ASSESSMENT OF LEFT VENTRICULAR ELECTROMECHANICAL ACTIVATION DURING RIGHT VENTRICULAR APICAL AND SEPTAL PACING

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ABSTRACT

Background: Right ventricular apical pacing, inducing asynchronous ventricular contraction, may impair cardiac function. Alternative sites of pacing particularly high septum may have more favorable hemodynamic profile, physiological LV activation and normal ventricular contraction pattern.

Aim of study: To find out alternative sites to RV apex for permanent pacemaker lead fixation which minimize LV dyssynchrony and subsequent complications.

Patients and methods: The study involved 86 patients; 43 patients with active pacemaker lead fixation in site which achieved narrowest intra-cardiac QRS duration named as group 1(case group) and 43 patients with active pacemaker lead fixation in RV apex named as group 2(control group). Echocardiography and six minute walk test were done for patients of both groups.

Results: high septal pacing was site which achieved the narrowest intra-cardiac QRS duration (100.27 ± 16.762 ms) when guided fluoroscopically and electrically and resulted into narrowest QRS duration on surface ECG (117.44 ± 7.89ms) when compared with RV apex (138.72± 12.77ms) ($p < 0.001$). RV apical pacing resulted into marked electromechanical delay and LV dyssynchrony evident by increase in IVMD (50.83 ± 15.59 ms), LVPEP (189.34 ± 36.14 ms), RVPEP (139.27 ± 24.58 ms) and SPWMD (121.13 ± 33.70 ms) in RV apex in comparison to other right ventricular sites where IVMD (27.86 ± 15.06 ms), LVPEP (105.39 ± 44.48 ms), RVPEP (77.79 ± 33.21 ms) and SPWMD (75.2195 ± 37.36 ms) ($p < 0.001$). Tissue Doppler Imaging revealed marked difference on the opposing LV segments mainly between mid septal and mid lateral in group 2 cases. EF decreased in both groups after 3 months of permanent pacemaker implantation but the decrease was more significant in group 2 (59.67 ± 6.38) in comparison to group 1 (60.46 ± 6.36) ($p < 0.001$). Six minute walk test was better in group 1 patients (458.95 ± 230.20 m) than group 2 patients (325.11± 224.49 m) ($p < 0.001$).

Conclusion: High septum is the ideal site for permanent pacemaker implantation especially when guided fluoroscopically and electrically by intra-cardiac catheter. Compared with RV apical pacing, it is associated with improvement in functional and hemodynamic parameters over long-term follow-up.

Key words: Pacemaker · Dyssynchrony · Echocardiography.

INTRODUCTION

Pacing from the right ventricular (RV) apex produces abnormal and prolonged left ventricular (LV) activation time with consequent mechanical dyssynchrony and dysfunction [(1)].

This deleterious effect has generated the utilization of alternative ventricular pacing sites with a more favourable haemodynamic profile. The septal areas, particularly the mid-RV septal and the RV outflow tract (RVOT) are the most commonly used sites where stimulation is relatively easy to achieve and is theoretically associated with a more physiological LV activation and ventri-cular contraction pattern [(2)].

However, such alternative pacing sites have yielded conflicting and contro-versial results most probably due to the multiplicity of possible lead positions [(3)].

Since the septal region of the LV normally depolarizes first, RVS pacing from close to the sites of early activation could achieve a more favorable LV contraction pattern. Such strategic sites could be found by endocardial mapping during PM implantation. Based on this concept, we investigated the utility of RVS endocardial mapping to identify optimal anatomical locations for lead placement. Such strategic sites could be found by endocardial mapping during PM implantation [(4)].

AIM OF THE WORK

The present study aims to find out alternative sites to RV apex for permanent pacemaker lead fixation which minimize LV dyssynchrony and subsequent complications.

PATIENTS AND METHODS

This retrospective case control study was conducted in Cardiology Department, Zagazig University Hospitals. We
included 86 patients admitted to the cardiology department with indications for permanent pacemaker based on electro-cardiographic data (2nd degree AV block, 3rd degree AV block and sick sinus syndrome).

