Permanent Cardiac Pacing in Children - Choosing the Optimal Pacing Site: A Multi-Center Study

Running title: Janoušek et al.; Optimal pacing site in children

Jan Janoušek, MD, PhD; Irene E. van Geldorp, MD; Sylvia Krupičková, MD, PhD; Eric Rosenthal, MD; Kelly Nugent, BSc; Maren Tomaske, MD; Andreas Früh, MD, Jan Elders, RN, MA; Anita Hippala, MD; Gunter Kerst, MD; Roman A. Gebauer, MD; Peter Kubuš, MD; Patrick Fria, MD; Fulvio Gabbarini, MD; Sally-Ann Clur, MBBCh, MSc, FCP(SA)Paed, PhD; Bert Nagel, MD; Javier Ganame, MD; John Papagiannis, MD, PhD; Jan Marek, MD; Svjetlana Tisma-Dupanovic, MD; Sabrina Tsao, MD; Jan-Hendrik Nürnberg, MD; Christopher Wren, MD; Mark Friedberg, MD; Maxime de Guillebon, MD; Julia Volaufova, PhD; Frits W. Prinzen, MD, PhD; Tammo Delhaas, MD, PhD for the Working Group for Cardiac Dysrhythmias and Electrophysiology of the Association for European Pediatric Cardiology

1Children’s Heart Ctr, Univ Hosp Motol, Prague, Czech Republic; 2Pediatric Cardiology; 24Dept of Physiology; 25Dept of Biomedical Engineering. Cardiovascular Rsch Inst Maastricht, Maastricht Univ Medical Ctr, Maastricht, The Netherlands; 3Evelina Children’s Hosp, London, UK; 4Univ Children’s Hosp, Zurich, Switzerland; 5Oslo Univ Hosp, Oslo, Norway; 6Dept of Cardiology, UMC St. Radboud, Nijmegen, The Netherlands; 7Dept of Pediatric Cardiology; Children’s Hosp, Univ of Helsinki and Helsinki Univ Central Hosp, Helsinki, Finland; 8Pädiatrische Kardiologie, Universitätsklinik für Kinder- und Jugendmedizin, Tübingen; 9Dept of Pediatric Cardiology, Univ of Leipzig, Heart Centre, Leipzig, Germany; 10Dept of Pediatric Cardiology, Children’s Hosp of Atlanta, Atlanta, GA; 11Pediatric Cardiology Division, Children’s Hosp Regina Margherita, Turin, Italy; 12Emma Children’s Hosp – Academic Medical Center, Amsterdam, and Center for Congenital Heart Anomalies Amsterdam-Leiden (CAHAL), Amsterdam, The Netherlands; 13Div of Pediatric Cardiology, Children’s Hosp, Medical University Graz, Austria; 14Pediatric Cardiology, Univ Hosp Leuven, Leuven, Belgium; 15Div of Pediatric Cardiology, Mitera Children’s Hospital, Maroussi, Greece; 16Pediatric Cardiology, Great Ormond Street Hosp, London, UK; 17Cardiology Section, Children’s Mercy Hospitals and Clinics, Kansas City, MO; 18Div of Cardiology, Children’s Memorial Hosp, Chicago, IL; 19Klinikum Links der Weser, Abt. Pediatric Cardiology, Bremen, Germany; 20Pediatric Cardiology, The Newcastle upon Tyne Hospitals, NHS Foundation Trust, Newcastle upon Tyne, UK; 21Div of Cardiology, The Hosp for Sick Children, Toronto, Canada; 22Dept of Congenital Heart Disease, Hôpital Cardiologique du Haut-Lévêque, Bordeaux Univ Hospitals, Bordeaux-Pessac, France; 23Biostatistics Program, LSU Health Sciences Ctr, Sch of Public Health, New Orleans, LA

Address for Correspondence:
Jan Janoušek MD, PhD
Children’s Heart Center, University Hospital Motol
V Úvalu 84
150 06 Prague 5
Czech Republic
Tel: +420 224432900
Fax: +420 224432920
E-mail: jan.janousek@lfmotol.cuni.cz

Journal Subject Codes: [11] Other heart failure; [120] Pacemaker; [41] Pediatric and congenital heart disease, including cardiovascular surgery
Abstract:

Background—We evaluated the effects of the site of ventricular pacing on left ventricular (LV) synchrony and function in children requiring permanent pacing.

Methods and Results—178 children (age <18 years) from 21 centers with atrioventricular block and a structurally normal heart undergoing permanent pacing were cross-sectionally studied. Median age at evaluation was 11·2 (inter-quartile range (IQR) 6·3-15·0) years. Median pacing duration was 5·4 (IQR 3·1–8·8) years. Pacing-sites were the free wall of the right ventricular (RV) outflow tract (RVOT, N=8), lateral RV (RVLat, N=44), RV apex (RVA, N=61), RV septum (RVS, N=29), LV apex (LVA, N=12), LV mid-lateral wall (LVLat, N=17), and LV base (LVB, N=7). LV synchrony, pump function and contraction efficiency were significantly affected by pacing-site and were superior in children paced at LVA/LVLat. LV dyssynchrony correlated inversely with LV ejection fraction (EF) (R=0·80, P=0·031). Pacing from RVOT/RVLat predicted significantly decreased LV function (LV EF <45 %; OR 10·72, CI 2·07-55·0, P= 0·005) whereas LVA/LVLat pacing was associated with preserved LV function (LV EF ≥55 %; OR 8·26, CI 1·46-47·62, P= 0·018). Presence of maternal auto-antibodies, gender, age at implantation, duration of pacing, DDD mode and QRS duration had no significant impact on LV EF.

