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Dynamics of N-terminal fragment of the brain natriuretic peptide as a marker and prognostic factors in patients with chronic heart failure and anaemia

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Abstract

Aim

To determine plasma levels of the N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) in patients with chronic heart failure (CHF) and anaemia during different treatments with the use of basic drugs and iron supplements.

Materials and methods

An open, randomized study included 208 patients aged 45-75 years (mean age 60.6±1.4) with New York Heart Association (NYHA) class I-IV CHF of ischaemic origin (mean class 3±0.85). Among 174 patients, there were 78 men (44.8%) and 95 women (55.2%). Depending on the therapy, all patients were divided into 4 groups: Group I received basic drugs only; Group II received basic drugs and methoxy polyethylene glycol-epoetin beta; Group III (which included patients with iron deficiency) received basic drugs and iron supplements; Group IV received combination therapy comprising basic drugs, methoxy polyethylene glycol-epoetin beta, and iron supplements. Before and after treatment, the levels haemoglobin, iron, ferritin, transferrin, erythropoietin, NT-proBNP, and systolic and diastolic function of the left ventricle were determined.

Results

In all groups of patients with CHF and anaemia, an increase in NT-proBNP plasma levels was diagnosed. During the therapy with basic drugs, a decrease in NT-proBNP plasma levels was not significant. In the three other groups with different combinations of therapy, a decrease in NT-proBNP plasma levels was statistically significant.

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Conclusion

These results reflect the prognostic value of determining NT-proBNP plasma levels in patients with CHF of ischaemic nature and anaemic syndrome in order to select an effective treatment and evaluation of treatment.

Keywords:

Chronic heart failure, anaemia, N-terminal of the prohormone brain natriuretic peptide

Introduction

In recent years, the relationship between chronic heart failure (CHF) and anaemia has been actively discussed. Main neurohumoral mediators in heart failure are divided into vasodilating (nitric oxide, natriuretic peptide (NP), [1] prostaglandins, adrenomedullin) and vasoconstricting (angiotensin, aldosterone, adrenaline, vasopressin, endothelin 1). Hormones that are natural antagonists of the renin-angiotensin system, sympathoadrenal system, aldosterone, and vasopressin refer to NP [1].

In 1988, the NP, isolated from guinea pig brain, was called brain natriuretic peptide (BNP) [2,3].

In CHF, BNP is produced mainly in the ventricles of the heart, although normally BNP gene expression is determined predominantly in the atrial tissue. Initially, BNP is synthesized as a prohormone (pro BNP 108), which is subsequently cleaved into biologically active C-terminal, BNP 32, and inactive N - terminal fragment (NT-pro BNP 76); and it is stored in the granules of cardiomyocytes [4]. Normally, BNP and NT-proBNP in equal picomolar concentrations are present in blood plasma. With the onset and progression of left ventricular (LV) dysfunction, NT-proBNP levels exceed BNP levels by 2-10 times. Comparison of the data of echocardiography with BNP levels showed the possibility of the diagnosis of systolic and diastolic dysfunction of the LV according to NP levels [5].

Together with the diagnostic and prognostic role of BNP, it can be also used in the plasma to monitor therapy in patients with severe CHF. Results of the study [6] showed that control of the BNP levels is an important criterion for evaluating the effectiveness of therapy.

The dynamics of BNP levels in patients with NYHA class II-IV CHF with ventricular tachycardia during amiodarone therapy was evaluated [7]. However, the results of the studies evaluating the effect of ß-blockers are contradictory [8-11]. In patients with isolated diastolic dysfunction, plasma BNP levels were significantly increased proportionally to the severity of diastolic dysfunction [4].

It is noted that according to BNP levels, a differential diagnosis of complex forms of CHF can be conducted; severity of LV dysfunction can be assessed; treatment tactics can be chosen; its performance can be monitored; and prognosis can be assessed. Leading pathophysiological form of CHF in patients with hypertension is LV diastolic dysfunction with preserved contractility of the heart. NT-proBNP is produced by the myocardium of the ventricles in response to stretching their walls and an increase in LV end-diastolic pressure [12]. Thus, the determination of BNP and its final fragment, NT-proBNP, enables to evaluate the effectiveness of a given therapy.

