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Correlation of B-type Natriuretic Peptide (BNP) with Left Ventricle Systolic Function Echocardiographic Parameters in Patients with Chronic Kidney Disease (CKD)

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Abstract

Introduction. BNP plasma levels are significantly increased in heart failure and have an excellent negative predictive value for left ventricular dysfunction. Measurement of BNP level is useful for "screening" in high-risk populations. It is suitable for detection of left ventricular hypertrophy (LVH) and/or dysfunction and risk assessment in the sub-acute phase of acute myocardial infarction in hypertensive patients. The aim of our study was to find whether BNP may correlate with the left ventricular systolic function, i.e. its echocardiographic parameters in chronic kidney disease (CKD) patients.
Methods. In a prospective study performed at the Department of Nephrology and Clinic for hemodialysis at the Clinical Center in Sarajevo we followed-up 80 patients stratified in three separate groups according to CKD stage (Stage III, IV and V) for two years, regardless of their cardiovascular symptoms. We analyzed levels of BNP before and after diuretic therapy or hemodialysis and echocardiographic characteristics of the left ventricle.
Results. There was a strong negative correlation between BNP values and the size of the EF before (rho=-0.692, $p<0.0001$) and after diuretic therapy (rho=-0.683, $p<0.0001$) for patients in CKD stage III, stage IV (rho=-0.314, $p>0.05$) and after diuretic therapy (rho=-495, $p<0.05$) Similarly, a negative correlation was found for BNP and EF values before (rho=-0.432, $p<0.05$) and after hemodialysis (rho=-0.556, $p<0.01$) for stage V CKD.
Conclusions. Our study confirmed that the value of BNP in CKD patients may represent a measure of left ventricular systolic function with a strong negative correlation with ejection fraction. BNP measurement is a reliable parameter for further follow-up and prognosis in patients with established left ventricular dysfunction, acute coronary syndrome and for estimation of the left ventricular dysfunction.

Key words: BNP, left ventricle systolic function, chronic renal disease

Introduction

B-type natriuretic peptide (BNP) is a hormone which is secreted from the ventricle in response to elevated volume and filling pressures. Levels of BNP depend on the presence or absence of chronic kidney disease (CKD). Along with the aging of the left ventricle (LV) and developed stiffness an increase in BNP is observed until it develops systolic or diastolic LV dysfunction. Cardiac and atrial natriuretic peptide (ANP) as well as the brain natriuretic peptide (BNP) act as key regulators of homeostasis of body fluid volume and blood pressure, by decreasing the retention of salt and water inhibiting the intensive action of the sympathetic nervous system and vasoconstrictor hormone secretion [1]. BNP plasma levels are significantly increased in heart failure. Measurement of BNP level is useful for "screening" in high-risk populations [2]. In addition, BNP has an excellent negative predictive value for left ventricular dysfunction. It is also suitable for "screening" in hypertensive patients for detection of left ventricular hypertrophy (LVH) and/or dysfunction (LVD) and risk assessment in the sub-acute phase of acute myocardial infarction. Measurement of BNP level is also useful for treatment monitoring and optimization of the heart failure therapy [3].
The question might be why, when and in which population we should determine the BNP? Of course it's not necessary to determine the BNP level in the entire population, but only in patients with positive cardiovascular (CV) anamnesis and in presence of CV risk factors. That's why the European Society of Cardiology guides for LVH diagnosis with BNP in these patients as an early diagnostic procedure.

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The normal value of BNP(<100pg/ml) is associated with high probability that the patient is without LVD. In cases of increased BNP values another diagnostic procedures should be carried out in order to establish a more detailed morpho-functional characteristics of the damaged myocardium.
However, BNP levels cannot replace echocardiography and similar techniques, because these methods provide different information. Thus, for cardiologists determination of the natriuretic peptides is a useful complementtary parameter to the standard clinical investigation of patients with LVD [4,5].

