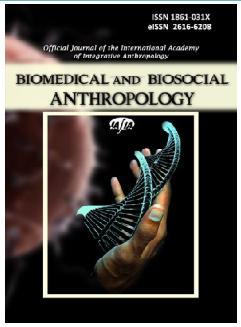
DOI: 10.31393/bba41-2020-02 Biomedical and Biosocial Anthropology, №41, Pages 11-17

ISSN 1861-031X eISSN 2616-6208

BIOMEDICAL AND BIOSOCIAL ANTHROPOLOGY

Official Journal of the International Academy of Integrative Anthropology

journal homepage: http://bba-journal.com



Comparative assessment of renal function by cystatin C level in patients with hypertension and extrasystole

Ivankova A. V., Kuzminova N. V., Lozinsky S. E., Ivanov V. P.
National Pirogov Memorial Medical University, Vinnytsia, Ukraine

ARTICLE INFO
Received: 26 October 2020
Accepted: 25 November 2020

UDC: 616.12-008.318.4:616.61-008.64

CORRESPONDING AUTHOR
e-mail: kuzminova5517@gmail.com
Kuzminova N. V.

Although the tight connection of the cardiovascular system and the kidneys is well known, using of cystatin C (Cys-C) opens new horizons in studying early renal failure stages. The study aimed to compare the functional status of the kidneys in patients with hypertension and extrasystole to the level of Cys-C. 156 patients with stage II hypertension (EH II) were examined. 124 of them had frequent symptomatic extrasystoles (74 - of supraventricular origin and 50 - ventricular), 32 patients had no arrhythmias, and were referred to the comparison group. The control group consisted of 30 healthy people with normal blood pressure (BP). All patients underwent a complete clinical examination, blood pressure measurement, daily blood pressure monitoring, daily electrocardiogram monitoring, echocardiography, and determination of renal function (creatinine, blood electrolytes, serum cystatin C) followed by calculation of glomerular filtration rate (GFR). The level of Cys-C in patients with hypertension was significantly higher ($p<0.001$) compared with healthy individuals. Among patients with arrhythmias, the highest level of Cys-C was noted in patients with ventricular arrhythmias. The correlation analysis showed that the level of Cys-C was higher in the presence of frequent extrasystoles (namely of ventricular origin), smoking, high blood pressure, increased systolic and pulse blood pressure, the presence of concentric left ventricular hypertrophy, dyslipidemia, increased creatinine level and decreased GFR. All three EH II patient groups had significantly lower GFR (calculated by creatinine level) ($p<0.001$). The lowest creatinine-based GFR was revealed in patients with ventricular extrasystole. All patients with EH II had significantly lower Cys-C based GFR than the control group ($p<0.001$). Mean Cys-C-based GFR values in patients with extrasystole were significantly lower than in patients without extrasystole ($p<0.03$). The analysis of GFR levels depending on the extrasystole origin was provided. The lowest level of GFR was recorded in patients with ventricular extrasystole. It was significantly different from the patients with supraventricular extrasystole ($p=0.02$). Our findings confirm the opinion of other researchers that Cys-C is an early marker of renal dysfunction in patients with hypertension, which is more sensitive than creatinine. Another finding is that ventricular extrasystole is more hemodynamically and metabolically unfavorable compared to supraventricular based on clinical and prognostic evaluation.

Keywords: *cystatin C, creatinine, glomerular filtration rate, essential hypertension, supraventricular extrasystole, ventricular extrasystole.*

Introduction

It is currently unknown how various forms of cardiac arrhythmias, including extrasystoles, affect the state of renal function in patients with essential hypertension. However, there is a lot of evidence that risk factors such as obesity, metabolic syndrome, hypertension, burden of cardiovascular history, type 2 diabetes, as well as the activation of inflammation, oxidative stress, and the renin-angiotensin-aldosterone mechanism are common for atrial fibrillation and renal dysfunction [4, 17, 20, 24]. A large number of studies aimed at studying the relationship between atrial fibrillation and renal dysfunction proved that not only renal dysfunction is a predictor of arrhythmias, but also the presence of arrhythmia is associated with an increased likelihood of further GFR decrease and increase of albuminuria due to deterioration of systemic and intrarenal hemodynamics. However, our knowledge about

early markers of renal dysfunction in patients with EH and concomitant extrasystole is incomplete and requires further specification [1, 2, 18, 22, 23].

The estimation of GFR is common in clinical practice for the assessment of the functional status of the kidneys, but its reduction occurs only when the number of functioning nephrons decreases, so it cannot serve as an early marker of kidney damage. This is a prerequisite for searching for more sensitive diagnostic methods [10, 14, 19].

