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Title- Impact of Paced QRS Duration on Left Ventricular Function in Patients with Chronic Single-Chamber Right Ventricular Apical Pacing

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ABSTRACT

Background: Permanent pacing can often lead to the deterioration of ventricular function with time, resulting in a gradual decline in cardiac performance. This study aimed to evaluate the impact of paced QRS duration (pQRSd) on left ventricle (LV) function in patients with single chamber right ventricular apex pacing.

Methods: This prospective, single-center study was conducted at a tertiary care center in India between November 2017 and January 2019. A total of 135 patients having atrioventricular disease received single chamber pacemaker implantation were enrolled. These patients were stratified in two groups, i.e., those with baseline pQRSd <150 ms those with baseline pQRSd ≥150 ms. The study outcomes were heart failure, changes in LV ejection fraction (LVEF), and alterations in LV dimensions.

Results: The mean age of patients was 65.92 ± 9.64 years and 59 (60.2%) were male. After one year of follow-up, the reduction in LVEF was significantly higher in patients with baseline pQRSd ≥150 ms as compared to patients with pQRSd <150 ms (P = 0.01). The elevation in LV end-diastolic diameter (LVEDD) was significantly higher patients with pQRSd ≥150 ms than in patients with pQRSd <150 (P = 0.01). Moreover, increase in LV end-systolic diameter (LVESD) was numerically higher in patients with pQRSd <150 ms as compared to patients with pQRSd ≥150 ms (P = 0.13).

Conclusions: Prolonged pQRSd has a negative impact on cardiac function, causing a decrease in LVEF and an increase in both LVEDD and LVESD, particularly in patients with baseline pQRSd ≥150 ms.

Keywords: Artificial pacing; heart failure; ventricular remodeling

INTRODUCTION

Atrioventricular (AV) block is an interruption or delay in electrical conduction from the atria to the ventricles caused by AV node or His-Purkinje conduction system abnormalities.(1) Cardiac pacing is a widely used treatment modality for patients with AV conduction disorders.(2) Single chamber right ventricular apex pacing involves implanting a pacemaker lead into the apex of the right ventricle. While this is effective in regulating the heart rhythm, it can also have an impact on the function of the left ventricle (LV). The placement of a pacing lead in the RV apex can produce an iatrogenic left bundle branch block (LBBB), which can cause electrical and mechanical dyssynchrony in the heart.(3) Such dyssynchrony can lead to increased workload and oxygen demand, altered cardiac hemodynamics, and ventricular remodeling, ultimately resulting in both systolic and diastolic dysfunction of the LV.(4,5) While this effect is of particular concern for patients with preexisting LV dysfunction at the time of pacemaker insertion, it can also affect those with normal cardiac function.(6,7) The development of mechanical dyssynchrony and LV dysfunction due to long-term RV pacing is a complex process that varies among individuals.(8)

Paced QRS duration (pQRSd), a measure of electrical activation of the ventricles during pacing, has shown predictive value for heart failure in patients receiving pacing therapy.(9) Understanding the impact of pQRSd on LV

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function in patients receiving single chamber RV apex pacing can provide valuable information on optimizing pacing parameters and can help improve patient outcomes. The impact of pQRSd on LV function has been inadequately studied in an Indian setting. Therefore, this study aimed to evaluate this impact in Indian patients receiving single chamber RV apex pacing for AV block.

METHODS

Study design and population

This prospective, single-center study was conducted at a tertiary care center in India. Between November 2017 and January 2019, 135 patients underwent single chamber pacemaker implantation for AV block at the institute. The study was approved by the institutional ethics committee and was conducted in accordance with the Declaration of Helsinki. The written informed consent was obtained from all participants or their designees.

Patients with AV block undergoing single chamber pacemaker implantation, and those willing to undergo regular evaluation and echo screening were included. Patients with structural heart diseases including valvular, congenital, or ischemic heart diseases, were excluded from the study. Additionally, patients with RV pacing of less than 90% on follow-up, and those not willing to give informed consent were also excluded.

