Correlation analysis of the relationship between B-type natriuretic peptide and selected echocardiographic parameters in patients with permanent pacemakers

Analiza korelacji pomiędzy peptydem natriuretycznym typu B a wybranymi parametrami echokardiograficznymi u pacjentów po wszczepieniu stymulatora serca na stałe

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Słowa kluczowe: peptyd natriuretyczny typu B, stymulacja serca, indeks objętości lewego przedsionka.

Abstract

Introduction: The present study was undertaken to evaluate the practical value of BNP measurements and echocardiographic left ventricular volume index in patients with permanent pacemakers because there are no such reports in the literature.
Aim of the research: The aim of the study was to reveal multiple correlations between BNP levels and selected echocardiographic parameters of the left atrium in patients with permanent pacemakers. In the literature there are reports on the significance of BNP values and left atrial size in patients with permanent pacemakers. The results of the present study appear to be of value in the outpatient assessment of these patients.
Material and methods: We analysed a group of 117 patients with permanent pacemakers (AAI/R 21 patients, DDD/R 59 patients, VVI/R 37 patients) and 48 healthy volunteers serving as the control group. BNP measurements were performed on venous blood samples using Triage meters. The Simpson method and the ellipse method were used to assess the left atrium on echocardiography.
Results: There was a significant correlation between BNP and maximum left atrial volume, minimum left atrial volume, and left atrial volume index in patients with AAI/R, DDD/R, and VVI/R pacemakers at 3 and 6 months after the implantation.
Conclusions: In patients after implantation of permanent pacemakers there are correlations between BNP values and echocardiographic left atrial parameters, especially in patients with DDD/R pacemakers. Left atrial function improves in patients with DDD/R pacemakers. Pacemaker check-up should be extended to include BNP measurements and echocardiographic assessment of the left atrium.

Streszczenie

Wprowadzenie: Przeprowadzono badania dotyczące przydatności praktycznej oznaczania peptydu natriuretycznego typu B (BNP) i badania echokardiograficznego wykorzystującego indeks objętości lewego przedsionka u chorych po wszczepieniu stymulatora serca na stałe.

Cel pracy: Celem przeprowadzonych badań było określenie korelacji pomiędzy BNP a wybranymi parametrami oceny echokardiograficznej lewego przedsionka u chorych po implantacji kardiostymulatora. W piśmiennictwie dostępne są prace dotyczące stymulacji stałej serca, wartości BNP po implantacji stymulatora oraz oceny echokardiograficznej lewego przedsionka. Również przeprowadzone badania własne wydają się potwierdzać znaczenie tych parametrów w ambulatoryjnej ocenie tej grupy chorych.
Materiał i metody: Przeanalizowano grupę 117 pacjentów ze wszczepionym stymulatorem serca na stałe (AAI/R 21 pacjentów, DDD/R 59 i VVI/R 37) oraz 48 zdrowych ochotników, stanowiących grupę kontrolną. Oznaczano BNP z próbki krwi żylnej za pomocą odczynników firmy Triage. Wykonywano badanie echokardiograficzne z oceną lewego przedsionka, wykorzystując metodę Simpsona i metodę elipsy.
Wyniki: Stwierdzono statystycznie istotne współczynniki korelacji pomiędzy BNP a objętością maksymalną lewego przedsionka, objętością minimalną lewego przedsionka i indeksem objętości lewego przedsionka w grupach AAI/R, DDD/R oraz VVI/R w ciągu 3 oraz 6 miesięcy po wszczepieniu stymulatora serca na stałe.
Wnioski: W trakcie obserwacji pacjentów po wszczepieniu stymulatora serca na stałe wykazano korelacje pomiędzy wartością BNP a parametrami echokardiograficznymi lewego przedsionka, szczególnie w grupie DDD/R. Po wszczepieniu stymulatora serca na stałe poprawiają się parametry czynności lewego przedsionka w grupie DDD/R. Kontrola chorych po implantacji kardiostymulatora może być wzbogacona o oznaczania BNP oraz wykonanie badania echokardiograficznego z oceną lewego przedsionka.

