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Blood pressure circadian rhythm abnormalities in patients with chronic kidney disease, stage 5

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Objective. *To detect clinical and laboratory characteristics of the course of arterial hypertension in patients with chronic kidney disease, 5 stage, receiving maintenance hemodialysis.*

Materials and methods. This study included 248 patients on maintenance hemodialysis therapy. All patients underwent 24h blood pressure monitoring (24h-ABPM) for 23,2±0,6h in order to detect abnormalities of blood pressure (BP) circadian rhythms and their relationship with metabolic parameters. Statistical analysis was performed using StatPlus 2009 software.

Results. *We found that a longer dialysis history was associated with a bigger number of patients with arterial hypotension rather than arterial hypertension (p<0,001). Daytime 24h-ABPM parameters correlated with office values of systolic BP (SBP) and diastolic BP (DBP) before hemodialysis: rSBP=0,52, p<0,01 and rDBP=0,65, p<0,01; during the procedure: rSBP=0,50, p<0,01 and rDBP=0,66, p<0,01, and after the procedure: rSBP=0,56, p<0,01 and rDBP=0,54, p<0,01. Night-peaker type of circadian rhythm was found in 34 patients (68%), whereas night levels of DBP were elevated in 22 (44%) patients. There were also patients with an insufficient decrease of nocturnal BP (non-dipper): 12 persons (24%) with corresponding SBP values and 16 (32%) with corresponding DBP values. Correlation analysis revealed the relationship between the morning SBP and DBP elevation value with urea levels (r=-0,77; p<0,001 and r=-0,87; p<0,001, respectively), potassium (r=-0,8; p<0,001 and r=-0,8; p<0,001, respectively), sodium (r=0,74; p<0,001 and r=-0,69; p<0,001, respectively), and phosphorus (r=-0,7; p<0,001 and r=-0,78;*

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p<0,001, respectively). There was also found a correlation between post-dialysis pulse pressure and the level of parathyroid hormone (rs=0,78; p<0,001), phosphorus (r=0,63; p<0,001), and calcium (r=0,57; p<0,001).

Conclusion. *Thus, long-term duration of dialysis is associated with an increase in the number of patients with arterial hypotension and a decrease in the number of patients with arterial hypertension. The majority of patients with AH had BP circadian rhythm abnormalities of non-dipper and night-peaker types. 24h-ABPM parameters correlate with electrolyte balance impairments (potassium, sodium, and phosphorus concentrations) and nitrogen metabolism (urea levels). Increased pulse pressure is associated with hypophosphatemia, hypercalcemia and elevated level of parathyroid hormone.*

Keywords: *arterial hypertension, 24h blood pressure monitoring, chronic kidney disease stage 5.*

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Cardiovascular diseases (CVD) represent the leading mortality cause in patients on maintenance hemodialysis (HD) [1, 2, 3, 4]. Arterial hypertension (AH) is a significant risk factor of cardiovascular complications in dialysis patients leading to disability and death, and, thus, determines the prognosis of the disease, as well as life duration and quality of life [5, 6, 7, 8]. In the dialysis population, hypertension is diagnosed in 55-88% of patients. According to the 2016 register, the percentage of HD patients with hypertension remains steadily high (61.1%) in Russia, in comparison to the previous years [9, 10].

Until recently, the question of the necessity and significance of 24-hour ambulatory blood pressure monitoring (ABPM) for patients on HD was debatable, since such patients on HD treatment showed a high correlation between BP values obtained during dialysis and blood pressure monitoring. The ABPM results were comparable to the values of office BP. The study of Ekart R. et al., conducted in 2009, showed that only blood pressure values obtained during the 24- or 48-hour ABPM were associated with the thickness of the blood vessels intima. In addition, a single measurement of "office" blood pressure in dialysis patients can's demonstrate the BP influence on the prognosis of the disease [11]. At the same time, Russian and foreign authors note a characteristic feature of hypertension in dialysis patients (on 85%) which is no decrease or a slight decrease of blood pressure (mainly nocturnal DBP). Since blood pressure is usually measured during the day, this can lead to an erroneous idea of good blood pressure control.

