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Role of B Type Natriuretic Peptide in Predicting Development of Ventricular Dysfunction in Patients on Single Chamber Permanent Right Ventricular Pacemaker with Structurally Normal Heart

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Abstract: ***Introduction: It is well known that level of BNP is high in single chamber pacing as compared to dual chamber pacing but whether raised level of BNP can predict development of ventricular dysfunction is not well known. Aims and Objectives: Relation between raised BNP and ventricular dysfunction. Effect of right ventricular apical pacing on blood level of BNP. Study Design: prospective, observational study. Results and Observations: The measured indices of RV dimension, were comparable between the patients at baseline, and after 3 months and 6 months of pacing. None of the patient developed dilatation of RV basal dimension at 6 months. One patient develop dilatation of RVmid for which p value was not significant (p=1.0). At baseline evaluation for interventricular dyssynchrony, none of the patient had interventricular dyssynchrony. After 3 months, 11.76% of the patients developed interventricular dysynchrony, and after six months of pacing, 33.33% of the patients had (p <0.0005).At the end of 6 months 70% of patients with raised BNP were having interventricular dysynchrony, as compared to only 9.68% of patients with normal BNP (P<0.0005). Conclusion: This study concluded that right ventricular apical pacing (≥ 90% pacing) for a period of 6 months does not deleteriously affect the ventricular structure and function, but gradually induces interventricular dysynchrony leading to stretching of ventricles and release of BNP.***

Keywords: PPI, BNP, Ventricular failure, Single chamber pacemaker, Interventriculardysynchrony

1. Introduction

B-type natriuretic peptide (BNP) is secreted from cardiomyocytes in response to stretching of cardiac wall. The BNP circulates as hormone. It induces vasodilation, natriuresis, and diuresis to protect cardiovascular system from the effect of volume overload. Plasma levels of either BNP or its inactive amino terminal fragment, NT-pro BNP are used as a clinical markers of left ventricular dysfunction.[1]Several studies have confirmed its its value as a "rule-out test" for heart failure (HF). The current European and North American heart failure guidelines suggests that the measurement of the plasma concentration of BNP can be useful in confirming or refuting a diagnosis of heart failure.[2] Levels of BNP can also be elevated in certain conditions other than heart failure e.g. acute coronary syndrome, sepsis, hyperthyroidism, severe lung disease, pulmonary embolism, pulmonary hypertension, cerebrovascular accidents, deep vein thrombosis. Level of BNP also increases with age and in patients with renal failure. Women tends to have higher BNP level than men.

The BNP has a half-life of approximately 20 min and is quickly cleared via several mechanisms. The NTproBNP, in contrast, has a longer half-life of approximately 1 to 2 h, leading to higher circulating levels and slower fluctuations compared with BNP, despite 1:1 secretion. Both peptides are influenced by renal function, but the effect seems to be greater for NTproBNP. However, the clinical implications of this seem to be modest, especially in patients with HF.[1]

The measurement of BNP is useful in distinguishing between cardiac and non-cardiac dyspnea. In patients with non-cardiac dyspnea, the BNP levels are considerably lower than in patients with cardiac dyspnea[3]. In the patients with cardiac dyspnea, the BNP levels are usually higher than 400 pg/ml. when the BNP level is less than 100 pg/ml it is unlikely that cardiac disorder is the cause of dyspnea. When levels are between 100-400 pg/ml, the sensitivity and specificity for diagnosis for heart failure is not high.

As a general guideline, in young, healthy adults, 90% will have BNP <25 pg/ml and NTproBNP <70 pg/ml. For acutely dyspneic patients, some have suggested cutoffs of BNP 100 pg/ml and NTproBNP 300 pg/ml to rule out heart failure[1].

Level of BNP also provide prognostic information in heart failure patients. Measurements obtained at the time of hospital admission for decompensated heart failure predict the likelihood of in-hospital mortality, and those obtained in the outpatient setting have been shown to predict morbidity and mortality.[4,5]

During normal activation, synchrony is observed between the ventricles (interventricular synchrony) and within each ventricle (intraventricular synchrony). During ventricular pacing, the initiation and the sequence of electrical ventricular activation are different from those in normal physiological circumstances. From the site of pacing, the electrical activation wave spreads over the ventricles through the slowly transmitting myocardium, instead of the rapidly conducting specialized conduction system. Slow

cell-to-cell transmission of the electrical impulse results in dysynchrony of electrical ventricular activation, with early activation of the myocytes close to the pacing site and delayed activation of the cells in remote regions. Consequently, early systolic shortening of the early-activated myocytes results in stretch of late-activated myocytes, at the onset of the ejection phase. When myocytes in remote regions are subsequently activated and start to contract, they contract even more powerfully due to the early systolic pre-stretching (known as the local Frank–Starling mechanism). Hence, electrical dysynchrony, as induced by ventricular pacing, results in a dyssynchronous contraction pattern. The mechanical dyssynchronous contraction pattern is associated with increase in BNP.

