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Original Research Article

Relationship between Echocardiographic Characteristics and NT-proBNP in Patients with Dual Chamber Pacemaker: A Prospective Follow up Study

Katerina Vitliyanova[1], Mariya Negreva[2*], Ivaneta Joncheva[3], Krasimira Prodanova[4]

[1]Second Multiprofile Hospital for Active Treatment of Sofia, Clinic of Cardiology, Sofia, Bulgaria

[2]Medical University of Varna "Prof. Dr.P. Stoyanov", First department of internal diseases, Varna, Bulgaria

[3]University Hospital for Active Treatment of Burgas, Clinic of cardiology, Burgas, Bulgaria

[4]Technical University of Sofia, Department of applied mathematics and informatics, Sofia, Bulgaria

***Corresponding Author's E-mail: mnegreva@abv.bg**

Abstract

Data on NT-proBNP serum levels and echocardiographic indices in patients with dual-chamber pacemaker are scarce. The purpose of this study is to explore the changes, if any in certain echocardiographic indices including LV volumes, LAV index, LVEF and levels NT-proBNP, and their relationships in patients with dual chamber pacing over the 24 weeks after the pacemaker implantation. Forty-five patients (20 women, and 25 men, mean age 72.1±9.0 years) were selected for the study with DDDR implanted pacemaker. At baseline (before the pacemaker implantation), on the 12th week and 24th week serum NT-proBNP levels was measured as well as echocardiographic parameters LVESV, LVEDV, LAVI and EF. The difference between the levels of NT-proBNP at 12th week were not significantly different as compared to the baseline values (546.88±41.74 vs 508.83±45.53pg/mL, p=0.54) but on the 24th week NT-proBNP significantly differed from the baseline mean value (649.00±43.04 vs 508.85±45.53pg/mL, p=0.029). LVESV, LVEDV and EF did not significantly changed over time (p>0.05). There was observed a trend to increase of LVESV reaching a borderline significance at 24th week (p=0.15). LAVI show statistically significant and stable increase over time as compared with the baseline values (p<0.001). Most significant changes occurred in NT-proBNP and LAVI values, notable at and after the 12th week after DCPM implantation. As markers of LA remodelling our results support measurement of NT-proBNP and LAVI values in the post pacemaker implantation follow up in case of DCPM has been implanted.

Keywords: Dual chamber pacemaker, NT-proBNP, LAVI

INTRODUCTION

Dual-chamber pacemakers (DCPM) sense and pace, both the atrium and the ventricle and are aimed to achieve atrioventricular synchrony in patients with complete AV – block. Dual chamber pacemaker has two leads, one in the right atrium and one in the right ventricle that correspond with normal heart activity and intrinsic depolarization. Currently the dual-chamber pacing is always preferred over the single chamber ventricular pacing except in patients with atrial flutter or fibrillation because physiologically they give time to the atria to empty in the ventricles and such way preserving the atrial kick (Dawood et al., 2021; Toff et al., 2005).

Most ofstudies suggested the negative effects of right ventricular (RV) pacing on the left ventricular (LV) structure and ejection fraction despite the beneficial effect on symptoms, functional capacity, and blood pressure control in patients with chronic heart failure (CHF) (Kruse et al., 1982; Boon et al., 1987). The results on the

relationship between NT-proBNP serum levels and echocardiographic indices in patients with DCPM are to some extend controversial. Left atrium (LA) assessment was also investigated but the data on correlation with biomarkers for heart failure are insufficient (Ferrari et al., 2014).

The purpose of this study is to explore the changes, if any in certain echocardiographic indices including LV volumes, LAvolume(LAVI) index, LVEF and levels NT-proBNP, and their relationships in patients with DCPM at baseline and over the 24 weeks.

