DEVICES

Medium-Term Effects of Septal and Apical Pacing in Pacemaker-Dependent Patients: A Double-Blind Prospective Randomized Study

LUIS MOLINA, M.D., D.Sc.,* RICHARD SUTTON, M.B., D.Sc.,† WILLIAM GANDOY, M.D.,‡
NICOLÁS REYES, M.D.,* SUSANO LARA, M.D.,* FROYLÁN LIMÓN, M.D.,*
SUSANA GÓMEZ, M.D.,* CONSUELO ORIHUELA, M.D.,§ LATIFE SALAME, B.Sc.,‡
and GABRIELA MORENO, B.Sc.‡

From the *Arrhythmia Laboratory of the Universidad Nacional Autónoma de México (UNAM) en Hospital General
de México, Mexico City, Medico; †Imperial College, London, UK; ‡Facultad de Medicina; and §Hospital Central Sur
Pemex, Tlalpan, Mexico

Background: *Pacing the right ventricle is established practice, but there remains controversy as to the optimal site to preserve hemodynamic function.*

Aims: *To evaluate clinical and hemodynamic differences between apical and septal pacing in pacemaker-dependent patients.*

Methods: *Patients receiving their first pacemaker for advanced atrioventricular block, with the atria in sinus rhythm, were randomized to receive apical (Group A) or septal (Group S) ventricular leads. After implant, with the device programmed VVI 70 beats/min fixed rate, patients underwent a 6-minute walk test and a transthoracic echocardiogram. Then, DDDR was programmed at nominal settings. The same tests were performed at 6 months and 12 months follow-up. If ventricular pacing was less than 98%, the patient was excluded.*

Results: *A total of 142 patients were included in the study. During the study year, 71 (50%) were excluded for not fulfilling the condition of 98% ventricular pacing. Groups A and S had 34 and 37 patients, respectively. Age and gender were similar in the groups. At implant, QRS duration was significantly greater in Group A (158 ms) than Group S (146 ms; P = 0.018), and the QRS axis was different: –74.5° in Group A and 1° in Group S (P < 0.001). At 1 year, the 6-minute walk improved significantly in both groups: Group A 15% (P = 0.048) and Group S 24% (P = 0.001). Left ventricular ejection fraction (LVEF) increased from 0.57 to 0.61 (P = 0.008) in Group S, without significant change in Group A.*

Conclusions: *After 1 year, pacemaker-dependent patients with septal ventricular leads have better clinical and functional (LVEF) outcome. (PACE 2014; 37:207–214)*

right ventricular pacing, pacemaker dependency, septal pacing, apical pacing, 6-minute walk, echocardiography

Background

Much has been said regarding the optimal right ventricular (RV) pacing site.[1–4] On one hand, there is the irrefutable proof of time: apical pacing has been used for over four decades without substantial damage or even beneficial[5,6] outcome in terms of heart function in patients who started with normal left ventricles; however, RV septal pacing has been argued to stimulate a more efficient ventricular contraction.[7,8]

The natural activation through the His-Purkinje system is, of course, the best way to depolarize the ventricular mass under normal circumstances,[8,9] irrespective of conduction or contractile disturbances. Any device that artificially depolarizes the heart will have some deleterious physiological effects.[10,11]

The physiological rationale behind pacing the septum rather than the apex is based on initiating the ventricular depolarization in the RV septal wall, across the base of the mitral septal papillary muscle, where the first activation vector normally

starts.[12,13] By doing so, the QRS duration will be shorter than that with pacing from the apex, and the ventricular contraction—in theory—will be more efficient. Pacing from the apex has a more "desynchronizing effect"[8] than pacing from the interventricular septum.

Pacemaker dependency is another crucial element to consider in artificial pacing. In nonpacemaker-dependent patients, the less stimulation, the better physiologic outcome.[14,15] The pacing site becomes an increasing problem when the patient requires pacing for a considerable part of the time.[16]

Material and Methods

After the Institutional Review Board approved the protocol, and written informed consent was obtained, patients were randomized to receive a septal or apical ventricular lead.