In patients treated with cardiac pacemakers, BNP or NT-pro BNP can reflect hemodynamic utility of different pacing modes. Physiological pacing preserving atrioventricular synchrony reduces ventricular wall stress and thus plasma BNP and NT-pro BNP concentration as compared with less physiological pacing.[6]

Various studies have shown that BNP increased in patients on pace maker and it is more in patients who are on single chamber right ventricular apical pacemaker as compared to dual chamber pace maker as a result of dyssynchrony caused by single chamber pacing.[8] Symptoms of heart failure are common in patients with pacemakers. Screening with NT-BNP is feasible and assists in the detection of important cardiac co-morbidity, particularly in patients with a dual chamber pacemaker.[7]

It is well known that level of BNP is high in single chamber pacing as compared to dual chamber pacing but whether raised level of BNP can predict development of ventricular dysfunction is not well known.

It was hypothesized that permanent pacing of right ventricle in patients of bradyarrythmias causes deterioration of right ventriclular and left ventricular functions and raised BNP level.

The research questions were

- Whether the patients on right ventricular apical pacemaker with raised BNP are prone to develop ventricular dysfunction.
- Is long term pacing of right ventricle, have a deleterious effect on ventricular functions, evident on echocardiography and
- Is the long term pacing of right ventricle, induce left ventricular dyssynchronny leading to left ventricular dysfunction, as assessed by echocardiography.

This study evaluated the development of ventricular dysfunction and role of BNP in predicting development of ventricular dysfunction in patients with structurally normal heart on single chamber right ventricular permanent pacemaker.

2. Aims and Objectives

1) Relation between raised BNP and ventricular dysfunction.
2) Effect of right ventricular apical pacing on blood level of BNP.

3. Material and Methods

Place of study
Department of cardiology, PGIMER, Dr R M L Hospital, New Delhi

Sample size
51 cases

Study design
This study was planned as a prospective, observational study and recruited 51 cases, as per the inclusion and exclusion criteria from Nov 2013 to March 2015. Last patient was enrolled on 30th of September. Blood sample for BNP level and 2 D Echocardiography for ventricular function was performed in all patients requiring right ventricular pacing for symptomatic bradyarrhythmia.

All patients recruited were undergone 2D echocardiographic and Doppler examination using Philips HD11XE machine, before the implantation of permanent pacemaker.

The following echocardiographic parameters were measured

1) **Right ventricular systolic function** was assessed as per the American society of echocardiography guidelines for assessment of right ventricular functions.[57]
2) **Intraventricular dyssynchrony** was assessed as described by Powel B.D. et al.[58]
   Using an M-mode/color Tissue Doppler Imaging recording from the parasternal short-axis view (at the level of the papillary muscles), the septal-to-posterior wall motion delay can be obtained, and a cutoff value of 130 ms or more was taken as a marker of intraventricular dyssynchrony.
3) **Interventricular dyssynchrony** was assessed as described by Bonakdar H.R. et al.[59]
   Interventricular dyssynchrony was defined as a 40 ms interventricular mechanical delay (IVMD) calculated as the difference between LV and right ventricular pre-ejection periods, measured between the onset of the QRS complex and, onset of aortic and onset of pulmonary ejection flows by pulsed-wave Doppler.
4) **Left ventricular function**
   a) Left ventricular ejectionfraction
   Left ventricular ejection fraction was calculated by modified simpson method, more than 55 % ejection fraction was taken as normal.
   b) Left ventricular internal diameter in systole
   Left ventricular internal diameter in systole was measured using 2D-targeted M-mode echocardiography at the level of the LV minor dimension, at the mitral chordae level. On follow up at 1 month in the pacemaker clinic device was interrogated and patients who did not satisfied the minimum pacing percentage (≥90%) criteria were excluded.

Patients who satisfied the criteria were evaluated at follow up by echocardiography for ventricular function, and ventricular dyssynchronny at three months and six months. The patients were also evaluated for functional class and

their peripheral blood sample for measuring BNP level was collected.

Inclusion and Exclusion Criteria

This study included

1) Adult patients
2) Patients having indication for permanent RV pacemaker implantation
3) Patients with normal LV function

Patients having any of the following conditions were excluded

1) Patients not satisfying the minimum pacing percentage of ≥90 %
2) Patients having low ejection fraction (< 55%)
3) Patients with conditions which causes elevation of BNP
   a) Renal failure.
   b) Cerebrovascular accidents
   c) Pulmonary thromboembolism
   d) Deep vein thrombosis
   e) Cirrhosis
   f) Hyperthyroidism
4) Patients suffering from diseases that can per se cause ventricular dysfunction
   a) COPD
   b) Pulmonary hypertension
   c) Moderate to severe Valvular heart disease
   d) Congenital structural heart disease
   e) History of CAD (past history of PTCA/CABG)

Statistical Analysis

Statistical significance was analyzed using the Unpaired "t" test/Mann-Whitney U test for comparisons of quantitative data between the different patient groups and Student's paired t-test/Wilcoxon Signed Rank sum Test for comparisons of data in the same patient group. For qualitative variables Chi-Square Test/Fischer's Exact Test was applied. P<0.05 was considered significant.