MATERIAL AND METHODS

Patient population and study protocol

Patient recruitment started from March 2019 to August 2021. Over this period, 144 consecutive patients (LVEF>50%) presented to the University hospitals in City of Burgas, St Deva Maria for device implantation. Screening was done only on patients with complete AV block with preserved sinus activity as an indication for dual chamber implantation. Of 144 patients, only 45(20 women, 25 men, mean age 72.1±9.0 years) patients met further the study criteria and were included in the study.

The study was approved by Local Ethics Committee in the University hospital of Burgas. All patients provided written informed consent.

Cases were eligible for inclusion if they were older than 18 years and had been diagnosed with AV – block and absence of considerable comorbidities, excluding presence of moderate arterial hypertension with optimal medical control defined in accordance with ESC 2018 recommendations. LV volumes and function were assessed by 2D echocardiography at baseline, at 12-week and 24-week post-pacing. Baseline assessment was done on the day after the implantation procedure.

The exclusion criteria included the presence of more than mild valve heart disease, ischaemic heart disease, survived acute coronary syndrome, coronary revascularization PCI/CABG, stable angina, uncontrolled arterial hypertension, diabetes mellitus, chronic heart failure, presence of inflammatory heart disease, congenital malformations and cardiomyopathies. Patients with poor echo windows, patients with atrial fibrillation or other types of arrhythmia that can affect stroke volume measurement, debilitated or cancer patients with expected survival less than 1 year and patients with previously implanted devices were excluded.

Pacemaker implantation and programming

The selected patients were implanted with dual chamber pacemaker programmed to DDDR mode in accordance with the requirements of the expert consensus of EHRA (Burri et al., 2021). The implanted pacemakers were Medtronic-Sphera DR MRI SureScan, with electrodes CapSure fix Novus MRI SureScan, 52 and 58 mm for the atrium and ventricle, respectively. During the procedure were placed electrodes with active fixation in the RA auricle and RV apex. Rate responsive mode was selected as it resulted in better patient quality of life and exercise tolerance. The procedure was done in accordance with all aseptic and antiseptic rules. Telemetric examination of the pacemaker was performed at the hospital discharge, on the 12^{th} and 24^{th} week after the pacemaker implantation. The proportion with constant RV stimulation reached over 80% of all participants.

Instrumental assessment

All patients underwent a detailed clinical examination and interview according to the standard protocol, to collect information on biologic and demographic data including age, gender, cardiovascular risk factors and blood pressure (systolic and diastolic).

All information on medical history, comorbidities, clinical characteristics and medications was documented. Instrumental assessment was conducted at admission, on the 12^{th} and the 24^{th} week. It included standard electrocardiogram obtained from 12-lead and transthoracic echocardiography.

Transthoracic echocardiography was undertaken with the patient in the left lateral decubitus position using a 3.5 MHz transducer and GE Healthcare Vivid S6(2013 GE Medical Systems, Israel Ltd.0 equipment. Standard M-mode was applied for obtaining left ventricle end-diastolic (LVEDD) and end-systolic diameters (LVESD). Standard two-dimentional images were examined off-line. Left ventricular end-systolic volumes (LVESV) and end-diastolic volumes (LVEDV) as well as the LVEF (%) were quantified using manual planimetry of conventional two- and four-chamber views and Simpson's technique (Lang et al., 2015). LAV was measured with two-dimentional echocardiography using manual planimetry of conventional four- and two chamber views at ventricular end systole and the biplane modified Simpson's method (Jiamsripong et al., 2008). LAVI was calculated by dividing LA volume by body surface area.

The same experienced echocardiographer carried out all examinations of each individual. Echocardiographic assessment of the left ventricular function was performed at baseline and on the 12^{th} and 24^{th} week.

Biochemical tests

Blood samples for standard biochemical analyses were taken at admission. NT-proBNP were measured at baseline (before the pacemaker implantation) on the 12 week and at the end of follow up.