Cys-C is the earliest and most informative marker of renal dysfunction, according to the KDIGO 2012 guidelines [21]. Cys-C is a basic peptide consisting of 122 amino acid residues with a molecular weight of about 13 kDa. It is an important extracellular inhibitor of cysteine proteases, which belong to the second type of cystatin superfamily. The active and mature form of Cys-C in humans is called the Cys-C monomer and consists of a single non-glycosylated polypeptide chain, the individual links of which are interconnected by disulfide bridges. The Cys-C monomer is present in almost all body fluids, but the largest amount is found in cerebrospinal fluid, milk, and semen. The level of this peptide can also be determined in urine and saliva [3, 7, 25].

Cys-C is freely filtered through the glomerular membrane due to its low molecular weight. Due to this, the level of Cys-C is relatively stable in the systemic circulation. It is a more sensitive marker of GFR reduction than creatinine because it could not be affected by factors such as age, gender, muscle mass, diet, physical activity, and race. It serves as an effective marker for early detection of renal failure, even at normal creatinine levels [16, 23].

The study aimed to compare the functional state of the kidneys in patients with hypertension and extrasystole based on the level of Cys-C.

Materials and methods

The study involved 156 patients with essential hypertension stage II (EH II). 124 of them (aged 27 to 75 years) had frequent symptomatic extrasystoles and formed the main clinical array of the study. 32 patients with EH II, but without cardiac arrhythmias (aged 32 to 72 years) were the comparison group. Among patients of the main array, 50 (40.3 %) were males and 74 (59.6 %) - females. The comparison group included 15 (46.9 %) men and 17 (53.1 %) women. Aside from that, 30 relatively healthy, normal people were assigned to the control group, which included 16 (53.3 %) men and 14 (46.7 %) women. The statistical analysis between the main group, comparison and control groups showed no significant differences ($p>0.05$) by age and sex, which indicated their age and sex homogeneity.

74 (59.7 %) of 124 patients with EH II and concomitant frequent extrasystoles had supraventricular (SVE) and 50 (40.3 %) had ventricular extrasystoles. Their arrhythmic history ranged from 1 to 27 years and averaged 8.062 ± 0.421 years.

Before participating in the study, all patients signed an informed consent form in accordance with the Declaration of Helsinki and the International Code of Medical Ethics.

All patients were examined in a complete, comprehensive clinical, laboratory, and instrumental examination, including the assessment of renal function, aiming to establish the underlying diagnosis and comorbidities before they entered the study.

Those who agreed to participate in the study were examined using the following methods: 1) general clinical and anthropometric examination, measurement of blood pressure (BP); 2) ECG with12 leads, daily ECG monitoring, daily blood pressure monitoring, echocardiography; 3) assessment of the functional state of the kidneys. The general clinical examination included the analysis of medical history, the establishment of the main and concomitant diagnosis, and the assessment of the inclusion-exclusion criteria. Then, patients were referred to the appropriate group.

Blood pressure was measured according to the recommendations of the Ukrainian Society of Cardiology (2013) using a sphygmomanometer (Microlife, Switzerland).

Electrocardiography in 12 leads was performed according to the standard method on an ECG device "UKARD" (Hungary).

Daily blood pressure monitoring (DBPM) and Holter ECG monitoring (HM ECG) were performed using the equipment "DiaCard" (JSC "Solvaig", Ukraine) according to the standard protocol.

Assessment of the structural and functional state of the heart was performed using an echocardiograph "My Lab 25" (Italy) in one- and two-dimensional modes with color, pulse and continuous-wave Doppler.

Assessment of the functional state of the kidneys was performed using the following tests: 1) the level of blood electrolytes (potassium and sodium) in mmol/l was determined by an ion-selective method using an electrolyte analyzer Easystat (USA); 2) blood creatinine level in μmol/l using the kinetically modified Jaffa method on a Cobas 6000 analyzer (with 501 modules) using the Roche Diagnostics test system (Switzerland). It should be noted that the study included only patients with a creatinine level which exceeded the reference values - 62-115 μmol/l in men and 53-97 μmol/l in women); 3) the serum level of Cys-C (ng/ml) was determined by an enzyme-linked immunosorbent assay using the "Human Cystatin C" set (BioVendor, Czech Republic, Lot: E18-091P01); 4) the glomerular filtration rate in ml/min /1.73 m^2 was calculated according to CKD-EPI formulas using online calculators: https://boris.bikbov.ru/2013/07/21/kalkulyator-skf-rascheta-skorosti-klubochkovoy- filtratsii (for creatinine) and https://medlabdiag.ru/calculators/clearance_cys (for Cys-C).

Statistical processing of the study results was performed using the software "Statistica" v. 12.0 (StatSoft) according to the recommendations for processing medical and biological research. The results were presented as a

value of median and quartile with an indication of 25 and 75 percentile, and as a percent (%) - for relative values. Comparison of relative values (%) was performed using the criterion χ^2. Absolute values were compared by the Kruskal-Wallis ANOVA test & the Median test. Spearman's rank correlation analysis was used to determine the relationship between certain parameters [11].

