Left Ventricular Dysfunction After Long-Term Right Ventricular Apical Pacing in the Young

M. Victoria T. Tantengco, MD, FAAC,* Ronald L. Thomas, PtID,† Peter P. Karpawich, MD, FAAC*

Detroit, Michigan

OBJECTIVES The goal of this study was to assess long-term global left ventricular (LV) function in patients paced from the right ventricular (RV) apex at a young age.

BACKGROUND Ventricular contraction asynchrony with short-term RV apical pacing has been associated with reduced LV pump function and relaxation. The long-term effect of RV apical pacing on global LV function in the young remains unknown.

METHODS Twenty-four patients with normal segmental anatomy paced from the RV apex (follow-up 1 to 19 years) underwent noninvasive assessment of global LV function with automated border detection echocardiography-derived fractional area of change (FAC), coupled with the Doppler index of myocardial performance (MPI). Data were analyzed from 24 RV-paced patients (mean follow-up 9.5 years, age 19 years, body surface area [BSA] 1.6 m², QRS duration 140 ms) and compared with 33 age- and BSA-matched control subjects (age 16.4 years, BSA 1.6 m²). Multiple linear regression analysis was performed to identify patient variables that can affect these indexes of LV function.

RESULTS Assessment of LV function (median follow-up 10 years) in 24 paced patients demonstrated impaired area- and Doppler flow-derived indexes of LV systolic and diastolic function, compared with those indexes of control subjects (FAC: 52% vs. 60%, p < 0.01; MPI: 0.46 vs. 0.34, p < 0.01). Paced QRS interval and age were found to significantly influence global LV contraction in these patients \( R^2 = 0.4 \) and the absence of any intracardiac shunt. Patients were verified to have normal LV function before pacemaker insertion. An electrocardiogram (ECG) was obtained from each patient before the echocardiogram.

CONCLUSIONS In the presence of impaired LV function with long-term RV apical pacing, alternative sites of ventricular pacing that simulate normal biventricular electrical activation should be explored to preserve function in pediatric patients in need of long-term pacing. (J Am Coll Cardiol 2001;37:2093–100) © 2001 by the American College of Cardiology.
tion (ABD) of the LV endocardial interface was accomplished from the parasternal short-axis view with on-line waveform display of the LV chamber area and the rate of area change per unit time (dA/dt) throughout the cardiac cycle, as illustrated in Figure 1.

This technique allows real-time calculation of the LV fractional area of change (FAC): \( \frac{(LV\text{ end-diastolic area} - LV\text{ end-systolic area})}{LV\text{ end-diastolic area} \times 100} \), as well as calculation of the LV peak emptying and peak filling rates (systolic-minimal and diastolic-maximal dA/dt, respectively), normalized to the LV end-diastolic area (s\(^{-1}\)). These measurements were taken from three to five consecutive cardiac cycles and averaged on-line for each of these three variables.

The LV ABD-derived area waveform during diastole readily demonstrates the three phases of ventricular filling: the initial rapid filling phase, followed by a period of diastasis and ending with the atrial contraction phase (9). The percent contribution to total LV filling due to these three phases of relaxation were calculated off-line and reported as additional indexes of diastolic function.

Doppler-derived myocardial performance index (MPI). Tei et al. (10) have forwarded a simple and reproducible noninvasive measure of quantifying ventricular function using Doppler flow-derived intervals. The MPI incorporates both systolic and diastolic aspects of function. It is defined as the sum of the isovolumetric contraction time and the isovolumetric relaxation time divided by the ejection time. This index has been shown to have an important prognostic value in patients with dilated cardiomyopathy and cardiac amyloidosis (10,11). Higher MPI values have been associated with more profound degrees of ventricular dysfunction. The MPI has also been shown to correlate well with known invasive indexes of LV systolic (peak \( +dP/dt \)) and diastolic (peak \( -dP/dt, \tau \)) function (12).

