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Original scientific paper

Impact of Hemoglobin Concentration on Plasma B-type Natriuretic Peptid Level and Left Ventricle Echocardiographics Characteristics in Chronic Kidney Disease Patients

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A B S T R A C T

Anemia is common in patients with chronic kidney disease (CKD) and contributes to cardiovascular alterations. Recent findings suggest that B-type natriuretic peptide (BNP) is a sensitive biomarker for left ventricular dysfunction, but relationship between hemoglobin and BNP in CKD patients is unclear. Hemoglobin, plasma BNP and serum creatinine levels were measured in 49 patients with CKD (without heart failure), divided in two groups according to the hemoglobin status (cut-off point 110 g/L). All patients underwent echocardiography in order to assess left ventricular (LV) morphology and function. The results showed that in the group of patients with hemoglobin levels under 110 g/L BNP levels were significantly elevated ($p<0.001$), as well as left ventricular mass index ($p<0.001$). Systolic and diastolic LV function were significantly better in patients with hemoglobin levels above 110 g/L ($p<0.001$). Hemoglobin levels were inversely related to BNP values ($r=–0.451$, $p<0.001$). Significantly negative correlation between BNP level and creatinine clearance ($p=0.009$), and significantly positive correlation between BNP level and left ventricular mass index (LVMI) were established. A similar but positive relationship was observed between hemoglobin levels and creatinine clearance ($p<0.01$). We established statistically significant negative correlation between hemoglobin levels and LVMI ($r=–0.564$, $p<0.001$). In conclusion, BNP and hemoglobin levels depend on the renal function. Anemia may contribute to elevated BNP levels in CKD patients, and may represent an important confounder of the relationship between BNP and cardiac alteration in these patients.

Key words: *hemoglobin, B-type natriuretic peptide, left ventricle, chronic kidney disease*

Introduction

Cardiovascular diseases are the leading cause of morbidity and mortality in patients with chronic kidney disease[1]. Left ventricular hypertrophy (LVH) is frequently observed cardiac alteration in these patients[2]. Pathogenesis of LVH in patients with chronic kidney disease is multifactorial and includes systolic hypertension, anemia, older age life, etc. Anemia is a basic characteristic of chronic kidney disease, and pathogenetically besides other factors includes the deficit of erythropoietin, abbreviated life of erythrocytes, the deficit of nutritional factors and disturbance of iron metabolism. In a state of relative tissue hypoxia, anemia causes peripheral vasodilatation as a compensatory response, and the peripheral vasodilatation and decrease of the blood viscosity resulting in an increased vein inflow as well as an increase in cardiac output. Cardiac output increases to meet metabolic needs and leads to the remodeling of left ventricle[3]. Studies so far have indicated that B-type natriuretic peptide (BNP) is a sensitive biomarker of left ventricular hypertrophy[4,5], and that anemia can have a significant impact on the concentration of B-type natriuretic peptide (BNP) in the plasma[6].

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The aim of this study was to determine the relationship between the concentration of hemoglobin in the blood and the concentration of BNP in plasma, and their impact on geometry of the left ventricle in patients with chronic kidney disease.

Patients and Methods

Patients

The study included 49 patients (19 men and 30 women) with chronic kidney disease (creatinine clearance <60 mL/min), without the need for renal replacement therapy. All patients were divided into two groups based on their hemoglobin status: the group with hemoglobin concentration lower than 110 g/L and the group with hemoglobin concentration higher than 110 g/L. The study was conducted at the Clinic of Nephrology, University Clinical Center in Sarajevo, during the period from September 2006 to December 2008. The study did not include patients with coronary heart disease, congenital heart malformations or heart failure.

Methods

Echocardiograph examination was carried out using ultrasonic recorder Toshiba SSH 140 with 2.5 MHz transducer and the cardiologist who was not familiar with the clinical patient data. Measurements of left ventricular posterior wall thickness (PWd), interventricular septal wall thickness (IVSd) and left ventricular internal diameter (LVIED) were made from long-axis parasternal position at the end of diastole. Left ventricular (LV) mass was calculated according to Devereux modified formula of the American Society of Echocardiography, and LV mass index was derived by dividing LV mass to body surface area. LVH was defined as the left ventricular mass index (LVMI) >131 g/m^2 for men and >100 g/m^2 for women in accordance with Framingham criteria[7]. Echocardiographic measurements in all patients were performed on the day when the blood sample was taken to measure the level of BNP.