4. Results and Observations

This study was done between November 2013 and March 2015 at RML Hospital New Delhi. Patients were recruited between November 2013 to September 2014. Total 98 patient underwent single chamber pacemaker implantation (VVI or VVIR). Twenty eight patients did not meet inclusion criteria, 18 patients had associated coronary artery disease and LV dysfunction, 4 patients had chronic kidney disease, 6 patients had COPD and therefore e excluded. Seventy patients were included, out of which 12 patients did not meet the required pacing percentage criteria (≥90%), and were excluded. Five patients were lost to follow up, and 2 patients expired. So a total of 51 patients were thus followed up for a period of 6 months and forms part of this study.

4.1 Indices of RV Dimension And Function

Indices of RV dimension

The measured indices of RV dimension, namely – basal, mid and longitudinal RV dimension, were comparable between the patients at baseline, and after 3 months and 6 months of pacing. (Tabulated below are the values for baseline, 3 and 6 months follow up). None of the patient developed dilatation of RV basal dimension at 6 months. One patient develop dilatation of RV mid for which p value was not significant (p=1.0). None of the patient develops dilatation of RV long axis.

Table 1: Basal, mid and long RV dimension (in mm) at baseline, 3 and 6 months

RV dimensions		Group 0 month n (%)	Group 3 months n (%)	Group 6 months n (%)	P value 0-3 months	P value 0-6 months	P value 3-6 months
Basal	Normal	51 (100%)	51 (100.00%)	51 (100%)			
Mid	Abnormal	0 (0.00%)	0 (0.00%)	1 (1.96%)	-	1.000	1.000
	Normal	51 (100%)	51 (100.00%)	50 (98.04%)			
Long	Normal	51 (100%)	51 (100.00%)	51(100.00%)			
Total		51 (100%)	51 (100.00%)	51(100.00%)			

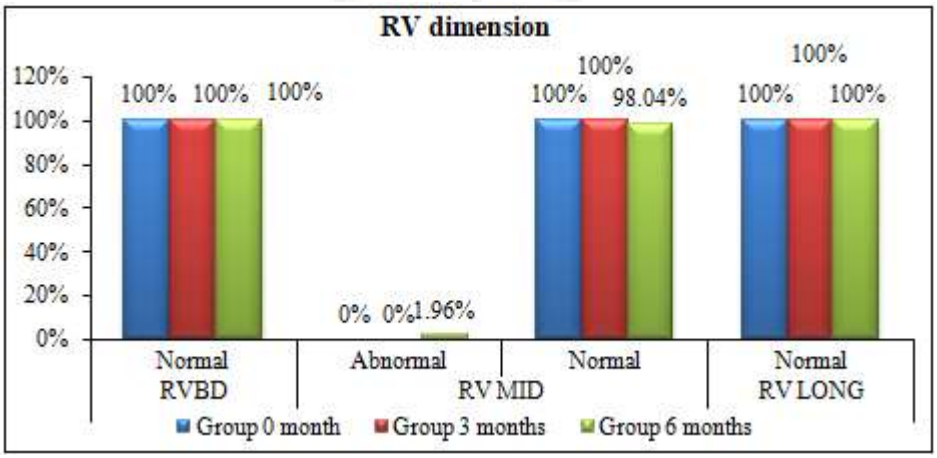

Figure 1: Showing RV dimension at 0, 3, and 6 months

4.2 Indices of RV Function

All the measured indices of RV function, TAPSE, TAPSV, RVSP, were comparable in patients at baseline, after 3 and 6 months of pacing. (Tabulated below are the values for baseline, 3 month and 6 month follow up evaluation). There was no decrease in TAPSE value at either 3 months or 6 months. TAPSV value decreased significantly at 6 months in 12 (23.53%) patients (p<0.0005).

Table 2: TAPSE (in mm) at baseline, 3 months and 6 months

TAPSE	Group			P value
	0 month	3 months	6 months	
Mean	18.57±1.5	18.86±1.56	18.78±1.51	0.497

TAPSV	Group			P value 0-3 months	P value 0-6 months	P value 3-6 months
	0 month n (%)	3 months n (%)	6 months n (%)			
Normal	51 (100.00%)	49 (96.08%)	39 (76.47%)	0.495	<0.0005	0.008
Decreased	0 (0.00%)	2 (3.92%)	12 (23.53%)			
Total	51 (100.00%)	51 (100.00%)	51 (100.00%)			