In some studies [13], an increase in NT-proBNP >128 pg/mL during 20 weeks in women with congenital heart disease was shown. It should be noted that the increase in BNP levels is accompanied by LV diastolic dysfunction during formation and progression of its hypertrophy [14-16]. The question of the relationship of changes of NT-proBNP plasma levels in patients with CHF and anaemic syndrome during treatment still remains little known and highly controversial.

The purpose of this study is to determine NT-proBNP plasma levels in patients with CHF and anaemia during different treatments using basic drugs and iron supplements.

Materials and methods

An open, randomized study included 208 patients aged 45-75 years (mean age 60.6±1.4 years) with NYHA class I-IV CHF of ischaemic origin (mean class 3±0.85). 158 patients had a history of myocardial infarction (MI) which happened from 1 to 10 years ago. According to the criteria for inclusion, 174 patients (78 (44.8%) men and 95 (55.2%) women) had clinical signs of CHF and anaemia. The mean duration of the disease was 16.5±1.2 years. Anaemia was diagnosed in women with haemoglobin levels (Hb) <11g/dL and in men with Hb levels <12g/dL.

Exclusion criteria were severe or malignant hypertension, acute disorders of cerebral circulation of <12 months, acute MI of 6 months, acute coronary syndrome, chronic obstructive pulmonary disease, and mental disorders.

All patients, depending on the therapy, were divided into 4 groups: Group I received only basic drugs

for CHF: angiotensin-converting enzyme (ACE) inhibitors, ß-blockers, diuretics, glycosides, nitrates; Group II received therapy of basic drugs and methoxy polyethylene glycol-epoetin beta; Group III (included patients with iron deficiency) received basic drugs and iron supplements; Group IV received combination therapy comprising basic drugs, methoxy polyethylene glycol-epoetin beta and iron supplements. Each group, depending on NYHA classification of CHF, was divided into A and B subgroups.

The subgroup IA included 27 patients with NYHA class I-II CHF of ischaemic origin and anaemia, and the subgroup IB included 22 patients with NYHA class III-IV CHF and anaemia. Of the 49 patients, 34 patients developed CHF as a result of NYHA class III-IV stable angina, and 15 patients had it as a result of postinfarction myocardiosclerosis. 8 patients were diagnosed with concomitant type 2 diabetes and 1 patient with hypertension.

Group II included 38 patients with CHF and anaemia treated with combination therapy of methoxy polyethylene glycol-epoetin beta at a dose of 0.60 mg/kg (50 units) once a month and basic drugs. If Hb levels increased by less than 10 g/L per month, the dose was increased by about 25% per month until an individual target Hb level was reached. If the rate of increase in Hb levels was more than 2 g/dL per month or Hb concentration rose, approaching 12 g/dL, the dose was reduced by about 25%. If Hb levels continued to rise, the treatment was stopped until Hb levels started to decline. Methoxy polyethylene glycol-epoetin beta was appointed to patients without iron deficiency. Iron deficiency was considered when ferritin levels were <100 µg//L and 299 µg/L if transferrin saturation was <20%. The mean age of patients was 59±1.5 years, including 18 men and 20 women. Group II was also, depending on the NYHA classification of CHF, divided into subgroups A and B. The subgroup IIA included 18 patients with NYHA class II CHF of ischaemic origin and anaemia, and the subgroup II B included 20 patients with NYHA class III CHF and anaemia. Of the 39 patients, 19 patients developed CHF as a result of stable angina, 19 patients developed CHF as a result of postinfarction myocardiosclerosis. 14 patients were diagnosed with concomitant type 2 diabetes, and 26 patients were diagnosed with hypertension.

Group III included 43 patients with CHF and anaemia treated with combination therapy of intravenous (IV) iron and basic drugs. Iron (III)-hydroxide sucrose complex was prescribed as Venofer at a dose of 200 mg 2 times per week during 5 weeks. Intravenous iron supplements were administered to patients with CHF and anaemia with iron deficiency. The mean age was 62.5±1.4 years, including 16 men and 27 women. Group III, depending on the NYHA classification of CHF, was divided into subgroups A and B. The subgroup IIIA included 20 patients with NYHA class I-II CHF of ischaemic origin and anaemia, and the subgroup IIIB included 23 patients with NYHA class III-IV CHF and anaemia. Of the 43 patients, 15 patients developed CHF as a result of the stable angina, and 28 patients developed CHF as a result of postinfarction myocardiosclerosis. 13 patients were diagnosed with concomitant type 2 diabetes, and 31 patients were diagnosed with hypertension.

