Left Ventricular Synchrony and Function in Pediatric Patients with Definitive Pacemakers

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Abstract

Background: Chronic right ventricular pacing (RVP) induces a dyssynchronous contraction pattern, producing interventricular and intraventricular asynchrony. Many studies have shown the relationship of RVP with impaired left ventricular (LV) form and function.

Objective: The aim of this study was to evaluate LV synchrony and function in pediatric patients receiving RVP in comparison with those receiving LV pacing (LVP).

Methods: LV systolic and diastolic function and synchrony were evaluated in 80 pediatric patients with either nonsurgical or postsurgical complete atrioventricular block, with pacing from either the RV endocardium (n = 40) or the LV epicardium (n = 40). Echocardiographic data obtained before pacemaker implantation, immediately after it, and at the end of a mean follow-up of 6.8 years were analyzed.

Results: LV diastolic function did not change in any patient during follow-up. LV systolic function was preserved in patients with LVP. However, in children with RVP the shortening fraction and ejection fraction decreased from medians of 41% ± 2.6% and 70% ± 6.9% before implantation to 32% ± 4.2% and 64% ± 2.5% ($p < 0.0001$ and $p < 0.0001$), respectively, at final follow-up. Interventricular mechanical delay was significantly larger with RVP (66 ± 13 ms) than with LVP (20 ± 8 ms). Similarly, the following parameters were significantly different in the two groups: LV mechanical delay (RVP: 69 ± 6 ms, LVP: 30 ± 11 ms, $p < 0.0001$); septal to lateral wall motion delay (RVP: 75 ± 19 ms, LVP: 42 ± 10 ms, $p < 0.0001$); and, septal to posterior wall motion delay (RVP: 127 ± 33 ms, LVP: 58 ± 17 ms, $p < 0.0001$).

Conclusion: Compared with RV endocardium, LV epicardium is an optimal site for pacing to preserve cardiac synchrony and function. (Arq Bras Cardiol. 2013;101(5):410-417)

Keywords: Ventricular Function, Left; Myocardial Contraction; Cardiac Pacing, Artificial; Child; Pacemaker, Artificial.

Introduction

Electric stimulation from the right ventricular (RV) apex and free wall induce a dyssynchronous contraction pattern characterized by early activation of RV and the interventricular septum and delayed activation of the left ventricular (LV) anterior wall. This produces mechanical and electrical interventricular asynchrony, along with intraventricular asynchrony[1]. Although these detrimental effects are tolerated by most pediatric patients, studies have shown that chronic RV pacing (RVP) is an important risk factor for acute and chronic impairment of LV function, structural remodeling of LV, and an increased risk of heart failure[2-5]. These adverse events occur in 6% and 13% patients after follow-up over approximately 10 years[2,5-8].

Alternative pacing sites have been investigated to preserve LV synchrony. Two retrospective studies of children with permanent LV epicardial pacing concluded that LV function can be preserved by chronic stimulation of the LV (LVP) free wall[9,10]. In addition, an study of pediatric patients with either LV dysfunction and RVP or intrinsic left bundle branch block demonstrated the possibility for improvement of LV function 1 month after single-site LVP[11].

The present study aimed to evaluate the evolution of LV function and synchrony after endocardial RVP in comparison with those after epicardial LVP.

Methods

Patients

A total of 130 pediatric patients who underwent pacemaker implantation in a single tertiary pediatric cardiology center were prospectively enrolled. The study included all children with either nonsurgical or surgical complete atrioventricular block (CAVB). Children were included when paced from both the RV endocardium (n = 40) and from the left ventricular epicardium (n = 40). We excluded the following patients: those aged >18 years at pacemaker implantation, those with <95% ventricular pacing, those with ≤1 year of permanent cardiac pacing, and those with clinical evidence or history of heart failure

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unrelated to CAVB at the time of pacemaker implantation. Table 1 depicts the demographic data of the paced children. The study protocol was approved by the institutional research ethics committee and written consent was obtained from the parents of all patients.

Pacing

Pacing lead positions were assigned according to implantation protocol data and confirmed by chest X-rays. LVP unipolar leads were implanted in the apical region, and inserted through a left lateral thoracotomy. All endocardial pacing leads were placed in the RV apex (RVA). Ventricular pacing (Ventricular Rate Modulated Pacing [VVI/VVIR]) was the predominant pacing mode. The study excluded patients who required a change in the pacing site between the initiation of pacing and evaluation.