The Doppler intervals were measured from the mitral inflow and LV outflow spectral Doppler data. The sum of the isovolumetric contraction and relaxation times was derived from the interval from the end of mitral inflow to the onset of the next mitral inflow signal minus the LV outflow ejection time. The isovolumetric relaxation time was directly obtained by measuring the interval from the end of the LV outflow spectral Doppler signal to the onset of mitral inflow, with optimal positioning of the sample volume in between the LV inflow and outflow tracts. Measurements were obtained and averaged from at least three consecutive beats.

Statistical analysis. Analysis of ABD- and Doppler-derived indexes of LV function for both study groups was accomplished using the Student independent-samples \( t \) test or the Mann-Whitney \( U \) test for parametric and nonpara-

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**Figure 1.** Image of on-line derivation of beat-to-beat changes in the left ventricle area throughout the cardiac cycle, obtained from the parasternal short-axis view using automated border detection by echocardiography. The inherent computer software algorithm allows instantaneous calculation of the fractional area of change (FAC), as well as the maximal rate of rise of LV pressure (+dA/dt) and −dA/dt normalized to the LV end-diastolic area. EDA = end-diastolic area; ESA = end-systolic area; PER = peak emptying rate; PFR = peak filling rate; TPFR = time to peak filling rate.
metric data, respectively. An alpha level (p value) ≤0.05 was considered statistically significant.

Multiple stepwise linear regression analysis was used to determine the association between LV function and patient pacing-related variables. Multiple regression represents a direct extension of simple regression. Instead of a single predictor variable (Y = B₁ · X₁ + A), multiple regression allows for more than one independent predictor variable (Y = B₁ · X₁ + B₂ · X₂ + B₃ · X₃ +...+A) in the prediction equation. One focuses on how well the equation fits the data, whether there are any significant linear relations and estimating the coefficients for the best-fitting prediction equation. In addition, one should realize the relative importance of the independent variables in predicting the dependent variable. When faced with many potentially useful variables, but with no guidance as to which should be used in the prediction equation, stepwise regression provides a method of selecting from a set of independent variables those which, in some limited sense, produce the best equation. As a filtering device to select promising predictors, or as an equation-building method when the analyst has no model in mind, stepwise regression is a frequently employed technique. The algorithm first computes the correlations between each independent variable and the dependent measure, then selects the variable with the highest correlation as the first variable in the equation (assuming it is statistically significant) and finally evaluates the equation. It then selects the independent variable that has the highest partial correlation (after adjusting for the existing variable in the equation) with the dependent measure, and if significant, this variable is added, as well. This process continues until there are no remaining variables with a significant linear relation to the dependent measure. This method was used to identify predictors of poor LV function in these patients.

RESULTS

Patient characteristics. A total of 24 patients were evaluated and compared with 33 age-, weight-, height- and BSA-matched control subjects. Patient demographic data and RV pacing data are presented in Table 1. Pacing was initiated at an average age of 10 ± 6.4 years for congenital complete atrioventricular (AV) block in 12 patients, sinus node dysfunction with or without atrial flutter in 4 patients and acquired AV block in 8 patients (postoperatively in 7). The duration of RV apical pacing ranged from 0.7 to 18.9 years (median 10), equally distributed as an epicardial or transvenous lead system and programmed as VVI/VVIR in 15 patients and DDD/DDDR in 9 patients. Pacemaker revision to a rate-responsive or dual-chamber system, or both, was performed in eight patients. The majority of the patients (23 of 24) exhibited 100% ventricular paced rhythm at the time of the study, with a mean paced heart rate of 73.5 ± 10.5 beats/min. The paced QRS intervals ranged from 80 to 180 ms (139.7 ± 27.1), with a mean QRS axis of −19°.

Clinical symptoms (New York Heart Association functional class II/III) were present in two patients, one of whom was maintained on digoxin and angiotensin-converting enzyme inhibitor therapy, and the other patient, since the time of this study, has successfully undergone heart transplantation. The rest of the patients were asymptomatic.

