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EFFECTIVENESS OF ARTERIAL HYPERTENSION CONTROL USING AMBULATORY BLOOD PRESSURE MONITORING IN PATIENTS IN THE REMOTE PERIOD AFTER MYOCARDIAL INFARCTION AND ISCHEMIC STROKE

A. Yagensky, M. Pavelko, Y. Oshtuk

Артеріальна гіпертензія – один з найважливіших модифікованих факторів ризику і її адекватний контроль є наріжним каменем первинної та вторинної профілактики. З іншого боку, надмірне зниження артеріального тиску може бути шкідливим, особливо у пацієнтів з ішемічними подіями в анамнезі.

Мета. *Оцінити добові коливання АТ за допомогою добового моніторування у пацієнтів з контрольованою за даними офісних вимірювань артеріальною гіпертензією у віддалений період після перенесеного інфаркту міокарда та ішемічного інсульту.*

Матеріали та методи. *До дослідження були залучені 64 пацієнти з артеріальною гіпертензією у віддалений період (щонайменше 6 місяців) після перенесеного інфаркту міокарда (38 пацієнтів) та ішемічного інсульту (26 пацієнтів) у яких впродовж трьох останніх місяців і мінімум двох візитів визначався систолічний артеріальний тиск в межах 120–139 мм рт. ст. та діастолічний артеріальний тиск 70–89 мм рт. ст. Пацієнти з вадами серця, важкими порушеннями ритму, вираженою серцевою недостатністю (NYHA III–IV) в дослідження не включались. Усім пацієнтам було проведено добове моніторування артеріального тиску. За рекомендаціями ESC/ESH 2018 р. оптимальним вважався контроль артеріального тиску при середньодобовому артеріальному тиску після інфаркту міокарда 130–140/70–79 мм рт. ст. у віці >65 років, 120–130/70–79 мм рт. ст. у віці ≤65 років; після ішемічного інсульту 120–130/<80 мм рт. ст. Усі значення менші оптимальних рівнів вважались зниженим артеріальним тиском, вищі оптимальних – підвищеним артеріальним тиском. Особлива увага зверталась на надмірне зниження артеріального тиску з обчисленням кількості епізодів надмірних знижень та їх тривалості протягом доби.*

Результати. *Середньодобові значення артеріального тиску відповідали визначенню оптимальних лише у 23,4 % пацієнтів з перенесеними ішемічними подіями. У 63,2 % пацієнтів після інфаркту міокарда середньодобові значення систолічного артеріального тиску та діастолічного артеріального тиску виявились*

нижчими від рекомендованих, а у пацієнтів після ішемічного інсульту ця кількість була значно меншою – 23,1 %. І, навпаки, у більше ніж половини пацієнтів після ішемічного інсульту (53,6 %) середньодобові рівні артеріального тиску перевищували рекомендовані. У пацієнтів після інфаркту міокарда ця цифра склала лише 13,2 %.

Надмірні зниження артеріального тиску зафіксовані у 58 з 64 пацієнтів (90,6 %), з яких у 54 такі епізоди спостерігались в денний час (84,3 %). Персистуюче (понад 1 годину) надмірне зниження артеріального тиску реєструвалось у 16 осіб (25,0 %), у 8 з яких персистуючих надмірних знижень артеріального тиску було ≥2/добу (12,5 %). Предикторами надмірних знижень артеріального тиску виявились чоловіча стать, перенесений інфаркт міокарда, прийом бета-блокаторів.

Висновки. *Пацієнти з артеріальною гіпертензією після інфаркту міокарда чи ішемічного інсульту потребують регулярного контролю рівня артеріального тиску навіть у випадках, коли рівень артеріального тиску певний час знаходиться в рекомендованих межах. При цьому необхідно враховувати ризик не лише підвищення, але і надмірного зниження артеріального тиску*

Ключові слова: *артеріальна гіпертензія, добове моніторування артеріального тиску, інфаркт міокарда, ішемічний інсульт, артеріальний тиск, артеріальна гіпотензія*

1. Introduction

Arterial hypertension (AH) is one of the most important modified risk factors and its adequate control is a cornerstone of primary and secondary prevention [1]. However, in most patients with cardiovascular disease, including myocardial infarction (MI) or stroke blood pressure (BP) remains high [2]. On the other hand, excessive reduction of BP can also be harmful, especially in patients with a history of ischemic events [3]. First of all, it is a question of excessive decrease in diastolic arterial pressure (DBP) in patients with coronary pathology. Thus, more than 25 years ago, a Framingham study found that low DBP (below 70 mm Hg) was associated with an increased risk of death in patients after myocardial infarction (MI) [3]. A 16-year follow-up of more than 5,000 MI patients with the well-known MRFIT project also found a correlation between low DBP and mortality [4].