Results

The method of variation statistics was used to determine the variation of serum Cys-C level in the general sample, in patients of different clinical groups and in practically healthy normotensive individuals (Fig. 1). In patients with EH, the level of Cys-C was significantly higher ($p<0.001$) compared with healthy individuals. The average value of Cys-C in all patients with EH was 1.162 (1.003; 1.371) mg/l, which was 23.3 % ($p<0.001$) higher than the corresponding level in healthy people. In a more detailed analysis, it was found that the average levels of Cys-C in patients with EH without arrhythmias were lower than in patients with EH and extrasystole. Among the patients with arrhythmias, the highest level of Cys-C was recorded in patients with frequent VE, which was significantly different from the corresponding level of Cys-C in patients with SVE (1.254 (1.101; 1.384) mg/l vs. 1.143 (1.000; 1.384) mg/l, $p<0.05$), patients without arrhythmias (1.254 (1.101; 1.384) mg/l vs. 1.011 (0.857; 1.237) mg/ml, $p<0.001$) and healthy individuals (1.254 (1.101; 1.384) mg/l vs. 0.892 (0.631; 1.043) mg/l, respectively, $p<0.001$).

The significance of intergroup differences in the level of Cys-C serum calculated by Kruskal-Wallis ANOVA test & Median test is shown in table 1.

In addition, we performed a Spearman Rank Order Correlation between Cys-C levels and various clinical, instrumental, and laboratory parameters (Table 2).

The results of Spearman's rank correlation analysis showed (see Table 2) that the serum Cys-C level demonstrated significant direct correlations with the

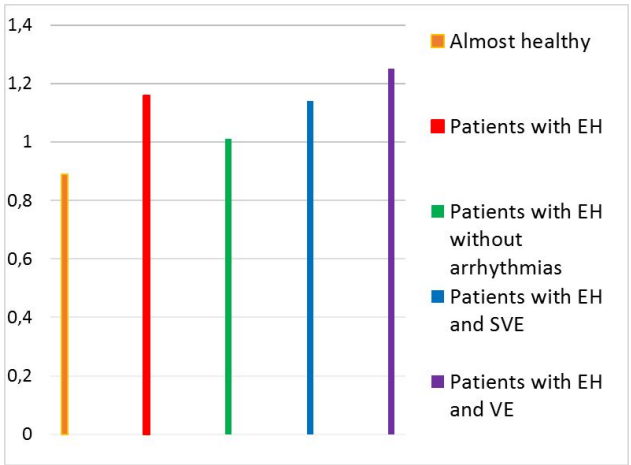


Fig. 1. Serum Cys-C level (in mg/l) in different clinical groups of patients.

Table 1. Differences in serum Cys-C levels between different clinical groups of patients.

Groups	1	2	3	4	5
1		<0.001	<0.05	<0.001	<0.001
2	<0.001		<0.01	>0.05	>0.05
3	<0.05	<0.01		<0.05	<0.001
4	<0.001	>0.05	<0.05		<0.05
5	<0.001	>0.05	<0.001	<0.05	

Notes: 1 - healthy individuals (n=30); 2 - all patients with EH (n=156); 3 - patients with EH without arrhythmia (n=32); 4 - patients with EH with SVE (n=74); 5 - patients with EH with VE (n=50).

Table 2. Significant associative correlations of Cys-C level with various clinical-instrumental and laboratory parameters (Spearman's rank order correlations).

Clinical, instrumental and laboratory parameters	Spearmen R	p-value
Presence of frequent extrasystole, points (1 - yes, 0 - no)	0.288	0.0003
Presence of frequent VE, points (1 - yes, 0 - no)	0.381	0.0001
Sex (1 - male, 0 - female)	-0.229	0.0041
High grade (III) EH, points (1 - yes, 0 - no)	0.312	0.0001
Smoking (1 - yes, 0 - no)	0.264	0.0009
SBPn, mm Hg (by ABPM data)	0.242	0.0221
PBP, mm Hg (by ABPM data)	0.344	0.0001
SBP ERV, mm Hg (by ABPM data)	0.266	0.0100
LVMI, g/m^2 (by EchoCG)	0.307	0.0007
RWT (by EchoCG)	0.284	0.0012
Concentric LV hypertrophy by Ganau, points (1 - yes, 0 - no) (by EchoCG)	0.299	0.0013
Number of VE (by ECG HM)	0.425	0.0001
Presence of paired VE, (1 - yes, 0 - no) (by ECG HM)	0.511	0.0001
Number of paired VE (by ECG HM)	0.402	0.0001
LDL-C, mmol/l	0.271	0.0003
AR, units	0.174	0.0222
Creatinine, mcmol/l	0.627	0.0001
GFR by CKD-EPI, ml/min/1.73 m^2	0.632	0.0001

Notes: VE - ventricular extrasystole, EH - essential hypertension, SBPn - mean night systolic blood pressure, PBPn - mean night pulse blood pressure, SBP ERV - Systolic blood pressure early rise velocity, LVMI - left venricular mass index, RWT - relative wall thickness, EchoCG - echocardiography, ECG HM - ECG Holter monitoring, LDL-C - low density lipoprotein cholesterol, AR - atherogenic ratio, GFR - glomerular filtration rate.

presence of frequent extrasystoles, regardless of their origin (r=0.29), with the presence of a ventricular extrasystole (r=0.38), high (III) degree of EH (r=0.31), smoking (r=0.26), mean night SBP and PBP (r=0.24 and r=0.34), rate of early rise of SBP (r=0.27), LVMI (r=0.31), relative myocardial wall thickness (r=0.28), presence of concentric LV hypertrophy (r=0.30), total number of VE

Table 3. Functional status of the kidneys in patients with hypertension and different origin of extrasystole (median (25.0th percentl; 75.0th percentl), or n (%)).

