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Role of homocysteine in atrial remodelling in atrial fibrillation

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ABSTRACT

High homocysteine levels seen in atrial fibrillation (AF) could be partly due to background coronary artery disease (CAD). We aimed to compare homocysteine concentrations between patients with or without AF carefully matched for history of CAD. We also aimed to determine association of homocysteine levels with atrial remodelling and risk of AF recurrence in study population with predominantly cardiac ischemic background. Homocysteine levels in 70 patients with paroxysmal or persistent AF with history of CAD and/or arterial hypertension who had undergone successful cardioversion were compared to 18 age, gender and co-morbidity matched patients with no history of AF. Left atrial size was measured by echocardiography and AF recurrence was recorded within 12-month follow up. Plasma homocysteine levels were significantly higher in AF patients than controls (9.9 ± 3.7 vs. 7.3 ± 2.0 µmol, respectively, p = 0.005). On univariate linear regression homocysteine levels were not related to echocardiographic parameters. However, after adjustment for age, gender, body mass index and history of CAD higher homocysteine levels were associated with increased left atrial diameter. During 1-year follow AF recurrence occurred in 42 (60%) of patients. On univariate logistic regression homocysteine was not related to AF recurrence, but the association became significant after adjustment for age, gender, body mass index and history of coronary artery disease. In conclusion, homocysteine levels are increased in AF patients with predominantly ischemic background and they are independently related to left atrial dilatation. In this patient population moderately-to-severely homocysteine increases rather than very severe homocysteine elevation is independently associated with increased risk of AF recurrences.

Keywords: Atrial fibrillation, atrial remodelling, homocysteine, left atrium, recurrence.

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INTRODUCTION

Atrial fibrillation (AF) affects 1.5 to 2% of general population and represents a major cause of morbidity and a socioeconomic burden (Camm et al., 2012). Recurrent AF paroxysms in patients with paroxysmal and persistent AF are associated with significant healthcare costs related to repeated admissions for cardioversion and they significantly affect patient quality of life.

Unfavourable cardiac remodelling in AF predisposes to the progressive nature of the arrhythmia (Schotten et al., 2011). Persistent or recurrent AF has been shown to contribute to electrical and structural changes of atrial cardiomyocytes thus predisposing to the arrhythmia self-perpetuation and resistance to conversion into sinus rhythm (Rossi et al., 2002). Despite increasing amount of data on pathophysiology of the phenomenon the detailed understanding of this process is far from complete (Dobrev and Ravens, 2003).

Chronic atrial stretch and geometric deformation play major roles in activation of the signalling pathways leading to cellular hypertrophy and diffuse interstitial

fibrosis (Schotten et al., 2003). It has been shown that atrial fibrosis in the setting of AF is the result of complex interplay between profibrotic signalling pathways, inflammation and oxidative stress (Pellman et al., 2010).

Homocysteine is known to be implicated in inflammation, excessive oxidative response and activation of metalloproteinases in endocardial cells (Bescond et al., 1999; Moshal et al., 2006). High levels of homocysteine are associated with increased risk of coronary artery disease and cerebrovascular disease (Whincup et al., 1999; Marcucci et al., 2004). Elevated levels of homocysteine have been also associated with presence of non valvular AF (Marcucci et al., 2004). High homocysteine levels in AF are associated with left atrial dilatation and increased risk of ischemic complications (Naji et al., 2010). Homocysteine levels correlated with LA diameter, and levels of type-1 collagen degradation marker (Shimano et al., 2008). Homocysteine levels were significantly elevated in the group of patients who developed AF during follow up (Naji et al., 2010). Increased risk of cardiovascular events (but not AF recurrence) in subjected with higher homocysteine levels has been suggested in patients treated by radiofrequency catheter ablation for AF (Shimano et al., 2008).

Given established relationship between high homocysteine levels and increased risk for atherogenesis (which could result in higher homocysteine in AF per se) in this study we aimed to assess whether homocysteine concentrations are increased in AF patients compared to those without AF and carefully matched for history of ischemic heart disease. We also aimed to determine association of homocysteine levels with atrial remodelling and risk of AF recurrence in the study population with predominantly cardiac ischemic background.

