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Features of Natriuretic Peptides in the Blood Plasma of Patients with Hypertrophic Cardiomyopathy

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Annotation: Hypertrophic cardiomyopathy (GKM), according to the current classification [1], is classified as primary cardiomyopathies, primarily a genetically determined disease of the heart muscle characterized by a complex set of specific morphofunctional changes and a steadily worsening course. The symptoms of the disease are varied and vague and are associated with hemodynamic disturbances - diastolic dysfunction against the background of massive hypertrophy of the left (CH Q) and or right ventricular myocardium, often asymmetric due to thickening of the interventricular septum (IVS), left ventricle (CH Q) with frequent development of outflow tract obstruction, myocardial ischemia, pathology of autonomic circulation regulation and disruption of electrophysiological processes in the heart [2-4]. The prognosis in GCM is variable, so one of the main challenges is to differentiate the risk of fatal complications of the disease, to look for available prognostic prognosis and criteria for evaluating the effectiveness of treatment [5].
Currently, the possibility of determining the level of circulating natriuretic peptides (NUP) as a biochemical sign of the severity of myocardial dysfunction and prognosis in patients with cardiovascular pathology is widely discussed. High levels of NUP in blood plasma have been shown to be an early and sensitive sign of CH Q dysfunction, associated with heart failure severity (HF) [6 - 8], as well as an increased risk of cardiovascular complications and death. In patients with HF and acute coronary syndrome [9-11].
Patients with HKM were also found to have increased NUP levels, possibly due to myocardial hypertrophy, increased CH Q filling pressure, and CH Q obstruction [12, 13]. However, the contribution of each of these components to the genesis of increased peptide secretion is unclear, and further studies are needed to compare the characteristics of clinical hemodynamic status and NUP levels in patients with HCM.
The aim of this study was to comprehensively study the main clinical and hemodynamic parameters and NUP levels in the blood plasma of patients with GKM.

Keywords: hypertrophic cardiomyopathy , natriuretic peptides, diastolic function.

Purpose of the study. To study the relationship between clinical baseline and hemodynamic parameters and levels of natriuretic peptides (NUP) in patients with hypertrophic cardiomyopathy (HCM). Concentrations of N-terminal NUP precursors of the brain and pupils (NT-proBNP) were detected in 110 patients with HCM (mean age 41.8 ± 13.9 years) with obstructive (n = 52) and non-obstructive (n = 58) forms of the disease. NT-proPNP) and conducted a comprehensive echocardiographic study. The composition of NUP in the blood does not depend on the age of the patients, the contractile function of the left ventricle (CHQ) and its volume. Patients with CHQ outflow tract obstruction have a higher functional class of heart failure, CHQ myocardial thickness and mass, and the size of the left atrium is larger than in patients with a non-obstructive form of the disease. High plasma levels of NT-proPNP and NT-proBNP are associated with the severity of heart failure and CHQ diastolic dysfunction, the severity of CHQ hypertrophy and mitral regurgitation, and the degree of

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CHQ outflow tract obstruction. In dead patients (n = 6), the level of NUP in the blood was higher than in survivors.

The aim of the study was to investigate the relationship between baseline clinical and hemodynamic parameters and levels of natriuretic peptides (NUPs) in patients with hypertrophic cardiomyopathy (GKM).

Materials and methods.
Concentrations of N-terminal precursors of cerebral and pupillary NUP (NT -proBNP) were detected in 110 patients with GCM (mean age 41.8 ± 13.9 years) with obstructive (n = 52) and non-obstructive (n = 58) forms of the disease. NT-proPNP) and conducted a comprehensive echocardiographic study.

Results.
The composition of NUP in the blood does not depend on the age of the patients, left ventricular (CH Q) contractile function and its volume. Patients with CH Q outflow tract obstruction had a higher functional class of heart failure, CH Q myocardial thickness and mass, and left atrium size greater than patients with a non-obstructive form of the disease. High plasma levels of NT-proPNP and NT-proBNP are associated with the severity of heart failure and CH Q diastolic dysfunction, the severity of CH Q hypertrophy and mitral regurgitation, and the degree of CH Q output pathway obstruction. Dead patients (n = 6) had higher NUP levels in the blood than survivors.

Conclusion. High levels of NT-proBNP and NT-proPNP in the blood plasma in patients with GKM are associated with diastolic dysfunction and CH Q myocardial hypertrophy, as well as the severity of hemodynamic and functional disorders.