Functional parameters of kidneys	Patients without extrasystole	Patients with EH and SVE	Patients with EH and VE	p
	Group 1 (n=32)	Group 2 (n=74)	Group 3 (n=50)	
Creatinine, mcmol/l	74.24 (58.37; 97.13)	85.02 (78.34; 92.11)*	89.33 (82.01; 94.07)*	$p_{1-2}>0.05$ $p_{1-3}>0.05$ $p_{2-3}>0.05$
Potassium, mmol/l	4.333 (4.09; 4.52)	4.209 (4.001; 4.333)	4.175 (4.022; 4.300)	$p_{1-2}>0.05$ $p_{1-3}>0.05$ $p_{2-3}>0.05$
Natrium, mmol/l	139.2 (138.1; 141.4)	142.3 (138.3; 145.4)	141.1 (139.0; 145.3)	**$p_{1-2}<0.05$** **$p_{1-3}<0.05$** $p_{2-3}>0.05$
(K/Na)*100	3.091 (2.864; 3.262)	2.922 (2.802; 3.083)*	2.922 (2.831; 3.052)*	**$p_{1-2}<0.05$** **$p_{1-3}<0.05$** $p_{2-3}>0.05$
GFR by CKD-EPI, ml/min/1.73 m^2	64.02 (42.17; 87.08)***	53.25 (46.34; 67.09)***	50.12 (44.24; 60.05)***	$p_{1-2}>0.05$ **$p_{1-3}<0.05$** $p_{2-3}>0.05$
GFR < 90 ml/min/1.73 m^2	26 (81.3 %)	72 (97.3 %)	49 (98.0 %)	**$p_{1-2}<0.01$** **$p_{1-3}<0.01$** $p_{2-3}>0.05$
GFR < 60 ml/min/1.73 m^2	13 (40.6 %)	47 (63.5 %)	37 (74.0 %)	**$p_{1-2}<0.05$** **$p_{1-3}<0.01$** $p_{2-3}>0.05$
GFR < 45 ml/min/1.73 m^2	9 (28.1 %)	15 (20.3 %)	15 (30.0 %)	$p_{1-2}>0.05$ $p_{1-3}>0.05$ $p_{2-3}>0.05$
Cys-C, mg/l	1.011 (0.857; 1.237)*	1.143 (1.000; 1.384)**	1.254 (1.101; 1.384)***	**$p_{1-2}<0.05$** **$p_{1-3}<0.001$** **$p_{2-3}<0.05$**
GFR by Cys-C, ml/min/1.73 m^2	74.12 (55.01; 94.21)***	63.11 (51.07; 74.23)***	54.17 (48.05; 65.22)***	**$p_{1-2}<0.05$** **$p_{1-3}<0.01$** **$p_{2-3}<0.05$**
GFR < 90 ml/min/1.73 m^2	23 (71.9 %)	68 (91.9 %)	48 (96.0 %)	**$p_{1-2}<0,01$** **$p_{1-3}<0.01$** $p_{2-3}>0.05$
GFR < 60 ml/min/1.73 m^2	10 (31.3 %)	31 (41.9 %)	32 (64.0 %)	$p_{1-2}>0.05$ **$p_{1-3}<0.01$** **$p_{2-3}<0.05$**
GFR < 45 ml/min/1.73 m^2	2 (6.3 %)	11 (14.9 %)	8 (16.0 %)	$p_{1-2}>0.05$ $p_{1-3}>0.05$ $p_{2-3}>0.05$

Notes: intergroup significance of absolute differences calculated by Kruskal-Wallis ANOVA test & Median test and percentages - by criterion χ^2; GFR - glomerular filtration rate; signs *, ** or *** indicate the significance of the difference compared with the control group (n = 30), at levels of <0.05, <0.01 and <0.001, respectively.

(r=0.43), the presence of paired VE (r=0.51), total number of paired VE (r=0.40), LDL cholesterol (r=0.27), atherogenic rate (r=0.17), creatinine (r=0.63) and glomerular filtration rate by CKD-EPI (r=0.63). At the same time, a significant inverse correlation was found between the level of Cys-C and the male sex (r= -0.23).

To assess the functional state of the kidneys, we determined the level of cystatin C and calculated GFR by the level of Cys-C (adapted formula CKD-EPI) in addition to routine determination of electrolytes, creatinine and calculation of GFR by the formula CKD-EPI (online calculator), (Table 3) [5, 13].

