

## Effects of right ventricular septal versus apical pacing on plasma natriuretic peptide levels

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### ABSTRACT

**Background:** To investigate the contribution of right ventricular (RV) pacing sites to the cardiac function, this study compares plasma B-type natriuretic peptide (BNP) levels during RV septal and apical pacing in patients implanted with a pacemaker. **Materials and Methods and Results:** Seventy-four consecutive patients with indication for permanent pacing were included. To provide for the possibility of appropriate subgroup analyses, patients were stratified according to their pacing mode into two groups: Those with dual chamber DDD(R)/VDD pacemakers (41 patients, mean age  $54.1 \pm 18.4$  years), and those with single chamber VVI pacemakers (33 patients, mean age  $60.6 \pm 18.4$  years). A prospective single-blinded randomized design was used. Randomization (1:1 way) was between lead placement on the RV septum or RV apex and occurred during the implant in both groups. Compared to baseline, a significant decrease in BNP ( $429.8 \pm 103$  pg/ml and  $291.7 \pm 138$  pg/ml, respectively) levels was observed during DDD(R)/VDD pacing after two months. In contrast, during VVI (R) pacing, a significant increase in BNP levels was observed ( $657.5 \pm 104$  pg/ml and  $889.5 \pm 139$  pg/ml, respectively). To determine the impact of pacing sites on cardiac function, we assessed the changes in BNP levels in each group separately. Despite the significant difference in the pattern of changes between the two groups ( $P < 0.02$ ), no significant changes were observed within groups regarding the acute effect of the pacing site (RV apex vs. RV septal) on BNP levels ( $P = NS$ ). **Conclusions:** Our main result showed no significant differences between pacing sites and concluded that hemodynamic improvement could be substantially influenced by pacing mode, more than by pacing site.

**Key words:** B-type natriuretic peptide, right ventricular apical pacing, right ventricular septal pacing

### INTRODUCTION

Several clinical and experimental studies have suggested that long-term right ventricular (RV) apical pacing deteriorates left ventricular (LV) function. They have demonstrated the

deleterious consequences of intraventricular conduction delay, particularly those produced by left bundle branch block (LBBB).<sup>[1-7]</sup> Alternative sites were tested with a view to optimize or stabilize LV function. Septal pacing seemed to better preserve cardiac performance in patients with normal LV systolic function,<sup>[8,9]</sup> however, its effects in patients with preexistent LV systolic dysfunction are unknown. Neurohumoral factors represent the natural response of the individual to heart failure. Among them natriuretic peptides, especially B-type natriuretic peptides (BNP), have been shown to be reliable and rapid markers for diagnosis in heart failure patients. BNP, which is

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released primarily in response to increased atrial and ventricular stress, is a marker of the severity of heart failure. Furthermore, BNP levels reflect hemodynamic changes elicited by different pacing modes, and BNP levels are significantly higher during asynchronous ventricular pacing than during atrioventricular sequential pacing.<sup>[10-12]</sup> It has been reported that BNP levels will change in patients with permanent cardiac pacing,<sup>[10-13]</sup> nevertheless, in fact, we do not exactly know how BNP levels change in different pacing sites, and we do not accurately know if RV septal pacing can really reduce BNP levels.

The primary objective of the present study was to demonstrate that RV septal pacing would better preserve ventricular function than RV apical pacing. The primary outcome measure is the change in BNP level at the end of the two-month follow-up period.

## MATERIALS AND METHODS

### Study population

Seventy-four consecutive patients with indications for permanent pacing were enrolled into the present study. Patients were implanted with either a dual or single-chamber pacemaker depending on whether the patient was in sinus rhythm or permanent atrial tachyarrhythmia. Exclusion criteria were symptomatic heart failure and any form of acute coronary syndrome within the previous month. During follow-up, patients were excluded if they had inadequate pacing lead position, or < 90% ventricular pacing ( $n=9$ ).

To provide for the possibility of appropriate subgroup analyses, patients were stratified according to their pacing mode into two groups: Those with DDD/VDD pacemakers and those with VVI pacemakers. Group I consisted of 33 patients with implanted VVI (R) pacemakers (mean age  $60.6 \pm 18.4$  years) and Group II had 41 patients with DDD (R)/VDD pacemakers (mean age  $54.1 \pm 18$  years). The hospital Ethical Committee approved the present study and all patients gave written informed consent prior to enrollment into the study.