Conclusions—The site of ventricular pacing has a major impact on LV mechanical synchrony, efficiency and pump function in children that require life-long pacing. Of the sites studied, LVA/LVLat pacing has the greatest potential to prevent pacing-induced reduction of cardiac pump function.

Key words: heart block; heart failure; pacemakers; pacing; pediatrics
Introduction

Right ventricular (RV) pacing has been used for decades in both adults and children. Recently, several large adult studies, smaller pediatric reports, and one larger pediatric survey have pointed towards the adverse effects of RV pacing. The incidence of left ventricular (LV) dysfunction in RV paced children ranged within a medium follow-up of less than a decade from 6.0 to 13.4%. The impact of pacing-induced dyssynchrony may be especially important in children with a prospect of life-long pacing that lasts for decades. This idea is nourished by findings that dyssynchronous LV activation causes pathologic remodeling and dysfunction.

Pediatric pacemaker therapy represents an optimal model for the evaluation of the long-term effects of different pacing-sites because, based on surgical preferences and in contrast to adults, various pacing-sites are used including LV epicardial pacing. In small single center reports and one larger retrospective survey pacing from the LV apex or free wall was associated with better preservation of LV function. The purpose of the current multi-center study was to evaluate the influence of different ventricular pacing-sites on long-term LV function in children with non-surgical atrioventricular (AV) block and a structurally normal heart, and to search for a mechanism for the difference in pump function between sites, by measuring mechanical synchrony and efficiency in a cross-sectional echocardiographic evaluation.

Patients and methods

Recruitment and demography

Patients were recruited from 21 centers providing pacemaker therapy for children (17 European and four North American) and had to fulfill the following inclusion criteria: presence of second or third degree AV block necessitating permanent cardiac pacing with >70% ventricular paced
beats, age <18 years at the time of primary pacemaker implantation, absence of any but trivial structural heart disease and of any known systemic illness potentially influencing cardiac function, duration of pacing >1 year, and no change in the ventricular pacing-site during the follow-up period. A total of 178 patients (female: 96, male: 82, complete AV block in 171) were included in the study with a median age at pacemaker implantation of 3.2, inter-quartile range (IQR) 0.2 – 7.0 years. AV block was congenital in 138 patients and diagnosed later during childhood in the remaining 40. Maternal auto-antibodies were present in 64 of the 136 mothers tested. Nine of the 178 patients had patent ductus arteriosus which was closed interventionally using coils prior to (N=3), at the time of (N=3), or after (N=3) pacemaker implantation. The retrospectively gathered data further included demographic parameters, pre-implantation LV size and function, New York Heart Association (NYHA) classification, and pacemaker implantation details (pacing-site as recorded by the implanting physician, lead type: endocardial vs epicardial, and initial pacing-mode and its change during the follow-up period).

Cross-sectional evaluation

After obtaining ethical approval by the hospital review committee and patient consent according to individual institutional guidelines, eligible patients were evaluated according to a pre-specified protocol including NYHA class assignment, 12-lead electrocardiogram (ECG), echocardiography, and, if not available in the patient files, a chest x-ray in the antero-posterior and lateral projections. The echocardiographic protocol consisted of: 1. two-dimensional grey scale loops of the parasternal long axis view, parasternal short axis view (at the level of papillary muscles), apical four-chamber and two-chamber views. Three cardiac cycles were recorded in each view along with simultaneous ECG tracing to allow for identification of QRS onset. 3.5 and 5 MHz transducers with a minimal frame rate of 30/s (ideally 60 - 90/s) were used. 2. Parasternal
long axis and short axis M-mode. 3. Pulsed Doppler of the RV- and LV-outflow tracts, pulsed transmitral Doppler, and qualitative assessment of mitral regurgitation (none = 0, mild = 1, moderate = 2 and severe = 3). Recordings were stored on CD/DVD as raw data from Vivid-GE systems and in DICOM format for other vendors.

**Data analysis**

All data were analyzed in a core lab (Children’s Heart Center, Prague, Czech Republic): 1. QRS duration was measured manually as the maximum value in any lead from ECG printouts with a sweep speed of 25 or 50 mm/s. 2. Approximate pacing-site assignment was performed using 12-lead ECG QRS morphology and axis and bi-plane chest x-rays to allow grouping into seven categories for the purpose of statistical evaluation: free wall of the RV outflow tract (RVOT), lateral RV wall (RVLat), RV apex (RVA), RV septum (RVS) (any position), LV apex (LVA), lateral LV wall (LVLat), and LV base (LVB). We used published algorithms for exact differentiation of the RV septal sites from the RVOT free wall sites⁰. Assignment to the RV lateral wall was performed in case of a leftward QRS axis along with left bundle branch block morphology. RV and LV apical pacing was characterized by superior axis and left and right bundle branch block morphology in lead I, respectively. Pacing was assigned to the LV lateral wall or LV base in case of a rightward QRS axis along with right bundle branch block morphology with further differentiation according to the biplane x-ray. 3. The following echocardiographic analysis, measurements and calculations were performed:

a) LV dimensions were measured from the parasternal long axis M-mode and expressed as z-scores using weight-related normal limits⁰. LV shortening fraction was calculated.

