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Are there any clinical associations with homocysteine and glycine plasma levels in patients with atrial fibrillation?

Czy istnieją jakieś kliniczne zależności między stężeniami homocysteiny i glicyny u pacjentów z migotaniem przedsionków?

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She is the author or co-author of 22 publications in national and international journals, including *Family Medicine & Primary Care Review* (Yatskevich K., Snezhitskiy V., Kurbat M., Stepuro T. The relationship between –C344/T aldosterone synthase (CYP11B2) gene polymorphism, enzyme activity level and increased risk of nonvalvular atrial fibrillation. *Fam. Med. Prim. Care Rev.* 2015; 17 (2): 136–139). She participated in many medical conferences of young scientists, including these held in Bialystok and Gdansk. Her main hobby is social activity. In 2013 she worked in television, hosting her own medical show called 'Doctor is listening to you!', where teaching physicians from the medical university were invited to discuss in the form of dialogue various medical problems, so the audience could ask questions. She would like to continue these activities in the future.

Abstract

Introduction. Atrial fibrillation (AF) is constantly associated with a complex of various factors that create a diversity of pathophysiological variants due to phenomenon of atrial remodelling. The aim of the study was to investigate clinical associations with plasma homocysteine (Hcy) and glycine (Gly) levels in patients with paroxysmal and persistent AF.

Materials and methods. The study included 94 patients with ischaemic heart disease and/or hypertension without significant structural myocardial damage — 48 subjects with paroxysmal AF (group 1) and 27 subjects with persistent AF (group 2). Control group consisted of 19 patients without history of AF. Echocardiography was performed to assess left atrium (LA) size and function. Plasma levels of Hcy and Gly were measured.

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Results. Patients with AF had significantly increased total plasma Hcy level. In group 2 there was a significant correlation between Hcy plasma level and LA-size. The Gly level > 349 μmol/L was found to be associated with a greater AF duration and was significantly more often in patients with AF existing for more than four years. Patients with Gly plasma level > 309 μmol/L and total Hcy plasma > 11.02 μmol/L showed significantly increased frequency of AF. Patients without AF showed Hcy plasma level < 11 μmol/L significantly more frequently (0% vs 29%) (p = 0.005).

Conclusion. There is an association between Hcy and Gly levels, atrial remodelling and the clinical course in patients with AF. It can be assumed that in a higher level of Hcy, increased Gly level may serve as a predictor of more pronounced structural and functional changes in the atria, but in such case it acts as a protective mechanism.

Key words: atrial fibrillation, homocysteine, glycine, fibrosis, left atrium, echocardiography, structural and functional remodelling

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Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, the incidence of which increases regularly with age [1].

Etiological and pathophysiological aspects of AF are complex and not fully understood. Currently, AF is considered as a result of complex various interconnected factors, such as electrophysiological, molecular, biological, genetic changes, the spectrum of which varies in each individual patient and creates a diversity of pathophysiological variants [2].

Two main theories of the AF pathogenesis — ectopic activity and focal "re-entry" mechanism, which require the presence of triggers and supporting substrate — has already been known, but even in their absence AF can exist. This occurs as a result of structural and electrical remodelling of the atria, which are characterized by the dilation and reduction of the effective refractory period. In addition, AF enhances the extracellular matrix proteins' expression and activation of atrial fibrosis [3].

Atrial conduction slowing result in electrical insulation of cardiomyocytes. Changes in the extracellular matrix are shown to be increase in the atria and to accumulate collagen in it, which leads to the development of fibrosis. These processes are defined as structural remodelling in AF [4].

However, a more detailed description, based on biochemical reactions that characterize the state of the connective tissue structures, also requires more investigations. It is known that collagen — the important exchange product of the connective tissue — is synthesized from proline (Pro) and lysine that undergo hydroxylation and are transformed into hydroxyproline (Hpro) and hydroxylysine. Therefore, Hpro can be considered as a marker of collagen formation. In the polypeptide strands, the small amino acid glycine (Gly) occurs at every third position, when Pro and Hpro account for 23% of the total residues.

