Permanent Cardiac Pacing in Children: Choosing the Optimal Pacing Site
A Multicenter Study

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 Hiippala, MD; Gunter Kerst, MD; Roman A. Gebauer, MD; Peter Kubuš, MD; Patrick Frias, MD; Fulvio Gabbarini, MD; Sally-Ann Clur, MB BCH, 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

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—One hundred seventy-eight children (aged <18 years) from 21 centers with atrioventricular block and a structurally normal heart undergoing permanent pacing were studied cross-sectionally. Median age at evaluation was 11.2 (interquartile range, 6.3–15.0) years. Median pacing duration was 5.4 (interquartile range, 3.1–8.8) years. Pacing sites were the free wall of the right ventricle (RV) outflow tract (n=8), lateral RV (n=44), RV apex (n=61), RV septum (n=29), LV apex (n=12), LV midlateral wall (n=17), and LV base (n=7). LV synchrony, pump function, and contraction efficiency were significantly affected by pacing site and were superior in children paced at the LV apex/LV midlateral wall. LV dyssynchrony correlated inversely with LV ejection fraction (R=0.80, P=0.031). Pacing from the RV outflow tract/lateral RV predicted significantly decreased LV function (LV ejection fraction <45%; odds ratio, 10.72; confidence interval, 2.07–55.60; P=0.005), whereas LV apex/LV midlateral wall pacing was associated with preserved LV function (LV ejection fraction ≥55%; odds ratio, 8.26; confidence interval, 1.46–47.62; P=0.018). Presence of maternal antiphospholipid antibodies, gender, age at implantation, duration of pacing, DDD mode, and QRS duration had no significant impact on LV ejection fraction.

Conclusions—The site of ventricular pacing has a major impact on LV mechanical synchrony, efficiency, and pump function in children who require lifelong pacing. Of the sites studied, LV apex/LV midlateral wall pacing has the greatest potential to prevent pacing-induced reduction of cardiac pump function. (Circulation. 2013;127:613-623.)

Key Words: heart block ■ heart failure ■ pacemakers ■ pacing ■ pediatrics

Received April 30, 2012; accepted December 18, 2012.

From the Children’s Heart Center, University Hospital Motol, Prague, Czech Republic (J.J., S.K., P.K.); Department of Pediatric Cardiology, Cardiovascular Research Institute Maastricht, Maastricht University Medical Center, Maastricht, Netherlands (J.E.v.G.); Evelina Children’s Hospital, London, United Kingdom (E.R., K.N.); University Children’s Hospital, Zurich, Switzerland (M.T.); Oslo University Hospital, Oslo, Norway (A.F.); Department of Cardiology, UMC St. Radboud, Nijmegen, Netherlands (J.E.); Department of Pediatric Cardiology, Children’s Hospital, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland (A.H.); Pädiatrische Kardiologie, Universitätsklinik für Kindermedizin und Jugendmedizin, Tübingen, Germany (G.K.); Department of Pediatric Cardiology, University of Leipzig, Heart Centre, Leipzig, Germany (R.A.G.); Department of Pediatric Cardiology, Children’s Hospital of Atlanta, Atlanta, GA (P.F.); Pediatric Cardiology Division, Children’s Hospital Regina Margherita, Turin, Italy (F.G.); Emma Children’s Hospital, Academic Medical Center, Amsterdam, and Center for Congenital Heart Anomalies Amsterdam/Leiden, Leiden, Netherlands (S.C.); Division of Pediatric Cardiology, Children’s Hospital, Medical University Graz, Graz, Austria (B.N.); Department of Pediatric Cardiology, University Hospital Leuven, Leuven, Belgium (J.G.); Division of Pediatric Cardiology, Mitera Children’s Hospital, Maroussi, Greece (J.P.); Department of Pediatric Cardiology, Great Ormond Street Hospital, London, United Kingdom (J.M.); Cardiology Section, Children’s Mercy Hospitals and Clinics, Kansas City, MO (S.T.-D.); Division of Cardiology, Children’s Memorial Hospital, Chicago, IL (S.T.); Klinikum Links der Weser, Abt Pediatric Cardiology, Bremen, Germany (J.N.); Department of Pediatric Cardiology, The Newcastle upon Tyne Hospitals, National Health Service Foundation Trust, Newcastle upon Tyne, United Kingdom (C.W.); Division of Cardiology, The Hospital for Sick Children, Toronto, Ontario, Canada (M.F.); Department of Congenital Heart Disease, Hôpital Cardiologique du Haut-Lévêque, Bordeaux University Hospitals, Bordeaux-Pessac, France (M.d.G.); BioStatistics Program, Louisiana State University Health Sciences Center, School of Public Health, New Orleans, LA (J.V.); Department of Physiology, Cardiovascular Research Institute Maastricht, Maastricht University, Maastricht, Netherlands (F.W.P.); and Department of Biomedical Engineering, Cardiovascular Research Institute Maastricht, Maastricht University, Maastricht, Netherlands (T.D.).