Level of plasma B-type natriuretic peptide was measured by the technique of enzymatic immunoassay using commercial kit assays AxSYM BNP on appliance AxSYM Abbott. Levels of BNP up to 100 pg/mL were considered as normal values. Concentration of hemoglobin in the blood and serum concentration of creatinine were determined by the routine laboratory methods. All measurements were performed at the Institute for Clinical Biochemistry at the University Clinical Center Sarajevo, the same day when the blood sample was taken. The level of creatinine clearance (mL/min) was calculated by using the Cockroft-Gault formula: (140-age) × body weight (kg) /0.81 × serum creatinine (ìmol/L), whose result for female persons is multiplied with the constant 0.85.

Statistics

Statistical analysis was performed using SPSS software (version 16). Data were expressed as means and standard deviation (SD) for normally distributed variables and as median with interquartile ranges for non-normally distributed data. Comparations between groups were made by Student's t-test and Mann-Whitney U test, for normally and non-normally distributed date. Coefficient of correlation was assessed by Spearman. We assumed a statistical significance for $p<0.05$.

Results

From a total of 49 observed patients with chronic kidney disease, 26 patients had blood level of hemoglobin below 110 g/L (average value 91.5 g/L) and 23 patients above 110 g/L (128.8 g/L). Demographic, laboratory and echocardiographic characteristics of patients per group are shown in Table 1. Between the tested groups there were no significant differences in age.

Average value of B-type natriuretic peptide concentration in the group of patients with severe renal anemia (Hgb<110 g/L) was significantly higher compared to the group of patients with a hemoglobin level above 110 g/L (median 922.6 pg/mL *vs.* 103.4 pg/mL, $p<0.001$, Figure 1). Value of creatinine clearance, expressed in mL/min, was significantly lower in the group of patients with a greater degree of renal anemia (33.8 mL/min *vs.* 62.7 mL/min, $p<0.001$).

Echocardiographic analysis indicates that LV mass index is significantly higher in renal patients with more pronounced anemia and lower creatinine clearance ($p<0.001$). Patients with hemoglobin levels higher than 110 g/L have a significantly better systolic (EF 57.2% *vs.* 54.2%, $p<0.001$) and diastolic LV function (E/A 0.90 *vs.* 0.75, $p<0.001$).

The inverse relationship of BNP concentration and the hemoglobin level of statistical significance in ob-

TABLE 1
CHARACTERISTICS OF THE CKD PATIENTS BY HEMOGLOBIN STATUS

	GROUP 1 (hemoglobin <110 g/L)	GROUP 2 (hemoglobin >110 g/L)
N	26	23
Age (years)	52.2±3.5	55.6±2.3
Hemoglobin (g/L)	91.5±2.4	128.8±2.5*
BNP (pg/ml)	922.6 [492.5–2066.7]	103.4* [42.2–430.3]
Creatinine clearance (ml/min)	33.8±2.4	62.7±7.9*
IMLV (g/m^2)	185.4±8.05	141.4±8.3*
EF (%)	54.2±2.3	57.2±1.2*
E/A	0.75±0.03	0.90±0.05*

Results are presented as mean ± standard deviation or as median with interquartile range
* $p<0.05$ in comparation with group 1(patients with hemoglobin status <110 g/L)

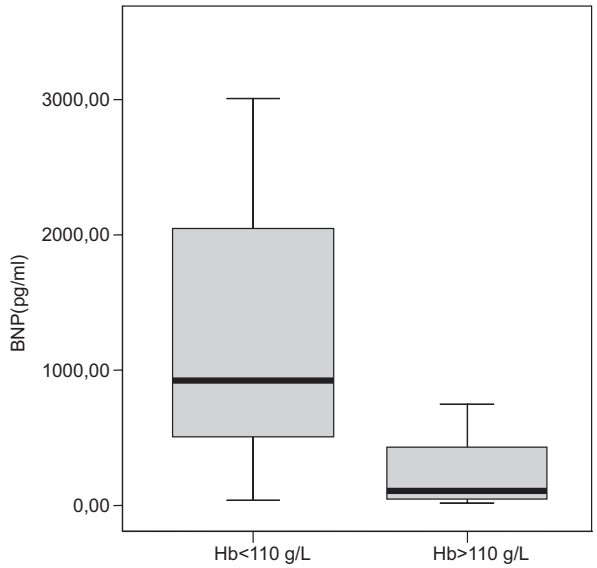

Fig. 1. Plasma BNP concentration in CKD patients by hemoglobin status. Bars indicate maximum and minimum value, while the square and its central bar are showing the intequartile range and median.

served patients with chronic kidney disease was showed (r=–0.451, p<0.001, Figure 2).

