

# CORRELATION ANALYSIS OF BNP CONCENTRATION AND RENAL FUNCTION PARAMETERS IN PATIENTS AFTER PERMANENT PACEMAKER IMPLANTATION

ANALIZA KORELACYJNA POMIĘDZY BNP A PODSTAWOWYMI PARAMETRAMI CZYNNOŚCI NEREK U CHORYCH PO WSZCZEPIENIU STYMULATORA SERCA NA STAŁE

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## SUMMARY

**Introduction:** The group of patients with implanted cardiac pacemakers is systematically increasing. Changes in the circulatory system after pacemaker implantation are related, amongst others, to the secretion of B-type natriuretic peptide (BNP) to the blood and changes in renal functions.

**Material and methods:** The study group consisted of 117 patients who underwent permanent implantation of a pacemaker with AAI/R, DDD/R or VVI/R pacing mode. On the day of the implantation, and within three and six months after the performed surgery, BNP, urea and creatinine levels were determined and creatinine clearance was estimated according to the MDRD formula.

**Results:** Significant correlations between plasma BNP level and the primary renal function parameters were observed before and after permanent pacemaker implantation.

**Conclusions:** Significant changes in serum creatinine and urea level as well as in eGFR are observed after pacemaker implantation. There are numerous correlations between the secretion of B-type natriuretic peptide into the blood and the primary renal function parameters.

**Key words:** cardiac pacing, B type natriuretic peptide, renal function, correlation analysis.

## STRESZCZENIE

**Wstęp:** Grupa pacjentów z wszczepionymi rozrusznikami serca systematycznie się powiększa. Zmiany w układzie krążenia zachodzące po implantacji stymulatora dotyczą m.in. wydzielania do krwi peptydu natriuretycznego typu B (BNP) oraz zmiany w zakresie czynności nerek.

**Material i metody:** Przebadano grupę 117 chorych z wszczepionymi na stałe rozrusznikami AAI/R, DDD/R i VVI/R. W dniu wszczepienia oraz trzy i sześć miesięcy po wykonanym zabiegu oznaczano stężenie BNP, mocznika i kreatyniny oraz szacowano klirens kreatyniny za pomocą wzoru MDRD.

**Wyniki:** Stwierdzono istotne korelacje pomiędzy wartościami BNP we krwi a podstawowymi parametrami czynności nerek. Korelacje te występowały zarówno w okresie przed wszczepieniem, jak i po wszczepieniu stymulatora serca na stałe.

### Wnioski:

1. Po implantacji stymulatora serca na stałe dochodzi do istotnych zmian podstawowych parametrów czynności nerek, takich jak kreatynina, mocznik i klirens kreatyniny.
2. Stwierdza się liczne korelacje pomiędzy wydzielanym do krwi peptydem natriuretycznym typu B a podstawowymi parametrami czynności nerek.

**Słowa kluczowe:** stymulacja serca, peptyd natriuretyczny typu B, czynność nerek, analiza korelacyjna.

## INTRODUCTION

The primary role of the electrical conduction system of the heart is to ensure autonomy in generation and conduction of action potentials leading to proper cyclic contractions of the heart muscle. The sinus node (the sino-atrial node) is the primary structure of the electrical conduction system. Anatomically, it is spindle-shaped and located around the mouth of the superior vena cava leading into the right atrium [1].

The stimulation is transmitted from the sinus node to the left atrium by the interatrial tract – Bachmann's bundle. Transmission of the action potential to the atrioventricular node is debatable. The prevailing view is that stimulations are transferred to the sinus node by atrial muscle without any special routes. Some are of the opinion, however, that there are three pathways of conduction – interstitial routes: anterior, central and posterior [2]. Next the stimulations are transmitted by the atrioventricular node and the bundle of His to the ventricles.