Data collection and follow-up

The clinical evaluation of the patients requiring permanent pacing was done as per the institute protocol. For electrocardiography, 12-lead ECGs were digitally recorded with MAC 5500 ECG recording devices (GE Healthcare, Waukesha, WI, USA). The maximum value from among all leads, averaged over three consecutive beats was considered as the pQRSd. Echocardiography was performed with the GE Vivid i machine (GE Healthcare, Chicago, IL, USA) by a single operator. The 2D echocardiogram of the LV in parasternal long axis view, parasternal short axis view, four chamber, and two chamber views were taken. Parasternal short axis views at the basal, mid, and apical levels were acquired to see the regional wall motion abnormality. LV ejection fraction (LVEF) was measured using biplane method according to modified Simpson's rule and fractional shortening method. Further echocardiographic measurements, viz. LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD) and LV end-diastolic volume (LVEDV) were analyzed. Mitral and tricuspid regurgitations were assessed qualitatively using color Doppler.

Data were collected immediately after pacemaker implantation, at 15 days, six months, and 12 months of follow-up. At each follow-up, clinical features were assessed, and pacemaker interrogation, electrocardiography and echocardiography were done. The study outcomes were heart failure, changes in LVEF, and alterations in LV dimensions.

Statistical analysis

Continuous data with normal distribution are presented as mean ± SD and categorical variables are shown as counts and percentages. A *P*-value of 0.05 was considered statistically significant. Statistical analyses were performed using Statistical Package for Social Sciences version 21.0 (IBM, Chicago, IL, USA).

RESULTS

Of the 135 patients, 98 were included for analysis. A total of 31 patients were excluded due to incomplete data, less than 90% ventricular pacing during follow-up, experiencing myocardial infarction or LV dysfunction. During the 12-month follow-up period, six patients died—two due to bronchogenic carcinoma and four due to unknown causes.

Table 1: Baseline characteristics of patients

Baseline characteristic (N=98)	n (%)
Age	
31–40 years	1 (1.0)
41–50 years	5 (5.1)
51–60 years	26 (26.5)
61–70 years	37 (37.8)
71–80 years	23 (23.5)
81–90 years	6 (6.1)
Male	59 (60.2)
Hypertension	48 (49.5)
Type 2 diabetes mellitus	24 (24.5)
Coronary artery disease	9 (9.2)
Hypothyroidism	4 (4.1)

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Cerebrovascular accident	2 (2.0)

The mean age of patients was 65.92 ± 9.64 years and 59 (60.2%) were male. Hypertension was the most common comorbidity affecting 48 (49.5%) patients, followed by type 2 diabetes mellitus in 24 (24.5%) patients (**table 1**). Complete heart block was the most common indication for pacemaker implantation in 84 (85.7%) patients, followed by high-degree AV block in 14 (14.3%) patients. All patients, except four who had a right bundle branch block pattern during pacing, demonstrated LBBB pattern on their baseline ECG.

Table 2: Change in cardiac parameters at six- and 12-months follow-up

Variable	Baseline (mean ± SD)	Six months (mean ± SD)	12 months (mean ± SD)	*P* value
pQRSd (ms)	155.63 ± 15.70	158.91 ± 11.28	164.79 ± 10.69	**<0.001**
LVEF (%)	56.21 ± 4.10	55.36 ± 4.22	54.49 ± 4.08	**0.01**
LVEDD (mm)	47.72 ± 3.31	48.12 ± 2.43	49.33 ± 2.46	**<0.001**
LVESD (mm)	**27.99 ± 3.41**	**28.93 ± 4.17**	**30.26 ± 2.99**	**<0.001**

LVEDD: Left ventricular end diastolic diameter; LVEF: Left ventricular ejection fraction; LVESD: Left ventricular end systolic diameter; pQRSd: Paced QRS duration

Table 3: Comparative change in cardiac parameters at six- and 12-months follow-up

Variable	Follow up	*P* value
pQRSd	Baseline *vs.* six months	**0.07**
	Baseline *vs.*12 months	**<0.001**
	Six months *vs.*12 months	**<0.001**
LVEF	Baseline *vs.* six months	**0.14**
	Baseline *vs.* 12 months	**0.004**
	Six months *vs.* 12 months	**0.14**
LVEDD	Baseline *vs.* six months	**0.31**
	Baseline *vs.* 12 months	**<0.001**
	Six months *vs.* 12 months	**0.003**
LVESD	Baseline *vs.* six months	**0.06**
	Baseline *vs.* 12 months	**<0.001**
	Six months *vs.* 12 months	**0.009**

LVEDD: Left ventricular end diastolic diameter; LVEF: Left ventricular ejection fraction; LVESD: Left ventricular end systolic diameter; pQRSd: Paced QRS duration

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The comparison between baseline, six months, and 12 months of changes in pQRSd, LVEF, LVEDD, and LVESD are given in **tables 2 and 3**.

