Original Article

Assessment of BNP Level in Patients with Single Chamber and Dual Chamber Pacemakers

J Kojuri, E Atabati, S Moslemi

Cardiovascular Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

Background: Recent years, have witnessed extended and continuous indication of cardiac pacing. However, increasing number of patients suffered new congestive heart failure (CHF) and aggravated CHF after pacing therapy. We used blood B type nutriuretic peptide (BNP) to predict the occurrence of CHF in patients with different types of pacemakers. To assess single N-terminal brain nutriuretic peptide (NT-pro BNP) as a predictor tool for ventricular dysfunction in different cardiac pacing mode.

Methods: Out of 480 consecutive patients with pacemaker more than 6 months, 79 patients with average age of 65±13, and more than 90% ventricular pacing participated in the present study. Those with CHF prior to pacemaker insertion were excluded. The patients underwent medical history and examination, echocardiography (M-mode, Doppler, and Tissue imaging) and blood sampling for pro-BNP. Twenty five, 12, and 42 patients had Dual chamber (DDDR), single chamber pacing with dual chamber sensing (VDDR), and Single chamber (VVIR) pacemakers respectively

Results: Single pro-BNP level in patient with DDDR and VDDR pacing was lower than in those with VVIR pacing ($P< 0.0001$) but in Echocardiography left ventricular (LV) dysfunction was not lower in DDDR than VDDR and VVIR pacing patients ($P= 0.190$).

Conclusion: Single level of pro-BNP is lower in double chamber pacing in comparison with single chamber pacing. Therefore, it seems that dual chamber pacing causes less LV dysfunction.

Keywords: NT- pro B-type natriuretic peptide (BNP), tissue Doppler, pacing

Introduction

Permanent cardiac pacemakers are widely used in modern cardiology practice, with implant rates ranging from 250 to 800 per million of the population per year, leading to 1000-3000 patients undergoing regular follow-up in a typical pacemaker centre.[1-3]

Use of pacemakers is not only limited to bradycardia but it opens a new era in therapy of heart failure and tachyarrhythmia, and the number of pacemaker treatment has increased year by year.[4,5] The prevalence of heart failure is high in patients with pacemakers due to their advanced age, high prevalence of atrial fibrillation[6-8] and prior myocardial infarction, and perhaps the effect of ventricular pacing itself.

Therefore, how to select reasonable pacing modes in different patients to reduce the incidence of CHF or relieving CHF symptoms in patient with CHF has become an important issue.[10-12] It is important to use blood B type natiuretic peptide (BNP) as a tool to predict the occurrence of arrhythmias and efficacy of cardiac resynchronization therapy in patient with pacing therapy.

The homodynamic effect of pacemakers may be due to intraventricular dyssynchrony caused by conventional pacing, altering the phase and magnitude of mechanical strain of both ventricles which is the main stimulus for BNP release.[13,14] Also non-physiological pacing modes such as single chamber VVIR pacing, by interrupting normal atrioventricular synchronization, may lead to altered LV diastolic filling and loading characteristics and, therefore, BNP release.[15-22]

For a screening test to become widely appli-

Correspondence:
J Kojuri
Cardiovascular Research Center, Faghihi Hospital, Zand Street, Shiraz, Iran.
Tel/Fax: +98-711-2343529
E-mail: kojurij@yahoo.com

Table 1. Demographic characteristics of the patients under study

	$DDD_{(R)}$	$VDD_{(R)}$	$VVI_{(R)}$	P value
Age (years)	61±13	62±15	65±13	0.23
Male/female	10/15	4/8	21/21	0.08
Duration after implantation (month)	53±26	42±24	56±27	0.12
Percent of Ventricular pacing	95±4	95±3	96±3	0.56

cable, it must be cost-effective, easy to administer and interpret, and the results should guide diagnosis and choice of treatment.[11,17,21] Pro BNP level can be easily obtained and is an efficient marker for detection and prognosis of LV dysfunction.

In this study, single N-terminal pro brain natriuretic peptide (NT-pro BNP) was measured as a predictor tool to detect left ventricular dysfunction in different cardiac pacing modes.[11,19,20]

Patients and Methods

This retrospective cohort study was carried out from September 2007 to June 2009, and comprised all patients referred to pacemakers' follow-up clinic.

The study included patients with permanent pacing more than 8 months with more than 90% ventricular pacing. Exclusion criteria were patients with LV dysfunction (CHF) prior to pacemaker insertion based on complete review of their charts and pace malfunction shown on pace analysis, and arrhythmias. A total of 79 cases were finally selected out of 480 patients. Echocardiography and venous sampling were performed for assessment of BNP level.

All patients underwent 2-D Doppler and tissue imaging by transthoracic echocardiography (VIVID 3-GE).