There are four primary kinds of permanent cardiac pacing: ventricular, atrial, dual and VDD stimulation. In VVI ventricular pacing, the pacing electrode, as well as the control electrode, are implanted in the apex of the right ventricular (or in the vicinity of the apex). Pacing, as well as control, occurs therefore involving only potentials of the muscle in the right ventricle. Dual-chamber pacing is more complicated. There are two electrodes in this pacing system. As in the VVI pacing, the ventricular electrode is implanted in the right ventricular. The atrial electrode is implanted in the right atrial appendage. Both control and pacing are dual-chamber. The VDD pacemaker, used since recently, is a one-electrode system. The electrode pacing the ventricle, as well as the one controlling the ventricular potentials, is anchored in the right ventricle. While the control rings are located along this electrode, at the atrium. They receive the atrium's own potentials without contact with the atrial muscle, through blood. Control of ventricular pacing occurs based on these potentials [3]. The ventricular electrode may be inhibited by own ventricular potentials if such are detected. In this case, the goal of physical stimulation using one and only one electrode is reached.

Determining the count of natriuretic peptides in the blood, especially that of B-type natriuretic peptide and NT-proBNP, currently plays a significant role in everyday clinical practice. An elevated concentration of natriuretic peptides may be observed in such cardiovascular disorders as heart failure, systolic and diastolic dysfunction, coronary heart disease, hypertension with features of left ventricular hypertrophy, valvular heart disease, and atrial fibrillation. Elevation

of BNP concentration in the serum may also occur in other disorders which influence the circulatory system indirectly, e.g. in acute pulmonary embolism, pulmonary hypertension, anaemia, chronic obstructive pulmonary disease, renal failure, septic shock and hyperthyroidism [4].

Determining natriuretic peptide concentration is a valuable diagnostic tool allowing for a quick differentiation of cardiac-origin and noncardiac-origin dyspnoea in case of doubt, which facilitates patient management at the emergency room. A high elevation of natriuretic peptides identified in the blood is characteristic of cardiac-origin dyspnoea. Values below 100 pg/mL speak against a diagnosis of heart failure (a probability below 2%). If the identified BNP value in the blood remains in the 100–400 pg/mL range and the patient gives in his medical records a positive history of heart failure, then the probability of heart failure remains within 75%. Whereas, if the BNP value obtained from a patient is higher than 400 pg/mL, then a diagnosis of heart failure and thus recognition of the dyspnoea reported by the patient as cardiac-origin dyspnoea, remains above 95% [5, 6, 7, 8].

In recent years, the number of implanted pacemakers has been increasing gradually. These are not only pacemakers implanted in different forms of electrical conduction system dysfunctions. Such devices are ever more often implanted in older patients with other accompanying diseases, i.a. heart and renal failure. What is more, a non-physiological course of stimulus propagation in the heart during artificial cardiac pacing may additionally exacerbate the symptoms of heart failure and indirectly impair kidney function.

The aim of the present study is to observe the relation between the values of plasma BNP, as a fundamental parameter of cardiac status, and renal function expressed by values of primary renal parameters in patients after permanent pacemaker implantation. The research also aims to attempt to answer the question to what degree B-type natriuretic peptide may be useful in monitoring patients with heart failure and renal failure.

## MATERIAL AND METHODS

184 people were pre-qualified for the research. Of this, 136 people constituted the group for study, that is patients qualified for permanent pacemaker implantation, and 48 healthy volunteers constituted the control group.

During a half-year-long observation, six patients have died and thirteen withdrew consent for further participation in the research. It was determined, as

a result of phone conversations, that the patients from that group are alive and under the care of a GP at their place of residence. Ultimately, 117 patients reached the completion of the research.

Thus, 117 patients with permanently implanted pacemakers and 48 healthy volunteers (constituting the control group) have been included in the final analysis. The patients were divided into four groups. 21 patients with implanted AAI/R pacemakers became part of Group I. 59 patients with implanted DDD/R pacemakers constituted Group II. 37 patients with implanted VVI pacemakers were Group III. 48 healthy volunteers of a similar age constituted the control group (Group IV).

