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IMPACT OF THE MTHFR GENE (GLU429ALA) POLYMORPHISM ON THE DEVELOPMENT OF CHRONIC HEART FAILURE IN PATIENTS WITH ISCHEMIC HEART DISEASE AND ITS CLINICAL–PROGNOSTIC SIGNIFICANCE

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ABSTRACT

The comparative analysis of mean homocysteine (Hcy) levels in patients with hyperhomocysteinemia (HHcy) among the studied groups showed that Hcy levels in patients with preserved EF (EF >50%) were significantly lower (21.2 ± 0.3 µmol/L) compared to patients with reduced EF (EF 40–49%: 22.9 ± 0.4 µmol/L and EF <40%: 24.0 ± 0.5 µmol/L) (p<0.001).

KEYWORDS: *Hyperhomocysteinemia, Chronic Heart Failure, Functional Class, Homocysteine.*

INTRODUCTION

Elevated levels of homocysteine can activate coagulation factors XII and V and enhance the expression of tissue factor (TF). In addition, impairment of protein C secretion—one of the natural inhibitors of the coagulation process and antiplatelet mechanisms—reduction in the activation of antithrombin III through glycosaminoglycans, as well as decreased thrombomodulin activity, are observed. A decline in the production of vasodilatory mediators, including nitric oxide (NO), by endothelial cells, along with endothelial injury, leads to an increase in von Willebrand factor, which may amplify platelet aggregation [3, p. 246; 4, p. 421].

The reduction in endothelial nitric oxide (NO) production is associated with a decrease in endothelial NO synthase activity caused by toxic products resulting from homocysteine-induced lipid oxidation. Consequently, hyperhomocysteinemia promotes endothelial dysfunction by accelerating atherogenesis and thrombus formation [5, p. 583].

The study included 103 patients diagnosed with chronic heart failure (CHF) based on clinical and instrumental data (mean age 63.6 ± 0.9 years) and 105 conditionally healthy volunteers (mean age 61.2 ± 1.4 years). In our study, the blood homocysteine (Hcy) level and the frequency of hyperhomocysteinemia (HHcy) were assessed in all patients and conditionally healthy individuals.

PURPOSE OF THE STUDY

The aim of our study was to determine the significance of blood homocysteine (Hcy) levels and the frequency of hyperhomocysteinemia (HHcy) in patients with chronic heart failure (CHF).

MATERIAL AND METHODS OF RESEARCH

The 103 patients included in the study who formed the main group were divided into subgroups according to the NYHA functional classification of CHF. Accordingly, the 1st subgroup (CHF II–FC) included 33 patients with a mean age of 60.2 ± 1.8 years. The 2nd subgroup (CHF III–FC) consisted of 37 patients with a mean age of 64.3 ± 1.4 years, and the 3rd subgroup (CHF IV–FC) included 33 patients with a mean age of 66.1 ± 1.6 years. Based on the identified aims and objectives, a research plan was developed. During the study, the accepted standards for CHF diagnosis were used, as well as instrumental, biochemical, and statistical analysis methods.

THE RESULTS OBTAINED AND THEIR DISCUSSION

In the next stage of our study, the blood homocysteine (Hcy) level and the frequency of hyperhomocysteinemia (HHcy) were evaluated in all patients and conditionally healthy individuals. According to the results, the plasma Hcy level in the main group consisting of 103 patients with CHF was 20.4 ± 0.5 µmol/L, which was significantly higher compared to the control group. In the control group, this value was 9.3 ± 0.6 µmol/L (p<0.001) (Table1).

The Hcy level was also significantly higher in all CHF subgroups compared with the conditionally healthy individuals: 18.0 ± 0.8 µmol/L in Group 1, 20.5 ± 0.7 µmol/L in Group 2, and 22.8 ± 0.7 µmol/L in Group 3 (p<0.001) (Table 1).

Moreover, it was found that the Hcy level increased significantly with the progression of CHF functional class among the subgroups.