Atrial fibrosis in AF is the result of a complex interaction not only of profibrotic signalling pathways. Activation of various matrix metalloproteinases (MMP) may also influence the collagen extracellular matrix disintegration [5]. Furthermore, it was shown that homocysteine (Hcy) may regulate MMP-2 and 9 activity [6], which can lead to structural and electrical remodelling.

The aim of our study was to search for clinical associations with homocysteine and Gly levels in patients with paroxysmal and persistent AF.

Materials and methods

Study population

Seventy-five patients admitted due to AF to the Arhythmology Department of the Grodno Regional Clinical Cardiology Centre (Belarus) have been observed.

These patients included 48 subjects with paroxysmal AF (group 1) and 27 subjects with persistent AF (group 2), without significant structural myocardial damage. Persistent AF was defined as AF which is sustained beyond seven days, or lasting less than seven days but necessitating pharmacological or electrical cardioversion. The study control group included 19 patients without history of AF. All participants had background history of ischaemic heart disease (IHD) and/or hypertension. Patients with thyroid dysfunction, acute stroke, acute myocardial infarction, acute myocarditis, known chronic heart failure (NYHA ≥ 2), diabetes, severe chronic diseases (e.g., severe renal or liver failure) or pregnancy were excluded from the study. Patients with diseases that lead to the Hcy metabolism disturbance and elevated levels of total plasma Hcy (B_{12}-deficiency anaemia, cancer and leukaemia, renal failure, systemic lupus erythematosus, rheumatoid arthritis) were also excluded, as well as patients taking vitamins B_6, B_{12}, folic acid and glycine drugs for less than 1 month prior to the study.

Routine laboratory and physical examinations were performed to eliminate cardiovascular diseases. All patients underwent instrumental and laboratory study after

signing an informed consent form that was approved by our institution's committee on human investigation. On the admission AF patients underwent pharmacological or direct current cardioversion. In all patients with persistent AF, cardioversion was performed with a transthoracic electrical shock of 200 to 360 J. No patient AF was terminated by radiofrequency catheter ablation. All patients were successfully cardioverted and remained in sinus rhythm at discharge. So, all study participants (in all groups) were in sinus rhythm during examination.

Laboratory methods

Plasma levels of total Hcy and Gly were measured after cardioversion by the method of high-performance liquid chromatography (HPLC Agilent 1100) with the use of Agilent ChemStation A10.01 software (HP, US) [7].

Echocardiography

Two-dimensional transthoracic echocardiography was performed using Philips IE-33 system (S5-1, 1–5 MHz, Philips, USA). The following parameters were obtained: left atrial (LA) systolic diameter, left ventricular (LV) end--systolic diameter, LV end-diastolic diameter, LV mass and LV mass index.

In additional to standard echocardiographic parameters, LA geometry and function were assessed by measurement of LA volume, LA volume index, LV stroke volume, LA ejection fraction using bi-plane area-length method as reported previously [8].

Statistical analysis

Normally distributed data are presented as mean ± standard deviation and non-normally distributed data are reported as median and interquartile range. For non--normal distribution of data, multiple comparisons among three groups were conducted by Kruskal-Wallis H test and differences between two groups were assessed by Mann--Whitney U test for post hoc analysis. Proportional data were compared with a chi square test. A one-way ANOVA test was used for assessing the statistical significance where appropriate. To identify the relationship between indicators of an abnormal distribution, the Spearman rank correlation coefficient (R) was used, and the Student's test for the normal distribution of the sign. For the assessment of significance of differences in the frequency of quality indicators the two-sided Fisher's exact test was used. General Classification Regression Tree Models analyse was used to determine how some indicators influence other variables, their hierarchy of influence, thereby defining its prognostic significance [9]. The differences were considered statistically significant when $p < 0.05$ (2-tailed). The analysis was performed using Statistica 6.0 software package (Statsoft, US).

Results

There were no significant differences in age, gender, renal function, history of coronary artery disease and hypertension between the study groups (Table 1), but there were significant differences in LA-parameters, that characterize its structure and function, in group 2 in comparison with other patient groups. It indicates more pronounced remodelling process in patients with persistent AF (Table 2).

