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DIFFERENCES IN CYSTATIN C LEVEL DEPENDING ON PARAMETERS OF DAILY BLOOD PRESSURE MONITORING IN PATIENTS WITH ESSENTIAL HYPERTENSION AND FREQUENT EXTRASYSTOLES

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156 patients with stage II essential hypertension were examined, among them, 124 had frequent symptomatic extrasystole and 32 patients did not have any heart rhythm disorders. Another 30 healthy persons were included in the control group. Complete clinical, laboratory and instrumental examinations were applied to all study participants, including daily blood pressure monitoring and cystatin C serum concentration. It was found that the level of cystatin C was significantly higher in hypertensive patients compared to controls ($p<0.001$). In turn, in the presence of extrasystoles, the mean cystatin C was significantly higher than in patients without extrasystoles ($p<0.05$). The highest level of cystatin C was noticed in patients with essential hypertension and ventricular extrasystole. It was significantly different from the patients with extrasystole of supraventricular origin ($p<0.05$) and patients without arrhythmias ($p<0.001$) or healthy individuals ($p<0.001$). Also, higher values of blood pressure and a relatively high level of serum cystatin C were found in patients with hypertension, which allows us to suspect the common pathophysiological mechanisms of an increase in the cystatin C level, values of blood pressure and the occurrence of frequent extrasystoles (especially of the ventricular origin).

Key words: hypertension, cystatin C, daily blood pressure monitoring, extrasystole.

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ЗМІНИ РІВНЯ ЦИСТАТИНУ С ТА ЙОГО ЗВ'ЯЗОК З ПОКАЗНИКАМИ ДОБОВОГО МОНІТОРУВАННЯ АРТЕРІАЛЬНОГО ТИСКУ У ПАЦІЄНТІВ НА ГІПЕРТОНІЧНУ ХВОРОБУ І ЧАСТУ ЕКСТРАСИСТОЛІЮ

Обстежено 156 хворих з гіпертонічною хворобою II стадії, серед них 124 мали часту симптомну екстрасистолію і 32 пацієнти не мали будь-яких порушень серцевого ритму. Ще 30 практично здорових осіб увійшли до групи контролю. Усім включеним у дослідження було проведено повне клініко-лабораторне та інструментальне обстеження, в тому числі добове моніторування артріального тиску та визначення рівня цистатину С. Виявлено, що у хворих на гіпертонічну хворобу рівень цистатину С був суттєво вищий, в порівнянні з контролем ($p<0,001$), при цьому при наявності екстрасистолії середній вміст цистатину С був достовірно вищий, ніж у пацієнтів без екстрасистол ($p<0,05$). Найвищий рівень цистатину С був зафіксований у хворих з гіпертонічною хворобою і шлуночковою екстрасистолією, що достовірно відрізнялось від відповідного рівня цистатину С у пацієнтів з суправентрикулярною екстрасистолією ($p<0,05$), пацієнтів без аритмій ($p<0,001$) та практично здорових осіб ($p<0,001$). Крім того було визначено, що для пацієнтів з гіпертонічною хворобою і відносно високим рівнем цистатину С сироватки характерні більш високі величини артеріального тиску, що дозволяє думати про існування спільних патофізіологічних механізмів між підвищенням рівня цистатину С, величинами артеріального тиску та наявністю частої екстрасистолії (особливо шлуночкового варіанту).

Ключові слова: гіпертонічна хвороба, цистатин С, добове моніторування артеріального тиску, екстрасистолія.

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Today, it is not exactly clear how various heart rhythm disorders, including extrasystoles, affect kidney function in patients with essential hypertension. However, there is evidence that risk factors such as obesity, metabolic syndrome, hypertension, cardiovascular disease, and type 2 diabetes, as well as mechanisms of progression such as, in particular, inflammation, oxidative stress, activation of the renin-angiotensin-aldosterone system, are common for heart arrhythmias and kidney dysfunction [2, 3, 7, 8]. A large number of studies are aimed at studying the relationship between atrial fibrillation and renal dysfunction, it has been proven that not only renal dysfunction is a predictor of the occurrence of arrhythmias, but also the presence of arrhythmia is associated with an increase in the probability of a further decrease in the rate of glomerular filtration and an increase in albuminuria due to the decline of systemic and intrarenal hemodynamics, however, early markers of renal dysfunction in patients with hypertension and concomitant extrasystole continue to be studied and require clarification [12, 13].