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Table 1
The average level of homocysteine in the main study group and the control group

Patients	Total patients n=103	Group 1 CHF FC II n=33	Group 2 CHF FC III n=37	Group 3 CHF FC IV n=33	control group n=43
Homocysteine	20.4±0.5*	18.0±0.8*	20.5±0.7*,**	22.8±0.7*,***	9.3±0.6

— the difference between the patient groups and the control group is statistically significant at p<0.001.** — the difference between Group 1 and Group 2 is statistically significant at p<0.001.*** — the difference between Groups 1 and 2 compared with Group 3 is statistically significant at p<0.001.

A comparative analysis of homocysteine (Hcy) distribution among the patients showed that in the group with CHF FC II, Hcy levels were elevated in 60.6% of cases, with a mean value of 21.4 ± 0.5 µmol/L. In patients with CHF FC III, Hcy was above normal in 78.4% of cases, with a mean value of 22.4 ± 0.5 µmol/L (p>0.05). Although there were no significant differences in the frequency and mean values of hyperhomocysteinemia (HHcy) between Groups II and III, an increasing trend in HHcy frequency was associated with a 2.4-fold higher risk of progression to higher CHF FC (78.4% vs 60.6%; χ^2=2.6; p=0.1; OR=2.4; 95% CI: 0.83–6.73)

In the CHF FC IV patient group, 87.9% showed increased plasma Hcy levels, with a mean value of 24.0 ± 0.5 µmol/L. The mean Hcy level in patients with HHcy in the CHF FC IV group was significantly higher compared to patients in CHF FC II and III groups (24.0 ± 0.5 µmol/L vs 21.4 ± 0.5 µmol/L and 22.4 ± 0.5 µmol/L, respectively) (p>0.05).

Although the increase in Hcy levels between CHF FC III and IV groups was not statistically significant, there was a weak trend toward a 2.0-fold higher likelihood of elevated Hcy in CHF FC IV patients (87.9% vs 78.4%; χ^2=1.1; p=0.3; OR=2.0; 95% CI: 0.54–7.38) (Figure 1).

Furthermore, the development of HHcy was associated with a significantly higher risk (4.7-fold) of severe CHF progression (CHF FC IV) compared to patients with CHF FC II (87.9% vs 60.6%; χ^2=6.4; p=0.01; OR=4.7; 95% CI: 1.34–16.57) (**Figure 1**).

