Short-Term Effects of Right-Left Heart Sequential Cardiac Resynchronization in Patients With Heart Failure, Chronic Atrial Fibrillation, and Atrioventricular Nodal Block

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Background—Single-site ventricular pacing in patients with heart failure, atrial fibrillation, and severe atrioventricular (AV) nodal block risks the generation of discordant contraction. Whether altering the site of stimulation can offset this detrimental effect and what role sequential right ventricular–left ventricular (RV-LV) stimulation might play in such patients remain unknown.

Methods and Results—Nine subjects with heart failure (ejection fraction, 14% to 30%), atrial fibrillation, and AV block were studied by pressure-volume analysis. Ventricular stimulation was applied to the RV (apex and outflow tract), LV free wall, and biventricular (BiV) at 80 and 120 bpm. BiV improved systolic function more than either site alone (dP/dt max, 810±83, 924±98, 983±102 mm Hg/s for RV, LV, BiV, respectively; *P<0.05*), although LV pacing was significantly better than RV pacing. However, only BiV improved diastolic function (isovolumic relaxation) over RV or LV alone. Similar results were obtained for both heart rates. RV pacing site did not alter the BiV effect, and concomitant stimulation of both RV sites did not improve function over each alone. Finally, varying RV-LV delay revealed optimal responses with simultaneous pacing.

Conclusions—Simultaneous BiV pacing acutely enhances both systolic and diastolic function over single-site RV or LV pacing in congestive heart failure patients with atrial fibrillation and advanced AV block. Sequential RV-LV stimulation offers minimal benefit on average and should perhaps be considered only in targeted subsets such as nonresponding patients. (*Circulation*. 2004;110:3404-3410.)

Key Words: atrial fibrillation • heart failure • pacing • physiology

Cardiac resynchronization therapy (CRT) with simultaneous stimulation of the right ventricle (RV) and left ventricle (LV) improves LV contractile function in patients with advanced heart failure and intraventricular conduction delay.1 Recent studies have proposed that some modest additional benefit may be obtained by use of sequential stimulation of the RV and LV, often with a small delay between them.2,3 Although both left and right preactivation had detrimental effects on LV function in one study,2 other short- and long-term investigations have found LV pacing to be as beneficial as BiV pacing.4–6 This has fueled controversy over the role of sequential stimulation in CRT.

An important caveat to prior studies investigating sequential stimulation and impact of pacing site is their need for ventricular preexcitation to achieve RV/LV capture. Varying delays and site may alter the influences of concomitant supraventricular activation (fusion) and atrial contraction. One way to remove such confounding factors is to study patients with chronic atrial fibrillation (AF) and advanced atrioventricular (AV) nodal block. Traditional single-site pacing induces dyssynchrony, whereas LV or biventricular (BiV) pacing with optimized stimulation timing may minimize this detrimental effect. Accordingly, the present study compared RV, LV, and BiV stimulation in individuals with advanced heart failure, chronic AF, and advanced AV block. The 2 aims of the study were to assess the impact of varying pacing site and site combinations in this setting and to determine the value of sequential RV-LV pacing to enhance cardiac function.

Patient Population
Nine consecutive patients (male; age, 65±11 years) with dilated cardiomyopathy (5 ischemic, 4 nonischemic), chronic AF, and advanced AV nodal block (s/p AV nodal ablation in 6 subjects) who agreed to participate in this investigation were studied. All patients had a traditional indication for bradycardia pacing. The Johns Hopkins Joint Committee on Clinical Investigation approved the study, and all participants provided written informed consent. All

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patients were on stable medical therapy for chronic heart failure. All patients were treated with a β-blocker, ACE inhibitor, or angiotensin receptor blockers, and all except 1 were treated with digoxin. Mean QRS duration was 152.4 ± 44 ms. One patient had a normal QRS pattern, 7 had left bundle-branch block pattern, and 1 had combined right bundle-branch block and left anterior hemiblock. All patients had already received or were referred for placement of a pacemaker for rate control with 100% capture. Mean ejection fraction (EF) was 24 ± 6%; 2 patients had severe and 2 patients had moderate mitral regurgitation.

Catheterization Protocol
The study group was instrumented with deflectable multipolar pacing catheters in the RV apex and lateral marginal cardiac vein. In 6 patients with prior excessive rapid ventricular response, AV node ablation was performed through the use of standard methods and ablation catheters. The ablation catheter was then repositioned at the high RV septum to serve as a second RV pacing site. A combined 6F dual pressure-volume (PV) catheter (Millar 550-768) was advanced through a 90-cm flexible long sheath (Arrow, CL-07690) and placed so that the pigtail tip lay at the distal LV apex. The catheter provided simultaneous proximal aortic and ventricular cavity micromanometer pressures and chamber volume, the latter by conductance method. Catheter volume was calibrated by matching to steady-state PV loops in 6 patients; in the remaining 3 subjects, a poor signal-to-noise ratio resulting from marked chamber dilation and low EF precluded analysis. This was evident at the time of the study and was not determined post hoc. Analysis of the steady-state PV loops was performed as previously described.