In clinical practice, measuring office BP does not always give a realistic picture of BP levels. Daily BP monitoring allows you to more objectively assess not only the average daily BP level, but also to detect its fluctuations. However, attention is traditionally focused on the ratio of day and night values of BP, the rise of BP in the morning, and indicators of BP variability [5]. The problem of excessive reduction of BP during the day has not been studied enough [6]. Such reductions can be especially dangerous in patients with a history of ischemic events. According to Antonioni L. et al. performed ABPM in 75 patients 3 weeks after MI [6]. The prognostic value of the examination was assessed after 12 months. The authors found that the decrease in the average daily level of DBP had a negative prognostic value. However, episodes of excessive decrease or increase during the day were not evaluated. The daily dynamics of BP in patients with acute stroke were evaluated using ABPM in several studies [7], including for assessing the effect of antihypertensive drugs [8, 9], however, data on the prognostic value of BP in the long term after ischemic stroke (IsI) are limited [10].

Therefore, the study of BP changes during the day in patients at very high risk, for example after MI or IsI is an important clinical and scientific task.

The aim of the research: Evaluate daily BP fluctuations using daily monitoring in patients with office-controlled hypertension in the remote period after myocardial infarction and ischemic stroke.

2. Materials and methods

The study was conducted on the basis of PC "Lutsk City Clinical Hospital" in 2018–2020. Sixty-four patients with AH and previous (at least 6 months) MI (39 patients, 64.1 % of them are men) and IsI (25 patients, 36.0 % of them are men) were enrolled in the study after voluntarily signing informed consent, in which during the last two visits to the clinic was determined by office systolic blood pressure (SBP) (120–139 mm Hg) and diastolic arterial pressure (DBP) (70–89 mm Hg). The study did not include patients with heart defects, severe heart failure (NYHA functional class >2) and left ventricular ejection fraction <40 %, symptomatic AH, atrial fibrillation, and frequent arrhythmias. The study was approved at a meeting of the Ethics Committee of PC "Lutsk City Clinical Hospital", minutes No. 741/1.1.10.18 from 02.10.2018.

All patients underwent ABPM with AVRM-04 (Meditech Ltd, Hungary). Prior to monitoring, patients were measured BP three times on the dominant arm. The average BP from the second and third measurements was taken into account. BP measurements were performed at 15-minute intervals during the day and every 30 minutes during the night. The average values of SBP, DBP, PBP and heart rate were estimated; SBP and DBP variability; night decrease and morning increase of BP, pressure load.

To assess the quality of AH control, patients were divided into several groups according to the recommendations of the European Association of Cardiologists for the treatment of AH in 2018 [1]. The optimal control group – patients whose mean BP values were within the recommended values for these categories. For patients

after MI younger than 65 years, the average daily systolic blood pressure (aSBP) in the range of 120–130 mm Hg, for patients aged 65 years and older aSBP in the range of 130–140 mm Hg. The average daily diastolic blood pressure (aDBP) is 70–79 mm Hg for both age categories. For patients after IsI – aSBP in the range of 120–130 mm Hg. Art. and aDBP below 80 mm Hg. Art. There are no restrictions on excessive aDBP reduction in the ESC/ESH recommendations. Probably due to the fact that there are currently no significant data on the deterioration of the prognosis with excessive reduction of aDBP in patients after stroke. Group of excessive BP reduction for patients after MI – aSBP<120 mm Hg, or aDBP<70 mm Hg. For patients after IsI – aSBP<120 mm Hg The group of elevated BP – patients in whom aSBP or aDBP were higher than optimal control.

Particular attention was paid to episodes of excessive BP reduction. Excessive lowering of blood pressure (EBPL) SBP was considered below 100 mm Hg during the day. Because once excessively low BP can be the result of various reasons, including technical, separately allocated persistent EBPL – excessive reduction of BP, reduction of BP below 100 mm Hg for at least an hour. In addition, such an indicator as EBPL load was calculated – the total EBPL time in percent during the day.