MATERIALS AND METHODS

Study population

Seventy patients with paroxysmal or persistent AF and preserved left ventricular ejection fraction who had undergone successful cardioversion were recruited in the Arrhythmology Department of the Grodno Regional Clinical Cardiology Centre (Grodno, Belarus). All patients had background coronary artery disease and/or arterial hypertension. Direct current electrical cardioversion was used in 24 (34%) patients and pharmacological cardioversion in 46 (66%) patients during 2 to 3 days after hospitalization. The AF patients were compared to 18 age, gender and co-morbidity matched patients with no history of AF. Patients with thyroid dysfunction, acute stroke, myocardial infarction or myocarditis, history of chronic heart failure (NYHA ≥2), diabetes, significant chronic diseases (e.g., severe renal or liver failure) or pregnancy were excluded from the study. AF recurrence post cardioversion was assessed in all AF patients during 1-year follow up. The study was approved by Grodno State Medical University ethics committee and all participants provided written informed consent for participation in the study.

Laboratory methods

Plasma levels of total homocysteine were measured after cardioversion. Blood samples taken with heparin as anticoagulant were centrifuged for 15 min at 600 g and stored at -70°C for batched analysis. For determination of Gly and Hcy a high performance liquid chromatograph (HPLC Agilent 1200) was used. The separation was performed on the column Zorbax Eclipse Plus C_{18}, 2.1×150 mm, 3.5 mcm. Mobile phase: 0.05 M NaH_2PO_4, 8.5 mM CH_3COOH, 40 mg/L EDTA, 1.8% acetonitrile. Flow rate 0.2 ml/min, column temperature 25°C, detection by fluorescence (379/510 nm). Blood plasma aminothiols were reduced with Tris (2-carboxyethyl)phosphine (TCEP) followed by derivatization with 7 fluorobenzo-2-oxo-1,3-diazole-4-sulfonate, ammonium salt (SBD-F). N-acetyl cysteine (NAC) was applied as an internal standard. The registering of chromatograms and their quantitative processing were carried out using the Agilent ChemStation A10.01 (Hewlett Packard, US). This was done in accordance with manufacturer recommendations.

Echocardiography

Two-dimensional transthoracic echocardiography was performed after cardioversion to sinus rhythm using Philips IE-33 system and broadband phased array probe (S5-1, 1-5 MHz, Philips, USA). Left ventricular end-diastolic volume and ejection fraction and left atrial diameter as per current guidance (Lang et al. 2015).

Statistical analysis

Normally distributed data are presented as mean ± standard deviation and non-normally distributed data are reported as median interquartile range. Normal data were compared using t-test and non-normal data were compared using Mann-Whitney test. Categorical variables were compared using chi^2 test. Linear regression analysis was used to establish associations between homocysteine levels and echocardiographic parameters in AF patients. Logistic regression analysis was used to determine predictive value of homocysteine (assessed as quartiles) for AF recurrence. A p-value of <0.05 was considered statistically significant. IBM SPSS Statistics 21 (IBM Inc, USA) software was used for statistical analyses.

RESULTS

There was no significant difference in age, gender, renal function, history of coronary artery disease and hypertension and brain natriuretic peptide levels between the study groups (Table 1). The plasma homocysteine levels were significantly higher in AF patients than controls (9.9 ± 3.7 vs. 7.3 ± 2.0 μmol, respectively, $p = 0.005$) (Figure 1).

There was correlation between total plasma Hcy levels and LA diameter in AF patients ($R = 0.45$, $p < 0.05$) (Figure 2).

On univariate linear regression homocysteine levels were not related to echocardiographic parameters. However, after adjustment for age, gender, body mass index and history of coronary artery disease higher homocysteine levels were associated with increased left atrial diameter (Table 2).

During 1-year follow AF recurrence occurred in 42 (60%) of patients. On univariate logistic regression homocysteine was not related to AF recurrence, but the

Table 1. Characteristics of the study groups.

Parameter	Atrial fibrillation	Controls	p value
Age, years	55 ± 9.3	54 ± 8.4	0.69
Male, n (%)	55 (79%)	12 (67%)	0.35
Coronary artery disease, n (%)	58 (83%)	13 (72%)	0.33
Hypertension, n (%)	56 (80%)	16 (89%)	0.51
Heart failure symptoms, n (%)	13 (19%)	1 (6%)	0.28
Body mass index, kg/m^2	30 ± 3.9	29 ± 3.5	0.38
eGFR, ml/min/1.73m^2	68 ± 13	72 ± 18	0.52
Homocysteine, µmol/L	9.9 ± 3.7	7.3 ± 2.0	0.005
Beta blocker, n (%)	42 (60%)	18 (100%)	0.0005
Aspirin, n (%)	23 (33%)	17 (94%)	0.0000
Statins, n (%)	58 (83%)	14 (78%)	0.73
ACE inhibitors, n (%)	55 (79%)	16 (89%)	0.51
Nitrates, n (%)	26 (37%)	10 (56%)	0.19
Left atrium diameter, mm	39 ± 3.8	36 ± 2.5	0.004
Left ventricular end diastolic volume	128 ± 24	124 ± 26	0.47
Left ventricular ejection fraction, %	64 ± 6.9	68 ± 4.9	0.06
Left ventricular mass, g	249 ± 55	224 ± 65	0.06
Left ventricular mass index, g/m^2	118 ± 24	105 ± 14	0.09

ACE, angiotensin enzyme inhibitors; eGFR, estimated glomerular filtration rate.