Significant negative relationship between level of hemoglobin and LV mass index, as well as significant positive relationship between level of BNP and LV mass index were demonstrated (Table 2).

At the same time creatinine clearance, as an indicator of endogenous renal function, shows a significant positive correlation with the hemoglobin value, and the inverse correlation with the BNP concentration. The level of BNP in plasma is shown as a negative indicator of systolic and diastolic LV function, while the hemoglobin is in positive correlation with ejection fraction of LV and with the parameter of diastolic LV function, E/A.

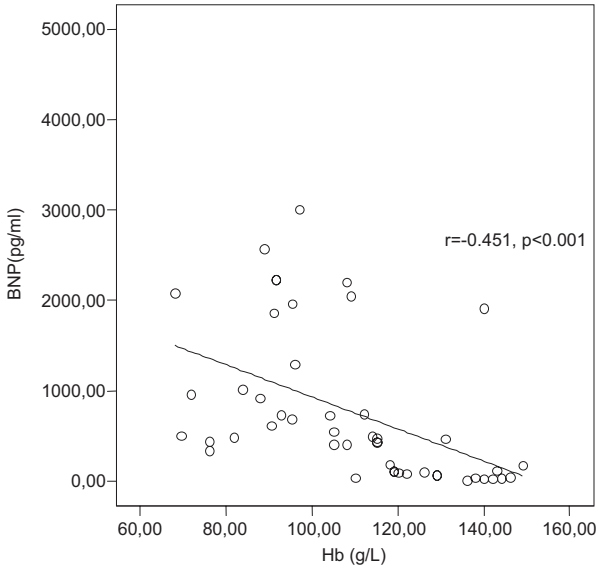

Fig. 2. Relationship between BNP and hemoglobin concentrations in CKD patients.

TABLE 2
CORRELATION BETWEEN HEMOGLOBIN AND BNP STATUS WITH ESTIMATED PARAMETERS IN ALL PATIENTS WITH CKD

	LV mass index	Creatinine clearance	EF	E/A
Hemoglobin	r=–0.564	r=0.594	r=0.148	r=0.335
	p<0.001	p<0.01	p=0.319	p=0.02
BNP	r=0.617	r=–0.569	r=–0.059	r=–0.319
	p<0.001	p=0.009	p=0.692	p=0.029

Discussion

Anemia associated with chronic kidney disease is defined with low hemoglobin values and accompanied with significant cardiovascular morbidity. Mechanisms of cardiovascular adjustment to anemia are reflected in the increasing cardiac output, initiated by the decrease of vascular peripheral resistance and increase of the heart rate and left ventricular contractility due to increase in concentration of catecholamines and non-catecholamines inotropic factors and chemoreceptor stimulation by hypoxia and increase in sympathetic nerve activity[3,8].

The results of our study clearly confirm the relationship between the degree of anemia and degree of kidney dysfunction, and the size of LV mass index. Patients with hemoglobin levels below 110 g/L have a significantly greater LV mass index and significantly poorer systolic and diastolic LV function.

At the same time it has been confirmed that renal patients with lower hemoglobin values have significantly higher values of BNP concentration. Identified significant negative correlation between hemoglobin status and BNP concentration in monitored patients, as well as between the level of creatinine clearance and BNP concentration, indicates that higher BNP concentrations, as anemia, may be the result of renal impairment.

This study has also confirmed significantly higher BNP concentrations in patients with more pronounced LV hypertrophy, and significant positive correlation of BNP levels with the LV mass index. This observation may reflect increased production of BNP in association with left ventricular hypertrophy. BNP is a polypeptide which is being synthesized as a preproBNP in the ventricular myocardium and enzymatically cleaved into proBNP. Prohormone (proBNP) is under the action of enzymes from the group of proteases cleaved to the biologically active form of BNP and amino terminal portion of prohormone – NTproBNP. Active hormone BNP is being excreted in ventricles in response to myocite stretching and is therefore believed to be a more sensitive indicator of the ventricular structure from other natriuretic peptides.

