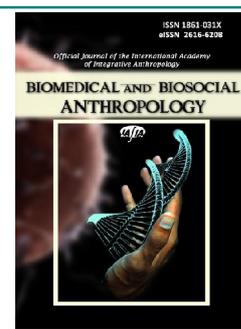




BIOMEDICAL AND BIOSOCIAL ANTHROPOLOGY

Official Journal of the International Academy
of Integrative Anthropology

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



The role of the brain natriuretic peptide gene polymorphism in the diagnostic use of the biomarker in myocardial dysfunction in men, residents of Podillya with comorbid essential hypertension and type 2 diabetes mellitus

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ARTICLE INFO

Received: 17 August, 2020

Accepted: 18 September, 2020

UDC: 616.12-008.331.1/.46:616.379-008.64:577.17:616-07-037

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There is a growing interest in the early detection of signs of myocardial dysfunction, especially in comorbid patients for timely prevention of progression of disease, reducing the risk of complications, improving their quality of life. The aim of the work was to optimize the diagnosis of myocardial dysfunction in men, residents of Podillya, taking into account the plasma concentration of brain natriuretic peptide (BNP) and polymorphism of the corresponding gene under conditions of comorbidity of essential hypertension (EH) with left ventricular hypertrophy (LVH) and type 2 diabetes mellitus (T2D). We examined 211 men: 79 persons without the signs of cardiovascular diseases, 62 patients with EH 2 and chronic heart failure (CHF) 0-I functional classes (FC) according to NYHA Classification and 70 - with EH 2 combined with T2D and CHF FC I-II. The examination included the determination of plasma concentration of BNP, the brain natriuretic peptide gene polymorphism (polymorphic locus T-381C), indices of doppler-echocardiography. The mathematical processing was performed using the standard statistical package Statistica 10. During the study, we calculated the primary statistical indicators, identified differences between groups on statistical grounds, made correlation and discriminant analysis. Diastolic dysfunction (DD) of the left ventricle (LV) was diagnosed in 45.16 % of patients in the group with EH 2, and 90 % in the group of comorbid patients. It was determined that men, residents of Podillya, with presence and absence of T2D, have dominating T381C genotype of the BNP gene. Lower plasma concentration of BNP that is peculiar for homozygous T381T genotype, in comparison with carriers of allele C of BNP gene and the average values of this biomarker in patients with DD may affect its informativeness in the diagnosis of myocardial dysfunction and requires a lower level of diagnosis. Appropriate borderline levels of BNP were determined for early diagnosis of DD in carriers of polymorphic variants of the BNP gene in men, residents of Podillya, with comorbid course of EH 2 and T2D. It is recommended to determine the genotype of the corresponding gene (polymorphic locus T-381C) and plasma level of BNP and focus on the calculated borderline levels of BNP to optimize the diagnosis of myocardial dysfunction in comorbid patients with EH 2 and T2D. For carriers of the T381T genotype it is ≥ 55.57 pg/ml, for carriers of the C allele (heterozygous T381C and homozygous C381C) of the BNP gene it is ≥ 69.13 pg/ml.

Keywords: essential hypertension, type 2 diabetes mellitus, diastolic dysfunction, the brain natriuretic peptide gene polymorphism.

Introduction

In today's world, the World Health Organization has identified the prevention and treatment of chronic non-communicable diseases as a priority project of the second decade of the XXI century, aimed at improving the quality of

life of the world's population [12]. Due to the high increase in prevalence, comorbid conditions need special attention, including the combined course of essential hypertension stage 2 (EH 2) and type 2 diabetes (T2D) [20]. Due to the

synergistic negative effect of hemodynamic stress inherent in EH and metabolic disorders inherent in T2D, this association is the most unfavorable prognostic sign for the development of congestive heart failure and cardiac death [11].

It is generally accepted that the early preclinical manifestation of heart disease in EH and T2D on the background of LVH is the development of DD, which is considered as a basis for further formation of CHF with preserved ejection fraction [17], which is detected by echocardiography. However, the method is expensive, sometimes limited in use due to socio-economic and anatomical factors, and concomitant pathology, including T2D, is a complicating background in the study, which causes difficulties in interpreting the data [13].

An additional tool for screening for subclinical ventricular dysfunction may be the neurohormonal profile of patients. In order to improve the individual strategy for the prevention of CHF at the stage of reversible changes in the comorbid course of EH and T2D, there is an urgent need to involve additional effective diagnostic biomarkers of myocardial dysfunction.