Pace analysis, under monitoring with pace analyzer, was done for all patients and the threshold level, sensivity and impedance were assessed in each case. Assessment of plasma level of NT-pro BNP blood was then made on 4 ml venous blood drawn from ante cubital vein, after 30 minutes in supine position[23] during the same visit. The plasma level of NT-pro BNP was measured by electrochemo luminescence method.

Statistical analysis

All analyses were performed using commercially available software (SPSS Chicago. IL.USA. edition, 15). Data are reported as mean ± standard deviation. Continuous variables between groups were compared by the unpaired student t-test. P value ≤ 0.05 was considered as statistically significant.

Table 2. Mean and Standard deviation of echocardiography data

	$DDD_{(R)}$	$VDD_{(R)}$	$VVI_{(R)}$	P value
EF	54±12	61±14	55±0.9	0.190
ESV^{cc}	45±29	43±22	40±23	0.750
PAT	117±23	105±18	109±26	0.271
Em cm/s	9.1±0.4	9.8±0.4	9.0±0.3	0.670
Am cm/s	1.1±0.4	1.1±0.4	1.1±0.8	0.915
Sm cm/s	5.2±.1	3.6±0.1	3.6±0.2	0.457
Tei index	0.59±0.19	0.69±0.16	0.80±0.34	0.017

EF: Ejection Fraction; ESV: end-systolic volume; PAT: Pulmonary acceleration time; Em: Tissue E wave; Am: Tissue A wave; Sm: Tissue systolic determinant

Results

Analysis performed on 79 patients with mean age of 65±13. The baseline data are presented in Table 1. There were no significant differences in regard to age and gender distribution between the 3 types of pace makers (DDDR-VDDR-VVIR).

The quality of echocardiography images in all patients was considered good or acceptable. Transthoracical echocardiography was performed to evaluate LV dysfunction.(Table 2) In Tissue Doppler imaging(TDI), Sm as a predictor of systolic dysfunction was defined normal and abnormal according to normal range (5.2±0.4) and Em as a predictor of diastolic dysfunction was defined normal if it was more than 10 cm/s. (Tables 3 and 4)

Table 3. Assessment of NT pro-BNP in 3 groups of pace makers

Type	No	Mean	Standard deviation	Minimum	Maximum
DDD(R)	25	211.55	178.30	42.29	674.30
VDD(R)	12	329.45	216.96	25.36	658.00
VVI(R)	42	764.48	447.42	103.93	1927.00
Total	79	523.42	435.77	25.36	1927.00

P values between DDD and VDD=0.08 and P value between VDD and VVI<0.0001)

Table 4. Systolic dysfunction in 3 groups of pace makers

Type of pace	Normal systolic function no (%)	Systolic dysfunction no (%)	P value
DDD(R)	9 (36)	14 (64)	
VDD(R)	3 (25)	9 (75)	0.510
VVI(R)	18 (25)	61 (75)	

The analysis of variance performed according to ANOVA method revealed that DDDR caused less LV systolic and diastolic dysfunction. (Table 5)

In regard to the age, there is no significant difference in the level of BNP between the three types of pacing. We therefore analyzed NT-pro BNP level (normal range=140-150 pg/ml) between 3 type of pacemaker (DDDR, VDDR, VVIR) using ANOVA method. As shown in Table 4, the average range of NT- pro BNP was lower in DDDR than in VDDR and VVIR (P< 0.001).

There was a significant reverse correlation between EF and NT- pro BNP according to Pearson correlation. In addition a significant direct correlation was found between Tei-index and NT-pro BNP(P=0.017), and between end systolic volume (ESV) and NT-pro BNP (P<0.05).

Table 5. Diastolic dysfunction in 3 groups of pace makers

Type of pace	Normal systolic function no (%)	Systolic dysfunction no (%)	P value
DDD(R)	17 (68)	8 (32)	
VDD(R)	6 (50)	6 (50)	<0.001
VVI(R)	9 (20)	33 (20)	

Discussion

BNP assay has recently been applied to cardiac pacing. Some investigations have shown that blood BNP levels could predict the occurrence of chronic AF in patients with sick sinus syndrome after VVIR pacing. BNP levels could also evaluate short, middle and long-term efficacy of CRT objectively and quantitatively. However, the changes of BNP levels in different periods and different pacing modes were not completely consistent according to published reports.[18,20,21,24]

BNP level in VVI(R) pacing was higher than that found in DDD(R) and AAI(R) pacing. BNP level in patients with different physiologic pacing were different, because some physiologic pacing such as VDD produced wide QRS complexes, which led to cardiac dyssynchronous contractions and raised the level of BNP.[24]

Hajime Horie et al concluded that plasma brain natriuretic peptide, like atrial natriuretic peptide, was influenced by the pacing mode, but not by electrical stimulation. Also low plasma brain natriuretic peptide was important in relation to physiological pacing.[25]