Introduction

Currently, in clinical practice five types of biomarkers can be identified and measured: neurohormonal biomarkers, biomarkers of myocardial injury, inflammatory biomarkers, biomarkers of organ dysfunction, and nonspecific laboratory markers. Neurohormonal biomarkers include natriuretic peptides (ANP, BNP, CNP, and other peptides), markers related to the renin-angiotensin-aldosterone system, and vasopressin [1].

Measurements of B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide contribute significantly to the assessment and stratification of risk in dyspnoeic patients admitted to the Intensive Coronary Care Unit and Emergency Department [2, 3]. The levels of peptides help to differentiate patients with dyspnoea. It is extremely important to differentiate respiratory dyspnoea from dyspnoea of cardiac origin, which is a sign of new or worsening heart failure. High levels of natriuretic peptides in the blood are characteristic of cardiac dyspnoea. Each patient with dyspnoea admitted to the Emergency Department undergoes physical examination, chest X-ray, ECG recording, and BNP measurements. A BNP level below 100 pg/ml indicates no heart failure (probability < 2%). A BNP levels between 100 and 400 pg/ml and a positive history of heart failure indicate a probability of heart failure of about 75%. A BNP level that is elevated above 400 pg/ml means that the probability of heart failure and cardiac origin of dyspnoea is above 95% [4–7]. Elevated BNP in the blood positively correlates with the prognosis and NYHA class, intraventricular pressure, and pulmonary artery pressure, whereas it negatively correlates with cardiac output [8, 9].

The left atrium performs three basic functions: it serves as a reservoir of blood received from pulmonary veins, a conduit for blood flowing to the left ventricle, and a booster pump compensating left ventricular systolic function loss [10–12]. Left atrial remodelling and adaptation occur as a result of various factors. The best-known factor for atrial remodelling is tachycardia as well as volume and pressure overload [13]. Left atrial assessment is based on a variety of echocardiographic parameters such as planimetric indices, and volume and functional parameters. Most of the parameters are widely studied in clinical trials [13, 14]. The most important planimetric indices include maximum and minimum volumes of the left atrium. In clinical practice, left atrial volume index (LAVI) is the most frequently used for atrial assessment. It is a derivative of left atrial volume indexed to body surface area. In adults the normal LAVI is 22 ±6 ml/m^2 [15]. The Simpson method and the ellipse method are recommended by the American Heart Association as the most useful for chamber quantification [15]. The LAVI may be significantly elevated in a variety of conditions. It is most frequently increased in atrial fibrillation, brain stroke, coronary artery disease, heart failure, renal failure, and diabetes mellitus [16–23].

Aim of the research

Studies on health problems in patients with permanent pacemakers are scarce. It is still not clear whether such directions of studies are warranted from a practical perspective. The present paper is an attempt to provide answers to some questions, especially from the viewpoint of the usefulness of BNP measurements in relation to left atrial echocardiographic parameters.

Material and methods

We analysed a group of 117 patients with permanent pacemakers, and healthy volunteers serving as the control group. The study population was divided into four groups: group I – 21 patients with an AAI/R pacemaker, group II – 59 patients with a DDD/R pacemaker, group III – 37 patients with a VVI pacemaker,

Table 1. Clinical characteristics of the study

Parameter	Group I (AAI/R)	Group II (DDR/R)	Group III (VVI/R)	Value of *p*
Age	72.4 ±7.7	73 ±7.94	74.11 ±7.14	
Gender (F/M)	12/9	30/29	17/20	
Medical history:				
Arterial hypertension	16	50	21	< 0.05
Coronary artery disease	14	35	19	> 0.05
Previous myocardial infarction	5	11	8	> 0.05
Compensated heart failure	8	16	20	< 0.05
Diabetes mellitus	9	16	9	> 0.05
Previous transient ischemic attack	4	5	4	> 0.05
Medication:				
ACE	15	40	30	> 0.05
ARB	4	11	4	> 0.05
β-Blockers	14	28	27	< 0.05
Ca blockers	3	12	7	> 0.05
Diuretics	5	18	3	> 0.05
Nitrates	5	3	1	> 0.05
Statins	12	22	22	> 0.05
Antidiabetic agents	9	9	9	> 0.05
Anticoagulants	4	28	28	> 0.05