Cystatin C (Cys C) serves as an early and most informative marker of renal dysfunction according to the KDIGO 2012 and 2020 guidelines [1, 4, 13, 15]. Cys C is freely filtered through the glomerular membrane, due to its low molecular weight. Because of this, the level of Cys C is relatively stable in

systemic circulation. It has been proven that this indicator is a more sensitive marker of a decrease in the glomerular filtration rate (GFR) than creatinine because it is not affected by factors like age, gender, muscle mass, eating habits, physical activity, and race. At the same time, it serves as an effective marker for the early detection of renal failure, even at normal creatinine levels [5, 9, 10, 14].

It is well-known that hypertension and extrasystole (especially of the ventricular origin), lead to remodeling and impaired function of the heart. In turn, cardiac remodeling is accompanied by certain inflammatory changes such as apoptosis, atrial fibrosis, calcium turnover disorders, and regulation of connexin, etc. [11, 12]. Cys C is often referred to inflammation marker because it is produced during inflammation by cells containing the nucleus, which can explain the increase in the level of this peptide in patients with hypertension and extrasystole.

The purpose of the study was to evaluate changes in cystatin C level and its relation with the daily blood pressure monitoring parameters in patients with hypertension and frequent extrasystole.

Materials and methods. The study includes 124 patients with stage II hypertension (EH II) and frequent symptomatic extrasystole ages of 27 to 75 (on average 58.2±0.9 years), who formed the main clinical array of the study. Among them, 74 patients had supraventricular (SVE) and 50 ventricular (VE) extrasystole. In addition, we examined 32 patients with EH II without any heart rhythm disorders (they were excluded by the Holter ECG Monitoring (HM ECG)) aged 32 to 72 (an average of 55.9±1.7) years, which formed a comparison group for the main clinical array. We also examined 30 people without cardiovascular and renal pathology, mean age of 53.1±0.3 years, who entered the control group. The statistical analysis between the main group, the comparison group, and the control group indicated the absence of significant differences ($p>0.05$) in the mean age of patients and the percentage of men and women, which evidenced the age and sexual homogeneity of the study participants.

A comprehensive clinical-instrumental and laboratory examination of all patients included: 1) general clinical and anthropometric examination and blood pressure measuring; 2) ECG in 12 standard leads 3) daily blood pressure monitoring (DBPM); 3) HM ECG; 4) Echocardiography in M-, B-, and D-modes; 5) ultrasound of carotid arteries; 6) biochemical examination: fasting glucose level, serum lipids levels, uric acid level; 7) assessment of the functional state of the kidneys (presence and level of microalbuminuria, serum electrolyte, cystatin C, and creatinine level followed by GFR calculation).

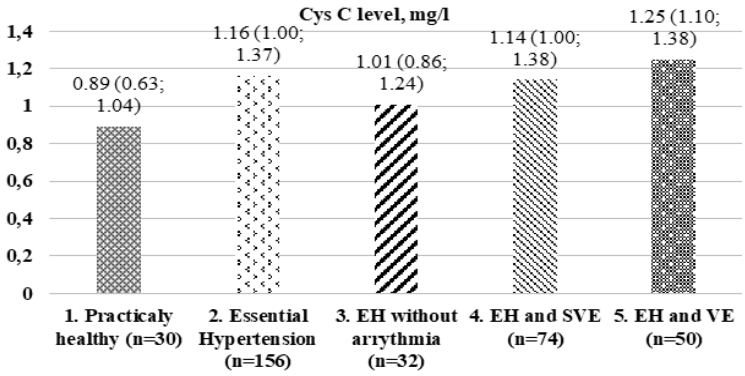

Fig. 1. Cystatin C level (mg/l) in different clinical groups. Note: The significances of intergroup differences by Kruskal-Wallis ANOVA test & Median test are shown in the table