Total plasma Hcy levels were significantly higher in patients with paroxysmal AF (9.42 (7.41–11.32) µmol and persistent AF 9.59 (7.27–12.4) µmol as compared to the control subjects (6.61 [5.8–8.82] µmol/L, $p = 0.005$ and $p = 0.001$, respectively) (Figure 1).

In the persistent AF group Hcy plasma concentration was positively correlated with LA systolic diameter ($R = 0.45$, $p = 0.03$) (Figure 2).

On the next step we used general regression tree model classification as a prediction model that can be represented as a decision tree. The Gly level > 349 µmol/L was found to be associated with a longer AF duration (Figure 3).

In order to analyse the relationship between Gly plasma level and AF duration, the all three patient groups (n = 94) were divided into two subgroups according to the Gly plasma levels (349 µmol/L). It was revealed that its level > 349 µmol/L was significantly more often in patients

Table 1. Characteristics of the studied patient groups

Patients' characteristics	Paroxysmal AF (n = 48)	Persistent AF (n = 27)	Controls (n = 19)	p value
Age, years	56 (50–64)	53 (46–61)	56 (49–61)	NS
Male gender, n [%]	37 (77)	22 (81)	12 (63)	NS
Hypertension, n [%]	39 (81)	22 (81)	17 (89)	NS
Coronary artery disease, n [%]	41 (85)	21 (78)	14 (74)	NS
eGFR [ml/min/1.73 m^2]	68 ± 13	66 ± 13	72 ± 18	NS

AF — atrial fibrillation; NS — no significant differences between there groups (by Kruskal-Wallis H test); eGFR — estimated glomerular filtration rate

Table 2. Echocardiographic parameters in studied patient groups

Parameters	Paroxysmal AF (n = 48)	Persistent AF (n = 27)	Control (n = 19)	p value
Left atrial parameters				
Systolic diameter [mm]	38 ± 3*	41 ± 4*#	36 ± 2	0.0015
Stroke volume [ml]	35 ± 10	30 ± 9	35 ± 10	NS
Diastolic volume [ml]	70 ± 16	78 ± 18*	61 ± 18	NS
Systolic volume [ml]	34 ± 14	47 ± 18*#	26 ± 9	0.0008
Systolic volume index [ml/m^2]	16 ± 6	24 ± 10*#	13 ± 4	0.0005
Diastolic volume index [ml/m^2]	34 ± 7	39 ± 10	31 ± 8	NS
Ejection fraction [%]	52 ± 11	37 ± 11*#	58 ± 7	0.0001
Left ventricular parameters				
Mass index [g/m^2]	118 ± 25	119 ± 22	105 ± 14	NS
End-diastolic volume [ml]	128 ± 20	131 ± 29	121 ± 26	NS
End-systolic volume [ml]	42 ± 10	52 ± 23*	37 ± 9	NS
Stroke volume [ml]	84 ± 14	79 ± 14	81 ± 17	NS
Ejection fraction [%]	66 ± 5	61 ± 8 *#	68 ± 5	0.0027

*Significant differences compared with control group; #significant differences compared with group 1; AF — atrial fibrillation; NS — no significant differences between there groups (by Kruskal-Wallis H test)