and group IV – 48 volunteers with similar age without any significant health problems. Patients with acute coronary syndromes up to 6 months before the implantation of pacemakers, active inflammation, brain stroke up to 6 months before the implantation, heart defects, heart failure NYHA class III and IV, cancers, respiratory failure, connective tissue diseases, muscular dystrophy, anaemia with haemoglobin 10 g/dl and less, and thyroid diseases were excluded from the study. Additionally, those with rates of paced beats below 75% during pacemaker check-up were not taken into account. The patients in the present study differed with respect to the presence of arterial hypertension and heart failure in the VVI/R and DDD/R groups. There were also differences in the use of certain medicines. However, there were no statistical differences in the use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers. The clinical characteristics and medication use in all study groups are summarised in Table 1. Patients were assigned to group I, II, and III if they were selected for pacemaker implantation according to the current guidelines, mainly the Recommendations for Cardiac Pacing and Resynchronisation of the Polish Cardiac Society published in 2007 and revised in 2010. Table 2 summarises patient selection for implantation. The study was approved by the Local Bioethics Committee (the Swietokrzyska Chamber of Physicians, ap-

Table 2. Patient selection for pacemaker implantation

Group I AAI/R	Sick sinus dysfunction with normal AV node function:
	a) sinus bradycardia
	b) bradycardia-tachycardia syndrome
Group II DDD/R	1. Sick sinus dysfunction:
	a) sinus bradycardia
	b) bradycardia-tachycardia syndrome
	2. Second-degree AV block with MAS episodes
	3. Third-degree AV block
Group III VVI/R	1. Third-degree AV block
	2. Atrial fibrillation with AV conduction disorders

proval no. 8/2009 of 19 May 2009) and carried out between January 2010 and January 2012.

BNP measurements were performed on venous blood samples collected in EDTA and centrifuged at 2000 G for 10 min to isolate plasma. Then, the samples were placed on the DXI 600 analyzer (Beckman Coulter) and the Triage meters were used for the quantitative assessment of BNP.

The Simpson method and the ellipse method, recommended by the American Heart Association [15], were used to assess the left atrium on echocardiography. The left atrial chamber is divided into a series of oval discs. The volume of the left atrium is the sum of the volumes of the individual discs. The lower atrial border is formed by the mitral valve ring. For practical reasons fundamental planimetric measurements were chosen for analysis, i.e. maximum left atrial volume (LAV_{max}; ml) calculated according to the following formula: $LAV_{max} = [\varpi/6 \times (LA_{max} \times LA_{short} \times La_{long})]$; minimum left atrial volume (LAV_{min}; ml) calculated according to the following formula: $LAV_{min} = [\varpi/6 \times (LA_{min} \times La_{short} \times LA_{long})]$; and left atrial volume index, which is the volume of the left atrium indexed to body surface area and expressed in ml/m^2. Normal LAVI was determined to be 22 ±6 ml/m^2. Echocardiograms were obtained using an ACUSON SEQUOIA device and a 3.5-Mhz transducer with the patient in the left lateral decubitus position, acquiring images in the parasternal long and short axis views.

Statistical analysis

In statistical analysis Spearman correlation rank-order coefficient was calculated because of the distribution and character of variables. The coefficient is used to test the strength of the relationship between the two variables, especially qualitative variables, and to put the observations in a certain order. The measure can also be used to test the relationship between quantitative variables if the number of observations is small.

Ranking the data involves putting the values in ascending (descending) order based on a specific variable and assigning new values. The data can be ranked from the smallest to the largest value or vice versa; however, the order must be identical for the two variables. If two or more values were the same, we averaged the ranks for the tied values. If the two variables move in the same (or generally the same) direction there is a positive correlation between the variables, but when the two variables move in the opposite direction the correlation is negative.

The numerical value of rank correlation coefficient falls in the range between –1 and +1 ($-1 \leq r_s \leq +1$), and it is interpreted in the same way as Pearson correlation coefficient, i.e. the greater the absolute value of a correlation coefficient, the stronger the relationship between the variables.