Statistical processing was performed using the software "Statistica" v.12.0 (StatSoft). The results are presented as the mean (M) and the mean error (m) for the quantitative values, as the median and the limit of the interquartile interval with the indication of 25 and 75 percentiles, and as percentages (%) for the relative values. A comparison of relative values (%) was performed using the criterion χ^2, values in independent samples – by Mann-Whitney and Kruskal-Wallis [5, 6].

Groups	1	2	3	4	5
1		<0.0001	0.04	0.0005	<0.0001
2	<0.0001		0.01	ns	ns
3	0.04	0.01		0.02	0.001
4	0.0005	ns	0.02		0.04
5	<0.0001	ns	0.001	0.04	

Results of the study and their discussion. The mean serum Cys C levels were established in the general sample, in patients of different clinical groups, and in healthy normotensive persons. In EH II patients, the average Cys C level was 1.16 (1.00; 1.37) mg/l, which was 23.3 % ($p<0.0001$) higher than the corresponding level in healthy persons. During more detailed analysis, it was found that the average Cys C level in patients with EH without arrhythmias was lower than in patients with EH and extrasystole. Among patients with arrhythmias, the highest level of Cys C was recorded in patients with frequent VE, which was significantly different from the corresponding Cys C level in patients with SVE (1.25 (1.10; 1.38) mg/l vs

1.14 (1.00; 1.38) mg/l, p=0.04), patients without arrhythmias (1.25 (1.10; 1.38) mg/l vs 1,01 (0.86; 1.24) mg/ml, p=0.001) and healthy persons (1.25 (1.10; 1.38) mg/l vs 0.89 (0.63; 1.04) mg/l respectively, p<0.0001) (fig. 1).

Three categories of patients were allocated according to the level of cystatin C: 1 – with relatively low (RL) level (value is less or equal to the 25 % quartile value); 2 – with intermediate level, and 3 – with relatively high (RH) level (value is greater or equal to the 75 % quartile value of Cys C in patients with EH (n=156)). Thus, in the RL group, the level of Cys C was ≤1.00, and in the RH group – ≥1.37 mg/l. For group 3, with an intermediate value, the limits were, respectively, within the range of 1.00-1.37 mg/l. Accordingly, the RL group includes 40, the intermediate group – 76, and the RH group – 40 patients, respectively.

After analysis of DBPM data depending on the level of Cys C, it can be argued that the average values of systolic and pulse blood pressure at night (SBP_n) and PBP_n) were significantly higher in patients with RH level of Cys C, which was significantly different from the corresponding values of Cys C in the RL group (148 (136; 159) vs 140 (127; 152) and vs 139 (129; 150) mm Hg, respectively, p<0.03; 70 (59; 76) vs 60 (54; 72) and vs 59 (50; 62) mm Hg, respectively, p<0.02). The speed of early morning systolic and diastolic blood pressure rises or morning surge (MS_SBP and MS_DBP) was also the highest in patients with RH Cys C levels, which was significantly different from patients with intermediate and RL Cys C levels (94 (58; 130) vs 82 (44; 108) and vs 81 (41; 99) mm Hg, respectively, p<0.04; 66 (51; 90) vs 51 (41; 79) and vs 48 (31; 79) mm Hg, respectively, p<0.04). The average diurnal index by diastolic blood pressure (DI_DBP) in patients with RH Cys C level was 14 %, which was significantly higher than in patients with RL level (9 %, p=0.04). The variability of systolic and diastolic blood pressure at night (Var SBP_n and Var DBP_n) in patients with Cys C levels reached critical values of 17 and 14 mm Hg., which was significantly higher than in patients with RL Cys C level (17 (10; 20) vs 11 (8; 15) mm Hg, p=0.03 and 14 (9; 17) vs 9 (7; 12) mm Hg, respectively, p=0.02) (Table 1).

