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DIAGNOSTIC SIGNIFICANCE OF NATRIUURETIC PEPTIDE IN ELDERLY PATIENTS WITH ISOLATED SYSTOLIC ARTERIAL HYPERTENSION

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Annotation. *The article solves the problem of determining the diagnostic value of natriuretic peptide (NT-pro BNP) in elderly patients with isolated systolic hypertension and chronic heart failure with preserved ejection fraction. NT-pro BNP levels above 220 pg / ml in combination with transmitral flow by type of relaxation disorder are early criteria for LV diastolic dysfunction.*

Keywords: *isolated systolic arterial hypertension, chronic heart failure natriuretic peptide, elderly age.*

It is estimated that 1-2% of the adult population of the developed countries have heart failure (HF) [3]. Among patients with clinical symptoms of heart failure in the form of shortness of breath, decreased exercise tolerance and edema of the lower extremities, 31-49% have a preserved ejection fraction (EF) of the left ventricle (LV) [9]. This pathology is an urgent public health problem. The proportion of patients with chronic heart failure and preserved LV EF in the population is higher than the proportion of people with CHF with reduced LV EF, but the mortality of patients with HF and preserved LV EF (LV CHFpEF) is high, which is an important clinical problem [6, 1, 2]. The initial stages of LV CHFpEF development have not been comprehensively studied, as most studies have focused on determining disease progression after hospitalization for acute CH decompensation [6]. Most patients complain of decreased exercise tolerance and shortness of breath long before HF decompensation. These symptoms are characteristic of the earlier phase of LV CHFpEF, but they are not specific [10]. Diagnosis of LV CHFpEF is complex and controversial. The European Society of Cardiology (ESC) recommends assessing LV diastolic function using tissue Doppler, transthoracic echocardiography (EchoCG) to determine LV myocardial mass index (MMI) and left atrial volume index (LAVI) and terminal fragment of brain natriuretic peptide (NT-pro BNP), in addition to cardiac catheterization [7]. Since the clinical manifestations of CHF are not specific enough, and when conducting echocardiographic examination (Echo-CG) it is not always possible to detect diagnostically significant changes and if CHF is suspected as an alternative diagnostic approach, it is advisable to determine laboratory biochemical markers in the blood. The European community of cardiologists recommends the determination of

natriuretic peptide (NT-pro BNP) and use the increase in its concentration as a diagnostic criterion in CHF with intermediate and preserved left ventricular ejection fraction (LV EF) [11]. However, at present, the diagnostic value of NT-pro BNP in elderly patients with isolated systolic hypertension and CHF with preserved EF has not been determined.

The aim of the study was to determine the diagnostic value of inactive N-terminal natriuretic peptide in the progression of chronic heart failure in elderly patients with isolated systolic hypertension.

The study is a fragment of research work of the Department of Pediatrics, Family Medicine and Clinical Laboratory Diagnostics of Dnipropetrovsk Medical Academy "Substantiation of integrated approaches to clinical and laboratory diagnosis, prevention and treatment of diseases of the cardiorespiratory system and comorbid conditions in the age aspect (state registration № U 004728".

Material and research methods. The study was conducted in compliance with the main provisions of the Declaration of Helsinki. Informed consent of patients was obtained. There were examined 134 elderly patients with isolated systolic arterial hypertension. The main group included 91 patients aged 71.1 ± 3.5 years with ISAH, LV EF> 50% and NT-pro BNP level> 125 pg / ml. Of them there were 61 women (67%) and 30 (33%) men. The comparison group consisted of 43 patients (27 women and 16 men aged 70.4 ± 3.7 years) with ISAH, LV EF> 50% and NT-pro BNP <125 pg / ml. The average duration of the disease in patients of the main group was 7.5 ± 1.0 years, in the comparison group - 7.1 ± 0.8 years. Both clinical groups were statistically comparable by age ($p = 0.902$ by t-test), sex ($p = 0.629$ by $\chi 2$) and duration of ISAH ($p = 0.796$ by t-test).

Diagnosis of CHF was performed according to the recommendations of the Ukrainian Association of Cardiologists (2017) and the recommendations of the European Society of Cardiology (2016) in the presence of symptoms and signs of heart failure, LV EF> 50% and natriuretic peptide (NT-pro BNP)> 125 pg / ml [8].

