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ORIGINAL ARTICLE

Chronic Left Ventricular Pacing Preserves Left Ventricular Function in Children

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Abstract Chronic right ventricular (RV) pacing can induce structural and functional cardiac deterioration. Because animal studies showed a benefit of left ventricular (LV) over RV pacing, this study compared the effects of chronic RV and LV pacing in children. Retrospectively, echocardiographic data were evaluated from 18 healthy children (control subjects) and from children undergoing chronic epicardial RV pacing (7 RVP) or LV pacing (7 LVP). Assessment included LV end-diastolic wall thickness (LVEDWT) and end-systolic wall thickness (LVESWT) as well as LV end-diastolic diameter (LVEDD) and end-systolic diameter (LVESD). The shortening fraction and eccentricity index (LV diameter/2 × LV wall thickness) were calculated as measures of LV function and eccentricity, respectively. Duration of QRS and septal posterior wall motion delay (SPWMD) were used as measures of electrical and mechanical dyssynchrony, respectively. A p value less than 0.05 determined significance. As the findings showed, LVEDD, LVESD, LVEDWT, and LVESWT were not significantly different between the groups. The shortening fraction was significantly lower in the RVP (21.7% ± 6.0%) than in the LVP (32.2% ± 5.2%) or control (29.3% ± 4.3%) children. The systolic LV eccentricity index was significantly larger in the RVP (1.8 ± 0.2) than in the LVP (1.4 ± 0.1) or control (1.4 ± 0.2) children. The SPWMD was significantly larger in the RVP (338 ± 20 ms) than in the LVP (−16 ± 14 ms) or control (−5 ± 35 ms) group, whereas QRS duration was similarly longer in the RVP (157 ± 10 ms) and LVP (158 ± 22 ms) groups compared than in the control group (69 ± 7 ms). The authors conclude that LV function in children is preserved by chronic pacing at the LV lateral wall.

Keywords Cardiac function · Children · Dyssynchrony · Pacing · Site · Ventricular

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In children and adults with congenital or acquired atrioventricular (AV) block, the ventricular pacing lead is traditionally positioned at the right ventricle (RV) [16, 19]. However, RV apex pacing causes an acute decrease in left ventricular (LV) function in animals [26], adults [6] and children [14, 36]. During chronic RV pacing in children, LV function, morphology [30, 31], and histology [15] are at risk for deterioration over time (for review see Karpawich [16]). Chronic RV pacing can eventually result in cardiac failure, which occurs in 6% to 7% of children [17, 20, 38]. Also, in adults, chronic RV apex pacing has deleterious effects (for review see Manolis [19]) and increases the risk of heart failure [1, 28].

Recognition of the possible harmful effects from RV apex pacing initiated the search for alternative ventricular pacing sites including the RV outflow tract, His bundle, LV wall, and biventricular pacing. Pacing at the His bundle is likely the superior approach [8], but appears to be

technically difficult, especially in children. Right ventricle outflow tract pacing does not provide a consistent beneficial hemodynamic effect compared with RV apex pacing [6]. During pacing at different RV septal sites, hemodynamic function varies widely, and the location of the RV septal site that leads to the less pronounced decrease in pump function also varies between hearts in canine experiments [22].

In adults with heart failure, both LV lateral wall pacing [3, 27] and biventricular (RV apex + LV lateral wall) pacing [3] acutely result in a better functional outcome than RV apex pacing. Also in adults, LV pacing alone seems to be as effective as biventricular resynchronization therapy, both in the acute situation [21] and after 6 months of pacing [33].

The current study aimed to investigate the long-term functional and structural outcome of epicardial RV and LV pacing in children. The study was performed retrospectively using echocardiographic and electrocardiographic (ECG) data from children undergoing chronic RV or LV pacing and from healthy children (control subjects).

Methods

Study Population and Pacing Characteristics

All children with normal cardiac anatomy and a ventricular pacemaker in the database of the Children's University Hospital in Zurich (Switzerland) were considered for inclusion in this study. The study included all children with congenital or acquired AV block (except for cardiomyopathy) undergoing chronic epicardial RV or LV pacing for rate control (minimum of 95% paced beats) for whom echocardiographic and ECG data were available.

