ORIGINAL ARTICLE

BIOMARKER AND ECHOCARDIOGRAPHIC CHARACTERISTICS OF HEART FAILURE IN PATIENTS HAVING ACUTE MYOCARDIAL INFARCTION COMBINED WITH DIABETES MELLITUS OF TYPE 2

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ABSTRACT

The aim: To investigate the level of B-type natriuretic peptide (BNP) and to establish its relationship with structural and functional indicators of the myocardium in patients having acute myocardial infarction (AMI), which is complicated by heart failure (HF) with concomitant type 2 diabetes mellitus (DM2).

Materials and methods: The study included 120 patients who were grouped by clinical diagnosis. Every patient underwent transthoracic echocardiography of the heart: left ventricular (LV) ejection fraction (EF), left ventricular myocardial mass index (LVMI), LV relative wall thickness (LVWT), BNP, HbA1c.

Results: LV EF was statistically significantly lower in group 2 compared with group 1. A significant difference was found. Significant difference between LVWT within indicators of groups 1 and 2 was found. There was a statistically significant increase of the LVMI in group 2 compared to group 1. Against the background of AMI, the formation of eccentric LVH prevailed in 61% cases. There was a statistically significant increase in BNP within the group of patients suffering of AMI with HF and concomitant DM2.

Conclusions: There was found a statistically significant increase in BNP in patients suffering of AMI with HF and concomitant DM2, which indicates a significant degree of damage to cardiomyocytes and causes an aggravating course of HF. The relationship between BNP and LV EF was revealed , which can be used to prognostic the severity of HF in this category of patients. A strong correlation between BNP and HbA1 was discovered, which indicates a burdensome unity of metabolic disorders that accelerate the development and progression of HF.

KEY WORDS: Myocardial infarction, diabetes mellitus, coronary heart disease, B-type natriuretic peptide, left ventricular remodeling

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INTRODUCTION

Acute myocardial infarction (AMI) is one of the leading causes of death worldwide [1,2]. European countries and the United States show examples of successful combating this problem, over 20 years mortality has decreased by more than 50% [3,2]. In Ukraine, the prevalence and incidence of coronary heart disease (CHD) is growing annually and is among the adult population – 34,9% and 26,8%, among people of working age – 26,7% and 23,1%, respectively [4]. The course and consequences of AMI determine comorbidities, including type 2 diabetes mellitus (DM2), one of the most common comorbid conditions in patients suffering of AMI. According to international registries published in the period since 2003 till 2018, the share of patients suffering of type 2 diabetes was (20-24)% of all hospitalized because of AMI, and among those cases of impaired carbohydrate metabolism – more than 50% [5,6].

Heart failure (HF) is considered to be one of the leading causes of premature death in patients having AMI. DM2 is one of the predictors of HF [7,8]. This is especially true of HF with preserved ejection fraction (EF) of the left ventricle (LV), the criterion for determining HF with preserved EF, according to the European Society of Cardiology, ranged from 40 to 50% [7,9,10]. The prevalence of HF shows a steady upward trend around the world, especially in patients with concomitant DM2, despite the progress in the prevention and treatment of AMI [8]. Modern clinical guidelines of various associations are improving the methods of early diagnosis, prevention and individual treatment of HF [7,11].

Biological markers that reflect different pathophysiological stages of HF remain important as a powerful tool for diagnosing acute and chronic HF, stratification of patients at high risk of HF and progression, and as a likely predictor of the effectiveness of HF treatment [12]. This is especially true for patients suffering of AMI with concomitant DM2, which requires a deeper understanding of the mutually aggravating mechanisms of comorbid pathology, which lead to the development and progression of HF.

The b-type natriuretic peptide (BNP) is actively released by cardiomyocytes in response to biomechanical stretching, volume overload, myocardial damage, ischemia, necrosis, reperfusion, metabolic or toxic damage [12,13]. Studies have shown a significant role of BNP in the early diagnosis of HF. Despite the fact that this peptide is called "brain natriuretic peptide", the center of the beginning of the synthesis of BNP is the ventricular myocardium, so it is recognized as an indicator of hemodynamic stress [14].

Asymptomatic LV dysfunction is of great importance, especially for patients having metabolic disorders, which requires improved methods of early diagnosis and prevention of HF.