b) LV volumes were measured from the apical 4-chamber and 2-chamber views using the Simpson’s biplane method. LV ejection fraction (EF) was calculated and graded as
follows: normal (LV EF ≥55%), subnormal (LV EF <55%) and significantly decreased (LV EF <45%).

c) Septal to posterior wall motion delay (SPWMD) was measured from the parasternal short axis M-mode. When maximum systolic motion was unclear, maximum systolic wall thickening was taken as the maximal excursion.

d) Inter-ventricular mechanical delay (IVMD) was calculated as the difference between left and right ventricular pre-ejection periods measured from QRS onset to the beginning of ventricular ejection using pulsed Doppler from the RV- and LV-outflow tracts.

Speckle tracking analysis was performed in 125/178 subjects with echocardiographic raw data available from Vivid-GE equipment (GE-Vingmed, Horten, Norway) using an EchoPac workstation. Longitudinal segmental strain was calculated in the apical 4- and 2-chamber views and radial strain in the parasternal short axis view according to standardized myocardial segmentation. Each of the three recorded cardiac cycles was inspected visually looking at both strain rate and strain curves and the one with least strain rate noise and unequivocally identifiable strain peaks was used for measurement. Segments automatically rejected by the software or those with unclear peaks were not used for analysis. Measurements were feasible in 938/1380 (68.0%) segments in the apical views and 625/660 (94.7%) segments in the short axis view. Peak segmental systolic deformation timing, defined as the time from QRS onset to peak systolic strain, was measured in each segment. Subsequently, mechanical delays were calculated as the median time between peak systolic strain: a) septal to lateral delay from the basal segments of the apical 4-chamber view; b) anterior to inferior delay from the basal segments of the apical 2-chamber view; and c) septal to lateral, anteroseptal to posterior and anterior to inferior delays from the parasternal short axis view. Further, a modified strain dyssynchrony index was
calculated. This index reflects wasted segmental contraction due to LV dyssynchrony. In brief, the difference between maximum and end-systolic strain (at the time of aortic valve closure as indicated by the end of systolic flow in the LV outflow tract) was measured in each segment and expressed as percentage of the respective maximum segmental strain. The proportion of wasted LV contraction was then separately calculated for the RV and LV pacing-sites from the 12 LV segments in the apical 4- and 2-chamber views (basal, mid and apical level) and from the 6 segments in the parasternal short axis view, respectively, as the sum of the segmental values divided by the number of segments. Wasted energy can result from premature end of shortening (maximum falls before aortic valve closure, as occurs in early activated regions) or from post-systolic shortening, as occurs in late-activated regions. To ensure correct delineation of aortic valve closure, measurements were rejected if the difference between the cardiac cycle length of the aortic outflow Doppler and respective speckle tracking measurement was greater than 10%.

Statistics

If not otherwise stated, continuous data are presented as raw means (standard deviations). Differences in demographic and informative variables between pacing sites were evaluated by one way analysis of variance using the Holm-Sidak method for pair-wise multiple comparisons or by the chi-square test, as appropriate. The continuous outcome variables characterizing LV function and synchrony were analyzed using a linear mixed model approach. Each model included the set of clinically informative additive covariates in addition to the main factor tested. The continuous covariates included age at implantation, pacing duration, and QRS duration. The dichotomous covariates were gender, presence of maternal antibodies, presence of congenital block, and DDD pacing. The main treatment factor included was the pacing site with seven levels or a combination of specific pacing sites. In all models the class variable “contributing
center” was included as an additive random effect. For the random center effect a simple covariance structure was assumed in all models. The statistical test of main treatment effect was an adjusted F-test with Kenward-Roger type adjustment of denominator degrees of freedom. For the “site” main effect, multiple comparisons were performed using the Tukey-Kramer adjustment. The two dichotomous variables calculated from LV EF with a cutting point of 45% and 55%, respectively, were analyzed by a generalized mixed linear model. The distribution of the response was set to be binomial and the probability of LVEF<45% (≥55%) was modeled by a log-link function. The covariates and main treatment effects were the same as for continuous variables. The data for dichotomous response are presented as odds ratios (95% confidence interval). The difference in the modified strain dyssynchrony index between RV and LV pacing was evaluated by the Mann-Whitney rank sum test. Correlation between two continuous variables was evaluated by linear regression. Inter-observer variability was tested by the coefficient of variation.9 SigmaPlot for Windows Version 12.0 (Systat Software Inc., San Jose, California, USA) and SAS Version 9.2 (SAS Institute Inc. 100 SAS Campus Drive Cary, NC 27513-2414, USA) were used for statistical analysis. Significance was accepted at the P < 0.05 level.

Results

Cross-sectional evaluation was performed at a median age of 11.2 (IQR 6.3-15.0) years. Median pacing duration was 5.4 (IQR 3.1–8.8) years.

Pacing-sites

In total, 97 patients were paced epicardially and 81 from the endocardium. Patients were not distributed equally with respect to pacing-site, reflecting the historical preference for RV pacing
(Figure 1). Demographic and clinical parameters are summarized in Table 1. Patients paced from the LVA were generally younger and had a shorter follow-up and QRS duration. Also, gender distribution and the proportion of DDD paced patients were not equal.