It is proved that a number of causes, in addition to LV dysfunction, can cause wide variability of BNP values and complicate clinical interpretation in comorbid patients: hereditary, sex features and metabolic changes [4, 5]. The latter requires clarification of the diagnostic significance of the genetic component - allelic polymorphism of the BNP gene (T-381C) in the analysis of plasma levels of the biomarker to detect early signs of myocardial dysfunction under the conditions of comorbidity of EH and T2D.

The aim of the study was to optimize the diagnosis of myocardial dysfunction taking into account the plasma concentration of BNP and polymorphism of the corresponding gene under conditions of EH comorbidity with LVH and T2D in men living in Podillya region.

Materials and methods

We examined 211 men aged 45 to 68 years (mean age 54.87 ± 0.89 years) living in the Podillya region of Ukraine. All individuals involved gave written informed consent to participate in the study. Patients underwent a comprehensive clinical-anamnestic, anthropometric and laboratory-instrumental examination, based on which they were diagnosed with EH, LV DD and CHF in accordance with the recommendations of the European and Ukrainian Association of Cardiologists for the diagnosis and treatment of hypertension and CHF [26, 29, 33]. Verification of the diagnosis of T2D was performed according to WHO criteria and in accordance with the order of the Ministry of Health of Ukraine dated 21.12.2012 № 1118 [8, 18].

Patients were divided into 3 groups, which are representative by age. The control group included 79 men in whom the results of objective and general clinical examination revealed no pathological changes in the circulatory system and endocrine system. The first main

group included 62 people with EH 2 and CHF not higher than FC I according to NYHA criteria. The second main group included 70 men with EH 2 in combination with moderate T2D. Among them, 58 (82.86 %) were diagnosed with CHF at level I, and 12 (17.14 %) - at level II FC according to NYHA. All patients had a preserved LV ejection fraction (EF). The average duration of EH in the studied patients was 8.23 ± 2.05 years, and T2D - 6.34 ± 3.03 years, respectively. The course of T2D in 61 people (87.14 %) is controlled.

Mandatory criteria for inclusion into the main groups: verified diagnosis of EH 2 1-3 degrees, lack of history and medical records of myocardial infarction, acute cerebrovascular accident, as well as the presence of symptoms, anamnestic indications for coronary heart disease (CHD), the development of which preceded the emergence of EH. 48 men of the 2nd main group had a concomitant diagnosis of coronary heart disease in the form of diffuse atherosclerosis, which was established 1-4 years after the main diagnosis of EH 2.

Exclusion criteria: symptomatic nature of hypertension, the presence of severe CHF (III-IV FC according to NYHA) with reduced LV EF (<40 %), T1D, decompensation of T2D, insulin therapy, diabetic nephropathy 4-5 years, chronic kidney disease non-diabetic origin, liver failure, chronic obstructive pulmonary disease and bronchial asthma, acquired heart defects, tumors, diseases of the blood system, concomitant inflammatory and endocrine diseases, except T2D.

The concentration of BNP in blood plasma was determined by ELISA using a standard kit from "Peninsula Laboratories Inc." (USA). The genomic DNA of the BNP gene for the determination of alleles of the polymorphic region (T-381C) was isolated by the phenol-chloroform method using a kit for isolation of DNA/RNA from blood serum (NPF "LiTech", Russia) in collaboration with the Institute of Genetic and Immunological Basis of Pathology and Pharmacogenetics of Ukrainian Medical Dental Academy, Poltava (Head of Laboratory - Doctor of Medicine, Professor Kaidashev I. P.). Echocardiography was performed to determine the parameters of intracardiac hemodynamics. The criterion of LV hypertrophy for men was considered to be $LV \text{ weight/height}^2.7 > 50 \text{ g/m}^2.7$ according to the recommendations of the European Association of Cardiologists for the diagnosis and treatment of hypertension (2018) [33]. Diastolic LV function was assessed according to current guidelines using pulsed Doppler echocardiography [14].

Statistical processing of the results of the study was performed on a personal computer using the standard statistical package Statistica 10. Calculated primary statistics, identified differences between groups on statistical grounds, performed correlation analysis.

Results

For the most part, the development of LV DD is the first stage of CHF formation in patients with EH, but with

Table 1. Types of disorders of diastolic heart function in patients from groups of comparison.