Table 1

Differences of DBPM parameters depending on Cyc C levels in patients with EH

DBPM indices	Cys C level, mg/l			P
	1. RL (n=40)	2.Intermediate (n=76)	3.RH (n=40)	
SBP, mm Hg	149 (139; 166)	148 (140; 160)	150 (139; 165)	ns
DBP, mm Hg	86 (78; 95)	86 (79; 95)	89 (78; 95)	ns
SBP_d, mm Hg	149 (140; 171)	150 (141; 164)	152 (142; 169)	ns
DBP_d, mm Hg	89 (77; 98)	91 (80; 98)	91 (79; 100)	ns
SBP_n, mm Hg	139 (129; 150)	140 (127; 152)	148 (136; 159)	**P1-3=0.03 P2-3=0.02**
DBP_n, mm Hg	80 (71; 85)	80 (72; 89)	78 (73; 86)	ns
PBP_d, mm Hg	59 (56; 73)	60 (54; 74)	60 (53; 69)	ns
PBP_n, mm Hg	59 (50; 62)	60 (54; 72)	70 (59; 76)	**P1-3=0.02 P2-3=0.009**
MS SBP, mm Hg/hour	81 (41; 99)	82 (44; 108)	94 (58; 130)	**P1-3=0.04 P2-3=0.01**
MS DBP, mm Hg/hour	48 (31; 79)	51 (41; 79)	66 (51; 90)	**P1-3=0.04 P2-3=0.03**
DI SBP, %	9 (4; 11)	9 (6; 12)	9 (2; 11)	ns
DI DBP, %	9 (4; 13)	11 (6; 14)	14 (7; 16)	**P1-3=0.04**
Var SBP_d, mm Hg	20 (15; 22)	18 (14; 21)	18 (16; 25)	ns
Var DBP_d, mm Hg	15 (11; 20)	15 (11; 19)	15 (12; 19)	ns
Var SBP_n, mm Hg	11 (8; 15)	14 (9; 17)	17 (10; 20)	**P1-3=0.03** *P2-3=0.06*
Var DBP_n, mm Hg	9 (7; 12)	11 (7; 16)	14 (9; 17)	**P1-3=0.02**

Note. The significance of intergroup differences calculated by the Kruskal-Wallis ANOVA test & Median test

Differences in percentages of patients with the “night-peaker” DBPM pattern were established in patients with RH and intermediate cystatin C levels, namely, 22.5 % vs 7.9 % (p=0.03), respectively. In addition, differences in the frequency of such daily patterns as “dipper”, “non-dipper”, and “night-peaker” were found among patients with different cystatin C levels. In the group of RH Cys C patients, a reduced number of patients with normal night pattern (“dipper”) was observed, which was significantly different from patients with intermediate and RL Cys C patients (30.0 % vs 38.2 % and 57.5 % respectively, p<0.04). 44.7 % of patients with intermediate Cys C level had insufficient night BP decrease (“non-

dipper"), which was statistically different from patients with RL Cys C level (25.0 %, p=0.04). The highest percentage of patients with night hypertension ("night-peaker") was observed in patients with RH Cys C level, which was significantly different from patients with intermediate level (12.5 % vs 2.6 %, p=0.03) (Table 2).