An additional risk of AMI in patients suffering of DM2 is hyperglycemia, which adversely affects the prognosis [8]. It is known that in the process of carbohydrate metabolism, glucose is non-enzymatically bound to proteins, including hemoglobin. Excessive non-enzymatic glycosylation, which is characteristic of hyperglycemia, alters the natural function of glycosylated proteins. Their constant excess leads to structural changes in cells and various complications inherent in diabetes. Glycosylation is mainly subject to hemoglobin A1 (HbA1), the determination of which by the method of cation exchange chromatography reveals several options: HbA1a, HbA1b and HbA1c. The most common of these is HbA1c, which accounts for approximately 60-80% of the total amount of glycosylated hemoglobin. [5]. An increase in its content in the blood leads to tissue hypoxia and the development of angiopathies, which is associated with insufficient oxygen saturation of the basement membranes of blood vessels. Determination of HbA1c is a measure of the risk of complications of diabetes and an effective means of monitoring its treatment [5].

Despite significant advances in the treatment of AMI, the mortality rate caused by HF in patients suffering of AMI in combination with type 2 diabetes remains high, with almost half of patients dying within five years of being diagnosed with HF [15]. The results of studies indicate that the prognosis in patients with HF with preserved EF and HF with reduced EF is comparable [11]. There is a constant increase in the number of such patients, which allows to identify the problem of HF with preserved LV EF and its intermediate level, as one of the non-infectious epidemics of the XXI century [15], this necessitates a deeper understanding of structural, functional and pathophysiological mechanisms of diseases. and progression of HF, which allows to optimize the diagnosis and develop a therapeutic strategy for the treatment of HF [8].

THE AIM

1. To investigate and evaluate the level of BNP concentration in the serum of patients with AMI, which is complicated by HF in combination with type 2 diabetes and without concomitant type 2 diabetes.
2. To establish a relationship between the levels of BNP and LV EF in patients suffering of AMI, which is complicated by HF in combination with type 2 diabetes and without concomitant type 2 diabetes.
3. To study the structural and functional parameters of the heart and to establish the type of geometry in patients with AMI with concomitant diabetes mellitus2, which is complicated by heart failure and without concomitant type 2 diabetes mellitus.
4. To determine the relationship between BNP and HbA1c in patients with AMI, which is complicated by HF in combination with type 2 diabetes.

MATERIALS AND METHODS

120 persons were examined , both males and females. The median age is 65 (59; 74) years. The diagnosis of AMI was established based on the results of clinical, electrocardiographic, biochemical indicators, according to the order of the Ministry of Health of Ukraine № 455 from 02.07.2014 "Unified clinical protocol of emergency, primary, secondary (specialized) and tertiary (highly specialized) care " [4]. According to the consensus of the American Association of Endocrinologists (AAE) and the American Diabetes Association (ADA). Hyperglycemia was considered to be an increase in venous glucose above 7,8 mmol/L. 38% (n=34) had a history of type 2 diabetes, in 62% (n=56) had no carbohydrate metabolism disorders at the time of hospitalization for AMI, in 29% (n=26) had been diagnosed and type 2 diabetes was detected for the first time. At the first stage, all patients were divided into 2 groups according to the clinical diagnosis: group 1 – AMI complicated by HF (n=30), group 2 – patients with AMI complicated by HF and concomitant type 2 diabetes mellitus (n=60). The class of acute CH was determined by the Killip-Kimbal classification [16]. In group 1 (n=30): Killip I was diagnosed in 73% (n=22) of patients, Killip II in 20% (n=6), Killip III in 7% (n=2). In group 2 (n=60): Killip I was diagnosed in 20% (n=12), Killip II in 48% (n=29), Killip III in 32% (n=19). For comparison, the 3-d control group (n=30) was formed of practically healthy people who did not have type 2 diabetes and were representative according to age and sex. All patients with AMI received therapy according to the order of the Ministry of Health of Ukraine № 455 from 02.07.2014 "Unified clinical protocol of emergency, primary, secondary (specialized) and tertiary (highly specialized) care for patients with acute coronary syndrome with ST-segment elevation", which included narcotic analgesics oxygen therapy on demand, nitrates, low molecular weight heparins (enoxiparin), disaggregants (aspirin, clopidogrel or ticagrelor), beta-blockers (in the absence of contraindications), angiotensin converting enzyme inhibitors or angiotensin II receptor blockers, statins. At the prehospital stage, all patients received loading doses of ticagrelor 180 mg or clopidogrel 300 mg, aspirin 150 mg, enoxoparin, depending on body weight. Patients who received systemic thrombolytic therapy were not included in the study. 87% (n=78) of patients underwent urgent coronary angiography with stenting of the infarct-dependent vessel, in 13% (n=12) coronary angiography was not performed due to patient refusal, or the presence of contraindications. Patients in groups 1 and 2 underwent a general clinical examination, general blood test, general urine test, coagulogram, creatinine and urea, total protein, total bilirubin, AST, ALT, total cholesterol, low and high density beta-lipoproteins, blood triglycerides, glucos, troponin I and MB CPK, BNP, HbA1c, transthoracic echocardiography of the heart with the determination of EF LV (Simson)%. LV myocardial mass index (LVMI) was calculated by the formula LVMI = LVM/BSA, where BSA is body surface area, LVM is LV myocardial mass,