Echocardiography

Echocardiographic evaluations were made before pacemaker implantation, immediately after, and at regular intervals during a mean follow-up period of 6.8 years. Data were obtained in the standard precordial positions with an appropriate transducer (5 MHz, Aloka Prosound 5500). Two experienced observers, blinded for the ventricular pacing site, performed one- and two-dimensional transthoracic echocardiography and Doppler evaluations. All examinations were performed in line with the recommendations of the Pediatric Council of the American Society of Echocardiography [12]; three measurements in random for every patient were made for each observer and the average of measurements was used for further analysis. Paraesternal M-mode images were used to measure LV end-diastolic and LV end-systolic diameters (LVEDD and LVESD, respectively). LV shortening fraction (LV SF) was calculated according to the formula[12]: LV SF = LVEDD − LVESD/LVEDD × 100. LV end-diastolic and LV end-systolic volumes (LVEDV and LVESV, respectively) were obtained using Simpson's biplane method, and indexed to body surface area and the ejection fraction (EF) calculated.

For a comprehensive diastolic evaluation, Doppler tissue imaging (DTI) was undertaken at the lateral and septal mitral valve annulus in the apical four-chamber view. The peak tissue E-wave (Ea) and A-wave (Aa) velocities were obtained, and the E/Ea ratio was also determined. LV isovolumic relaxation time was used to assess diastolic function, and it was considered as the period from the end of aortic flow to the beginning of mitral inflow in the apical five-chamber view.

Myocardial 2D strain was performed to assess ventricular synchrony in the four-chamber and long-axis views. The following parameters were evaluated:

Interventricular mechanical delay, measured as the time difference between the LV and RV pre-ejection times.

Septal to lateral mechanical delay, calculated as the maximum time difference between the earliest and latest peak myocardial systolic velocity of two opposing segments.

Table 1 - Study population: clinical and pacing data

	All patients	RV pacing	LV pacing
Patients	80	40	40
Age (years)	12.5(5.2)	14.6(4.3)	10.3(6.1)
Age at first implantation (years)	7.2(4.0)	8.1(3.1)	6.3(4.9)
Total duration of pacing (years)	6.8(4.3)	6.3(2.6)	7.2(3.2)
Gender (male/female)	80(49/31)	40(26/14)	40(23/17)
Structural heart disease	46(57.5)	22(55.0)	24(60.0)
Atrial septal defect	3(3.75)	-	3(10.0)
Ventricular septal defect	5(6.25)	4(10.0)	1(2.5)
Tetralogy of Fallot	17(21.25)	8(20.0)	9(22.5)
Double outlet right ventricle	9(11.25)	6(15.0)	3(7.5)
Subvalvular aortic stenosis	7(8.75)	3(7.5)	4(10.0)
Valvular pulmonary stenosis	2(2.5)	1(2.5)	1(2.5)
Persistence ductus arteriosus	3(3.75)	-	3(7.5)
Definitive pacing indications			
Nonsurgical CAVB	42(52.5)	22(55.0)	20(50.0)
Surgical CAVB	38(47.5)	18(45.0)	20(50.0)
Stimulation mode			
DDD/DDDR	9(11.3)	9(22.5)	-
VVI/VVIR	63(78.7)	23(57.5)	40(100)
VDD/VDDR	8(10.0)	8(20.0)	-

Data are presented as the mean value ± SD or number (%) of patients. CAVB: complete atrioventricular block; DDD: dual chamber pacing and sensing; LV: left ventricular; RV: right ventricular; VDD: ventricular pacing with dual chamber sensing; VVI: ventricular pacing and sensing.

Septal to posterior wall motion delay (SPWMD), determined as the delay between peak systolic inward motion of the interventricular septum, and the left posterior wall.

LV mechanical delay, measured as the maximum difference between the initial and last peak systolic 2D strain in any of the 12 LV segments.

Statistics

Data are presented as mean ± standard deviation. For analyzing the differences in continuous variables between the RVA pacing (RVAP) group and LVP group, t-tests were used. Correlations between variables were assessed using Pearson's correlation (r value). Logistic regression was performed to determine the predictors of impaired left ventricular function. Significance was accepted at a p value of ≤0.05. The software package Medcalc for Windows (Version 11.3) was used for statistical work up.

Results

Patient characteristics

A total of 80 patients with a mean age of 12.5 ± 5.2 years were evaluated. The demographic data and clinical characteristics of study are presented in Table 1. Pacing indications were postsurgical CAVB (n = 38) and nonsurgical CAVB (n = 42). In total, 57.5% patients had structural heart disease, with 79.2% having undergone surgical correction. Tetralogy of Fallot was the congenital cardiac disease with the highest rate of postoperative CAVB. Neither the mean age at first implantation nor the duration of pacing showed significant differences between the two pacing groups. All patients with LVP received a single-chamber pacemaker, whereas 23 children (57.5%) that were paced from the RVA received VVI/VVIR pacing.