Data were acquired during the most recent outpatient clinic visit of children with chronic RV pacing (RVP, $n = 7$) or LV pacing (LVP, $n = 7$) and evaluated retrospectively. For the children who underwent a pacing lead replacement, the last echocardiography and the ECG data before the replacement were evaluated to exclude the effects of changes in the pacing site between the initiation of pacing and the moment the data were obtained. In addition, for a small number of patients (3 RVP and 4 LVP), the echocardiographic preimplantation data were of sufficient quality for assessment and are presented to provide an estimation of the baseline characteristics.

Bipolar steroid-eluting pacing leads (Medtronic CapSure Epi 10366 or 4968; Medtronic Inc., Minneapolis, MN, USA) were implanted in all children and connected to various pulse generators. Pacemaker lead positioning was purely determined by the surgical approach preferred by surgeons [9]. Through a sternotomy or using a subxyphoidal approach, RV pacing leads were implanted and positioned at the RV apex ($n = 6$) or RV free wall ($n = 1$). Left ventricular pacing leads were implanted through a left lateral thoracotomy and placed at the LV mid lateral wall [9].

Table 1 depicts the characteristics of the paced children. Before pacemaker implantation and during the follow-up period, none of the patients had clinical symptoms of heart failure, received any cardiovascular drugs, or had echocardiographic signs of cardiac failure. The control group consisted of 18 healthy children who visited the outpatient clinic for an innocent cardiac murmur. This retrospective study was approved by the local ethics committee and performed according to their guidelines.

Echocardiographic Evaluation

Echocardiographic data were obtained in the standard precordial positions with appropriate transducers (7.5-, 5.0-, 3.5-, and 2.5-MHz; Vivid 7; General Electric Healthcare, UK; or Philips Sonos 5500; Philips, Best, The Netherlands). Data were stored either digitally or on VHS videotapes, then subsequently digitized offline. End-diastolic and end-systolic frames of the parasternal short-axis views were further analyzed using Matlab software (The Mathworks Inc., Natick, MA, USA).

Two observers, blinded to the study group of the patient, each performed three independent measurements in random order for every patient. The average of the measurements performed by the two observers was used for further analysis. A representative example of a processed echocardiographic image is depicted in Fig. 1.

Body surface area was calculated using the formula of Du Bois and Du Bois [10]:

$$\text{Body surface area } (\text{m}^2) = 0.20247 \times \text{length}\,(\text{m})^{0.725} \times \text{weight}\,(\text{kg})^{0.425}.$$

Left ventricular end-diastolic diameter (LVEDD) and LV end-systolic diameter (LVESD) were measured bidirectionally (Fig. 1) and averaged to minimize over- or underestimation in case of an asymmetric mechanical activation pattern. To estimate the degree of LV dilation and to compare patients of different ages and weights, LVEDD was expressed as a z-score of normal [5].

Shortening fraction (SF) as a measure of cardiac function was defined as:

$$\text{SF}(\%) = (\text{LVEDD} - \text{LVESD}) / \text{LVEDD} \times 100.$$

Regional changes in LV wall thickness were assessed by measuring the LV wall in six consecutive regions at

Table 1 Patient and pacemaker characteristics[a]

Patient	Sex (M/F)	Pacing indication	Prepacing SPWMD (ms)	Prepacing shortening fraction (%)	Pacing mode	Pacing duration (years)	Age at end of study (years)
RVP-1	F	C-AVB III			DDD	6.9	8.7
RVP-2	M	C-AVB III	70	28	DDD	2.2	9.4
RVP-3	F	C-AVB III (Mat. SLE)			VVI	6.3	6.3
RVP-4	F	A-AVB II	65	38	DDD	2.5	4.3
RVP-5	F	C-AVB III			DDD	2.3	4.4
RVP-6	F	C-AVB II	10	40	DDD	2.5	8.4
RVP-7	F	C-AVB III (Mat. SLE)			VVI	4.9	4.9
LVP-1	M	C-AVB III			VVI	5.5	6.8
LVP-2	F	A-AVB III	−5	40	DDD	1.5	11.1
LVP-3	F	C-AVB II, long QT			DDD	4.8	4.4
LVP-4	M	A-AVB II, SSS	45	35	DDD	3.3	7.4
LVP-5	M	C-AVB III	20	39	DDD	2.5	3.7
LVP-6	F	C-AVB III	35	33	DDD	6.3	10.6
LVP-7	M	C-AVB III (Mat. SLE)			VVI	2.8	2.8