Results

In the present study, 3 months after AAI/R pacemaker implantation, there was a significant correlation between BNP and maximum left atrial volume (q = 0.55, t = 2.89), minimum left atrial volume (q = 0.67, t = 3.93), and left atrial volume index (q = 0.60, t = 3.24) (Table 3 and Figure 1). At 3 months after DDD/R pacemaker implantation there was a significant correlation between BNP and maximum left atrial volume (q = 0.39, t = 3.18), minimum left atrial volume (q = 0.40, t = 3.34), and left atrial volume index (q = 0.40, t = 3.29) (Table 3). At 6 months after DDD/R pacemaker implantation there was a significant correlation between BNP and maximum left atrial volume (q = 0.47, t = 4.03), minimum left atrial volume (q = 0.49, t = 4.28), and left atrial volume index (q = 0.50, t = 4.40) (Table 3 and Figure 2). At 3 months after VVI/R pacemaker implantation there was a significant correlation between BNP and maximum left atrial volume (q = 0.54, t = 3.77), minimum left atrial volume (q = 0.59, t = 4.32), and left atrial volume index (q = 0.56, t = 4.02) (Table 3 and Figure 3). At 6 months after VVI/R pacemaker implantation there was a significant correlation between BNP and maximum left atrial volume (q = 0.39, t = 2.49), minimum left atrial volume (q = 0.37, t = 2.39), and left atrial volume index (q = 0.38, t = 2.45) (Table 3).

Discussion

It has been 55 years since the first permanent pacemaker implantation. In 2012, 756 permanent pacemakers were implanted per million inhabitants in Poland and 923 per million inhabitants in Europe [24]. Pacemaker therapy has become a vast specialist domain in cardiology. The rapid development of cardiac pacing provided an impulse for a search for non-invasive tests to be used for the evaluation of patients with permanent pacemakers.

Recently, a number of randomised studies have been performed to assess cardiac function based on BNP measurements in patients with heart failure. Maisel *et al.* in 464 patients, Troughton *et al.* in 106 patients, and Cohen-Salal *et al.* in 1327 patients [25–28] demonstrated the clinical usefulness of BNP measurements to monitor patients with heart failure and to estimate their risk of dying.

There are also interesting non-randomised studies evaluating BNP in patients with permanent pacemakers. Kafkas *et al.* analysed 67 patients with DDD/R and VVI/R pacemakers and demonstrated significantly elevated BNP values at 30 days after the implantation. The increase was probably a result of right ventricular apex pacing. It was therefore concluded that BNP is an early marker of structural and functional myocardial changes in patients with permanent pacemakers [29].

Table 3. Correlation analysis of the relationship between B-type natriuretic peptide and selected echocardiographic parameters of left atrium in patients selected for AAI/R pacing at 3 months after the implantation, DDD/R at 3 and 6 months after the implantation, and VVI/R at 3 and 6 months after the implantation

Variables	B-type natriuretic peptide in pg/1000 μl			
	No. of patients	Spearman correlation coefficient (*q*)	Test value (*t*)	Value of *p*
V_{max}	21	0.55	2.89	< 0.01
V_{min}	21	0.67	3.93	< 0.001
LAVI	21	0.60	3.24	< 0.01
DDD/R 3 months:				
V_{max}	59	0.39	3.18	< 0.01
V_{min}	59	0.40	3.34	< 0.01
LAVI	59	0.40	3.29	< 0.01
DDD/R 6 months:				
V_{max}	59	0.47	4.03	< 0.001
V_{min}	59	0.49	4.28	< 0.001
LAVI	59	0.50	4.40	< 0.00
VVI/R 3 months:				
V_{max}	37	0.54	3.77	< 0.001
V_{min}	37	0.59	4.32	< 0.001
LAVI	37	0.56	4.02	< 0.001
VVI/R 6 months:				
V_{max}	37	0.39	2.49	< 0.05
V_{min}	37	0.37	2.39	< 0.05
LAVI	37	0.38	2.45	< 0.05

Sadowski and Wożakowska-Kapłon followed up 28 patients with AAI/R and DDD/R pacemakers and did not find elevated BNP values at 6 months [30]. However, Wang *et al*. in 105 patients with DDD/R and VVI/R pacemakers found a clear relationship between BNP levels, mode of pacing, and NYHA class [31].