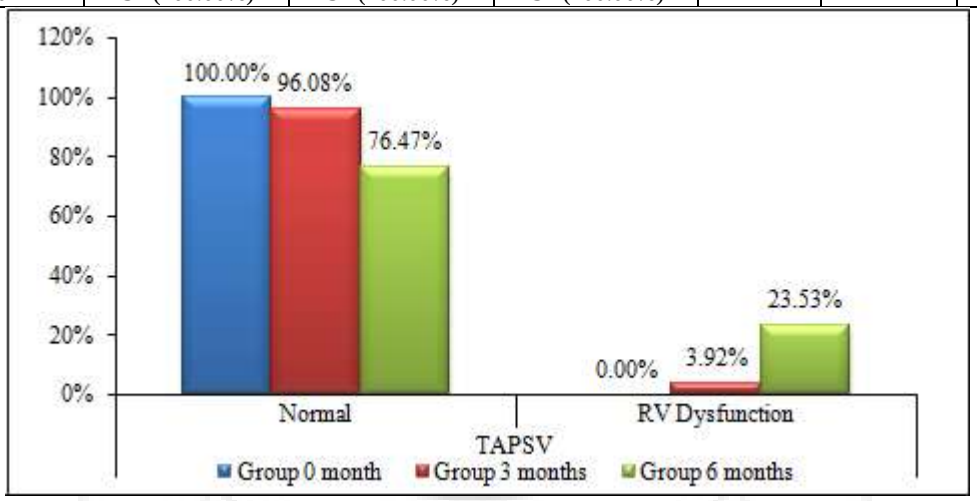

Figure 2: Showing TAPSV at 0, 3, and 6 months.

4.3 Effect of Pacing Onleft Ventricular Ejection Fraction

LVEF ≥55 % is considered as normal and patients had LVEF <55% considered to have LV dysfunction. Baseline LVEF of patient cohort was 60.29 ±2.39%. On follow up at 3 months the mean LVEF was 61.56 ±3.04 %, which was not significantly different than the baseline, and at 6 months follow up, LVEF was 61.80 ±3.88% which was not significantly different than the baseline LVEF. Only one patient developed systolic dysfunction for which p value was not significant (p=1.0).

Table 3: LVEF at 0. 3, and 6 months

LVEF	Group			P value 0-3 months	P value 0-6 months	P value 3-6 months
	0 month n (%)	3 months n (%)	6 months n (%)			
Deranged	0 (0.00%)	1 (1.96%)	1 (1.96%)	1.000	1.000	1.000
Normal	51 (100.00%)	50 (98.04%)	50 (98.04%)			
Total	51 (100.00%)	51 (100.00%)	51 (100.00%)			

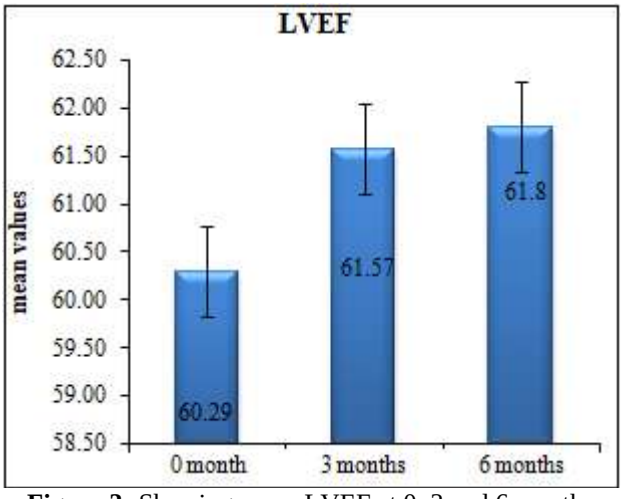

Figure 3: Showing mean LVEF at 0, 3 and 6 months

LV Dimension

None of the patients developed dilatation of LV when compared to baseline. The mean baseline LVESD in patient group was 4.67 ±0.33cm. After 3 months, mean LVESD in the patient group (4.7 ±0.3cm) not statistically from the baseline. After 6 months LVESD in the patient group was 4.72 ±0.3cm, which was not significantly different (p =0.074).

Table 4: Showing LV dimension in systole and diastole at 0, 3, and 6 months.

LV dimension	LVESD		
	0 month n (%)	3 month n (%)	6 month n (%)
Abnormal	0(0%)	0 (0.00%)	0 (0.00%)
Normal	51(100%)	51 (100%)	51 (100%)
Total	51(100%)	51 (100%)	51 (100%)

Dyssynchrony Assessment

Interventricular dyssynchrony

At baseline evaluation for interventricular dyssynchrony, none of the patient had interventricular dyssynchrony. The mean baseline value was 27.71±6.87ms. After 3 months, 11.76% of the patients developed interventricular dysynchrony, and after six months of pacing, 33.33% of the patients had (p <0.0005).

After 3 months of pacing, the mean interventricular delay in the pacing cohort was significantly more than baseline (31.55 ± 7.66 vs 27.71±6.87ms, p = <0.0005) and at 6 months the mean interventricular delay had further increased from the baseline (35.8 ± 10.89 vs 27.71±6.87 ms p = <0.0005).