SPWMD, septal-to-posterior wall motion delay; RVP, right ventricular pacing group; III, third degree; C-AVB, congenital atrioventricular (AV) block; DDD, atrial and ventricular sensing and pacing; Mat. SLE, maternal systemic lupus erythematosus; VVI, ventricular sensing and pacing; A-AVB, acquired AV block; II, second degree; LVP, left ventricular pacing group; SSS, sick sinus syndrome

[a] Available shortening fraction and SPWMD data before pacemaker implantation are presented

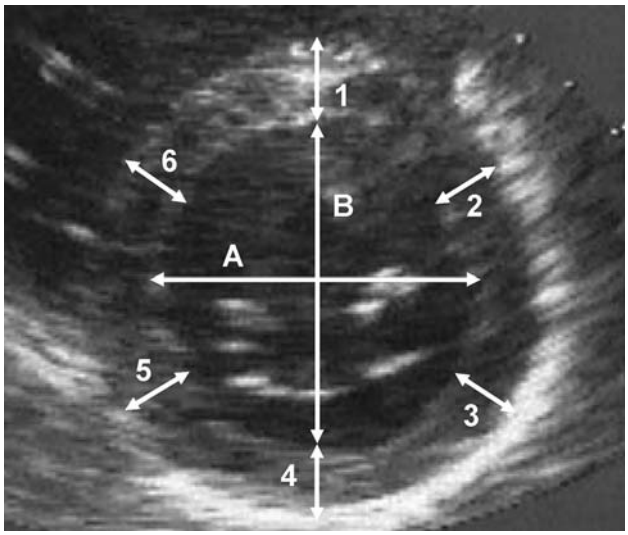

Fig. 1 Representative echocardiographic short-axis view. Six regions are indicated for wall thickness determination (*arrows*) and the inner diameter of the left ventricle (LV). The LV diameter was determined bidirectionally as the mean of diameters A and B

end-diastole and end-systole on short-axis views (Fig. 1). The mean of these six regions was used as the mean LV end-diastolic wall thickness (LVEDWT) and the mean LV end-systolic wall thickness (LVESWT). Again, LVEDWT was expressed as a *z*-score of normal.

The eccentricity index of the LV (as a measure of fiber stress) was calculated as follows:

$$\text{LV eccentricity index} = \text{LV diameter} / (2 \times \text{mean LV wall thickness}).$$

Septal posterior wall motion delay (SPWMD), as a measure of intraventricular mechanical synchrony, was obtained from short-axis M-mode echocardiographic images and defined as the time delay between the earliest peak of systolic inward movement of the septum and the opposite LV posterior wall [23, 24, 41].

Electrocardiographic Evaluation

Duration of QRS was assessed from the surface ECG during sinus rhythm (control group), RV pacing (RVP group), and LV pacing (LVP group) and used as a measure for synchrony of electrical ventricular activation.

Statistical Analysis

Statistical analysis was performed using one-way analysis of variance (ANOVA) on every parameter. Only if ANOVA showed a significant difference was further analysis with Tukey comparison used to identify statistical differences between the different study groups. A p value less than 0.05 determined statistical significance. Data are presented as mean ± standard deviation. For echocardiographic measures, the interobserver correlation (r value) was assessed using Pearson product-moment correlation.

Results

Study Population

The characteristics of the RVP and LVP groups are presented in Table 1. Unless specified, the etiology of the AV block was not identified. Age and body surface area were not significantly different between the groups (RVP group: 6.6 ± 2.2 years and 0.9 ± 0.2 m^2, respectively; LVP group: 6.7 ± 3.3 years and 0.9 ± 0.3 m^2; control group: 4.8 ± 3.7 years and 0.7 ± 0.3 m^2). The duration of ventricular pacing was not significantly different between the two paced groups (RVP: 3.9 ± 2.1 years vs LVP: 3.8 ± 1.8 years).