Long-term RV apical pacing and LV FAC. Left ventricular contraction, depicted by the ABD echocardiography-derived FAC, was reduced in this particular group of patients who had long-term RV apical pacing (52.0 ± 10.4%), compared with control subjects (59.8 ± 5.8%, p < 0.01), as shown in Figure 2. However, this was not accompanied by a decrease in LV peak emptying rates in the paced group (3.7 ± 1.5 s⁻¹) versus the control group (3.7 ± 0.6 s⁻¹).

The LV end-diastolic area, indexed to BSA, was comparable between the patient and control groups (10.0 ± 2.7 vs. 8.9 ± 2.8 cm²/m²). This was accompanied by a larger indexed LV end-systolic area found in the long-term pacing group versus the control group (4.9 ± 2.4 vs. 3.6 ± 1.5 cm²/m², p < 0.05), accounting for the reduced FAC found in these patients.

Long-term RV pacing and LV diastolic function (ABD by echocardiography). There was a trend toward reduced LV chamber peak filling rates in the patient group (4.6 ± 1.2 s⁻¹) versus the control group (5.2 ± 1.1 s⁻¹, p = 0.06). There were no differences found, however, between the paced versus control group in the proportion of LV filling attributed to rapid early filling (80.8% vs. 80.2%), diastasis (4.9% vs. 5.2%) or atrial contraction (14.2% vs. 14.6%).

Long-term RV pacing and LV MPI. Assessment of LV contraction and relaxation with Doppler MPI (Fig. 3) demonstrated diminished global function in the patient group (0.46 ± 0.13) versus the control group (0.34 ± 0.08). This can be attributed to the shorter LV ejection interval found in the patients who had long-term RV apical pacing (272 ± 16 ms) versus the control subjects (294 ± 19 ms, p = 0.001), without being accompanied by any difference in isovolumetric relaxation or contraction time between the two study groups.

Predictors of LV function in patients with RV apical pacing. Eleven patient variables—gender, age, BSA, heart rate, age at which pacing was started, duration of pacing, QRS interval, QRS axis, pacing mode, pacemaker lead system and previous intracardiac surgery—were assessed by multiple stepwise linear regression analysis to determine their association with the LV FAC. Table 2 lists the variables that appeared to be significant determinants of long-term LV function in the 24 patients studied, including their regression coefficients with the estimated precision (standard error) and 95% confidence intervals of the coefficients. The coefficient of multiple determination (R²) was 0.39 between the paced QRS interval, in combination with patient age, and the measured LV FAC. Interestingly, the
The duration of RV apical pacing, previous cardiopulmonary bypass with intracardiac surgery and QRS axis were not found to be significant predictors of LV function in these patients. Figure 4 illustrates the inverse relationship between LV FAC and paced QRS duration (r² = 0.24, b = -0.19, p = 0.015). The two patients with the longest QRS interval (176 and 180 ms) also had the lowest FAC and were the same patients who had cardiac symptoms.

DISCUSSION

Right ventricular apical pacing; comparison with previous studies. Invasive indexes of LV systolic function have been shown to be impaired with short-term RV apical pacing in both animal and human studies. The maximal rate of rise of LV pressure (peak +dP/dt) has been consistently reduced with RV apical pacing, compared with either right atrial pacing or the intrinsic sinus rhythm (1,4,5,13). Experimental animal studies have shown that RV outflow tract pacing, compared with atrial pacing, produced dyssynchronous contraction between the LV septal wall and the opposing lateral wall (2,3). Right ventricular pacing resulted in paradoxical septal motion, with early shortening in the LV septal-free wall dimension relative to the anteroposterior wall, inducing septal bulging and late septal shortening, which cause lateral wall systolic lengthening.