Statistical processing of the obtained material was performed using the statistical program STATISTICA for Windows 12.5. The results are presented as the mean±standard deviation (M±m), the number of variants (n). With the normal distribution of quantitative variables to compare the two groups used Student's t-test for independent samples. When comparing several groups, the significance of the difference between all groups in general was determined by analysis of variance. Pearson's chi-square (χ^2) independence criterion was used to test the hypothesis of the independence of two features. To compare the qualitative characteristics (frequency tables) used the criterion χ^2 and Fisher's exact test. Bilateral values with $p<0.05$ were evaluated as reliable.

3. Results

The study included 64 patients, 30 women (46.9 %) and 34 men (53.1 %). 38 people had a history of MI (59.4 %), 26 people (40.6 %) had IsI. The mean age of the subjects was 63.5±10.5 years. The mean time from event to examination was 4.3±3.0 years. Thirteen patients (20.3 %) were diagnosed with diabetes mellitus (DM), 21 (32.8 %) had a history of smoking, of which 12 subjects (18.8 %) continued to smoke after a cardiovascular event. In 48 people (75.0 %) there was overweight, of which 21 (32.8 %) were obese. The average creatinine clearance was 91.1±32.5 ml/min.

As shown in Table 1, among patients after IsI, the predominant number were women, the groups did not differ in age, time from event to examination, frequency of risk factors such as DM and smoking.

All patients took antihypertensive drugs, an average of 2.3±0.9 drugs. In particular, angiotensin-converting enzyme inhibitors (ACE inhibitor) received 37 patients (57.8 %), angiotensin receptor blockers (ARB) – 17 (26.6 %), calcium channel blockers (CCB) – 19 (29.7 %), diuretics – 30 (46.9 %), beta-blockers – 42 (65.6 %). In addition to antihypertensive drugs, patients received statins – 60 people (93.8 %), acetylsalicylic acid (ASA) – 55 (85.9 %). The analysis of treatment depending on the event did not reveal a significant difference between the groups in the average number of drugs (Table 1). Patients after MI were more likely to receive beta-blockers (BB). There was also a clear trend towards more frequent use of diuretics, ARB and CCB in patients with IsI.

Table 1

General characteristics of patients included in the study depending on the ischemic event

Indicator	MI (n=38)	IsI (n=26)	p
Women, %	43.3	56.7	0.01
Age, years	62.3±11.9	65.0±8.0	0.32
BMI, kg/m^2	28.8±4.0	28.1±4.4	0.50
Time from event to examination, years	4.8±3.5	3.6±2.3	0.26
Creatinine clearance, ml/min	94.6±31.0	86.0±34.5	0.30
DM, %	23.7	15.4	0.41
Smoking, %	23.7	11.5	0.15
Antihypertensive drugs, number	2.3±0.8	2.3±1.0	0.97
ACE inhibitor, %	63.2	50.0	0.29
ARB, %	18.4	38.5	0.07
CCB, %	21.1	42.3	0.06
BB, %	86.8	34.6	0.0001
Diuretics, %	36.8	61.5	0.05
Office SBP, mm Hg	127.3±21.1	142.0±21.5	0.008
Office DBP, mm Hg	79.2±15.6	83.1±11.6	0.25
Office PBP, mm Hg	48.1±15.4	58.7±15.0	0.008
Office heart rate, beats/min	69.2±12.8	71.2±10.2	0.48

Patients underwent BP measurements before the ABPM procedure. It was found that despite the fact that in all patients during the last two visits BP was less than 140/90 mm Hg, in 24 (37.5 %) patients before the installation of the ABPM monitor it was higher than the indicated figures. Elevated BP was found significantly more often in patients after IsI – 16 patients out of 26 (61.5 %) than after MI – 8 out of 38 (21.1 %) (61.5 % vs. 21.1 % after MI) p=0.001. The ABPM results showed that the average daily BP values were elevated in 14 people after IsI (53.9 %) and 5 patients with MI (13.2 %), p=0.01. In addition, in 9 (14.1 %) patients recorded BP figures below 110/70 mm Hg. All 9 patients with lower BP levels had a history of MI. When performing ABPM, the average number of measurements was 84.9±5.3 per patient and did not differ significantly between groups. There was a high percentage of successful measurements – 90.2± ±7.8 %. The mean SBP was 123.8±13.0 mm Hg, DBP –

73.3±8.7 mm Hg, pulse blood pressure (PBP) – 50.3± ±9.3 mm Hg., heart rate (HR) – 67.2±8.1 rpm. The variability of SBP was 11.8±3.0 mm Hg, DBP – 14.9±4.6 mm Hg. The average night decrease in SBP was 5.0±8.0 %, DBP was 8.2±8.9 %. Morning increase in SBP was observed at the level of 39.7±21.7 mm Hg, DBP – 34.4±21.1 mm Hg.