There is a correlation between the absence of nocturnal decrease in BP and the severity of damage to target organs of the cardiovascular system. Previous studies have shown that an increase in nocturnal blood pressure by more than 30% was as an independent factor of the left ventricular hypertrophy onset and progression. At the same time, left ventricular hypertrophy may be associated with an increase in total peripheral resistance, which, in turn, in patients on HD, is due to an increased vascular wall stiffness and an increased return wave [12, 13]. The simplest clinical method which can reflect arterial stiffness is the pulse pressure (PP) calculation.

Thus, ABPM in dialysis patients represents a necessary diagnostic method which determines the further management of the patient.

Objective of the study: to identify clinical and laboratory features of AH in patients with chronic kidney disease (CKD) on the 5th dialysis stage.

Materials and methods

The study included 248 patients with CKD stage 5, M / F = 129/119, aged from 18 to 61 years, who were receiving the HD treatment in the hemodialysis units of the Udmurt Republic (Izhevsk, Glazov, Votkinsk, Mozhgi, Sarapul). The dialysis was performed using devices 4008S ("Fresenius", Germany) and Dialog + (B. Braun, Germany) 3 times per week for 4–4.5 hours via polysulfone dialyzers. The Kt / V adequacy index for urea was higher than 1.2 and was 1.43 ± 0.09.

In regard to the blood pressure level, all patients were divided into three groups. The first group consisted of 173 patients with elevated BP. This group included 120 patients with grade-I hypertension, 42 patients with grade-II hypertension and 11 patients with III-grade hypertension, according to the Russian Society of Cardiology (RSC) guidelines (2004, 2010) and ESH/ESC guidelines (2013). Patients with differ-

Table 1. **Distribution of patients with different BP level depending on their dialysis history**

Dialysis history	Normal BP N=28 patients (%)	AH (%) N=173 patients (%)	Arterial hypotension N=47 patients (%)	p
Up to 1 year	8(28.6)	54(31.2)	7(14.9)	$p_{1-2}>0.05$ $p_{2-3}<0.05$ $p_{1-3}>0.05$
2-5 years	5(17.8)	69(39.9)	11(23.4)	$p_{1-2}<0.05$ $p_{2-3}>0.05$ $p_{1-3}>0.05$
6-10 years	7(25)	29(16.8)	11(23.4)	$p_{1-2}>0.05$ $p_{2-3}>0.05$ $p_{1-3}>0.05$
More than 11 years	8(28.6)	21(8.5)	18(38.3)	$p_{1-2}>0.05$ $p_{2-3}<0.001$ $p_{1-3}>0.05$

Note: p – significance of difference between groups according to Pearson criterion χ^2

ent hypertension grades were comparable on age and sex and had AH history of 13,4±1,1years.

The second and the third group consisted of 28 and 47 patients with normal and low BP respectively. The groups were comparable on age and sex.

Patients' examination program included general and special methods. 50 patients underwent blood pressure monitoring during 23,2±0,6 hours (using the IECG-DP-NS-01 device, 2008) in order to reveal circadian rhythm of BP abnormalities and their relationship with metabolic parameters. The correlation between the 24h-ABPM values and biochemical parameters according to diagnostic standards for patients on hemodialysis, such as, creatinine 780.45 + 199.9 μmol /L), urea (29.4 + 6.9 mmol /L), potassium (5.33 + 0.47 mmol /L), sodium (137.7 + 2.1 mmol /L), calcium (2.52 + 0.5 mmol /L), phosphorus (2.1 + 0.4 mmol /L), alkaline phosphatase (311.7+ 155.2 U /L), total cholesterol (5,1 + 1,2 mmol /L), parathyroid hormone (PTH) 526 [252; 895] pg /L was studied. Local Ethics Committee permission was obtained before the start of the study.

Statistical analysis of obtained results was carried out using the BioStat (2009, version 4.03.) and Microsoft Excel 2010 application programs. Statistical analysis was performed using parametric and non-parametric statistical methods. The data were described as M ± m. The reliability of the research results was confirmed by Student's criterion (t) value calculation. The χ^2 criterion was used to reveal the differences between groups according to their qualitative characteristics. Pearson (r) and Spearman (rs) correlation analysis was also applied.