All patients underwent their first pacemaker implant, using active fixation ventricular leads in the septum and passive fixation in the apex, for documented complete atrioventricular (AV) block. All patients' atria were in sinus rhythm; none was in atrial fibrillation (AF). All the apical and septal positions were radiographically documented in relation to anatomic landmarks. Figure 1 illustrates the range of positions considered to be septal. No attempt was made to achieve right ventricular outflow tract (RVOT) pacing.[17,18] Once pacing was established, measurements of paced QRS duration and axis in the frontal plane leads were obtained.[17]

At the end of the first week after implant, a transthoracic echocardiogram was obtained (Model HD11XE, Phillips Healthcare, Eindhoven, the Netherlands). Only one operator acquired all the echocardiographic images and calculated all parameters. This operator's intraobserver reproducibility was 3–4%. During this period, all patients also had a 6-minute walk test.

Pacing Protocol

Once the generator was implanted, it was programmed as VVI (ventricular pacing only) at a fixed rate of 70 beats/min. This was determined to be a control phase, as far as possible to normalize the different clinical states of those entering the trial, before undertaking the echo and the 6-minute walk.

After the echo was obtained and the 6-minute walk performed, the pacemaker was reprogrammed as DDDR (dual chamber pacing and the rate response mechanism ON) with default pulse output. The AV interval was programmed at nominal values: 120 ms for sensed P waves and 150 ms for paced atrial activation.

Patients were then evaluated at the third month, to reduce the generator's output to three
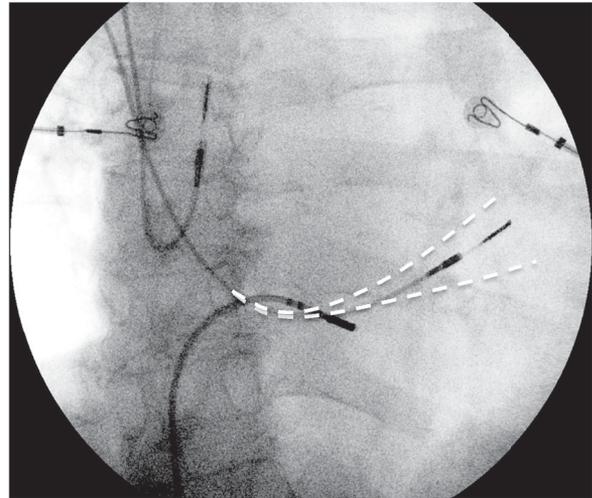
Panel A
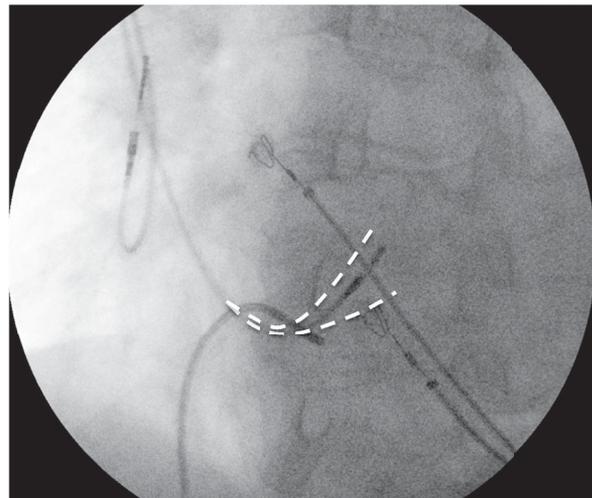
Panel B

Figure 1. *Right ventricular lead placement. This chest radiograph shows a typical septal pacing position in right anterior oblique (RAO) in Panel (A), and left anterior oblique (LAO) in Panel (B) projections with acceptable ranges of position drawn in. No leads were positioned outside these limits.*

times threshold value. Six months after implant, a second echocardiogram was performed in addition to another 6-minute walk test. Finally, 6 months later (1 year after implant), the same two examinations were repeated (Fig. 2).

The lead placement was blinded to the patient and to the physician conducting the clinical follow-up.