Left ventricle: long-term size, function and synchrony.

At the end of the follow-up period, LVEDD in patients with RVAP increased significantly over both the corresponding baseline values (40 ± 6.0 vs. 32 ± 3.1, p < 0.001) and the values of the LVP group (40 ± 6.0 vs. 35 ± 4.2, p < 0.001) (Table 2). SF in the RVP group was significantly lower than before pacing (32 ± 4.2 vs. 41 ± 2.6, p < 0.001) and was lower than that in the LVP group (32 ± 4.2 vs. 39 ± 5.2, p < 0.001). The LV EF was normal in children with LVP after long-term cardiac stimulation, but tended to worsen in the RVAP group (70 ± 6.9 vs. 64 ± 2.5, p < 0.001). A similar tendency has not been observed with LV diastolic function at any pacing site during follow-up (Table 3).

All the echocardiographic parameters reflecting both interventricular and intraventricular dyssynchrony were affected in patients with RVAP (Table 4). Interventricular mechanical delay was significantly larger in the RVAP group (66 ± 13 ms) than in the LVP group (20 ± 8 ms); similarly, septal to lateral wall motion delay (RVP: 75 ± 19 ms; LVP: 42 ± 10 ms, p < 0.0001) and SPWMD (RVAP: 127 ± 33 ms; LVP: 58 ± 17 ms, p < 0.0001) were altered in patients with receiving RVAP but not LVP. In addition, RVAP was associated with global LV dyssynchrony, as evidenced by a prolonged LV mechanical delay (69 ± 6 ms) compared with LVP (30 ± 11 ms).

Five patients developed dilated cardiomyopathy (6.3%). The clinical and echocardiographic data of these patients are shown in Table 5. Three variables were identified as significant predictors of LV dysfunction: RVAP [odds ratio (OR) = 11.3, p < 0.001], septal to lateral wall mechanical delay (OR = 12.1, p < 0.001), and septal to posterior wall motion delay (OR = 11.6, p < 0.001). However, in those patients receiving RVAP, there was no correlation between either EF and SPWMD (R^2 = 0.283, p = 0.077) or EF and septal to lateral mechanical delay (R^2 = −0.013, p = 0.935) (Figure 1). No correlations were found between late LV failure diagnosis, pacing mode, duration of stimulation, presence of structural heart disease or other echocardiographic indices of dyssynchrony.

Discussion

The main finding of our study is that RV apical pacing in pediatric patients with or without structural heart disease produces LV remodeling and dyssynchrony. Moreover, the research confirms that LVP is a safe site of stimulation when seeking to prevent the dyssynchronous effect of chronic cardiac pacing.

Table 2 – Evolution of left ventricular systolic function

Parameter	RVA pacing		LV pacing		p value *	p value **	p value ***	p value ****
	Before PM implant	Last follow-up	Before PM implant	Last follow-up				
LVEDD (mm)	32(3.1)	40(6.0)	33(3.6)	35(4.2)	<0.001	0.024	0.187	<0.001
LV SF (%)	41(2.6)	32(4.2)	40(4.3)	39(5.2)	<0.001	0.351	0.211	<0.001
LV EF (%)	70(6.9)	64(2.5)	70(6.8)	69(3.6)	<0.001	0.413	1.000	<0.001

*Data are presented as the mean ± SD. EF: ejection fraction; LV: left ventricular; LVEDD: left ventricular end-diastolic diameter; PM: pacemaker; RVA: right ventricular apex; SF: shortening fraction. * RVA pacing before vs. last follow-up. ** LV pacing before vs. last follow-up. *** RVA pacing before vs. LV pacing before. **** RVA pacing last follow-up vs. LV pacing last follow-up.*

Table 3 - Left ventricular diastolic function at last follow-up

Parameter	RVAP	LVP	p
LV IVRT (ms)	63(10.5)	65(8.7)	0.356
Ea (cm/s)	19(2.4)	18(3.6)	0.147
Aa (cm/s)	9(2.3)	10(3.1)	0.105
E/Ea	5.1(2.2)	5.3(1.5)	0.636

Data are presented as the mean ± SD. Aa: peak A wave by Doppler tissue imaging; Ea: peak E wave by Doppler tissue imaging; E/Ea: relation between peak E wave by transmitral Doppler flow and peak E by Doppler tissue imaging; LV IVRT: left ventricular isovolumic relaxation time; LVP: left ventricular pacing; RVAP: right ventricular apical pacing.