Vasodilatation and hemodynamic alteration in renal anemia contribute to an increase in venous blood return

to the heart and the gradual development of LVH. Left ventricular hypertrophy is eccentric, characterized by increase of LV internal diameter and normal attitude of the wall thickness toward diameter of the cavity, as it occurs in other forms of load volume. It is known that LV mass increases with kidney disease progression[9]. Expansion of the ventricular wall in response to volume expansion and increase of pressure in the ventricle, together with neurohumoral stimulation, induces BNP secretion. Significantly higher values of BNP in renal patients with greater LV mass index, and significantly positive correlation between BNP levels and LV mass index, as well as significantly negative correlation of BNP values with diastolic function of hypertrophic myocardium indicates that the BNP is a sensitive indicator of ventricular structure and function.

Significantly higher levels of BNP in the presence of the higher level of kidney failure could be the result of combining renal failure and the presence of cardiac disease, respectively LV hypertrophy. Mark et al.[10] showed that the level of BNP depends on renal and cardiac dysfunction, as well as numerous factors associated with the progression of kidney diseases, including the anemia and LVH. Study by Knudsen et al.[6] suggests that anemia may contribute to the increase of BNP level in the absence of heart failure, and that anemia contributes significantly to the relation between BNP concentrations and cardiac function, as well as prognosis.

In conclusion, results of our study indicate that the levels of hemoglobin and the levels of BNP depend on renal function, but also there is causal relation between anemia, levels of BNP and cardiac alterations, such as LV hypertrophy in chronic kidney disease. Anemia may contribute to elevated BNP levels in CKD patients, and may represent an important confounder of the relationship between BNP and cardiac alteration in these patients.

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UTJECAJ KONCENTRACIJE HEMOGLOBINA NA RAZINU NATRIURETSKOG PEPTIDA TIPA B I EHOKARDIOGRAFSKE KARAKTERISTIKE LIJEVE SRČANE KLIJETKE U BOLESNIKA SA KRONIČNOM BUBREŽNOM BOLESTI

SAŽETAK

Anemija je često prisutna u bolesnika sa kroničnom bubrežnom bolesti (KBB) i doprinosi pojavi kardiovaskularnih promjena. Noviji nalazi sugeriraju da je natriuretski peptid tipa B (BNP) senzitivan biomarker disfunkcije lijeve srčane klijetke, ali je odnos između hemoglobina i BNP-a u bolesnika sa KBB još nejasan. Razine hemoglobina, plazmatskog BNP-a i serumskog kreatinina su mjerene u 49 bolesnika sa KBB (kreatinin klirens <60 mL/min), razdijeljene u dvije grupe prema statusu hemoglobina (točka razdvajanja 110 g/L). Svim pacijentima je urađena ehokardiografija u cilju utvrđivanja morfologije i funkcije lijeve srčane klijetke (LK). Rezultati pokazuju da su u grupi bolesnika sa razinom hemoglobina iznad 110 g/L, razine BNP-a bile signifikantno povećane ($p<0,001$), kao i indeks mase lijeve klijetke ($p<0,001$). Sistolna i dijastolna funkcija LK su bile signifikantno bolje u bolesnika sa razinom hemoglobina iznad 110 g/L ($p<0,001$). Razine hemoglobina su u inverznom odnosu sa razinom BNP-a ($r=–0,451$, $p<0,001$). Utvrđena je signifikantna negativna korelacija između razine BNP-a i kreatinin klirensa ($p=0,009$), te signifikantna pozitivna korelacija između razine BNP-a i indeksa mase lijeve klijetke (IMLK). Sličan, ali pozitivan odnos je uočen između razina hemoglobina i kreatinin klirensa ($p<0,01$). Utvrdili smo statistički signifikantnu negativnu korelaciju između razina hemoglobina i IMLK ($r =–0,564$, $p<0,001$). U zaključku, razine BNP-a i hemoglobina su ovisne od bubrežne funkcije. Anemija može doprinositi povećanju razina BNP-a u bolesnika sa KBB, te može predstavljati značajan čimbenik odnosa između BNP-a i srčanih promjena u ovih bolesnika.