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# Blood concentrations of B-type natriuretic peptide and N-terminal prohormone B-type natriuretic peptide as markers of left ventricle diastolic function in patients with chronic renal failure

## Koncentracije B-tipa natriuretskog peptida i N-terminalnog prohormon B-tipa natriuretskog peptida u krvi kao pokazatelji dijastolne funkcije leve komore kod bolesnika sa hroničnom bubrežnom insuficijencijom

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**Abstract**

**Background/Aim.** Patients with chronic renal failure (CRF) have increased cardiovascular morbidity and mortality. It is unknown which biomarkers best describe the degree of diastolic dysfunction in patients with CRF. The aim of this study was to determine the correlation between B-type natriuretic peptide (BNP), N-terminal prohormone brain natriuretic peptide (NTproBNP) and left ventricular diastolic dysfunction (DD-LV) with the degree of CRF. **Methods.** The study included 100 adult patients with CRF without major cardiac and cerebral incidents who did not start actively treating CRF. According to the degree of CRF, the patients were divided into two groups: G1 (moderate degree), glomerular filtration rate (GFR) ≥ 30 mL/min/1.73 m², and G2 (more severe degree), GFR < 30 mL/min/1.73 m². Blood concentrations of BNP and NTproBNP were measured and Doppler echocardiographic measurement performed to estimate diastolic dysfunction (DD-LV). According to the degree of DD-LV, all the patients were divided into two groups: DD-LV1 (mild diastolic dysfunction) and DD-LV2 (severe diastolic dysfunction). According to the degree of CRF and DD-LV, the patients were divided into four groups: I (G1, DD-LV1), II (G1, DD-LV2), III (G2, DD-LV1) and IV (G2, DD-LV2). **Results.** There was a highly significant statistical correlation between BNP and NTproBNP with GFR ($p < 0.001$), and DD-LV with BNP ($p < 0.023$) and NTproBNP ($p = 0.035$). In patients with DD-LV2, a statistically significantly higher BNP concentrations were registered in patients with G2 ($p < 0.001$). Unlike BNP in the patients with diastolic dysfunction DD-LV1 and those with diastolic dysfunction DD-LV2, significantly higher concentrations of NTproBNP were registered in the patients with G2 (DD- LV1: $p = 0.006$; DD-LV2: $p < 0.001$). **Conclusion.** Biomarkers BNP and NTproBNP are not the best predictors in the assessment of diastolic dysfunction because they are correlated with the degree of renal insufficiency.

**Key words:**
**kidney failure, chronic; glomerular filtration rate; ventricular function, left; natriuretic peptides; biological markers; sensitivity and specificity.**

**Apstrakt**

**Uvod/Cilj.** Bolesnici sa hroničnom bubrežnom insuficijencijom (HBI) imaju povećan kardiovaskularni morbiditet i mortalitet. Nije poznato koji biomarkeri najbolje opisuju stepen dijastolne disfunkcije kod bolesnika sa HBI. Cilj ove studije bio je da se utvrdi povezanost koncentracije B-tipa natriuretskog peptida (BNP), N-terminalnog prohormon moždanog natriuretskog peptida (NTproBNP) i dijastolne disfunkcije leve komore (DD-LV) sa stepenom HBI. **Metode.** U studiju je bilo uključeno 100 odraslih bolesnika sa hroničnom bubrežnom bolesti koji nisu imali srčane i cerebralne incidente i nisu započeli akti-