Grouping of patients:

these patients were divided into two groups, group 1 (case group) include 43 patients where permanent pacemaker leads were inserted into any of the following RV positions (High septum, Mid septum, Lower septum, Right ventricular outflow tract (RVOT) and Right ventricular (RV) free wall) selected according to which site had the narrowest intra-cardiac QRS duration after pacing on these sites by intra-cardiac catheter and group 2 (control group) include 43 patients where Permanent pacemaker active leads were inserted directly into right ventricular (RV) apex.

Exclusion criteria:

We excluded patients with atrial fibrillation, ejection fraction less than 50%, ischemic heart disease, rheumatic valvular heart disease, any myocardial disease as myocarditis and Congenital heart block.

Pacemaker implantation:

All patients included in group 1 were undergone RV mapping by intra-cardiac catheter inserted throw femoral vein into RV with pacing into high septum, mid septum, low septum, RVOT and RV free wall which radiographically documented in relation to anatomic landmarks. The active pacemaker lead was fixed into the site with narrowest intra-cardiac QRS duration after intra-cardiac pacing. While patients in group 2, the active pacemaker lead was inserted directly into RV apex.

Echocardiography:

Echocardiographic recordings were made using a HP SONOS (USA), GE Vivid E9 (Norway) and Philips envisor (Netherlands). Images were obtained using a 2.5 MHz transducer.

Conventional echocardiography

Complete standard echocardiography, including measurements of Left ventri-cular end systolic dimension (LVESD), Left ventricular end diastolic dimension (LVEDD), left ventricular ejection fraction (EF) calculated with modified biplane method of Simpson, Left ventri-cular end systolic volume (LVESV), Left ventricular end diastolic volume (LVEDV), Left atrium dimension (LA), Right atrium dimension (RA) and Right ventricular dimension (RV) was perfor-med at baseline after 3 days and was repeated at 3-month follow-up exami-nations.

Inter-ventricular dyssynchrony

Pulsed-wave Doppler velocity signals were recorded from the right and left ventricular outflow tracts to measure the inter-ventricular mechanical delay (IVMD) (time from the beginning of QRS to the start of pulmonary or aortic flow). The difference between pre-ejection times (IVMD) was used as an indicator of synchronicity between right and left ventricular contraction.[5,6].

Intra-ventricular dyssynchrony

Intra-ventricular mechanical delay could be determined on the basis of the simple M-mode-derived septal to post-erior wall motion delay (SPWMD). SPWMD was the difference between the time from the onset of ECG-derived Q wave to the initial peak posterior displacement of the septum, and the time from the onset of QRS to the peak systolic displacement of posterior wall with 100% sensitivity, 63% specificity and 85% accuracy.[7][8]

Various PW Tissue Doppler parameters had been proposed [9] as the time interval between the onset of ECG derived QRS and the Sm peak (= time to Sm peak) and the time interval between the onset of QRS and the onset of Sm (= time to Sm onset), which correspond to LV PEP .[10] Dyssynchrony was also assessed by using the measure of electromechanical delay (the time between the beginning of the QRS complex and the peak systolic wave of tissue Doppler) in the basal and mid regions of different opposing left ventricular walls. [11][12]..

Six minute walk test

Six minute walk test is a simple, low tech, safe and well established self-paced assessment tool to quantify functional exercise capacity and is a good predictor for morbidity and mortality in various diseases in adult populations. [13] it was performed at 5th day after permanent pacemaker implantation for all patients with comparing the results with the expected from all patients.[14]

STATISTICAL ANALYSIS

Statistical analysis was performed using the Statistical Package for Social Sciences version 16.0 (SPSS for Windows 16.0, Inc., Chicago, IL, USA).

Regarding the main measured parameters, the differences in both groups (1) diseased and (2) control group were tested by using independent samples t-test and homogeneity of variances was analyzed by the Levene's test. Results were expressed as Mean ± standard deviation (SD).

Categorical data are presented as absolute numbers and percentages within brackets. A $\chi 2$ analysis or Fisher exact test was used to compare these variables when expected cell frequency was less than five.

Correlations between categorical data are done using spearman correlation coefficient. All P values were based on a 2-tailed distribution, and the correspond-ding P value: non-significant (NS) difference if $P > 0.05$, significant (S) difference if $P < 0.05$, and highly significant (HS) difference if $P < 0.001$.