LV function

LV shortening fraction, biplane ejection fraction and the end-systolic volume index (both available in 157/178 patients) were different between pacing-sites, whereas the z-score of the LV end-diastolic dimension and the end-diastolic volume index did not differ. LVA and LVLat pacing yielded significantly higher shortening fraction and EF than RV pacing-sites (Figure 2). LV EF was not significantly different between RVS and RVA pacing. Patients with RVOT and RVLat pacing had the largest scatter in LV EF with the lower quartile as low as <38 % in the RVOT group (Figure 2B). Patients with subnormal LV EF (<55 %) were almost exclusively confined to RV pacing-sites or LV base pacing whereas the vast majority of patients paced from the LV apex or lateral wall had completely preserved LV function (Figure 3). As compared to the pre-implantation values the decrease in LV shortening fraction was significant for all RV pacing-sites and absent in the LV paced groups (Figure 4). Comparing the best and clinically most commonly used RV site (i.e. RVA) with the combination of optimal LV sites (LVA and LVLat) still yielded a significant difference in favor of LV pacing (Table 2). To elucidate the potential effect of maternal auto-antibodies, presence of congenital AV block, gender, age at implantation, pacing duration, DDD pacing and QRS duration on LV function these variables were introduced as covariates. Pacing-site was the only significant predictor of both LV EF and shortening fraction (p<0.0001 for both) whereas none of the covariates reached significance. RVOT/RVLat pacing was the only independent predictor of significantly decreased LV EF (<45 %) whereas LVA/LVLat pacing was associated with preservation of LV function (LV EF >55 %, DOI: 10.1161/CIRCULATIONAHA.112.115428

Downloaded from http://circ.ahajournals.org/ by guest on May 28, 2017
Table 3 and 4). To allow for comparison with a recent multicenter retrospective survey, we also analyzed LV function by whether they were RV epicardial, RV endocardial or LV paced. Results were similar to the previous findings with LV pacing being superior to RV endocardial or epicardial pacing in terms of LV shortening fraction, LV EF, and change in LV shortening fraction as compared to pre-implantation values (Table 5). No difference was found between RV apical epicardial and endocardial pacing.

LV dyssynchrony

The inter-ventricular and intra-LV delays were significantly different between pacing-sites (Figure 5). LV EF and the septal to posterior wall motion delay for the individual pacing-sites are depicted in Figure 6. Segmental strain analysis by speckle tracking confirmed this mechanical dyssynchrony pattern (Figure 7 and 8A, B). RV pacing consistently produced delayed LV ejection and a mechanical contraction delay between the septum and LV free wall with least negative effect of the RVA pacing-site. In contrast, during LVA and LVLat pacing both inter- and intra- ventricular dyssynchrony were minimal. Pacing-sites located towards the LVB resulted in a reversed intra LV dyssynchrony pattern with early free wall and late septal motion. LV EF was significantly dependent on the degree of LV dyssynchrony (Figure 8C).

Contraction efficiency

The proportion of wasted LV contraction due to dyssynchrony measured by a modification of the strain dyssynchrony index was significantly higher during RV pacing than during LV pacing for both radial and longitudinal systolic function: median 8.3 (IQR 5.7-14.5) vs 3.1 (2.2-3.5) %, P =0.002 and 6.2 (IQR 5.0-8.2) vs 2.1 (1.2-3.5) %, P <0.001, respectively.

Inter-observer agreement

Inter-observer agreement (JJ, IvG) was calculated in a total of 28/178 patients. Pacing-site
assignment was equal in 27/28 patients. The following coefficients of variation were achieved in the parameters tested: biplane LV ejection fraction (EF) = 9.7%, inter-ventricular mechanical delay = 5.7%, septal to posterior wall motion delay = 11.2%, inter-segmental mechanical delay from two-dimensional strain = 0.9%.

**Discussion**

This is the first cross-sectional multi-center study showing significant differences between various ventricular pacing-sites in terms of LV synchrony, function and contraction efficiency in a large group of children that are chronically paced for complete AV block in the absence of structural heart disease. The results can be summarized as follows:

1. LV apical and LV lateral wall pacing are associated with the best preservation of LV function, which appears related to preserved mechanical synchrony and contraction efficiency.
2. RV pacing-sites carry a high risk for a negative effect on LV performance, coinciding with significant mechanical asynchrony and contraction inefficiency. This effect is most pronounced for RV lateral and outflow tract pacing and less with RV apical pacing.
3. Non-targeted RV septal pacing does not show any advantage over RV apical pacing.
4. LV basal pacing produces a significant reversed pattern of LV dyssynchrony and should probably not be the preferred LV pacing-site.
5. The presence of maternal auto-antibodies is not associated with decreased LV function and could not be confirmed as a modifier of the response to pacing-induced LV dyssynchrony.

