ORIGINAL ARTICLE

PROGNOSTIC SIGNIFICANCE OF BLOOD MARKER OF HYPERTROPHY– CARDIOTROPHIN-1 WHEN CARRYING DIFFERENT VARIANTS OF ITS GENE IN MEN WITH ESSENTIAL HYPERTENSION

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Maryna O. Matokhniuk, Oleksandr V. Limanskiy, Olena V. Maiko, Vadym Zhebel, Oleksandra K. Shevchuk, Irina K. Palii
VINNYTSIA NATIONAL PIROGOV MEMORIAL MEDICAL UNIVERSITY, VINNYTSIA, UKRAINE

ABSTRACT

The aim: To improve diagnosis of essential hypertension with left ventricular hypertrophy and chronic heart failure in men citizens of Podillya region in Ukraine by determining the plasma levels of cardiotrophin-1 in patients with different CT-1 gene variants.

Materials and methods: A total of 70 men with no signs of cardiovascular disease and 100 patients with essential hypertension were examined. Among those, 50 participants had hypertension and left ventricular hypertrophy. Other 50 patients had hypertension complicated by chronic heart failure.

Results: It was established that in patients with essential hypertension the frequency of the pool of genotypes GA + AA is higher than the genotype GG ($p < 0.05$). Plasma CT-1 levels ≥ 122,895 pg / ml can be used for early diagnosis left ventricular hypertrophy, and the cut-off level is ≥ 303.81 pg / ml (sensitivity 85.7%, specificity 92%) for screening diagnosis of essential hypertension complications in the form of chronic heart failure.

Conclusions: In patients with essential hypertension of varying severity, the GA+AA genotypes of CT-1 gene was found to be dominant. They had higher levels of plasma concentration CT-1. The threshold levels of CT-1 for screening diagnosis of essential hypertension with hypertrophy and chronic heart failure in males (who were residents of the Podillya region of Ukraine) were evaluated.

KEY WORDS: Cardiotrophin-1, essential hypertension, left ventricular hypertrophy, chronic heart failure, polymorphism of cardiotrophin-1 gene

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INTRODUCTION

According to the Framingham study, the presence of left ventricular hypertrophy (LVH) doubles the incidence of cardiovascular events. An increase in LV wall thickness in patients with essential hypertension (EH) by 1 mm can be associated with an increased risk of dying by 7 times. The significance of myocardial hypertrophy as an independent predictor of cardiovascular complications in EH when assessing myocardial viability has been proved. [1,2].

At a certain stage of LVH development myocardial fibrosis and a number of other pathomorphological ones begin to form shifts, which ultimately lead to myocardial dysfunction and heart failure (CHF), which results in frequent hospitalizations and increased mortality of people with EH. This encourages the search for biomarkers for accurate diagnosis of LVH and prediction of CHF, especially in the early stages of the disease. Finding a solution to this problem requires an assessment of both the state of myocytes and myocardial connective tissue. One of the biomarkers that can help answer the above questions is cardiotrophin-1 (CT-1).

CT-1 is a member of the superfamily of cytokines interleukin IL-6 and is considered as one of the key regulators of hypertrophy and cardiomyocyte hyperplasia. CT-1 also affects the intensity of apoptosis and myocardial sensitivity to ischemia and collagen proliferation and secretion [3,4].

CT-1 releases its biological effects by interacting with the heterodimeric receptor gp130 and the receptor of leukemia inhibitory factor (LIFR), which causes intracellular activation of Janus kinase (Jaks) type I and II, as well as tyrosine kinase. It is shown that the expression of CT-1 is increased in response to stretching of the heart chambers and increased myocardial stiffness even before the increase in natriuretic peptides [5].

An important role in properties and the expression of CT-1 may belong to the polymorphism of the genes that encode it in particular at position rs8046707 G / A, and according to its biomarker value. Of particular interest is this aspect when using CT-1 not only as a biomarker of CHF, but also to clarify the state of the myocardium in such genetically dependent pathology as EH.