Analysis of the data showed that the average creatinine level in patients with extrasystole did not exceed the reference values and differed significantly only compared with healthy individuals (85.02 μmol/l in patients with SVE and 89.33 μmol/l in patients with VE versus 70.08 μmol/l, p<0.05). Patients with extrasystole had higher sodium levels than patients without extrasystole (142.3 mmol/l in patients with SVE and 141.1 mmol/l in patients with VE versus 139.2 mmol/l, p<0.05). The level of sodium in patients of the control group was 140.4 mmol/l, and had no significant difference

compared with patients in the clinical array and the comparison group. The rate (K/Na)*100 in patients with extrasystole was significantly lower than in patients without arrhythmia (2.922 vs. 3.091 p<0.05) and practically healthy individuals (2.922 vs. 3.082, p<0.05). GFR (creatinine-based) in all 3 groups of patients with EH was significantly lower than in healthy individuals (64.02 ml/min/1.73 m^2 in patients without extrasystole, 53.25 ml/min/1.73 m^2 in patients with SVE and 50.12 ml/min/1.73 m^2 in patients with SE against 91.12 ml/min/1.73 m^2, respectively, p<0.001). The lowest GFR (calculated by creatinine) was revealed in patients with VE. It differed significantly from patients without extrasystoles (50.12 vs. 64.02 ml/min/1.73 m^2, p<0.05). The distribution of patients by GFR showed that 98.0 % of patients with VE and 97.3 % of patients with SVE had a GFR of less than 90 ml/min/1.73 m^2, which was significantly different from patients without arrhythmias (81.3 %; p<0.01). The level of GFR of less than 60 ml/min/1.73 m^2 was found in 74.0 % of patients with VE and in 63.5 % of patients with SVE. It was statistically different from patients without extrasystole (40.6 %, p<0.05). The level of GFR of less than 45 ml/min /1.73 m2 was determined in 28.1 % of patients in the comparison group, in 20.3 % of patients with EH and SVE, and in 30.0 % of patients with EH and VE. There were no statistically significant differences between groups. The mean level of Cys-C in patients with frequent extrasystoles was significantly higher compared with patients without arrhythmias (p<0.05) and healthy individuals (p<0.01) (see Fig. 1). At the same time, the highest level of Cys-C was noted in patients with a VE, which was significantly different from patients with SVE (1.254 vs. 1.143 mg/l, p<0.05) and patients without extrasystole (1,011 mg/l, p<0.001). It was noted that the average values of GFR calculated by Cys-C were higher than the corresponding values of GFR calculated by creatinine. GFR by Cys-C in all patients with EH was significantly lower than in the control group (74.12 ml/min/1.73 m^2 in patients without extrasystole, 63.11 ml/min/1.73 m^2 in patients with SVE and 54.17 ml/min/1.73 m^2 in patients with VE against 94.08 ml/min/1.73 m^2, respectively, p<0.001). Mean GFR values calculated by Cys-C in patients with extrasystole were significantly lower than in patients without extrasystole (54.17 ml/min/1.73 m^2 in patients with VE and 63.11 ml/min/1.73 m^2 in patients with SVE versus 74.12 ml/min/1.73 m^2, p<0.05). Analysis of GFR levels depending on the place of extrasystole's origin showed the lowest GFR level in patients with VE. It differed significantly from patients with SVE (54.17 vs. 63.11 ml/min/1.73 m^2, p <0.05). GFR of less than 90 ml/min/1.73 m^2 was met in 96.0 % of patients with VE and in 91.9 % of those with SVE, while in the comparison group it was significantly rarer (71.9 %; p<0.01). The highest percentage of patients with GFR of less than 60 ml/min/1.73 m^2 was found in patients with frequent VE, and it differed significantly from patients with SVE and without arrhythmias (64.0 % vs. 41.9 % and vs. 31.3 %, p<0.05). A GFR of less than 45 ml/min/1.73 m2 was met in 6.3 % of patients in the comparison group, in 14.9 % of patients with SVE, and in 16.0 % of patients with VE. The differences between them were non-significant (see Table 3).

Discussion

The tight connection between the cardiovascular system and the kidneys is well known. Their relationships are multifaceted and work as a kind of feedback. In this context, the kidney can play a role of target organ, but also take an active part in the formation of systemic metabolic and vascular pathological processes. Dysfunction of any link leads to activation of the renin-angiotensin-aldosterone system and sympathetic hyperactivation, the development of endothelial dysfunction and chronic systemic inflammation. Thus, a complex pathogenic cycle is closed, leading to the progression of heart and kidney dysfunction, remodeling of the myocardium and vascular wall, increased morbidity and mortality. This pathophysiological mechanism in modern medicine is called the cardiorenal continuum [7, 8, 9].