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vno lečenje HBI. Prema stepenu HBI bolesnike smo podelili u dve grupe: G1 (umereni stepen), glomerularna filtracija (GFR) ≥ 30 mL/min/1,73 m², i G2 (teži stepen), GFR < 30 mL/min/1,73 m². U krvi su određene koncentracije BNP i NTproBNP, a dopler ehokardiografskim merenjem procenjena je dijastolna disfunkcija leve komore (DD-LV). Prema stepenu DD-LV bolesnici su podeljeni u dve grupe: DD-LV1 (blaga dijastolna disfunkcija) i DD-LV2 (teška dijastolna disfunkcija). Prema stepenu HBI i DD-LV bolesnici su podeljeni u četiri grupe: I (G1, DD-LV1), II (G1, DD-LV2), III (G2, DD-LV1) i IV (G2, DD-LV2). **Rezultati.** Utvrđena je visokoznačajna statistička korelacija BNP i NTproBNP sa GFR ($p < 0,001$), a DD-LV sa BNP ($p < 0,023$), odnosno NTproBNP ($p = 0,035$). Registrovane su statistički značajno više koncentracije BNP kod bolesnika sa DD LV2, nego kod bolesnika sa G2 ($p < 0,001$). Za razliku od BNP, kod bolesnika sa disfunkcijom DD-LV1, ali i onih sa disfunkcijom DD-LV2, registrovane su statistički značajno veće koncentracije NTproBNP kod bolesnika sa G2 (DD-LV1: $p = 0,006$; DD-LV2: $p < 0,001$). **Zaključak.** Biomarkeri BNP i NTproBNP nisu najbolji prediktori u proceni dijastolne disfunkcije jer su u korelaciji sa stepenom hronične bubrežne insuficijencije.

**Ključne reči:**
**bubreg, hronična insuficijencija; glomerulska filtracija; srce, funkcija leve komore; natriuretski peptidi; biološki pokazatelji; senzitivnost i specifičnost.**

## Introduction

Patients with chronic renal failure (CRF) have increased cardiovascular risk for development of cardiovascular morbidity and mortality [1–4]. In these patients more than 50% of death outcomes is due to cardiovascular diseases [5], while before dialysis 40% of patients have cardiovascular diseases [6]. Until now, heart failure has been most frequently accounted to the patients with end-stage renal disease (ESRD) who are already on dialysis. There are only a few studies which have examined the correlation between mild decrease of renal function and cardiac function [7–9]. It has been proved than even the mildest damage of renal function (GFR < 90 mL/min/1.73 $m^2$) significantly increases cardiovascular risk [10–12].

Determination of non-traditional cardiovascular risk factors and cardiac biomarkers in patients with CRF revealed increased cardiovascular morbidity and mortality in the second and third stage of chronic renal disease [13]. Diastolic dysfunction (DD) usually precedes the left ventricular (LV) systolic dysfuntion [14] and it is related with morbidity and mortality in patients with ESRD on dialysis [15]. Diastolic dysfunction in patients with preserved systolic function and ESRD is also a significant risk factor for cardiovascular morbidity and mortality [16, 17]. The European Society of Cardiology suggests that natriuretic peptide (BNP) or N-terminal pro b-type natriuretic peptide (NTproBNP) may serve as markers of heart failure because they point to the heart failure in patients with preserved left ventricular ejection fraction [18]. NTproBNP is also a useful non-invasive marker of atherosclerosis in the renal disease [13].

The aim of our study was to determine if BNP, NTproBNP and the left ventricular diastolic dysfunction may serve as predictors of cardiovascular risk in patients with chronic renal failure at the pre-dialysis stage.

## Methods

After obtaining Institutional Ethical Committee's approval, 100 adult patients with CRF were included in the prospective sectional study. All the patients were examined and recruited in our Outpatient Department. Study inclusion criteria comprised CRF patients without previous cerebral or heart complications or current active treatment for CRF. According to the stage of the renal function, glomerular filtration rate (GFR), clearens of creatinine was determined using the formula CKD-EPI ($GFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{age} \times 1.018$ [if a female]) and expressed as mL/min/1.73 $m^2$ [19] divided initially into five groups: (GI) GFR 90−120 mL/min; (GII) GFR 60−89 mL/min; (GIII) GFR 30−59 mL/min; (GIV) GFR 15−29 mL/min i (GV) GFR ≤ 15 mL/min. Afterwards, all the patients were divided into two groups. The first group, G1 with GFR ≥ 30 mL/min/1.73$m^2$, comprised of totally 60 patients with milder renal insufficiency (GFR I-III). The second group G2 with GFR < 30 mL/min, comprised of totally 40 patients with more severe degree of the renal insufficiency (GFR IV−V). Study exclusion criteria comprised of patients without previous cardiovacular and cerebrovascular diasease, malignancies, autoimmune disorders and other chronic diseases which might have an impact on results.