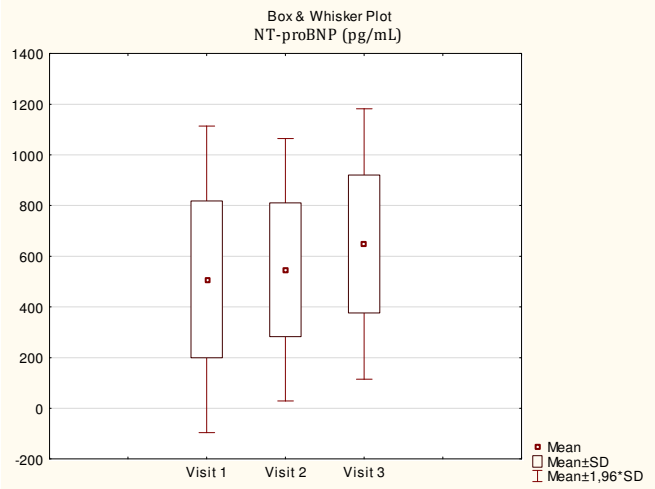

Figure 1. Serum NT-proBNP (pg/mL) over the follow up: at baseline, on the 12th and the 24th week after the pacemaker implantation.

Serum NT-proBNP levels were measured with immunoassay. Blood samples were collected with a BD Vacutainer Serum Tubes (Becton Dickinson, NJ, USA). Samples were centrifuged up to 1 h after sampling and were stored at –20° until assayed. NT-proBNP levels were determined using the commercialy available kit MAGLUMI NT-pro BNP,Lotus GlogalCo., London UK with intra-assay coefficient of variation ≤10% and inter-assay coefficient of variation ≤15%. The sensitivity determined by the manufacturer was less than 12.5 pg/ml.

Statistical analyses

Statistical analyses were done using STATISTICA version 13.3.0, StatSoftInc., USA. The data are summarised in terms of frequencies and percentages for categorical variables, and bymeans and standard deviations (SD) for continuous variables. Group comparisons were made with t-test of student for independent samples. Simple linear regression was used to investigate the independent relations of the variables LVESV, LVEDV, LAVI and EF to NT-proBNP. The model function for a simple linear regression was:

$y=B_0+B_1x+e,$

where **y** is the predicted value of the dependent variable (y) for any given value of the independent variable (x), B_0 is the intercept, the predicted value of y when the x is 0, B_1 is the regression coefficient (slope). Slope give us information about how much we expect y to change as x increases, x is the independent variable (the variable we expect is influencing y) and e is the error of the estimate, or how much variation there is in our estimate of the regression coefficient.The coefficient of determination (r^2) is use as a measure how well a statistical model predicts the values of NT-proBNP. As it is known r^2 provides a measure of how well observed outcomes are replicated by the model, based on the proportion of total variation of outcomes explained by the model.

In all analyses, statistical significance was considered achieved at a value of $p<0.05$.

RESULTS

Additionally to the age and gender distribution the studied mean BMI of the investigated patients was 27.45 ± 0.64 cm/m^2 with frequency of well controlled mild to moderate hypertension 86.6% (39) of all study patients.

NT-proBNP

Mean values of serum NT-proBNP at baseline of were 508.85±45.53 pg/ml. There was an increase in values over the follow at each visit: 546.93±41.74 and 649.00±43.04 (Figure 1). The difference between the levels of NT-proBNP at week 12th were not significantly different as compared to the baseline values (546.88±41.74 vs 508.83±45.53pg/mL, p=0.54) but on the 24th week NT-proBNP significantly differed from the baseline mean value (649.00±43.04 vs 508.85± 45.53pg/mL, p=0.029).