Due to the paucity of preimplantation echocardiographic data, no statistical analysis was performed on these data. It seems likely from available preimplantation echocardiograms (3 RVP and 4 LVP) that mechanical asynchrony during AV nodal escape rhythm was irrelevant because SPWMD was 48 ± 33 ms in the RVP group and 23 ± 22 ms in the LVP group. Furthermore, available data suggest no preimplantation difference in shortening fraction between the two groups (RVP: 35.4% ± 6.2% vs LVP: 36.5% ± 3.3%).

Structural Echocardiographic Outcome

Interobserver reproducibility was good for LVEDD ($r = 0.96$), LVESD ($r = 0.95$), mean LVEDWT ($r = 0.90$), and mean LVESWT ($r = 0.94$). Among the three study groups, LVEDD, LVESD, mean LVEDWT, and mean LVESWT did not differ significantly (Table 2). No significant differences in LV wall thickness between different regions of the heart were observed in any of the study groups (data not shown).

Table 2 Echocardiographic structural results[a]

	RV pacing group	LV pacing group	Control group
LVEDD (mm)	39.5 ± 6.8	39.4 ± 6.1	34.2 ± 6.8
z-score	0.6 ± 0.9	0.4 ± 0.7	0.0 ± 0.9
LVESD (mm)	31.0 ± 6.9	26.7 ± 4.3	24.2 ± 5.2
LVEDWT (mm)	7.4 ± 2.1	7.4 ± 1.3	6.3 ± 1.2
z-score	1.5 ± 1.4	1.3 ± 0.9	0.8 ± 0.5
LVESWT (mm)	8.7 ± 1.9	9.2 ± 1.3	8.2 ± 1.4

RV, right ventricular; LV, left ventricular; LVEDD, LV end-diastolic diameter; LVESD, LV end-systolic diameter; LVEDWT, mean LV end-diastolic wall thickness; LVESWT, mean LV end-systolic wall thickness

[a] There are no significant differences between groups

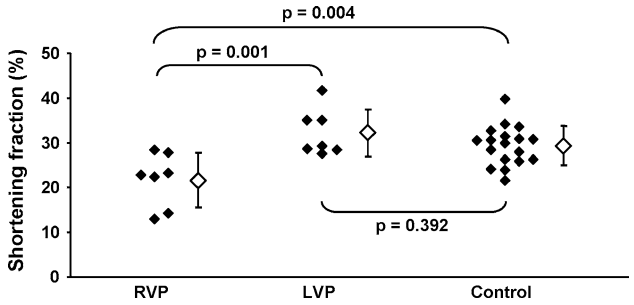

Fig. 2 Shortening fraction in the study groups. Closed symbols represent individual data. Open symbols represent group average ± standard deviation. LVP, left ventricular pacing group; RVP, right ventricular pacing group

Functional Echocardiographic Outcome

After chronic epicardial pacing, the shortening fraction was significantly lower in the RVP group (21.7% ± 6.0%) than in the LVP group (32.2 ± 5.2%) or the control group (29.3% ± 4.3%, nonsignificant difference between the control and LVP groups, Fig. 2). The end-systolic LV eccentricity index was significantly higher in the RVP group (1.8 ± 0.2) than in the LVP (1.4 ± 0.1) or control (1.4 ± 0.2) group (nonsignificant difference between the LVP and control groups, Fig. 3).

At end-diastole, the LV eccentricity index was not significantly different between the study groups (RVP: 2.7 ± 0.3; LVP: 2.7 ± 0.6; control: 2.7 ± 0.4). The SPWMD was similar in the control (−5 ± 35 ms) and LVP (−16 ± 14 ms) groups, with good interobserver reproducibility ($r = 0.97$). As compared with the control and LVP groups, the SPWMD in the RVP group (338 ± 20 ms) was significantly different ($p < 0.001$).