This study strongly supports previous findings of a retrospective pediatric report showing a decrease in LV function specifically due to RV free wall pacing. Our results also confirm data on
preservation of LV function with LV apical or LV lateral wall pacing\(^0\) including a large retrospective pediatric multi-center survey\(^0\) and a recently published experimental study\(^0\). Our current report does not show any superiority of RV septal over RV apical pacing. This is in line with another experimental work published by Mills et al. few years ago\(^0\). Some clinical studies showed promising results using RV septal lead placement,\(^0\) but clear benefit from RV septal pacing has not yet been demonstrated in a randomized trial, except when the lead is positioned in the His-bundle.\(^0\)

RV pacing (contrary to LV pacing) was associated with depressed systolic function and induced a consistent decrease in LV systolic function compared to pre-implantation values. This decrease was functionally well tolerated as no difference in the NYHA class was observed between the pacing-sites. However, given the cross-sectional design of the study, patients suffering from symptomatic heart failure may have been missed because they were upgraded to a biventricular system, were transplanted or died. The incidence of patients suffering from heart failure due to RV pacing has been reported to range from 6.0 to 13.4% in previous pediatric reports.\(^0\)

Results of this study further indicate that LV pacing may be a substitute for primary biventricular pacing which has recently been shown to preserve LV function in chronically paced adults.\(^0\) As demonstrated by Tomaske et al. and Vanagt et al. in small descriptive pediatric reports,\(^0\) LV pacing may also be used instead of biventricular pacing to improve LV function which has been compromised from long-term RV pacing.

QRS duration was not a multivariable predictor of decreased LV function as it reflects the total electrical activation time but not the sequence of activation. Recently, a sub-analysis of the MADIT-CRT trial has shown that left bundle branch block morphology rather than QRS
duration is the prerequisite for the efficacy of cardiac resynchronization therapy. This implies that a specific activation pattern is more important than total asynchrony. Our study indicates that the negative effects of LV dyssynchrony produced by RV pacing, are preventable by LV pacing irrespective of QRS duration.

The presence of maternal auto-antibodies in the setting of congenital AV block was not found to be a component of the individual reactivity to the pacing-induced LV dyssynchrony as opposed to a study showing association of autoimmune AV block with dilated cardiomyopathy. None of the patients who were paced from the LV showed decreased LV function, despite the presence of maternal auto-antibodies in a significant portion. RV pacing-induced LV dysfunction has previously been reported in the absence of maternal auto-antibodies in children with surgical AV block and could be effectively corrected by an upgrade to biventricular pacing. All these findings support our statement that the pacing-site plays a crucial role in the development of pacing-associated LV dysfunction.

Study limitations

This study has limitations related to the unequal number of patients in each pacing-site group, significant differences in age at primary implantation and duration of pacing, as well as the accuracy of the retrospective assessment of the pacing-site using surgical records, biplane x-ray and 12-lead ECG. However, neither age nor duration of pacing was a multi-variable predictor of LV dysfunction and pacing-site localization could be performed with acceptable inter-observer variability. Also there is some degree of uncertainty about the exact proportion of fully captured paced beats during the entire pacing period. However, the vast majority of patients had complete AV block (171/178) with a low probability of spontaneous rhythm. Moreover, all available 12-lead ECGs showed a permanently paced rhythm in all cases. The lack of AV synchrony as
present in the VVI(R) paced patients may have been another confounder. The pacing mode was, however, not a factor influencing LV function in any of the analysis performed. Additionally, biplane LV ejection fractions were not available in all patients. The differences between pacing sites could be, however, confirmed by the analysis of LV shortening fractions. Also, the study protocol did not include RV evaluation and potentially negative effects of LV pacing on RV function could thus not be assessed. One of the legitimate statistical concerns is that a certain bias in the analysis of the mean response is introduced due to the fact that the patients were not randomized with respect to pacing sites. However, in our approach we addressed this limitation by including all available confounders in all analyzed models as covariates. Propensity score adjustment might be considered an alternative approach. We haven’t applied it here since the basic assumption for the propensity score analysis, that no additional confounders exist than those collected on patients, was not verifiable.

Conclusions
The site of ventricular pacing has a major impact on LV mechanical synchrony, efficiency and pump function in children that require life-long pacing. Of the sites evaluated in the present study, LVA/LVLat pacing has the greatest potential to prevent pacing-induced reduction of cardiac pump function, whereas RVOT/RVLat pacing is associated with a high risk of LV dysfunction. Although associated with a mild decrease in LV EF in approximately one half of the patients, RVA pacing is well tolerated in the majority. These data may guide clinicians in selecting proper pacing strategies in a population which will be subjected to several decades of permanent cardiac pacing and in which the aim to optimally preserve LV synchrony and function should be mandatory. Surgical access to the LV is possible using existing tools and at no
additional costs: the subxiphoid approach in younger children or, in older ones, a left lateral thoracotomy with an excellent cosmetic result. The results of the present study also provide an important clinical confirmation of previously published experimental research.

**Funding Sources:** JJ, PK and SK were supported by the grant of the Internal Grant Agency of the Ministry of Health of the Czech Republic NT 12321-3/2011 and by the Project (Ministry of Health, Czech Republic) for conceptual development of research organization 00064203 (University Hospital Motol, Prague, Czech Republic). IEvG was supported by a Dr. E. Dekker Grant for Research Fellow in Pediatric Cardiology, Dutch Heart Foundation, NHS-2010T078.

**Conflict of Interest Disclosures:** FWP received research grants from Medtronic, Boston Scientific, MSD, EBR Systems and Proteus Biomedical.