Ehocardiography

The invetsigated echocardiographic indices LVESV, LVEDV and EF did not significantly changed over time (Table 1). There was observed a trend to increase of

Table 1. Dynamics in echocardiographic indices over the follow up

Ehocardiographic characteristics	Visit 1*	p Visit 1 vs Visit 2	Visit 2**	p Visit 2 vs Visit 3	Visit 3***	p Visit 1 vs Visit 3
LAVI (mL/m²)	20.03±0.71	<0.001	27.42±1,34	<0.001	27.05±1.51	<0.001
LVEDV (mL/m²)	51.98±1.97	>0.05	51.94±1.63	>0.05	51.62±1.81	>0.05
LVESV (mL/m²)	24.50±0.77	>0.05	24.23±0.88	>0.05	26.05±0.72	>0.05
LVEF (%)	57.36±0.66	>0.05	56.23±0.65	>0.05	56.13±0.69	>0.05

*at baseline; ** at 12th week, *** at 24th week

Table 2. The estimated parameters of the linear models with dependant variable NT-proBNP.

Explanatory variable	Intersept	Slope	Coefficient of determination
LVESV	-1123.14	722.91	0.85
LVEDV	19354.11	-362.32	0.97
LAVI	274.45	11.83	0.68
LVEF	5114.46	-80.36	0.76

LVESV reaching a borderline significance at 24th week (p=0.15). Concerning the LAVI the results show statistically significant and stable increase over time as compared with the baseline values.

Using mean values of the data at baseline; at 12th week, at 24th week for NT-proBNP and for each of the indexes LVESV, LVEDV, LAVI and EF we built four simple linear regression models to invetsigate the relationship between the values of NT-proBNP and the indexes. The coefficient of determination (r^2) is use as a measure how well a statistical model predicts the values of NT-proBNP. The estimated parameters of the linear models, with explanatory variables LVESV, LVEDV, LAVI and EF are given in Table 2.

Estimated values of the slope for LVESV and LAVI were positive, so values of NT-proBNP increased as LVESV and LAVI increased. The slopes for LVEDV and EF were negative, so values of NT-proBNP decreased as LVEDV and EF increased. The r^2 value show that 85% of the variation in the values of NT-proBNP were explained by the values of LVESV and the corresponding percentages for LVEDV were 97%, for LAVI 68% and for EF-76%.

DISCUSSION

The present paper is focused on measuring the changes and the relationship between the selected echocardiographic characteristics, and short term NT-proBNP in relation to dual-chamber pacing. Investigation of NT-proBNP and echocardiographic response in patients with dual chamber pacemaker is under research to define the subjects at risk of worsening cardiac function. It is also related to the general efforts to find out ease and credible noninvasive tests for clinical assessment of such patients.

Many studies revealed the prognostic role of NT-proBNP measurement in monitoring cardiac function in patients with permanent pacemakers (Troughton et al., 2004; Troughton 2009). NT-proBNP is an early marker of heart failure, cardiac dyssnchrony, and its secretion is stimulated by left ventricular pressure, left ventricle wall stress and volumetric overload (Naegeli et al., 2007; Naqvi and Chao, 2021; Krittayaphong et al., 2008; Rahsepar et al., 2021).

Our results on the dynamic of NT-proBNP values are concordant with those obtained by other studies as well (Michael., 2006). The increase in NT-proBNP is previously observed in patients with DDDR pacemakers with right ventricular apical pacing (Sriratanasathavorn et al., 2013).

DCPM is shown to lead to LV dyssynchrony, systolic dysfunction, elevation of left and right atrial pressures and the subsequent LA enlargement explaining the observed in our study dynamics in LAVI values. (Psychari et al., 2010); Ahmed et al., 2014)

In support to our results Kafkas et al. demonstrated in 67 patients with DDD/R and VVI/R pacemakers that BNP values increase, marking the structural and functional myocardial changes in patients with right apical placement of the electrode of DCPM (Kafkas et al., 2011). Similarly to our results, Wang et al. in a study on 105 patients with DDD/R and VVI/R pacemakers found a significant relationship between BNP levels, mode of pacing, and NYHA class (Wang et al., 2005). Sielski, et al also confirmed that the patients with DDD pacemakers showed an increase in BNP values between the investigated time points (Sielski., 2015). According to some investigators, however BNP values in patients with AAI/R and DDD/R pacemakers did not change over the 6 months follow up (Sadowski and Wożakowska-Kapłon, 2008). The controversity of the results between the conducted studies could be explained with the difference

in the characteristics of the investigated patients as well specific methodologic issues including study design.