Correspondence to Jan Janoušek, MD, PhD, Children’s Heart Center, University Hospital Motol, V Úvalu 84, 150 06 Prague 5, Czech Republic. E-mail jan.janousek@lfmotol.cuni.cz

© 2012 American Heart Association, Inc.

Circulation is available at http://circ.ahajournals.org

DOI: 10.1161/CIRCULATIONAHA.112.115428
Right ventricular (RV) pacing has been used for decades in both adults and children. Recently, several large adult studies,1–3 smaller pediatric reports,4–7 and a larger pediatric survey8 have pointed toward 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%.7 The impact of pacing-induced dyssynchrony may be especially important in children with a prospect of lifelong pacing that lasts for decades. This idea is furthered by findings that dysynchronous LV activation causes pathological remodeling and dysfunction.9 Pediatric pacemaker therapy represents an optimal model for the evaluation of the long-term effects of different pacing sites because, on the basis of surgical preferences and in contrast to adults, various pacing sites are used, including LV epicardial pacing. In small single-center reports10–14 and a larger retrospective survey,1 pacing from the LV apex or free wall was associated with better preservation of LV function. The purpose of the present multicenter study was to evaluate the influence of different ventricular pacing sites on long-term LV function in children with nonsurgical atrioventricular 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.

Clinical Perspective on p 623

Methods

Recruitment and Demography

Patients were recruited from 21 centers providing pacemaker therapy for children (17 European and 4 North American) and had to fulfill the following inclusion criteria: presence of second- or third-degree atrioventricular 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 atrioventricular block in 171) were included in the study, with a median age at pacemaker implantation of 3.2 years and interquartile range (IQR) of 0.2 to 7.0 years. Atrioventricular block was congenital in 138 patients and diagnosed later during childhood in the remaining 40. Maternal anticonvulsant agents were present in 64 of the 136 mothers tested. Nine of the 178 patients had patent ductus arteriosus that was closed interventionally with the use of coils before (n=3), at the time of (n=3), or after (n=3) pacemaker implantation. The retrospectively gathered data additionally included demographic parameters, preimplantation LV size and function, New York Heart Association classification, and pacemaker implantation details (pacing site as recorded by the implanting physician; lead type [endocardial versus epicardial]; and initial pacing mode and its change during the follow-up period).

Cross-sectional Evaluation

After ethical approval by the hospital review committee and patient consent according to individual institutional guidelines were obtained, eligible patients were evaluated according to a prespecified protocol including New York Heart Association class assignment, 12-lead ECG, echocardiography, and, if not available in the patient files, a chest x-ray in the anteroposterior and lateral projections. The echocardiographic protocol consisted of the following: (1) 2-dimen- sional gray scale loops of the parasternal long-axis view, parasternal short-axis view (at the level of papillary muscles), and apical 4-chamber and 2-chamber views; (2) 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 per second (ideally 60–90 per second) were used; (2) parase- nteral long-axis and short-axis M mode; and (3) pulsed Doppler of the RV outflow tract (RVOT) and LV outflow tract, pulsed transmural 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 Digital Imaging and Communications in Medicine format for other vendors.

Data Analysis

All data were analyzed in a core laboratory (Children’s Heart Center, Prague, Czech Republic). First, 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. Second, approximate pacing site assignment was performed with the use of 12-lead ECG QRS morphology and axis and biplane chest x-rays to allow grouping into 7 categories for the purpose of statistical evaluation: free wall of the RVOT, lateral RV wall, RV apex, RV septum (any position), LV apex, lateral LV wall, and LV base. We used published algorithms for exact differentiation of the RV septal sites from the RVOT free wall sites.15 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 were 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. Third, the following echocardiographic analysis, measurements, and calculations were performed:

(1) LV dimensions were measured from the parasternal long-axis M-mode and expressed as Z scores with the use of weight-re- lated normal limits.16 LV shortening fraction was calculated.