Patients who had the following disorders were excluded from the research: acute coronary syndrome that occurred within 6 months prior to implantation, an active inflammatory process, a stroke 6 months prior to implantation, heart defects, NYHA scale class III and IV heart failure, cancer diseases, respiratory insufficiency, connective tissue diseases, muscular dystrophy, anaemia with haemoglobin at 10 g/dl and below, thyroid diseases.

A qualification for permanent implantation of a pacemaker of a given type, made on the basis of commonly accepted qualification criteria, mainly including the Guidelines for Cardiac Pacing and Cardiac Resynchronization of the Polish Cardiac Society from 2007 with amendments in 2010 was the requirement for inclusion in the research in groups I, II and III.

The characteristics of the patients are presented in table 1.

*The methodology for determining plasma BNP level.* Determination of BNP level was done from a sample of EDTA venous blood, after 10 minutes of centrifugation at 2000 G in order to obtain plasma. Next, the samples were placed in a DXI 600 system.

Determination was done with the help of Triage reagents and using a Beckman Coulter DXI 600 immunochemical analyser.

*Analysis of renal function parameters (urea and creatinine).* Determination was done using an OLYMPUS AU 680 analyser. Determination was done through urea in serum samples. Determination of creatinine levels was done using an OLYMPUS AU 680 analyser. The creatinine clearance value was used to analysis of renal function parameters. To simplify, the real value of creatinine clearance was not determined, we used eGFR index, which is an accurate indicator of renal function in stead. We used the MDRD formula. This formula was created based on the patients with chronic renal insufficiency the participants of Modification of Diet in Renal Disease study.

Statistical analysis was accomplished on the basis of Levene's test of homogeneity of variance, the Pearson chi-squared test, the Kruskal-Wallis ANOVA by ranks test and the Friedman ANOVA test.

## RESULTS

Before permanent pacemaker implantation, higher creatinine levels and lower creatinine clearance levels were observed in all examined groups compared to the control group. Urea levels remained unchanged compared to the control group. After implantation, a decrease of urea levels in the blood was observed in the group with an implanted AAI/R pacemaker and an increase of those levels in the group with an implanted VVI/R pacemaker. Creatinine levels and creatinine clearance levels remained unchanged.

These were the levels of primary renal parameters of patients after permanent pacemaker implantation:

Table 1. Statistical analysis of age distribution in the examined groups and the control group

|                               | Age [in years]  |  |  |  |
|-------------------------------|---|--|--|--|
|                               | control group   | group I                                    | group II                                   | group III                                  |
| Number of patients            | 48  | 21   | 59   | 37   |
| Minimum                       | 53.00   | 53.00                                      | 53.00                                      | 60.00                                      |
| Maximum                       | 86.00   | 85.00                                      | 88.00                                      | 88.00                                      |
| Median                        | 74.50   | 75.00                                      | 74.00                                      | 75.00                                      |
| Mean value                    | 71.79   | 72.43                                      | 73.39                                      | 74.11                                      |
| Standard deviation            | 9.26  | 7.72                                       | 7.94                                       | 7.14                                       |
| Skewness                      | -0.56   | -0.71                                      | -0.76                                      | -0.42                                      |
| Feature distribution analysis | the Shapiro-Wilk Test<br>W = 0.93 p > 0.05  | the Shapiro-Wilk Test<br>W = 0.95 p > 0.05 | the Shapiro-Wilk Test<br>W = 0.94 p > 0.05 | the Shapiro-Wilk Test<br>W = 0.95 p > 0.05 |
| Statistical analysis          | Levene's test of homogeneity of variance = 1.68 p > 0.05<br>The F analysis of variance test = 0.66 p > 0.05 |  |  |  |

Analysis did not show a statistically significant difference of age in the examined groups.