Material and methods

In a prospective study performed at the Department of Nephrology and Clinic for hemodialysis at the Clinical Center in Sarajevo we followed-up 80 patients stratified in three separate groups according to CKD stage (Stage III, IV and V) for two years, regardless of their cardiovascular symptoms. We analyzed levels of BNP before and after diuretic therapy or hemodialysis and echocardiographic characteristics of the left ventricle.
Group A: 28 patients, CKD stage III (GFR 30-60 ml/min/1.73m²), 12 males, mean age 65.3±19.36 years and 16 females, mean age 67.7±13.51 years.
Group B: 25 patients, CKD stage IV (GFR 15-29 ml/min/1.73m²), 15 males, mean age 58.3±13.51 years and 10 females, mean age 69.2±11.41 years.
Group C: 27 hemodialysis patients, CKD stage V (GFR< 15 ml/min/1.73m²), 16 males, mean age 50.5±16.52 years and 11 females, mean age 62.6±17.70 years.
All patients were subjected to detailed personal medical history, physical examination, BMI calculation, ECG, echocardiography at the beginning and end of study, and laboratory tests (BNP and TnII) before/after diuretic therapy and hemodialysis.
Hemodialysis of bicarbonate type, and low and high-flow dialyzers with programmed ultrafiltration (UF) were used.
Echocardiography was performed on the machine Hewlett Packard 5500 Sonors, Philips Inc.
Left ventricle mass as a sign of myocardial hypertrophy was determined based on the formula for calculation of left ventricle mass by the Penn convention:

$$\textbf{LV mass}=1{,}04\,[(\text{LVIDd}+\text{IVS}+\text{LVPWd})^3-(\text{LVIDd})^3]+13{,}6\ \text{g}$$

where LVIDd-left ventricle in diastole dimension, IVS-interventricular septum thickness in diastole and LVPW-posterior wall thickness in diastole. Left ventricle volume as a sign of myocardial hypertrophy was determined using the following formula:

$$\textbf{Volume LV (RWT)} = 2x\ (\text{LVPWd}/\text{LVIDd})$$

where LPWd-posterior wall thickness in diastole, LVIDd-left ventricle in diastole dimension.
BNP concentration was determined by immunoassay (quantitative determination of BNP in human plasma), centrifuged at room temperature at 3000 rpm for 3 minutes (ARCHITECTE 2000 SR machine).
We used descriptive and analytical method for statistical analysis. The groups were compared with the Student's *t*-test for normally distributed variables; the Mann Whitney U-test was used for skewed variables distribution and x^2 test for categorical values. SPSS statistical software (version 13.0 SPSS) was used for the analysis, and $p<0.005$ level was considered significant. Data were presented as mean ± standard deviation.

Results

Out of 80 patients**,** 19 patients had normal value of BNP (BNP<100) and regular EF (EF 53-66%). Five patients with normal values of BNP had a lower EF (EF approximately 52-40%).

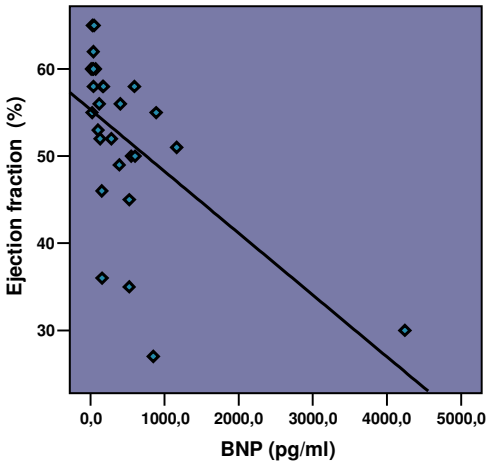

Fig. 1. Correlation between BNP and ejection fraction size in stage III CKD before therapy (rho=-0,692; p<0,0001). Results of the individual values of BNP (pg/ml) compared to the size of the ejection fraction (%) of patients in stage III CKD, before the use of diuretic therapy