Inclusion criteria were the presence of clinical symptoms and signs of heart failure (HF), LV EF> 50%, natriuretic peptide (NT-pro BNP)> 125 pg / ml, and elderly patients.

Criteria for non-inclusion in the study were obesity, lung disease, diabetes mellitus, acute coronary syndrome, atrial fibrillation and palpitation, severe conduction disorders, heart defect, cardiomyopathy, systemic connective tissue disease, thyroid disorders, severe liver and kidney failure, cancer and alcohol abuse.

Plasma NT-pro BNP were determined by chemiluminescent enzyme-linked immunosorbent assay on an Immulite 1000 (USA) analyzer.

The structural and functional state of the heart was studied using one- and two-dimensional echocardiography (ECHO-CG) on the device "Esaote.my lab class C" by the standard methods according to the recommendations of the American Society of Echocardiography and the European Echocardiography Association [5]. Volume findings of LV and left atria (LA) were calculated by the disc method (Simpson) and were indexed by total body area (TBA).

Transmitral flow was assessed according to the recommendations of the

European Association of Cardiovascular Imaging and the American Association of Echocardiography [7]. To assess the diastolic function of the left ventricle there was determined E/A - the ratio of the maximum rate of early diastolic filling (E) to the flow rate during atrial systole (A) - the most studied indicator of LV diastolic function. Together with the indicator E, this ratio allows the gradation of diastolic dysfunction into three types: relaxation disorders, pseudonormal and restrictive type.

Statistical processing of the study data was performed using the methods of parametric and nonparametric analysis using the software package Statistica v. 6.1 (serial № AGAR909E415822FA). The hypothesis of the normality of the distribution of quantitative data was tested by the Shapiro-Wilk test at $p < 0.01$. The average data are presented as an arithmetic mean (M) with a standard error (m), relative - as an absolute value and percentage. The statistical significance of differences in mean values was assessed by Student's t-test for independent samples taking into account the homogeneity of variances (Fisher's test), relative values by Pearson's $\chi 2$ correspondence criterion, including the Yates correction at small values. To analyze the correlation between different factors Pearson's pairwise correlation method (r) was used. Differences were considered significant at $p < 0.05$.

Results and discussion. In 76 (83.5%) of the studied patients the main clinical complaint was shortness of breath during exercise. 80 (87.9%) patients noted general weakness, rapid fatigue during exercise Fifty (54.9%) patients had a disturbed heart rhythm. 16 (17.6%) patients noted the presence of edema of the lower extremities. Drowsiness and agitation were present in 23 (25.3%) patients of the main group.

The six-minute walk test (SMWT) was performed with each patient twice with an interval of 4-5 hours. The condition of patients who were able to cover from 300 to 425 m in 6 minutes corresponded to moderate CHF - II functional class (FC), from 150 to 300 m - moderate CHF - III FC, less than 150 m - severe CHF -IV FC. Among 91 patients with ISAH and CHF, 72 (79.1%) patients were diagnosed with II FC CHF, and 19 (20.9%) - III FC CHF.

Numerous studies in primary practice have shown that serum levels of brain natriuretic propeptide (NT-proBNP) <125 pg /ml by 95 99% exclude the presence of CH of any type.

The level of NT-pro BNP depending on FC CHF and a distance of 6 minutes' walk is shown in Figure 1.

There is a significant difference in the level of NT-pro BNP between II (227.1 ± 10.1) and III (397.1 ± 17.3) FC CHF. The presence of a direct relationship between the level of NT-pro BNP and FC CHF is confirmed by the correlation coefficient equal to $r = + 0.58$ ($p < 0.05$).

Thus, against the background of increasing LV diastolic dysfunction from II to III FC CHF with preserved ejection fraction in elderly patients with ISAH, a progressive increase in the level of NT-pro BNP was registered, which allows to consider this indicator as a marker of desease severity in patients in this category.

Thus, in elderly patients with ISAH and CHF, the level of NT-pro BNP can be used

to assess the disease severity and objectify FC CHF.