RESULTS

The demographic data, the under-lying causes of permanent pacemaker and QRS duration before and after permanent pacemaker implantation are summarized in Table 1. There were no statistical significant difference between the two groups regarding to age, gender and the cause of permanent pacemaker insertion (p >0.05). After permanent pacemaker insertion, there was highly statistical significant difference among both groups in QRS duration with statistical significant decrease in QRS duration in group 1 and statistical significant increase in QRS duration in group 2. (117.44 ± 7.89 versus 138.72 ± 12.77 ms) (< 0.001).

Table (1): The demographic data, the underlying causes of permanent pacemaker and QRS duration before and after permanent pacemaker implantation.

Variables	Group 1	Group 2	P-value
Number	43	43	
Age (years)	65.97 ± 10.52	68.62 ± 9.04	0.21
Male gender (n)(%)	31(72.1%)	34(79.1%)	0.45
QRS duration (msec)			
Pre-pacemaker	136.51 ± 12.32	120.69 ± 9.101	< 0.001*
Post-pacemaker	117.44 ± 7.89	138.72 ± 12.77	< 0.001*
Underlying disease (n)			
2^{nd} deg HB/CHB/SSS	5/35/3	5/34/4	0.92

N (number), HB (heart block), CHB (complete heart block), SSS (sick sinus syndrome) and P-value (probability of chance).

The intra-cardiac QRS duration of various positions after RV mapping with intra-cadiac catheter and the sites of permanent pacemaker leads fixation in group 1are listed in Table 2. there was no statistical significant difference between different positions in QRS duration (> 0.05) but there was highly statistical significant increase in number and percentage of patients with the narrowest QRS duration measured in High septum and consequently had lead fixation in this position(34 patients and 79.1%)(< 0.001)

Table (2) intra-cardiac QRS duration of different RV positions and sites of permanent pacemaker lead fixation

	Intra-cardiac QRS duration (ms)	P- value	Site of permanent pacemaker lead fixation		P-value
			No	% within the group	
High septum	100.27 ± 16.76	> 0.05	34	79.1	< 0.001*
Mid sepum	108.69 ± 16.51		5	11.6	
Lower septum	114.79 ± 14.75		2	4.7	
RVOT	110.95 ± 16.38		1	1.2	
RV free wall	130.44 ± 13.64		1	1.2	

RVOT (right ventricular outflow tract) and RV (right ventricle)

Table (3): Echocardiographic variables measured in both groups after 3 days and follow up after 3 months of permanent pacemaker implantation

parameters	Echocardiography after 3 days			Echocardiography after 3 months		
	Group 1	Group 1	P -value	Group 1	Group 2	P -value
LVESD (mm)	50.04 ± 4.71	50.09 ± 5.33	p> 0.05	50.34 ± 5.31	50.97 ± 6.35	p> 0.05
LVEDD (mm)	32.67 ± 4.96	30.93 ± 4.73	p> 0.05	33.06 ± 5.62	32.44 ± 6.53	p> 0.05
EF (%)	60.95 ± 5.40	61.32 ± 4.23	p> 0.05	60.46 ± 6.36	59.67 ± 6.38	p < 0.05*
LA (mm)	34.16 ± 4.09	33.41 ± 5.31	p> 0.05	34.23 ± 4.19	33.58 ± 5.42	p < 0.05*
RA (mm)	28.20 ± 2.68	30.18 ± 5.02	p> 0.05	28.72 ± 3.24	31.90 ± 5.97	p < 0.05*
RV (mm)	26.18 ± 4.06	26.46 ± 4.63	p> 0.05	26.83 ± 4.26	27.72 ± 5.28	p < 0.05*
LVESV (ml)	49.74 ± 8.54	49.32 ± 6.03	p> 0.05	50.72 ± 9.67	52.13 ± 10.06	p < 0.05*
LVEDV (ml)	127.88 ± 19.93	134.65 ± 19.36	p> 0.05	128.72 ± 21.04	137.32 ± 20.31	p < 0.05*
IVMD (ms)	27.86 ± 15.06	50.83 ± 15.59	p < 0.001*	28.58 ± 15.45	51.39 ± 15.95	p < 0.001*
LVPEP (ms)	105.39 ± 44.48	189.34 ± 36.14	p < 0.001*	107.32 ± 45.28	191.55 ± 36.56	p < 0.001*
RVPEP (ms)	77.79 ± 33.21	139.27 ± 24.58	p < 0.001*	78.51 ± 33.75	140.90 ± 24.51	p < 0.001*
SPWMD (ms)	75.2195 ± 37.36	121.13 ± 33.70	p < 0.001*	79.04 ± 39.92	122.46 ± 33.84	p > 0.05
Time to SM peak-time to SM onset (ms)	40.72 ± 16.57	64.4651 ± 16.15	p < 0.001*	41.09 ± 17.19	65.69 ± 16.72	p < 0.001*