Table 4 – Echocardiographic measurements of LV synchrony for the study cohort

Parameter	RVAP	LVP	p
SPWMD (ms)	127(33)	58(17)	<0.001
Septal to lateral wall motion delay (ms)	75(19)	42(10)	<0.001
Interventricular mechanical delay (ms)	66(13)	20(8)	<0.001
LV mechanical delay (ms)	69(6)	30(11)	<0.001

Data are presented as the mean ± SD. LV: left ventricular; LVP: left ventricular pacing; SPWMD: septal to posterior wall motion delay; RVAP: right ventricular apical pacing.

Table 5 – Patients with dilated cardiomyopathy related to ventricular pacing

No.	Age (years)	Diagnosis	Structural heart disease	Pacing period (years)	Pacing site	Pacing mode	LVEDD (mm)	LV EF (%)	LV SF (%)
1.	10	CAVB	-	3.6	RV apex	DDD	53	44.0	22.0
2.	8	Surgical CAVB	VSD	6.2	RV apex	VVI	48	48.7	24.5
3.	12	Surgical CAVB	TOF	9.5	RV apex	DDD	50	48.2	24.3
4.	6	CAVB	-	2.8	RV apex	VVI	44	52.0	26.5
5.	15	BAVT	-	4,6	RV apex	VDD	54	42.3	21.0

CAVB: complete atrioventricular block; DDD: dual chamber pacing and sensing; EF: ejection fraction; LV: left ventricle; LVEDD: left ventricular end-diastolic diameter; RV: right ventricle; SF: shortening fraction; TOF: tetralogy of Fallot; VDD: ventricular pacing with dual chamber sensing; VSD: ventricular septal defect; VVI: ventricular pacing and sensing.

Evolution of LV systolic and diastolic function in RV apical pacing:

Endomyocardial biopsies taken from the mid-RV septal region in paced patients have detected histopathological abnormalities. These consist of prominent subendocardial Purkinje cells with an increase in variable-sized, focal areas of dystrophic calcification and myofibrillar disarray[13]. These findings are the result of stress vectors and myocardial shearing forces resulting from asynchrony of electrical ventricular activation, with early activation of myocytes close to RVA, and delayed activation of cells in remote regions[1]. This heterogeneity in electrical activation of the myocardium is accompanied with changes in the mechanical activation pattern of LV[14]. An animal study has demonstrated the presence of rapid early-systolic shortening in early-activated regions, with premature relaxation of these sites, and prestretching of late-activated regions[15]. Because of the low LV pressure, contraction of the early-activated myocardium is inefficient. Furthermore, against high LV pressures, a vigorous late-systolic contraction occurs in regions with delay. This imposes loading on the earlier activated territories, which undergo paradoxical systolic stretch[16]. The abnormal contraction pattern of different regions of LV, results in a redistribution of myocardial strain, and less effective contraction[15]. Decreases in contractility and relaxation together with histological abnormalities lead to the detriment of left ventricular function.

Clinical data about the deleterious effect of chronic RVP in children remain controversial, with some researches supporting a negative impact[13,17,18], whereas others have obtained conflicting results[19, 20]. The present study found a significant deleterious effect of RV apical pacing on systolic LV function, with an incidence of 6.3% in patients with dilated cardiomyophathy, which is concordant with previous

data (6.0%–13.4%)[2,5-8]. RV apical pacing was a predictive factor for the deterioration of LV function [OR = 11.3, 95% confidence interval (CI) = 2.1–63.8, p < 0.001]. Gebauer et al[5] evaluated LV function in 82 pediatric patients with either nonsurgical or postsurgical CAVB. In their research, the only significant risk factor for the development of LV dilatation and dysfunction was the presence of epicardial RV free wall pacing (OR = 14.3, 95% CI = 2.3–78.2, p < 0.001). Therefore, although epicardial RV free wall stimulation may induce more LV dyssynchrony, our findings suggest that RVAP results in the same degree of asynchronous activation, abnormal contraction and decreased pump function.

The impact of RV apical stimulation on LV diastolic function has not been extensively explored, even in pediatric populations. Previous research in animal models have demonstrated the deterioration of diastolic parameters[21,22]. Litwin et al[21] for example found a significant alteration of the diastolic filling parameters on radionuclide left ventriculography, such as time to peak filling rate and negative rate of LV pressure rise in ventricular paced dogs[21]. Similarly, Aoyagi et al[22], found a prolongation of the LV isovolumic relaxation time (IVRT) that was dependent on the degree of wall motion asynchrony[22]. Although our data showed a detrimental effect on synchrony in the RVP group, the LV IVRT did not change during follow-up. In addition, Kolettis et al[23] studied the acute hemodynamic status of 20 adult patients with dual-chamber sequential pacing, determining increased IVRT to be a measure of LV diastolic function deterioration[23]. Similarly, on the basis of the hypothesis that RV impairment precedes LV dysfunction, Dwevedi et al[24] found a significant increase in IVRT and deceleration time following 1 month of single-chamber RVP, which continued to increase progressively until 6 months[24]. They confirm that LV diastolic and systolic functions are