In the present study the most significant changes occurred in NT-proBNP and LAVI values, notable at and after the 12th week after DCPM implantation. The increase of LAVI the most frequently used echocardiographic measure for atrial assessment and its correlation with the NT-proBNP values, is an important point of discussion (Lang et al., 2005). Left atrial remodeling is a result of various factors including both tachycardia and volume and pressure overload related to atrial fibrillation, coronary artery disease and heart failure (Thomas et al., 2002; Pagel et al., 2003; Hoit et al., 1998; Pritchett et al., 2003); Takemoto et al., 2005; Gottdiener et al., 2006). We found that the LAVI values were higher than normal at baseline and significantly increasing over the follow up after the implantation of the permanent pacemaker as compared with the baseline values. This result is supported by other studies on the significance of left atrial size in patients with permanent pacemakers (Kubica et al., 1990). Nielsen et al. in a follow up study of 2.9 ±1.1 years found significant increase of the LA size in patients with DDD/R accompanied by the significant decrease in LVEF (Nielsen et al., 2003). Psychiari et al. have not detected changes in left atrial and ventricular size in 60 patients with AAI/R and DDD/R pacemakers. Although the LA and LV size did not change over the study the authors found significant differences of tissue Doppler echocardiography (Psychiari et al., 2010; Takeichi et al., 1998)

LVEF in our study did not change significantly at any point of investigation over the follow up and there was observed a significant inverse relationship between NT-proBNP and LVEF. The relationship between NT-proBNP and LVEF in our study was similar to the found by Koç et al. negative correlations between NT-proBNP and left ventricular ejection fraction (Koç et al., 2009).

There are two options for the preservation of the LV function over the follow up in our study with the first option relating the setup of time of atrial and ventricular contraction of the DCP. The second option considers the insufficient time to register the reduction in LVEF in terms of the relative shortness of the defined in our study follow up. The absence of a decrease in LVEF, increase in NT-proBNP values as well as the observed increase in LAVI values puts on consideration the time, sequence and sensitivity of echocardiographic changes in the in the first 24 weeks after the PM implantation. The data on correlations between BNP values and echocardiographic dimensions of the left atrium in patients with permanent pacemakers are scarce as most of the conducted studies focused on the correlations with the LV function. Previous data showed significant correlations between BNP values and echocardiographic LA parameters, especially in patients with DDD-R pacemakers (Sielsk et al., 2015).

The observed in our study increase in LVESV is a finding of concern because the left ventricular volume is shown to be a powerful predictor of mortality in patients with CV disease but also in healthy subjects (Banjamin et al., 1995). It is of scientific interest to follow such patients for longer time to identify the subsequent dynamics and significance of values in the context of the rest of echocardiographic parameters and NT-proBNP.

CONCLUSION

We found high baseline values of both NT-proBNP and LAVI in the studied patients. The values of NT-proBNP increase as LVESV and LAVI increase. The underlined discussed mechanisms of that changes include compromised hemodynamics, myocardial stretching and increased wall stress in studied patients both before and after the PM implantation. Both LVEDV and LVEF correlate inversely with the NT–proBNP values although both parameters stayed stable and did not change significantly over the follow up. The borderline increase of LVESV and its correlation with NT-proBNP values in our study is a cause of concern. Consistent elevation of NT-pro BNP values and significant increase in LAVI according to our results are good predictors of short term changes after pacemaker implantation. Our results support measurement of NT-proBNP and LAVI values in the post pacemaker implantation follow up in case of DCPM has been implanted.

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