In this context, GFR plays an important role. Its reduction should be considered as an independent risk factor for the progression of cardiovascular pathology and cardiovascular mortality [2, 12]. A series of large population-based studies have shown that even an initial decrease in renal function with serum creatinine levels within normal limits or slightly elevated, is accompanied by a tremendous increase in cardiovascular morbidity and mortality [13, 14, 16]. A lot of studies have confirmed that the deterioration of the functional state of the kidneys in patients with hypertension is associated with a poor cardiovascular prognosis [15, 21, 22, 23]. Such conclusions prompted researchers to identify and study in detail early markers of renal dysfunction, in particular Cys-C.

We determined and compared the average level of Cys-C in patients with stage II EH without cardiac arrhythmias, in patients with EH and frequent extrasystoles, taking into account their supraventricular or ventricular origin. We did a detailed analysis of the relationship between serum Cys-C levels and different clinical and instrumental and laboratory parameters in this cohort of patients, as well as a comparative assessment of the functional status of the kidneys based on Cys-C and creatinine serum levels. The average level of Cys-C in patients with EH II was significantly higher than in healthy individuals (p<0.001). Mean Cys-C levels in patients with EH and extrasystoles were higher than in patients with EH but without arrhythmias (p<0.05). The level of Cys-C was the highest in patients with frequent VE among all patients with arrhythmias. It was significantly different from the corresponding level of Cys-C in patients with SVE (p<0.05), patients without arrhythmias (p<0.001), and healthy people (p<0.001). EH and extrasystole (especially the ventricular) are known contributors to heart remodeling and dysfunction. It is known that heart remodeling is accompanied by certain inflammatory changes (apoptosis, atrial fibrosis, disorders of calcium transfer and regulation of connexin, etc.) [2, 4, 6].

Cys-C is frequently referred to as an inflammatory marker because it is produced during inflammation by cells containing the nucleus [2, 6], which may explain why the level of this peptide is higher in patients with hypertension and extrasystole.

Spriman's correlation analysis revealed an association between Cys-C levels and the following parameters: the presence of frequent extrasystoles (in particular VE and paired VE), frequency of VE per 1 hour, the total number of paired VE, smoking, high grade of blood pressure, elevated means of night SBP and PBP, early SBP rise, LVMI, RWT, presence of LV concentric hypertrophy, increased LDL and atherogenic ratio, increased creatinine and decreased GFR. It suggests the existence of common pathophysiological mechanisms between increasing levels of Cys-C, known risk factors, and cardiovascular diseases. Our data confirms the point of view that Cys-C is currently the "gold standard" and prognostic marker that determines kidney function [3, 19, 21] and simultaneously serves as an additional indicator of cardiovascular risk.

The average creatinine level in patients with EH and extrasystole was significantly higher when compared to healthy individuals. The presence of frequent extrasystoles in patients with stage II EH was associated with an increased cystatin C and serum sodium level, a decrease in the K/Na ratio, and a decrease in the GFR determined by Cys-C. In addition, all patients were ranged depending on the meaning of GFR, because a number of meta-analyses have identified a critical level of GFR associated with the increase in cardiovascular risk and overall mortality, which is approximately equal to 75 ml/min/1.73 m^2 [3, 12, 13, 15, 16]. In addition, all patients were ranged depending on the meaning of GFR, taking into account that some meta-analyses identified a critical level of GFR approximately equal to 75 ml/min/1.73 m^2, which was associated with an increase in cardiovascular risk and overall mortality [3, 12, 13, 15, 16]. In patients with stage II EH, the presence of a VE was associated with the highest level of Cys-C, a decrease in GFR (both creatinine and cystatin-C based), and an increase in the number of patients with Cys-C based GFR of less than 60 ml/min/1.73 m^2. The mean GFR values calculated by Cys-C were higher than the corresponding values of GFR calculated by creatinine. It is known that Cys-C today is used as a more accurate and sensitive marker of renal dysfunction than creatinine [12, 15].

Our study suggests that patients with stage II EH had a decrease in GFR compared with healthy individuals. In turn, the lowest GFR (both creatinine and Cys-C based) was found in patients with stage II EH and frequent VE. Some authors have described more severe hemodynamic and metabolic disorders in the case of ventricular extrasystole. It might be a suitable explanation of our results, but it needs further study. [1, 4, 20].

In the future, it is advisable to provide a deeper investigation of the Cys-C properties in patients with hypertension and various comorbid conditions, and other cardiovascular diseases. The implementation of diagnostic methods based on this marker requires re-equipment of laboratories, training of laboratory personnel and physicians to calculate Cys-C-based GFR, but it may improve the diagnosis and stratification of cardiovascular risk in our country.

Conclusions

1. The level of Cys-C was significantly higher in patients with EH, compared to the control ($p<0.001$), while in the presence of extrasystole, the mean level of Cys-C was significantly higher than in patients without extrasystoles ($p<0.05$). The highest level of Cys-C was found in patients with EH and VE. It differed significantly from the corresponding level of Cys-C in patients with SVE ($p<0.05$), patients without arrhythmias ($p<0.001$), and healthy persons ($p<0.001$).