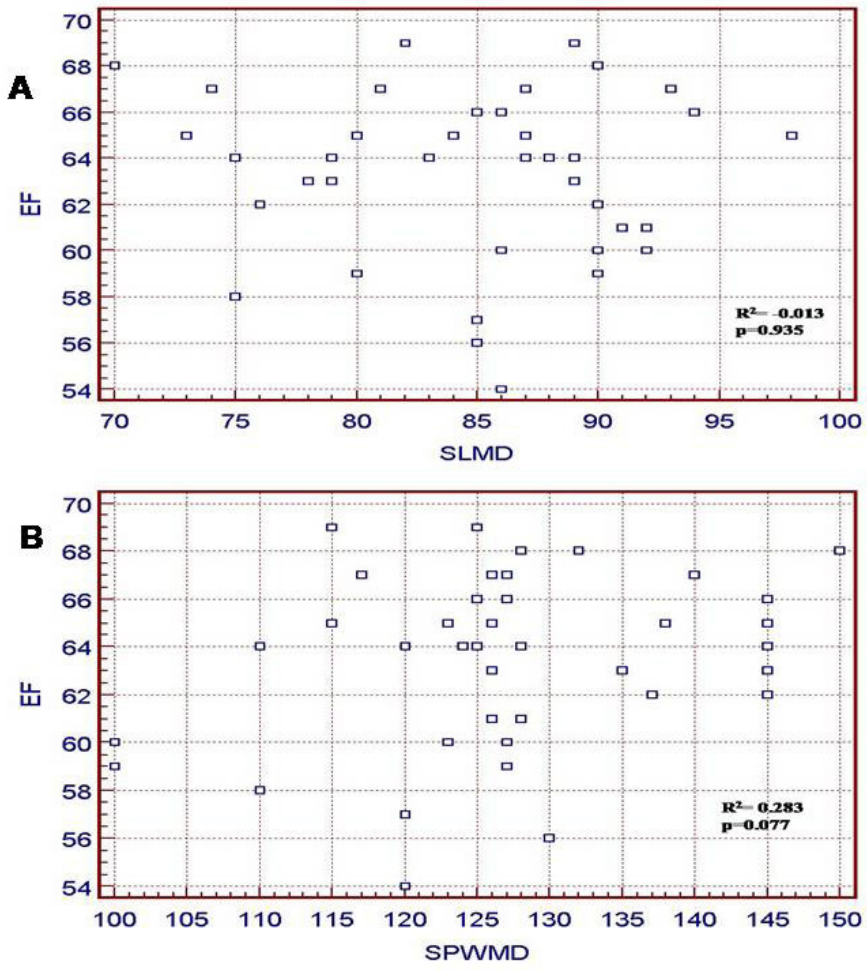

Figure 1 - *Correlation between EF and electromechanical delay variables in patient with RVA pacing. A) EF and SLMD. B) EF and SP. EF: ejection fraction, SLMD: septal to lateral mechanical delay, SPWMD: septal to posterior wall motion delay.*

deranged in many conditions secondary to involvement of the right ventricle[24]. However, in our study, 57.5% patients presenting with congenital cardiovascular defects such as atrial septal defect, pulmonary stenosis, tetralogy of Fallot or double-outlet right ventricle, which are conditions that improve RV function, diastolic dysfunction was absent and so was a correlation between the presence of structural heart disease and late LV failure. The contradiction with the findings of Dwevedi et al[24] could possibly be explained because 47.5% of the study population had a corrected congenital cardiac defect, and that we excluded patients with clinical evidence of ventricular dysfunction. Results and conclusions from pacing studies in adult patients cannot be extrapolated to the pediatric population because of differences in comorbid diseases and potential causes of ventricular dyssynchrony.

Left ventricular dyssynchrony: LVP vs. RVP

We postulate that the sequence of activation is a major determinant of cardiac pump function, as previous researches have shown[25,26]. Stimulation from the LV free wall induces a prior activation of the LV lateral wall, preventing paradoxical movement of the septum, and resulting in a better hemodynamic response when compared with RV pacing[27]. Moreover, a physiological apex-to-base sequence is induced, producing a synchronous electrical activation and contraction at the LV circumferential level[28].