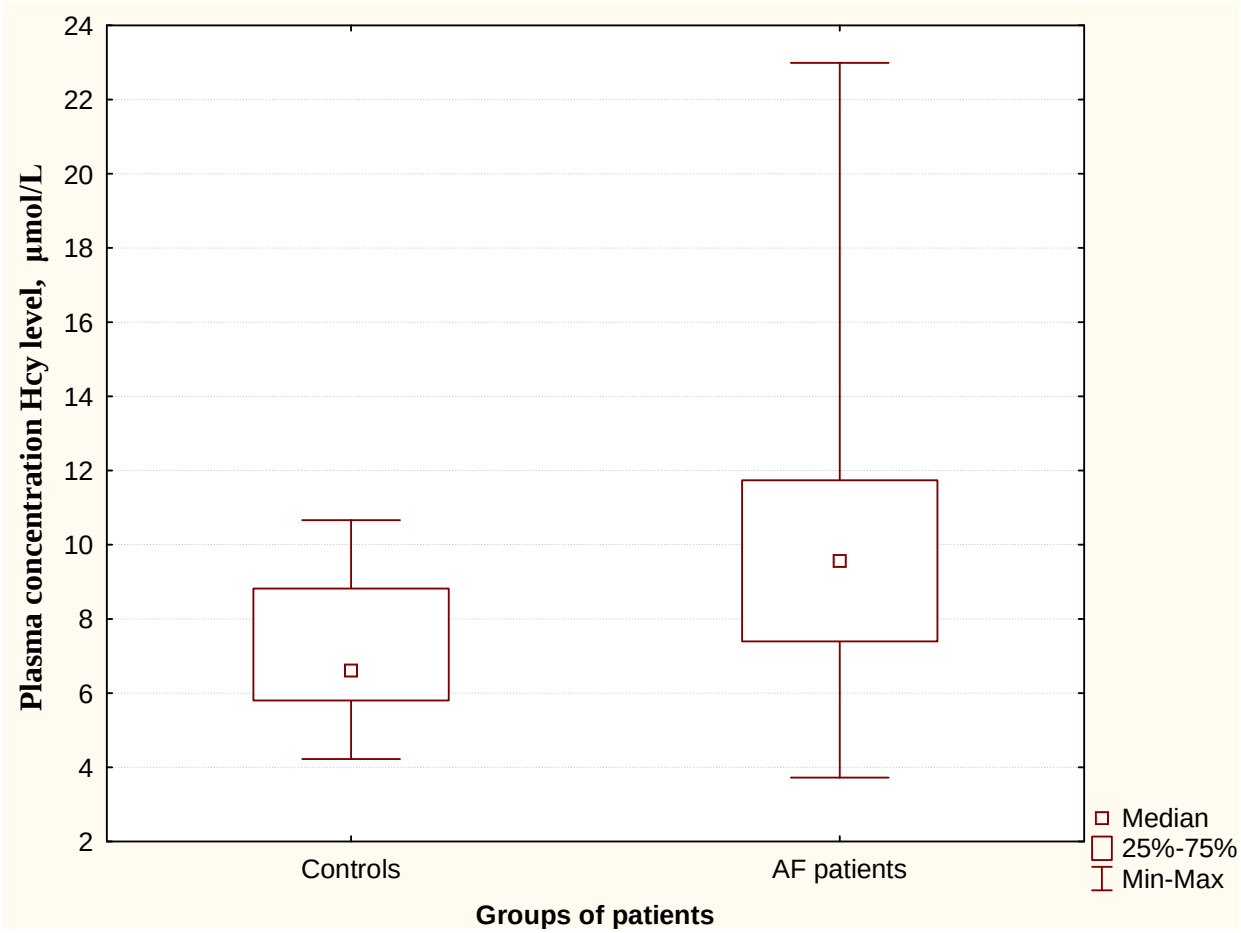

Figure 1. Plasma concentration Hcy level in the studied patients groups.