**References:**


Table 1. Demographic, clinical and pacing parameters according to the ventricular pacing site

<table>
<thead>
<tr>
<th>Parameter</th>
<th>RVOT(^1)</th>
<th>RVLat(^2)</th>
<th>RVA(^3)</th>
<th>Pacing-site</th>
<th>RVS(^4)</th>
<th>LVA(^5)</th>
<th>LVLat(^6)</th>
<th>LVB(^7)</th>
<th>Overall p-value</th>
<th>p&lt;0.05 between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>8</td>
<td>44</td>
<td>61</td>
<td>29</td>
<td>12</td>
<td>17</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>7 (87.5)</td>
<td>21 (47.7)</td>
<td>33 (54.1)</td>
<td>11 (37.9)</td>
<td>1 (8.3)</td>
<td>6 (35.3)</td>
<td>3 (42.9)</td>
<td>-</td>
<td>0.016</td>
<td>-</td>
</tr>
<tr>
<td>CCAVB (%)</td>
<td>6 (75.0)</td>
<td>35 (79.5)</td>
<td>47 (77.0)</td>
<td>20 (69.0)</td>
<td>9 (75.0)</td>
<td>16 (94.1)</td>
<td>5 (71.4)</td>
<td>-</td>
<td>0.467</td>
<td>-</td>
</tr>
<tr>
<td>Maternal ABs (N)</td>
<td>5/3/0</td>
<td>16/22/6</td>
<td>19/27/15</td>
<td>12/13/4</td>
<td>7/2/3</td>
<td>5/3/9</td>
<td>0/2/5</td>
<td>-</td>
<td>0.644</td>
<td>-</td>
</tr>
<tr>
<td>yes/no/unknown (%)</td>
<td>(62.5/37.5/0.0)</td>
<td>(36.4/50/13.6)</td>
<td>(31.1/44.3/24.6)</td>
<td>(41.4/44.8/13.8)</td>
<td>(58.3/16.7/25)</td>
<td>(29.4/17.6/52.9)</td>
<td>(0/28.6/11.4)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDD preimpl. [z-score]</td>
<td>1.64 (1.06)</td>
<td>1.81 (1.79)</td>
<td>1.79 (1.74)</td>
<td>2.11 (1.96)</td>
<td>1.71 (2.13)</td>
<td>1.49 (0.86)</td>
<td>1.53 (1.98)</td>
<td>0.980</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVSF preimpl. (%)</td>
<td>42 (5)</td>
<td>38 (7)</td>
<td>41 (7)</td>
<td>43 (7)</td>
<td>40 (5)</td>
<td>42 (8)</td>
<td>41 (5)</td>
<td></td>
<td>0.359</td>
<td>-</td>
</tr>
<tr>
<td>LVEF preimpl. (%)</td>
<td>65 (14)</td>
<td>66 (12)</td>
<td>62 (12)</td>
<td>61 (14)</td>
<td>68 (14)</td>
<td>60 (11)</td>
<td>64 (5)</td>
<td></td>
<td>0.632</td>
<td>-</td>
</tr>
<tr>
<td>Age at impl. [years]</td>
<td>3.52 (5.61)</td>
<td>2.85 (3.64)</td>
<td>5.32 (4.29)</td>
<td>6.76 (5.43)</td>
<td>1.69 (2.50)</td>
<td>3.78 (4.61)</td>
<td>6.34 (6.32)</td>
<td>0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at follow-up [years]</td>
<td>7.02 (5.38)</td>
<td>9.73 (4.50)</td>
<td>12.62 (4.91)</td>
<td>12.78 (4.36)</td>
<td>4.08 (2.98)</td>
<td>10.08 (5.68)</td>
<td>11.72 (5.17)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of pacing [years]</td>
<td>3.51 (1.77)</td>
<td>6.87 (3.85)</td>
<td>7.31 (4.25)</td>
<td>6.02 (4.21)</td>
<td>2.38 (0.97)</td>
<td>6.30 (4.02)</td>
<td>5.39 (3.84)</td>
<td>0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DDD pacing at follow-up (%)</td>
<td>6 (75.0)</td>
<td>11 (25.0)</td>
<td>33 (54.1)</td>
<td>16 (55.2)</td>
<td>6 (50.0)</td>
<td>10 (58.8)</td>
<td>6 (85.7)</td>
<td>0.007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QRS duration at follow-up [ms]</td>
<td>143 (13)</td>
<td>157 (20)</td>
<td>157 (21)</td>
<td>146 (19)</td>
<td>127 (23)</td>
<td>158 (25)</td>
<td>177 (22)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA at follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ABs = antibodies; CCAVB = congenital complete AV block; LVA = LV apex; LVB = LV base; LVEDD = LV end-diastolic dimension; LVEF = LV ejection fraction; LVLat = lateral LV wall; LVSF = LV shortening fraction; N = number of patients; RVA = RV apex; RVLat = lateral RV wall; RVOT = free wall of the RV outflow tract; RVS = RV septum. Data are presented as N (percent) or mean (standard deviation).
Table 2. Comparison of LV function between RV apical and LV apical + lateral wall pacing

<table>
<thead>
<tr>
<th>Pacing site</th>
<th>RVA</th>
<th>LVA + LVLat</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>61</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>LVSF [%]</td>
<td>34 (7)</td>
<td>40 (6)</td>
<td>=0.0007</td>
</tr>
<tr>
<td>Change in LVSF [units]</td>
<td>-7 (9)</td>
<td>-1 (9)</td>
<td>=0.044</td>
</tr>
<tr>
<td>(compared to preimpl. values)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF [%]</td>
<td>54 (6)</td>
<td>61 (6)</td>
<td>=0.0015</td>
</tr>
<tr>
<td>LVESVi [ml/m2 BSA]</td>
<td>29 (9)</td>
<td>21 (5)</td>
<td>=0.260</td>
</tr>
</tbody>
</table>

Data are presented as mean (standard deviation).
LVESVi = left ventricular end-systolic volume index. For other abbreviations see Table 1.