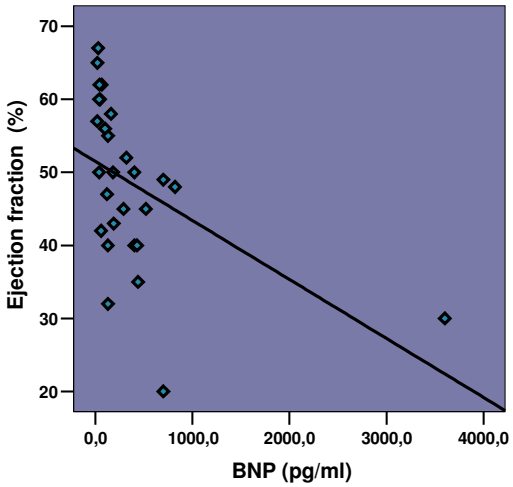

Fig. 2. Correlation between BNP and ejection fraction size in stage III CKD after therapy (rho=- 0,683; p<0,0001). Results of the individual values of BNP (pg/ml) compared to the size of the ejection fraction (%) of patients in stage III CKD after the use of diuretic therapy

None of the patients with normal values of BNP had extremely low EF (EF <40%).
Based on the results of this study, the total number of patients (80) 22 patients with normal BNP value (BNP<100) did not have verified LVH on echocardiography, while three of them with normal BNP value had verified LVH.
Thirteen (13) patients with an elevated BNP value (BNP>100) did not have verified LVH, while 42 of them with elevated BNP value had verified LVH on echocardiography.
Based on the assumption of investigated association between the value of BNP and EF (LVEF) we present some interesting observations.
In patients with stage III CKD before use of diuretic therapy there was strong negative correlation between BNP and EF values (rho=-0.692; p<0.0001) (Figure 1.).

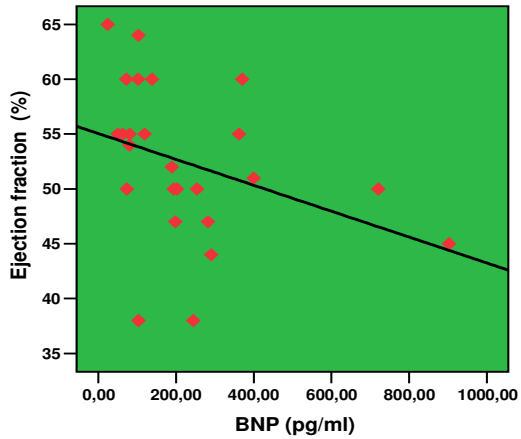

Fig. 3. Correlation between BNP and ejection fraction size in stage IV CKD after therapy (rho=-0.495; p<0.05). Results of a single value of BNP (pg / ml) compared to the size of the ejection fraction (%) of patients in stage IV CKD and after the use of diuretic therapy.

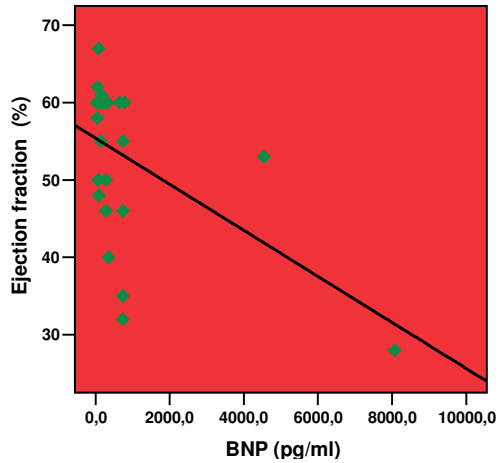

Fig. 4. Correlation between BNP and ejection fraction size in HD patients before dialysis (rho=-0.432; p<0.05). Eesults of a single value of BNP (pg/ml) compared to the size of the ejection fraction (%) in HD patients before hemodialysis.

In these patients, even after the use of diuretic therapy negative correlation between BNP values and the size of the EF was confirmed (rho=-0.683, p <0.0001) (Figure 2).