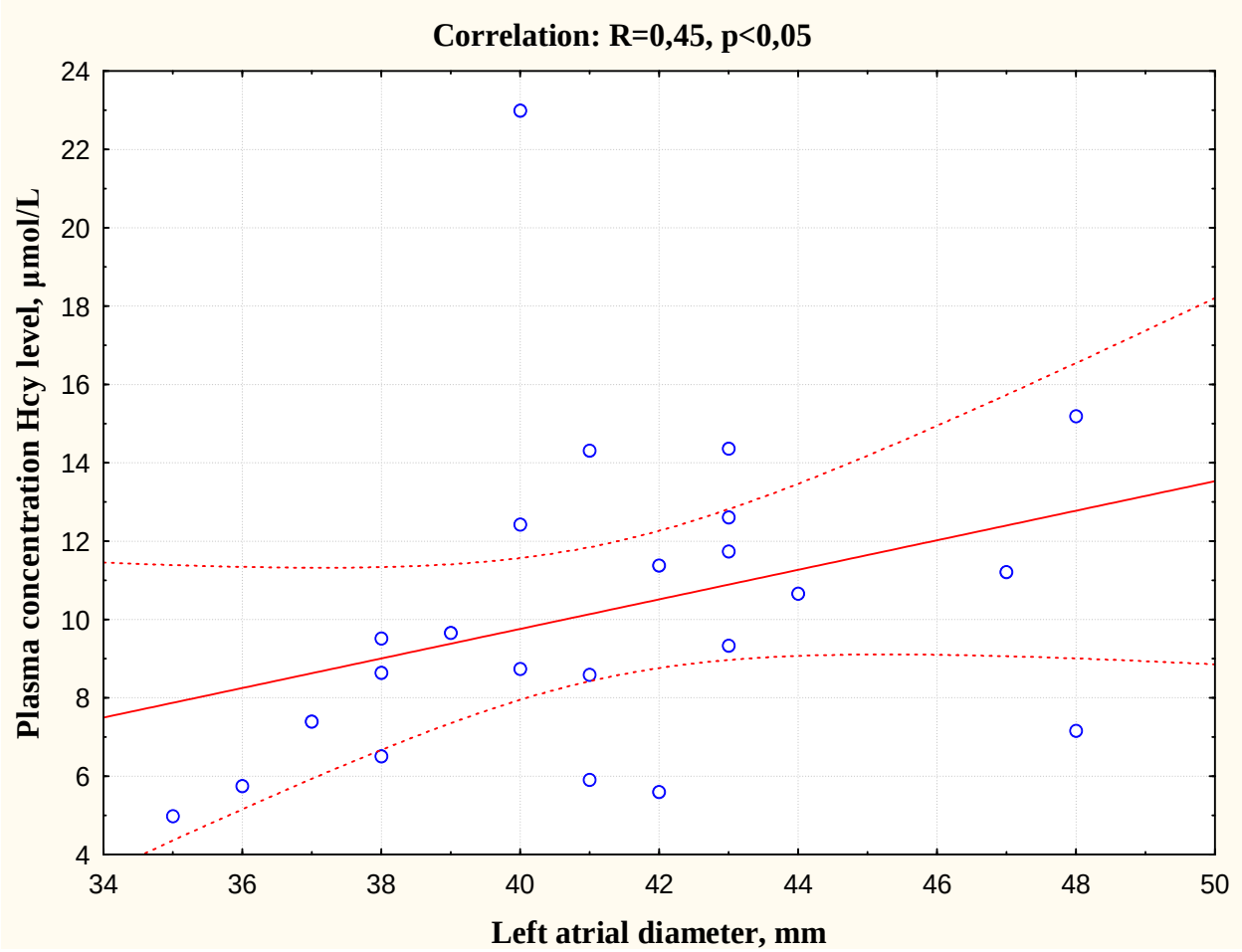

Figure 2. Correlation between total plasma Hcy levels and LA diameter in AF patients.

Table 2. Predictive value of homocysteine on regression analysis.

	Univariate analysis		Multivariable analysis*	
Linear regression: predictive value of homocysteine for echocardiographic parameters				
	β (B ± standard error)	p value	β (B ± standard error)	p value
Left atrial diameter	0.21 (0.22 ± 0.13)	0.095	0.26 (0.27 ± 0.13)	0.04
LV end-diastolic volume	-0.03 (-0.18 ± 0.81)	0.83	0.00 (0.00 ± 0.85)	1.00
LV ejection fraction	-0.06 (-0.12 ± 0.23)	0.61	-0.10 (-0.18 ± 0.24)	0.46
Logistic regression: predictive value of homocysteine quartiles for AF recurrence				
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Quartile 2 vs. 1	0.71 (0.19-2.69)	0.62	1.60 (0.28-9.29)	0.60
Quartile 3 vs. 1	3.11 (0.72-13.4)	0.13	8.29 (1.21-56.6)	0.03
Quartile 4 vs. 1	1.63 (0.41-6.46)	0.49	1.53 (0.31-7.66)	0.61

*Adjusted for age, gender, history of coronary artery disease and hypertension and body mass index; AF, atrial hypertension; B, regression coefficient; CI, confidence interval; LV, left ventricular.

association became significant after adjustment for age, gender, body mass index and history of coronary artery disease (Table 2).