Materials and methods
We examined 110 patients (69 men and 41 women, mean age 41.8 ± 13.9 years) with a diagnosis of G KM based on the recommendations of the International Committee of GM Specialists (ACC / ESC) [5]. All patients underwent a comprehensive examination, including 12 ECG recordings, 24-hour ECG monitoring, echocardiography (E x G), and determination of blood concentrations (NT-proBNP and NT- proPNP) of the N-terminal parts of the brain and puzzle NUP precursors. was completed .) . Patients were included in the study during inpatient follow-up 5–7 days after discontinuation of previous drug therapy.
An obstructive form of the disease was identified in 52 (47%) patients, which was CH Q In OT maximum pressure gradients - 25 mm Hg and increase gone about information _ _ based on detected . Art. A paroxysmal form of pupillary fibrillation (AF) was observed in 9 (8.2%) patients with persistent, 13 (11.8%) patients.
ExokG is recorded on MINDRAY's HDI 5000 ultrasound device. During the study, standard one- and two-dimensional indicators of CH Q function, CH Q myocardial mass index (CH QMI) were calculated using the field length method. In addition, Doppler parameters of CH Q diastolic function (DF) were evaluated: CH Q isovolumic relaxation time (IBV); early (E) and late (A) CH Q maximum rate of diastolic filling and their ratio (E / A); left ventricular (DT) early diastolic filling slows blood flow. The pressure gradient in CH Q was determined according to the standard method using a continuous wave Doppler study. In addition, the degree of mitral regurgitation was assessed in each case, given the high incidence of mitral valve insufficiency in patients with GCM. However, both the depth of penetration of the regurgitant flow into the left pupil cavity (CH B) and the width of its isthmus and the density of the regurgitant flow were taken into account. DF was not assessed in 9 patients with persistent MA because CH Q filling of MA was more dependent on hemodynamic load in CH Q than its corresponding diastolic properties. In addition, 3 more patients experienced technical difficulties in determining the optimal quality of transmitral flow. Based on transmitral flow parameters, central hemodynamic data, and analysis of clinical presentation in 98 subjects, CH Q diastolic filling types were identified: normal, impaired relaxation, pseudonormal, or restrictive (adapted to diagnostic criteria). [14]).
It is known that NUPs are divided into biologically active C-terminal and inactive N-terminal fragments before entering the bloodstream. The latter is characterized by a longer half-life and high concentrations in blood

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plasma, which makes it easier to determine their content than to determine the content of C-terminal fragments for diagnosis [15 - 17]. In this study, we determined the levels of NUP N-terminal precursors.

Venous blood samples from patients were placed in ethylenediaminetetraacetate (EDTA) tubes, and the plasma formed after centrifugation was immediately frozen and stored at -70 ° C until analysis. Plasma levels of NT-proBNP and NT-proPNP were determined by enzyme immunoassay using NT-proBNP and NT-proANP (1-98) kits from Biomedica (Austria). According to the manufacturer of the kit, the upper limit of the norm for NT-proBNP is 350 fmol / ml, and for NT-proBNP is 1945 fmol / ml. According to these "intersection points", an increase in the level of puzzle NUP was detected in 96 (87%) patients, the brain - in 85 (77%) patients.

Statistical processing of the results was performed using the software package STATISTICA 6.0 (Stat Soft). The differences were considered significant at $p < 0.05$

Research results

It shows the main clinical and hemodynamic characteristics of patients examined with general GCM, as well as two groups depending on the presence / absence of CH Q outflow tract obstruction.

HF symptoms (functional class II-III - NYHA FC) were detected in 76% of patients, and complete absence of functional limitations was noted in only 6 (5.4%) young patients (all had no CH Q obstruction). With the increase in HF FC, a gradual increase in the level of CH Q hypertrophy was noted, a more pronounced enlargement of the LA cavity was noted, which indicated an increase in diastolic dysfunction of the CH Q CH diastolic dysfunction.

As the functional limitations increased, an increase in the content of cardiac NUPs was noted (Fig. 1). However, differences in NT-proBNP content between the considered subgroups of patients began to be significant with HF FC and with NC-proBNP content with FC II. Nevertheless, the correlation analysis revealed that functional impairments were significantly associated with both NUP levels.

The composition of peptides does not depend on the age and sex of patients, left ventricular contractile function and its volume. However, a moderate correlation was found between both peptide levels and left ventricular filling type, FC heart failure rate, and hypertrophy rate (CH QMI). Weaker, but still significant, NUP levels were related to the transverse measurement of LA, the ratio of LA / final diastolic measurement - EDD, the magnitude of the pressure gradient at CH QOT, and a number of individual Doppler parameters of transmitral diastolic. flow The transverse dimension of LA is more closely related to the N-proCNP content, and the degree of mitral regurgitation is significantly correlated only with this peptide (Table 2). Patients with obstructive GKM are characterized by more pronounced functional impairments than patients without CH Q obstruction, greater Q thickness and mass of CH Q myocardium, greater LA size, and LA / ER ratio, with persistent or paroxysmal pupillary fibrillation. were more likely to The condition of patients with CH QOT obstruction is more consistent with II-III HF FC than in patients without such obstruction (87 and 67%, respectively, $p < 0.05$). It should be noted that the mean level of NUP in these patients was significantly higher . The majority of patients examined (91%) had some diastolic abnormalities, and 63% had severe diastolic dysfunction (pseudonormal or restrictive type CH Q filling).