Table 2

The values of DBPM parameters depending on the level of Cys C in patients with EH

Daily BP pattern	Cys C level, mg/l			P
	1. RL (n=40)	2.Intermediate (n=76)	3.RH (n=40)	
SBP daily pattern				
Dipper, n (%)	15 (37.5 %)	29 (38.2 %)	14 (35.0 %)	ns
Non-dipper, n (%)	18 (45.0 %)	39 (51.3 %)	15 (37.5 %)	ns
Night-peaker, n (%)	5 (12.5 %)	6 (7.9 %)	9 (22.5 %)	**P2-3=0.03**
Over-dipper, n (%)	2 (5.0 %)	2 (2.6 %)	2 (5.0 %)	ns
DBP daily pattern				
Dipper, n (%)	23 (57.5 %)	29 (38.2 %)	12 (30.0 %)	**P1-2=0.04 P1-3=0.01**
Non-dipper, n (%)	10 (25.0 %)	34 (44.7 %)	17 (42.5 %)	**P1-2=0.04**
Night-peaker, n (%)	3 (7.5 %)	2 (2.6 %)	5 (12.5 %)	**P2-3=0.03**
Over-dipper, n (%)	4 (10.0 %)	11 (14.5 %)	6 (15.0 %)	ns

Note: The intergroup difference is calculated by the χ^2 criterion.

The close relationship between the cardiovascular system and the kidneys is well known. The relationship between kidney dysfunction and the cardiovascular system is multifaceted and built on a feedback loop. In this context, the kidney can act as a target organ and take an active part in the formation of systemic metabolic and vascular pathological processes [6, 7]. In a series of large population studies, it is shown that even an initial decrease in kidney function, when the level of creatinine in the blood serum is within the normal range or slightly elevated, is accompanied by a dramatically increase in cardiovascular morbidity and mortality [1, 4, 9]. Several studies confirmed that the deterioration of the functional state of the kidneys in patients with hypertension is associated with the worsening of the cardiovascular prognosis [11, 12]. Such data prompted researchers to identify and study in detail earlier markers of renal dysfunction, such as microalbuminuria and cystatin C.

Based on the result of our study we established that in patients with EH II, the average level of Cys C was significantly higher compared to healthy individuals (p<0.0001). Moreover, in patients with EH II and extrasystole, the level of Cys C was significantly higher (p<0.02) than in patients with EH II without arrhythmias. The highest level of cystatin C was noted in patients with EH and ventricular extrasystole, which was significantly different from the corresponding level of cystatin C in patients with supraventricular extrasystole (p<0.05), patients without arrhythmias (p<0.001) and healthy individuals (p< 0.001). At the same time, a relatively high level of cystatin C (≥ 1.37 mg/l) was associated with higher values of blood pressure and other DBPM parameters as well as with higher frequency of the night-peaker profile in SBP and DBP, which suggests the existence of common pathophysiological mechanisms between an increase of cystatin C, blood pressure values and the presence of frequent extrasystoles (especially of the ventricular origin). Our data confirms the opinion of some scientists that cystatin C should be attributed not only to markers of renal dysfunction, but also to markers of inflammation and assessment of the state of the cardiovascular system [13, 14, 15].

Conclusions

1. The mean level of cystatin C in patients with EH was significantly higher compared to the control group (p<0.0001). In the presence of extrasystole, the mean Cys C level was much higher than in patients without heart rhythm disorders (p<0.02). The highest level of Cys C was recorded in patients with EH and VE, which was significantly different from the corresponding Cys C level in patients with SVE (p=0.04), patients without arrhythmias (p=0.001) or healthy persons (p<0.0001).

2. The relatively high level of cystatin C (≥1.37 mg/l) was determined in 40 patients with EH (26 %) and was associated with higher values of SBP_n, PBP_n, MS_SBP, MS_DBP, DI_DBP, Var SBP_n, Var DBP_n, greater frequency of "night-peaker" pattern by SBP and DBP.

3. The intermediate level of cystatin C (1.00-1.37 mg/l) was recorded in 76 patients (49 %) and was associated with a higher frequency of the "non-dipper" daily BP pattern.

4. The relatively low level of cystatin C (≤1.00 mg/ml) was revealed in 40 patients (26 %) and was associated with a higher frequency of BP "dipper" daily pattern.

Continuation of further research in this direction will make it possible to improve knowledge of the pathogenesis of the development and progression of cardiovascular diseases and their connection with the development of kidney damage, and will allow improving the methods of diagnosis, treatment and prognosis of such a difficult category of patients.

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