Systolic time intervals were measured from LV and aortic pressure tracing using the following definitions. Pre-ejection activation time was the interval from the pacing spike to crossover of LV and aortic pressures (aortic valve opening). Ejection time was the interval between aortic valve opening and the dicrotic notch, and systole period was the sum of activation and ejection time (ie, time interval from pacing spike to end of ejection). The diastole period was the total cycle length minus systolic period, and the ratio between diastole time to RR interval was calculated for each heart rate.

Effects of pacing site and heart rate were evaluated by 2-way repeated measures ANOVA with site and heart rate as categorical variables and a Tukey test for post hoc multiple comparisons. The effects of different interval delays were analyzed similarly by 1-way repeated-measures ANOVA. Results are presented as mean ± SD except when noted otherwise.

Results

Influence of Altering Pacing Site and Site Combinations
Figure 1 shows comparisons between RV apex, LV lateral, and combined simultaneous BiV pacing on cardiac function. Systolic function improved significantly with both LV and BiV compared with RV apex pacing at both heart rates (P < 0.0001), with a somewhat greater response in dP/dtmax (P < 0.001) from BiV. This was accompanied by increases in arterial pulse pressure, systolic pressures, stroke work, and EF. In contrast, diastolic relaxation indexed by dP/dtmin and mono-exponential time constant (τ) improved only with BiV pacing. Individual responses to pacing in different loci and heart rate for dP/dtmax and dP/dtmin are shown in Figure 2.
Results for varying pacing sites are provided in Table 1. Systolic function and diastolic function were nearly identical with RV apex or outflow tract pacing or their combined stimulation. The addition of an LV stimulation site (BiV) enhanced function similarly when used in conjunction with RV apex compared with RV outflow pacing for all but EF, which was better when LV pacing was combined with RV apex stimulation.

Although the relative benefit of BiV over RV pacing was similar at normal (80 bpm) and high (120 bpm) mean heart rates, there were heart rate interactions on net ejection. In particular, cardiac output changed by $-22\%$ at the faster heart rate (120 versus 80 bpm) when hearts were paced from the RV apex, whereas it rose 18% and 26% if the same hearts were paced with BiV or LV stimulation ($P<0.05$ for interaction effect; Figure 3). This was due to a somewhat greater change in stroke volume ($-47\%$ versus $-20\%$ and $-9\%$, RV versus BiV and LV, respectively) for RV pacing compared with the other 2 modes ($P=0.06$). There was a borderline greater decline in preload (but unchanged end-systolic volume) with RV apex pacing ($P=0.13$) that likely underlay the fall in stroke volume and output. This indicates that the benefit of LV or BiV over RV pacing applied not only to basal function but also importantly to rate-dependent systolic ejection reserve.

To further explore the mechanisms for the differential rate effect on cardiac output, we examined systolic and diastolic time intervals (Table 2). Pre-ejection time was shorter with BiV than LV or RV pacing and did not change with heart rate. Ejection time was similar among the 3 pacing modes at both heart rates. Thus, the systolic period was shorter and the diastolic period was accordingly longer with BiV compared with LV or RV at both rates. Increasing the heart rate worsened this disparity, reducing the relative diastolic period (relaxation and filling) by 55% with RV pacing, 60% with LV

**Table 1. Systolic and Diastolic Function With Different RV Pacing Modes**

<table>
<thead>
<tr>
<th>Pacing Mode</th>
<th>dP/dt$_{max}$, mm Hg/s</th>
<th>Aortic Pulse Pressure, mm Hg</th>
<th>dP/dt$_{min}$, mm Hg/s</th>
<th>EF, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV apex</td>
<td>817±87</td>
<td>36.3±7.4</td>
<td>−793±135</td>
<td>21.7±6</td>
</tr>
<tr>
<td>RV septal</td>
<td>845±50</td>
<td>35.7±9.1</td>
<td>−826±131</td>
<td>15.2±7</td>
</tr>
<tr>
<td>Bi-focal RV</td>
<td>839±83</td>
<td>37.3±7.5</td>
<td>−844±121</td>
<td>19.9±6</td>
</tr>
<tr>
<td>RV septal with LV</td>
<td>979±82$^*$</td>
<td>39.5±8.5$^*$</td>
<td>−896±95$^*$</td>
<td>25.5±6</td>
</tr>
<tr>
<td>RV apex with LV</td>
<td>988±107$^*$</td>
<td>39.8±8.5$^*$</td>
<td>−908±112$^*$</td>
<td>30.3±9$^*$</td>
</tr>
</tbody>
</table>

$^*$P<0.05 vs RV apex.
pacing, and 47% with BiV stimulation (P<0.001 for interaction effect).

