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Correlation analysis of atrial natriuretic peptide concentration, echocardiographic left atrial and left ventricular dimensions, and renal function parameters in patients after permanent pacemaker implantation

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Abstract

Background: *Atrial endocrine function was established in the second half of the 20th century, confirming the role of artial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) in the physiology of the cardiovascular system. The present study was undertaken to evaluate changes in ANP and echocardiographic parameters within the first month after VVI and DDD pacemaker implantation and to evaluate correlations between the parameters.*

Methods: *The study population consisted of group I — 20 VVI patients aged 71–90 years (mean age 77.5 ± 5.9) and group II — 20 DDD/VDD patients aged 49–81 years (mean age 68.9 ± 11). Fifteen healthy volunteers aged 58–80 years (mean age 72.7 ± 2.8) served as controls. Correlations between ANP levels and cardiac cavity dimensions and between ANP and parameters of renal function were studied.*

Results: *Blood levels of ANP decreased after pacemaker implantation: in the VVI group from 168.61 ± 81.95 pg/1000 μL to 118.04 ± 61.06 pg/1000 μL at 7 days and to 121.4 ± 71.90 pg//1000 μL at 30 days; and in the DDD/VDD group from 134.89 ± 83.11 pg/1000 μL to 104.96 ± ± 57.09 pg/1000 μL at 7 days and to 110.82 ± 53.32 pg/1000 μL at 30 days. There was a significant correlation between ANP levels and left atrial size in the DDD/VDD group — 0.598 (p = 0.005) and 0.593 (p = 0.005) and left ventricular dimensions — 0.499 (p = 0.024) and 0.485 (p = 0.030).*

Conclusions: *ANP decreases significantly after pacing implementation in patients selected for implantation of VVI and DDD/VDD pacemakers. ANP correlates significantly with echocardiographic measurements in patients selected for DDD/VDD pacemakers, but no significant correlation is observed in VVI patients qualifying for permanent pacemaker due to atrioventricular block.* (Cardiol J 2009; 16, 2: 157–163)

Key words: ANP, VVI, and DDD pacing, correlation analysis

Table 1. Clinical data.

Clinical data	Group I (n = 20)	Group II (n = 20)	P
Previous myocardial infarction	5 (25%)	10 (50%)	> 0.05
Stable coronary disease	14 (70%)	14 (70%)	> 0.05
Compensated heart failure	17 (85%)	13 (65%)	> 0.05
Type 2 diabetes	6 (30%)	2 (10%)	> 0.05
Hypercholesterolemia	8 (40%)	15 (75%)	< 0 05

Introduction

Assessment of natriuretic peptides in blood provides important clinical information, especially in cases of heart failure, arterial hypertension, coronary artery disease, and cardiac arrhythmias.

The endocrine function of the heart was first established in 1956 when Kisch described osmophilic granules in the atrial muscle of a guinea pig [1]. In 1981 de Bold et al. [2] reported that rat atrial extracts given intravenously had a stimulatory effect on urinary water and sodium excretion.

The most important natriuretic peptides are: atrial natriuretic peptide (ANP), consisting of 28 amino acids; brain natriuretic peptide (BNP), consisting of 32 amino acids; and C-type natriuretic peptide (CNP), consisting of 22 amino acids [3, 4]. The principal stimulus for ANP secretion, and therefore increase in serum ANP concentration, is mechanical distension of atrial myocytes. Increased atrial wall tension causes ANP secretion. Increased atrial mechanical load raises the ANP concentration in blood serum [5, 6].

Mechanical atrial wall stretch is linked to increased ANP secretion [7]. It is the first response to unfavourable hemodynamic changes. A further compensatory mechanism involves vasodilator effects. Urinary sodium excretion and diuresis are increased whereas secretion of vasopressin, aldosterone, and renin is reduced [8]. In response, ANP concentration and BNP secretion are increased.

Assessment of ANP and BNP concentrations is a useful tool for monitoring patients with heart failure. Clinical evidence shows that BNP is a predictor of morbidity and mortality in heart failure patients [9, 10]. It is especially important in the asymptomatic phase of the disease when BNP levels may predict the development of symptoms [11, 12].