It has been confirmed in studies in both animals and children that LV pumping function approximating to that of normal ventricular conduction results from pacing at the inferoapical LV septum and the epicardium of LV apex[28-30]. The resultant synchronous contraction is predominantly because of quick engagement of the impulse into the LV endocardial layers, and subsequent fast apex-to-base conduction along all wall segments of LV[30]. Mills et al[30], in their research in dogs with experimental complete AV block, demonstrated that LV apical pacing can produce a moderate electrical dyssynchrony with normal levels of myocardial efficiency, contractility and relaxation after 4 months of LVP[30].

In our study, indices of dyssynchrony such as septal-to-lateral wall motion delay and SPWMD were identified as predictors of LV dysfunction. This finding demonstrated, once again, the consequences of impairment of normal ventricular activation. Apical RVP produces early activation of the RV wall, followed by that of the LV septum and then the LV lateral wall[30]. Early activation of the basal septum induces segmental contraction that is unopposed by the delayed activation of the remaining LV myocardium, which leads to systolic septal bulging[9]. Long activation times around the LV circumference (29–49 ms) during RV apical pacing, produces abnormal distribution of mechanical work and blood flow, mechanical dyssynchrony, and incoordination of contraction; there is then a consequential negative impact on contractility, relaxation, and external efficiency[30].

Research by van Geldorp et al[10], compared the ventricular function and synchrony in 18 healthy children and patients with chronic RVP and LVP. In this study, the RVP group also showed a decreased LV SF. Similarly, the systolic LV eccentricity index, and the duration of posterior septal wall motion delay were significantly longer in this group than in the LVP or control groups[10]. In addition, Gebauer et al[31] evaluated LV synchrony and function in 32 patients paced epicardially from the RV free wall, the LV apex and the RVA; RV free wall pacing and SPWMD were found to be negative predictors of LVEF[31]. Of note, Tomaske et al[9] showed that a decreased LV EF and greater LV dyssynchrony was associated with children receiving RV pacing[9]. In addition, a significant correlation was established between decreased LVEF and the severity of mechanical dyssynchrony measured by the septal-to-lateral wall delay and LV mechanical delay[9].

Clinical implications

Our data confirm the benefit of chronic LV pacing on LV synchrony and function. The results of our study support the view that epicardial LVP is the optimal pacing site in pediatric populations; observations in small cohorts support the use of an LV pacing site when chronic pacing is indicated in children[9,10,31]. It has also been demonstrated that LV lateral wall pacing can be as effective as biventricular pacing in patients with congestive heart failure[32,33]. For example, Vanagt et al. reported the case of a 2-year-old girl with congenital CAVB and heart failure induced by RVP, who recovered LV function following LV apical pacing[34]. Furthermore, in children with LV dysfunction and dyssynchrony caused by long-term RVP, small case series have shown improvements in function 1 month after single-site LVP[11].

Alternative sites for pacing have also been investigated[35-40]. His-bundle pacing induces a normal physiological sequence of activation, and therefore prevents dyssynchrony and the deleterious effects on LV function[35,36]; however the anatomical characteristics of this region make this a challenging procedure that could be difficult in a pediatric population. Alternatively, the RV outflow has been proposed[37,38], although the results are controversial[39,40], and do not support stimulation from this site in children. In our institution, we advocate the implantation of LV epicardial leads via a left lateral thoracotomy, resulting in stable thresholds as well as good cosmetic results.

Study limitations

Because of a lack of diastolic evaluation prior the first implantation, we could not compare the DTI measurement before and after permanent pacing; nevertheless, the results at the last follow-up showed a preserved diastolic function using the DTI echocardiographic method.

Conclusions

Chronic RVP was associated with LV remodeling, dyssynchrony, and systolic dysfunction in our pediatric population. This is consistent with previous findings. Because of the benefits of chronic LV pacing, we believe that it should be proposed as the optimal site when permanent cardiac stimulation is required in children.

Author contributions

Conception and design of the research: Ortega MC, Ricardo GS; Acquisition of data, Analysis and interpretation of the data, Statistical analysis and Critical revision of the manuscript for intellectual content: Ortega MC, Morejón AEG, Ricardo GS; Writing of the manuscript: Ortega MC.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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References