Influence of Varying RV-LV Stimulation Delay

Figure 4 shows an example PV loops depicting the effect of varying the delay between RV-LV stimulation on global LV function. With increasing RV prestimulation, the loops became progressively thinner and slanted leftward (likely reflecting worsening mitral regurgitation) (Figure 4A). Simultaneous RV-LV stimulation was superior to having any RV preactivation. However, minimal further impact was observed with LV preactivation. However, minimal further impact was observed with LV preactivation was never superior to simultaneous BiV or LV-only stimulation.

Discussion

The main new findings in this study are that in patients with AF, AV nodal block, and chronic heart failure, BiV pacing acutely enhances both systolic and diastolic function compared with RV-only or LV-only stimulation. As a single site, however, LV stimulation improves systolic function considerably and similarly to BiV. Importantly, these data are obtained without confounding influences of supraventricular conduction or timing and effect of atrial systole. Furthermore, we show that sequential BiV pacing offers little additional benefit over simultaneous pacing in these patients and that the precise RV pacing site has little impact on the result.

Prior reports have generally found that LV-only pacing has comparable or even better effects on cardiac function than BiV pacing. Such studies have been performed in patients with sinus rhythm and with an existing intraventricular conduction defect.4,5,9 The mechanisms by which LV-only pacing works remain somewhat controversial.10 Fusion with electrical activity from the AV node is a possibility;11–13 however, experimental data have suggested that electrical synchrony is not a prerequisite for mechanical synchrony.14 Another possible explanation is that early activation of the lateral wall is preferable to the septum, ie, that dyssynchrony associated with right bundle-branch block–type delay is less than that associated with left bundle-branch block–type delay.10 This is consistent with regional motion analysis of left versus right bundle-branch block, where initial prestretch of the opposing wall is greater with early septal activation.14 By eliminating any possibility of electrical fusion, the present data support the latter hypothesis, particularly with respect to systolic function. Improved diastolic function was observed only with BiV stimulation, indicating that single-site LV pacing may still induce some intraventricular dyssynchrony that can affect relaxation. Myocardial relaxation is influenced by chamber load and homogeneity of activation.15–18 In previous work, we did not find an improvement in ventricular relaxation with resynchronization therapy,4 and Auricchio et al13 found that CRT had only a modest effect on relaxation. This may, however, reflect the more complex influence of

<table>
<thead>
<tr>
<th>TABLE 2. Systolic and Diastolic Time Intervals at Different Heart Rates and Pacing Sites</th>
<th>Pre-Ejection Time, ms</th>
<th>Ejection Time, ms</th>
<th>Systole Time, ms</th>
<th>Diastole Time, ms</th>
<th>Diastole/RR, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pacing Site</td>
<td>HR 80 bpm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVP</td>
<td>205±25</td>
<td>259±22</td>
<td>464±27</td>
<td>286±27</td>
<td>38.1±3.6</td>
</tr>
<tr>
<td>LVP</td>
<td>211±14</td>
<td>259±23</td>
<td>470±23</td>
<td>286±27</td>
<td>37.3±3.0</td>
</tr>
<tr>
<td>BiV</td>
<td>179±16*</td>
<td>264±26</td>
<td>443±22*</td>
<td>307±22*</td>
<td>41.2±3.0*</td>
</tr>
<tr>
<td>Pacing Site</td>
<td>HR 120 bpm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVP</td>
<td>203±23</td>
<td>211±16</td>
<td>413±21</td>
<td>87±11</td>
<td>17.3±4.1</td>
</tr>
<tr>
<td>LVP</td>
<td>203±23</td>
<td>213±15</td>
<td>421±17</td>
<td>79±17</td>
<td>15.7±3.5</td>
</tr>
<tr>
<td>BiV</td>
<td>172±15†</td>
<td>216±21</td>
<td>388±14†</td>
<td>112±14†</td>
<td>22.3±2.8†</td>
</tr>
</tbody>
</table>

HR indicates heart rate; RVP, RV pacing; and LVP, LV pacing. Values are mean±SD.