A correlation was found between the degree of diastolic dysfunction and HF heart failure. In addition, CH Q myocardial hypertrophy increased with increasing Q Q DF disorders. A pseudonormal or restrictive type of CH Q filling (associated with an increase in diastolic pressure in the CH Q cavity) was detected in 68% of patients with obstruction and 59% without CH QOT obstruction.

In general, an increase in the content of NUPs with CH Q DF disorders was noted, which can also be seen when comparing the average concentrations of peptides in patients with varying degrees of severity of CH Q diastolic dysfunction (Fig. 2) and when. conduct a correlation analysis (see Table 2). However, patients with small and severe disorders of CH Q DF differed significantly in NUP levels (590.2 ± 428.7 and 927.2 ± 811.2 fmol / ml for NT-proBNP, $p < 0$, 01; 3208.2 ± 1289, 4 and 4248.9 ± 4648.9). Fmol / ml for NT-proPNP, $p < 0.001$).

57 (52%) patients had grade II or higher mitral regurgitation. However, CH Q obstruction was noted in 52 (47%) patients, confirming the key role of anterior systolic displacement of mitral valve leaflets in the formation of a systolic pressure gradient in CH Q and mitral regurgitation.

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An increase in LA transverse dimension was noted with an increase in mitral regurgitation: in people with small ("trace") regurgitation it was 4.06 ± 0.62 cm, small / moderate - 4.37 ± 0.59 cm (compared to p <0.05). With size in patients with mild regurgitation), mean / severe - 5.35 ± 0.82 cm (p <0.01 less than in patients with less severe regurgitation). A similar pattern was found with respect to CH Q hypertrophy: the stronger the regurgitation, the more pronounced the hypertrophy. Thus, if the mean CH QMI was 106 ± 18 g / m2 in patients without regurgitation, 135 ± 26 g / m2 in patients with grade II, and 149 ± 35 g / m2 in patients with grade III. the last two cases p <0.05 compared with CH QMI in patients without regurgitation).
Both NUP levels have been reported to increase with the severity of mitral regurgitation. In the correlation analysis, only the dependence on the level of NT-proPNP was identified.
The presence of MA in patients with GKM was associated with higher levels of NT-proPNP than in patients with sinus rhythm. Thus, the average level of the peptide in the permanent form of MA is 7125.2 fmol / ml, in the paroxysmal form - 5970.6 fmol / ml, with a sinus rhythm.
- 4224.7 fmol / ml. It should be noted that such dynamics of NT-proPNP coincided with a change in LA volume, which is characterized by a gradual increase in the rate of intrabulhythmic arrhythmogenic disturbance (from sinus rhythm to constant AF form). hemodynamics. As for NaT-proBNP, unlike NaT-proPNP, there were no significant differences in mean levels of this peptide in the blood between small groups of patients with sinus rhythm and MA. During follow-up (average 3 years), 6 patients died. Of these, 3 had a restrictive type of CH Q diastolic filling in all 3 patients with persistent form of pupillary fibrillation and sinus rhythm. In addition, dead patients were characterized by higher NUP levels than survivors (№T-proBNP: 7575.1 ± 2219.9 and 4225.4 ± 2443.1 fmol / ml, p <0.002; №T-proBNP: 1029, 02.3 and 023+). +688.2 fmol / ml, respectively, p <0.05).

