of taking the drugs.

2. In clinical practice, the most informative method for assessing the effectiveness of blood pressure control is the ABPM in the management of patients with hypertension.

3. The results obtained necessitate the widespread introduction into clinical practice ABPM in order to avoid under- and overdiagnosis of AH.

4. According to our data, the treatment mode does not significantly affect the short-term variability of blood pressure, determined by the standard deviation from the mean BP and the root-mean-square value of the difference between consecutive BP measurements for a given time period.

**Prospects for further research.** It seems perspective to evaluate the effect of various treatment modes on short-term variability of BP using other variability indices that are less susceptible to external factors.

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