Group IV included 44 patients with CHF and anaemia treated with combination therapy of methoxy polyethylene glycol-epoetin beta, IV iron, and basic drugs. Methoxy polyethylene glycol-epoetin beta was administered in a dose of 50 IU once a month, and iron (III)-hydroxide sucrose complex (Venofer) in a dose of 200 mg 2 times per week for 5 weeks. IV iron was administered to patients with CHF and anaemia with iron deficiency. The mean age of patients was 59.9±1.2 years, including 19 men and 25 women. Group IV was also, depending on the NYHA classification of CHF, divided into subgroups A and B. The subgroup IVA included 24 patients with NYHA class I-II CHF of ischaemic origin and anaemia, and the subgroup IVB included 20 patients with NYHA class III-IV CHF and anaemia. Of the 44 patients, 17 patients developed CHF as a result of NYHA class III-IV stable angina and 27 patients developed CHF as a result of postinfarction myocardiosclerosis. 19 patients were diagnosed with concomitant type 2 diabetes and 30 patients were diagnosed with hypertension.

In each group, the patients were divided according to sex, age, duration of disease, and treatment strategy. The distribution of the patients with CHF and anaemia in groups and their clinical characteristics are shown in Table 1.

The control group included 34 patients with NYHA class I-IV CHF of ischaemic origin without anaemia. The mean age of patients was 58.4±1.6 years; mean duration of disease 14.2±2.1 years; there were 21 women and 13 men. The control group was also like the main groups divided into subgroups A and B: the subgroup A included 16 patients with NYHA class I-II CHF of ischaemic origin without anaemia; the subgroup B included 18 patients with NYHA class III-IV CHF of ischaemic origin without anaemia. Table 2 shows the demographic and clinical characteristics of the patients in the control group.

Table 1. **Clinical characteristics of patients from the main groups and laboratory parameters from the subgroups**

Indicators	I group n=49		II group n=38		III group n=43		IV group n=44	
	n	%	n	%	n	%	n	%
NYHA class I CHF and anaemia	11	22.5%	–	–	1	2.3%	2	4.5%
NYHA class II CHF and anaemia	16	32.6%	18	47.3%	19	44.2%	22	50%
NYHA class III CHF and anaemia	17	34.7%	20	54.1%	16	37.2%	17	38.6%
NYHA class IV CHF and anaemia	5	10.2%	–	–	7	16.2%	3	6.8%
MI	15	30.6%	19	51.4%	28	65.1%	27	61.3%
Hypertension	11	2%	26	68.4%	31	72.1%	30	68.2%
Type 2 diabetes	8	16.3%	14	37.8%	13	30.2%	19	43.2%
Previous treatment:								
ACE inhibitors	40	81.6%	30	78.9%	37	86%	30	86.4%
Angiotensin II receptor blockers	9	18.4%	8	21.1%	14	32.6%	14	31.8%
Nitrates	39	79.6%	25	67.5%	28	65.1%	32	72.7%
Diuretics	27	55%	21	56.7%	40	93%	42	95.5%
Digoxin	4	8.1%	5	13.5%	8	18.6%	7	15.9%
ß-blockers	41	83.7%	29	78.3%	39	90.7%	32	72.7%
Amiodarone	29	76.3%	21	55.2%	19	44.1%	17	38.6%
Ivabradine	10	20.4%	8	21.6%	11	25.6%	8	18.2%
Laboratory indicators	**Subgroup IA**	**Subgroup IB**	**Subgroup IIA**	**Subgroup IIB**	**Subgroup IIIA**	**Subgroup IIIB**	**Subgroup IVA**	**Subgroup IVB**
Hb, g/L	103.8±1.3	104.0±30	100.2±3.2	87.9±4.3	101.2±1.9	103±2.1	97.8±2.2	94.6±2.5
Hematocrit, %	47.2±6.8	48.0±7.5	38.1±1.5	38.8±1.3	39.1±1.5	38.5±1.2	41.8±1.4	53.3±9.7 1
Iron, µmol/mL	14.7±1.3	15.8±1.3	17.2±1	17.1±2.1	14.4±1.4	15.5±0.8	18.1±4.1	2.8±1.3
Plasma ferritin, µg/L	45.2±10.2	50.5±11	160.3±23.5	127.6±24.8	77.8±15.8	90.6±15.8	42.3±7.7	63.3±12.4
Transferrin saturation,%	<20%	<20%	>20%	>20%	<20%	<20%	<20%	<20%
Erythropoietin, IU/mL	18.6±6.1	24.1±6.4	7.3±1.8	12.8±5.7	7.2±1.8	50.1±19.1	2.8±0.4	3.7±0.8
NT-proBNP, pg/mL	1500±415.2	1173±144.9	1779.5±206.9	1817.5±170.2	2245.4±175.1	2421±154	2478.4±201.7	2306.1±260.5