Table 4: Change in cardiac parameters according to pQRSd

Variable	Follow-up	pQRSd <150 ms (n=35)	pQRSd ≥150 ms (n=63)
		Mean ± SD	Mean ± SD
LVEF (%)	Baseline	58.96 ± 1.07	**54.69 ± 4.36**
	Six months	58.65 ± 1.40	**53.52 ± 4.14**
	12 months	58.23 ± 1.26	**52.41 ± 3.58**
	Change in % at 12 months as compared to baseline	−1.21 ± 2.94	**−3.91 ± 6.24**
LVEDD (mm)	Baseline	45.89 ± 1.37	**48.75 ± 3.63**
	Six months	47.80 ± 1.94	**48.30 ± 2.67**
	12 months	48.40 ± 1.93	**49.84 ± 2.58**
	Change in % at 12 months as compared to baseline	2.51 ± 2.65	**1.11 ± 4.01**
LVESD (mm)	Baseline	26.46 ± 0.95	**28.84 ± 3.94**
	Six months	27.54 ± 1.87	**29.70 ± 4.85**
	12 months	29.46 ± 1.93	**30.70 ± 3.37**
	Change in % at 12 months as compared to baseline	**3.04 ± 2.29**	**1.82 ± 4.07**

LVEDD: Left ventricular end diastolic diameter; LVEF: Left ventricular ejection fraction; LVESD: Left ventricular end systolic diameter; pQRSd: Paced QRS duration

Table 5: Comparative change in cardiac parameters according to pQRSd

Variable	Follow up	*P* value	
		pQRSd < 150 ms	pQRSd ≥ 150 ms
LVEF	Baseline *vs.* six month	0.31	**0.10**
	Baseline *vs.* 12 month	0.01	**0.002**
	Six month *vs.* 12 month	0.16	**0.12**
	Baseline *vs.* six month *vs.* 12 month	0.06	**0.008**
	Comparison of both groups regarding change in % at 12 month as compared to baseline	**0.01**	
LVEDD	Baseline *vs.* six month	0.001	**0.40**
	Baseline *vs.* 12 month	0.001	**0.004**
	Six month *vs.* 12 month	0.15	**0.004**
	Baseline *vs.* six month *vs.* 12 month	<0.001	**0.01**
	Comparison of both groups regarding change in	**0.06**	

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	% at 12 month as compared to baseline		
LVESD	Baseline *vs.* six month	0.007	**0.24**
	Baseline *vs.* 12 month	0.001	**0.01**
	Six month *vs.* 12 month	0.001	**0.17**
	Baseline *vs.* six month *vs.* 12 month	<0.001	**0.04**
	Comparison of both groups regarding change in % at 12 month as compared to baseline		**0.13**

LVEDD: Left ventricular end diastolic diameter; LVEF: Left ventricular ejection fraction; LVESD: Left ventricular end systolic diameter; pQRSd: Paced QRS duration

A total of 35 patients had baseline pQRSd <150 ms and 63 patients had pQRSd ≥150 ms. LVEF of patients in the former group slightly reduced numerically from 58.96 ± 1.07% at baseline to 58.65 ± 1.40% at six months and 58.23 ± 1.26% at 12 months (*P* = 0.06). In the latter group, however, LVEF significantly reduced from 54.69 ± 4.36% at baseline to 53.52 ± 4.14% at six months, and further reduced to 52.41 ± 3.58% at 12 months (*P* = 0.008). The reduction of LVEF was significantly higher in patients with pQRSd ≥150 ms as compared to patients with pQRSd <150 ms (*P* = 0.01) (**tables 4 and 5**).