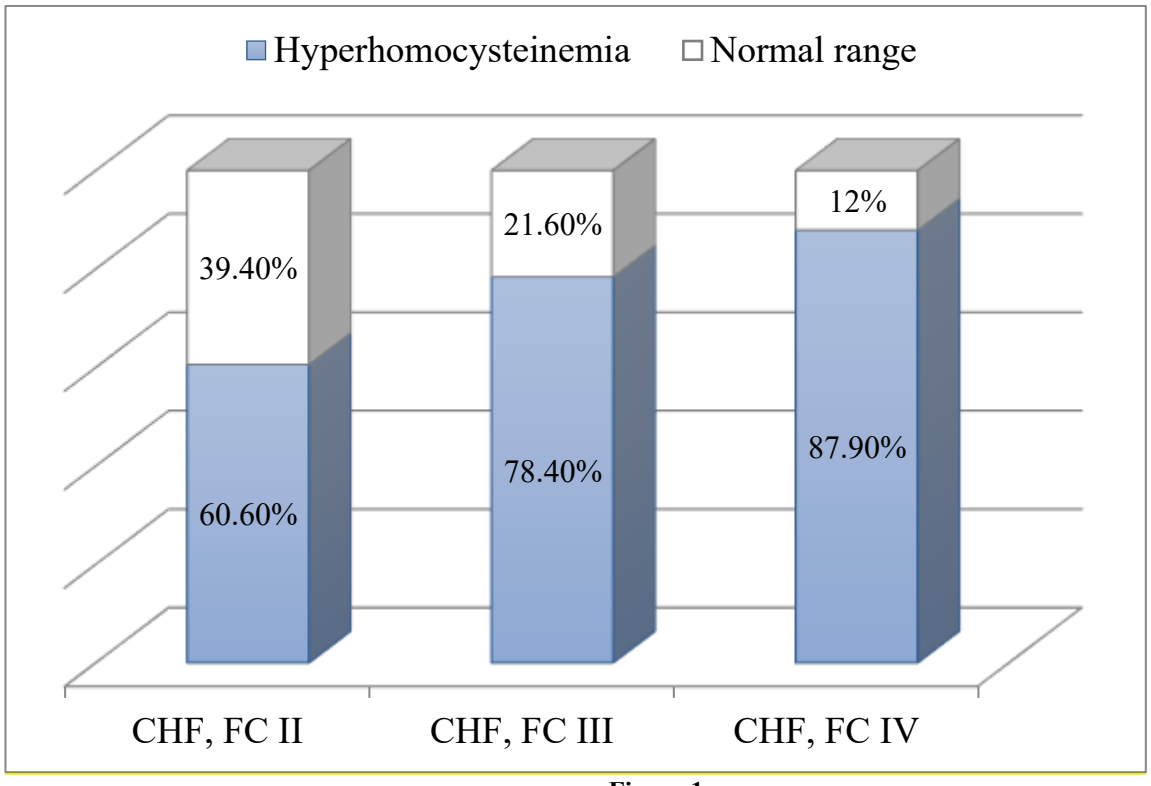


Figure 1

Frequency of hyperhomocysteinemia in patients with CHF depending on functional class (FC)

The results of the study on the relationship between the mean homocysteine (Hcy) level and the frequency of hyperhomocysteinemia (HHcy) with left ventricular ejection fraction (EF) in patients with CHF led to the following conclusion: the group of patients with preserved EF (EF >50%) had the lowest Hcy levels, which were significantly lower compared to patients with reduced EF (EF 40–49% and <40%) (18.3 ± 0.6 µmol/L vs 21.7 ± 0.7 µmol/L and 25.2 ± 0.7 µmol/L, p<0.001) (Table 2).

Moreover, the differences between Groups 2 (EF 40–49%) and 3 (EF <40%) were also statistically significant (p<0.001), and Hcy levels were notably higher in patients with EF <40%

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compared to those with relatively reduced EF (25.2 ± 0.7 μmol/L vs 21.7 ± 0.7 μmol/L) (Table 2).

Table 2
Mean homocysteine levels in patients with CHF depending on left ventricular ejection fraction (EF)

Patients	EF >50% n=60	EF 50-40 n=23	EF<40 n=20
Homocysteine (μmol/L)	18.3± 0.6	21.7 ± 0.7*	25.2 ± 0.7*,**

– Statistically significant difference between Groups 1 and 2–3 ($p<0.001$)
** – Statistically significant difference between Groups 2 and 3 ($p<0.001$)

The frequency of hyperhomocysteinemia (HHcy) in the studied groups was as follows: 65.0% in patients with preserved EF (EF >50%), 87.0% in the group with EF 40–49%, and 95.0% in patients with EF <40%. Thus, in patients with CHF, the presence of HHcy was associated with a significantly higher risk of reduced left ventricular ejection fraction: 3.6-fold for EF 40–49% compared to EF >50% (87.0% vs 65.0%; $\chi^2=3.9$; $p=0.05$; OR=3.6; 95% CI: 0.96–13.50) and 10.2-fold for EF <40% compared to EF >50% (95.0% vs 65.0%; $\chi^2=6.8$; $p=0.009$; OR=10.2; 95% CI: 1.28–81.87).

CONCLUSION

Thus, an increase in plasma homocysteine (Hcy) above the reference values in patients with CHF indicates a higher risk of disease progression and may contribute to a more severe course, i.e., a significant reduction in left ventricular ejection fraction in these patients.

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