QRS Duration

The duration of QRS was 69 ± 7 ms in the control group, and significantly longer ($p < 0.001$) in both paced groups

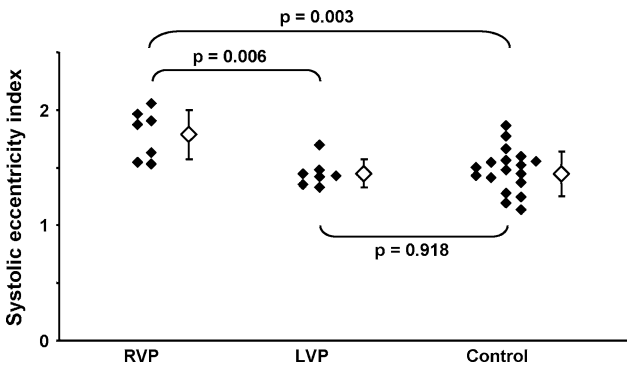

Fig. 3 End-systolic left ventricular eccentricity index in the study groups. For legends see Fig. 2

(RVP: 157 ± 10 ms vs LVP: 158 ± 22 ms; nonsignificant difference between RVP and LVP).

Discussion

To our knowledge, this is the first study to compare the long-term effects of RV and LV pacing in children. The current study supports the finding of previous studies that chronic RV pacing can be detrimental to LV function [16, 19, 30, 31]. Chronic RV pacing is associated with deleterious LV remodeling [15, 31] and decreased LV function [30] in the young (for a review, see Karpawich [16]) and in adults (for review see Manolis [19]). More importantly, the current study shows that during chronic epicardial LV pacing (mean duration, >3½ years), LV function and structure are maintained at the level of healthy control children. Therefore, the pacing site appears to be an important determinant for cardiac function and structure in children.

Pacing Site and LV Structure

Animal experiments showed asymmetrical hypertrophy during pacing [35], because early-activated regions of the LV had a low workload due to a low-pressure gradient at this early activation phase. Low workload results in hypotrophy, whereas late-activated regions hypertrophy as they are stretched before activation and thus must perform higher myocardial work (local Frank-Starling effect). Remarkably, we did not find differences in regional wall thicknesses during pacing, possibly because the quality of images was not appropriate to distinct regional changes in wall thicknesses.

Relation Between Pacing Site and LV Function

In parallel with the acute decrease in cardiac pump function during RV pacing [14, 36], chronic RV pacing significantly depressed shortening fraction in the current study. Furthermore, the LV eccentricity index was significantly increased after chronic RV pacing. This eccentricity index provides an approximation of fiber stress because fiber stress increases in proportion to the result for the following equation [2, 7]:

$$\text{LV pressure} \times (\text{LV cavitydiameter}/\text{LV wall thickness})$$

from this equation, it can be deduced that at a similar LV pressure, an increase in LV cavity diameter or a decrease in LV wall thickness will result in higher fiber stress. Although neither LV nor aortic pressures were assessed for the children in this study, the increased eccentricity index in RV-paced children may indicate increased fiber stress.

Left ventricular pacing neither increased the eccentricity index nor decreased the shortening fraction after more than 3 years of pacing. Superior hemodynamic performance during LV pacing compared with RV pacing probably is caused by a more favorable balance between interventricular synchrony [13], intraventricular synchrony [36], and the sequence of electrical ventricular activation [26] during LV pacing. The idea that the sequence of activation is an important determinant of cardiac pump function is supported by other studies as well [25, 26].

During RV pacing, a left bundle branch block pattern of activation is created [16, 19, 26, 36]. In the current study, RV-paced children showed significant intraventricular mechanical dyssynchrony, with motion of the interventricular septum toward the LV posterior wall more than 300 ms before the first peak of inward LV posterior wall movement. This motion pattern of the interventricular septum is caused by the pressure developments within each ventricle. If the interventricular septum and the LV free wall are activated after the RV free wall, RV pressure increases before LV pressure is built up. This causes early systolic bulging of the interventricular septum into the LV [18].

Cardiac resynchronization therapy with biventricular pacing increases cardiac function after surgery for patients with congenital heart disease compared with intrinsic activation [13, 42]. Experience with chronic biventricular pacing in children is sparse, but a multicenter study showed promising results with regard to cardiac function after 4 months of resynchronization therapy [11], and biventricular pacing proved effective in the treatment of six children with RV pacing-induced heart failure [20]. In adults with congestive heart failure, chronic LV lateral wall pacing (single-site, short AV delay) can be as effective as biventricular pacing [4, 12, 33]. To our knowledge, the effect of chronic biventricular pacing in children has not been compared with LV lateral wall pacing alone.