Blood samples for determination of BNP and NTproBNP concentration were harvested after 12 h of starvation. Analysis were performed using a SIMENS/ADVIA Centaur XP : principle CMIA (direct chemiluminescence, Munich-Germany, 2012), and the levels of NT-proBNP in plasma were determined by electroluminescence assay Roche Cobas e 601: principle "ECLIA„ (Basel, Switzerland, 2004).

Echocardiographic study was performed on a Simens 141148, type Acuson SC 2000, with a matric probe 4D for 2D live heart recording 4 z1c (Munich, Germany, 2012). Diastolic function was determined by measuring the following echocardiographic parameters in M-mode: E and A wave velocity, E/A ratio, isovolumetric relaxation time (IVRT), Doppler tissue echocardiography (DTE) as well as by tissue Doppler imaging measurement of E/Ea ware velocities.

According to the degree of DD-LV all the patients were divided into two groups: DD-LV1 – mild diastolic dysfunction (DD-N, DD-I), and DD-LV2, severe diastolic dysfunction (DD-II, DD-III, DD-IV).

According to the degree of CRF and DD-LV all the patients were divided into four gropus: I (G1, DD-LV1), mild chronic renal disease and mild diastolic dysfunction (n = 11), II (G1, DD-LV2), mild chronic renal failure and severe diastolic dysfunction (n = 48), III (G2, DD-LV1), severe chronic

renal failure and mild diastolic dysfunction (n = 5); and IV (G2, DD- LV2), severe chronic renal failure and severe diastolic dysfunction of the left ventricle (n = 36).

## Results

Within a period from June 1, 2014 to March 31, 2015 we recruited and analyzed 100 patients of whom 61 were men and 39 women. The demographic data were as follows: mean age 56.75 ± 10.60, average body mass index (BMI) 27.25 ± 4.02 kg/m$^2$, active smokers 20%, former smokers 29% and non-smokers 51%. Arterial hypertension (HTA) was noted in 93% of the patients. Mean sistolic blood pressure was 132.30 ± 17.98 mmHg and mean diastolic blood pressure was 81.60 ± 10.02 mmHg (Table 1).

The most frequent causes of renal disease were chonic glomerulonephritis (20), kidney stones (19), arterial hypertension (18), kidney cysts (13), diabetes mellitus (13), adult policystic kidney disease (12), nephritis tubulointerstitialis (3) and isolated erythrocyturia (2).

The distribution of basic causes of renal disease for which patients required physician's attention and the most frequent disorder that caused ESRD was not equal (Table 1).

Comparison of the concentrations of BNP and NTproBNP in the group of patients with different degree of CRF (G1 and G2) revealed a highly significant statistical corellation $p < 0.001$. In the patients with different degree of diastolic dysfunction (DD-LV1 and DD-LV2) a statistically significant difference was oberved for BNP ($p = 0.023$ and for NTproBNP $p = 0.035$) (Table 2).