Statistical Analysis

The sample size was estimated with a confidence level of 95% and error margin of 5%. We inserted International data[18] into the following
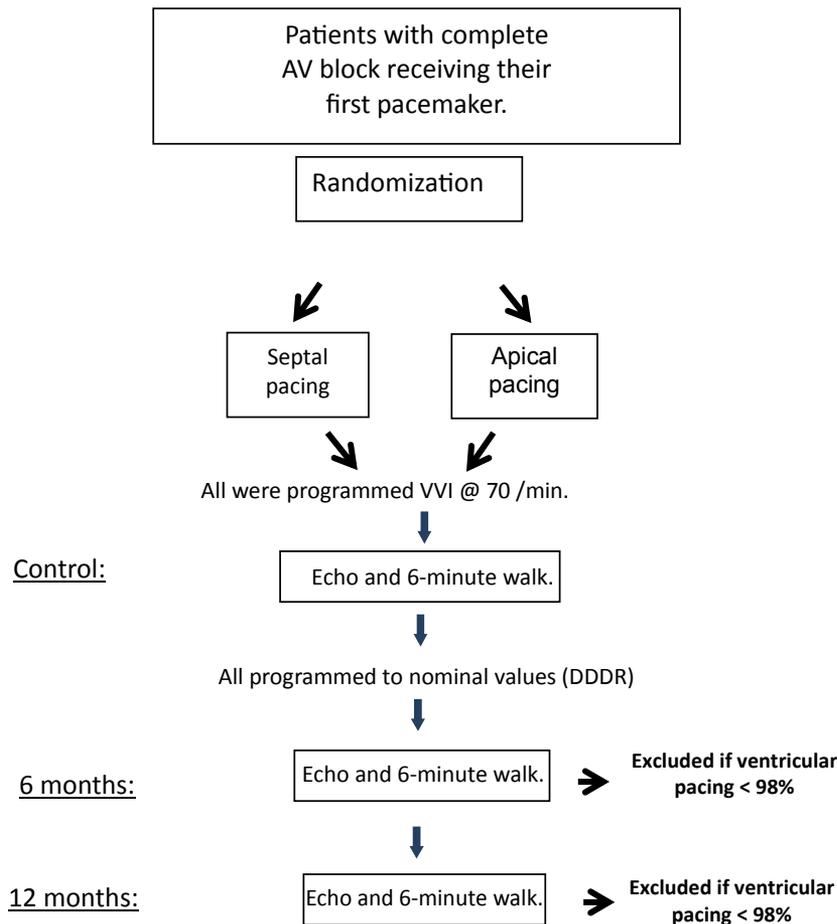
Figure 2. *Study flow chart. AV = atrioventricular; Echo = echocardiogram.*

equation:

$$n = \frac{Z^2 \, [(P)\,(1-P)]}{e^2}$$

where Z (1.96) is the value for a 95% level of confidence, e (0.05) is error margin, and P (0.04) is the prevalence reported for the world population.

The population needed to achieve statistical strength was 59 subjects. Anticipating high rates of dropout because of the prospective exclusion criterion (below), we included 142 patients.

In order to determine which test had to be carried out, the data were analyzed to define if it had "Gaussian" characteristics with the Kolmogorov-Smirnov test.

We used the nonparametric Mann-Whitney U test to determine significant differences between variables that did not adjust to a normal distribution. For the normally distributed variables, the Student's *t*-test was used. To verify the significance, we performed a Monte Carlo (MC) test for 10,000 samples. This method was preferred

over calculating Type I error and Power with classical theoretical distributions for asymptotic conditions, as clinical data are often not normally distributed.[19]

Patients

Patients receiving their first pacemaker for documented complete persistent AV block were randomized to septal or apical pacing. We used a "complete randomization" method (simple randomization) that is equivalent to a coin toss.[20,21]

Patients were included regardless of their age, gender, or underlying pathology. None had clinical evidence of severe congestive heart failure (CHF) as defined by New York Heart Association class IV.

Exclusion Criteria

All patients were followed-up every 3 months. They were excluded if ventricular pacing was less than 98% of the time, regardless of atrial

Left Ventricle Ejection Fraction
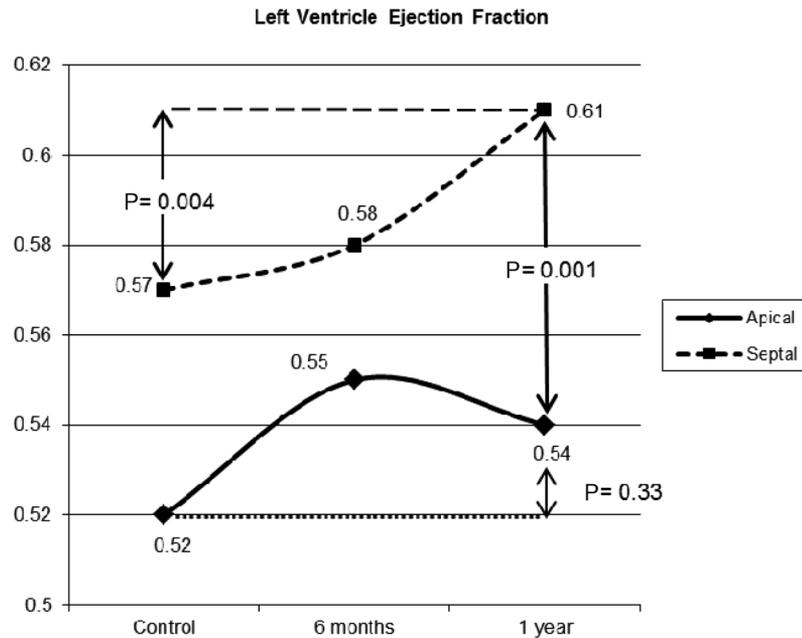
Figure 3. *Ejection fraction changes. This figure shows the left ventricular ejection fraction plotted for the apical and septal groups at control, 6 months and 1 year.*