*P<0.05 vs RVP at 80 bpm; †P<0.05 vs RVP at 120 bpm.
preactivation and atrial contraction on chamber load present during sinus rhythm. Removing this factor in the present study revealed a significant advantage of BiV over other modes of stimulation on chamber relaxation.

This is the first study to assess the hemodynamic response to various ventricular stimulation methods as a function of varying heart rate. This is important because most symptomatic improvement relates to exertional tolerance and not rest symptoms. Increasing heart rate could theoretically alter electrical delay and thus mechanical activation sequence, thereby changing its impact on net chamber function. We found that the relative benefits of BiV and LV pacing over conventional RV stimulation at normal resting heart rates were not just maintained but enhanced at faster rates. Moreover, diastolic filling was better at a higher heart rate with BiV and LV compared with RV pacing. Systolic intervals were shorter with BiV, allowing longer diastolic time intervals for a given heart rate. This was especially evident at rapid heart rate and contributed to better diastolic filling with BiV pacing. Because systolic intervals were similar between RV and LV pacing, the improved diastolic filling at a high heart rate with LV pacing should be attributed to different factors such as a decrease in mitral regurgitation and a change in the time delay between RV and LV contraction. The latter can improve LV filling by changing ventricular...
interaction and allowing the LV to fill before the development of external restraint from the RV.\textsuperscript{19}

Several recent studies have suggested a potential advantage of using an alternative RV pacing site instead of the apex, specifically placement along the mid to upper infundibular tract.\textsuperscript{20,21} In addition, some have suggested that simultaneous RV stimulation at both the apex and outflow tract can lead to sufficient resynchronization effect to potentially obviate the need for an LV lead.\textsuperscript{22} The latter hypothesis is particularly attractive given the complexity of LV lead placement. However, our data indicate that RV lead position has little to no impact on the CRT results and that simultaneous dual-site RV stimulation behaves like single-site RV stimulation. In addition, when RV is combined with LV pacing, the site of concomitant RV pacing makes little difference.

This is the first study to examine the influence of sequential BiV pacing in patients with AF. Several prior studies have examined this modality in patients with heart failure, basal conduction delay, and sinus rhythm. Sogaard et al\textsuperscript{2} first examined this modality in patients with heart failure, basal concomitant RV pacing makes little difference. In addition, when RV is combined with LV pacing, the site of concomitant RV pacing makes little difference.

The present study should be contrasted to those in several recent studies of AF patients. Puggioni et al\textsuperscript{3} reported a small increase in systolic function with LV compared with RV pacing in patients with chronic AF but did not contrast BiV and LV pacing. Simantirakis et al\textsuperscript{4} more recently compared RV, LV, and BiV stimulation in patients with AF and essentially normal systolic function after AV nodal ablation and found nearly identical but modest (10%) benefits from LV and BiV pacing. Myocardial relaxation was not different between the 3 pacing modes.\textsuperscript{24} The present study was conducted in patients with marked cardiac failure and a delay in relaxation, with values of both dP/dt\textsubscript{max} and dP/dt\textsubscript{min} <60% of those in the prior study. This likely explains the greater impact between pacing modes (~25% difference) and effects on relaxation.

**Study Limitations**

We tested interventricular delay intervals of \(\approx 40\) ms rather than very short delays. In patients in sinus rhythm, optimal RV-LV delay varies between 12 and 20 ms\textsuperscript{2} and can be as high as 60 ms.\textsuperscript{3} Given the shape of the derived relations (Figure 5), however, it is unlikely that a clinically significant response was overlooked. The calibration method of the conductance catheter was not based on contemporaneous assessment of absolute volume, but this would not affect the results, which depended solely on relative changes within each patient as a result of the pacing protocol. The inadequacy of the volume signal in 30% of patients is expected, given the extent of chamber dilation and cardiodepression, and we found consistent results in arterial pulse pressure (which reflects output) in patients with or without an interpretable volume signal. Because of the invasive nature of our study, only a small sample of patients were studied in only the short-term setting. Therefore, our results may not predict clinical BiV outcomes during medium- or long-term follow-up. The small sample size may not have allowed detection of modest but clinically meaningful effects of RV lead position or sequential BiV pacing.

**Conclusions**

Short-term RV pacing, regardless of site or combination of sites, is hemodynamically inferior to BiV or LV pacing in heart failure patients with chronic AF lacking supraventricular conduction. This effect is perhaps even greater at faster heart rates. Sequential RV-LV stimulation offers minimal benefit over simultaneous pacing.

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**Disclosure**

Drs Kass and Berger serve as consultants to Guidant. Drs Kramer and Spinelli and Craig Reister are Guidant employees. The other authors have no relationships to disclose.

**References**


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