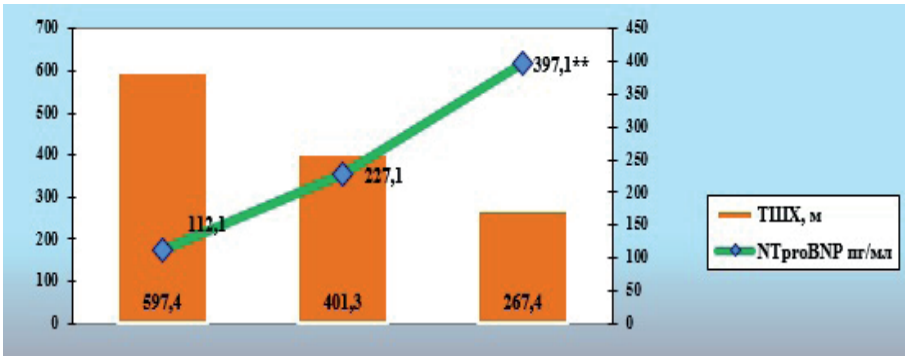

Fig. 1. NT-pro BNP level depending on FC CHF and a 6 minutes' walk distance
*Note. ** - p <0.001 for the group with FC II.*

Analysis of transmitral flow allows us to assert the heterogeneity of LV diastolic dysfunction in elderly patients with ISAH and CHF with preserved LV EF. As a result of the study, the following types of LV diastolic dysfunction were registered: relaxation disorders and pseudonormal type. Analysis of disorders of LV diastolic function and its remodeling profile proved that in patients with ISAH, LV diastolic dysfunction develops against the background of a concentric variant of the LV geometric structure, namely, concentric hypertrophy and concentric remodeling. In patients of the main group, concentric LVH prevailed - 73 (80.2%) patients, and in the comparison group concentric remodeling – 25 (58.1%) patients ($p < 0.01$ by criterion $\chi 2$). Concentric remodeling in patients with ISAH and CHF was diagnosed in 18 (19.8%) patients. Concentric LVH was verified in 18 (41.9%) patients of the comparison group ($p < 0.01$). The aortic stiffness index (ASI) was calculated as the ratio between PAP and stroke volume. ASI in patients of the main group significantly exceeded the value of that in patients of the comparison group - 1.18 ± 0.02 against 0.73 ± 0.02; $p < 0.001$. A direct correlation between ASI LVMMI ($r = +0.487$; $p < 0.001$) and ASI and LVRWT ($r = +0.223$; $p = 0.011$) was proved, which indicates the effect of vascular stiffness on LV remodeling in patients with ISAH and CHF . The value of LAVmax., regardless of gender, exceeded 58 ml, and the level of LAVImax. exceeded 34 ml / m2, which indicates a significant contribution of LA to the filling of the left ventricle in patients with ISAH with CHF EF.

The level of NT-pro BNP depending on the profile of diastolic function of the left ventricle is presented in Fig.2.

Analysis of NT-pro BNP showed that in general in the group of patients with ISAH and CHF with a preserved ejection fraction of left ventricular, this indicator has higher values (262.6 ± 11.0 pg / ml. pg/ml), compared with this marker in patients with ISAH without CHF (112 ± 10.1 pg / ml), which reflects the severity of cardiovascular disorders in these patients.

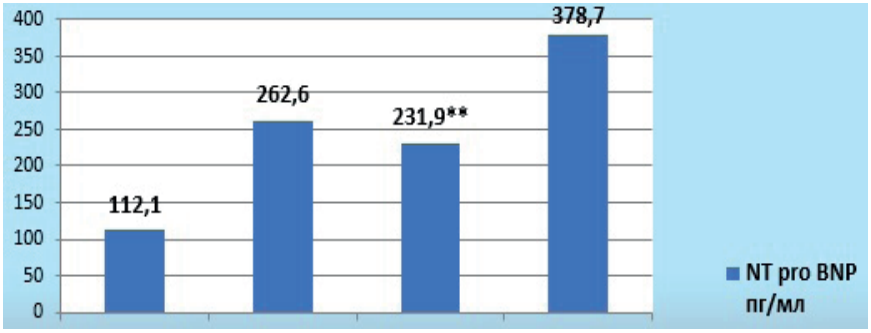

Fig. 2. The level of HT-pro BNP depending on the profile of diastolic function of the left ventricle.
*Note. ** - p <0.001 with indicators of the group with pseudonormal type of DF disturbance.*

The relationship between the profile of diastolic dysfunction and the level of NT-pro BNP was also revealed (Fig. 2). As LV DD progressed from RD to pseudonormal type of LV filling, the level of the indicator significantly increased from (231.9 ± 10.2) pg / ml to (378.7 ± 18.4) pg / ml. A direct correlation (r = + 0.64; p <0.05) between the E /A ratio and the NT-pro BNP concentration was recorded.