(2) LV volumes were measured from the apical 4- and 2-chamber views with the Simpson 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 <55%).

(3) Septal to posterior wall motion delay was measured from the parasternal short-axis M mode.17 When maximum systolic motion was unclear, maximum systolic wall thickening was taken as the maximal excursion.

(4) Interventricular mechanical delay was calculated as the dif- ference between LV and RV pre-ejection periods measured from QRS onset to the beginning of ventricular ejection with the use of pulsed Doppler from the RVOT and LV outflow tract.

Speckle tracking analysis was performed in 125 of 178 subjects with echocardiographic raw data available from Vivid-GE equipment (GE-Vingmed, Horten, Norway) with the use of an Echocap 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.18,19 Each of the 3 recorded cardiac cycles was inspected visually with examination of both strain rate and strain curves, and the one with the least strain rate noise and unequivocally identifiable strain peaks was used for mea- surement. Segments automatically rejected by the software or those with unclear peaks were not used for analysis. Measurements were feasible in 938 of 1380 segments (68.0%) in the apical views and 625 of 660 segments (94.7%) 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, as follows: (1) septal to lateral delay from the basal segments of the apical 4-chamber view; (2) anterior to inferior delay from the basal segments of the apical 2-chamber view; and (3) sep- tal to lateral, anteroseptal to posterior, and anterior to inferior delays

Circulation 623–633 February 5, 2013
from the parasternal short-axis view. Furthermore, a modified strain
dysynchrony index²⁰ was calculated. This index reflects wasted segment-
contraction due to LV dysynchrony. 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 calculated separately for the RV and LV pac-
ing sites from the 12 LV segments in the apical 4- and 2-chamber
views (basal, mid, and apical levels) 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 re-
sult from premature end of shortening (maximum falls before aortic
valve closure, as occurs in early-activated regions) or from postsysto-
tic shortening (as occurs in late-activated regions). To ensure cor-
rect delineation of aortic valve closure, measurements were rejected
if the difference between the cardiac cycle length of the aortic outflow
Doppler and the respective speckle tracking measurement was >10%.

Statistical Analysis
If not otherwise stated, continuous data are presented as raw means
(SDs). Differences in demographic and informative variables be-
tween pacing sites were evaluated by 1-way ANOVA with the use
of the Holm-Sidak method for pairwise multiple comparisons or by
the χ² test, as appropriate. The continuous outcome variables char-
acterizing LV function and synchrony were analyzed with the use
of a linear mixed model approach. Each model included the set of
clinically informative additive covariates in addition to the main fac-
tor 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 7 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 with the use of the

Table 1. Demographic, Clinical, and Pacing Parameters According to Ventricular Pacing Site

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pacing Site</th>
<th>Overall</th>
<th>P&lt;0.05 Between Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>RVOT [1] Lateral</td>
<td>8</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>RV Wall [2]</td>
<td>44</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>RV Apex [3]</td>
<td>61</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>RV Septum [4]</td>
<td>29</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>LV Apex [5]</td>
<td>12</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Lateral LV Wall [6]</td>
<td>17</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>LV Base [7]</td>
<td>7</td>
<td>...</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>7 (87.5)</td>
<td>21 (47.7)</td>
<td>33 (54.1)</td>
</tr>
<tr>
<td></td>
<td>11 (37.9)</td>
<td>1 (8.3)</td>
<td>6 (35.3)</td>
</tr>
<tr>
<td></td>
<td>3 (42.9)</td>
<td>0.016</td>
<td></td>
</tr>
<tr>
<td>CCAVB, n (%)</td>
<td>6 (75.0)</td>
<td>35 (79.5)</td>
<td>47 (77.0)</td>
</tr>
<tr>
<td></td>
<td>20 (69.0)</td>
<td>9 (75.0)</td>
<td>16 (94.1)</td>
</tr>
<tr>
<td></td>
<td>5 (71.4)</td>
<td>0.467</td>
<td></td>
</tr>
<tr>
<td>Maternal antibodies, yes/no/unknown, n (%)</td>
<td>5/3/0 (62.5/37.5/0)</td>
<td>16/22/6 (36.4/50/13.6)</td>
<td>19/27/15 (31.1/44.3/24.6)</td>
</tr>
<tr>
<td>LV end-diastolic dimension, mm</td>
<td>1.64 (1.06)</td>
<td>1.81 (1.79)</td>
<td>1.79 (1.74)</td>
</tr>
<tr>
<td>LV end-diastolic dimension, Z score</td>
<td>0.66 (1.06)</td>
<td>0.83 (1.79)</td>
<td>0.75 (1.74)</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>65 (14)</td>
<td>66 (16)</td>
<td>62 (12)</td>
</tr>
<tr>
<td>Age at implantation, y</td>
<td>3.52 (5.61)</td>
<td>2.85 (3.64)</td>
<td>5.32 (4.29)</td>
</tr>
<tr>
<td>Age at follow-up, y</td>
<td>7.02 (5.38)</td>
<td>9.73 (4.50)</td>
<td>12.62 (4.91)</td>
</tr>
<tr>
<td>Duration of pacing, y</td>
<td>3.51 (1.77)</td>
<td>6.87 (3.85)</td>
<td>7.31 (4.25)</td>
</tr>
<tr>
<td>DDD pacing at follow-up, n (%)</td>
<td>6 (75.0)</td>
<td>11 (25.0)</td>
<td>33 (54.1)</td>
</tr>
<tr>
<td>QRS duration at follow-up, ms</td>
<td>143 (13)</td>
<td>157 (20)</td>
<td>157 (21)</td>
</tr>
<tr>
<td>NYHA classification at follow-up</td>
<td>1.03 (0.17)</td>
<td>1.00 (0.00)</td>
<td>1.00 (0.00)</td>
</tr>
</tbody>
</table>