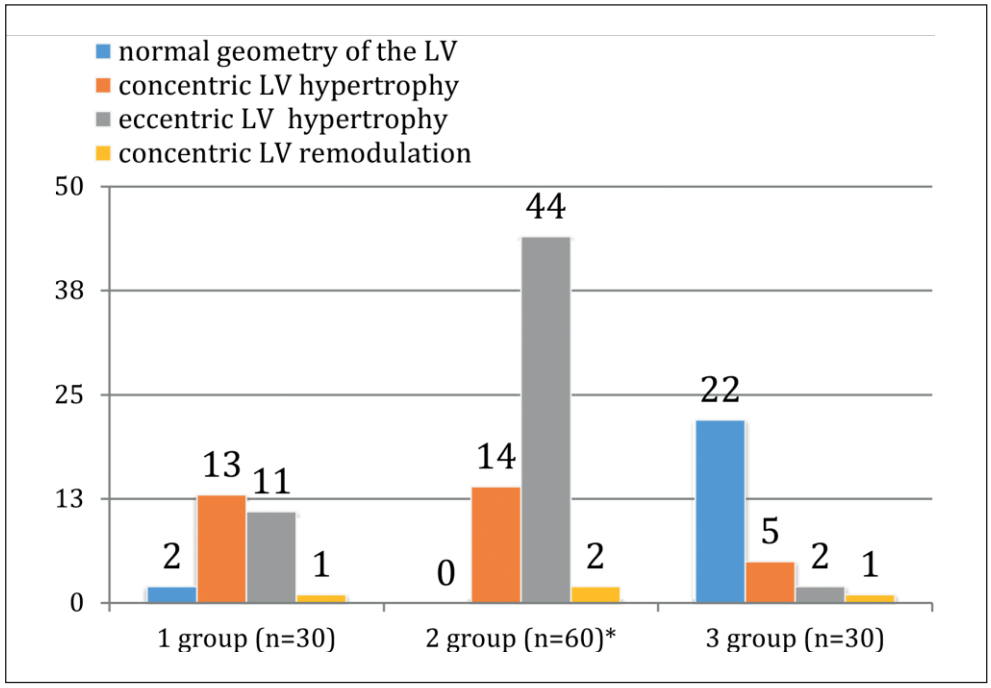

Fig. 1. Types of geometry of the left ventricle of the heart in the examined patients.
Note: comparison of the AMI + DM2 group with the AMI group;
* – p <0,05;

for the calculation of LVM used the formula: LVM = 1,05 [(IVST + LVPWT + EDD) 3 – EDD 3] – 14, where IVST is the thickness of the interventricular membrane in diastole, LVPWT is the thickness of the posterior wall of the LV in diastolol, EDD is the end-diastolic size of the LV. Body surface area (BSA) – according to the formula of RD Mosteller [17]: BSA (m2) = √ (weight (kg) * height (cm) ÷ 3600). To determine the type of LV remodeling, the relative wall thickness of the LV (LVWT) was determined by the formula: LVWT = (LVPWT + IVST) /EDD, where LVPWT is the thickness of the posterior LV wall in diastole; IVST – the thickness of the interventricular septum; EDD is the final diastolic size of the LV.

Types of LV remodeling were determined by A. Genau [18]:
- normal geometry of the LV (LVMI – N; LVWT <0,42);
- concentric LV remodeling (LVMI <N; LVWT> 0,42);
- concentric LV hypertrophy (LVMI > N; LVWT > 0,42);
- eccentric LV hypertrophy (LVMI > N; LVWT <0,42).

The control group underwent bicycle ergometry to exclude coronary heart disease, HbA1c, BNP, echocardiography with the determination of LV EF, LVWT, LVMI.