At the initial stage in hospital, patients underwent some tests and examination, namely their medical history and complaints were studied; heart rate and blood pressure on both arms were measured; general clinical blood and urine tests, electrolyte composition of the blood, levels of lipids, glucose, creatinine, uric acid and hepatic enzymes were also checked.

All patients had levels of Hb, iron, ferritin, transferrin, erythropoietin, NT-proBNP, and parameters of systolic and diastolic LV function before and after treatment determined. All patients underwent a follow-up examination after 1 month. Echocardiography and Doppler echocardiography were performed again after 20 weeks. LV ejection fraction in patients with NYHA class I CHF was ⩽50%, with class II ⩽45%, with class III ⩽35%, and with class IV ⩽25%.

Statistical analysis

Software packages of Excel and Statistica were used for statistical processing of the results. Data were analyzed using paired Student's t-test. Differences were considered significant at $P<0.05$.

Results

According to the results, NT-proBNP plasma levels decreased in the subgroup IA from 1500±415.2 pg/mL to 962.6±164.7 pg/mL (P=1.2) and in the subgroup IB from 1173±144.9 pg/mL to 874.3±129.1 (P=1.5). In patients with CHF and anaemia, the dynamics of NT-proBNP during the treatment with basic drugs was not significant. And the confirmation of these insignificant results was observed among patients with mild, moderate, and severe CHF.

Table 2. **Clinical characteristics of patients from the control group and laboratory indicators from its subgroups A and B**

Indicators	Control group, n=34	
NYHA class I CHF and anaemia	n	%
	1	2.9%
NYHA class II CHF and anaemia	15	44.1%
NYHA class III CHF and anaemia	17	50%
NYHA class IV CHF and anaemia	1	2.9%
MI	13	38.2%
Hypertension	17	50%
Type 2 diabetes	11	32.4%
Previous treatment:		
ACE inhibitors	30	88.2%
Angiotensin II receptor blockers	4	11.8%
Nitrates	13	38.2%
Diuretics	33	97.1%
Digoxin	13	38.2%
ß-blockers	27	79.4%
Amiodarone	14	41.1%
Ivabradine	9	26.5%
Laboratory indicators	**Subgroups of the control group**	
	A	**B**
Hb, g/L	125.1±1.1	126.8±1.2
Hematocrit,%	54.8±1.8	53.5±1.2
Iron, µmol/mL	16.3±0.7	16.3±1.2
Plasma ferritin, µg/L	143.8±26.8	149.9±27.5
Transferrin saturation,%	>20%	>20%
Erythropoietin, IU/mL	13.3±4.7	14.4±3.9
NT-proBNP, pg/mL	1545.6±204.5	1688.5±187

NT-proBNP plasma levels in the subgroup IIA decreased from 1779.5±206.9 pg/mL to 837.3±198.6 pg/mL (P<0.01). NT-proBNP plasma levels in group II decreased from 1817.5±170.2 pg/mL to 999.6±160.9 pg/mL (P<0.01). Attention was drawn to the fact that patients with CHF and anaemia during the treatment with a combination of basic drugs and methoxy polyethylene glycol-epoetin beta had positive dynamics of NT-proBNP which was statistically significant. These changes were observed among patients with mild, moderate, and severe CHF.

NT-proBNP plasma levels in the subgroup IIIA decreased from 2245.4±175.1 pg/mL to 1128.7±118 pg/mL (P<0.001); in the subgroup IIIB decreased from 2421±154 pg/mL to 1782±184.4 pg/mL (P<0.05). In patients with CHF and anaemia during the treatment with a combination of basic drugs and IV iron, positive dynamics of NT-proBNP was significant. Reliability of the results in patients with mild CHF was observed more often than in patients with moderate and severe CHF.