1. van Geldorp IE, Vanagt WY, Prinzen FW, Delhass T. Chronic ventricular pacing in children: toward prevention of pacing-induced heart disease. Heart Fail Rev. 2011;16(3):305-14.
2. Moak JP, Barron KS, Hougen TJ, Wiles HB, Balaji S, Sreeram N, et al. Congenital heart block: development of late-onset cardiomyopathy, a previously underappreciated sequela. J Am Coll Cardiol. 2001;37(1):238-42.
3. Tantengco MV, Thomas RL, Karpawich PP. Left ventricular dysfunction after long-term right ventricular apical pacing in the young. J Am Coll Cardiol. 2001;37(8):2093-100.
4. Karpawich PP, Mital S. Comparative left ventricular function following atrial, septal, and apical single chamber heart pacing in the young. Pacing Clin Electrophysiol. 1997;20(8 Pt 1):1983-8.
5. Gebauer RA, Tomek V, Salameh A, Marek J, Chaloupecký V, Gebauer R, et al. Predictors of left ventricular remodeling and failure in right ventricular pacing in the young. Eur Heart J. 2009;30(9):1097-104.
6. Kim JJ, Friedman RA, Eidem BW, Cannon BC, Arora G, Smith O, et al. Ventricular function and long-term pacing in children with congenital complete atrioventricular block. J Cardiovasc Electrophysiol. 2007;18(4):373-7.
7. Vatasescu R, Shalganov T, Paprika D, Kornyei L, Prodan Z, Bodor G, et al. Evolution of left ventricular function in pediatric patients with permanent right ventricular pacing for isolated congenital heart block: a medium term follow-up. Europace. 2007;9(4):228-32.
8. Chiesa P, Cuesta A, Dutra S, Matto S, Morales J, Giudice J, et al. Miocardiopatía dilatada en la edad pediátrica por marcapasos con estimulación en el ápex del ventrículo derecho. Arch Pediatr Urug. 2008;79(2):125-38.
9. Tomaske M, Breithardt OA, Bauersfeld U. Preserved cardiac synchrony and function with single-site left ventricular epicardial pacing during mid-term follow-up in paediatric patients. Europace. 2009;11(9):1168-76.
10. van Geldorp IE, Vanagt WY, Bauersfeld U, Tomaske M, Prinzen FW, Delhaas T. Chronic left ventricular pacing preserves left ventricular function in children. Pediatr Cardiol. 2009;30(2):125-32.
11. Tomaske M, Breithardt OA, Balmer C, Bauersfeld U. Successful cardiac resynchronization with single-site left ventricular pacing in children. Int J Cardiol. 2009;136(2):136-43.
12. Lai WW, Geva T, Shirali GS, Frommelt PC, Humes RA, Brook MM, et al; Task Force of the Pediatric Council of the American Society of Echocardiography; Pediatric Council of the American Society of Echocardiography. Guidelines and standards for performance of pediatric echocardiogram: a report from the task force of the pediatric council of the American Society of Echocardiography. J Am Soc Echocardiogr. 2006;19(12):1413-30.
13. Karpawich PP, Rabah R, Hass E. Altered cardiac histologic following apical right ventricular pacing in patients with congenital atrioventricular block. Pacing Clin Electrophysiol. 1999;22(9):1372-7.
14. Tops LF, Schalij MJ, Bax JJ. The effect of right ventricular apical pacing on ventricular function and dyssynchrony implications for therapy. J Am Coll Cardiol. 2009;54(9):764-76.
15. Badke FR, Boinay P, Covell JW. Effects of ventricular pacing on regional left ventricular performance in the dog. Am J Physiol. 1980;238(6):H858-67.
16. Prinzen FW, Hunter WC, Wyman BT, McVeigh E. Mapping of regional myocardial strain and work during ventricular pacing: experimental study using magnetic resonance imaging tagging. J Am Coll Cardiol. 1999;33(6):1735-42.
17. Tantengco MV, Thomas RL, Karpawich PP. Left ventricular dysfunction after long-term right ventricular apical pacing in the young. J Am Coll Cardiol. 2001;37(8):2093-100.
18. Thambo JB, Bordachar P, Garrigue S, Laffite S, Sanders P, Reuter S, et al. Detrimental ventricular remodeling in patients with congenital heart block and chronic right ventricular apical pacing. Circulation. 2004;110(25):3766-72.
19. Sagar S, Jahangir A, Friedman PA. Long-term right ventricular apex pacing in patients with congenital AV block does not have a detrimental effect on ventricular function. Circulation. 2004;110(3):345-6.
20. Shalganov TN, Paprika D, Vatasescu R, Kardoss A, Mihalcz A, Kornyei L, et al. Mid-term echocardiographic follow up of left ventricular pacing in pediatrics patients with and without structural heart disease. Cardiovasc Ultrasound. 2007;5:13.
21. Litwin SE, Gorman G, Huang SK. Effect of different pacing modes on left ventricular relaxation in closed chested dogs. Pacing Clin Electrophysiol. 1989;12(7 Pt 1):1070-6.
22. Aoyagi T, Iizuka M, Takahashi T, Ohya T, Serizawa T, Momomura S, et al. Wall motion asynchrony prolongs time constant of left ventricular relaxation. Am J Physiol. 1989;257(3 Pt 2):H883-90.
23. Kolettis TM, Kyriakides ZS, Tsiapras D, Popov T, Paraskevaides IA, Kremastinos DT. Improved left ventricular relaxation during short-term right ventricular outflow tract compared to apical pacing. Chest. 2000;117(1):60-4.
24. Dwivedi SK, Bansal S, Puri A, Makharia MK, Narain VS, Saran RK, et al. Diastolic and systolic right ventricular dysfunction precedes left ventricular dysfunction in patients paced from right ventricular apex. Indian Pacing Electrophysiol J. 2006;6(3):142-52.
25. Rinzen FW, Peschar M. Relation between the pacing induced sequence of activation and left ventricular pump function in animals. Pacing Clin Electrophysiol. 2002;25(4 Pt 1):484-98.
26. Puggioni E, Brignole M, Gammage M, Soldati E, Bongiorni MG, Simantirakis EN, et al. Acute comparative effect of right and left ventricular pacing in patients with permanent atrial fibrillation. J Am Coll Cardiol. 2004;43(2):234-8.
27. Little WC, Reeves RC, Arciniegas J, Katholi RE, Rogers EW. Mechanism of abnormal interventricular septal motion during delayed left ventricular activation. Circulation. 1982;65(7):1486-91.