The study did not include patients with concomitant myocardial damage: unstable angina, secondary hypertension, persistent atrial fibrillation or flutter, dilatation, hypertrophic and secondary cardiopathy, acute left ventricular failure: Killip IV, autoimmune hematological diseases, mental disorders, endocrine disorders (except for patients with DM), patients with acute renal and hepatic insufficiency, agonists and cancer patients.

The type of distribution of the obtained data was performed according to the Shapiro-Wilk criterium. Parametric statistics methods were used when distribution was normal, in particular one-way analysis of variance (ANOVA) with Bonferroni correction. When the data had a distribution different from normal, the Kraskel-Wallis criterium with the Dunn test was used. The obtained data are presented as the mean value with standard error (M±m) or median and interquartile range (Me (Q25-Q75) according to the type of distribution. The correlation was analyzed by the Spearman's test, because one of the variables had not normal distribution. Differences between groups were considered statistically significant with a probability of error of the null hypothesis p<0,05, which is common in biomedical studies.

RESULTS

Analysis of echocardiographic data showed that the left ventricular ejection fraction (Simson),% (LV EF) was statistically significantly lower in patients of group 2 compared with group 1 and a significant difference was found (p<0,05) in patients of LV EF group 2 decreased by 10% (p<0,05) compared to patients of group 1 (Table 1). When estimating the relative wall thickness of the left ventricle (LVWT), a significant difference was found between the indicators of groups 1 and 2 (p<0,05) (Table I). The data obtained and their analysis indicate significant structural and functional disorders in the left ventricular heart muscle, which determines the severity of AMI and confirms the negative impact of type 2 diabetes on the development and prognosis of HF, so control over LV remodeling processes, both acute and the postinfarction period needs more detailed attention.

The division of patients according to the types of LV geometry of the heart is illustrated in Figure 1. In group 2 there is no normal LV geometry, which provides better diastolic filling and systolic emptying. It was found in only 6,7% of respondents in group 1. Against the background of AMI, the formation of eccentric LVH prevailed – in 61% of cases in both groups. Eccentric LV hypertrophy was

Table I. Indicators of trasthoracic echocardiography of the heart in patients having acute myocardial infarction complicated by heart failure with and without concomitant diabetes mellitus.

Indicator	1 group – AMI (n=30)	2 groups - AMI + DM2 (n=60)	3 groups (n = 30)
LV EF (Simson),%	49,1±1,8	44,1±1,6*	58,1±3,0
LVWT	0,44±0,01	0,47±0,01*	0,36±0,03
LVMI, g/m 2	122,2±7,2	134,5±8,4*	85,1±8,5

Note: comparison of the AMI + DM2 group with the AMI group; * – p <0,05;

Table II. Glycosylated hemoglobin in patients with acute myocardial infarction complicated by heart failure with or without concomitant type 2 diabetes.

Indicator	1 group – AMI (n=30)	2 groups - AMI + DM2 (n = 60)	3 groups (n = 30)
HbA1c,%	5,4±0,3	7,5±0,4*	5,1±0,2

Note: comparison of the AMI + DM2 group with the AMI group; * – p <0.05.

Table III. Indicators of natriuretic peptide in patients with acute myocardial infarction complicated by heart failure with or without concomitant type 2 diabetes mellitus.

Indicator	1 group AMI (n=30)			2 groups AMI + DM2 (n=60)			3 groups (n=30)		
BNP, pg/ml	Me	25%	75%	Me	25%	75%	Me	25%	75%
	325,3	302,2	348,4	423,7*	364,6	482,8	45,4	37,6	53,2

Note: comparison of the AMI + DM2 group with the AMI group;* – p <0.05;

more often registered in group 2 than in group 1 by 29,5%. Most patients in group 1 had concentric LV hypertrophy. Comparison of LVMI and LVWT with BNP, which reflects the course of HF, showed a higher incidence of acute heart failure above Killip II in patients with concomitant type 2 diabetes with eccentric LV hypertrophy, which prevailed over data in concentric LV hypertrophy by 49% (p<0,05) (Figure 1).

Inpatients with AMI, left ventricular hypertrophy was detected in 98%. At AMI in patients with concomitant type 2 diabetes mellitus 33,3% more often registered areas of LV hypokinesia, thinning of certain segments of the posterior wall of the LV and IVST, 14% developed LV aneurysm. The obtained data indicate the severity of HF in patients with comorbid pathology and confirm the negative impact of type 2 diabetes on the structural and functional parameters of the heart.