The result of present study demonstrated that single NT- pro BNP level in patients with DDDR and VDDR pacing was lower than that found in patients with VVIR pacing. Additionally, in echocardiography LV dysfunction was lower in DDDR than in VDDR and VVIR pacing patients.[18,9] Our data was consistent with previous observations and suggested that LV dyssynchrony was implicated in deteriorating ventricular function in single chamber pacing.[20,21] RV pacing produces an electrical activation sequence similar to the left bundle branch block pacing at any ventricular site. This would affect the natural pattern of activation and contraction since the electrical wave front conductes more slowly through the ventricular myocardium than His- Purkinje system. Moreover, there may be disturbed systolic interaction of the paced myocardium with remote regions during RV pacing.[18,22,26,27] During pacing, myocardial fiber shortening occurs earlier in paced region, and can be a systolic burden to the remote region.[16,18,20] At the end of ejection period, the paced region starts myocardial lengthening while the remote region continues myocardial shortening.

Disorganized ventricular contraction may induce heterogeneous chamber stretch, cumulatively stimulating BNP secretion. In the RV pacing the free wall segments contracted later than the septal segment, which may support aforementioned explanation. Heterogeneous ventricular contraction can also be associated with net reductions of ventricular pressure rise and decline, with a resultant decrease in ventricular systolic and diastolic function.[18,22,26] Shortening of LV filling time during pacing may also reduce coronary blood flow, predisposing to further impairment of ventricular function. Moreover, during RV pacing, there may be asymmetric hypertrophy,[9,20,22,27] which is most pronounced in the latest-activated region.

Dual chamber pacing preserves atrial-ventricular synchrony and decreases ventricular end-diastolic pressure and increases cardiac output. This may have key effect on decrease of BNP and improving systolic and diastolic function especially in diseased myocardium. How this effect can improve survival and quality of life needs further studies.

Single level of NT-pro BNP is lower in double chamber pacing in comparison with single chamber pacing. Therefore, dual chamber pacing may cause less LV dysfunction for better synchrony and harmonized contracture in myocardium.

Acknowledgement

This work was financially supported by Vice Chancellor for Research of Shiraz University of Medical Science. The authors declare that they have no conflicts of interest.

References

1 Bernstein AD, Parsonnet V. Survey of cardiac pacing and defibrillation in the United States in 1993. *Am J cardiol* 1996;**78**:187-96. [8712141]

2 Mond HG. The world survey of cardiac pacing and defibrillation: calendar year 1991-Asia pacific, Middle East, South America. *Pacing Clin Elect* 2001;**24**:856-62. [1138810]

3 Toff WD, Skehan JD, De Bono DP, Camm AJ. The United Kingdom pacing and cardiovascular events (UKPACE) trial. United Kingdom Pacing and Cardiovascular Events. *Heart* 1997;**78**:221-3. [9391280]

4 Tung AS, Roberts RS, Kerr C, Gillis AM, Green MS, Talajic M, et al. Relationship between pacemaker dependency and the effect of pacing mode on cardiovascular outcomes. *Circulation* 2001;**103**:3081-5. [11425772]

5 Sinha AM, Filzmaier K, Breithardt OA, Kunz D, Graf J, Markus KU, et al. Usefulness of brain natriuretic peptide release as a surrogate marker of the efficacy of long-term cardiac resynchronization therapy in patient chronic heart failure. *Am J Cardiol* 2003;**91**:755-8. [12633819]

6 Horie H, Tsutamoto T, Minia k, Hayash M, Kito O, Kinoshita M. Brain natriuretic peptide predicts chronic atrial fibrillation after ventricular pacing in Patient with Sick Sinus Syndrome. *Jpn. Circ J* 2000;**64**:965-70. [1119429]

7 Maisael A. B-type natriuretic peptide levels: diagnostic and management of congestive heart failure. *Cardiol Clin* 2001;**19**:557-71. [11715177]

8 Molhoek SG, Bax JJ, van Erven L, Bootsma M, Steendijk P, Lentjes E, et al. Atrial and brain natriuretic peptide as markers of response to resynchronisation therapy. *Heart* 2004;**90**:97-8. [14676258]

9 Sudon T, Kangowa K, Minamino N, Mastuo H. A new natriuretic peptide in porcine brain. *Nature* 1988;**32**:78-81. [2964562]

10 McNairy M, Gardetto N, Clopton P, Garcia A, Krishnaswamy P, Kazanegra R, et al. Stability of B-type natriuretic peptide levels during exercise in patient with congestive heart failure: implications for out patient monitoring with natriuretic peptide. *Am Heart J* 2002;**143**:406-11. [11868044]