28. Peschar M, de Swart H, Michels KJ, Reneman RS, Prinzen FW. Left ventricular septal and apex pacing for optimal pump function in canine hearts. J Am Coll Cardiol. 2003;41(7):1218-26.

29. Vanagt WY, Verbeek XA, Delhaas T, Mertens L, Daenen WJ, Prinzen FW. The left ventricular apex is the optimal site for pediatric pacing: correlation with animal experience. Pacing Clin Electrophysiol. 2004;27(6 Pt 2):837-43.

30. Mills RW, Cornelussen RN, Mulligan LJ, Strik M, Rademakers LM, Skadsberg ND, et al. Left ventricular septal and left ventricular apical pacing chronically maintain cardiac contractile coordination, pump function and efficiency. Circ Arrhythm Electrophysiol. 2009;2(5):571-9.

31. Gebauer RA, Tomek V, Kubus P, Razek V, Matejka T, Salameh A, et al. Differential effects on the site of permanent epicardial pacing on the left ventricular synchrony and function in the young: implications for lead placement. Europace. 2009;11(12):1654-9.

32. Blanc JJ, Bertault-Valls V, Fatemi M, Gilard M, Pennec PY, Etienne Y. Midterm benefits of left univentricular pacing in patients with congestive heart failure. Circulation. 2004;109(12):1741-4.

33. Touiza A, Etienne Y, Gilard M, Fatemi M, Mansourati J, Blanc JJ. Long-term left ventricular pacing: assessment and comparison with biventricular pacing in patients with severe congestive heart failure. J Am Coll Cardiol. 2001;38(7):1966-70.

34. Vanagt WY, Prinzen FW, Delhaas T. Reversal of pacing induced heart failure by left ventricular apical pacing. N Engl J Med. 2007;357(25):2637-8.

35. Deshmukh P, Casavant DA, Romanyshyn M, Anderson K. Permanent, direct His-bundle pacing: A novel approach to cardiac pacing in patients with normal His-Purkinje activation. Circulation. 2000;101(8):869-77.

36. Zanon F, Baracca E, Aggio S, Pastore G, Boaretto G, Cardano P, et al. A feasible approach for direct his-bundle pacing using a new steerable catheter to facilitate precise lead placement. J Cardiovasc Electrophysiol. 2006;17(1):29-33.

37. Hillock RJ, Stevenson IH, Mond HG. The right ventricular outflow tract: a comparative study of septal, anterior wall, and free wall pacing. Pacing Clin Electrophysiol. 2007;30(8):942-7.

38. Mond HG, Hillock RJ, Stevenson IH, McGavigan AD. The right ventricular outflow tract: the road to septal pacing. Pacing Clin Electrophysiol. 2007;30(4):482-91.

39. Kipta A, Steinwender C, Kammler J, Leisch F, Hofmann R. Long-term outcomes in patients with atrioventricular block undergoing septal ventricular lead implantation compared with standard apical pacing. Europace. 2008;10(5):574-9.

40. de Cock CC, Meyer A, Kamp O, Visser CA. Hemodynamic benefits of right ventricular outflow tract pacing: comparison with right ventricular apex pacing. Pacing Clin Electrophysiol. 1998;21(3):536-41.