In CKD patients with stage IV before diuretic therapy the correlation between BNP and EF (rho=-0.314, p>0.05) was not found. However, after the administration of adequate diuretic therapy in these patients a strong, negative correlation between BNP and EF values (rho=- 0.495, p<0.05) was demonstrated (Figure 3).
In CKD patients with stage V before HD therapy there was strong, negative correlation between BNP and EF values (rho=-0.432, p<0.05) (Figure 4), which was maintained after dialysis (rho=-0.556, p<0.01) (Figure 5).

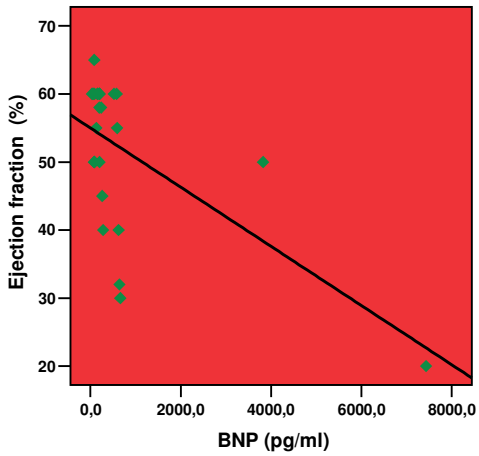

Fig. 5. Correlation between BNP and ejection fraction size in HD patients after hemodialysis (rho=- 0.556; p<0.01). Results of a single value of BNP (pg/ml) compared to the size of the ejection fraction (%) in HD patients after hemodialysis.

In order to verify LVH on echocardiography in addition to EF, the following parameters were also measured: left ventricular mass, volume of the left ventricle and left ventricular shortening fraction (FS).
Mean BNP level in serum of patients with CKD stage III with LVH before diuretic therapy (654.31±223.07) was significantly higher than mean BNP level in serum of patients without LVH (58.43±15.48, p<0.0005).
Similar pattern of mean BNP level in serum of CKD stage III patients with LVH after the use of diuretic therapy (530.73±188.24) was significantly higher than the mean BNP level in serum of patients with CKD stage III without LVH (59.28±13.68, p<0.0005).
In addition, we observed that CKD stage III patients with elevated BNP levels (BNP>100 pg/ml) have LVH, whereas patients with baseline values of BNP (BNP≤100 pg/ml) didn't have LVH on echocardiography. The mean BNP value in patients with LVH was greater compared to mean BNP level in patients without LVH before and after diuretic therapy.
In contrast, there was no correlation between the BNP levels and LVH parameters in patients with CKD stage III before use of diuretics, neither between BNP levels and left ventricular volume, nor between BNP and fractional shortening.
Nevertheless, in patients with CKD stage III we found a strong, positive correlation between fractional shortening (FS) and left ventricular volumes before and after ad-

ministration of diuretic therapy (rho=0.587, p<0.001 (Figure 6) before diuretic therapy; rho=0.592, p<0.001 after diuretic therapy) (Figure 7).

Mean BNP level in serum of CKD stage IV patients with LVH before use of diuretic therapy (464.00±100.34) was significantly higher compared to CKD stage IV patients without LVH (125.22±32.65, p<0.001).

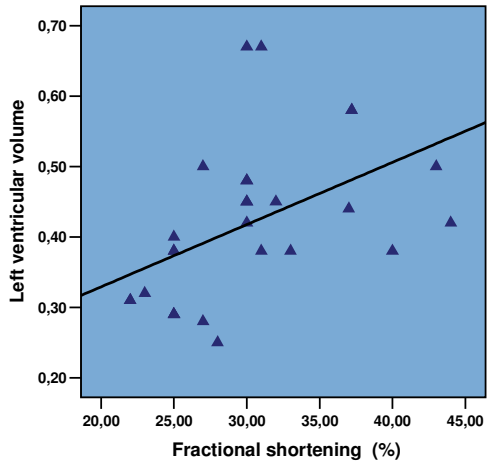

Fig. 6. Correlation between fractional shortening and left ventricular volume (rho=0,587; p<0,001). Values of fractional shortening (FS) and left ventricular volume (LVV) in patients in stage III CKD before diuretic therapy.