THE AIM

To improve diagnosis of essential hypertension with LVH and CHF in men citizens of Podillya region in Ukraine by determining the plasma levels of CT-1 in patients with different CT-1 gene variants.

MATERIALS AND METHODS

During the study we examined 170 middle-aged male residents of Podillya region. 100 men of the main group

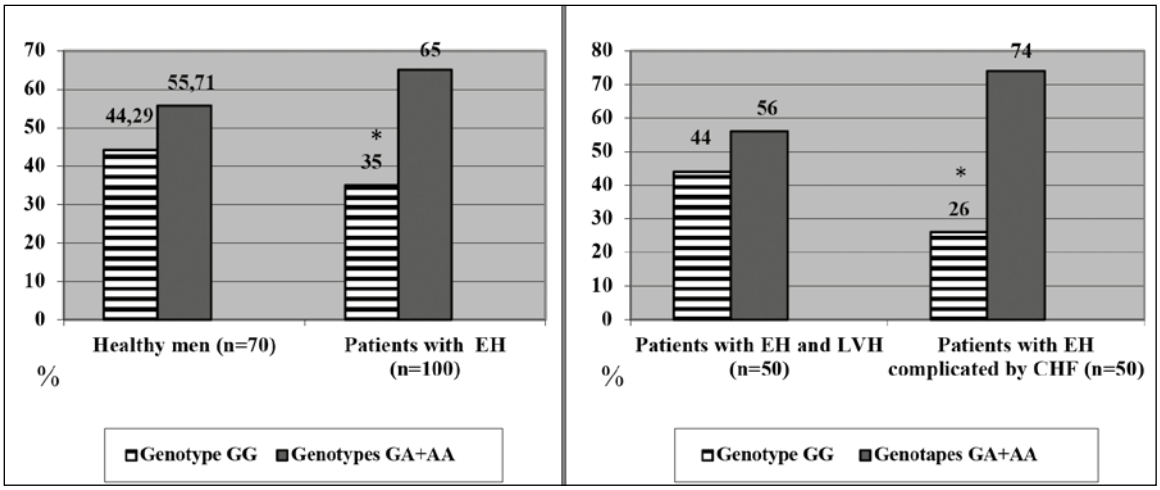

Fig. 1. The distribution of the CT-1 gene genotypes frequencies in men citizens of Podillya region in the healthy patients and the patients with EH and LVH and EH complicated by CHF (%).
Note: The difference is significant (p≤0,05) when compared to: * – GG genotype within each group.

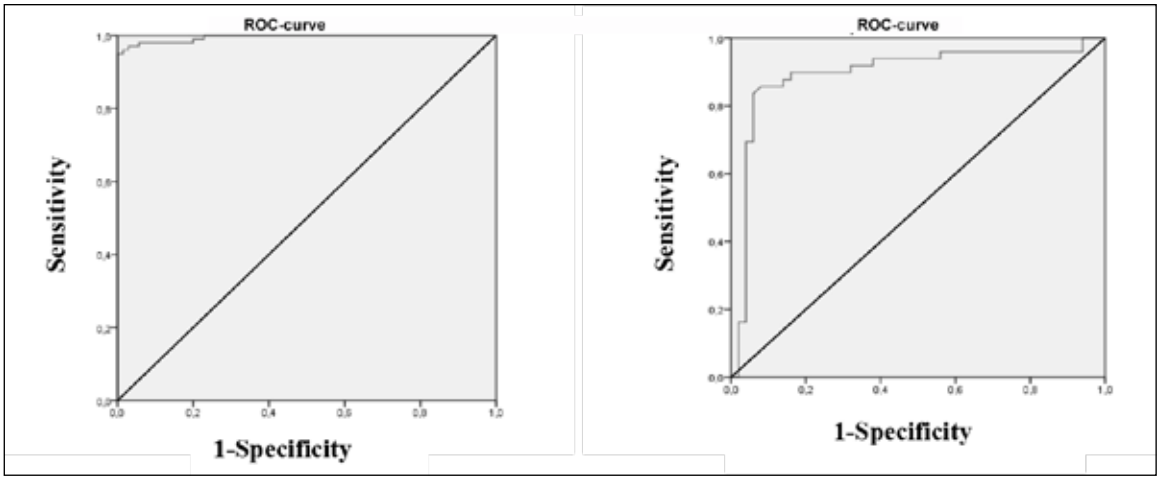

Fig. 2. ROC-curve to determine the cut-off level of CT-1 in blood plasma during the development of LVH in EH and EH complicated by CHF.