DISCUSSION

The study shows for the first time that only moderately

high (that is, third quartile) but not the highest (that is, forth quartile) plasma homocysteine concentrations are associated with increased risk of AF recurrence in patients with paroxysmal/persistent AF, vast majority of whom had background coronary artery disease. These data contrast to previous study done in AF patients predominantly free from coronary artery disease (that is, in about 10% of patients only), where the top homocysteine quartile was linked to significantly increased AF recurrence, but no association was seen with atrial diameter. The discrepancy could be partly explained by difference in the study populations, particularly in view of recognised link between coronary artery disease and homocysteine (Whincup et al., 1999; Marcucci et al., 2004).

Nevertheless, based on available data it is not stipulated whether there is a causal relationship between elevated homocysteine levels and atrial remodelling. The association of higher Hcy levels with increased left atrial diameter, LV end-diastolic volume and LV ejection fraction in patients with AF in our work indicates that paroxysmal or persistent can be constantly associated with the phenomenon of atrial remodeling characterized by electrical and structural changes of cardiomyocytes that are in response for arrhythmia self-perpetuation and resistance to sinus rhythm conversion. Left atrial (LA) volume has been shown to be significantly associated with LV chamber remodeling, diastolic dysfunction, and the degree of mitral regurgitation in patients with dilated cardiomyopathy (Rossi et al., 2002). However, unlike the LV, the structural basis for atrial chamber remodeling process in HF has not been characterized. On the other hand, there exist both experimental and clinical evidence that AF itself is able to promote fibrosis (Burstein and Nattel, 2008).

The differences could also be related to the fact the Naji et al. (2010) compared patients with the top quartile homocysteine to all three other quartiles analysed together, thus not providing separate results for patients with moderately increased homocystein. Of note, our data on independent relationship between increased homocysteine and atrial dilatation agree with the report by Marcucci et al. (2004) thus extending the knowledge regarding AF patients with predominantly ischemic backgound.

Homocysteine is commonly related to coronary atherosclerosis, which could further predispose to AF, thus leading to higher homocysteine in patients with the arrhythmia. However, participants of this study were carefully matched for the presence of the background ischemia and other major cardiac or renal co-morbidity. The study indicates that high homocysteine can be directly involved in AF pathogenesis rather than via pathogenesis of AF risk factors (e.g., coronary artery disease).

Mechanisms linking higher (but not highest) homocysteine levels with AF recurrence and left atrial remodelling remain uncertain. They may involve role of homocysteine in oxidative stress and reduced nitric oxide bioavailability as it was shown in animal heart tissue (Burstein and Nattel, 2008). Also experimental data indicate that homocysteine may induce metalloproteinase activity in endocardial cells thus promoting atrial fibrosis (Bescond et al., 1999; Moshal et al., 2006). Also, homocysteine could cause electro-physiological disturbances of potassium currents in human atrial myocytes and predisposes to oxidative stress and reduced nitric oxide bioavailability in animal heart tissue (Suematsu et al., 2007; Cai et al., 2007). Moreover, it is well recognised that high levels of homocysteine promote development and progression of coronary artery disease and a possibility remains that homocysteine-related more advanced coronary artery disease could be partly responsible for the increased rate of AF relapses (Whincup et al., 1999; Marcucci et al., 2004). Indeed, increased homocysteine has been shown to be associated with ischemic events in patients with AF (Marcucci et al., 2004). Admittedly there are no firm data at present to prove direct causative relationship between homocysteine and AF. It is likely that interactions between homocysteine and atrial remodelling/AF recurrence are complex with more than one mechanism involved. It is possible that very high homocysteine levels may trigger mechanisms involved in atrial fibrosis. Also, no clinical data are currently available on whether pharmacological reduction in homocysteine could produce any beneficial effects in AF.

Conclusions

Homocysteine levels are increased in AF patients with predominantly ischemic background and they are independently related to left atrial dilatation. In this patient population moderately-to-severely homocysteine increase rather than very severe homocysteine elevation is independently associated with increased risk of AF recurrences.

Limitations

This is a relatively small observational study, which limits the scope of multivariable analysis. Also, mechanistic insight into mechanisms mediating high homocysteine levels with atrial dilatation and AF recurrence was beyond the scope of the study and needs to be addressed separately.

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