Results

In our study, the number of patients with dialysis history of up to one year was 54 for the group with elevated BP (31.2% of all patients with elevated pressure), 8 for those with normal BP (28.6%), 7 – with low BP (14.9%; see Table 1). Among patients with the dialysis history of 2-5 years, there were mostly individuals with elevated blood pressure – 69 persons (39.9%; p <0.01). In the group with dialysis history of 6-10 years, the distribution of patients with different levels of blood pressure was statistically unreliable. In the group with dialysis history of more than 11 years, low blood pressure was observed in 18 (38.3%) patients, normal BP – in 8 patients (28.6%), elevated BP – in 21 (8.5%) patients (p <0.001). Therefore, a longer dialysis history leads to a decrease in the number of individuals with hypertension and an increase in the number of those with hypotension (Table 2).

Patients with AH underwent 24h-ABPM (Table 3). It was found that average integral indicators of SBP

Table 2. **"Office" BP values in patients on maintenance HD**

Parameter, mm Hg	**BP, mm Hg. (N=248)**
SBP in the beginning of the HD procedure (M±m).	135.3±1.5
DBP in the beginning of the HD procedure (M±m).	81.8±0.8
SBP in the end of the HD procedure (M±m)	133.7±1.9
DBP in the end of the HD procedure (M±m)	80.5±0.9

Table 3. **24h BP monitoring parameters in patients with arterial hypertension**

Parameter	SBP (N=50)	DBP (N=50)
Average integral value for 24 hours, mm Hg.	144.2±5.8	94.2±3.8
Average integral diurnal value, mm Hg.	143.7±6.4	93.9±3.9
Average integral nocturnal value, mm Hg.	145.9±5.5	95.2±4.3
Hypertonic time index	70.8±18.6	74.4±16.3
Magnitude of Morning Surge in BP (MSBP), mm Hg.	4.3±6.5	3.5±4.7
RoR (morning rate of rise), mm Hg/hour	1.8±1.9	1.1±1.7
Nocturnal BP decrease rate	-2.2±2.4	-0.14±2.6

and DBP exceeded the permissible values and were, respectively, 144.2 ± 5.8 mm Hg and 94.2 ± 3.8 mm Hg for 24 hours, 143.7 ± 6,4mm Hg and 93.9 ± 3.9 mm Hg for the day hours, 145,9±5,5 mm Hg and 95,2±4,3 mm Hg for the night hours. As shown in the table, the SBP and DBP time index is significantly increased, which indicates not a transient, but a stable character of hypertension. Diurnal ABPM values correlated with the "office" SBP and DBP values before the hemodialysis procedure : 136.8 ± 5.8 mm Hg and 82.5 ± 3.9 mm Hg (r_{SBP} = 0.52, p <0.01 and r_{DBP} = 0.65, p <0.01), during the hemodialysis procedure: 133.8 ± 5.7 m Hg and 84.2 ± 3.5 mm Hg (r_{SBP} = 0.50, p <0.01 and r_{DBP} = 0.66, p <0.01), after the hemodialysis procedure: 134.8 ± 7.9 mm Hg and 82.9 ± 3.9 mm Hg (r_{SBP} = 0.56, p <0.01 and r_{DBP} = 0.54, p <0.01).

It is well-known the BP undergoes significant fluctuations in the course of a day; these daily fluctuations reflect the circadian rhythm which is characterized by a BP decrease during the night sleep and a rapid increase at the moment of awakening or immediately before it. Night-peaker circadian rhythm, characterized by paradoxical nocturnal hypertension, i.e. a distinct BP elevation at night, occurred in 34 (68%) patients; DBP elevation was observed in 22 (44%) patients (Figure 1). The morning BP elevation value was negative in 16 (32%) patients for SBP and 22 (44%) patients for DBP: therefore, in these cases, there is a decrease and not an increase in the morning BP. There were also individuals with an insufficient decrease in nocturnal BP (non-dipper): 12 (24%) persons for SBP, and 16 (32%) persons for DBP. Normal diurnal rhythm (Dipper) was observed in 4 (8%) patients for SBP and 12 (24%) patients for DBP. There was no patient with an excessive decrease in nocturnal BP in our study.

