Electrical Resynchronization
A Novel Therapy for the Failing Right Ventricle

Anne M. Dubin, MD; Jeffrey A. Feinstein, MD; V. Mohan Reddy, MD; Frank L. Hanley, MD; George F. Van Hare, MD; David N. Rosenthal, MD

Background—Many patients with congenital heart disease develop right ventricular (RV) failure due to anatomy and prior therapy. RV problems may include right bundle-branch block (RBBB), volume loading, and chamber enlargement. Because the failing RV may have regional dyskinesis, we hypothesized that resynchronization therapy might augment its performance.

Methods and Results—We studied 7 patients with RV dysfunction and RBBB, using a predefined pacing protocol. QRS duration, cardiac index (CI), and RV dp/dt were measured in 4 different pacing states. Atrioventricular pacing improved CI and RV dp/dt at peak and decreased QRS duration as compared with atrial pacing or sinus rhythm.

Conclusions—Atrioventricular pacing in patients with RBBB and RV dysfunction augments RV and systemic performance. RV resynchronization is a promising novel therapy for patients with RV failure. (Circulation. 2003;107:2287-2289.)

Key Words: pacing ■ heart defects, congenital ■ heart failure

Right heart failure is an important cause of late morbidity in congenital heart disease.1-3 Whereas left ventricular (LV) failure is well studied, the therapeutic approach to right ventricular (RV) failure is largely empirical, and clinical trial data are nearly nonexistent.

Regional dyskinesis is common in LV systolic dysfunction, impeding global cardiac contractility and relaxation. Restoring mechanical synchronization with biventricular pacing improves hemodynamics and bioenergetics.4 Resynchronization improves cardiac contractility without the increase in oxygen demand that accompanies inotropic therapies.5 Trials have demonstrated improved exercise tolerance, although survival benefit is uncertain.6

In contrast to LV dysfunction, the failing RV is poorly understood. Prior surgery often produces right bundle-branch block (RBBB).7 Tricuspid or pulmonary insufficiency may cause RV enlargement. These alterations may decrease RV ejection fraction.8 The motion of the interventricular septum often becomes paradoxic in these circumstances, indicating an abnormal RV activation sequence.9 Thus, RV dyskinesis appears to be a reasonable therapeutic target. We hypothesized that there would be an acute hemodynamic benefit from electrical resynchronization of the failing RV.

Methods
This was an unblinded, acute intervention. Eligibility criteria included RV dysfunction determined by echocardiography or angiography, sinus rhythm, and RBBB on the ECG (QRS ≥120 ms). Exclusion criteria were concomitant LV failure or anatomy precluding temporary pacing. Patients enrolled in this study had clinically indicated cardiac catheterization. The Stanford University Human Subjects Committee approved the protocol.

Patients were sedated for study. A pressure-tip catheter (Millar Instruments) was placed in the RV. Pacing catheters were inserted transvenously into the right atrium and RV. Data from the Millar catheters were passed through an isolation amplifier, digitized with the use of Powerlab hardware (ADInstruments) at a sampling rate of 400 Hz, and analyzed using custom software written in Labview (National Instruments).

Data were collected under the following conditions: sinus rhythm, atrial pacing (AOO) at a rate 10% faster than baseline, atrioventricular pacing (DOO) at the same rate as atrial pacing at 3 different RV sites, and atrial pacing again (AOO) to ensure that the patient’s condition remained stable during the study. Condition order of DOO pacing at the different RV sites was randomly assigned. For DOO pacing, an atrioventricular delay of 90% of the PR interval was chosen to facilitate RV capture yet minimize the effect of a shortened AV delay on ventricular function. Three separate RV pacing sites were used: apex, outflow tract, and septum. All pacing conditions were maintained for 2 minutes to obtain a steady state before data collection.

The primary outcomes were change in cardiac index (CI) and change in RV dp/dt max. CI was determined by using the Fick method, assuming constant oxygen consumption during the study. AOO pacing was used as the study baseline to eliminate the effect of heart rate alteration.

Data were analyzed by using repeated-measures ANOVA and χ² as appropriate. A value of P=0.05 was taken as significant.
Results

Patient Characteristics
Seven patients (4 males) were studied. Diagnoses included tetralogy of Fallot and aortic stenosis status after Ross procedure. Baseline characteristics are shown in the Table.

Hemodynamic Measures
The Table shows baseline data. CI was generally normal, aside from 1 patient in whom the CI was 1.12 L/min per m². RV systolic and diastolic pressures were elevated.

Cardiac Index
CI was calculated in all patients for all states. Mean CI in sinus rhythm was 2.86±1.19 L/min per m², with no significant change in CI from sinus rhythm to AOO pacing (mean increase of 8%; \( P=NS \)). The mean CI with DOO pacing was 3.4±1.4 L/min per m², which represented an increase of 17±8% compared with AOO pacing (\( P=0.04 \); Figure). One patient increased CI by 44% during resynchronization. Six of the seven patients increased CI during resynchronization.

dP/dt_max
dP/dt_max did not change between sinus rhythm and AOO pacing (mean increase of 0%; \( P=NS \)). There was a highly significant increase in dP/dt_max during DOO pacing, from 289±149 to 354±188 mm Hg/s (mean increase of 22% with resynchronization pacing; \( P=0.01 \); Figure).