Table 5: Showing interventricular dyssynchrony at 0, 3 and 6 months

Interventriular Dyssynchrony	Group			P value 0-3 months	P value 0-6 months	P value 3-6 months
	0 month n (%)	3 months n (%)	6 months n (%)			
Yes	0 (0.0%)	6 (11.76%)	17 (33.3%)	0.027	<.0005	0.017
No	51 (100%)	45 (88.24%)	34 (66.6%)			
Total	51 (100%)	51 (100%)	51 (100%)			

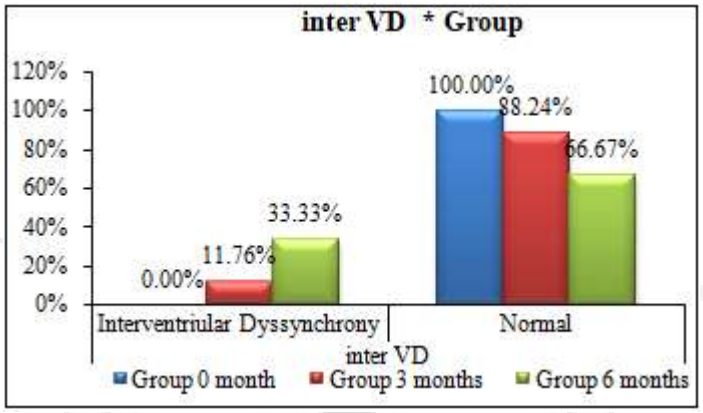

Figure 4: Showing interventricular dysynchrony at 0, 3 and 6 months

Intraventricular Dyssynchrony

At baseline evaluation using M-mode, the septal-to-posterior wall motion delay of > 130 ms, was not seen in any patient. None of the patients developed intraventricular dysynchrony at 3 months or 6 months. At baseline mean intraventricular delay was 71.12±18.68 which increased to 73.9±17.84 at 3 months and 75.35±17.57 at six months which was statistically significant (p= 0.022).

Table 6: Showing various parameters at 0, 3, and 6 months and p value

	Sample size	Mean ± SD	Inter quartile Range	P value 0-6 months
Inter VD 0month	51	27.71 ± 6.87ms	22 - 33	<.0005
Inter VD 3 month	51	31.55 ± 7.66ms	28 - 37.500	
Inter VD 6 month	51	35.8 ± 10.89ms	28 - 44	
Intra VD 0 month	51	71.12 ± 18.68ms	64 - 81	0.022
Intra VD 3month	51	73.9 ± 17.84ms	67.250 - 85.500	
Intra VD 6month	51	75.35 ± 17.57ms	66.250 - 89	
LVEF 0 month	51	60.29 ± 2.39%	60 - 60	0.002
LVEF 3 month	51	61.57 ± 3.04%	60 - 64.750	
LVEF 6month	51	61.8 ± 2.88%	60 - 64	
LVSD 0 month	51	4.67 ± 0.33cm	4.500 - 4.875	0.074
LVSD 3 month	51	4.7 ± 0.3cm	4.500 - 4.900	
LVSD 6 month	51	4.72 ± 0.3cm	4.500 - 5	
PASP 0 month	51	19.12±4.01mm Hg	16 - 20	<.0005
PASP 3 month	51	22.75±5.49 mm Hg	18.500 - 26	
PASP 6month	51	25.18±7.11 mm	20 - 29.500	
		Hg		
RV LONG 0month	51	6.87 ± 0.38 cm	6.700 - 7.100	0.002
RV LONG 3 month	51	6.98 ± 0.4cm	6.800 - 7.100	
RV LONG 6 month	51	7.01 ± 0.43cm	6.800 - 7.275	
RV MID 0month	51	2.94 ± 0.29cm	2.705 - 3.100	<.0005
RV MID 3month	51	3.02 ± 0.22cm	2.900 - 3.200	
RV MID 6month	51	3.1 ± 0.2cm	3 - 3.200	
RVBD 0 month	51	2.65 ± 0.25cm	2.500 - 2.800	<.0005
RVBD 3 month	51	2.81 ± 0.24cm	2.700 - 2.900	
RVBD 6month	51	2.96 ± 0.33cm	2.800 - 3.175	
TAPSE 0month	51	18.57 ± 1.5mm	17.250 - 19.750	0.497
TAPSE 3 month	51	18.86 ± 1.56mm	18 - 20	
TAPSE 6 month	51	18.78 ± 1.51mm	18 - 20	
TAPSV 0month	51	11.9 ± 1.31cm/sec	11.025 - 13	<.0005
TAPSV 3 month	51	11.17 ± 1.15cm/sec	10.400 - 11.400	
TAPSV 6 month	51	10.78 ± 1.22cm/sec	10.100 - 11.300	

Effect of Pacing on BNP Level

At baseline 41.18% of patients had raised BNP level. In most of patients BNP level decreased after 24 hour of pacing. At 24 hour 27.45% had raised BNP as compared to 41.18% of baseline. At 3 months 29.41% and at 6 months 39.22% had raised BNP level which was statistically not significant (p=1). BNP Value less than 100 taken as normal more than 100 taken as abnormal.