In 1958 Sening in Stockholm was the first person to implant a cardiac pacemaker in a patient with a third-degree atrioventricular block [13, 14]. The first pacemaker implantation in Poland was performed by Kieturakis in Gdansk in 1963 [14]. Since that time, the situation has changed and we have witnessed tremendous progress in cardiac pacemakers and pacing leads. The indications for cardiac pacing have extended beyond the management of atrioventricular blocks and conduction disorders [14] and include cardiac resynchronization therapy, pacing to prevent atrial fibrillation, and permanent pacing in long QT syndrome [15].

Patients with severe atrioventricular conduction defects receive VVI, DDD, and VDD pacemakers.

The present study was undertaken to evaluate changes in ANP and echocardiographic parameters during the first month after VVI and DDD pacemaker implantation and to evaluate correlations among studied parameters.

Methods

The study included a total of 55 patients of whom 40 had second- and third-degree atrioventricular blocks. Group I consisted of 20 patients with an implanted VVI pacemakers, aged 71–90 years (mean age 77.5 ± 5.9 years), and group II, 20 patients with DDD/VDD pacemakers, aged 49–81 years (mean age 68.9 ± 11 years). The control group (group III) consisted of 15 healthy volunteers ranging in age from 58 to 80 years (mean age 72.7 ± ± 2.8 years). Those with cardiac defects, acute myocardial infarction, unstable angina pectoris, decompensated heart failure, acute and chronic respiratory diseases, anemia, thyroid diseases, or neoplastic processes were excluded from the study. Patients were entered for the study if their ECG strips or Holter recording showed second- or third-degree atrioventricular conduction defects and they qualified for permanent pacing. Table 1 summarizes the clinical data.

VVI pacemakers were implanted in patients with paroxysmal block and atrioventricular conduction defects without retrograde ventriculoatrial conduction and in patients with motoric dysfunction. DDD/VDD pacemakers were implanted in physically active patients (irrespective of age), patients with

retrograde ventriculoatrial conduction, and in patients with clinical manifestations of heart failure.

Plasma αANP was measured in all the three groups. Blood samples for the determination of plasma αANP were drawn before, and 7 days and 30 days after, pacemaker implantation. In the control group, αANP concentration was measured only once. Blood was sampled at rest (supine position) from patients arriving in the morning until noon. Six millilitres of full blood was sampled in tubes containing 1 mg/mL EDTA and 500–1000 KIU/mL Trasylol and centrifuged at 4°C for 30 min at 2000 g. Isolated serum was frozen at –15 to –30°C. ANP concentration was measured using double-antibody radioimmunoassay kit (Human αANP-RIA system RPA 512, Amersham) [16].

Transthoracic echocardiography was performed in all the patients and the controls. Echocardiograms were obtained from pacemaker patients on three occasions: before, 7 days, and 30 days after the system placement. The controls underwent echocardiographic examination only once. The study was performed in the morning between 9.00 and 12.00 with an Acuson Sequoya device and 3.5 MHz probe.

Those with poor-quality echocardiographic images were excluded from further analysis. The value of each parameter was averaged from three measurements. The study was performed on the patients in the left decubitus position. M-mode images were obtained in the parasternal long and short axis and in apical two- and four-chamber views. Doppler technique was used to measure the flow of blood. The following echocardiographic parameters were selected for analysis:

Left atrial parameters

LA max [cm] — maximum left atrial dimension in the M-mode parasternal long axis view — measured from the left atrial posterior wall to the inner aortic surface.

LA min [cm] — minimum left atrial dimension in the M-mode parasternal long axis view — measured from the left atrial posterior wall to the inner aortic surface.

LATEF — left atrial total emptying fraction = LA max – LA min/LA min [17–19].

Parameters of left ventricular systolic function

LVEDD [cm] — left ventricular end-diastolic dimension in the M-mode parasternal long axis view, immediately below the mitral valve — measured between the posterior wall inner surface and the left ventricular inner surface of the ventricular septum.

LVESD [cm] — left ventricular end-systolic dimension in the M-mode parasternal long axis view, immediately below the mitral valve — measured between the posterior wall inner surface and the left ventricular inner surface of the ventricular septum.