Discussion

It is known that cardiac NUPs in the form of prohormones (proBNPs and proPNPs) are present in the secretory granules of pupillary and ventricular cardiomyocytes and are broken down into biologically active C-terminal fragments before being released into the bloodstream; PNP and MNP and inactive N-terminal parts, viz. T-proPNP number and T-proBNP number. ANP and BNP bind to specific receptors and cause natriuresis, diuresis, vasodilatation, inhibit renin, angiotensin II, aldosterone production, have antiproliferative and antifibrotic effects, have cytoprotective effects, and inhibit cardiomyocyte hypertrophy does. Increased myocardial stress (“heart wall stress”) is the main stimulus for the synthesis and secretion of peptides [9, 16, 18]. The object of our study is a special, "hospital" group of patients with GKM with one or another symptomatology and significant functional disorders, with a predominance of patients with asymptomatic forms of the disease in the general population, and often it diagnosed only at autopsy. [19].
In this paper, NT-proPNP and NT-proBNP levels in the blood plasma of patients with GKM are related to heart rate and severity of CH Q diastolic dysfunction, severity of CH Q hypertrophy, degree of mitral regurgitation, and presence. puzzle fibrillation. In addition, patients with CH Q outflow tract obstruction had more pronounced clinical, hemodynamic, and functional impairments, and correspondingly higher NUP levels in the blood.
It is known that NUP levels are closely related to the presence and severity of HF. This also applies to patients with HCM previously shown [20] and confirmed by the results of this study. Given the high prevalence of heart failure, it seems logical that severe CH Q diastolic dysfunction (92% of cases) in the patients we examined was a major cause of functional limitations in GCM. In our study, a moderately significant correlation was found between the composition of both peptides and the type of CH Q filling. However, the lowest levels of NUPs were noted in patients with a normal type of diastolic filling, and the highest levels in their blood plasma were noted in patients with the most severe, restrictive-type disorders. In the transition from isolated relaxation disorder to pseudo-normalization, a fundamental “hemodynamic jump” occurs, the left ventricular diastolic filling pressure increases, which enhances NUP production. Similar results were obtained in a number of other studies in which an increase in NUP levels was noted with increasing diastolic dysfunction and an increase in CH Q filling pressure [21 - 23]. Thus, CH Q diastolic dysfunction, which forms the basis of hemodynamic disturbances in GCM and determines the clinical presentation of the disease, appears to be the main trigger for NUP secretion in this disease. Given the data from the correlation analysis, it should be noted that №H-proBNP and №H-proBNP also reflect DF and FC HF disorders to the same extent

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in patients with GKM. In this case, NUP can act as a marker that accurately reflects both the severity of the clinical manifestations of the disease and the severity of the underlying pathophysiological process (diastolic dysfunction). There is a stronger correlation between №T-proBNP levels and the severity of CH Q hypertrophy and CH QOT obstruction. zi due to differences. this affects the increase in peptide levels. A very close correlation was shown between NLP levels and the level of CH Q hypertrophy, which is not surprising since myocardial hypertrophy is one of the leading causes of diastolic dysfunction in patients with HKM. A number of authors have shown that detection of puzzle NUP in cardiomyocytes of the interventricular septum of patients with GCM is more pronounced with interstitial fibrosis, cardiomyocyte hypertrophy, and myofibrillar architectonics disturbances [13], compared with cardiomyocytes that do not contain this peptide. In addition, there is evidence that BNP CH Q, which results in puzzles, is an important predictor of myocardial mass in patients with hypertrophy [24].

It is known that the presence of CH Q obstruction leads to a significant increase in CH Q myocardial systolic tension. In a study by K. Nasegawa et al. [12] No BNP was found on interventricular septum biopsies in patients with non-obstructive GCM. In the obstructive form of the disease, CH Q end-diastolic pressure (EDB) was significantly higher in patients with BNP in biopsy samples than in patients not in biopsy samples. Previously, CH Q obstruction has been shown to be one of the possible causes of increased BNP levels in patients with GCM [25].

CH Q obstruction has an effect on NUP synthesis, which leads not only to systolic tension of CH Q myocardium, but also to mitral insufficiency generated in GCM, mainly due to anterior systolic displacement of mitral valve nodes. This indicates that there is a significant correlation between the ENP level not only with the degree of mitral regurgitation, but also with the magnitude of the pressure gradient in the CH QOT. In contrast to BNP, which responds to an increase in pressure in the CH Q cavity, the main stimulus for ANP synthesis is elongation of the LA wall, which is an overload of pus volume relative to pressure (diastolic dysfunction) (mitral regurgitation, pupillary fibrillation). known to be more characteristic . . This was convincingly demonstrated in our study. Thus, the transverse dimension of LA (note that volume overload is associated with more pronounced atriomegaly than pressure overload) was more closely related to puzzle peptide content, and the degree of mitral regurgitation was only related to this peptide level. . In addition, patients with pupillary fibrillation and patients with sinus rhythm also differ from each other only in the level of ANP. The mechanisms for increasing ANP and BNP levels in HCM are shown in the figure. 3.

Because of the low number of deaths recorded during follow-up, it would be incorrect to draw conclusions about the prognostic significance of determining NUP levels in patients with GKM. And yet, it should be noted that the patients who died were characterized by high levels of NUP in their blood plasma. Apparently, high levels of NUP indicate a more pronounced severity of hemodynamic disturbances and electrical instability of the myocardium, and the detection of a significant increase in NUP levels in the blood in patients with GCM requires a more proactive treatment tactic. to such patients.

Thus, determining the level of hemodynamic and functional disorders and the level of NUP, which reflects the resulting pathophysiological processes in the hypertrophied myocardium, can be used as an additional diagnostic indicator of the severity of the condition in patients with GCM. Depending on the dynamics of these levels, it is possible to assess the severity of the disease and the effectiveness of drug therapy.

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