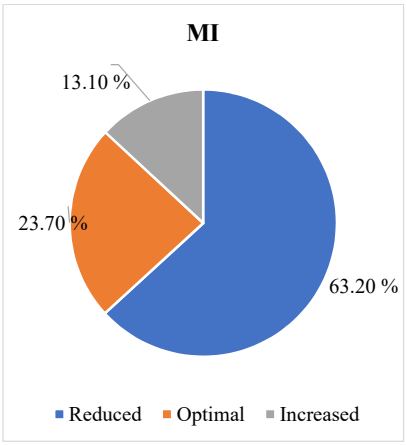
The results of ABPM separately by groups are shown in Table 2. All SBP and DBP were higher in patients after IsI. Higher SBP variability was also found in this group, especially during the day. The analysis of the data shows that the average values of daily SBP in patients after IsI were slightly higher than the optimal recommended in this category of patients, while in patients after MI, on the contrary, slightly lower. The average values of daily DBP in both groups were within the optimal parameters, although in this case the average value of DBP after MI was closer to the lower limit of the optimal value.

Of course, the average values do not reflect the whole picture and cannot indicate the effectiveness of BP control in the subjects. To analyze the effectiveness of AH control and in accordance with the recommendations of ESC/ESH 2018 [1] according to the results of ABPM, patients were divided into three groups. The first was patients with optimal control of AH – daily average BP after MI 130–140/70–79 mm Hg at the age of >65 years, 120–130/70–79 mm Hg at the age of ≤65 years; after IsI 120–130/<80 mm Hg. All values below the optimal levels were considered low BP, higher than optimal – elevated BP.

As shown in Fig. 1, in patients after MI and after IsI with controlled BP during the last two outpatient visits, only one in four according to the ABPM results, the average values of SBP and DBP remained within optimal limits according to the latest ESC/ESH recommendations in 2018. Interestingly, the percentage of patients with the optimal BP level was virtually independent of the previous ischemic event. Whereas a significant difference was found between the groups in the direction of BP deviations. In 24 (63.2 %) patients after MI, the average daily values of SBP or DBP were lower than recommended, while in patients after IsI this number was significantly lower – 6 (23.1 %). Conversely, in more than half of the patients after IsI (14 people – 53.9 %) the average daily BP levels exceeded the recommended ones. In patients after MI, this figure was only 5 (13.2 %). Thus, we found a fundamental difference between patients after MI and IsI with controlled AH according to office measurements.

According to the results of ABPM, patients after IsI had higher office SBP and office PBP, did not differ in office DBP and heart rate (Table 2). When estimating the average daily values of BP, individuals after IsI had a higher average daily SBP, DBP, PBP, there was no difference in the average daily heart rate.

Given the large number of patients with BP levels below our recommended level, an in-depth evaluation of EBPL episodes was performed. Such episodes were considered to be a decrease in SBP less than 100 mm Hg or a decrease in DBP less than 70 mm Hg. Given that excessive BP deviations can be caused, inter alia, by technical problems, it was decided to analyze the presence and frequency of prolonged (persistent) episodes of BP reduction lasting at least 1 hour. The number of both EBPL and persistent EBPL was determined in each patient. In addition, such an indicator as EBPL load was calculated.



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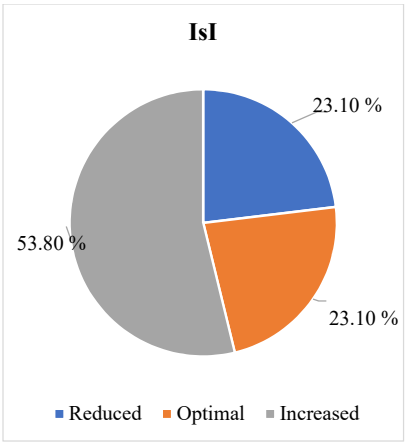

b

Fig. 1. BP levels in MI and IsI groups according to ESC 2018 recommendations: *a* – MI; *b* – IsI