### Study design

A prospective single-blinded randomized design was used in both groups. Randomization (1:1 way) was between lead placement on the RV septum or RV apex and occurred during the implant. An implanted RV pacing lead was implanted at the RV septal position or RV apex using any commercially available active fixation lead via an axillary

or subclavian puncture and in the case of dual-chamber pacemakers, an active atrial lead was fixed for the right appendage. The procedure for implantation of the RV septal lead was defined in the study protocol as to be performed by advancing the lead out the pulmonary artery, withdrawing the lead until it dropped below the pulmonic valve, and then advancing the lead into the high septum. The distal electrode was placed at the junction between the upper and middle septal segments, in a position to obtain the shortest pace-mapped QRS. Proper lead positioning was confirmed by multiple fluoroscopic views and surface electrocardiogram ECG.

Post-implantation chest X-ray and ECGs were given to confirm appropriate lead positions. The lower and upper pacing rate limits and sensor settings were individually programmed according to patient needs. All the implanted RV pacing leads were positioned at a stable position to obtain a satisfactory pacing threshold value (mean:  $1.3 \pm 0.7$  V, at a pulse width of 0.5 ms). All study patients had successful device replacement procedure without any complication.

Among patients with VVI pacemakers, the final positions of the RV leads were at the septum in 15 patients and at the RV apex in 18; in patients with DDD/VDD pacemakers the final lead positions were at the septum in 24 and at the RV apex in 17.

Plasma samples for the determination of plasma BNP were drawn before and two months after pacemaker implantation.

### B-type natriuretic peptide measurement

Venous blood was taken from an antecubital vein in gel-filled tubes after the patient had been in a supine position for at least 15 min. At randomization and at the end of each study period, a venous blood sample was collected in tubes containing potassium Ethylenediaminetetraacetic acid EDTA. Specimens were centrifuged at 3000 rpm (15°C for 10 min) and separated plasma was immediately assayed. All samples were plasma natriuretic peptide concentrations were measured with a specific immunoradiometric assay for human BNP using a highly sensitive, commercially available, enzyme-linked immunoassay (Biomedica Gruppe, Austria) and reported in pg/ml.

### Statistical analysis

Continuous data are expressed as mean  $\pm$  SE. A paired Student's *t* test analysis was used for comparison within groups and a non-specified Student's *t* test analysis for comparison between groups; all were done as two-sided

tests. Categorical variables were compared by Chi-square analysis or Fisher's exact tests and summarized by proportion in each category. Covariance analyses were used to compare variables between the two groups with adjustment for the pre-pacing values of these variables. We compared clinical characteristics including BNP levels between two groups using the  $\chi^2$  and Mann-Whitney U tests. Factors associated with BNP levels were examined using the Mann-Whitney U test and linear regression analysis. Factors with a probability of  $<0.1$  on univariate analysis were entered into a multivariate analysis. All statistical analyses were completed using the SPSS 15 software package. A two-sided  $P < 0.05$  was considered statistically significant.

## RESULTS

The baseline characteristics of patients are shown in Table 1. To provide for the possibility of appropriate subgroup analyses, patients were divided according to their pacing mode into two groups after randomization: those with DDD/VDD(R) pacemakers and those with VVI (R) pacemakers. Group I consisted of 33 patients with implanted VVI (R) pacemakers (mean age  $60.6 \pm 18.4$  years, 15 men) and Group II had 41 patients with DDD/VDD (R) pacemakers (mean age  $54.1 \pm 18$  years, 16 men). The primary implant indication was sick sinus syndrome in 14 patients, high-degree atrioventricular AV block in 35 patients, and a combination of these two disorders in 25 patients. The telemetrically assessed percentage of ventricular paced beats was  $98 \pm 0.3\%$  in the DDD /VDD(R) mode and  $98 \pm 0.8\%$  in the VVI (R) mode ( $P=NS$ ).

There was no significant difference in the age, gender distribution, percentage of ventricular pacing and QRS duration before implantation, the medications, hypertension, diabetes and coronary artery diseases between groups.

**Table 1: Baseline characteristics**

Age (year)	$57.2 \pm 18$
Male sex (n)	31
Type of pacemaker (n)	
DDD( R )/VDD	41
VVI ( R )	33
Functional class (n)	
NYHA I	51
NYHA II	23
Primary implant indication (n)	
Sinoatrial nodal disease	14
Atrioventricular nodal disease	35
Combination of both	25