2. Spearman's correlation analysis revealed a direct relationship between Cys-C levels and frequent extrasystole, in particular of ventricular origin (presence of frequent VE, frequency of VE per 1 h, presence of paired VE, and the total number of paired VE per day), known cardiovascular risk factors, such as smoking and a high degree of hypertension, some indicators of DBPM (mean night SBP, PBP, early SBP rise), concentric LV hypertrophy, LVMI and RWT, metabolic risk factors (LDL cholesterol, AR) and indicators of renal function (creatinine and GFR). These results prove the ability to use Cys-C as a prognostic marker of renal dysfunction and increased cardiovascular risk in patients with hypertension.

3. In patients with stage II EH, the presence of frequent extrasystoles is associated with an increase in Cys-C, sodium, decreased potassium to sodium ratio, decreased renal filtration function, as determined by Cys-C-based GFR, and an increase in the number of patients with GFR of less than 90 (for creatinine and Cys-C-based) and less than 60 ml/min/1.73 m^2 (for creatinine-based). In patients with stage II EH, the presence of VE is associated with the highest level of Cys-C, a decrease in GFR (both creatinine- and Cys-C-based) and an increase in the number of patients with Cys-C-based GFR of less than 60 ml/min/1.73 m^2.

4. In patients with stage II EH there is a decrease in GFR, compared with healthy individuals. The lowest GFR (both creatinine- and Cys-C-based) was reported in patients with stage II EH and frequent VE. It allows to consider extrasystole of the ventricular origin as more hemodynamically and metabolically unfavorable than supraventricular and to use it as an important clinical marker of metabolic disorders.

References

[1] Arnlov, J., Ingelsson, E., Sundstrom, J., & Lind, L. (2010). Impact of body mass index and the metabolic syndrome on the risk of cardiovascular disease and death in middle-aged men. *Circulation,* 121(2), 230-236. doi: 10.1161/CIRCULATIONAHA.109.887521

[2] Bansal, N., Zelnick, L. R., Alonso, A., Benjamin, E. J., de Boer, I.

H., Deo, R., ... & Heckbert, S. R. (2017). eGFR and Albuminuria in relation to risk of Incident Atrial Fibrillation: A Meta-Analysis of the Jackson Heart Study, the Multi-Ethnic Study of Atherosclerosis, and the Cardiovascular Health Study. *Clin. J. Am. Soc. Nephrol,* 12(9), 1386-1398. doi: 10.2215/CJN.01860217

[3] Dangle, P. P., Ayyash, O., Kang, A., Bates, C., Fox, J., Stephany, H., & Cannon Jr, G. (2017). Cystatin C-calculated glomerular filtration rate - a marker of early renal dysfunction in patients with neuropathic bladder. *Urology,* (100), 213-217. doi: 10.1016/j.urology.2016.08.011

[4] Hoogendijk, M. G., Geczy, T., Yap, S., & Szili-Torok, T. (2020). Pathophysiological mechanism of premature ventricular complexes. *Front Physiol*, (11), 406. doi: 10.3389/fphys.2020.00406

[5] Inker, L. A., Eckfeldt, J., Levey, A. S., Leiendecker-Foster, C., Rynders, G., & Manzi, J. (2011). Expressing the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) cystatin C equations for estimating GFR with standardized serum cystatin C values. Am. J. Kidney. *Dis. Off J. Natl. Kidney Found,* 58(4), 682-684. doi: 10.1053/j.ajkd.2011.05.019

[6] Jin, L. L., You, L., & Xie, R. Q. (2018). Value of cystatin C in predicting atrial fibrillation recurrence after radiofrequency catheter ablation. *Journal of geriatric cardiology: JEH*, 15(12), 725-731. doi: 10.11909/j.issn.1671-5411.2018.12.008

[7] Kayukov, I. G., Smirnov, A. V., & Emanuel, V. L. (2012). Цистатин С в современной медицине [Cystatin C in modern medicine]. *Нефрология - Nephrology,* 16(1), 22-39.

[8] Kharchenko, E. P. (2015). Сердечная недостаточность при кардиоренальных синдромах [Heart failure in cardiorenal syndromes]. *Терапевтический архив - Therapeutic archive*, (1), 85-91.

[9] Kurjata, A. V., & Cherkasova, A. V. (2015). *Артериальная гипертензия при хронической болезни почек [Arterial hypertension in chronic kidney disease].* ДМА МОЗ України - DMA of the Ministry of Health of Ukraine.