Data are presented as number (percentage) or mean (SD). Numbers in square brackets and in the P value column refer to pacing site categories. CCAVB indicates congenital complete atrioventricular block; LVEDD, left ventricular end-diastolic dimension; LV EF, left ventricular ejection fraction; LVSF, left ventricular shortening fraction; NYHA, New York Heart Association; and RVOT, free wall of the right ventricular outflow tract.
Tukey-Kramer adjustment. The 2 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 LV EF <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 intervals). The difference in the modified strain dyssynchrony index between RV and LV pacing was evaluated by the Mann-Whitney rank sum test. Correlation between 2 continuous variables was evaluated by linear regression. Interobserver variability was tested by the coefficient of variation.\(^2\)

**Figure 2.** Left ventricular (LV) function at cross-sectional follow-up. A, LV shortening fraction (SF). B, LV ejection fraction (EF). C, LV end-systolic volume index (LVESVi). The dotted line shows the division between normal and subnormal values. LVA indicates LV apex; LVB, LV base; LVLat, lateral LV wall; RVA, right ventricular apex; RVLat, lateral right ventricular wall; RVOT, free wall of the right ventricular outflow tract; and RVS, right ventricular septum.

**Figure 3.** Proportion of patients with decreased left ventricular (LV) ejection fraction (EF) (<55%). LVA indicates LV apex; LVB, LV base; LVLat, lateral LV wall; RVA, right ventricular apex; RVLat, lateral right ventricular wall; RVOT, free wall of the right ventricular outflow tract; and RVS, right ventricular septum.

**Figure 4.** Change in left ventricular (LV) shortening fraction (SF) from preimplantation to cross-sectional follow-up. Dotted line indicates no change. LVA indicates LV apex; LVB, LV base; LVLat, lateral LV wall; RVA, right ventricular apex; RVLat, lateral right ventricular wall; RVOT, free wall of the right ventricular outflow tract; and RVS, right ventricular septum.
Table 2. Comparison of LV Function Between RV Apical and LV Apical Plus Lateral Wall Pacing

<table>
<thead>
<tr>
<th>Pacing Site</th>
<th>RV Apex</th>
<th>LV Apex+Lateral Wall</th>
<th>LV Apex+Lateral Wall</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>61</td>
<td>29</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>LVSF, %</td>
<td>34 (7)</td>
<td>40 (6)</td>
<td>0.0007</td>
<td></td>
</tr>
<tr>
<td>Change in LVSF, SF units (compared with preimplantation values)</td>
<td>−7 (9)</td>
<td>−1 (9)</td>
<td>0.044</td>
<td></td>
</tr>
<tr>
<td>LV EF, %</td>
<td>54 (6)</td>
<td>61 (6)</td>
<td>0.0015</td>
<td></td>
</tr>
<tr>
<td>LVESVi, mL/m² BSA</td>
<td>29 (9)</td>
<td>21 (5)</td>
<td>0.260</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean (SD). BSA indicates body surface area; EF, ejection fraction; LV, left ventricular; LVESVi, LV end-systolic volume index; LVSF, LV shortening fraction; and RV, right ventricular.

version 12.0 (Systat Software Inc, San Jose, CA) and SAS version 9.2 (SAS Institute Inc, Cary, NC) 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 LV apex were generally younger and had a shorter follow-up and QRS duration. In addition, gender distribution and the proportion of patients with DDD pacing were not equal.