- in Group I, the level of urea in the blood three months after the permanent AAI/R pacemaker implantation decreased from  $45.19 \pm 13.24$  mg/dl to a value of  $37.52 \pm 8.56$  mg/dl ( $p > 0.05$ ). Within 6 months after pacemaker implantation, the level of urea in the blood decreased to a value of  $41.10 \pm 8.59$  mg/dl and was lower with statistical significance in comparison to the starting period before pacemaker implantation;
- in Group II, the level of urea in the blood three months after implantation of a DDD/R pacemaker increased with statistical significance from  $41.61 \pm 20.54$  mg/dl to a value of  $45.24 \pm 15.04$  ( $p < 0.01$ );
- in Group III, the level of urea in the blood three months after implantation of a VVI/R pacemaker increased with statistical significance from  $44 \pm 46$  mg/dl to a value of  $48.46 \pm 16.62$  ( $p < 0.01$ ). Within 6 months after the VVI/R pacemaker implantation, the value of urea in the blood amounted to  $47.00 \pm 13.46$  and was higher with statistical significance in comparison to the starting period ( $p < 0.01$ );
- in Group I, the level of creatinine in the blood three months after the permanent AAI/R pacemaker implantation decreased from  $1.35 \pm 0.28$  mg/dl to a value of  $1.29 \pm 0.30$  mg/dl ( $p > 0.05$ );
- in patients from Group II, the level of creatinine in the blood three months after DDD/R pacemaker implantation changed from a value of  $1.16 \pm 0.32$  mg/dl to a value of  $1.16 \pm 0.28$  ( $p > 0.05$ ).

No statistically significant changes were observed in terms of creatinine clearance levels in the patients after permanent pacemaker implantation.

As a result of performed correlation analysis, the following positive correlation coefficients were stated between the level of plasma BNP and the values of primary renal function parameters:

- within 3 months after permanent implantation of a DDD/R type pacemaker, statistically significant correlation coefficients were stated between B-Type Natriuretic Peptide and creatinine clearance level ( $q = -0.35$ ,  $t = -2.86$ ); detailed results are presented in figure 1;
- within 6 months after permanent implantation of a DDD/R type pacemaker, statistically significant correlation coefficients were stated between B-Type Natriuretic Peptide and the level of urea in the blood ( $q = 0.42$ ,  $t = 3.44$ ); detailed results are presented in figure 2;
- before permanent pacemaker implantation in Group III (a VVI/R pacemaker), statistically significant correlations were stated between the levels of B-Type Natriuretic Peptide and the level of urea in the blood ( $q = 0.38$ ,  $t = 2.46$ ), the level

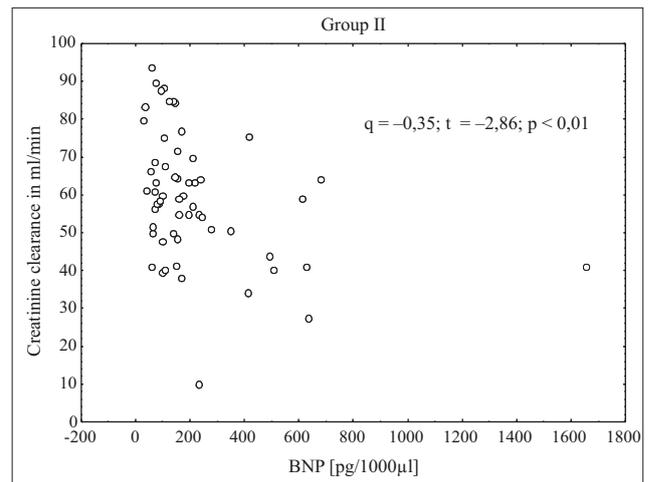


Fig. 1. Correlation between BNP and eGFR in DDD/R group three months after pacemaker implantation

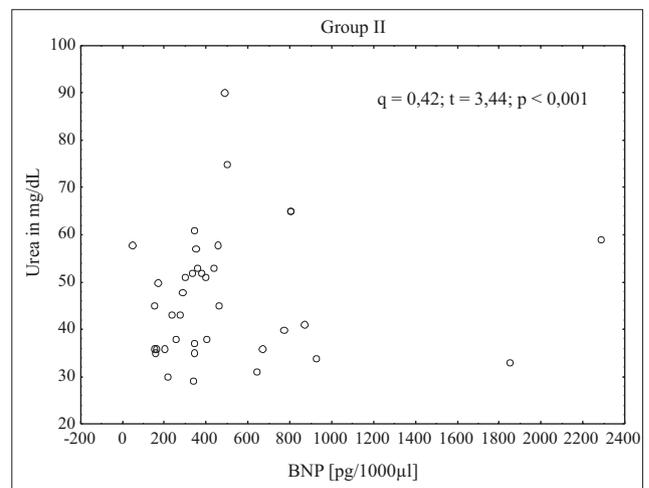


Fig. 2. Correlation between BNP and urea level in DDD/R group six months after pacemaker implantation