Table 7: showing patients with raised and normal BNP at 0, 24 hr, 3 and 6 months

BNP value pg/ml	Group			
	0 month n(%)	24 hours n(%)	3 months n(%)	6 months n(%)
<100	30 (58.82%)	37 (72.55%)	36 (70.59%)	31 (60.78%)
≥100	21 (41.18%)	14 (27.45%)	15 (29.41%)	20 (39.22%)
Total	51 (100.00%)	51 (100.00%)	51 (100.00%)	51 (100.00%)
P Value	0-24hr	24hr-3months	3-6 months	0-3 months
	0.211	1.000	0.404	0.300

Mean BNP level at baseline was 144.84±167.21 pg/ml which was decreased to 96.26±91.41 after 24 hour of pacing with significant p value (<0.0005). Mean level of BNP at 3 months (106.83±99.38) was also lower than that at baseline but value was not significant (P=0.253). At six months mean value was higher than that at base line (146.81±167.36 vs 144.84±167.21) but it was statistically not significant (P=0.959). As compared to 3 months increase in level of BNP was statistically significant (p<0.005).

Table 8: showing mean BNP level at 0, 24 hr, 3 and 6 months

BNP AT	Mean ± SD	P value	P value 3-6 months
Baseline	144.84 ± 167.21	<.0005	<0.005
24 HR	96.26 ± 91.41		
3 Month	106.83 ± 99.38	0.253	
6 Month	146.81 ± 167.36	0.959	

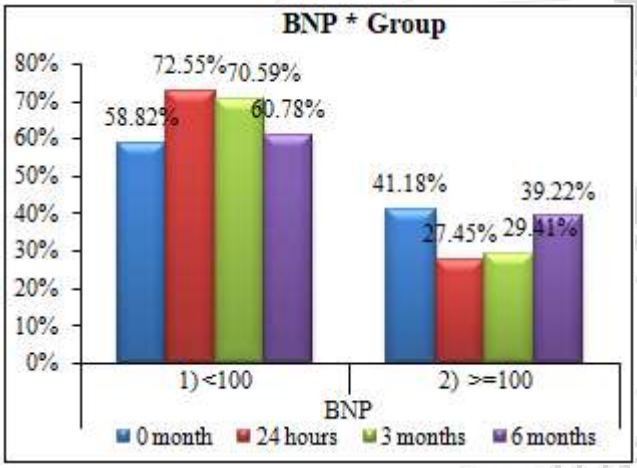

Figure 5: Showing patients with raised and normal BNP level

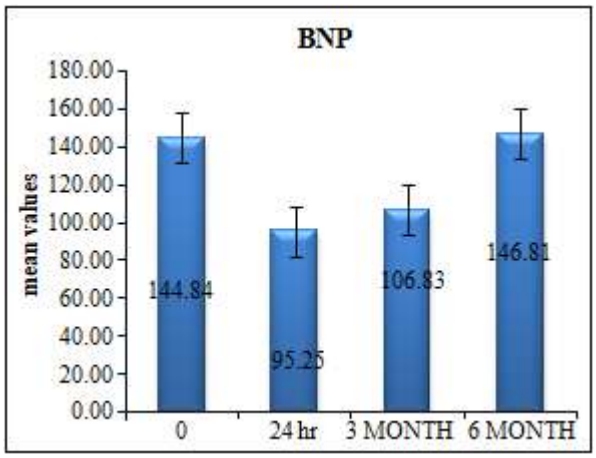

Figure 6: Showing mean BNP level at 0, 24 hr, 3 and 6 months.

Relation between Ventricular Dysynchrony and BNP Levelinterventricular Dysynchrony

At the end of 3 months 6 patient (11.76%) developed interventricular dysynchrony. Out of 6 patients 2 were having normal BNP level and 4 patients having raised BNP level (P=0.054). At the end of 6 months 70% of patients with raised BNP were having interventricular dysynchrony, as compared to only 9.68% of patients with normal BNP (P<0.0005). At the end of 3 months also interventricular dysynchrony was more common in patients with raised BNP level but that was statistically not significant (P 0.054).

Table 9: Correlation between BNP and interventricular dysynchrony at 3 months

Interventriular Dyssynchrony	BNP 3 MONTH		Total n (%)	P value
	1) <100 n (%)	2) >=100 n (%)		
yes	2 (5.56%)	4 (26.67%)	6 (11.76%)	0.054
No	34 (94.44%)	11 (73.33%)	45 (88.24%)	
Total	36 (100.00%)	15 (100.00%)	51 (100.00%)	

Table 10: BNP and interventricular dysynchrony at 6 months

Interventriular Dyssynchrony	BNP 6MONTH		Total n (%)	P value
	1) <100 n (%)	2)>=100 n (%)		
Yes	3 (9.68%)	14 (70.00%)	17 (33.33%)	<.0005
No	28 (90.32%)	6 (30.00%)	34 (66.67%)	
Total	31 (100.00%)	20 (100.00%)	51 (100.00%)	