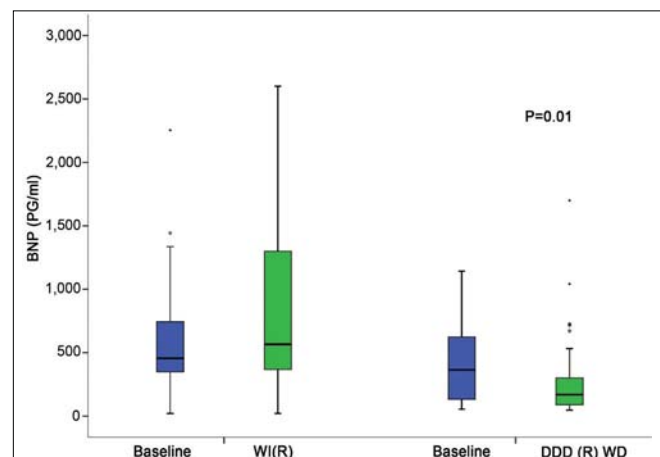
Compared to baseline, a significant decrease in BNP ( $429.8 \pm 103$  pg/ml and  $291.7 \pm 138$  pg/ml, respectively) levels was observed during DDD/VDD (R) pacing after two months. In contrast, during VVI (R) pacing, a significant increase in BNP levels was observed ( $657.5 \pm 104$  pg/ml and  $889.5 \pm 139$  pg/ml, respectively) [Figure 1].

Table 2 shows the important characteristics of the study subgroups according to pacing site (RV apex group and RV septal group).

In Group I, 18 patients were randomized to RV apex pacing and 15 to septal pacing. In Group II, 17 patients were randomized to RVA pacing and 24 to RV septal pacing. To determine the impact of pacing sites on

**Table 2: Characteristics of the study subgroups according to pacing site (RVA group and RV septal group)**

	DDD (R )/VDD		VVI (R )	
	RV septal	RVA	RV septal	RVA
Age (year)	$56.3 \pm 19$	$51.1 \pm 16$	$58 \pm 21$	$64 \pm 13$
Male sex (n)	9	7	5	10
Ejection fraction(%)	$54.2 \pm 10$	$48.7 \pm 8.6$	$48.5 \pm 13$	$50.7 \pm 13$
LA size (mm)	$40.0 \pm 3.7$	$51.1 \pm 16$	$40.1 \pm 5$	$43.4 \pm 5$
Functional class (n)				
NYHA I	16	11	11	13
NYHA II	8	6	4	5
Primary implant indication (n)				
Sinoatrial nodal disease	2	1	6	5
Atrioventricular nodal disease	13	10	5	7
Combination of both	9	6	4	6



**Figure 1:** Plasma concentrations of BNP in patients with a VVI pacing mode compared with DDD mode

cardiac function, we assessed the changes in BNP levels in each group separately. Table 3 shows the association between BNP levels and pacing sites (RV apex vs. RV septal). The result was a significant difference in the pattern of changes between the two groups [ $P < 0.02$ , Figure 1]; nevertheless, no significant changes were observed within groups regarding the acute effect of pacing site (RV apex vs. RV septal) on BNP levels [Figure 2a and 2b] ( $P=NS$ ).

This pattern of change in the BNP level was consistently present using multivariate analysis while considering confounding factors such as sex, age, left ventricular ejection fraction LVEF, and different pacing indications.

Despite the increase in BNP levels in patients with the VVI mode, compared with those with the DDD(R) / VDD mode, the pacing sites had no effect on BNP levels, irrespective of the pacing mode.

In Group I, 12 patients were randomized to RV apex pacing and 16 to septal pacing. In Group II, 13 patients were randomized to RVA pacing and 17 to RV septal pacing. To determine the impact of pacing sites on cardiac function, we assessed the changes in BNP levels in each

group separately. Table 3 shows the association between BNP levels and pacing sites (RV apex vs. RV septal). The result was a significant difference in the pattern of changes between the two groups [ $P < 0.02$ , see Figure 1]; nevertheless, no significant changes were observed within groups regarding the acute effect of the pacing site (RV apex vs. RV septal) on BNP levels [Figure 2] ( $P=NS$ ).

This pattern of change in the BNP level was consistently present using multivariate analysis while considering confounding factors such as sex, age, LVEF, and different pacing indications.