with EH with LVH, whose average age was 50,65±0,46 years. Among them, 50 men with EH with LVH (stages 1 and 2), with saved systolic function and CHF I-II classes according to NYHA Classification, whose average age was 50,62±0,73 and 50 men with EH complicated by CHF stage IIA, II-III classes according to NYHA Classification, whose average age was 51,86±0,81. 70 healthy men whose age was (48,81±0,78) did not differ from patients with EH and constituted the control group (p>0.05).

Exclusion criteria of the study were: secondary hypertension, renal and liver dysfunction, coronary heart disease the onset of which was before EH, endocrine, hematological, neoplastic and autoimmune disorders, patients with EH complications: myocardial infarction, acute cerebrovascular accident. These diseases were excluded

by collecting complaints, the results of an objective and general clinical examination (including, if necessary, pre-diagnosis of coronary heart disease), as well as a detailed analysis of outpatients' cards.

Genotyping of the CT-1 gene (rs8046707) was conducted using polymerase chain reaction (PCR) after isolation of genomic DNA from white blood cells of venous blood. This study was carried out jointly with the Research Institute of the genetic and immunological bases of pathology and pharmacokinetics "Ukrainian Medical Stomatological Academy" (Poltava, the head is prof. I.P. Kaidashev). The CT-1 concentration in plasma was determined by using ELISA method on enzymelinked immunosorbent analyzer "Humareader single» (Germany).

The mathematical processing was performed on a personal computer using a standard statistical package STATISTICA 10. Structural and functional parameters of the myocardium were evaluated using ultrasound of the heart.

RESULTS

The frequency distribution of the CT-1 gene genotypes in the men included in the study, residents of the Podillya region of Ukraine, corresponded to the Hardy-Weinberg equilibrium. Because of the relatively small number of patients with the AA genotype, we combined the patients with GA and AA genotypes in the carriers of the genotypes GA +AA.