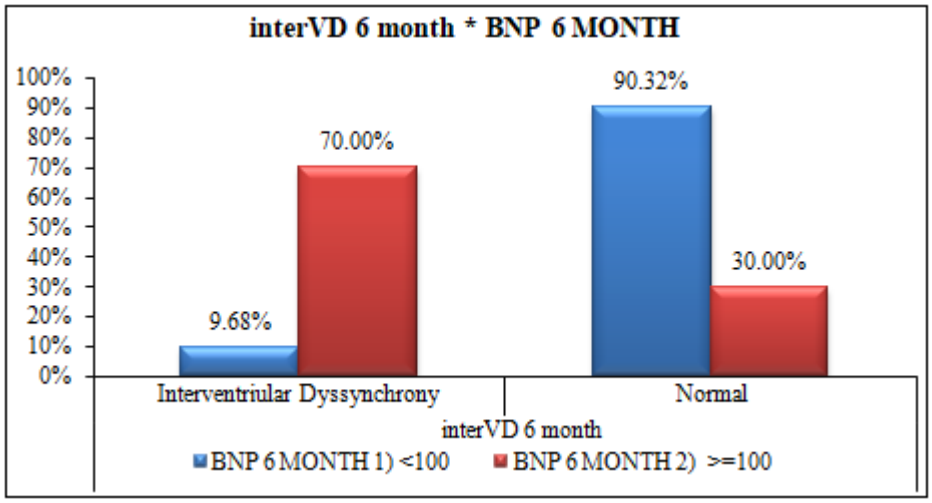

Figure 7: Relation between BNP and interventricular dysynchrony

Intra Ventricular Dyssynchrony

None of the patients developed intra ventricular dyssynchrony either at 3 months or at 6 months.

Relation between BNP Level, LVEF and LV Dimension

At the end of 3 months only one patients developed ventricular dysfunction and BNP level was normal in that patient(P=1.0). At the end of 6 months no more other patient developed LV dysfunction. None of the patients developed dilatation of LV at 3 or 6 months.

Table 11: Showing LVEF and BNP level at 3 months

LVEF	BNP3MONTH		Total n (%)	P value
	1) <100 n (%)	2) >=100 n (%)		
Decreased	1 (2.78%)	0 (0.00%)	1 (1.96%)	1.000
Normal	35 (97.22%)	15 (100.00%)	50 (98.04%)	
Total	36 (100%)	15 (100%)	51 (100%)	

Table 12: Relation between LVEF and BNP level at 6 months

LVEF	BNP		Total n(%)	P value
	1) <100 n(%)	2) ≥100 n(%)		
Decreased	1 (3.23%)	0 (0.00%)	1 (1.96%)	1.000
Normal	30 (96.7%)	20(100%)	50 (98%)	
Total	31 (100%)	20 100%)	51 (100%)	

Relation between Level of BNP, RV Function and RV Dimension

Only one patient developed dilatation of RV at mid level. Level of BNP was raised in that patient but it was not statistically significant (P = 0.392). None of the patients developed dilatation of RV basal and long axis.

Table 13: Showing relation between RV dimension and BNP level at 6 months

RV Dimensions		BNP 6MONTH		P value
		1) <100 n(%)	2) >=100 n(%)	
RVBD	Normal	31 (100%)	20 (100%)	0.392
Mid	normal	31 (100%)	19(95%)	
	Dilated	0 (0.00%)	1(5%)	
Long	Normal	31(100%)	20(%)	

None of the patients had TAPSE less than 16 at the end of three or six month. But 2 patients had RV dysfunction in the form of TAPSV less than 10 at the end of 3 months and at the end of 6 months 12 patient had TAPSV level less than 10. Out of 12, 5 patients were having normal BNP and 7 patients had raised BNP (P=0.121).

Table 14: Showing relation between BNP level and TAPSV at 3 and 6 month

TAPSV	BNP level				P value 0-3 month	P value 0-6 month
	3month n (%)		6 month n (%)			
	<100	>=100	<100	≥100		
Normal	35 (97.2%)	14 (93.3%)	26 (83.87%)	13 (65.00%)	0.506	0.121
Decreased	1 (2.7%)	1 (6.6%)	5 (16.13%)	12 (23.53%)		
Total	36 (100%)	15 (100%)	31 (100.00%)	51 (100.00%)		

5. Discussion

In this study 51 patients of permanent single chamber pacing (> 90 % pacing requirement) were followed up for 6 months. They were evaluated at 0, 3,and 6 months for the symptom class, serum BNP level, left ventricular dimension, left ventricular systolic function, dyssynchrony, and right ventricular function and dimension.

The measured indices of RV dimension, namely – basal, mid and longitudinal RV dimension, and the measured indices of RV function were comparable between the patients. In this study, RV function and dimension were unaltered by RV pacing at a follow up of 3 and 6 months, signifying that RV apical pacing does not deleteriously affect RV function till 6 months of pacing.

This study is comparable to the study of Nunes MCP et al, who in their study of 85 permanent pacing patients, found no significant deterioration in RV function and dimension, after a mean RV pacing for 89 months. [42]

Friedberg MK et al, who studied 17 patients (mean age 12 yrs and structurally normal hearts), referred for accessory pathway ablation, also found no significant change in global RV function assessed by RV dP/dT, from baseline, and one minute of RV pacing. [43]

In this study only 1 out of 51 patients developed LVEF of less than 55 % after 6 months of continuous pacing and BNP level was normal in that patients. This is similar to study by J Kojuri et al. of 480 consecutive patients with pacemaker more than 6 months, It was found that NT pro-BNP level was higher in patient with single chamber pacing than dual chamber pacing but Echocardiographically left ventricular (LV) dysfunction was not higher in single chamber pacing than dual chamber pacing (P= 0.190).[44] That shows that patients on single chamber pacemaker may have raised BNP without having LV dysfunction.