Group	Normal transmitral blood flow (TBF)	Indefinite TBF	TBF by type of relaxation disorder - DD I degree	TBF by type of pseudo normalization - DD II degree	p
Patients with EH 2 (n=62)	43.55% (n=27) (1)	11.29% (n=7) (2)	33.87% (n=22) (3)	9.68% (n=6) (4)	$p_{2-1}<0.05$ $p_{4-1}<0.05$
Patients with EH 2 and T2D (n=70)	-	10.00% (n=7) (5)	68.57% (n=48) (6)	21.43% (n=15) (7)	$p_{6-5}<0.01$ $p_{7-6}<0.01$
p		-	$p_{6-3}<0.01$	$0,05<p_{7-4}<0.1$	

additional adverse effects on the myocardium of such a comorbid disease as T2D, conditions are created for its accelerated development [28], which was confirmed in the study: LV DD in the group with EH 2 diagnosed in 43.55 % of people (n=28), while in the group of comorbid patients - in 90 % of people (n=63) (Table 1).

Plasma levels of BNP in men with LV DD in the isolated course of EH was 82.00 ± 4.01 pg/ml, while in comorbid with diabetes 2 - 105.99 ± 3.76 pg/ml ($p<0.01$). Spearman's rank correlation method was used to identify correlations between BNP concentration and hemodynamic parameters characterizing myocardial diastolic function in men with different EH 2 course (Table 2).

According to the obtained results, it was found that in men with an isolated course of EH 2, the plasma level of BNP significantly correlates directly with the values of E/A, E/E' and vice versa - with the values of IVRT and DT. In comorbid patients with T2D, a direct correlation was also found between the level of BNP and the E/E' index, whereas the correlation with the value of DT was inverse. The presence of correlations between the above indicators may indicate the possibility of using BNP as a marker for the assessment of LV DD in patients with different EH courses.

Since it is known that the expression of such a biomarker as BNP may depend on the genetic characteristics of patients, requires clarification of the role of allelic polymorphism of the BNP gene (locus T-381C) in the diagnostic process in different variants of EH [10, 15]. In both main groups of patients, as well as in the control group, the distribution of polymorphic genotypes of the BNP gene corresponded to the Hardy-Weinberg equilibrium. No significant differences in the distribution of genotype frequencies in the comparison groups were found, the T381C variant of the BNP gene dominated ($p\leq 0.05$). Due to the small number of C381C homozygotes, for greater accuracy of comparative analysis in all comparison groups, it was decided to combine individuals with T381C and C381C genotypes into one group - carriers of the C allele of the BNP gene (Fig. 1).

In the first main group of patients with DD was found in 50.0 % (n=11) homozygotes T381T and 42.5 % (n=17) carriers of the C allele, and in the second main group of comorbid patients with T2D - in 100 % (n=24) and 84.78 % (n=39), respectively. In order to assess the possible variation of the plasma level of the biomarker in the carrier of polymorphic variants of the BNP gene in individuals with DD, a corresponding comparative analysis was performed

in the comparison groups. In homozygotes of T381T of the BNP gene, the plasma level of the biomarker corresponded to 63.27 ± 6.83 pg/ml in the isolated course of EH and 97.05 ± 6.21 pg/ml in comorbid with T2D ($p<0.01$), while in carriers of the C allele, respectively 94.12 ± 1.50 pg/ml and 111.5 ± 4.6 pg/ml ($p<0.05$).

In both study groups, the plasma levels of the biomarker in the T381T homozygotes of the BNP gene were significantly lower than in the C allele carriers ($p<0.01$). Thus, the lower plasma concentration of BNP, which is characteristic of homozygotes T381T, compared with carriers of the C allele of the BNP gene and the average plasma level of the biomarker in patients with DD in groups may affect its informativeness in detecting myocardial dysfunction.

Table 2. Indicators of correlation of BNP plasma level and hemodynamic parameters of myocardium in men with different course of EH 2.

Indicator	Patients with EH 2 (n=62)		Patients with EH 2 and T2D (n=70)	
	R	p	R	p
E/A, c.u.	+0.25	<0.05	+0.21	<0.05
IVRT, ms	-0.29	<0.05	-0.15	>0.05
DT, ms	-0.36	<0.01	-0.20	<0.05
E/E'	+0.36	<0.01	+0.25	<0.05

Note: R - Spearman's correlation coefficient.