LV Function

LV shortening fraction, biplane EF, and the end-systolic volume index (both available in 157 of 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. LV apex and lateral LV wall pacing yielded significantly higher shortening fraction and EF than did RV pacing sites (Figure 2). LV EF was not significantly different between RV septum and RV apex pacing. Patients with RVOT and lateral RV wall 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). Compared with preimplantation values, the decrease in LV shortening fraction was significant for all RV pacing sites and absent in the LV paced groups (Figure 4). Comparison of the best and clinically most commonly used RV site (ie, RV apex) with the combination of optimal LV sites (LV apex and lateral LV wall) still yielded a significant difference in favor of LV pacing (Table 2). To elucidate the potential effect of maternal autoantibodies, presence of congenital atrioventricular 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/lateral RV wall pacing was the only independent predictor of significantly decreased LV EF (<45%), whereas LV apex/lateral LV wall pacing was associated with preservation of LV function (LV EF ≥55%; Tables 3 and 4). To allow for comparison with a recent multicenter retrospective survey,4 also analyzed LV function by whether subjects were RV epicardial, RV endocardial, or LV paced. Results were similar to the previous findings,8 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 compared with preimplantation values (Table 5). No difference was found between RV apical epicardial and endocardial pacing.

LV Dyssynchrony

The interventricular and intra-LV delays were significantly different between pacing sites (Figure 5). LV EF and 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 (Figures 7, 8A, and 8B). RV pacing consistently produced delayed LV ejection and a mechanical contraction delay between the septum and LV free wall with the least negative effect of the RV

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 ≥45%</th>
<th>P</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender, %</td>
<td>50.0</td>
<td>45.4</td>
<td>0.810</td>
<td>0.83 (0.19–3.81)</td>
</tr>
<tr>
<td>Congenital atrioventricular 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, y</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 lateral RV wall 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, y</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 (SD). CI indicates confidence interval; EF, ejection fraction; LV, left ventricular; RV, right ventricular; and RVOT, free wall of the RV outflow tract.
apex pacing site. In contrast, during LV apex and lateral LV wall pacing, both interventricular and intraventricular dysynchrony were minimal. Pacing sites located toward the LV base 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, as follows: median 8.3% (IQR, 5.7–14.5%) versus 3.1% (2.2–3.5%) (P=0.002) and 6.2% (IQR, 5.0–8.2%) versus 2.1% (1.2–3.5%) (P<0.001), respectively.

Interobserver agreement (J.J., I.E.v.G.) was calculated in a total of 28 of 178 patients. Pacing site assignment was equal in 27 of 28 patients. The following coefficients of variation were achieved in the parameters tested: biplane LV EF=9.7% (IQR, 5.0–14.9%) versus 3.1% (2.2–3.5%) (P<0.001) and 6.2% (IQR, 5.0–8.2%) versus 2.1% (1.2–3.5%) (P=0.002), respectively.

Table 4. Factors Associated With Preserved LV Function (LV EF ≥55%)

<table>
<thead>
<tr>
<th>Variable in Model</th>
<th>LV EF ≥55%</th>
<th>LV EF &lt;55%</th>
<th>P</th>
<th>Odds Ratio (95% CI)</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 atrioventricular 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, y</td>
<td>4.24 (4.46)</td>
<td>4.69 (4.83)</td>
<td>0.425</td>
<td>0.95 (0.84–1.08)</td>
</tr>
<tr>
<td>LV apical and lateral LV wall pacing, %</td>
<td>29.2</td>
<td>4.7</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>0.972</td>
<td>0.98 (0.29–3.35)</td>
</tr>
<tr>
<td>Pacing duration, y</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 (SD). CI indicates confidence interval; EF, ejection fraction; and LV, left ventricular.