Table 3. Risk factors for decreased LV function (LV EF <45 %)

<table>
<thead>
<tr>
<th>Variable in model</th>
<th>LV EF &lt;45 %</th>
<th>LV EF &gt;45 %</th>
<th>p-value</th>
<th>Odds ratio (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>50.0 %</td>
<td>45.4 %</td>
<td>0.810</td>
<td>0.83 (0.18-3.81)</td>
</tr>
<tr>
<td>Congenital AV block</td>
<td>75.0 %</td>
<td>77.5 %</td>
<td>0.783</td>
<td>0.72 (0.07-7.42)</td>
</tr>
<tr>
<td>Maternal autoantibodies</td>
<td>61.5 %</td>
<td>43.6 %</td>
<td>0.406</td>
<td>2.51 (0.28-22.35)</td>
</tr>
<tr>
<td>Age at implantation [years]</td>
<td>4.39 (4.79)</td>
<td>4.49 (4.66)</td>
<td>0.592</td>
<td>0.93 (0.72-1.21)</td>
</tr>
<tr>
<td>RVOT and RVLat pacing</td>
<td>62.5 %</td>
<td>24.8 %</td>
<td>0.005</td>
<td>10.72 (2.07-55.60)</td>
</tr>
<tr>
<td>DDD pacing</td>
<td>50.0 %</td>
<td>48.2 %</td>
<td>0.520</td>
<td>1.77 (0.31-10.25)</td>
</tr>
<tr>
<td>Pacing duration [years]</td>
<td>4.94 (3.32)</td>
<td>6.44 (4.13)</td>
<td>0.115</td>
<td>0.60 (0.75-1.06)</td>
</tr>
<tr>
<td>QRS duration [ms]</td>
<td>154 (26)</td>
<td>154 (22)</td>
<td>0.477</td>
<td>1.02 (0.97-1.07)</td>
</tr>
</tbody>
</table>

Data are presented as percentage or mean (standard deviation).
Abbreviations see Table 1.

Table 4. Factors associated with preserved LV function (LV EF ≥55 %)

<table>
<thead>
<tr>
<th>Variable in model</th>
<th>LV EF &gt;55 %</th>
<th>LV EF &lt;55 %</th>
<th>p-value</th>
<th>Odds ratio (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>36.1 %</td>
<td>54.1 %</td>
<td>0.086</td>
<td>0.45 (0.18-1.12)</td>
</tr>
<tr>
<td>Congenital AV block</td>
<td>73.6 %</td>
<td>80.5 %</td>
<td>0.972</td>
<td>0.98 (0.29-3.35)</td>
</tr>
<tr>
<td>Maternal autoantibodies</td>
<td>41.1 %</td>
<td>49.3 %</td>
<td>0.103</td>
<td>0.37 (0.11-1.23)</td>
</tr>
<tr>
<td>Age at implantation [years]</td>
<td>4.24 (4.46)</td>
<td>4.69 (4.83)</td>
<td>0.323</td>
<td>0.94 (0.82-1.07)</td>
</tr>
<tr>
<td>LVA and LVLat pacing</td>
<td>4.7 %</td>
<td>29.2 %</td>
<td>0.018</td>
<td>8.26 (1.46-47.62)</td>
</tr>
<tr>
<td>DDD pacing</td>
<td>45.8 %</td>
<td>50.6 %</td>
<td>0.455</td>
<td>1.50 (0.52-4.33)</td>
</tr>
<tr>
<td>Pacing duration [years]</td>
<td>5.88 (3.78)</td>
<td>6.64 (4.30)</td>
<td>0.425</td>
<td>0.95 (0.84-1.08)</td>
</tr>
<tr>
<td>QRS duration [ms]</td>
<td>149 (22)</td>
<td>158 (23)</td>
<td>0.593</td>
<td>0.99 (0.97-1.02)</td>
</tr>
</tbody>
</table>

Data are presented as percentage or mean (standard deviation).
Abbreviations see Table 1.
Table 5. Differences between RV epicardial, endocardial and LV pacing

<table>
<thead>
<tr>
<th>Pacing-site</th>
<th>RV epicardial</th>
<th>RV endocardial</th>
<th>LV</th>
<th>Overall</th>
<th>Between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVSF [%]</td>
<td>31 (5)</td>
<td>33 (7)</td>
<td>40 (6)</td>
<td>&lt;0·0001</td>
<td>1,2 vs 3 &lt;0.001</td>
</tr>
<tr>
<td>Change in LVSF [SF units]</td>
<td>-9 (9)</td>
<td>-8 (9)</td>
<td>-1 (9)</td>
<td>0.023</td>
<td>2 vs 3 = 0.0235</td>
</tr>
<tr>
<td>LVEF [%]</td>
<td>52 (8)</td>
<td>53 (7)</td>
<td>60 (6)</td>
<td>&lt;0·0001</td>
<td>1,2 vs 3 &lt;0.001</td>
</tr>
</tbody>
</table>

Data are presented as mean (standard deviation). Abbreviations see Table 1.