In recent years, increasing attention is being paid to heart rate (HR), which is considered an independent risk factor for cardiovascular complications. It is important to note that some authors tend to consider tachycardia an indicator of an increase in the activity of the autonomic nervous system. Patients included in this study had the heart rate of 76 [74,8; 81,8] beats/min during the 24h-ABPM. This parameter exceeded the reference values in 12 patients (24%). Kerdo vegetative index corresponded to the prevalence of parasympathetic tone in 44 patients (88%), of sympathetic tone in 6 patients (12%), and it's average value was –20.2 ± 5.5.

Also, various authors note the role of pulse pressure in the development of cardiovascular events [14]. When measuring "office" blood pressure, the pulse pressure at the beginning and in the end of the hemodialysis procedure was 53.5 ± 1.0 mm Hg and 53.3 ± 1.2 mm Hg, respectively (p> 0.05). The distribution of the pulse pressure level was as follows: 127 (51.2%) patients had elevated values, 88 (35.5%) patients had normal values, and 33 (13.3%) patients had borderline values. The correlation analysis revealed a relationship between the pulse pressure at the end of the hemodialysis procedure and the level of PTH (rs = 0.78; p <0.001), phosphorus (r = 0.63; p <0.001) and calcium (r = 0.57; p <0.001).

Via correlation analysis, there was also found a relationship between the SBP and DBP morning elevation magnitude and the level of urea (r = -0.77; p <0.001 and r = –0.87; p <0.001, respectively), potassium (r = –0.8; p <0.001 and r = –0.8; p <0.001, re-

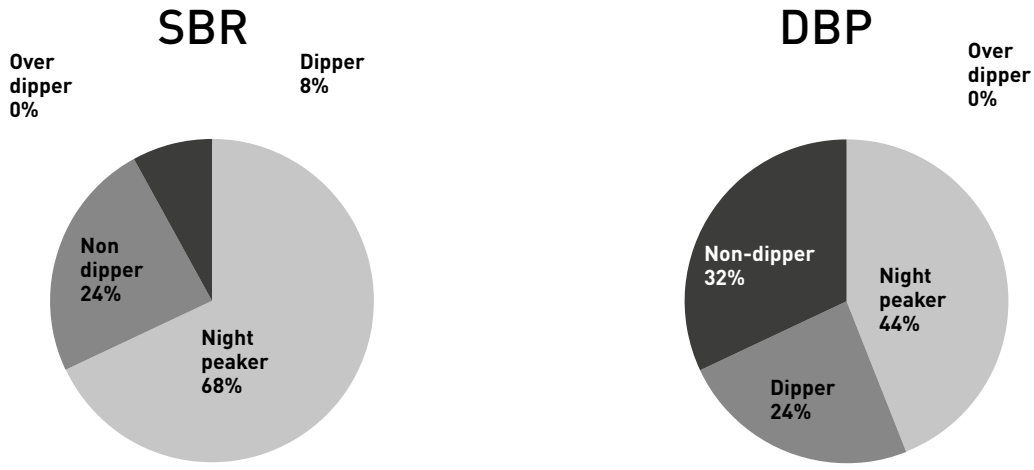

Figure 1. BP circadian rhythm features in patients with AH

spectively), sodium (r = 0.74; p <0.001 and r = 0.69; p <0.001, respectively) and phosphorus (r = –0, 7; p <0.001 and r = –0.78; p <0.001, respectively). These correlations indicate that the higher the concentration of metabolites (urea and creatinine) and ions (potassium, sodium, phosphorus) in the blood is, the greater is the likelihood of nocturnal hypertension. In our study, the morning BP elevation magnitude was the only 24h-ABPM parameter to be correlated with biochemical parameters (Table 4).

Table 4. **Correlation of biochemical parameters and the magnitude of morning BP surge**

Parameter	magnitude of morning SBP surge (r)	magnitude of morning DBP surge (r)
Urea	-0,77**	-0,87**
Potassium	-0,8**	-0,8**
Phosphorus	-0,7**	-0,78**
Sodium	0,74**	0,69**

Note: correlation coefficient reliability - **p<0,001;

Discussion

The results of our research show that BP values depend on the duration of the hemodialysis therapy history. With a longer dialysis history, an increase in hypotonic patients number and the decrease in the hypertonic patients number can be observed (p<0,001). It may be associated with the heart failure progression, when there is a decrease in the ejection fraction, and, consequently, a BP decrease [15]. Myocardial remodeling develops under the influence of various urotoxins (FGF-23, urea, potassium, PTH, renin, etc.) and chronic mechanical overload of the myocardium [16, 17, 18].