LVESD (left ventricular end systolic diameter), **LVEDD** (left ventricular end diastolic diameter), **LA** (left atrium), **RA** (right atrium), **RV** (right ventricle), **LVESV** (left ventricular end systolic volume), **LVEDV** (left ventricular end diastolic volume), **IVMD** (interventricular mechanical delay), **LVPEP** (left ventricular pre-ejection period), **RVPEP** (right ventricular pre-ejection period), **SPWMD** (septal to posterior wall motion delay), **Time to SM peak-time to SM onset** (time to S- wave peak – time to S wave onset) .

Echocardiographic variables mea-sured in both groups immediately after 3 days and the follow up after 3 months are listed in Table 3. In echocardio-graphy done after 3 days, there were no statistically significant difference between two groups in LVESD, LVEDD, EF, LA, RA, RV, LVESV and LVEDV (> 0.05) while there were highly significant increase in IVMD (27.86 ± 15.06 ms versus 50.83 ± 15.59 ms), LVPEP (105.39 ± 44.48 ms versus 189.34 ± 36.14 ms), RVPEP (.79 ± 33.21 ms versus 139.27 ± 24.58 ms), SPWMD (75.2195 ± 37.36 versus 121.13 ± 33.70 ms) and Time to SM peak-time to SM onset (40.72 ± 16.57 ms versus 64.4651 ± 16.15 ms)(< 0.001) in group 2 in comparison to group 1. After 3 months still no statistically significant difference between two groups in LVESD and LVEDD but there were statistically significant increase in LA (34.23 ± 4.19 mm versus 33.58 ± 5.42 mm), RA (28.72 ± 3.24 mm versus 31.90 ± 5.97 mm), RV (26.83 ± 4.26 mm versus 27.72 ± 5.28 mm), LVESV (50.72 ± 9.67 ml versus 52.13 ± 10.06 ml) and LVEDV (128.72 ± 21.04 ml versus 137.32 ± 20.31 ml)(< 0.05). also highly significant increase in IVMD (28.58 ± 15.45 ms versus 51.39 ± 15.95 ms), LVPEP (107.32 ± 45.28 ms versus 191.55 ± 36.56 ms), RVPEP (.51 ± 33.75 ms versus 140.90 ± 24.51 ms)and Time to SM peak-time to SM onset (41.09 ± 17.19 ms versus 65.69 ± 16.72 ms)(< 0.001).

Stepwise regression analysis between patients in group 1 was done with the dependent variable the pacemaker insertion site (either high septum position or other sites) and independent variables EF, LVESV, LVEDV, RV, RA, SPWMD, IVMD and 6MWT Table 4. There was no statistical significant correlation bet-ween the different variables and the insertion sites (p > 0.05).

Table (4): Stepwise regression analysis between pacemaker insertion site and different echocardiographic parameters and 6MWT in group 1

Independent variables	Dependant variable	r	P -value
EF (%)		- 2.354	
RVESV (ml)		1.025	
RVEDV (ml)		2.021	
RV (mm)	Insertion site	4.361	> 0.05
RA (mm)		1.365	
SPWMD (ms)		2.369	
IVMD (ms)		3.025	
6MWT (m)		- 1.231	

RA (right atrium), **RV** (right ventricle), **LVESV** (left ventricular end systolic volume), **LVEDV** (left ventricular end diastolic volume), **IVMD** (interventricular mechanical delay), **SPWMD** (septal to posterior wall motion delay) and **6MWT** (six minute walk test)