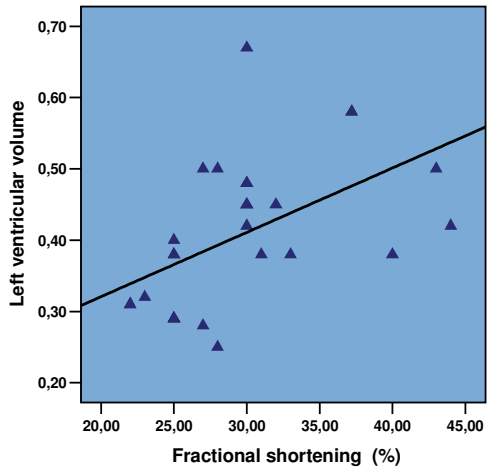

Fig. 7. Correlation between fractional shortening and left ventricular volume (rho=0.592; p<0.001). Values of fractional shortening (FS) and left ventricular volume (LVV) in patients in stage III CKD after diuretic therapy.

Mean BNP levels in CKD stage IV patients with LVH after the use of diuretics (359.85±71.52) was significantly higher compared to patients with CKD stage IV without LVH (118.77±25.16, p<0.001).

The mean BNP levels in serum of patients with CKD stage V (HD) with LVH before hemodialysis (1173.59±530.35) was significantly higher than those in CKD patients stage V (HD) without LVH (119.28±19.12, p<0.0005).

The mean BNP levels in patients with CKD stage V (HD) with LVH after hemodialysis (1025.63±481.16) was significantly higher compared to the mean BNP levels in CKD stage V patients (HD) without LVH (115.32±16.76, p<0.0005).

There was no correlation between BNP levels and left ventricular mass, left ventricular volume and fractional shortening in patients with CKD stage V (HD) before hemodialysis. However, a strong negative correlation between values of fractional shortening and left ventricular mass in HD patients before hemodialysis (rho=-0.680, p<0.0001 (Figure 8)), as well as a negative correlation between values of fractional shortening and left ventricular mass in HD patients after hemodialysis (rho=- 0.748, p <0.0001) was observed (Figure 9).

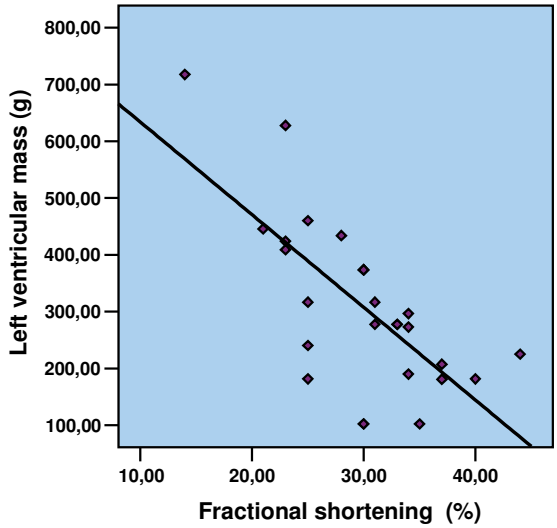

Fig. 8. Correlation between fractional shortening and left ventricular mass (rho=-0.680; p<0.0001). Values of fractional shortening (FS) and left ventricular mass (LVM) in HD patients before hemodialysis.

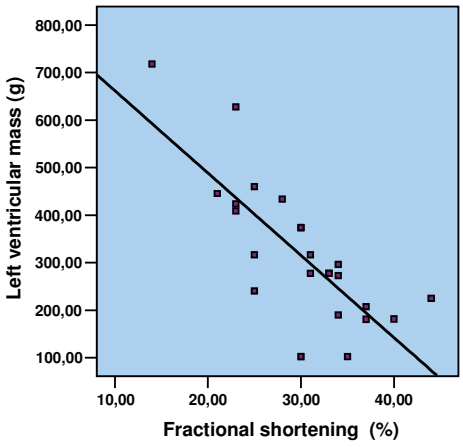

Fig. 9. Correlation between fractional shortening and left ventricular mass (rho=-0.748; p<0.0001). Values of fractional shortening (FS) and left ventricular mass (LVM) in HD patients after hemodialysis.