In the present study in 117 patients with various types of pacemakers followed up for 6 months initial BNP values were higher in all study groups compared with the controls. Patients with DDD pacemakers showed an increase in BNP values between consecutive time points. In the remaining groups the differences were not significant. The increase in BNP indicating haemodynamic deterioration is encountered in patients with DDD pacemakers in whom right ventricular apical pacing, but not right ventricular outflow tract septal pacing, was used. This mode of pacing is haemodynamically unfavourable, but it is still used due to procedural simplicity and good late effects as regards ventricular lead positioning in the right ventricular apex. An alternative site to apical pacing is the right ventricular outflow tract with active lead fixation. Unfortunately, active fixation leads are not widely used in Kielce. Other results of the present study

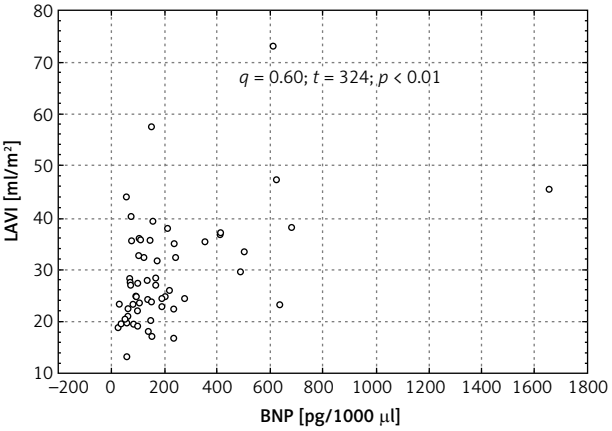

Figure 1. Analysis of correlations between type B natriuretic peptide (BNP) levels in the blood and left atrial volume index (LAVI) in group I (AAI) at 3 months after pacemaker implantation

are concordant with those obtained by other investigators. BNP values are lowest in patients with physiological pacemakers, and highest in patients with VVI pacing. BNP is an early marker of heart failure, and

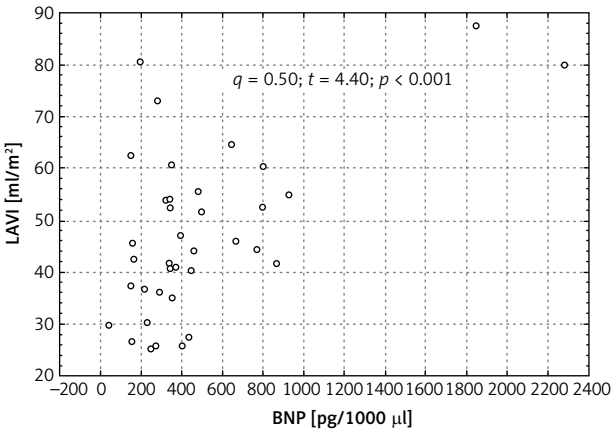

Figure 2. Analysis of correlations between type B natriuretic peptide (BNP) levels in the blood and left atrial volume index (LAVI) in group II (DDD/R) at 6 months after pacemaker implantation

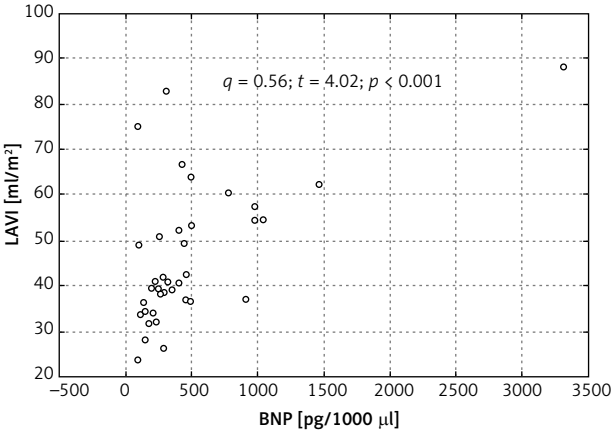

Figure 3. Analysis of correlations between type B natriuretic peptide (BNP) levels in the blood and left atrial volume index (LAVI) in group II (VVI/R) at 3 months after pacemaker implantation

its secretion is stimulated by left ventricular pressure and volumetric overload. These phenomena may be caused by intra-ventricular dyssynchrony due to right ventricular apical pacing. Dyssynchrony with RV pacing has a similar mechanism to left bundle branch block (LBBB) and leads to systolic dysfunction, which causes elevation of left and right atrial pressure. Elevated atrial pressure leads to enlargement of the volume of this chamber. VVI pacing is associated with complete AV dyssynchrony; also, many of the patients with this type of pacing have atrial fibrillation, which results in loss of atrial contraction and significantly reduces cardiac output. A DDD pacemaker enables more physiological stimulation with atrial contraction if the timing of atrial and ventricular contraction is correctly set up. The most physiological pacing is AAI, which provides native ventricular activation.