EBPLs were recorded in 58 of 64 patients (90.6 %), of whom 54 such episodes were observed during the day (84.3 %). Persistent EBPL was registered in 16 people (25.0 %), 8 of whom had persistent EBPL ≥2/day (12.5 %). There was a tendency that patients with persistent EBPL had MI in more cases (23.7 % vs. 7.7 % after IsI, p=0.09) and received fewer antihypertensive drugs (1.8±0.9 against 2.4±0.9, p=0.06). There were no differences in age, sex, BMI, creatinine clearance, DM, smoking, type of antihypertensive drugs used. The distribution of EBPL and persistent EBPL depending on the etiology is shown in Table 2. There was a tendency to more frequent detection of persistent EBPL in the group after MI (23.7 % vs. 7.7 % after IsI, p=0.09), individuals with persistent EBPL used less the number of antihypertensive drugs (1.8±0.9 vs. 2.4±0.9 drugs, p=0.06). The groups did not differ in other parameters. Among patients who had at least one episode of EBPL, patients with MI had a significantly higher number of EBPLs that persisted in EBPL. The EBPL load was also statistically higher in the MI group.

The analysis of the main indicators on groups depending on the level of office BP measured before the

beginning of ABPM was carried out. Examined with low levels of office BP were more men, people after MI, smokers. This cohort of patients received ARBs and diuretics less frequently. In other respects, individuals with varying degrees of office BP did not differ. Persons with office BP <120 mm Hg had more episodes of EBPL during ABPM (9.8±12.8 vs. 2.8±3.0 episodes in the group with office BP>140 mm Hg, p=0.01) and persistent EBPL (0.8±1.6 vs. 0.1±0.3, respectively, p=0.03). In patients with office blood pressure <120 mm Hg lower average daily SBP (112.9±9.2 mm Hg and 134.0±10.2 mm Hg, p=0.00001), DBP (68.9±7.6 mm Hg) were registered. Against 77.3±9.5 mm Hg, p=0.003), pulse BP (44.0± ±7.9 mm Hg and 56.5±7.5 mm Hg, p=0.00001), there was no difference in heart rate (70.2±7.8 beats/min against 66.1±7.6 beats/min, p=0.11).

Table 2

The main indicators of ABPM depending on the ischemic event

Indicator	IM (n=36)	IsI (n=28)	p
Average daily SBP, mm Hg	118.0±10.6	132.2±11.5	0.00004
Average daily DBP, mm Hg	71.1±9.0	76.6±7.2	0.01
Average SBP, day, mm Hg	120.2±11.0	133.9±11.6	0.00001
Average DBP, day, mm Hg	73.5±9.4	78.3±7.1	0.02
Average SBP, night, mm Hg	113.0±12.0	128.8±15.4	0.00002
Average DBP, night, mm Hg	67.0±10.5	73.2±9.7	0.02
Average daily HR, beats/min	67.4±8.3	66.9±8.1	0.78
Daily variability SBP, mm Hg	14.0±4.6	16.1±4.7	0.07
Daily variability DBP, mm Hg	11.8±3.0	11.9±3.0	0.88
EBPL, %	92.1	80.8	0.17
Number of patients with persistent EBPL, %	31.6	15.4	0.14
EBPL episodes, number*	8.4±9.9	3.2±3.2	0.02
Episodes of persistent EBPL, number*	0.7±1.4	0.1±0.3	0.03
EBPL load, % per day *	14.6±13.7	6.4±4.8	0.01

*Notes: * – only patients with at least one episode of EBPL were considered*

Given the data that patients with lower SBP have a statistically higher incidence of ELBP and persistent EBPL, the analysis of patients with an average daily level of SBP<110 mm Hg, SBP<120 mm Hg. and DBP<70 mm Hg. Thus, patients with an average daily SBP<110 mm Hg were more often men, after MI, with DM, smokers, received BB, did not accept CCB; increased BMI, younger age were registered; had fewer episodes of EBPL and persistent EBPL. Individuals with an average daily SBP<120 mm Hg were more often men, after MI, took BB, did not take ARB, CCB, diuretics; had fewer episodes of EBPL and persistent EBPL. In turn, examined with an average daily DBP<70 mm Hg were after MI, did not take ARB, were older, and also had fewer episodes of EBPL and persistent EBPL.