Tissue Doppler imaging is a sophisticated echocardiographic tech-nique that permits measurement and timing of myocardial systolic (and diastolic) velocities. there were no statistical significant difference between the two groups regarding to the difference in tissue doppler imaging of most opposing LV segments including (basal septal and basal lateral), (basal anterior and basal inferior) and (mid anterior and mid inferior) but there was statistical significant difference between the two groups in tissue doppler imaging of mid septal and mid lateral segments (<0.05) in echocardiography done after 3 days of permanent pacemaker insertion. After 3 months, still there was no statistical significant difference between the two groups regarding to the difference in tissue doppler imaging of mid anterior and mid inferior segments only (> 0.05) but there were highly statistical significant difference between the two groups in tissue doppler imaging of other segments including (basal septal and basal lateral), (basal anterior and basal inferior) and (mid septal and mid lateral) (< 0.001). **Table 5**

Table (5): Tissue doppler imaging of opposing LV segments after 3 days and follow up after 3 months of PPM insertion

Opposing walls	differences	After 3 days				P - value	After 3 months				P - value
		Group 1		Group 2			Group 1		Group 2		
		NO	%	NO	%		NO	%	NO	%	
Basal septal – basal lateral (ms)	< 60ms	33	76.7	26	60.4	> 0.05	28	65.1	9	20.9	<0.001*
	≥ 60ms	10	23.3	17	396		15	34.9	34	79.1	
Mid septal – Mid lateral (ms)	< 60ms	30	69.7	20	46.5	< 0.05*	28	65.1	11	25.5	<0.001*
	≥ 60ms	13	30.3	23	53.5		15	34.9	32	74.5	
Basal anterior – Basal inferior (ms)	< 60ms	35	81.3	32	74.4	> 0.05	34	79.0	14	32.5	<0.001*
	≥ 60ms	8	18.7	11	25.6		9	21.0	19	67.5	
Mid anterior – Mid inferior (ms)	< 60ms	34	79.0	30	69.7	> 0.05	34	79.0	24	55.8	>0.05
	≥ 60ms	9	21.0	13	30.3		9	21.0	19	44.2	

Six minute walk test was performed by all patients and there was highly statistical increase in the distance (458.95 ± 230.20 m versus 325.11 ± 224.49 m) and percentage of walked distance in relation to expected for every patient (71 ± 30.78 % versus 49.67 ± 31.05 %.) (< 0. 001) in group 1 in comparison with group 2. (Table 6)

Table (6) six minute walk test in both groups

	Group 1	Group 2	P - value
Achieved distance (m)	458.95 ± 230.20	325.11 ± 224.49	< 0.001*
Achieve percentage (%)	71 ± 30.78	49.67 ± 31.05	< 0.001*

DISCUSSION

An increasing amount of data has recently raised questions about the safety of RV apical pacing [13]. Several published studies [14] demonstrated that more than 40% of the heart beats are paced from the right ventricular apex, an increase in the incidence of atrial firillation, heart failure, hospitalizations and even death is observed.

In our study, QRS duration was a major predictor for long term deter-ioration of LV function and development of heart failure. There was highly statistical significant decrease in QRS duration in group 1 patients (p < 0.001) and highly statistical significant increase in QRS duration in group 2 patients (p < 0.001) after PPM insertion. Many studies [15] revealed that the duration of the QRS during septal pacing remained compare-able to that recorded at the implantation while In right ventricular paced patients, QRS duration increased significantly (average 165 ± 10 ms, with values always > 130 ms). The DAVID (Dual Chamber with VVI Implantable Defbrillator) trial **(Wilkoff et al., 2002)** suggested that RV apical pacing was associated with an increased risk of death and hospitalization for heart failure in patients with an implantable defibri-llator [16]. Some studies could not demonstrate any significant difference of the LV dyssynchrony indices between patients with narrow or wide

QRS complex after the RV apical and septal pacing. [17].