**Table 1**

**Baseline characteristics of the patients in relation to glomerular filtration rate (GFR) groups**

| Parameters | Total | Glomerular filtration rate groups | | Probability |
|---|---|---|---|---|
| | | G1 | G2 | (*p*) |
| Age (years), mean | 56.75 | 55.95 | 57.28 | 0.54 |
| BMI (kg/m$^2$), mean | 27.25 | 26.69 | 27.63 | 0.25 |
| Gender (%) | | | | |
| male | 61.0 | 60.0 | 61.7 | 0.97 |
| female | 39.0 | 40.0 | 38.3 | |
| Smoking (%) | | | | |
| nonsmoker | 51.0 | 52.5 | 50.0 | |
| former smoker | 29.0 | 27.5 | 30.0 | 0.96 |
| current smoker | 20.0 | 20.0 | 20.0 | |
| Arterial hypertension (%) | 93.0 | 97.5 | 90.0 | 0.29 |
| Basic disorder, % (n) | | | | n.s. |
| chronic glomerulonephritis | 20 | 27.5 | 15.0 | |
| nephrolithiasis | 19 | 5.0 | 28.3 | |
| arterial hypertension | 18 | 25.0 | 13.3 | |
| diabetes mellitus | 13 | 15.0 | 11.7 | n.s. |
| cystic kidney disease | 13 | 0.0 | 21.7 | |
| adult polycystic renal disease | 12 | 20.0 | 6.7 | |
| tubulo-interstitial nephritis | 3 | 7.5 | 0.0 | |
| isolated erithrocyturia | 2 | 0.0 | 3.3 | |
| Total | 100 | 100 | 100 | |

**BMI − body mass index; G1 − GFR ≥ 30 mL/min/1.73 m$^2$ (modest degree of the chronic renal failure); G2 − GFR < 30 mL/min/1.73 m$^2$ (more severe degree of the chronic renal failure).**

**Table 2**

**Clinical and biochemical parameters in relation to glomerular filtration rate (GFR) and LVDD groups**

| Parameters | Median (interquartile range) | | Mann-Whitney |
|---|---|---|---|
| | G1 | G2 | test |
| BNP (pg/mL) | 20.2 (7.5−44.1) | 54.9 (22.7−135.5) | z = 3.846 $p < 0.001$ |
| NTproBNP (pmol/L) | 8.7 (4.3−20.5) | 73.6 (29.4−210.0) | z = 6.116 $p < 0.001$ |
| | DD–LV1 | DD–LV2 | |
| BNP (pg/mL) | 15.7 (6.8−50.8) | 29.0 (14.5−88.4) | z = 2.26 $p = 0.023$ |
| NTproBNP (pmol/L) | 9.7 (5.2−35.3) | 24.5 (7.6−90.6) | z = 2.11 $p = 0.035$ |

**BNP − B-type natriuretic peptide; NTproBNP − N-terminal pro-brain natriuretic peptide; DD-LV1 − milder degree of the left ventricular diastolic dysfunction (LVDD); DD-LV2 − more severe degree of LVDD; G1 − GFR ≥ 30 mL/min/1.73 m$^2$ (modest degree of the chronic renal failure); G2 − GFR < 30 mL/min/1.73 m$^2$ (more severe degree of the chronic renal failure).**

Comparison of the concentration of BNP with the group of patients with the same degree of GFR impairment but with the different degree of left ventricular diastolic dysfunction (Table 3) did not reveal a statistically significant difference (G1: $p = 0.124$; G2: $p = 0.281$). In the patients with diastolic dysfunction DD-LV2, higher statistically significant concentration of BNP were registered in the patients with simultaneous dysfunction G2 ($z = 3.498$; $p < 0.001$) (Table 3).

in the group G V (50.8 years). The specificity of comparison existed between the second and the fifth group of GFR, as well as with the fourth and the fifth group of GFR ($p < 0.01$). Comparison of GFR and BMI did not shows statistically significant difference ($p > 0.188$). Comparison of age and diastolic dysfunction revealed that patients below 50 years (mean age 48.27) had normal left ventricular systolic function, but the patients from 50 to 70 years had diastolic