rhythm (sinus or pacing). This was a prospective exclusion by protocol. An "underlying rhythm" test to ensure the persistence of complete AV block was performed at every visit. The application of the protocol led to late exclusion in 71 patients, but it determined that, as planned at the outset, only persistently pacemaker-dependent patients completed the study.

Methods

Ventricular leads were Medtronic® models Capsurefix® Novus 5076 for the screw-in (active) and Capsure® SP 5024 passive fixation (Medtronic Inc., Minneapolis, MN, USA), placed according to randomization in the septum or the RV apex. To achieve the midseptal position, a custom curved stylet was shaped as has been described,[22,23] or by simply pulling down the lead from the pulmonary artery until it was parallel to the midseptal endocardium.[24]

The tip of the lead was verified to be in the midseptum using the left anterior oblique and right anterior oblique (RAO) projections (Fig. 1).

The apical position was attained in the RAO projection, placing the lead as far and inferiorly as possible. No diaphragmatic stimulation was observed.

The generators used were Medtronic® model Kappa, series 400, 700, and 900 (Medtronic Inc.).

Results

A total of 142 patients had a pacemaker successfully implanted. Correct location was confirmed in all cases, and no dislodgements occurred. No major complications were observed during implant.

After 1 year, 71 patients registered >98% ventricular pacing: 34 were in Group A, and 37 in the septal (S) Group. The 71 excluded patients recovered some degree of AV conduction and hence had a pacing percentage of less than 98%.

Both groups of patients completing the follow-up were pacemaker dependent, and inhibition of pacing provoked symptomatic ventricular pauses or intense bradycardia.

Mean age of Group A was 72 ± 12, similar to the Group S, 69 ± 12 (P = ns). Likewise, 40% of patients in Group A were male, and 49.7% in Group S (P = ns).

Parameters Obtained during Implant

Of both groups, 12 had a femoral temporary pacing lead placed during the procedure (seven in Group A and five in Group S).

For this reason, only 27 in Group A had a spontaneous R wave with a median value of 12.1 mV, compared with 32 patients with an R wave of 8.9 mV in Group S (P = ns).

Other acute values such as impedance (765 Ω for Group A and 778 Ω for Group S) and threshold

Table I.

Data at Implant

	Group A	Group S	P Value
Age ± SD	72 ±12	69 ± 12	
Gender (% males)	40.3	49	
R-wave amplitude (mV)[a] (IR)	12.1 (8.5)	8.9 (6.2)	0.15
Impedance (Ω)[a] (IR)	765 (288)	778 (269)	
Threshold (V)[a] (IR)	0.6 (0.4)	0.5 (0.3)	
QRS axis (°)[a] (IR)	−74.5 (29)	1 (90)	<0.001
QRS duration (ms)[a] (IR)	158 (29.5)	146 (45.5)	0.018

[a]Values presented as medians.
IR = interquartile range; SD = standard deviation.

(0.6 V for Group A and 0.5 for Group S) were not significantly different between groups (P = ns).

During pacing, the QRS duration was longer in Group A patients (158 ms) than Group S (146 ms; P = ns). The QRS axes were highly statistically different: −74.5° in the Group A and 1° for the septal position (P < 0.001; Table I).

Acute Results Obtained during the First Week after Implant

These are the results while the patients had the device programmed in VVI mode at 70 beats/min.

For both groups, the 6-minute walk was possible in 32 and 36 patients in groups A and S, respectively. In Group A, the distance was 383 ± 177 m and 386 ± 114 m the Group S (Table II).