EF — left ventricular ejection fraction calculated according to the Teicholtz formula.

Creatinine clearance was measured using a colorimetric kinetic Jaffe assay. In an alkaline environment, creatinine forms coloured complexes with picric acid. Absorption enhancement measured for 500 nm wavelength is proportional to creatinine concentration. Creatinine is measured in serum and daily urine. Total creatinine urinary excretion is 1.0–2.5 g/day. Creatinine clearance reference values are 75–110 mL/min. Measurements are made using an automated analyzer Ra 1000 Technicon [20].

Quantitative variables were presented as the arithmetic mean, median (if not normally distributed), and standard deviation [21].

Statistical analysis was performed using parametric Student's t-test and non-parametric U Mann--Whitney test. ANOVA was used for the normally distributed data. The RIR Turkey test was used for comparisons [21].

The study was approved by the local bioethical committee and all patients gave their informed consent.

Results

Assessment of the changes in blood ANP concentrations during the study revealed significant differences in group I (VVI pacing) and in group II (DDD pacing) between baseline and 7 days, and between baseline and 30 days after implantation.

Left atrial systolic dimension at baseline differed significantly from that at 30 days in group I (VVI pacing). Left atrial diastolic dimension at baseline differed significantly from that at 7 days and at 30 days in group I (VVI pacing). There was a significant difference in left atrial total emptying fraction between baseline and day 30, and between day 7 and day 30, in group II (DDD pacing).

Left ventricular systolic dimension at baseline differed significantly from that at 7 days in group II (DDD pacing). Left ventricular ejection fraction differed significantly between baseline and day 7 and between baseline and day 30 in group I (VVI pacing).

There was a significant difference in blood urea levels between baseline and day 7, and between

Table 2. Changes in atrial natriuretic peptide and echocardiographic parameters over time in patients with VVI and DDD pacing.

Parameters	Before implantation	7 days after implantation	30 days after implantation	P		
				7 days *vs.* baseline	30 days *vs.* baseline	30 days *vs.* 7 days
VVI						
ANP [pg/1000 μL]	168.61 ± 81.95	118.04 ± 61.06	121.40 ± 71.90	< 0.01	< 0.05	NS
LASD [mm]	32.40 ± 5.63	31.35 ± 4.36	29.40 ± 5.53	NS	< 0.05	NS
LADD [mm]	42.95 ± 4.75	40.75 ± 3.97	39.60 ± 4.13	< 0.05	< 0.01	NS
LATEF (%)	24.50 ± 6.59	22.80 ± 7.17	25.95 ± 8.74	NS	NS	NS
LVSD [mm]	37.05 ± 7.36	36.80 ± 7.91	36.55 ± 7.21	NS	NS	NS
LVDD [mm]	54.80 ± 9.79	54.00 ± 9.15	53.60 ± 6.57	NS	NS	NS
LVEF (%)	53.05 ± 6.07	54.85 ± 5.22	55.15 ± 5.99	< 0.01	< 0.05	NS
Urea [mg/dL]	56.45 ± 21.59	52.10 ± 19.90	42.45 ± 7.95	< 0.05	< 0.01	< 0.05
CC [ml/min]	72.07 ± 19.31	76.12 ± 17.80	84.98 ± 17.91	NS	< 0.01	< 0.01
DDD/VDD						
ANP [pg/1000 μL]	134.89 ± 83.11	104.96 ± 57.09	110.82 ± 53.32	< 0.01	< 0.05	NS
LASD [mm]	29.05 ± 6.29	27.70 ± 5.33	27.00 ± 5.95	NS	NS	NS
LADD [mm]	37.55 ± 7.07	37.25 ± 6.17	37.70 ± 6.35	NS	NS	NS
LATEF (%)	22.95 ± 7.47	25.05 ± 8.23	28.05 ± 9.06	NS	< 0.01	< 0.05
LVSD [mm]	39.35 ± 10.47	37.90 ± 10.32	37.65 ± 9.47	< 0.05	NS	NS
LVDD [mm]	55.90 ± 9.49	55.70 ± 9.55	54.75 ± 8.21	NS	NS	NS
LVEF (%)	53.75 ± 10.00	55.05 ± 10.15	54.40 ± 10.70	NS	NS	NS
Urea [mg/dL]	47.30 ± 14.91	46.40 ± 13.06	44.80 ± 11.40	NS	NS	NS
CC [ml/min]	82.32 ± 15.85	84.63 ± 13.21	96.86 ± 18.22	NS	< 0.01	< 0.01