QRS Duration
The QRS duration at baseline was 163±39 ms (range 110 to 240 ms). This decreased for every patient during DOO pacing, with a statistically significant decrease overall to 126±31 ms (\( P=0.001 \)). The pacing site that produced the narrowest QRS duration was associated with the greatest improvement in CI for 6 of 7 patients (\( P=0.01 \)). There was no apparent relationship between the site that produced the narrowest QRS duration and the site that produced the best RV dP/dt_max.

Discussion
Heart failure due to LV dysfunction is an important cause of death and disability in the United States. LV resynchronization represents a major therapeutic advance for selected heart failure patients, with both hemodynamic and clinical benefits.

For many forms of congenital heart disease, it is RV failure rather than LV failure that is clinically important. Many congenital heart lesions lead to long-term complications of RV function, through a combination of volume loading, pressure loading, and surgically induced myocardial injury.

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Baseline Characteristics and Hemodynamic Data of Study Subjects

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>23.6 (18.7)</td>
<td>1.7</td>
<td>53</td>
</tr>
<tr>
<td>Height, cm</td>
<td>147 (42)</td>
<td>70</td>
<td>178</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>66.5 (38)</td>
<td>9.3</td>
<td>81</td>
</tr>
<tr>
<td>Baseline cycle length, ms</td>
<td>828 (123)</td>
<td>590</td>
<td>1000</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>166 (39)</td>
<td>140</td>
<td>200</td>
</tr>
<tr>
<td>Hemoglobin, gm/dL</td>
<td>13.2 (2.8)</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>NYHA class</td>
<td>2–4</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Cardiac index, L/min per m²</td>
<td>2.85 (1.19)</td>
<td>1.12</td>
<td>4.60</td>
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<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>114 (23)</td>
<td>90</td>
<td>148</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>69 (14)</td>
<td>54</td>
<td>88</td>
</tr>
<tr>
<td>RV peak pressure, mm Hg</td>
<td>54 (36)</td>
<td>26</td>
<td>130</td>
</tr>
<tr>
<td>RV/LV ratio</td>
<td>0.47 (0.25)</td>
<td>0.18</td>
<td>0.94</td>
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<tr>
<td>RV minimum pressure, mm Hg</td>
<td>4 (5)</td>
<td>0</td>
<td>12</td>
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<tr>
<td>RV end-diastolic pressure, mm Hg</td>
<td>14 (9)</td>
<td>5</td>
<td>28</td>
</tr>
<tr>
<td>RV dP/dt_max, mm Hg/s</td>
<td>289 (151)</td>
<td>149</td>
<td>548</td>
</tr>
</tbody>
</table>

Change in CI and dP/dt with resynchronization. Figure illustrates the change in CI (A) and dP/dt (B) achieved with DOO pacing as compared with AOO pacing. Subjects are plotted individually in black, with the mean value for the group shown in gray. The y axis in A indicates the CI in L/min per m², whereas the y axis in B indicates dP/dt_max, in mm Hg/s.
As in the LV, RV dysfunction often manifests as dilatation and dyskinesis.

In contrast to the LV, RV failure is less well understood, particularly from a therapeutic perspective. In fact, to our knowledge, there is no therapy for RV dysfunction that is well supported by experimental evidence.

Our data demonstrate the feasibility of RV resynchronization. In a group of patients with moderate to severe RV dysfunction, improvement during at least one pacing condition was seen in all patients. Benefit was demonstrated by an increase in RV dP/dt max, a well-validated index of ventricular systolic performance.11,12 We selected this as our primary RV outcome because it can be measured independently of ventricular geometry and is insensitive to changes in afterload. Although dP/dt max is affected by alterations in preload, there is no reason to believe that the pacing intervention altered preload acutely, particularly because heart rate was held constant. Therefore, the change in RV dP/dt max in this study most likely indicates an improvement in intrinsic contractility. The average increase in dP/dt max was 22% in our patients. This is a somewhat greater change than was recently described for LV resynchronization (14%).4 To place this in perspective, Nelson and colleagues3 have recently shown that an infusion of 10 to 25 μg/kg per min of dobutamine produced an increase in LV dP/dt max of 42%.

In addition to the benefit shown in RV performance, resynchronization of the RV consistently improved systemic CI. This finding has several potential explanations. RV resynchronization may have exerted a favorable effect on interventricular interaction, improving LV diastolic performance. Alternatively, the RV may have played a key role in limiting LV output in this group of patients. In either case, the improvement in CI reinforces the potential impact of this therapy on overall cardiovascular hemodynamics. This finding also illustrates a potential role of RV resynchronization in settings of acute RV failure, such as the patient undergoing surgical repair of tetralogy of Fallot.

In LV failure, QRS duration is a good indicator of potential benefit from resynchronization, but the change in QRS duration during pacing does not necessarily correlate with the magnitude of benefit achieved.13,14 In our series, there did not appear to be a good relationship between the site that optimized QRS duration and the site that optimized RV function. However, there was a strong relationship between the degree of QRS improvement and the increase in CI. This relationship needs confirmation in a larger series.

**Limitations**

This is a preliminary study with a small number of heterogeneous subjects. The role of atrioventricular delay, which has been shown to be important in some studies, was not investigated.15 Our data demonstrate acutely improved hemodynamics but do not prove that there will be clinical benefit in a more chronic setting.

**Conclusion**

RV resynchronization is a novel therapy that improves RV function acutely in selected patients. In view of the essential role of the RV in many forms of congenital heart disease, this therapy should be tested more comprehensively to determine the potential clinical benefit. Populations of particular interest include those with acute RV failure from surgical repair and patients with chronic RV failure due to underlying congenital heart disease.

**Acknowledgment**

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**References**


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