A comparison of glycosylated hemoglobin (HbA1c) in groups 1 and 2 revealed a significant difference between the indicators (p <0,05), which indicates the presence of diabetes and confirms the negative impact of carbohydrate metabolism disorders on the structural and functional parameters of the heart (Table II).

When comparing the natriuretic peptide (BNP) of groups 1 and 2, a statistically significant increase in BNP was found in the group of patients with AMI with HF and concomitant diabetes mellitus (p<0,05) (Table III). This indicates LV myocardial ischemia, impaired myocardial structure and function and confirms the negative impact of carbohydrate disorders on the course of HF, which is confirmed by a significant deterioration in echocardiography in the group of patients with AMI with concomitant type 2 diabetes.

The comparison of parameters between both experimental groups and control group have demonstrated statistically significant differences which are caused by main disease. In second experimental group its comorbidity with DM2 have been considering as influencing factor of these findings.

The correlation analysis revealed a strong relationship between BNP and HbA1c (r=0,713, p=0,009), which indicates the unity of the process of development and course of HF in patients with AMI with concomitant type 2 diabetes.

DISCUSSION

Manifestations of HF depend on LV remodeling, which includes damage to heart cells and extracellular matrix, followed by cell hypertrophy, apoptosis and necrosis of cardiomyocytes, activation and proliferation of fibroblasts, leading to widespread fibrosis and myocardial dysfunction. This process is characterized by progressive ventricular dilatation followed by systolic dysfunction with decreased EF. Early remodeling is characterized by stretching and thinning of the myocardium, dilatation and spherification of the left ventricle. Under these conditions, excessive stretching of the viable myocardium compensates for the decrease in myocardial mass that develops as a result of the lesion. Much attention is paid to patients having heart failure with preserved EF in which have a completely different phenotype and biochemical features different from traditional ones. Therefore, there is a need to identify their characteristics and predictors of negative myocardial remodeling in patients with AMI. This is especially true for patients with metabolic disor-

ders, namely with concomitant diabetes mellitus 2. It is proved that DM2 is a key marker of risk of developing diabetic complications, especially HF [2].

Due to the peculiarities of pathophysiological processes that lead to the development of heart failure as a result of myocardial remodeling after AMI, there is a need to stratify the risk of prognostic myocardial changes based on certain parameters. In addition to the clinical characteristics included in the prognostic scales, BNP is used as a biological marker of the clinical severity of HF.

BNP is a biomarker that has high laboratory sensitivity and specificity and can be used for early diagnosis in order to optimize the choice of treatment, monitoring the effectiveness of therapy

and predicting the consequences of the disease in patients. Its increase at the beginning of the ischemic process in the myocardium before complications depends on the degree of damage to myocardial cells, as evidenced by the deterioration of echocardiography and has a close correlation with HbA1c, which confirms the negative impact of metabolic disorders on the development of HF and evidence of unity.

The study confirms that the degree of LV dilatation in patients with AMI is closely related to comorbidities, in this case DM2. LV dilatation plays an important role in the development of HF. This study confirms a positive correlation between the level of BNP and LV EF, which allows to predict further changes in the geometry, LV function with the development and progression of HF. According to our data, the level of BNP was higher in patients with AMI and concomitant type 2 diabetes, and LV EF was much lower, which confirms the negative impact of metabolic disorders on the development and further progression of HF in this comorbid pathology.

Determination of LVMI and LVWT made it possible to distinguish between LV geometry types in the examined patients. The results of the study confirmed that heart remodeling in patients with AMI is complex and heterogeneous process that requires an individual approach. From our point of view, taking into account indexed indicators provides a better and more individual analysis.

CONCLUSIONS

1. A statistically significant increase in the level of the biomarker of natriuretic peptide in patients with comorbid pathology (AMI with HF and concomitant diabetes mellitus), which indicates a significant degree of cardiomyocyte involvement and causes a severe course of HF has been established.
2. The relationship between BNP and LV EF, which can be used to prognostically assess the severity of HF in this category of patients has been revealed.
3. In patients with AMI, LV geometry is interrelated with the presence of comorbid pathology and confirms the negative impact of type 2 diabetes on the structural and functional parameters of the heart, which determines the severity of HF.
4. A strong correlation between natriuretic peptide and glycosylated hemoglobin in patients with comorbid pathology has been established as a basic biomarker, indicating the aggravating unity of metabolic disorders that accelerate the development and progression of HF.

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