The remaining data were acquired from the transthoracic echocardiogram: fractional shortening, left ventricular end-systolic volume, and left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic dimension were very similar in the two groups (Table II). The only parameter that showed significant difference between groups was left ventricular end-diastolic dimension (P = 0.028).

Control values for left ventricular ejection fraction (LVEF) were 0.52 ± 0.1 for Group A, and 0.57 ± 0.1 for Group S (P = ns).

Follow-Up

Patients were subjected to the same clinical examinations (6-minute walk and echocardiogram) as in the acute phase after 6 months and 1 year. At 6 months, there were no significant

Table II.

Data at the First Week after Implant

	Group A	Group S	P Value
6-minute walk (m) ± SD	383 ± 177	386 ± 114	
Fractional shortening (%) ± SD	0.37 ± 0.09	0.38 ± 0.1	
LVESV (mL) ± SD	35.6 ± 27.1	33.7 ± 26.2	
LVEDV (mL) ± SD	70.6 ± 34.0	66.2 ± 32.1	
LVEDD (mm)[a] (IR)	50 (8)	45 (7)	0.028
LVESD (mm) ± SD	31.7 ± 8.9	29.8 ± 8.1	
LAD (mm) ± SD	38.9 ± 5.4	38.8 ± 7.0	
LVEF ± SD	0.52 ± 0.1	0.57 ± 0.1	

[a]Values presented as medians.
IR = interquartile range; LAD = left atrial dimension; LVEDD = left ventricular end-diastolic dimension; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic dimension; LVESV = left ventricular end-systolic volume; SD = standard deviation.

differences between groups or with respect to control values.

After 1 year, we compared changes between groups (Table III) and within each group (Table IV). Comparing control values with 1-year results, the distance covered during the 6-minute walk, Group A patients increased from 383 ± 177 to 452 m (18% P = 0.018), though in Group S, the increment was from 386 ± 114 to 480 m (24% P = 0.002; MC = 0.002, 95% confidence interval [CI] = 0.001–0.003).

At the end of the follow-up period, the difference in LVEF between the groups was significant (S: 0.61, A: 0.54; P = 0.001; MC = 0.002, 95% CI = 0.001–0.003; Fig. 3). Likewise, LVEF increased seven percentage points in the Group S (0.57 ± 0.1 to 0.61, P = 0.004; MC = 0.002, 95% CI = 0.001–0.002) compared with the nonsignificant change (P = 0.33) from 0.52 ± 0.1 to 0.54 in Group A patients. None of the other parameters was statistically different.

Discussion

This study has shown in patients with ventricular pacemaker dependency using a randomized double-blind single-center prospective design, that there is significant improvement in LVEF and 6-minute walk distance, with septal RV

Table III.

One Year Follow-Up

	Group A	Group S	P Value
6-minute walk (m)[a] (IR)	452 (133.3)	480 (94.8)	
Fractional shortening (%) ± SD	0.38 ± 0.09	0.37 ± 0.08	
LVESV (mL) ± SD	31.8 ± 20.7	32.6 ± 24.7	
LVEDV (mL) ± SD	61.9 ± 22.2	67.6 ± 29.9	
LVEDD (mm) ± SD	46.9 ± 6.2	45.4 ± 9.4	
LVESD (mm) ± SD	28.9 ± 5.8	28.8 ± 5.3	
LAD (mm) ± SD	37 ± 8.5	37 ± 6.4	
LVEF[a] (IR)	0.54 (0.11)	0.61 (0.07)	0.001

[a]Values presented as medians.
For abbreviations please see Table II.

pacing—over a period of 1 year—compared with RV apical pacing.

Perhaps, the most important feature of this study is the high degree of pacemaker dependency. Most reports on the differences between septal and apical pacing have not considered this facet,[1–3,25–27] which remains important because the ideal pacing site has not been definitively demonstrated. This failure to demonstrate the ideal pacing site may, at least in part, be due to intermittent AV block with its implied percentage

of normal or near-normal AV conduction. The main prospective exclusion criterion was ventricular pacing for less than 98% of the time throughout the follow-up period. Not only were patients being paced almost all the time, but also the "underlying rhythm" test demonstrated they did not have AV conduction that could compete with the pacemaker. This was not manipulated by programming short AV intervals. Hence, the clinical progress of the patients in this study was a consequence of ventricular pacing only. Thus, the influence of normally conducted beats was eliminated.