Dynamics of NT-proBNP plasma levels in the subgroup IVA was negative. Their levels decreased from 2478.4±201.7 pg/mL to 1128.7±118 pg/mL (P<0.001). In the subgroup IVB, NT-proBNP plasma levels decreased from 2306.1±260.5 pg/mL to 1314.8±159.51 pg/mL (P<0.01). Compared with baseline values, patients with CHF and anaemia during the treatment with a combination of methoxy polyethylene glycol-epoetin beta, IV iron, and basic drugs, had significant positive dynamics of NT-proBNP. High reliability of the results was observed in patients with mild, moderate, and severe CHF.

Comparison of the results showed that NT-proBNP plasma levels were diagnosed high in all groups and subgroups of patients with CHF and anaemia. NT-proBNP plasma levels decreased in patients with CHF and anaemia during all 4 compared treatment tactics. However, a decrease in NT-proBNP plasma levels during the treatment with basic drugs in the subgroups IA and IB was not significant. In contrast to the results of Group I, three other groups and their subgroups had a significant decrease in NT-proBNP plasma levels. Attention was drawn to the degree of reduction in NT-proBNP plasma levels in these three groups. The compared results, indicating differences in a decrease of NT-proBNP plasma levels according to applied treatment strategy, are presented in Table 3.

Table 3. **Comparable figures of decrease of NT-proBNP plasma levels from patients with CHF and anaemic syndrome**

Groups and subgroups	NT-proBNP levels before treatment, pg/mL	NT-proBNP levels after treatment, pg/mL	P	Δ,%
Control A	1545.6±204	–		
Control B	1688.5±187	–		
IA	1500±415	962.6±164.7	1.2	–35.83
IB	1173±144.9	874.3±129.1	1.5	–25.46
IIA	1779.5±206.9	837.3±198.6	<0.01	–29.01
IIB	from 1817.5±170.2	999.6±160.9	<0.01	–45
IIIA	2245.4±175.1	1128.7±118	<0.001	–49.73
IIIB	2421±154	1782±184,4	<0.05	–26.4
IVA	from 2478.4±201.7	1128.7±118	<0.001	–54.45
IVB	2306.1±260.5	1314.8±159.51	< 0.01	–42.98

Discussion

According to the results, patients with CHF and anaemic syndrome, during the therapy with basic drugs, had an insignificant decrease in NT-proBNP plasma levels. This implies that the main therapy for patients in this category should primarily be the treatment of anaemia. In patients with CHF and anaemic syndrome during therapy, the most significant decrease in NT-proBNP plasma levels was observed in the subgroup IVA. Among severely affected patients of this subgroup, a reduction in NT-proBNP plasma levels was -42.98% (P<0.01). In patients with NYHA class I-II CHF and anaemia, a triple combination of IV iron with methoxy polyethylene glycol-epoetin beta reduces NT-proBNP plasma levels to the greatest degree by -54.45 (P<0.001). When comparing the results of different treatments in patients with NYHA class I-II CHF and anaemia, a marked reduction in NT-proBNP plasma levels by -29.01% (P<0.01) was found in patients who had erythropoietin therapy, methoxy polyethylene glycol-epoetin beta, and a greater reduction in NT-proBNP plasma levels by -45% (P<0.01) in severely affected patients of this category.

Group III patients with CHF and anaemia treated with IV iron had the most reduced NT-proBNP plasma levels, by -49.7% (P<0.001), in moderately affected patients; on the other hand, the least reduced NT-proBNP plasma levels, by -26.4% (P<0.05), were in severely affected patients.

The literature also suggests that in presence of anaemia in patients with CHF, its treatment with methoxy polyethylene glycol-epoetin beta or IV iron reduces NT-proBNP plasma levels. The greatest reduction of NT-proBNP plasma levels was observed during combination therapy of methoxy polyethylene glycol-epoetin beta and IV iron [13,17].

Conclusion

The results of the study reflect the prognostic value of determining NT-proBNP plasma levels in patients with CHF of ischemic origin and anaemic syndrome in order to select correct treatment and evaluate the effectiveness of treatment.

Conflict of interest: None declared

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