Table 1. Right Ventricular Apical Pacing Data of Patients Paced for 1 to 19 Years

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yrs)</th>
<th>BSA (m²)</th>
<th>HR (beats/min)</th>
<th>Duration of Pacing (years)</th>
<th>Pace Mode (Initial/Revised)</th>
<th>Lead System</th>
<th>QRS Duration (ms)</th>
<th>QRS Axis (°)</th>
<th>Diagnosis</th>
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<tr>
<td>1</td>
<td>13.1</td>
<td>1.6</td>
<td>70</td>
<td>0.7</td>
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<td>2</td>
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<td>0.7</td>
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<td>129</td>
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<tr>
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<td>8</td>
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<td>9.9</td>
<td>VVI Epicardial</td>
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<td>136</td>
<td>110</td>
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<tr>
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<td>10.2</td>
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<td>84</td>
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<td>6.8</td>
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<td></td>
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<td>-35</td>
<td>Sinus node dysfunction/atrial flutter</td>
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<td>149</td>
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<tr>
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Mean ± SD 19.5 ± 8.1  1.6 ± 0.4  73.5 ± 10.5  9.5 ± 4.8  139.7 ± 27.1  (-19 ± 79)

ACA VB = acquired complete atrioventricular block; ASD = atrial septal defect; AVSD = atrioventricular septal defect; CCA VB = congenital complete atrioventricular block; postop. = postoperative; RFA = radiofrequency ablation; TVR = tricuspid valve replacement for Ebstein’s anomaly of the tricuspid valve; VSD = ventricular septal defect.
VVI mode versus the AAI mode, with no substantial changes in LV ejection, contributed by the lateral and inferior walls, between the three pacing modes. A similar pattern of LV systolic dysfunction was found with VVI pacing with or without AV synchrony, compared with AAI pacing with Doppler echocardiographic markers of ventricular systolic work (15).

Ventricular asynchrony with RV pacing has also been shown to be associated with impaired LV relaxation. Short-term RV pacing in dogs resulted in a decreased rate of isovolumic pressure decline (longer relaxation time constant, or tau), slower peak segment lengthening rate and a slower LV chamber peak filling rate, compared with right atrial pacing (6). A similar pattern of LV diastolic dysfunction with AV sequential pacing versus atrial pacing was found only in patients with evidence of impaired systolic function (1), with unchanged indexes of ventricular relaxation in patients with normal LV ejection fractions.

Our study has provided parallel evidence of impaired ABD area and Doppler echocardiography-derived variables of global LV systolic and diastolic function in patients who had long-term pacing from the RV apex. Left ventricular dysfunction in these patients was shown by 1) reduced LV FAC accompanied by a larger LV end-systolic area; and 2) an impaired MPI associated with a decrease in LV ejection time. Left ventricular shortening appeared to be influenced by the paced QRS interval and patient age. Moreover, the presence of cardiac symptoms tended to correlate with extreme prolongation of the paced QRS duration.

**Mechanisms of LV dysfunction.** Histologic findings of the LV free wall obtained after three to four months of RV apical pacing in both young and adult animals have specifically demonstrated focal areas of dystrophic calcification, myofibrillar disarray, prominent subendocardial Purkinje cells with an increase in variable-sized and disorganized mitochondria (16, 17). Recently, Karpawich et al. (7) have detected similar histopathologic abnormalities in paced patients. These endomyocardial biopsies were taken from the mid-RV septal region within 3 to 12 years of RV apical pacing. Histopathologic abnormalities seen after pacing were not present from biopsies taken before pacing. These changes may be the result of repetitive abnormal myocardial shearing forces and stress vectors secondary to the presence of an aberrant electrical activation sequence initiated from the RV apex, instead of normal electrical firing from the high septal His bundle region (18). The presence of ventricular contraction-relaxation asynchrony, coupled with such histologic abnormalities, could provide the mechanical and anatomic substrate(s) for the eventual untoward development of ventricular dysfunction in these patients.