The use of active or passive fixation ventricular leads[22,28,29] was not associated with dislodgements or differences in any of the acute values during implant.

Data obtained after 1-year follow-up were analyzed with a Kolmogorov-Smirnov test to define the normality of the distribution determining selection of Student's *t*-test or Mann-Whitney U test for statistical significance.

The most remarkable disparities during implant were the R-wave amplitude and the QRS axis. For the R wave, little has previously been stated[30]: we found a persistent statistically nonsignificant lower R wave in the septal position (P = 0.15). This could reflect purely the confluent depolarization vectors at the apex or possibly a trend toward significance. The QRS axis pacing from the RV apex directs all vectors toward a left superior angle, although there are opinions opposing this statement.[31] Our findings were that there was a highly significant difference in QRS vectors of septal and apical pacing.

There remains controversy over QRS duration. Some authors have described[32,33] a faster

Table IV.

Changes at Apical versus Septal Site

	Apical Changes			Septal Changes		
	Initial	Final	P Value	Initial	Final	P Value
6-minute walk (m)	383 ± 177	452[a]	0.018	386 ± 114	480[a]	0.002
Fractional shortening	0.37 ± 0.09	0.38 ± 0.09		0.38 ± 0.1	0.37 ± 0.08	
LVESV (mL)	35.6 ± 27.1	31.8 ± 20.7		33.7 ± 26.2	32.6 ± 24.7	
LVEDV (mL)	70.6 ± 34.0	61.9 ± 22.2		66.2 ± 32.1	67.6 ± 29.9	
LVEDD (mm)	50[a]	46.9 ± 6.2		45[a]	45.4 ± 9.4	
LVESD (mm)	31.7 ± 8.9	28.9 ± 5.8		29.8 ± 8.1	28.8 ± 5.3	
LAD (mm)	38.9 ± 5.4	37 ± 8.5		38.8 ± 7.0	37 ± 6.4	
LVEF	0.52 ± 0.1	0.54[a]	0.33	0.57 ± 0.1	0.61[a]	0.004

[a]Values presented as medians; for interquartile ranges please refer to Tables I–III. The remaining values are presented with ±SD.
For abbreviations, please see Table II.

depolarization with a beneficial hemodynamic consequence from septal pacing.[31,33–35] The possible small variations in septal position of the pacing electrode[36] could have some influence on the outcome. In these observations, the Group S had the QRS 12 ms shorter than those with apical stimulation (P = 0.018). This observation had no acute hemodynamic effect, but it may explain the favorable results we detected at 1 year.

Concerning the first week after implant, when patients had the device programmed in VVI mode at a fixed rate of 70 beats/min, we observed nonsignificant differences: LVEF was slightly better in the Group S (0.57 ± 0.1 vs 0.52 ± 0.1). The LVEDV was also modestly smaller in the Group S (66.2 ± 32.1 vs 70.6 ± 34.0).

Six months after implant, there were no significant improvements in any of the evaluated parameters. This coincides with the findings of others in acute and short-term studies.[5,25]

The most remarkable changes within a group and dissimilarities between the groups were seen after 1 year.

Considering the 6-minute walk, there were no differences between groups, although within both sets of patients we found important increments: those with the apical lead increased 18% (from 383 ± 177 m to 452 m), whereas the septal group had an increment of 24% (from 386 ± 114 m to 480 m). Although both groups had a significant rise, that of the septal group was clearly superior (Table IV).

One possible reason for the remaining echocardiographic/anatomical parameters not improving may be the relatively brief follow-up period.[5,37]

Just as stated in our hypothesis, the LVEF showed a considerable increment within the septal group, and had an important divergence from apical pacing. Even though the absolute values are not substantially different, we consider that the septal curve shows a clear tendency toward a better LVEF compared with the changes in the apical pacing group.

Limitations

Although this is a single-center study with a relatively small number of patients, the absolute pacemaker dependency, we believe, makes this report a relevant contribution to the RV pacing site controversy.

The follow-up period was relatively brief, though sufficient to demonstrate significant differences between groups.

Conclusion

We have shown that after 1-year follow-up in persistently pacemaker-dependent patients, with no clinical evidence of severe CHF, midseptal ventricular lead placement is superior to the apical location. We observed significant improvements in both clinical (6-minute walk) and functional (LVEF) parameters.

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