Table 5. Differences Between RV Epicardial, RV Endocardial, and LV Pacing

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></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>&lt;0.001, 1.2 vs 3</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>0.0235, 2 vs 3</td>
</tr>
<tr>
<td>LV EF, %</td>
<td>52 (6)</td>
<td>53 (7)</td>
<td>60 (6)</td>
<td>&lt;0.0001</td>
<td>&lt;0.001, 1.2 vs 3</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD). Numbers in square brackets and in the P value column refer to pacing site categories. EF indicates ejection fraction; LV, left ventricular; LVSF, LV shortening fraction; and RV, right ventricular.

Discussion

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, including a large retrospective pediatric multicenter survey and a recently published experimental study. Our present report does not show any superiority of RV septal over RV apical pacing. This is in agreement with another experimental work published by Mills et al a few years ago. Some clinical studies showed promising results with the use of RV septal lead placement, 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.

RV pacing (in contrast to LV pacing) was associated with depressed systolic function and induced a consistent decrease in LV systolic function compared with preimplantation values. This decrease was functionally well tolerated because no difference in New York Heart Association 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.5–7 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.26 As demonstrated by Tomaske et al27 and Vanagt et al28 in small descriptive pediatric reports, LV pacing may also be used instead of biventricular pacing to improve LV function that has been compromised from long-term RV pacing.

QRS duration was not a multivariable predictor of decreased LV function because it reflects the total electric activation time but not the sequence of activation. Recently, a subanalysis of

![Figure 5](http://circ.ahajournals.org/)

**Figure 5.** A, Interventricular mechanical delay (IVMD). B, Septal to posterior wall motion delay (SPWMD). To allow for comparisons between pacing sites, statistical significance is calculated for absolute measurement values. Dotted line indicates interventricular/intra-ventricular synchrony. LVA indicates left ventricular apex; LVB, left ventricular base; LVLat, lateral left ventricular wall; RVA, right ventricular apex; RVLat, lateral right ventricular wall; RVOT, free wall of the right ventricular outflow tract; and RVS, right ventricular septum.

![Figure 6](http://circ.ahajournals.org/)

**Figure 6.** Approximate pacing sites as assessed from biplane chest x-rays and 12-lead ECG and color-coded absolute values of left ventricular (LV) ejection fraction (EF) (A) and septal to posterior wall motion delay (SPWMD) (B) in each specific patient. RV indicates right ventricle. Adapted with permission from Netter FH. Atlas of Human Anatomy. 2nd ed. Hansen JT, consulting ed. Teterboro, NJ: Icon Learning Systems; 1997; plates 205 and 213 (pacing sites are not part of the original image and were added by the authors).
The Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT) has shown that left bundle-branch block morphology rather than QRS duration is the prerequisite for the efficacy of cardiac resynchronization therapy.\(^2\)\(^9\) 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 autoantibodies in the setting of congenital atrioventricular block was not found to be a component of individual reactivity to pacing-induced LV dyssynchrony as opposed to a study showing association of autoimmune atrioventricular block with dilated cardiomyopathy.\(^3\)\(^0\) None of the patients who were paced from the LV showed decreased LV function, despite the presence of maternal autoantibodies in a significant portion. RV pacing–induced LV dysfunction has been reported previously in the absence of maternal autoantibodies in children with surgical atrioventricular block and could be effectively corrected by an upgrade to biventricular pacing.\(^3\)\(^1\),\(^3\)\(^2\) All of 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 with the use of surgical records, biplane x-ray, and 12-lead ECG. However, neither age nor duration of pacing was a multivariable predictor of LV dysfunction, and pacing site localization could be performed with acceptable interobserver variability. In addition, 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 atrioventricular 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 atrioventricular synchrony as present in the patients with VVI(R) pacing may have been another confounder. The pacing mode was, however, not a factor influencing LV function in any of the analyses performed. Additionally, biplane LV EFs were not available in all patients. The differences between pacing sites, however, could be confirmed by the analysis of LV shortening fractions. In addition, the study protocol did not include RV evaluation, and potentially negative effects of LV pacing on RV function could therefore not be assessed. One of the legitimate statistical concerns is that a certain bias in the analysis of the mean response is introduced because 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 have not applied it here because the basic assumption for the propensity score analysis, that no additional confounders exist other 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 who require lifelong pacing. Of the sites evaluated in the present study, LV apex/lateral LV wall pacing has the greatest potential to prevent pacing-induced reduction of cardiac pump function, whereas RVOT/lateral RV wall pacing is associated with a high risk of LV dysfunction. Although it is associated with a mild decrease in LV EF in approximately one half of the patients, RV apex pacing is well tolerated in the majority. These data may guide clinicians in selecting proper pacing strategies in a population that 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 with the use of existing tools and at no additional cost: the subxiphoid approach in younger children or, in older ones, a left lateral thoracotomy with an excellent cosmetic result.33

The results of the present study also provide an important clinical confirmation of previously published experimental research.22,23,34,35
Sources of Funding
Drs Janoušek, Kubuš, and Krupičková were supported by a 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). Dr van Geldorp was supported by a Dr E. Dekker Grant for Research Fellow in Pediatric Cardiology, Dutch Heart Foundation (NHS-2010T078).