LVEDD significantly increased from 45.89 ± 1.37 mm at baseline to 47.80 ± 1.94 mm at six months, and further to 48.40 ± 1.93 mm at 12 months (*P* <0.001) in patients with pQRSd <150 ms. Similarly, in patients with pQRSd ≥150 ms, LVEDD slightly reduced at six months (48.30 ± 2.67 mm) compared to baseline (48.75 ± 3.63 mm), and then increased at 12 months (49.84 ± 2.58 mm) (*P* = 0.01). The rise in LVEDD was significantly higher in patients with pQRSd <150 ms as compared to patients with pQRSd ≥150 ms (*P* = 0.01) (**tables 4 and 5**).
In patients with pQRSd <150 ms, LVESD significantly increased from 26.46 ± 0.95 mm at baseline to 27.54 ± 1.87 mm at six months, and to 29.46 ± 1.93 mm at 12 months (*P* <0.001). In patients with pQRSd ≥150 ms, LVESD also increased from 28.84 ± 3.94 mm at baseline to 29.70 ± 4.85 mm at six months and further to 30.70 ± 3.37 at 12 months (*P* = 0.04). The increase in LVESD was numerically higher in patients with pQRSd <150 ms as compared to patients with pQRSd ≥150 ms (*P* = 0.13) (**tables 4 and 5**).

Table 6: Pearson correlation between baseline pQRSd values and cardiac parameters at 12 months

Parameter at 12 months	Pearson correlation coefficient (r) with baseline pQRSd values (*P* value)		
	pQRSd < 150 ms	**pQRSd ≥ 150 ms**	**All patients**
LVEF	0.01 (0.97)	−0.44 (<0.001)	**−0.71 (< 0.001)**
LVEDD	−0.31 (0.06)	0.35 (0.005)	**0.36 (< 0.001)**
LVESD	**−0.44 (0.008)**	**0.46 (0.001)**	**0.36 (< 0.001)**

LVEDD: Left ventricular end diastolic diameter; LVEF: Left ventricular ejection fraction; LVESD: Left ventricular end systolic diameter; pQRSd: Paced QRS duration

Table 7: Relationship between pQRSd and LVEF change at baseline, six months, and 12 months follow-up

Time point	LVEF (%)	pQRSd, n (%)		Total	*P* value using Fisher's exact test
		< 150 ms	≥ 150 ms		

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Baseline	< 50	0 (0.0%)	7 (11.1%)	7 (7.1%)	**0.04**
	≥ 50	35 (100.0%)	56 (88.9%)	92 (92.9%)	
Six months	< 50	0 (0.0%)	14 (22.2%)	14 (14.3%)	**0.002**
	≥ 50	35 (100.0%)	49 (92.1%)	84 (85.7%)	
12 months	< 50	0 (0.0%)	10 (15.9%)	10 (10.2%)	**0.01**
	≥ 50	35 (100.0%)	53 (84.1%)	88 (89.8%)	
Total		**35 (100.0%)**	**63 (100.0%)**	**98 (100.0%)**	

LVEF: Left ventricular ejection fraction; pQRSd: Paced QRS duration

Table 6 depicts the Pearson correlation between pQRSd at baseline with different variables at 12 months. pQRSd had a negative correlation with LVEF ($r = -0.71$, $P < 0.001$) and positive correlations with both LVEDD ($r = 0.36$, $P < 0.001$) and LVESD ($r = 0.36$, $P < 0.001$). The relation between pQRSd and LVEF changes at baseline, six months, and 12 months is given in **Table 7**.

DISCUSSION

A prolonged pQRSd is an indicator of delay in ventricular activation, which can be due to several factors such as conduction abnormalities, myocardial damage, or LV dysfunction. When the activation of the ventricles is delayed, it can cause asynchrony in the contraction of different regions of the LV. This alters the LV functions, causing a decrease in LVEF and an increase in LV dimensions which are hallmarks of LV dysfunction.

Various researchers have studied the impact of pacing on LV function for over two decades. For instance, Sumiyoshi and colleagues conducted a retrospective analysis of 114 patients who underwent permanent pacemaker implantation for AV block.(10) They found that patients with a prolonged pQRSd (>180 ms) exhibited a significantly higher prevalence of underlying heart disease (83% *vs.* 32%, $P < 0.001$), reduced LVEF (49 ± 17% *vs.* 68 ± 10%, $P < 0.001$), and increased LVEDD (57.1 ± 7.9 mm *vs.* 48.5 ± 5.6 mm, $P < 0.001$) than those with pQRSd <180 ms. The authors concluded that prolonged pQRSd can serve as an important sign of impaired LV systolic function and more advanced underlying heart disease.(10)