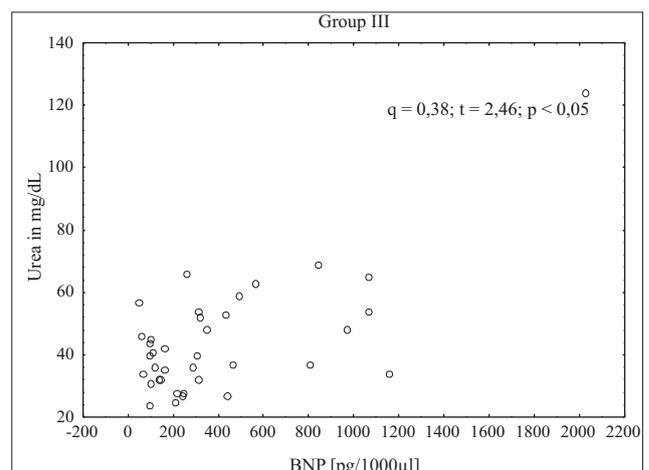


Fig. 3. Correlation between BNP and urea in VVI/R group before pacemaker implantation

of creatinine in the blood ( $q = 0.35$ ,  $t = 2.22$ ) and the value of creatinine clearance ( $q = -0.38$ ,  $t = -2.42$ ). Detailed results were presented in figures 3, 4 and 5.

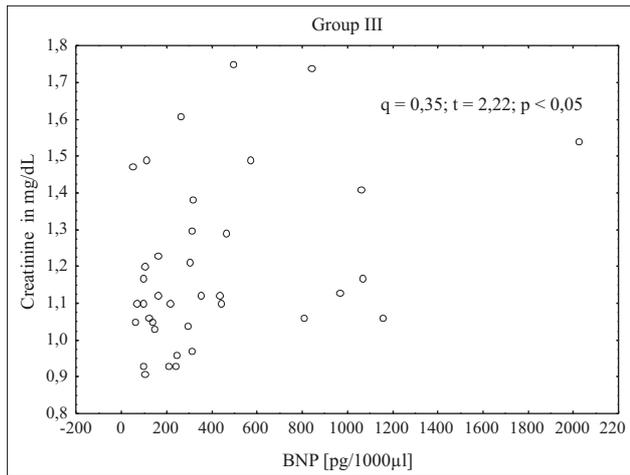


Fig. 4. Correlation between BNP and serum creatinine in VVI/R group before pacemaker implantation

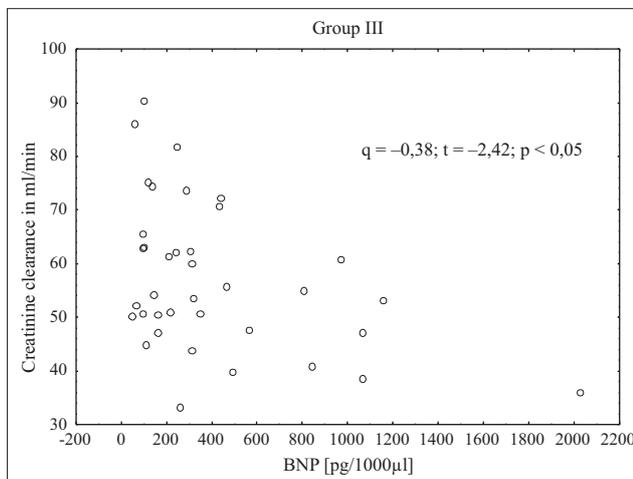


Fig. 5. Correlation between BNP and eGFR in VVI/R group before pacemaker implantation

No statistically significant correlation coefficients were stated during the remaining cases of correlation analysis of B-Type Natriuretic Peptide levels with primary renal function parameters.