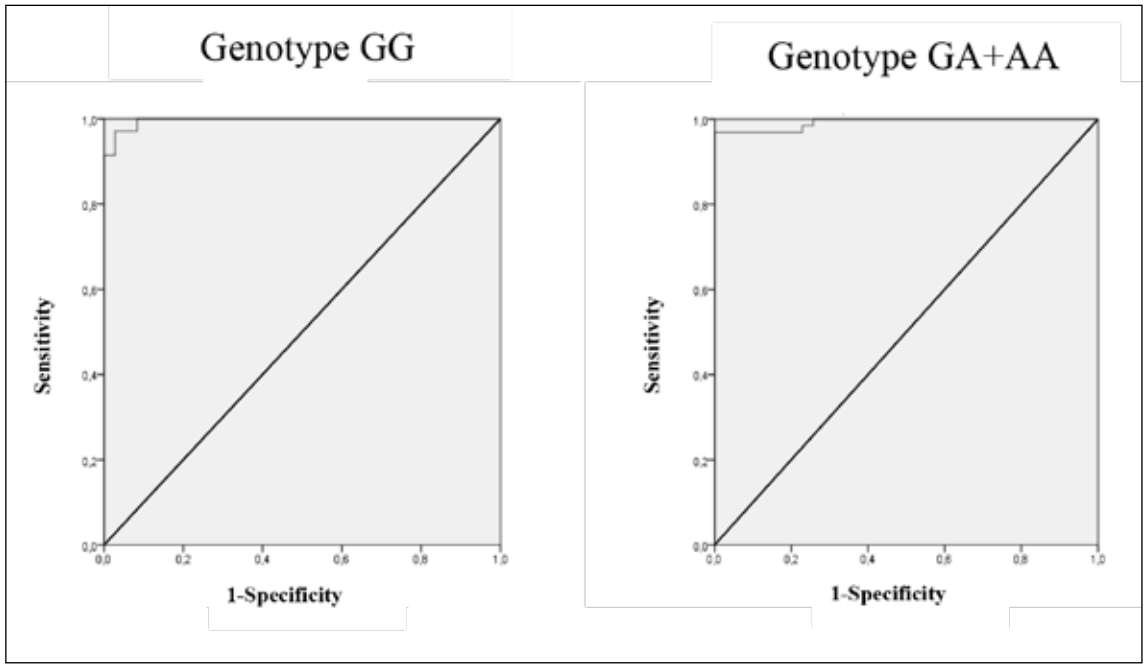

Fig. 3. ROC-curve to determine the cut-off level of CT-1 in blood plasma during the development of LVH in carriers of polymorphic variants of the CT-1 gene.

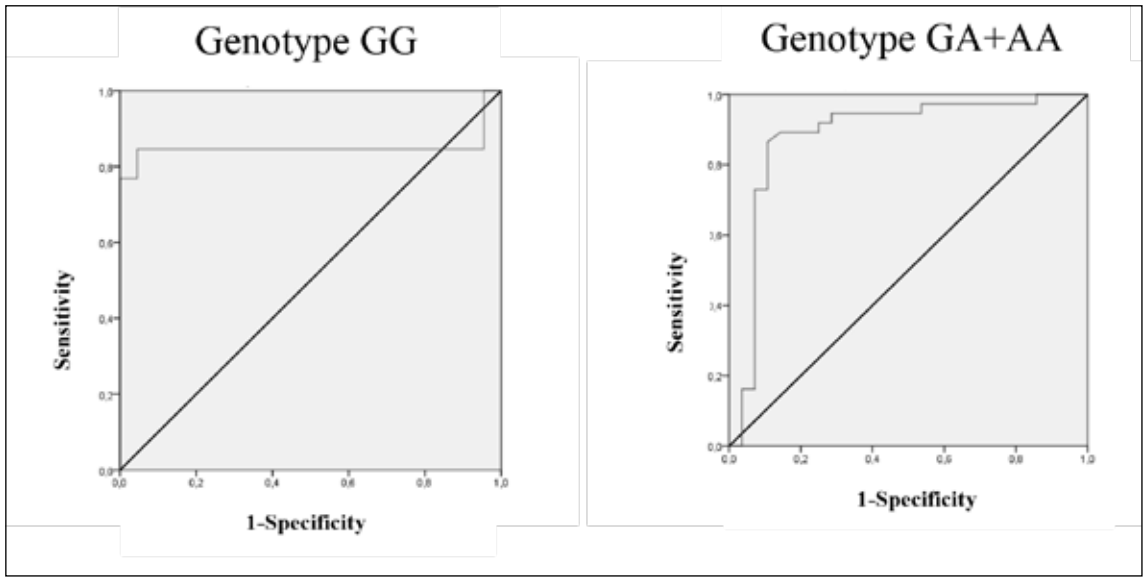

Fig. 4. ROC-curve to determine the cut-off level of CT-1 in blood plasma relative to the development of complicated EH, in carriers of polymorphic variants of the CT-1 gene.

In the control group, there were no significant differences in frequency carriage of the genotype variants of the CT-1 gene (p> 0.05).

In individuals with EH in general, the frequency of the GG genotype of the CT-1 gene was less than -35.00% (n = 65), which is below the pool of genotypes GA + AA -65.00% (n = 35) (p <0.05). However, in men with EH and LVH, the frequency of carriers of the GG genotype is 44.00% (n = 22), and the pool of genotypes GA + AA is 56.00% (n = 28) (p> 0.05). Among patients with EH complicated by CHF stage IIA, the frequency of GG genotype was 26.00% (n = 13), the pool of GA + AA genotypes was 74.00% (n = 37) (p <0.05). That is, among the studied contingent with EH reviews the pool of genotypes GA + AA of the CT-1 gene, at the expense of people with CHF. (Fig.1).