The duration of QRS was not significantly different between the two paced groups in our study despite the significantly different hemodynamic and mechanical performance. This is consistent with other studies, in which QRS duration during pacing was not related to cardiac function [25, 36, 42]. It is important to bear in mind that QRS duration reflects total biventricular activation time, whereas intraventricular mechanical synchrony and sequence of electrical ventricular activation [26] probably are more important determinants of LV function [19, 36]. Given the absence of a consistent correlation between cardiac function and QRS duration in acute and chronic pacing studies, we discourage the use of QRS duration as a tool for the selection of an optimal epicardial pacing site in children.

Clinical Application

We apply and advocate the use of LV pacing sites when chronic epicardial pacing is indicated in children. We do so because chronic LV pacing has proved superior to RV pacing in terms of LV function and relative systolic dimensions in the current study, and because in some case reports, RV pacing-induced heart failure was successfully treated with single-site LV pacing [29, 32, 37]. However, once implantation of LV epicardial leads is started, it is of major clinical importance to know which site, apex, or free wall should be preferred. In an acute-pacing study, LV apex pacing increased pump function compared with RV pacing, whereas there was no benefit of LV free wall pacing [36]. Nevertheless, the current study shows that LV lateral wall pacing preserves LV function.

These findings could be explained by subtle differences in LV lateral wall pacing sites. In the aforementioned study [36], the pacing lead was placed at the base of the LV lateral wall, whereas in the current study, the location of the LV pacing lead was halfway between the LV apex and the base of the LV lateral wall (mid lateral wall).

The hypothesis that the exact pacing site at the LV lateral wall influences the effect of LV pacing is supported by the following experiment. In an established animal left bundle branch block (LBBB) model [39, 40], we investigated the hemodynamic improvement of four epicardial LV pacing sites. Pacing was applied to seven dogs with experimental LBBB at four LV pacing sites: apex, apical lateral wall, mid lateral wall, and base of the lateral wall, respectively. At all sites, pacing was performed after the same short AV delay to avoid fusion with intrinsic activation. The averaged maximum rate of LV pressure rise (LVdP/dt|max) from all beats during one ventilation cycle, measured with a catheter tip manometer, was used as a measure of LV function. Compared with LBBB, LVdP/dt|max was significantly increased by pacing at the LV apex ($18\% \pm 11\%$; $p = 0.005$), LV apical lateral wall ($11\% \pm 6\%$; $p = 0.001$), and LV mid lateral wall ($7\% \pm 6\%$; $p = 0.020$), whereas no significant improvement in LV function occurred during pacing at the base of the LV lateral wall ($3\% \pm 10\%$; $p = 0.413$).

Although pacing at the LV apex caused the most pronounced improvement in LV function, it is not easy to come within reach of this particular pacing site using established endovenous or minimal surgical techniques. However, pacing at epicardial LV mid lateral wall sites also resulted in improved LV function and is easily accessible through a left lateral thoracotomy. This approach is surgically reliable and provides excellent cosmetic and functional results in children [9].

Study Limitations

Although the number of patients studied in the current series was small, we consider the study groups to be comparable because body surface area, age, and duration of pacing were similar, and none of the patients had structural heart disease.

Because echocardiographic image quality deteriorates during long-term storage [34], we were hampered in our retrospective evaluation, especially in the evaluation of preimplantation data. We therefore could not achieve a longitudinal follow-up evaluation of all the patients and could not perform statistical analysis of echocardiographic preimplantation data. Therefore, the possibility that some of the differences between chronically RV- and LV-paced children were preexisting cannot entirely be excluded.

The main disadvantage of this study is its retrospective design. The positive effects of single-site LV pacing observed in this study, as well as the practical advantages of single-site over multisite ventricular pacing, strongly advocate further investigation on LV pacing in prospective multicenter studies.

Conclusion

Left ventricular function in children is preserved by chronic pacing at the LV lateral wall, whereas chronic RV pacing causes a decrease in shortening fraction and a higher systolic eccentricity index.

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