In our study, the majority of patients in group 1 had narrowest intra-cardiac QRS duration in high septum despite there were no statistical significant difference between different RV position in intra-cardiac QRS dura-tion. These results were consistent with **Gianni et al., 2012** whom revealed that the high septal region of the LV normally depolarizes first and high right ventricular septal pacing close to the sites of early activation could achieve the narrowest intra-cardiac QRS duration. [18] The cause of this concordant was using both fluoroscopic and electrical guiding to select the optimal site which achieved narrowest intra-cardiac QRS duration. In contrast to **Padeletti et al., 2007** which could not demonstrate any significant difference between RV outflow tract and right ventricular septum in intra-cardiac QRS duration because they used fluoroscopic guiding only. [17]

3 days after PPM implantation, there were no statistical significant differrence between the two groups regarding to LVESD, LVEDD, LA, RA, RV, LVESV, LVEDV and LVEF (> 0.05). But there were highly statistical significant increase in IVMD, LVPEP, RVPEP and Time to SM peak-time to SM onset in group 2 in comparison to group 1. In three months follow up echocardiography, still there were no statistical significant difference between the two groups regarding to LVESD and LVEDD (>0.05) while there were statis-tical significant difference between the two groups regarding to LA, RA, RV, LVEF, LVESV, IVMD, LVPEP, RVPEP, SPWMD and Time to SM peak-time to SM onset (> 0.001) with increase in all these parameters in group 2 in comparison to group 1 except LVEF which decreased in both groups but the decrease was more significant in group 2. Many studies agreed with these results [15, 19, 20] and revealed that patients with LV dyssynchrony after long term RV pacing showed a decrease in LV ejection fraction, with an increase in LV volumes and LV end-diastolic diameter indicating LV dilatation. Also revealed an increase in SPWMD after long-term RV pacing. The OPSITE (Optimal Pacing SITE) study [21] compared RV pacing and biventricular pacing in patients with permanent AF undergoing AV node ablation. After 6 months, patients with RV pacing had a significant lower LV ejection fraction as compared to biventricular pacing. In addition, NYHA functional class was significantly lower with RV pacing as compared to biventricular pacing. This is discordant with **Goo-Yeong et al., 2005** [22] which showed that after pacemaker implant-ation, LV volume and ejection fraction did not significantly change. None of the echocardiographic measures of dyssy-nchrony showed a significant difference according to the pacing site. Also Aortic pre-ejection time and SPWMD in patients with a pacemaker were longer compared to those of normal controls, but there was no significant difference. According to the PROSPECT trial, [23] no single echocardiographic measure of dyssynchrony may be recommended because of the poor reproducibility.

There was no statistical significant difference between the two groups regarding to the difference in tissue doppler imaging of most opposing LV segments except mid septal and mid lateral segments in echocardiography done after 3 days of PPM insertion which became highly significant after 3 months. So the difference in tissue doppler imaging of mid septal and mid lateral segments was the earliest to reveal difference after permanent pacemaker insertion and could be used as early predictor of dyssynchrony and possibility of occurrence of complica-tions. This was proved by many studies [24,25] which showed that TDI was significantly larger in patients with permanent pacing as compared with control patients and was significantly larger in patients in patients with apical pacing as compared to septal pacing particularly the septal-to-lateral delay.

Six minutes walk test as predictor of improvement of clinical status or to trace the change in exercise capacity was performed by all patients and there was highly statistical increase in the distance (458.95 ± 230.20 m versus 325.11 ± 224.49m) and percentage of walked distance in relation to expected for every patient (71 ± 30.78 % versus 49.67 ± 31.05 %.) (< 0.001) in group 1 in comparison with group 2. These results were concordant with **Eraldo et al., 2015** [15] and also with **Occhetta et al., 2015** [26] which revealed that Exercise tolerance, expressed in meters walked in 6 min, was better in patients with PHstimulated patients than in RVA-stimulated patients but the difference was not significant. on the contrary **Kypta et al., 2006** [27] which revealed that analyzed 98 pacing dependent patients regarding exercise capacity at 3 days, 3 months, and 18 months after the pacemaker implant-ation. All changes from baseline to 18 months were statistically not different between septal and apical stimulation.

CONCLUSION

The present study showed that high septum was the ideal site for permanent pacemaker implantation especially when guided fluoroscopically and electrically by intra-cardiac catheter. High septum achieved the narrowest intra-cardiac QRS duration and also the narrowest surface ECG which associated with better echocardiographic and clinical outcomes. Furthermore Doppler echo-cardiography was a good diagnostic and predictive investigation for immediate and late complications of permanent pacemaker implantation. Finally six minute walk test was the test of choice to evaluate clinical status and functional capacity of the patients.

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