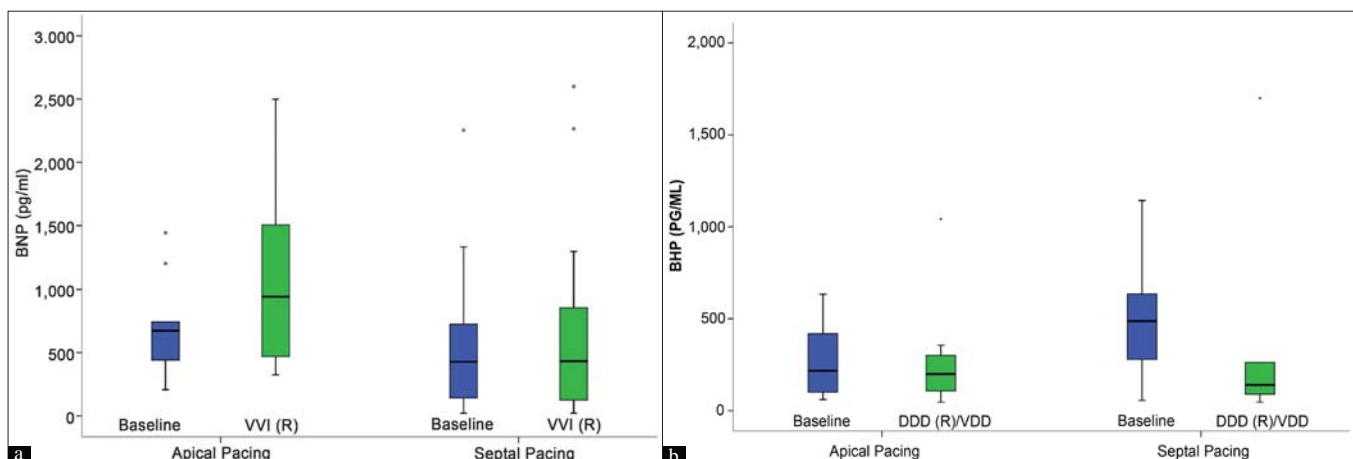
Despite the increase in BNP levels in patients with the VVI mode compared with those with DDD(R) / VDD mode, the pacing sites had no effect on the BNP levels, irrespective of the pacing mode.

## DISCUSSION

Evidence-based clinical trials in cardiac pacing designed to determine the most physiologic pacing mode have shown an increased risk of heart failure and/or mortality associated with chronic RVA pacing independent of the pacing mode.<sup>[2,3]</sup> Although several studies have investigated the acute and chronic effects of pacing from alternative RV sites outside of the apex, the optimal RV pacing lead location for patients with a standard indication for ventricular pacing, remains controversial.<sup>[14-16]</sup> Even though data suggest that RV septal pacing is not inferior to RVA pacing, the clinical benefits of pacing from alternative RV sites have not yet been established.<sup>[8,9,17-19]</sup> Victor *et al.*,<sup>[20]</sup> did not find significant differences between RV apex and right ventricular outflow tract RVOT pacing after three months with respect to functional class, LVEF, duration of exercise and maximum oxygen uptake. Similar results come from

**Table 3: BNP levels ( pg/ml) according to pacing site (Subgroup analysis)**

	Septal pacing	RVA pacing	P value
DDD (R)/VDD			
Pre	494.9 ± 296	310.9 ± 292	$P=0.07$
Post	367.4 ± 417	288.4 ± 289	
VVI (R)			
Pre	677.06 ± 662	836.3 ± 576	$P=0.4$
Post	702.6 ± 796	1140.3 ± 792	



**Figure 2(a and b):** The changes observed within groups regarding the acute effect of pacing site (RV apex vs. RV septal) on BNP levels



the ROVA study. This study showed that in patients with congestive heart failure CHF, LV dysfunction and chronic AF undergoing permanent pacing, RVOT and dual-site RV pacing shorten but do not normalize paced QRS duration and do not consistently improve quality of life QOL or other clinical outcomes after three months as compared with RVA pacing. In contrast, Mera *et al.*,<sup>[8]</sup> reported that in 10 patients with LV dysfunction, who underwent AV junction ablation, LVEF was higher after two months of high septal RVOT than RV apex pacing. More recently, Tse *et al.*,<sup>[9]</sup> randomized 24 patients, none of whom had CHF or LVEF <50%, to long-term RVOT or RV apex pacing. Between months 6 and 18 after initiation of pacing, LVEF declined ( $55\% \pm 3\%$  to  $47\% \pm 3\%$ ) and myocardial perfusion defects increased during RV apex but not RVOT pacing.

The purpose of our study was to assess if RV septal pacing, compared to RV apex pacing, would impact cardiac function using the parameter BNP. It is well known that different cardiac pacing modes have different effects on patients' hemodynamics; however, it is not yet known how BNP levels change in different cardiac pacing sites.

In this small randomized study, we showed that plasma concentrations of BNP were higher in patients with a VVI pacing mode compared with a DDD mode [ $P=0.02$ , see Figure 1] which is consistent with previously published studies.<sup>[21,22]</sup> Our main result showed no significant differences between pacing sites and concluded that hemodynamic improvement could be substantially influenced by pacing mode, more than by pacing site.

## Limitations of the study

The main limitation of this study was the small number of patients. Potential limitations in the study design may have affected our results. Beneficial or deleterious effects of longer pacing durations from alternative RV sites could not be addressed by this study. The present data is also limited by the fact that the study patients did not undergo follow-up echocardiograms and 6-min walk tests.

## CONCLUSIONS

The present study showed no significant differences between pacing sites and concluded that hemodynamic improvement could be substantially influenced by pacing mode, more than by pacing site.

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