**Table 3**

**Concentration of BNP and NTproBNP regarding the corresponding clinical groups**

| Parameter | Groups | Number of patients, median (interquartile range) | | Probability |
|---|---|---|---|---|
| | | DD-LV1 | DD-LV2 | |
| BNP (pg/mL) | G1 | n = 11<br>15.2 (1.7−37.2) | n = 48<br>22.0 (9.6−44.1) | z = 1.538<br>$p < 0.124$ |
| | G2 | n = 5<br>44.7 (15.8−56.6) | n = 36<br>57.3 (23.4−142.0) | z = 1.127<br>$p = 0.281$ |
| Probability | | z = 1.567<br>$p = 0.138$ | z = 3.498<br>$p < 0.001$ | |
| NTproBNP (pmol/L) | G1 | n = 11<br>6.6 (3.8−11.7) | n = 48<br>9.2 (4.3−23.6) | z = 0.983<br>$p = 0.326$ |
| | G2 | n = 5<br>60.6 (24.8−69.3) | n = 36<br>80.0 (29.7−219.5) | z = 1.037<br>$p = 0.324$ |
| Probability | | z = 2.61<br>$p = 0.006$ | z = 5.595<br>$p < 0.001$ | |

**BNP − B-type natriuretic peptide; NTproBNP – N-terminal pro-brain natriuretic peptide; DD-LV1 − milder degree of the left ventricular diastolic dysfunction; DD-LV2 − more severe degree of the left ventricular diastolic dysfunction; G1 − glomerular filtration rate (GFR) ≥ 30 mL/min/1.73 m$^2$ (modest degree of the chronic renal failure); G2 − GFR < 30 mL/min/1.73 m$^2$ (more severe degree of the chronic renal failure).**

Comparison of the concentration of NTproBNP with the group of patients with the same degree of GFR impairment but with the different degree of left ventricular diastolic dysfunction (Table 3) did not reveal a statistically significant difference (G1: $p = 0.326$; G2: $p = 0.324$). Contrary to BNP, in the patients with left ventricular diastolic dysfunction DD-LV1, as well as those with DD-LV2, a statistically significantly higher concentration of NTproBNP was registered in the patients with simultaneous diastolic dysfunction G2 (DD- LV1: $p = 0.006$; DD-LV2: $p < 0.001$) (Table 3).

Normal diastolic function (DD-N) was observed in 14% of the patients while diastolic dysfunction (DDI, II, III ) was observed in 86% of the patients. The most severe degree of diastolic dysfunction (DD-IV) was not observed in any single patient. However, DD-III was observed in the patients with GFR ≤ 60 mL/min/1.73 m$^2$.

The impaired values of diastolic dysfunction, BNP and NTproBNP were more prevalent among men.

The distribution of impaired values according to gender (men-women) was as follows: DD 54 (90.1%) : 31 (79.5%), BNP 22 (55%) : 18 (45%), NTproBNP (52.5%) : 19 (47.5%), respectively.

Comparison of age in respect to GFR showed a statistically significant difference ($p < 0.001$). In the groups G II and G IV were the oldest patients (61.80 *vs* 61.10 years, respectively). On the other hand, the youngest patients were dysfunction (DDI, DDII and DDIII degree). A correlation of diastolic dysfunction and age revealed a statistically significant difference ($p < 0.001$).

According to the BMI all the patients were classified as moderately obese (BMI: 25−29.9 kg/m$^2$). Comparison of diastolic dysfunction and BMI did not reveal a statistically significant difference ($p > 0.220$).

## Discussion

The values of BNP, NTproBNP and left ventricular diastolic dysfunction were corellated with the stage of chronic renal failure in hundred patients, divided in two groups, G1 and G2. The group G1 comprised of 60 patients with mild degree of CRF (GFR > 30 mL/min), while the group G2 included 40 patients with more severe degree of CRF (GFR < 30 mL/min).