CC — creatinine clearance; LVEF — left ventricular ejection fraction; LVDD — left ventricular diastolic dimension; LVSD — left ventricular systolic dimension; LATEF — left atrial total emptying fraction; LADD — left atrial diastolic dimension; LASD — left atrial systolic dimension

baseline and day 30, as well as between day 7 and day 30, in group I (VVI pacing). Creatinine clearance differed significantly between baseline and day 30 and between day 7 and day 30 in both groups (VVI and DDD pacing).

After pacemaker implantation, ANP concentration decreased in the VVI and DDD/VDD groups. We observed significant differences. We did not observe significant differences between left atrial and left ventricular dimensions in either group. Left atrial total emptying fraction in the group DDD//VDD and left ventricular ejection fraction in the group VVI improved after pacemaker implantation. Renal parameters improved in both groups. Table 2 summarizes changes in ANP and echocardiographic parameters over time in patients with VVI and DDD pacing.

At baseline in patients with second- and third-degree atrioventricular conduction defects there was a significant correlation between serum ANP concentration and maximum and minimum left atrial dimension (p < 0.05) in group II. The correlation coefficients were 0.598 and 0.593, respectively.

There was also a significant correlation between ANP levels and left ventricular diastolic and systolic dimensions in group II (p < 0.05). The correlation coefficients were 0.499 and 0.485, respectively.

In the control group (group III), we found no significant correlation between ANP levels and left atrium, or left ventricular dimension and renal function. Table 3 summarizes the assessment of the correlations. Figures 1–3 show significant correlation coefficients between blood ANP concentrations and left atrial and left ventricular function parameters.
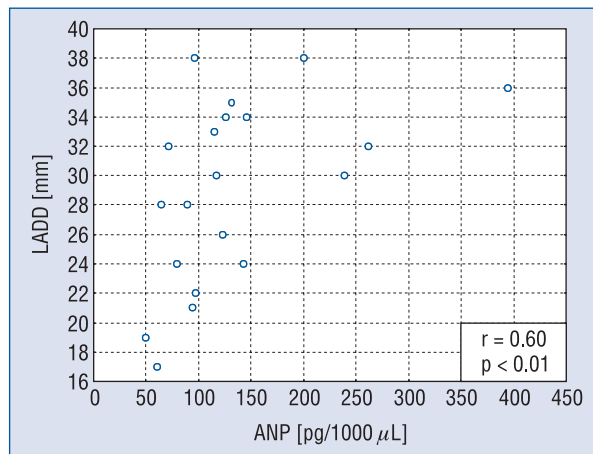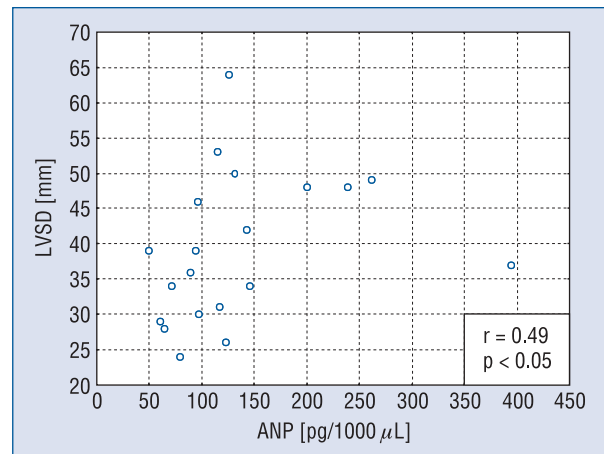
Discussion

At baseline, prior to permanent pacemaker implantation, there was a positive correlation between serum ANP concentration and left atrial minimum and maximum dimensions in patients with DDD/VDD pacing systems. In these patients there was also a positive correlation between ANP concentration and left ventricular systolic and diastolic dimension. In all patients with VVI and DDD/VDD pacing systems

Table 3. Correlation between blood atrial natriuretic peptide concentrations and selected parameters of left atrial and left ventricular function, and renal function, in groups I, II, and III.