This suggests that the level of natriuretic peptide in elderly patients with ISAH and CHFpEF reproduces the state of tension of the heart wall. That is, with increasing diastolic pressure in the left ventricular cavity, the secretion of brain natriuretic hormone increases, which indicates that the level of NT-pro BNP reliably reflects the degree of existing diastolic disorders in patients with ISAH. In patients with LV DF by type of relaxation disorder in all cases, the level of NT-pro BNP exceeded 220 pg / ml.

When conducting an individual analysis in 66 (72.5%) patients of the main group E/A was in the range of 0.66 ± 0.01, and the level of Nt-pro BNP was in the range of 221.7-242.1 pg/ml, which corresponded to type I (relaxation disorder) of DD. In 25 (27.5%) patients with E/A values within 1.28 ± 0.01, the level of NT-pro-BNP corresponded to the range of 360.3-397.1 pg/ml, which was regarded as type II (pseudonormalization) of DD.

Therefore, an increase in NT-pro BNP levels above 220 pg/ml is an early criterion for LV diastolic dysfunction.

Thus, to more accurately determine the type of left ventricular DD in elderly patients, we recorded the maximum rate of transmitral diastolic flow in the period of early (E) and late (A) diastolic filling of the left ventricle and their ratio (E/A). Additionally, natriuretic peptide (NT-pro-BNP) and left atrial volume index were determined.

As a result of the study, we established criteria for early diagnosis of diastolic LV dysfunction in patients with CHF, namely an increase in NT-pro BNP levels above 220 pg/ml in combination with transmitral blood flow by type of relaxation disorder with E/A <0.8 and ASI > 1.18 ± 0.02/

Thus, the level of NT-proBNP is an important addition not only to the clinical data,

but also a criterion that can improve the diagnosis of CHF in patients with ISAH at the primary level of examination and choose the right management tactics.

Discussion. Based on the peculiarities of physiological changes in the elderly, the course of heart failure is characterized by nonspecific clinical symptoms. Therefore, the transition from one type of diastolic dysfunction to the next does not correspond to the classical course of diastolic changes. Consideration of these changes is of great importance for early diagnosis of diastolic disorders in these patients. Taking into account the above, the use of only echocardiographic indicators does not allow to detect early manifestations of LV diastolic dysfunction in the elderly with ISAH and CHF. Consequently, the NT-pro BNP level should be used as an additional criterion.

Therefore, NT-pro BNP is first a marker of the severity of CHF in elderly patients with ISAH, as evidenced by a direct correlation ($r = + 0.58$; $p < 0.05$) between the level of NT-pro BNP and FC CHF, the second - a marker for the diagnosis of LV diastolic dysfunction, as indicated by a direct correlation ($r = + 0.64$; $p < 0.05$) between the ratio of E/A and the concentration of NT-pro BNP. NT-pro BNP levels above 220 pg / ml are an early criterion for LV diastolic dysfunction.

Early diagnosis of types of diastolic dysfunction is necessary for a reasonable differentiated treatment of patients of this age category with ISAH and CHF with preserved LV EF.

Conclusions. 1. NT-pro BNP is a marker of the severity of CHF in elderly patients with ISAH and chronic heart failure with preserved left ventricular EF Between the level of NT-pro BNP and FC CHF a direct correlation ($r = + 0.58$; $p < 0.05$) is established.

2. NT-pro BNP is a marker for the diagnosis of LV diastolic dysfunction. A direct correlation was found between the E/A ratio and the concentration of NT-pro BNP ($r = + 0.64$; $p < 0.05$).

3. The level of NT-pro BNP over 220 pg/ml together with the disturbance of transmitral flow by type of relaxation disorder with a value of $E / A < 0.8$ and IJA> 1.18 ± 0.02 in patients with ISAG are early criteria for disorder of LV diastolic function.

Prospects for further research are to develop differentiated treatment of patients with isolated systolic hypertension and chronic heart failure with preserved left ventricular EF.

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