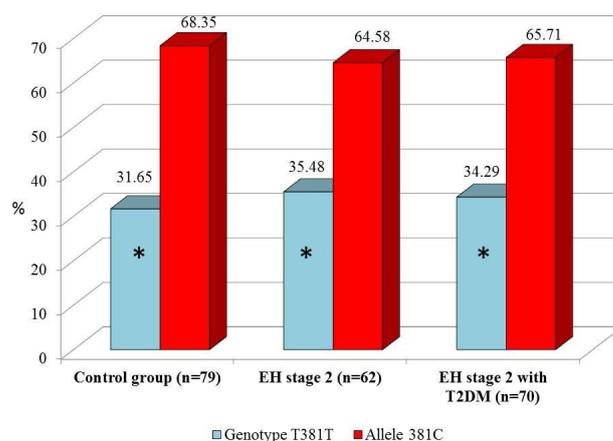


Fig. 1. Frequency of distribution of BNP alleles gene in comparison groups among men, inhabitants of Podillya, (%). Note: * - the difference is significant ($p\leq 0.05$) when compared with the C allele within the group.

It should be noted that the limit level of BNP 35 pg/ml, which is recommended to confirm the high probability of CHF regardless of LV EF [32] showed insufficiently high specificity (55.32 %) in comorbid patients with T2D, where BNP levels are probably higher than in isolated cases of EH course [2]. The identified features led to the calculation of appropriate informative cut-off levels of BNP for the diagnosis of LV DD in carriers of different polymorphic variants of the BNP gene among patients with EH 2 and T2D. For this purpose, we used the formula of Antamonov M. Yu. [22]. When determining the threshold level of the indicator, and during the discriminant analysis, sensitivity, specificity, infallibility, false-negative and false-positive responses were established according to the proposed methods [35].

In the isolated course of EH, the threshold levels of informativeness of the studied biomarker for men, residents of Podillya, carriers of different genotypes of the BNP gene were presented in previous studies by the Department of Internal Medicine of the Medical Faculty № 2 National Pirogov Memorial Medical University, Vinnytsya [23].

In the comorbid course of EH 2 and T2D in men, residents of Podillya for carriers of genotype T381T threshold level of informativeness BNP for the detection of LV DD is ≥ 55.57 pg/ml (sensitivity - 95.83 %, specificity - 97.87 %, infallibility - 97.10 %, infallibility - 97.10 %, false negative response - 4.17 %, false-positive response - 2.13 %), while for carriers of the C allele (heterozygote T-381C and homozygote C381C) it is ≥ 69.13 pg/ml (sensitivity - 89.13 %, specificity - 82.22 %, infallibility - 85.71 %, false-negative response - 11.11 %, false positive response - 17.78 %).

Discussion

T2D has the highest additional negative impact on short-term and long-term prognosis in patients with both asymptomatic and clinically pronounced LV dysfunction. That is why there is a growing interest in the early detection of signs of myocardial dysfunction, especially in comorbid patients with T2D in a timely manner to prevent disease progression, reduce the risk of complications, improve their quality of life. Since clinical and instrumental manifestations of comorbid cardiovascular and metabolic pathology complicate the diagnosis of early stages of CHF, in patients with T2D list of examinations should rationally include the definition of valid biomarkers, such as BNP [19, 32], which was used in this study.

Although the main reason for the increase in the production of BNP is considered to be the volume overload of the heart cavities [31], the interpretation of the plasma concentration of the biomarker takes into account factors that can change its levels, among which sex [9, 27] and heredity [7] plays some role. That is why only men living in the Podillya region were involved in the formed group.

Currently, a promising approach is to further study the determining role of the polymorphism of the BNP gene, which participates in the coding of the corresponding biomarker and to determine the need to take into account

these genetic features in the diagnostic process in EH, including comorbid T2D.

Our data are consistent with the results of a study by Takeishi et al., who examined 2,970 Japanese adults with CHF and found that, regardless of sex, carriers of the 381C allele of the BNP gene had a higher plasma biomarker level, while the T381T genotype was associated with the lowest in blood plasma [30].

Similar results were obtained by Costello-Boerrigter L. C. in a mixed cohort of North Americans with EH. Inheritance of BNP gene genotypes with the presence of the 381C allele has been shown to be associated with high peptide concentrations. The authors indicate that refined genotype points may be useful in the diagnosis of asymptomatic LV dysfunction, or in compensated chronic LV dysfunction when some patients fall into the diagnostic gray area [10].