Group	r/p	Left atrial function			Left ventricular function			Renal function		
		LA max	LA min	LATEF	LVEDD	LVESD	EF	Urea	Creatinine	CC
I	r	0.038	−0.057	0.221	−0.128	−0.044	−0.349	−0.336	−0.320	0.057
	p	0.871	−0.244	0.347	−0.548	−0.188	0.131	0.146	0.168	0.810
II	r	0.598	0.593	−0.124	0.499	0.485	−0.120	0.259	-0.001	0.257
	p	0.005	0.005	0.601	0.024	0.030	0.612	0.269	0.994	0.272
III	r	−0.001	−0.254	0.159	0.285	0.189	0.007	−0.175	−0.028	−0.267
	p	0.994	0.360	0.571	0.302	0.498	0.979	0.531	0.919	0.334

EF — ejection fraction; LVEDD — left ventricular end-diastolic dimension; LVESD — left ventricular end-systolic dimension; CC — creatinine clearance; LA — left atrial; LATEF — left atrial total emptying fraction

Figure 1. Correlation between blood atrial natriuretic peptide (ANP) concentrations and left atrial diastolic dimension (LADD) prior to pacemaker implantation in group II (DDD); r = 0.598, p = 0.005.

Figure 2. Correlation between blood atrial natriuretic peptide (ANP) concentrations and left ventricular systolic dimension (LVSD) prior to pacemaker implantation in group II (DDD); r = 0.485, p = 0.030.

there was a positive correlation between ANP concentration and left atrial maximum dimension.

At 7 days after permanent pacemaker implantation there was a significant correlation between serum ANP concentration and creatinine clearance in patients with DDD/VDD pacing systems. There was also a significant correlation between ANP values and left atrial maximum dimension in all patients with VVI and DDD/VDD pacing systems.

At 30 days after permanent pacemaker implantation there was a significant correlation between serum ANP concentration and left ventricular systolic and diastolic dimension in patients with VVI pacing systems. There was also a significant correlation between ANP concentration, left ventricular

systolic and diastolic dimension, and left ventricular ejection fraction in all patients with VVI and DDD/VDD pacing systems.

There was a positive correlation between changes in ANP concentration and changes in left atrial total emptying fraction in patients with VVI pacing systems.

In patients with DDD/VDD pacing systems there was a positive correlation between changes in ANP concentration and changes in left ventricular systolic dimension.

In all patients with VVI and DDD/VDD pacing systems there was a significant correlation between changes in ANP concentration and left ventricular systolic dimension.
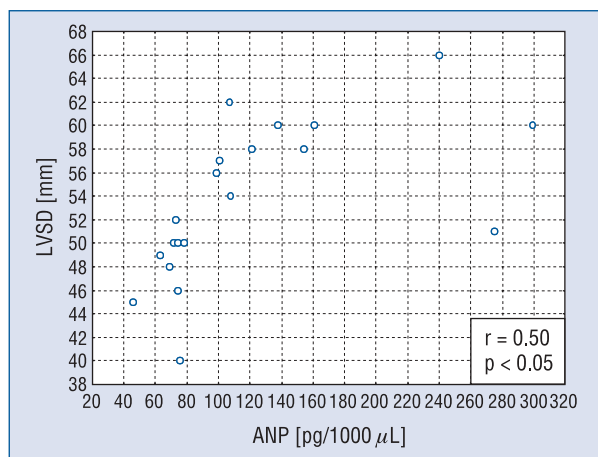
Figure 3. Correlation between blood atrial natriuretic peptide (ANP) concentrations and left ventricular systolic dimension (LVSD) at 30 days after pacemaker implantation in group II (DDD); r = 0.495, p = 0.040.

At 30 days after permanent pacemaker implantation there was a significant correlation between changes in serum ANP concentration and changes in left ventricular minimum dimension in patients with DDD/VDD pacing systems. There was also a significant correlation between changes in ANP concentration and changes in left atrial minimum dimension in all patients with VVI and DDD/VDD pacing systems.