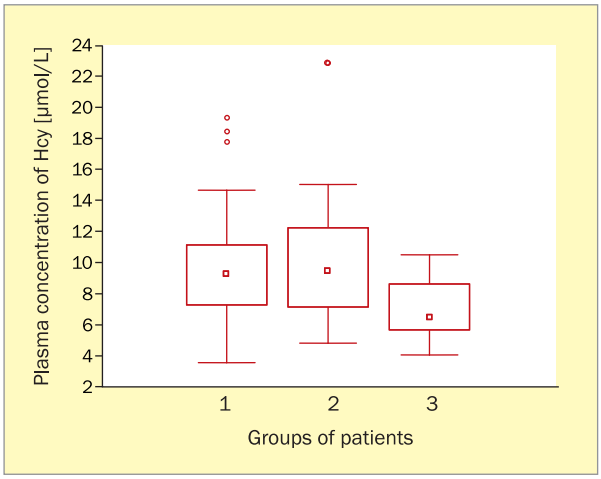

Figure 1. Plasma concentration of homocysteine (Hcy) in the studied patients

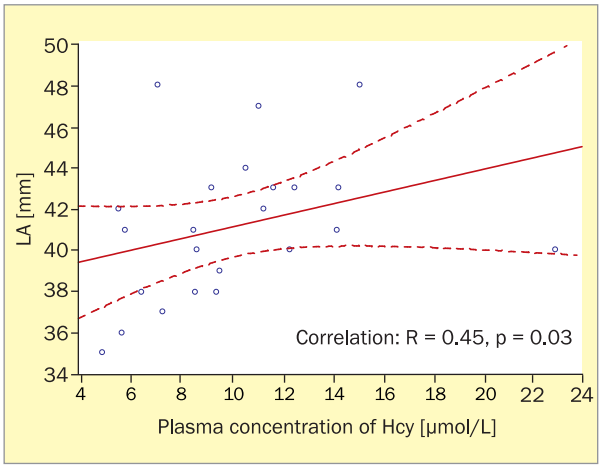

Figure 2. Correlation between homocysteine and left atrial (LA) systolic diameter in patients with persistent atrial fibrillation (group 2); Hcy — homocysteine

with AF existing for more than four years (46% vs 22%) (p = 0.05) (Table 3).

We have also found that the Gly plasma level > 309 µmol/L level when total Hcy plasma level was > 11.02 µmol/L is associated with a significant AF frequency increase (Figure 4).

All studied patient groups (n = 94) were divided into two subgroups according to Hcy plasma levels (11 µmol/L). In the subgroup of patients without AF, Hcy plasma level was < 11 µmol/L (0% vs 29%) (p = 0.005), whereas we observed different number of AF rhythm disorders per year when Hcy plasma concentration was > 11 µmol/L (Table 4).

Discussion

Unfortunately, regulatory roles of amino acids in metabolism have long been ignored. It was tactically assumed, without much evidence, that humans could synthesize sufficient amounts of all nonessential amino acids, and growing evidence from cell culture and animal studies

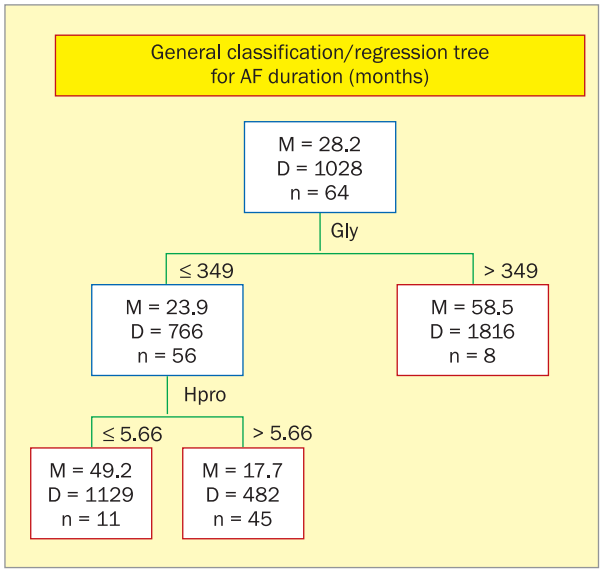

Figure 3. Classification of atrial fibrillation (AF) duration depending on the glycine (Gly) plasma level; M — mean value; D — a dispersion of the sample; Hpro — hydroxyproline