In the control groups of GG genotype owners, the main level of CT-1 in blood plasma was lower – 55.77 ± 2.53 pg/ml than the carriers of the pool of genotypes GA + AA – 92.46 ± 1.54 pg / ml and, accordingly, below in men with EH carriers of different genotypes of the CT-1 gene.

In men with asymptomatic EH and EH complicated by CHF, the plasma concentration of CT-1 is higher in carriers of the pool of genotypes GA + AA, respectively, 272.71 ± 12.57 pg/ml and 359.05 ± 5.79 pg/ml (p <0, 05) than in carriers of the GG genotype of the CT-1 gene (respectively 189.50 ± 9.51 pg/ml and 322.81 ± 27.01 pg/ml

Table 1. Indicators of ROC-analysis for the diagnosis of LVH and CHF in carriers of polymorphic variants of the CT-1 gene.

Group	«Cut off value»	AUC	p	Sensitivity, %	Specificity, %
LVH	122,89 pg / ml	0,995±0,003	p<0,05	95%	100%
LVH in carriers of the GG genotype	113,25 pg / ml	0,99±0,004	p<0,05	97,1%	98%
LVH in carriers of the GA+AA genotype	161,5 pg / ml	0,993±0,006	p<0,05	96,9%	100%
CHF	303,81 pg / ml	0,895±0,038	p<0,05	87,5%	92%
CHF in carriers of the GG genotype	266,955 pg / ml	0,850±0,096	p<0,05	84,6%	95%
CHF in carriers of the GA+AA genotype	323,32 pg / ml	0,884±0,050	p<0,05	86,5%	89,2%

(p <0.05)). Therefore, in men with the GG genotype and the GA + AA genotype with EH complicated by CHF, the level of the peptide is significantly higher than in persons without signs of cardiovascular pathology and in persons with asymptomatic EH (p <0.05).

The obtained data allowed us to calculate the boundary levels using ROC-analysis CT-1 in blood plasma for early diagnosis of LVH and CHF in men with EH, carriers of different variants of the genotype CT-1. This data can be used in the examination of large contingents of the population to identify persons who then need to conduct a full, including ultrasound examination of the heart and have appropriate treatment prescribed in cases of family examination (suspected hereditary pathology) and in expert cases, and in case of impossibility of instrumental examination because of various anatomical defects of the chest.

According to the Swets classification [6], the area under the ROC curve from 0.5 to 0.7 indicates low model accuracy, the model with the area under the ROC curve from 0.7 to 0.9 can be used in practice and the area under the ROC-curve above 0.9 characterizes highly accurate model. Based on the ROC-curve, which is presented in Fig. 2, sensitivity and specificity for different boundary points were calculated.

The area under the AUC curve according to ROC-analysis for the determination of CT-1 in blood plasma in the presence of EH and LVH of varying severity is 0.995 ± 0.003 [95% CI from 0.988 to 1.00;] which indicates the excellent quality of the obtained models. The cut-off point equal to ≥ 122,89 pg/ml 89% sensitivity and 92% specificity with an AUC equal to 93% This calculation allows to establish the cut-off level of CT-1 in blood plasma (sensitivity-95%, specificity-100%) in such a structural state of the myocardium as LVH. The area under the AUC curve according to ROC analysis for CT-1 is 0.895 ± 0.038 [95% CI from 0.822 to 0.969;], which indicates a very good quality of the obtained model. The obtained data indicate that the level of CT-1 in blood plasma ≥ 303.81 pg / ml (sensitivity – 85.7%, specificity-92%) can be considered as a boundary for the diagnosis of EH complicated by CHF.

However, it is also necessary to take into account possible deviations from the presented parameters in carriers of different variants of the genotype of the CT-1 gene, because the plasma concentrations of this biomarker in the respective subgroups differ.