11 Wilkoff BL, Cook JR, Epstein AE, Greene HL, Hallstrom AP, Hsia H, et al. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. *JAMA* 2002;**288**:3115-23. [12495391]

12 Nielsen JC, Bottcher M, Nislsen TT, Pedersen AK, Andersen HR. Regional myocardial blood flow in patients with sick sinus syndrome randomized to long-term single chamber atrial or dual chamber pacing- effect of pacing mode and rate. *J Am Coll Cardiol* 2000;**35**:1453-61. [10807447]

13 Lee MA, Dae MW, Langloerg JJ, Griffin JC, Chin MC, Finkbeiner WE, et al. Effect of long-term right ventricular apical pacing on left ventricular perfusion. *J Am Coll Cardiol* 1999;**24**:225-32. [8006270]

14 Villacorta H, Duarte A, Duarte NM, Carrano A, Mesquita ET, Dohmann HJ, et al. The role of B-type natriureitc peptide in the diagnosis of congestive heart failure in patient presenting to an emergency department with dyspnea. *Arq Bras Cardiol* 2002;**79**:569-72. [12532240]

15 Yoshimura M, Yasue H, Okumura K, Ogawa H, Jougasaki M, Mukoyama M, et al. Different secretion patterns of atrial natriuretic peptide and brain natriuretic peptide in patients with congestive heart failure. *Circulation* 1993;**87**:464-9. [8425293]

16 Wakakura M. Radionuclide study of left ventricular function and regional myocardial perfusion in patients with a DDD pacemaker. *Kaku Igaku* 1992;**29**:561-72. [1434070]

17 Nielsen JC, Andersen HR, Thomsen PE, Thuesen L, Mortensen PT, Vesterlund T, et al. Heart failure and echocardiographic changes during long-term follow-up of patients with sick sinus syndrome randomized to single-chamber atrial or ventricular pacing. *Circulation* 1999;**97**:987-95. [9529267]

18 Kawanishi Y, Ito T, Suwa M, Terasaki F, Futai R, Kitaura Y. Effect of left ventricular Dyssynchrony on plasma B-type Natriuetic peptide levels in patients with long-term Right ventricular apical pacing. *Int Heart J* 2008;**49**:165-73. [18475016]

19 van Oosterhout MF, Prinzen FW, Arts T, Schreuder JJ, Vanagt WY, Cleutjens JP, et al. Asynchronous electrical activation induces asymmetrical hypertrophy of the left ventricular wall. *Circulation* 1998;**98**: 588-95. [9714117]

20 Sogaard P, Egeblad H, Pedersen AK, Kim WY, Kristensen BO, Hansen PS, et al. Sequential versus simultaneous biventricular resynchronization for sever heart failure. *Circulation* 2002;**106**:2078-84. [12379577]

21 Edvardsen T, Gerber BL, Garot J, Bluemke DA, Lima JA, Smiseth OA. Quantitative assessment of intrinsic regional myocardial deformation by Doppler strain rate echocardiography in humans: validation against three-dimensional tagged magnetic resonance imaging. *Circulation* 2002;**106**:50-6. [12093769]

22 Bader H, Garrigue S, Lafitte S, Reuter S, Jaïs P, Haïssaguerre M, et al. Intra left ventricular electromehcanical asynchrony. A new independent predictor of sever cardiac events in heart failure patient. *J Am Coll Cardiol* 2004;**43**: 48-56. [14736445]

23 Maffei S, Del Ry S, Prontera C, Clerico A. Increase in circulating levels of cardiac natriuretic peptide after hormone replacement therapy. *Clin Sci (Lond)* 2001;**101**:447-53. [1167244]

24 Wang RX, Li XR, Jiang WP, Liu ZH, Yang XJ, Xiao CH, et al. Observation of blood B-type natriuretic peptide level changes in different periods and different cardiac pacing modes. *Chin Med J (Engl)* 2005;**118**:1384-7. [16157035]

25 Horie H, Tsutamoto T, Ishimoto N, Minai K, Yokohama H, Nozawa M, et al. Plasma brain natriuretic Peptide as a Biochemical Marker for Atrioventricular Sequence in Patients with Pacemakers. *Pacing Clin Electrophysiol* 1999;**22**:282-90. [10087542]

26 Leon AR, Greenberg JM, Kanuru N, Baker CM, Mera FV, Smith AL, et al. Cardiac resynchronization in patient with congestive heart failure and chronic atrial fibrillation effect of upgrading to biventricular pacing after chronic right ventricular pacing. *J Am Coll Cardiol* 2002; **39**:1258-63. [11955841]

27 Feigenbaum H, Armstrong W, Ryan T, Ovid Technologies I. Feigenbaum's echocardiography: Lippincott Williams & Wilkins Philadelphia, PA; 2005.