Disclosures
Dr Prunen received research grants from Medtronic, Boston Scientific, MSD, EBR Systems, and Proteus Biomedical.

References
Permanent cardiac pacing that starts in childhood will continue for decades. The observed reduction in left ventricular (LV) function in right ventricular–paced children is only the beginning of a process that will likely develop further over subsequent decades. Thus, the aim to preserve LV synchrony and function should be mandatory. The site of ventricular pacing has a major impact on LV mechanical synchrony, efficiency, and pump function in children who require lifelong pacemaker therapy. These clinical findings have provided an important confirmation of previously published experimental research. Pediatric patients with a systemic LV who are scheduled for epicardial lead implantation should be paced from the LV apex or free wall, whereas the right ventricular free wall and outflow tract should be avoided. Transvenous leads may still be placed in the right ventricular apex given that it had the least negative hemodynamic influence of all right ventricular pacing sites. These patients, however, should be monitored for changes in ventricular performance. The mentioned principles may be applied to all children with a systemic LV and either spontaneous or surgical atrioventricular block. Care should be taken to place the leads at the LV apex rather than the LV base because the inverse pattern of electromechanical dyssynchrony caused by LV basal pacing might be detrimental in the long term. Given the fast developments in pacemaker technology and the expected introduction of leadless pacing systems with a potential for an easy application of LV pacing, our findings may also have importance for the future strategy of pacemaker therapy in adults.

**CLINICAL PERSPECTIVE**

Permanent cardiac pacing that starts in childhood will continue for decades. The observed reduction in left ventricular (LV) function in right ventricular–paced children is only the beginning of a process that will likely develop further over subsequent decades. Thus, the aim to preserve LV synchrony and function should be mandatory. The site of ventricular pacing has a major impact on LV mechanical synchrony, efficiency, and pump function in children who require lifelong pacemaker therapy. These clinical findings have provided an important confirmation of previously published experimental research. Pediatric patients with a systemic LV who are scheduled for epicardial lead implantation should be paced from the LV apex or free wall, whereas the right ventricular free wall and outflow tract should be avoided. Transvenous leads may still be placed in the right ventricular apex given that it had the least negative hemodynamic influence of all right ventricular pacing sites. These patients, however, should be monitored for changes in ventricular performance. The mentioned principles may be applied to all children with a systemic LV and either spontaneous or surgical atrioventricular block. Care should be taken to place the leads at the LV apex rather than the LV base because the inverse pattern of electromechanical dyssynchrony caused by LV basal pacing might be detrimental in the long term. Given the fast developments in pacemaker technology and the expected introduction of leadless pacing systems with a potential for an easy application of LV pacing, our findings may also have importance for the future strategy of pacemaker therapy in adults.
Permanent Cardiac Pacing in Children: Choosing the Optimal Pacing Site: A Multicenter 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, Svetlana Tisma-Duponovic, Sabrina Tsao, Jan-Hendrik Nürnberg, Christopher Wren, Mark Friedberg, Maxime de Guillebon, Julia Volaufova, Frits W. Prinzen and Tammo Delhaas

Circulation. 2013;127:613-623; originally published online December 30, 2012;
doi: 10.1161/CIRCULATIONAHA.112.115428

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/127/5/613

An erratum has been published regarding this article. Please see the attached page for:
/content/127/15/e550.full.pdf

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/
In the article by Janoušek, “Permanent Cardiac Pacing in Children: Choosing the Optimal Pacing Site: A Multicenter Study,” which was published in the February 5, 2013 issue of the journal (Circulation. 2013;127:613-623), an error occurred in Table 4.

The values in the “LV apical and lateral LV wall pacing, %” row were reversed under the LVEF ≥55% and LVEF <55% columns.

The error has been corrected in the current online version of the article. The authors regret the error.