[10] Kuzminova, N. V., Ivankova, A. V., Ivanov, V. P., & Lozinsky, S. E. (2017). Diagnostic and prognostic value of cystatin C as an early marker of renal dysfunction in patiens with cardiovascular pathology. *Medical business,* (7-8), 17-23. doi: 0.31640/JVD.7-8.2018(3)

[11] Kuzminova, N. V., Ivankova, A. V., & Lozinsky, S. E. (2019). State of kidney function and features of metabolic status changes in patients with different forms of extrasystols. *World of medicine and biology,* 3(69), 83-89. doi: 10.26724/2079-8334-2019-3-69-83-89

[12] Lashkul, D. A. (2014). Структурно-функціональні зміни серця у хворих на хронічну серцеву недостатність ішемічного генезу, що асоційована з нирковою дисфункцією [Structural and functional changes of the heart in patients with chronic heart failure of ischemic origin associated with renal dysfunction]. *Запорожский медицинский журнал - Zaporozhye medical journal*, 2(83), 18-21.

[13] Levey, A. S., Stevens, L. A., Schmid, C. H., Zhang, Y. L., Castro, A. F., Feldman, H. I., … & Coresh, J. C. K. D. (2009). CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann. Intern. Med.* 150(9), 604-612. doi: 10.7326/0003-4819-150-9-200905050-00006

[14] Li, X., Lin, H., Wang, S., Guan, L., & Wang, Y. (2016). Association of microalbuminuria with metabolic syndrome among aged population. *BioMed Research International*, (6), 226-233. doi: 10.1155/2016/92412788

[15] Pottel, H., Delanaye, P., Schaeffner, E., Dubourg, L., Eriksen, B. O., Melsom, T., ... & Ebert, N. (2017) Estimating glomerular filtration rate for the full age spectrum from serum creatinine and cystatin C. *Nephrol. Dial. Transplant,* 32(3), 497-507. doi: 10.1093/ndt/gfw425

[16] Ronco, C., McCullough, P., Anker, S. D., Anand, I., Aspromonte, N., Bagshaw, S. M., ... & Acute Dialysis Quality Initiative (ADQI) consensus group. (2010). Cardio-renal syndromes: report from the consensus conference of the acute dialysis quality initiative. *European heart journal,* 31(6), 703-711. doi: 10.1093/eurheartj/ehp507

[17] Sirenko, U. M. (2018). Рекомендації ESC та ESH з лікування артеріальної гіпертензії [ESC and ESH recommendations for the treatment of hypertension]. *Артеріальна гіпертензія - Hypertension,* 5(61), 258.

[18] Sivolap, V. D., & Lashkul, D. A. (2015). Маркери фіброзу міокарда та функція нирок у хворих на хронічну серцеву недостатність ішемічного ґенезу з фібриляцією передсердь [Markers of myocardial fibrosis and renal function in patients with chronic heart failure of ischemic origin with atrial fibrillation]. *Український медичний часопис - Ukrainian medical journal,* 3(107), 77-79.

[19] Sherief, L. M., Youssef, D. M., Sherbiny, H. S., Abdelkhalek, E., Talaat, M., & Khalifa, N. A. (2017). Screening of renal dysfunction among Burkitt lymphoma survivors by novel markers. *Hematology,* 22(5), 265-273. doi: 10.1080/10245332.2016.1259713

[20] Skibchyk, V. A., Bablyak, S. D., & Matvienko, Yu. O. (2019). Артеріальна гіпертензія і фібриляція передсердь: небезпечна "дружба", яку не можна ігнорувати [Hypertension and atrial fibrillation: a dangerous "friendship" that cannot be ignored]. *Артеріальна гіпертензія - Hypertension*, 3-4(65-66), 103-109. doi: 10.22141/2224-1485.3-4.64-65.2019.177851

[21] Stevens, P. E., & Levin, A. (2013). Kidney Disease: Improving global Outcomes (KDIGO) CKD Work group. KDIGO 2012 Clinical Practice guideline for the for the Evaluation and Management of Chronic Kidney Disease. *Ann. Intern. Med.* 158(11), 825-830. doi: 10.7326/0003-4819-158-11-201306040-00007

[22] Unger, T., Borghi, C., Charchar, F., Khan, N. A., Poulter, N. R., Prabhakaran, D., ... & Schutte, A. E. (2020). 2020 International Society of Hypertension global hypertension practice guidelines. *Hypertension,* 75(6), 1334-1357. doi: 10.1161/HYPERTENSIONAHA.120.15026

[23] Voronenko, Yu. V., Shekera, O. G., & Ivanov, D. D. (2015). Актуальні питання нефрології в практиці сімейного лікаря [Current issues of nephrology in the practice of family medicine]. *Сімейна медицина - Family medicine*, (7), 64-87.

[24] Watanabe, H., Watanabe, T., Sasaki, S., Nagai, K., Roden, D. M., & Aizawa, Y. (2009). Close bidirectional relationship between chronic kidney disease and atrial fibrillation: the Niigata preventive medicine study. *American heart journal,* 158(4), 629-636. doi: 10.1016/j.ahj.2009.06.031

[25] Zhu, Z., Zhong, C., Xu, T., Wang, A., Peng, Y., Xu, T., ... & He, J. (2018). Prognostic significance of serum cystatin C in acute ischemic stroke patients according to lipid component levels. *Atherosclerosis,* (274), 146-151. doi: 10.1016/j.atherosclerosis.2018.05.015