Discussion

These results have shown that an increase in BNP concentrations in serum of CKD patients with stage III before and after administration of diuretic therapy, lead

to a reduction in the size of the EF. Patients with CKD (stage III, IV and V) have elevated BNP levels compared to healthy population at the same age, even in the absence of congestive heart failure. This might be due to decreased renal clearance, increased stress on the myocardium, left ventricle hypertrophy, subclinical ischemia and remodeling, and fibrosis. However, the limited value of BNP in diagnosis of congestive heart failure should be adjusted in patients with GFR <60 ml/min.
According to the study of Forfia *et al.*, who monitored 40 patients in an Intensive Care Unit, 63% of patients in various CKD stages and without diagnosed congestive heart failure had BNP values between 100-250 pg/ml [6]. Hence and in addition to our observations, BNP value in patients with different stages of CKD associated with congestive heart failure has only a limited value for BNP of 200 pg/ml instead of 100 pg/ml as previously considered. Hence, BNP of 390 ng/L might be considered a weak predictor of adverse cardiovascular events in patients on hemodialysis [6].
As expected, the HD patients have higher BNP levels compared to patients in other CKD stages (III and IV) [7] that might be explained by the high prevalence of left ventricle structural and functional abnormalities.
We have confirmed the positive correlation between BNP levels and LVH and an inverse correlation with the ejection fraction (EF) [7-9]. Naganuma *et al*. have prospectively monitored a cohort of 164 patients for 36 months, showing the BNP correlation with LVH, cardiovascular diseases and diabetes mellitus [8]. Zoccali *et al*. monitored the levels of ANP and BNP and performed echocardiography in 246 CKD patients, without clinical evidence of congestive heart failure. They showed significant association between both natriuretic peptides and left ventricle mass index, LVH and ejection fraction [9].
Our results showed a negative correlation between BNP levels and ejection fraction in all groups of patients before and after diuretic therapy or hemodialysis, except in patients with CKD stage III, before diuretic therapy, where the correlation was not significant. However, we could not find any correlation between BNP and left ventricle mass, left ventricle volume and fraction shortening. Hence, the question is what might be the reason for such an inconsistency in correlations between the above-mentioned parameters in our study. The first possible explanation might be the insufficient number of patients included in the study (n=80). Another reason may be the drug effect that was not recorded when personal history data were collected, and finally the intraobserver variation i.e. the individual approach in determining of the parameters of LVH on echocardiography.
Given that BNP is secreted in response to the increase in myocardial wall stretch, it is hypothesized that the circulating BNP might be a useful marker of volume status. A few studies have investigated the relationship between BNP levels and volume load, but the direct evidence still lacks [10].
Several limitations should be considered in interpreting our results. Firstly, we used a single baseline measurement for BNP at the start and end of the study. We did not use average values during the follow-up. Secondly, we considered only plasma levels of BNP, we did not measure plasma levels of NT-pro-BNP. Thirdly, the follow-up period was relatively short, only two years (a longer follow-up period might produce more relevant results).

Conclusions

Study results show that the BNP value in CKD patients may represent a measure of left ventricular systolic function and correlate well with echocardiographic parameters. BNP levels correlate directly with left ventricular mass index and left ventricular hypertrophy, and negatevely with ejection fraction. Correlation of the BNP levels and ejection fraction is negative and statistically significant. The BNP level may be useful for risk stratification and administered therapy in CKD patients. Measurement of the BNP level is important in the prognosis of the outcome in patients with established left ventricle dysfunction, acute coronary syndrome and for estimation of the likelihood of ventricle dysfunction.
Testing of natriuretic peptides (BNP) is perhaps the greatest advance in the diagnosis of congestive heart failure since theintroduction of echocardiography. However, tests of BNP can not be used independently, they provide additional information.
Their sensitivity and negative predicitive value makes them suitable for elimination of congestive heart failure with high certainty. Conversely, increasing their levels goes in line with the increase of their specificity and positive predictive value.

Conflict of interest statement. None declared.

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