4. Discussion

Because AH is a major risk factor in patients after MI and stroke, its monitoring requires special attention. Regular visits to the doctor with BP measurement and correction of therapy are the basis of such control. However, the proportion of patients in whom BP is within the recommended limits according to our data does not exceed 25 % [11, 12]. This study included patients who had BP below 140/90 mm Hg as a result of two consecutive visits to the doctor during the last 2 months. Before monitoring in 24 people (37.5 %) BP was higher. And only in 13 (20.3 %) patients this increase was not confirmed during ABPM. Moreover, ABPM results showed that more than half of the patients after IsI had BP values higher than optimal. This again indicates the lack of effectiveness of AH treatment, especially in patients after stroke.

The negative prognostic value of excessive BP reduction has recently been established. According to the results of a number of population studies, the so-called "phenomenon of the U-curve" – a negative prognostic effect of BP reduction [13–15]. First of all it is a question of excessive decrease in DBP at patients with coronary pathology. Thus, more than 25 years ago, a Framingham study found that low DBP (below 70 mm Hg) was associated with an increased risk of death in patients after MI. Reduction of SBP less than 120 mm Hg was accompanied only by a tendency to worsen the prognosis [3]. A 16-year follow-up of more than 5,000 MIpatients with the well-known MRFIT project also found a correlation between low DBP and mortality [4]. In patients with HF (most after MI), lower BP levels were also associated with an increase in mortality during the year of follow-up [19].

In general, data on ABPM in patients after MI and IsI are quite limited. Antonioni L. et al. performed ABPM in 75 patients 3 weeks after MI [6]. The prognostic value of the examination was assessed after 12 months. The authors found that the mean value of diastolic BP had a significant prognostic value. In all 10 patients who died, this figure was below 70 mm Hg. The daily dynamics of BP in patients with acute stroke were evaluated using ABPM in several studies [7], including to assess the effect of antihypertensive drugs [8, 9], however, data on the prognostic value of BP in the long term after IsI is limited [10].

Our study showed that a large proportion of patients with "controlled" AH during ABPM have figures that are outside the optimal BP. Of particular concern is that most patients after MI and the majority of patients after IsI show a significant reduction in both SBP and DBP. In 25 % of patients, these reductions were quite long – at least for an hour. Part of the cause of excessive BP reduction may be systolic dysfunction of the left ventricle. We did not perform echocardiography imme-

diately prior to ABPM, but the study included patients who had a left ventricular ejection fraction of at least 40 % in the last 6 months and a heart failure of no more than NYHA class II.

Study limitations. A certain limitation of this study is the fact that when conducting ABPM, we used the recommended office levels of BP to assess the quality of AH control. However, to date, there are only recommendations for BP levels in ABPM in the diagnosis of AH, the target levels of BP in treatment, including in patients with ischemic events have not yet been established. Therefore, we used the recommended office BP values for these patient categories.

Thus, in the treatment of AH in patients after MI or stroke, attention should be paid not only to increase BP, but also to prevent its excessive reduction, especially in patients with MI.

Prospects for further research. The presence of episodes of excessive BP reduction in patients with ischemic events can theoretically lead to serious complications. However, this thesis should be confirmed in prospective studies with ABPM with an assessment of the prognostic value not only of the average daily values of BP, but also its fluctuations during the day. Another promising area of research is the search for predictors of excessive BP fluctuations and the possibility of reducing these fluctuations.

5. Conclusions

1. According to the results of ABPM, optimal BP levels are registered in less than 25 % of patients after myocardial infarction and ischemic stroke. The average daily BP was higher in patients after stroke, in 53.6 % the level of average daily BP was higher than optimal. In patients after myocardial infarction, this figure was only 13.2 %. In 63.2 % of patients after myocardial infarction, the average daily BP values were lower than recommended.

2. At least one episode of excessive BP reduction was recorded in 58 of 64 patients (90.6 %). Persistent (over 1 hour) excessive decrease in BP was registered in 16 (25.0 %) individuals, in 8 of whom persistent excessive reductions in blood pressure were ≥2/day (12.5 %).

3. Predictors of excessive reductions in BP were gender male, myocardial infarction, beta-blockers.

4. Patients with AH after myocardial infarction or ischemic stroke require regular monitoring of BP levels, even in cases where BP levels are within the recommended range for some time. It is necessary to take into account the risk not only of increasing but also of excessive decrease of BP.

Conflict of interests

The authors declare that they have no conflicts of interest.

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