Comparing serum ANP concentrations in patients with VVI and DDD/VDD pacing systems, we found that serum ANP decreased in patients with both types of pacing devices. Further analysis of absolute ANP values revealed that patients with DDD/VDD pacing devices are characterized by increased dynamics of reduction in ANP concentration after permanent pacemaker implantation.

VVI pacemakers were implanted in patients with paroxysmal block and atrioventricular conduction defects without retrograde ventriculoatrial conduction, and in patients with motoric dysfunction. DDD/VDD pacemakers were implanted in physically active patients (irrespective of age), patients with retrograde ventriculoatrial conduction, and patients with clinical manifestations of heart failure. Measurement of blood ANP concentrations prior to pacemaker implantation had no impact on the choice of pacing mode. If the information on ANP levels had been available earlier, it would have been possible to alter patient selection criteria for pacing mode. Changes in blood ANP concentrations might have also been a result of the natural course of the disease. It is of vital importance to analyze carefully the patient's clinical data, taking into account the manifestations of heart failure (Table 1).

The correlation between ANP levels and other parameters is of major interest. Analysis revealed that ANP values are linked to parameters of left atrial function. The relationship is especially strong in patients with DDD/VDD pacing devices. In such patients the reduction in ANP secreted from cardiac atria is associated with improved left atrial hemodynamics and renal function.

The presence of positive correlations between ANP concentrations and left atrial and left ventricular dimensions, as well as renal function parameters, may provide a clue to the choice of pacing mode in a given group of patients. Routine assessment of ANP levels prior to pacemaker implantation would provide useful prognostic information from a clinical viewpoint.

Analysis of ANP levels prior to pacemaker implantation and at consecutive time intervals demonstrates higher ANP concentrations and larger changes in its levels in patients with VVI pacing. There is a clear correlation between ANP changes and left atrial function parameters. As left ventricular function was comparable in both groups, it may be concluded that, based on ANP assay, the patients had been inappropriately selected for pacemaker implantation. VVI pacemakers had been implanted in patients with higher ANP levels, that is, in those with more advanced heart failure. According to guidelines, such patients should receive a DDD pacemaker. The information on ANP levels was not available prior to patient selection for pacemaker implantation in this study. It appears that ANP assay is an important prognostic tool supporting the diagnostic process in patients qualifying for pacemaker therapy.

Left ventricular and left atrial function in patients with left ventricular impairment was examined in the large multicentre clinical study, CONSENSUS II. Erriksson et al. performed a subgroup analysis in 53 patients with post-myocardial infarction left ventricular impairment [22]. They assessed the correlation between left atrial dimension, left ventricular dimension and serum ANP concentration, measured by radioimmunology. There was a negative correlation between ANP and left atrial dimension (r = –41), and a positive correlation between left ventricular systolic parameters and ANP secretion measured by radioimmunology (r = 40).

In a similar study, Irzmański et al. [17] assessed ANP and BNP levels in patients with idiopathic arterial hypertension and left ventricular hypertrophy.

They found a positive correlation between ANP and BNP levels and left ventricular posterior wall thickness, ventricular septal thickness, and left ventricular mass index. Increased ANP and BNP levels were predictors of hypertension complications.

In another study, Irzmański et al. [18] assessed ANP and BNP levels in relation to endothelin-1 in patients with arterial hypertension. There was a strong correlation between ANP, BNP, and endothelin-1 levels and left ventricular posterior wall thickness, and between ventricular septal thickness and left ventricular mass index on echocardiography in hypertensives.

Hayashi et al. [19] demonstrated a similar correlation between ANP levels and left atrial dimension in patients with mitral stenosis.

Summing up, the correlation between ANP levels and echocardiographic parameters of the left atrium and left ventricle varies and may provide useful clinical information.

Conclusions

1. ANP decreases significantly after implementation of pacing in patients qualified for implantation of VVI and DDD/VDD pacemakers.
2. ANP correlates significantly with echocardiographic measurements in patients qualified for DDD/VDD pacemakers, but no significant correlation is observed in VVI patients qualified for pacemaker due to atrioventricular blocks.

Acknowledgements

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