Other investigators have demonstrated changes in regional myocardial perfusion abnormalities and apical wall

![Figure 2](image.png)
motion abnormalities and redistribution of LV wall mass with RV pacing (19,20). These changes may represent myocardial structural maladaptations resulting from localized or regional changes in mechanical work load. Burkoff et al. (21) demonstrated a reduction in the slope of the end-systolic LV pressure-volume relationship with RV free-wall pacing compared with atrial pacing. Using isolated animal heart preparations, the normalized LV force-interval relationship, which is reflective of beat-to-beat alterations in the amount of intracellular calcium supplied to the myofilaments, was similar between right atrial and RV free-wall pacing (22). Therefore, the presence of reduced LV contraction associated with RV apical pacing is probably not based on diminished intracellular calcium released from the sarcoplasmic reticulum.

**Alternative ventricular pacing sites.** There is growing evidence to support that LV free-wall pacing, and not RV pacing, improves LV contraction in patients with heart failure and intraventricular conduction delay (23,24). Left ventricular epicardial (VDD mode) pacing, either through a prograde or retrograde approach, resulted in increased LV maximal dP/dt, increased stroke work, lower end-systolic volume, higher systolic blood pressure and lower pulmonary capillary wedge pressure, compared with either RV apical, mid-septal or outflow tract pacing. Biventricular pacing has not been shown to consistently enhance contraction over LV free-wall pacing.

The potential benefit of pacing from non-RV apical sites that can theoretically closely simulate the normal cardiac electrical activation sequence needs to be further explored. Normalization of the paced QRS duration with septal pacing has been shown to be associated with nearly normal ventricular contraction patterns and normal histologic findings, compared with that found in young animals that had RV apical pacing (25).

**Study limitations.** The limitations inherent in this study include the absence of sequential echocardiographic variables of LV function in each patient, which certainly provides stronger evidence for progressive ventricular dysfunction found with long-term RV-apical pacing, as well as
the limited number of patients with available long-term follow-up data. Previous intracardiac surgical repair with inherent cardiopulmonary bypass can be construed as a confounding variable that could adversely affect long-term ventricular function. Other studies, however, have shown that LV function appears to be preserved long after successful surgical correction of intracardiac defects (26,27).

On-line derivation of ventricular function using echocardiography-derived ABD requires sharp definition of the LV endocardial border. This, in turn, is largely operator-driven, despite image enhancement with lateral gain compensation and longer backscatter data integration times, resulting in a reduction in image speckle noise, compared with that found with conventional scanning (8). In our study, reproducible definition of the entire LV endocardium was more readily attained from the parasternal short-axis over the apical four-chamber view. Using the parasternal short-axis dimension of the LV, off-line and on-line measurements of the LV end-diastolic area were similar to each other (adjusted $r^2 = 0.94$). A biplane approach in the assessment of changes in the LV area will certainly provide more complementary wall segments and may provide additional insights into the contribution of septal-posterior wall contraction asynchrony, inherent in RV apical pacing, to global LV function.

The Doppler-derived MPI is an attractive alternative to quantification of overall cardiac function. Calculation of the ratio of isovolumetric contraction and relaxation times to the ejection time has been previously shown to be applicable over a wide range of heart rates (50 to 110 beats/min), independent of blood pressure, as opposed to considering these variables alone (10,28). This index, however, may be affected by alterations in ventricular preload, even under constant contractility conditions (29). Therefore, differences in MPI that may be reflective of changes in preload could conceivably be corrected for by incorporating the Doppler-derived LV stroke volume, in the absence of significant aortic and mitral valve regurgitation.

Conclusions. Long-term ventricular pacing from the RV apex appears to be associated with LV systolic and diastolic dysfunction. Near synchronization of ventricular contraction with LV pacing may preserve long-term ventricular function, especially in young patients in need of permanent pacing.

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Reprint requests and correspondence: Dr. Tantengco, Pediatric Cardiology, 2nd Floor, Children’s Hospital of Michigan, 3901 Beaubien Boulevard, Detroit, Michigan 48201. E-mail: mtanteng@dmc.org.

REFERENCES