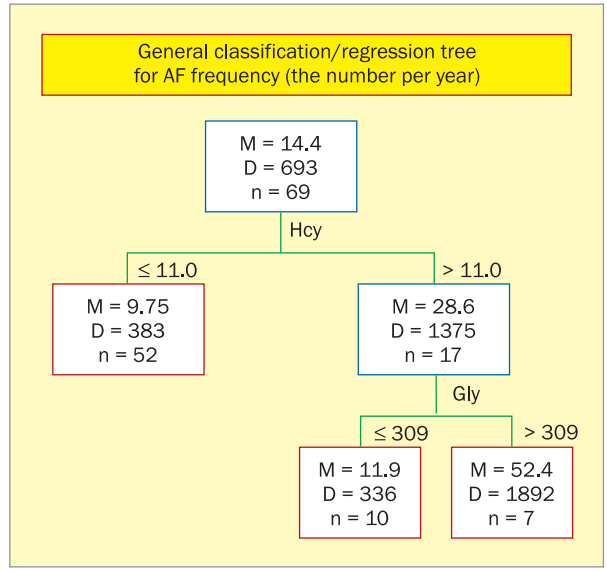

Figure 4. Atrial fibrillation (AF) frequency classification depending on homocysteine (Hcy) and glycine (Gly) plasma levels; M — mean value; D — a dispersion of the sample

Table 3. The relationship between glycine (Gly) plasma level and atrial fibrillation (AF) duration

AF duration	Gly < 349 µmol/L (n = 79)		Gly > 349 µmol/L (n = 15)		p value
	n	[%]	n	[%]	
No AF	16	20	3	20	NS
New-onset AF	18	23	2	13	NS
6 months–1 year	10	13	1	7	NS
Up to 4 years	18	23	2	13	NS
More than 4 years	17	22	7	46	0.05*

*Significant difference between two subgroups; NS — no significant differences between there groups (by Kruskal-Wallis H test)

Table 4. The relationship between homocysteine (Hcy) plasma level and atrial fibrillation (AF) frequency

AF frequency	Hcy < 11 µmol/L (n = 65)		Hcy > 11 µmol/L (n = 29)		p value
	n	[%]	n	[%]	
No AF	19	29	0	–	0,005*
New on-set AF	13	20	8	28	NS
Up to 2 per year	7	10	7	24	NS
3–9 per year	12	18	5	17	NS
More than 10 per year	14	21	9	31	NS

*Significant difference between two subgroups; NS — no significant differences between there groups (by Kruskal-Wallis H test); NS — nonsignificant

shows that some of the traditionally classified nonessential amino acids can play important roles in multiple signalling pathways, thereby regulating gene expression, intracellular protein turnover and oxidative defence [10]. There are many data indicating Hcy as an independent modifiable risk factor for cardiovascular disease [11, 12].

Data based on the Hcy receptor effects leads to the important conclusion: one of the leading factors in pathobiochemical mechanism of this amino acid action is a mitochondrial dysfunction that dysregulates the Ca^{2+} homeostasis.

Under HHcy, the percentage of contractile cells, the maximum speed rate, the maximum rate of relaxation and amplitude of Ca^{2+} transfer in the myocardium is significantly reduced [13].

Recently, it was demonstrated that Hcy was able to act as an antagonist of the N-methyl-D-aspartate (NMDA) receptors on its glutamate binding site. At the same time, Gly is the agonist of these receptors on the glycine binding site. Hcy can play role as an antagonist at glutamate binding site of NMDA-R and as a partial agonist on the Gly binding site. Rosenquist et al. [14] showed in their work that the NMDA receptor co-agonist Gly provided a highly significant level protection against Hcy-induced developmental abnormalities.

It has been shown that NMDA-receptors are widely represented in organs and various tissues including human heart [15]. Many studies highlight the role of these receptors in the development of cardiovascular pathology. In human myocardium they are concentrated in the nerve terminals, ganglia, conductive fibres, and cardiomyocytes including atrial myocytes [16]. It has been found that high levels of Hcy induce heart failure and arrhythmias by acting on NMDA-receptors [17, 18].

There are few studies that explored the relationship between increased Hcy level and remodelling in AF. So, mechanisms of fibrosis and myocardium remodelling are partially associated with the Hcy action on NMDA-receptors. Chronic Hcy activation of NMDA receptors induces cardiomyocytes hypertrophy and intramitochondrial nitroxide stress, which in turn increase the level of cytoplasmic Ca^{2+} and lead to increase in reactive oxygen species (ROS) production and apoptosis [17, 19]. As a result, mitochondrial MMP-9 increased activity as well as the disintegration and translocation of connexin-43 [16, 20] reduce the elastin/collagen ratio, increase interstitial collagen deposition between myocytes and endothelial cells and lead to fibrosis underlying arrhythmias manifestations [21].