However, in a large, prospective EPIC-Norfolk study (USA), on a mixed cohort of individuals, researchers did not find a significant association between the rs198389 genotypes of the BNP gene and the risk of heart failure. The mean follow-up time was 12.6 years. The results did not differ significantly in the presence of EH, obesity and coronary heart disease. According to the authors, a possible explanation may be that the physiological activation of the BNP system in conditions of enhanced mechanical deformation of the heart may block small genetically determined differences in the levels of BNP. In addition, it is possible that a slight genetic influence on certain subtypes of CHF syndrome associated with the polymorphism of the gene may not affect the risk of developing general heart failure [24].

However, according to Berezikova E. N. in practically healthy individuals of the Russian population, carriers of the genotype C381C gene BNP, the plasma level of NT-pro BNP (inactive BNP precursor) was significantly higher than in carriers of the genotype T381T. The T allele and the TT genotype of the T-381C polymorphic locus of the BNP gene were associated with a high risk of development, severity and adverse course of CHF in patients with coronary heart disease, and the C allele and the CC genotype proved to be protective factors [3].

In the South Chinese population, it was also found that the rs198389 polymorphism of the BNP locus may be an additive additional genetic factor influencing the progression of LV dysfunction in patients with coronary heart disease and dyslipidemia [34].

Researchers from Iran have shown that the T-381C polymorphism in the BNP gene affects the plasma level of BNP, where the CC genotype and C allele are associated with higher BNP levels in 70 cardiac patients. There was no statistically significant difference in the distribution of genotyping and frequency of alleles between groups of patients with cardiovascular disease (acute coronary syndrome, etc.) and a healthy control group [1].

There are isolated studies on the study of BNP gene polymorphism in patients with cardiovascular disease in

Ukraine. Pashkova Yu. P. and co-authors found that in the control group, as well as in men with EH 2-3 and CHF stage II A, residents of Podillya, the plasma concentration of BNP is probably lower in homozygotes T381T gene BNP than in carriers of the C allele associated with higher levels of systolic blood pressure and diastolic blood pressure, pronounced eccentric LVH, decreased LV EF. Researchers suggest that the carrier of the T381T genotype of the BNP gene is one of the pathogenetic factors in the development of CHF [23]. It should be noted that patients with T2D were not included in the study.

Foreign works on the role of BNP gene polymorphism in patients with T2D is of great interest. Meirhaeghe A. and co-authors analyzed the relationship between the risk of developing T2D, plasma BNP concentration and T381C polymorphism in the French population. Subjects with genotype CC had lower plasma sugar concentrations, which was associated with a lower risk of developing T2D and higher plasma levels of BNP compared with carriers of the T allele. According to the authors, these data together indicate that relatively high BNP expression may protect against T2D [17].

A promising cohort study of the European population also analyzed the relationship between NT-proBNP levels in the blood, taking into account the T381C polymorphism of the corresponding gene and the risk of developing T2D. The authors combined the results with existing meta-analysis data from 11 studies with control cases and concluded potential the causal role of the BNP system in the etiology of T2D [24].

These data suggest that the role of the BNP gene polymorphism and possibly the associated plasma level of the biomarker in the diagnosis of both DD and CHF in various clinical situations remains debatable to this day. It is considered expedient to continue research in this direction, which can provide additional potential during the use of BNP for diagnostic purposes in screening examinations and in expert cases.

Conclusions

1. The diagnostic value of BNP in patients with EH and comorbid T2D is higher taking into account the polymorphism of the gene encoding the expression of this biomarker. In order to improve diagnostic strategies for assessing cardiovascular risk and predicting the development of DD in comorbid patients with EH and T2D, it is recommended to determine the genotype of the corresponding gene (polymorphic locus T381C) together with the plasma level of BNP.

2. In case of EH 2 in combination with T2D and carriers of the T381T genotype, the threshold level of BNP is ≥ 55.57 pg/ml (sensitivity - 95.83 %, specificity - 97.87 %, infallibility - 97.10 %, false-negative response - 4.17 %, false-positive response - 2.13 %) allows to detect LV DD, while for carriers of the C allele (heterozygote T-381C and homozygote C381C of the BNP gene) it is ≥ 69.13 pg/ml (sensitivity - 89.13 %, specificity - 82.22 %, infallibility - 85.71 %, false-negative response - 11.11 %, false positive response - 17.78 %).

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