In another study, Miyoshi *et al*. conducted a prospective analysis of pQRSd during RV pacing in 92 permanently paced patients over a mean period of 53 ± 16 months.(11) Using a cutoff value of 190 ms, the authors observed that a prolonged pQRSd significantly predicted the onset of CHF (46.6% *vs.* 11.6%, $P < 0.05$). Moreover, patients with pQRSd values ≥190 ms had significant deterioration of LV function parameters such as a decreased LVEF (53.0 ± 14.6% *vs.* 62.8 ± 12.3%, $P < 0.05$), elevated LVEDD (60.0 ± 10.4 mm *vs.* 48.9 ± 7.4 mm, $P < 0.05$), and increased LVEDD (43.2 ± 11.5 mm *vs.* 32.1 ± 8.1 mm, $P < 0.05$), compared to those with pQRSd of <190 ms.(11)

In a case-control study involving patients who received permanent RV apical pacing, Pan *et al*. found a correlation between pQRSd and the structure and function of the LV.(12) Specifically, pQRSd was found to be negatively correlated with LVEF ($\beta = -109.25$, $P < 0.001$). Additionally, there were significant positive correlations between pQRSd and both LVEDD and LVESD dimensions ($\beta = 1.59$ and 1.54, respectively; $P < 0.001$).(12)

The PREDICT-HF trial led by Chen and colleagues found that patients with pQRSd between 160–190 ms (group 2) and ≥190 ms (group 3) exhibited significantly lower LVEF than those with pQRSd <160 ms (group 1) (51.8 ± 10.5% vs. 56.6 ± 9.7%, group 2 *vs.* group 1, $P = 0.006$; 43.2 ± 10.9% *vs.* 56.6 ± 9.7%, group 3 *vs.* group 1; $P = 0.001$).(9) Moreover, the LVEF in group 3 remained significantly lower than that in group 2 at the 3-year mark (43.2 ± 10.9% *vs.* 51.8 ± 10.5%, group 3 *vs.* group 2; $P = 0.001$). This trend was also observed during the 1- and 2-year follow-up periods.(9)

In another study, Sharma *et al.* determined the association between pQRSd and LV function in patients with permanent RV pacing.(13) They found that patients with pQRSd >130 ms showed a decrease in LVEF after one year of follow-up (54.7% *vs.* 52.9%; $P = 0.031$). However, LVEF was found to be preserved in patients with pQRSd ≤130 ms (56.6% *vs.* 54.9%; $P = 0.151$).(13)

A shorter duration of pQRSd is indicative of physiological conduction via the His-Purkinje system, whereas a longer pQRSd implies activation of a larger myocardial mass through muscle conduction prior to the entry of the ectopic activation front into the normal conduction system. Our findings are consistent with those of previous studies. In our study, patients with pQRSd ≥ 150 ms had a significantly greater reduction in LVEF compared to those with pQRSd <150 ms ($P = 0.01$). The rise in LVEDD was significantly higher in patients with pQRSd <150 ms as compared to

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patients with pQRSd ≥ 150 ms (P = 0.01). Moreover, the increase in LVESD was numerically higher in patients with pQRSd <150 ms as compared to patients with pQRSd ≥150 ms (P = 0.13). Taken together, the reduction in LVEF, and the increase in LVEDD and LVESD suggest a worsening LV function in patients with pQRSd ≥150 ms.

Limitations

This study has a few limitations. First, this was a non-randomized observational study conductedat a single center. Second, the sample size wa s relatively small, and the follow-up duration was short. Third, we did not conduct a systematic evaluation and analysis of echocardiographic parameters related to LV dyssynchrony and structural remodeling. Fourth, manual measurements of pQRSd and LVEF may be subject to inter- as well as intra-observer variability.

Conclusions

In conclusion, our study highlights the negative impact of prolonged pQRSd on cardiac function. Our findings suggest that a prolonged pQRSd is associated with a decrease in LVEF and an increase in both LVEDD and LVESD. The effect is more pronounced in patients with a baseline pQRSd ≥150 ms. These findings have important clinical implications; however, further research is warranted to identify effective interventions that can improve cardiac function in patients with prolonged pQRSd.

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