The association between Hcy and Gly in the nervous tissue cells was shown earlier. It has been revealed that at Gly physiologic concentrations toxic Hcy levels to neurons lies in the millimolar range. However, when under pathological conditions the Gly level in the nervous system grows (stroke, head trauma), Hcy neurotoxicity can significantly exceed its neuroprotective activity as antagonist of this process. That is, the Hcy cyto- and neurotoxicity is the result of excessive NMDA receptor activation in hyperhomocysteinaemia (HHcy) [15]. It could explain why Hcy partially inhibits the NMDA-receptors on the glycine binding site and Gly can reduce these effects [22].

Conclusions

In our study we investigated the association between Hcy and Gly levels, atrial remodelling and the clinical course in patients with AF. It can be assumed that in a higher level of Hcy (> 11 µmol/L) Gly plasma level may serve as a predictor of more pronounced structural and functional changes in the atria, but in this case the effect of Gly level increasing is likely to be a protective mechanism of HHcy in paroxysmal and persistent AF. This fact may explain the relationship of elevated Gly levels to a greater AF duration and AF frequency. Although such conclusions would be expected from theoretical point of view, of course, further analyses are needed in this case.

Interest of our study is focused on the fact that in patients with paroxysmal and persistent AF with coronary artery disease and/or hypertension not only a significant Hcy level increase occurs, but the relationship of its level > 11 µmol/L to LA-size and AF rhythm disorders per year was also revealed.

In conclusion, AF is not a rare condition in either general population or patients with hypertension or IHD, and it is also associated with increased risk of morbidity and mortality. Therefore, new approaches of identification of atrial remodelling that increases the likelihood of AF, especially when it seems to be relatively stable, could contribute to its prevention, prognosis and treatment.

Conflict of interest(s)

The authors declare no conflict of interest.

Streszczenie

Wstęp. Migotanie przedsionków (AF) wiąże się z kompleksem różnych czynników, które tworzą wiele mechanizmów w wyniku zjawiska przebudowy przedsionków. Celem pracy było zbadanie klinicznych zależności między stężeniami homocysteiny (Hcy) i glicyny (Gly) we krwi pacjentów z napadowym i przetrwałym AF.

Materiały i metody. Zbadano 94 pacjentów ze współistniejącymi chorobą niedokrwienną serca i/lub nadciśnieniem tętniczym bez uszkodzenia mięśnia sercowego — 48 pacjentów z napadowym AF (grupa 1) i 27 chorych z utrwalonym AF (grupa 2). Za pomocą echokardiografii oceniano strukturalno-funkcjonalny stan lewego przedsionka. Mierzono także stężenia homocysteiny i glicyny w osoczu krwi.

Wyniki. U pacjentów z AF stężenie Hcy we krwi było znacznie wyższe. W grupie 2 zidentyfikowano znaczące korelacje między wartościami Hcy i Gly i parametrami echokardiograficznymi lewego przedsionka, charakteryzując jego strukturę i funkcję. Stężenie Gly ponad 349 μmol/l było skojarzone z dłuższym czasem występowania AF i znacznie częściej dotyczyło pacjentów z AF istniejącym od ponad 4 lat. Stężenie Gly przekraczające 309 μmol/l przy wartości Hcy ponad 11,02 μmol/l wiązało się ze wzrostem częstotliwości AF. U pacjentów bez AF wartość Hcy znamiennie częściej wynosiła poniżej 11 μmol/l (0% *v.* 29%) (p = 0,005).

Wnioski. Istnieje związek między stężeniami Hcy i Gly, przebudową przedsionka i przebiegiem klinicznym u pacjentów z AF. Można założyć, że wyższa wartość Hcy i zwiększenie stężenia Gly mogą być bardziej przydatne w przewidywaniu wyraźnych zmian strukturalnych i funkcjonalnych w przedsionku, jednak w takim przypadku służą jako mechanizm ochronny.

Słowa kluczowe: migotanie przedsionków, homocysteiny, glicyna, echokardiografia, lewy przedsionek, strukturalna i funkcjonalna przebudowa przedsionków

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