Echocardiographic measurements of the left atrium are of major importance for cardiovascular assessment and prognosis not only in patients with cardiac diseases but also in healthy subjects. Left atrial dimensions provide important information in patients with left ventricular dysfunction, mitral regurgitation, and atrial fibrillation. Left ventricular volume is a powerful mortality indicator in patients after myocardial infarction. Those with smaller left atrial size and signs of left ventricular systolic dysfunction have a better prognosis than the remaining patients [32–34].

There are studies on the significance of left atrial size in patients with permanent pacemakers. Kubica *et al.* analysed 114 patients with various types of pacemakers (VVI, AAI, DDD) and found significant differences in left atrial volume on echocardiography in patients with VVI pacing as compared with other types [35]. Nielsen *et al.* obtained echocardiographic measurements of the left atrium, left ventricle, and left ventricular ejection fraction in patients with AAI/R and DDD/R pacing followed up for 2.9 ±1.1 years. Patients with AAI/R pacing did not show any significant differences in echocardiographic measurements of the left atrium, left ventricle, and left ventricular ejection fraction. In patients with DDD/R left atrial size increased significantly whereas LVEF significantly decreased [36]. Psychiari *et al.* studied 60 patients with known sick sinus syndrome having AAI/R and DDD/R pacemakers. Left atrial and left ventricular size did not change, but there were significant differences in tissue Doppler [37].

In the present study the maximum left atrial volume, minimum left atrial volume, and left atrial volume index were significantly higher before the implantation of permanent pacemakers as compared with the controls. After the implantation the values did not change significantly in any of the groups.

Correlation analysis of the relationship between BNP and echocardiographic parameters of the left atrium and left ventricle provides important information on the cardiovascular system in patients with heart failure and diabetes mellitus. Dencker *et al.* in a study of 33 patients with poorly regulated type 2 diabetes demonstrated significant correlations between BNP and end-systolic left atrial volume. Certain echocardiographic parameters and their correlation with BNP values may be useful in the assessment of patients with glycaemia disorders [38]. Takeichi *et al.* analysed 92 patients presenting with various cardiovascular diseases: previous myocardial infarction, arterial hypertension, right bundle branch block, and hypertrophic cardiomyopathy. Echocardiography revealed significant correlations between end-diastolic volume, total left atrial fraction, and atrial natriuretic peptide (ANP) in the blood [39]. Koç *et al.* in a large group of 100 patients with heart failure found signifi-

cant negative correlations between NT-proBNP and left ventricular ejection fraction [40].

There are no reports in the literature showing correlations between BNP values and echocardiographic dimensions of the left atrium in patients with permanent pacemakers.

In the present study there was a significant correlation between BNP values and echocardiographic parameters. The most significant correlations occurred between BNP and maximum left atrial volume, minimum left atrial volume, and left atrial volume index, mainly at 3 months after DDD/R pacemaker implantation.

The present study in a group of 117 patients demonstrated the usefulness of extended patient evaluation before and after the implantation of permanent pacemakers. After the implantation there are significant haemodynamic changes such as modulations of BNP values and alterations in echocardiographic parameters of the left atrium. It is therefore helpful to analyse these parameters before and after the implantation. Pacemaker check-up should be extended to include measurements of heart failure markers such as BNP. Echocardiographic evaluation should include measurements of left atrial size and function in patients after pacemaker implantation.

Conclusions

In patients after the implantation of permanent pacemakers there are correlations between BNP values and echocardiographic left atrial parameters, especially in patients with DDD/R pacemakers. Left atrial function improves in patients with DDD/R pacemakers. Pacemaker check-up should be extended to include BNP measurements and echocardiographic assessment of the left atrium.

Conflict of interest

The authors declare no conflict of interest.

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