The area under the AUC curve according to ROC analysis to determine the level of CT-1 in blood plasma in GG homozygotes is 0.99 ± 0.004 [95% CI from 0.988 to 1,000;], in carriers of the pool of genotypes GA + AA (Fig. 3) – 0.993 ± 0.006 [95% CI from 0.981 to 1,000;] which indicates the excellent quality of the obtained models. The cut- off CT-1 in blood plasma for the diagnosis of LVH in carriers of the GG genotype is ≥ 113,255 pg / ml (sensitivity – 97.1%, specificity-98%) and in carriers of GA+AA genotype ≥ 161.5 pg / ml (sensitivity – 96 , 9%, specificity – 100%).

The area under the AUC curve according to ROC analysis for the determination of CT-1 in blood plasma in carriers of the GG genotype is 0.850 ± 0.096 [95% CI from 0.662 to 1,000;], in carriers of the GA + AA genotype pool – 0.884 ± 0.050 [95% CI from 0.785 to 0.982;] (Fig. 4) which indicates a very good quality of the obtained model. These data indicate that in male homozygotes GG the level of CT-1 in blood plasma ≥ 266,955 pg / ml (sensitivity – 84.6%, specificity – 95%), and in carriers of the genotype GA + AA ≥ 323.32 pg / ml (sensitivity- 86.5%, specificity – 89.2%) allows to diagnose CHF.

The data presented in table 1 shows that the obtained results have a very good quality of the model, sensitivity and specificity for the diagnosis of LVH on the background of EH and CHF in men.

DISCUSSION

Thus, among 40 to 60 years old men, residents of the Podillia region in Ukraine who are patients with EH the frequency of registration of the pool of genotypes GA + AA was higher than in the group of patients with EH heterozygotes GG.

In a study done by Lutz S Z, Franck O et al. in the German population, it was found that the GA genotype is most common among Germans [7]. In both German and Ukrainian populations, the AA genotype is rarely identified.

In the study of plasma concentrations of CT-1 it was found that men with EH and LVH have significantly higher level those in the control group and in turn levels than persons with EH, complicated by CHF (p <0, 05). In men with EH of varying severity, the plasma concentration of CT-1 is significantly higher in carriers of the GA + AA genotype of the CT-1 gene. (p <0.05). In a meta-analysis conducted by K. Song, the plasma concentration of CT-1 not only increases with EH, but also has a prognostic value for the development of CHF [8]. In a study conducted by Kolesnik M.Yu. among the residents of Ukraine there was an increase in the concentration of the marker depending on the severity of impaired glucose metabolism. The results were such that in men with EH without impaired glucose metabolism, the concentration of the marker was 176.1 (106.5-436.2) pg / ml, in the presence of insulin resistance in combination with EH, the level of CT-1 in blood plasma 282.2 (119.5-650.2) pg / ml [9]. The study clarified the diagnostic limits for the confirmation of LVH in EH and CHF.

CONCLUSIONS

In 40-60 years old male residents of Podillya who were patients with EH the frequency of the pool of genotypes GA + AA is higher than the genotype GG (p <0.05) due to patients with CHF.

Plasma CT-1 levels ≥ 122,895 pg / ml can be used for early diagnosis of myocardial changes such as LVH, and the cut-off level is ≥ 303.81 pg / ml (sensitivity 85.7%, specificity 92%) for screening diagnosis of CHF.

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ORCID and contributorship:

Maryna O. Matokhniuk: 0000-0001-5968-0512[A,B,C,D]
Oleksandr V. Limanskiy: 0000-0002-5725-1340[A,B]
Olena V. Maiko: 0000-0002-6392-3289 [A,E]
Vadym M. Zhebel: 0000-0002-6542-9313[A,E,F]
Oleksandra K. Shevchuk: 0000-0001-6795-5969[A,E]
Irina K. Palii: 0000-0002-8000-1702 [A,E]

Conflict of interest:

The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Maryna O. Matokhniuk
Vinnytsia National Pirogov Memorial Medical University
56 Pirogov Str., Vinnytsia, Ukraine
tel: +380682137788
e-mail: marina.s.a8604@gmail.com

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