More than a half of patients (51.2%) had an elevated level of pulse BP. Some authors associate the pulse pressure increase with an increase of the main arteries rigidity [14]. We found a correlation between pulse pressure and the level of PTH, phosphorus and calcium (p <0.001). It is known that the CKD and secondary hyperparathyroidism progression leads to medial sclerosis, or Mönckeberg's arteriosclerosis, which is characterized by sclerotic lesion of the arterial media of elastic or elastic-muscular arteries and manifests as the media necrosis, sclerosis or calcinosis. [19].

Therefore, the severity of calcium-phosphorus metabolic disturbances has a direct impact on the CVD prognosis in this cohort of patients. A review of seven studies (EWPHE, HEP, MRC1, MRC2, SHEP, Syst-Eur and STOP) showed that PP was an independent risk factor of death from cardiovascular disease [20]. According to Klassen P.S. (2002) and USRDS Waves 3 and 4 Study (2010) in patients with HD, the risk of death increased by more than 10% with an increase in post-dialysis PP by 10 mm Hg. [21, 22, 23]. Thus, the pulse pressure control and the effective correction of calcium-phosphorus metabolism represent significant prognostic factors.

In November 2017, the American College of Cadiology and the American Heart Association presented new guidelines for hypertension, where new approaches to patient management and diagnosis were established. Thus, the target level of blood pressure, regardless of comorbid pathology, was established to be less than 130/80 [24]. Russian guidelines, though, regard hypertension today in the same way as the guidelines of the European Society of Cardiology and the European Society of Hypertension (2013) [25] do: target blood pressure for all patients with hypertension, regardless of risk, should be less than 140/90 mm Hg, and exactly 130–135 / 80–85 mm Hg [26]. At the same time, a large study showed that if the post-dialysis SBP is less than 120 mm Hg, there is an increase in the incidence of cardiovascular events in patients on HD [27]. Another study was conducted to check this data: it included 649 hemodialysis patients and showed that that hypertension, on the contrary, was associated with better survival, while patients with hypotension had a higher mortality rate [28]. It is also worth noting that hypotension episodes during dialysis often provoke fatal arrhythmias, which is the main cause of sudden death in dialysis patients.

The first guidelines on the target level of blood pressure in the dialysis cohort of patients appeared in Japan (2014), where target BP values were defined as from 130 to 159 mm Hg for SBP and from 70 to 89 mm Hg for DBP. [29]. Thus, both hypertension and hypotension after the HD session are associated with an increased risk of death.

The results obtained by us show that the "office" BP values are highly correlated with diurnal 24h-ABPM values, but do not reflect nocturnal blood pressure, and, therefore, do not assess the degree of hypertension in dialysis patients. The overwhelming majority of patients with hypertension had a circadian rhythm disorder of the non-dipper type, which is characterized by an insufficient nocturnal decrease of BP, and the night-peaker type, characterized by paradoxical nocturnal hypertension. According to Agarwal R. Pro (2015), 24h-ABPM was the best way to predict mortality risks in comparison to the "office" and "home" BP measurement[30]. But for today the 24h-ABPM is not widely used due to low availability of equipment and

certain practical difficulties for the patient. Therefore, it is necessary to include the 24-hours blood pressure monitoring in the medical care standards for dialysis patients, and, in prospect, the 24-hours monitoring of blood pressure via radial artery applanation tonometry.

Conclusion

Arterial hypertension occurs in 69.8% of patients on maintenance hemodialysis in the Udmurt Republic. With an increase of the dialysis history, there can be observed a decrease in the number of patients with arterial hypertension and an increase in the number of patients with arterial hypotension. Most patients with hypertension have circadian rhythm abnormalities of non-dipper and night-peaker types.

We also revealed a relationship between 24h-ABPM values and ionic balance changes (potassium, sodium, phosphorus), as well as nitrogen metabolism indicators (urea level). The increase in pulse pressure was associated with hyperphosphatemia, hypercalcemia and an increased PTH level. 24h-BPM is indispensable for an adequate hypertension diagnostics and, together with antihypertensive therapy, for an effective correction of calcium-phosphorus metabolism.

Conflict of interest: None declared

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