Comparison of concentration of BNP and NTproBNP with the stage of chronic renal disease (G1 and G2) showed a highly statistical significant difference ($p \leq 0.001$). Comparison of the concentration of BNP and NTproBNP with the degree of left ventricular diastolic dysfunction revealed a statistically significant difference for BNP ($p = 0.023$), and for NTproBNP ($p = 0.035$), respectively. In the patients with diastolic dysfunction DD-LV2 a statistically higher concentration of BNP was registered simultaneously with diastolic dysfunction G2 ($z = 3.498$; $p < 0.001$). In contrary to BNP,

in the patients with diastolic dysfunction DD-LV1 as well as in those with simultaneous diastolic dysfunction DD-LV2, a statistically higher concentration of NTproBNP was registered in the patients with simultaneous diastolic dysfunction G2 (DD-LV1: $p = 0.006$; DD-LV2: $p < 0.001$). A positive correlation was obtained by comparing BNP, NTproBNP [19–21] and diastolic dysfunction with the stage of chronic renal disease [22, 23]. Statistical analysis by comparison data for BNP, NTproBNO, left ventricular diastolic dysfunction, age and stage of chronic renal disease revealed a statistically significant difference ($p < 0.001$).

The most signifficant finding was obtained by correlation of diastolic dysfunction with the stage of chronic renal disaease where we noticed impaired diastolic function of the left ventricle (DDI, II, III degrees) in 86% of the patients. Impaired diastolic dysfunction of the left ventricle was present already in the group G-I in 60% of the patients, in G-II, G-III and G-IV in 90% of the patients, and in G-V in terminal stage of the chronic renal disease in 95% of the patients. The most frequent was DD-II in 57% of the patients, thereafter DD-I in 24% of the patients, while the most rare was DD-III in 5% of the patients. DDIII of severe degree was not present in the groups G-I and G-II, however it was present in the groups GIII, GIV and GV in the patients whose GFR was $\leq 60$ mL/min/1.73 m$^2$. The most severe degree of diastolic dysfunction (DD-IV) was not observed in any single patient.

Our results show, as in some other studies, that even the smallest impairment of renal function GFR < 90 mL/min/1.73 m$^2$ is related to the signifficant increase of cardiovascular risk [11, 24–26].

A higher increase in the concentration of NTproBNP observed in the third stage of chronic renal disease was in accordance with the previous study [13] which allows us to explain why this is a risk group with an increased risk for cardiovascular morbidity and mortality. Concentration of BNP was in positive correlation with the degree of GFR, too. In the group G-I an increased concentration of BNP was immanent in 5% the patients, and in the group G-V in 65% of the patients, respectively.

Comparison of diastolic dysfunction with the concentrations of BNP and NTproBNP showed that an increased concentration of BNP and NTproBNP was followed by the degree of diastolic dysfunction up to the moderate level (DD-II). Noteworthy, DD-III and increased concentration BNP were frequently observed in women while NTproBNO in men.

A correlation of gender, BMI, and smoking status with GFR, diastolic dysfunction and an increased concentration of BNP and NTproBNP, did not show a signifficant difference. Comparison of left ventricular function with age showed that patients over 48 had impaired diastolic function.

The results shown in our group of patients might have greater importance because they point out to the signifficant impairment of diastolic function with only moderate impairment of glomerular filtration G-II (GFR < 90 mL/min/1.73 m$^2$). An increased concentration of BNP and NTproBNP are in correlation with GFR. Diastolic dysfunction of the left ventricle is in correlation with the stage of chronic renal disease, arterial hypertension and its evolution as well as with age. Non-conventional cardiovascular risk factors and cardiac biomarkers during the early stage of chronic renal failure may serve as predictors of heart failure.

## Conclusion

The values of BNP, NTproBNP and diastolic dysfunction are in correlation with the degree of renal failure. The impaired values of these parameters are also present in the early stages of renal failure, so they may serve for estimation of cardiovascular risk in patients with chronic renal failure at the predialysis stage in whom high cardiac morbidity and mortality can be expected.

We think that the simultaneous follow-up of renal function and cardiovascular risk is neccessary in patients with chronic renal failure at the predialysis level.

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