## DISCUSSION

Chronic kidney disease, defined as a reduction of glomerular filtration, and proteinuria occur more frequently in patients with heart failure. In large-scale population research, chronic kidney disease concerns 7% of patients above 30 years of age and this is increasing systematically, and concerns approximately 23–36% of patients above the age of 65 [9].

Initial parameters of renal function during different types of stimulation have been investigated in animal experiments and clinical trials. Yoneda et al. reported that during ventricular stimulation in anesthetized dogs (pacing with increasing frequencies 200–250 beats/

min), no significant increase of maximal urinary excretion of sodium was observed [10]. Seymour et al. in their experimental studies in conscious, unstressed dogs observed a decrease of renal filtration from  $168 \pm 19$  ml/min to  $96 \pm 9$  ml/min and reduced sodium excretion from  $36 \pm 5$  to  $10 \pm 4$  mEq/d after rapid ventricular pacing (260 beats/min) [11].

A number of studies have been done or are being done in the field of EBM in patients with heart failure and chronic kidney disease [12, 13]. However, in the analysis of the available references only a few reports of tests were found, where the theme was to evaluate heart failure, renal function, natriuretic peptides blood excretion and permanent cardiac pacing. Williams et al. found in their experimental research that rapid ventricular pacing reduces plasma renin activity, vasopressin secretion and increases creatinine clearance. It does not, however, influence excretion of sodium ions in urine [14]. Also Mark et al., in a large-scale research encompassing patients with different stages of chronic kidney disease found significant correlations between renal function and the levels of BNP and ANP in the blood [15]. Sielski et al. examined 40 patients after VVI/R and DDD/R pacemaker implantation. An increase of atrial natriuretic peptide levels after implantation and significant changes in primary renal function parameters were found. Atrial natriuretic peptide proved to be useful in monitoring patients after pacemaker implantation [16]. In a study concerning the same group of patients, significant correlations between the levels of atrial natriuretic peptide, primary renal function parameters and echocardiographic measurements of the left atrium and the left ventricle were also found [17].

In the author's own research, no significant differences in the levels of urea in the blood were found in patients before permanent pacemaker implantation when comparing the control group and all of the examined groups. The level of creatinine, however, was higher in the examined groups compared to the control one, and the value of creatinine clearance – lower. After pacemaker implantation, the level of urea in the blood decreased in patients with an AAI/R pacemaker and in patients with an implanted DDD/R pacemaker. Whereas, in patients with an implanted VVI/R pacemaker the level of urea after implantation increased. The level of creatinine in the blood of patients after pacemaker implantation did not change. The value of creatinine clearance also did not change in patients after pacemaker implantation. In the carried out correlation analysis, significant correlations between the values of primary renal parameters and secretion of B-type natriuretic peptide into the blood were found.

## CONCLUSIONS

1. After permanent pacemaker implantation, significant changes take place in primary renal function parameters such as creatinine, urea and creatinine clearance.
2. Numerous correlations between B-type natriuretic peptide secreted in to the blood and primary renal function parameters were found. There are:
  - a) positive correlation between BNP and creatinine clearance in the group DDD/R;
  - b) positive correlation between BNP and urea value in the group DDD/R;
  - c) positive correlation between BNP and urea value in the group VVI/R;
  - d) positive correlation between BNP and creatinine value in the group VVI/R;
  - e) positive correlation between BNP and creatinine clearance in the group VVI/R.

## SUMMING-UP

An annually increasing number of implantable devices requires precise control and a thorough examination of the controlled patient. During this control, it is important not only to check the technical parameters of the device, but also to thoroughly examine the patient and to control some biochemical parameters which may indicate a deviation from the norm in the work of the circulatory and excretory system. Natriuretic peptide of B type can possibly be the crucial parameter for monitoring renal function in patients after permanent pacemaker implantation.

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