Various other studies have reported development of LV dysfunction[42,61]. Nunes MCP et al[42] showed that RV apical pacing induced interventricular dysynchrony in 60% of patients and reduced LVEF.

Tops LF et al in their study of 55 permanent pacing patients after a mean follow up of 3.8 yrs also found significant decrease in LVEF from baseline only in the patients developing dyssynchrony (48 ± 7% to 43± 7%) and that, those having dyssynchrony had lower LVEF than those who did not.[61]

Tantengco MVT et al, in their study comparing 24 permanent RV paced patients to 33 healthy controls, found a significant decrease in left ventricular systolic function (measured by fractional area change) of patients as compared to controls, at a mean follow up of 9.5 years. [62] In this study only 7.6 % patients developed reduction in LVEF of less than 55% at 6 months. Other studies have however reported a higher incidence of LV dysfunction on follow up.

Less incidence of LV dysfunction in our study may be because of short duration of follow up. Most studies which showed decrease LV function have followed patients for longer duration.

After 6 months of pacing, there was no significant change in LV or RV dimensions. The mean LVESD was not significantly different from baseline. One patient developed RV mid level dilatation but that was statistically not significant. There was no relation between BNP level and LV or RV dimensions. This was in contrast to other studies which showed increase in LV and RV dimensions.[61,62.] Tops LF et al,[61] in their study of 55 permanent pacing patients after a mean follow up of 3.8 yrs found that increase in left ventricular end systolic volume (measured Echocardiographically) from baseline, was significant only in the patients developing dyssynchrony and not in those without dyssynchrony.

Tantengco MVT et al,[62] in their study comparing 24 permanent RV paced patients to 33 healthy controls, found a significant increase in left ventricular end systolic area (measured by echocardiography) in patients as compared to controls, at a mean follow up of 9.5 years.

Nunes MCP et al,[42] in their study of 85 permanent pacing patients followed up for a minimum period of 6 months found that, left ventricular end systolic diameter measured Echocardiographically, was significantly higher in the subgroup of patients developing dyssynchrony than those without dyssynchrony.

At the end of 3 months 6 patient (11.76%) developed interventricular dyssynchrony. Out of 6 patients 2 were having normal BNP level and 4 patients having raised BNP level (P=0.054).At the end of 6 months 17 patients (33.3%) developed interventricular dyssynchrony.70% of patients with raised BNP were having interventricular dysynchrony, as compared to only 9.68% of patients with normal BNP (P<0.0005). It was because patients with interventricular dysynchrony have altered contraction pattern and myocardial stretching that leads to secretion of BNP. At the end of 3 months also interventricular dysynchrony was more common in patients with raised BNP level but that was statistically not significant (P 0.054).

This was similar to study by A.S. Algazzar et al studied a group of 40 patients with implanted VVI and DDD pacemakers. Mean BNP level in VVI pacing was higher than DDD pacing after two months with P value = 0.001 while comparison after 6 months showed P value =0.023. There was a statistically significant difference between both groups in results of aortic preejection delay (APED) (P value of <0.05). BNP was correlated to APED (r= 0.651 and P value = 0.001) and pacing percentage (r = 0.687 and P value = 0.00). So it is Concluded that Loss of atrioventricular synchrony in VVI mode leads to a significant difference in LV dyssynchrony between both groups. BNP level is correlated to LV dyssynchrony and pacing percentage.[45]

None of the patients developed intraventricular dysynchrony, but the mean septum to posterior wall delay increased from 71.12±18.68 at base line to 75.35±17.57 at 6 months. This is in contrast to studies showing development of intraventricular dysfunction.[42,63] Nunes MCP et al,[4] who in their study of 85 permanent pacing patients followed up for a minimum period of 6 months found interventricular dyssynchrony in 60 % of the patients, and intraventricular dyssynchrony assessed by SPWMD in 36 %, and 60% patients using 12 segment model.

Thambo JB et al,[63] in their study of 23 adults with permanent pacing requirement, for congenital AV block, after a mean follow up of 10 yrs found that the measures of Interventricular dyssynchrony, intra-LV dyssynchrony, extent of LV myocardium displaying delayed longitudinal contraction, and septal-to-posterior wall-motion delay, were significantly higher after chronic RV pacing than in controls.

Lack of development of intraventricular dysynchrony in our study may be because of small sample size, short duration of follow up and variable method of dyssynchrony assessment and short duration of follow up.

Five (9.8%) patients developed pulmonary hypertension, which was not reported in other studies. Even though p value (0.369) was not significant but it needs further evaluation with large sample size and longer duration of follow up.

6. Future Scope

The sample size was small (n=52). Another limitation was the relatively short follow up of 6 months so the long term effects of pacing could not be not assessed. It is possible that RV dysfunction might appear at a longer follow up.

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