Figure Legends:

Figure 1. Number of patients and distribution of pacing sites per center (not corresponding with contributing center numbering). LVA = LV apex; LVB = LV base; LVLat = lateral LV wall, RVA = RV apex; RVLat = lateral RV wall; RVOT = free wall of the RV outflow tract; RVS = RV septum.

Figure 2. LV function at cross-sectional follow-up. A. LV shortening fraction. B. LV ejection fraction. C. LV end-systolic volume index. The dotted line shows the division between normal and subnormal values. LV EF = LV ejection fraction; LVESVi = LV end-systolic volume index; LV SF = LV shortening fraction; for other abbreviations see Figure 1.

Figure 3. Proportion of patients with decreased LV ejection fraction (<55 %). EF = ejection fraction; for other abbreviations see Figure 1.

Figure 4. Change in LV shortening fraction from pre-implantation to cross-sectional follow-up. Dotted line = no change. Abbreviations see Figure 1.
**Figure 5.** A. Inter-ventricular mechanical delay. B. Septal to posterior wall motion delay. To allow for comparisons between pacing sites statistical significance is calculated for absolute measurement values. Dotted line = inter-/intraventricular synchrony. IVMD = inter-ventricular mechanical delay; SPWMD = septal to posterior wall motion delay; for other abbreviations see Figure 1.

**Figure 6.** Approximate pacing-sites as assessed from biplane chest x-rays and 12-lead ECG and color-coded absolute values of A. LV ejection fraction and B. septal to posterior wall motion delay in each specific patient. LV = left ventricle; RV = right ventricle. Adapted with permission from: Netter FH. Atlas of Human Anatomy. Second Edition. Hansen JT, Consulting Editor, Icon Learning Systems, Teterboro, New Jersey, 1997; Plate 205 and 213 (pacing sites are not part of the original image and were added by the authors).

**Figure 7.** A. Mechanical activation pattern in RV free wall pacing showing early peak negative 2D strain in the basal and mid-ventricular septum (yellow arrow) and late negative strain peak in the LV free wall (red arrow). An extensive septal to lateral mechanical dyssynchrony with a delay of 300 ms is present. B. Left ventricular apical pacing with mechanical activation starting at the apex (yellow arrows) and proceeding to the base (red arrows) resulting in almost complete septal to lateral mechanical synchrony.

**Figure 8.** A. Cumulative LV dyssynchrony A. using longitudinal strain in the apical four- and two-chamber views and B. using radial strain in the parasternal short axis view. C. Relationship between the degree of cumulative LV dyssynchrony using radial strain and LV ejection fraction. Ant-Inf delay = anterior to inferior delay; As-Post delay = anteroseptal to posterior delay; Sept-Lat delay = septal to lateral delay; other abbreviations see Figure 1.
Figure 1
Figure 2A
Figure 2B
Figure 2C
Figure 4
Figure 5A
Figure 5B
Figure 6A
Figure 6B
Figure 7A
Figure 7B
Cumulative LV dyssynchrony from longitudinal strain [ms]

<table>
<thead>
<tr>
<th>Pacing site</th>
<th>Sept-Lat delay</th>
<th>Ant-Inf delay</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVOT</td>
<td>0</td>
<td>-50</td>
</tr>
<tr>
<td>RVLat</td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td>RVA</td>
<td>-150</td>
<td>0</td>
</tr>
<tr>
<td>RVS</td>
<td>-100</td>
<td>100</td>
</tr>
<tr>
<td>LVA</td>
<td>-150</td>
<td>-100</td>
</tr>
<tr>
<td>LVLat</td>
<td>-100</td>
<td>-150</td>
</tr>
<tr>
<td>LVB</td>
<td>-50</td>
<td>-50</td>
</tr>
</tbody>
</table>

Figure 8A
Figure 8B

Bar chart showing cumulative left ventricular (LV) dyssynchrony from radial strain at various pacing sites:

- RVOT
- RVLat
- RVA
- RVS
- LVA
- LVLat
- LVB

Legend:
- Sept-Lat delay
- As-Post delay
- Ant-Inf delay
Permanent Cardiac Pacing in Children - Choosing the Optimal Pacing Site: A Multi-Center Study

Jan Janousek, Irene E. van Geldorp, Sylvia Krupicková, Eric Rosenthal, Kelly Nugent, Maren Tomaske, Andreas Früh, Jan Elders, Anita Hiippala, Gunter Kerst, Roman A. Gebauer, Peter Kubus, Patrick Frias, Fulvio Gabbarini, Sally-Ann Clur, Bert Nagel, Javier Ganame, John Papagiannis, Jan Marek, Svjetlana Tisma-Dupanovic, Sabrina Tsao, Jan-Hendrik Nürnberg, Christopher Wren, Mark Friedberg, Maxime de Guillebon, Julia Volaufova, Frits W. Prinzen and Tammo Delhaas

Circulation. published online December 30, 2012;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/early/2012/12/30/CIRCULATIONAHA.112.115428