Biventricular Pacing Decreases Sympathetic Activity Compared With Right Ventricular Pacing in Patients With Depressed Ejection Fraction

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Background—Although there have been few studies in which the hemodynamic effects of right ventricular (RV) and left ventricular (LV) pacing were compared with those of biventricular (BV) pacing, the autonomic changes during these different pacing modes remain unknown. We hypothesized that BV pacing results in improved hemodynamics and a decrease in sympathetic nerve activity (SNA) compared with single-site pacing.

Methods and Results—Thirteen men with a mean ejection fraction of 0.28±0.7 were enrolled in the study. Arterial blood pressure (BP), central venous pressure (CVP), and SNA were recorded during 3 minutes of right atrial (RA)-RV, RA-LV, and RA-BV pacing at a rate 10 beats faster than sinus rhythm. BP was greater during LV (151±7/85±3 mm Hg) and BV (151±6/85±3 mm Hg) pacing than during RV pacing (146±7/82±3 mm Hg) (P<0.05). There were no differences in CVP among all pacing modes (P=0.27). SNA was significantly less (P<0.02) during both LV (606±35 U) and BV (582±41 U) pacing compared with RV pacing (685±32 U) (P<0.02). Although not statistically significant (P=0.08 to 0.14), there was a trend for patients with a narrow QRS to have a lower mean BP and higher SNA during LV pacing than during BV pacing (r=0.42 to 0.49).

Conclusions—LV-based pacing results in improved hemodynamics and a decrease in SNA compared with RV pacing in patients with LV dysfunction regardless of the QRS duration. (Circulation. 2000;102:1027-1032.)

Key Words: heart failure • pacing • nervous system, autonomic

Conventional pacing of the right heart with a short atrioventricular (AV) delay was used as an adjunctive therapy in patients with drug-resistant congestive heart failure until prospective studies showed no improvement or even deterioration with pacing.1–3 Today, dual chamber pacing is used only for the treatment of symptomatic bradyarrhythmias. On the other hand, preliminary results with biventricular (BV) pacing have shown improvement in New York Heart Association (NYHA) functional class and exercise tolerance in patients with depressed ejection fraction and intraventricular conduction delay.4 This improvement is thought to be the result of correction of the electrical and mechanical asynchrony of the left heart. To our knowledge, few studies5–8 have compared the hemodynamic effect of single-site versus multisite pacing in patients with depressed ejection fraction, and no studies have considered the autonomic changes during these different pacing modes.

Therefore, the purpose of the present study was to compare BV pacing with right ventricular (RV) and left ventricular (LV) pacing in patients with depressed ejection fraction. Arterial blood pressure (BP), central venous pressure (CVP), and muscle sympathetic nerve activity (SNA) with microneurography were measured during sinus rhythm and single-site and multisite pacing at rates slightly above normal sinus rhythm. We hypothesized that BV pacing results in improved hemodynamics and a decrease in sympathetic activity compared with single-site pacing.

Methods

Patients
The study was performed at the Dallas Veterans Affairs Medical Center and was approved by the institutional review board. Informed consent was obtained from all patients, and all procedures were conducted in accordance with institutional guidelines. All patients with a clinical indication for programmed electrical stimulation and a depressed ejection fraction (<0.35) were screened for the study. Patients were excluded if they had a history of insulin-dependent diabetes mellitus or a history or signs of peripheral neuropathy. A total of 13 patients were enrolled in the study, and the recordings from these subjects form the basis of the present study.

Experimental Protocol
After acceptable recordings of SNA were obtained, the following protocol was performed. Arterial BP, CVP, and sympathetic neural

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responses to 3 minutes of pacing were recorded during right atrial (RA)-RV, RA-LV, and RA-BV pacing. The sequence was chosen at random with a 1-minute recovery time and a 1-minute repeat baseline value obtained between each pacing mode.

Electrophysiological Studies
Patients were studied in the drug-free postabsorptive state after informed consent was obtained. Three quadripolar catheters were inserted percutaneously and positioned in the high lateral RA, RV apex, and across the tricuspid valve for His-bundle recording. Next, a 2.5F multipolar catheter (Cardima Inc) was introduced from the femoral vein via a guiding catheter and positioned in the lateral cardiac vein for LV pacing. Atrial and ventricular pacing thresholds were then measured, and pacing was performed at twice diastolic pacing threshold.

Measurements
Efferent, postganglionic muscle SNA was recorded from the right peroneal nerve as previously described. Briefly, a sterile microelectrode was inserted into a fascicle of the peroneal nerve near the fibular head. The nerve signals were amplified, filtered (70 to 2000 Hz), rectified, and discriminated. Raw nerve signals were integrated (time constant 0.05 s) to produce a mean voltage display for quantitative analysis. Muscle sympathetic neural bursts during sinus rhythm were readily recognized by their tight temporal relationship to the sinus cardiac cycle, their increasing frequency during Valsalva maneuvers, the occurrence of large bursts accompanying premature ventricular beats, and their failure to respond to arousal stimuli or stroking of the skin. The SNA was quantified as the total activity derived from the sum of the area of the SNA bursts for a given time period. Area was used for these analyses because compared with the burst amplitude, it more appropriately reflects the changes in SNA associated with the wide variations in arterial BP that can occur during ventricular pacing. Arterial BP was directly recorded with a 5F catheter inserted into the right femoral artery. CVP was continuously recorded with a catheter placed in the right atrium via the right femoral vein. Heart rate (HR) was derived from continuous ECG recording of at least 2 leads (typically leads II and V1).

Statistics
All data sets were tested for normality with a Kolmogorov-Smirnov test. Group comparisons of RV, LV, and BV pacing were performed with a 1-way ANOVA with a repeated measure design. When main effect differences were obtained, post hoc comparisons were performed with a Tukey’s multiple range test to distinguish individual differences between pacing conditions. A rank sum test was used for post hoc comparisons in which normality failed. A linear regression was used to assess the relation of QRS duration to the difference between LV and BV pacing for each variable. For all analyses, significance was set at an α level of 0.05.

Results
Patient Characteristics
All patients were men with a mean age of 66±8 years. The mean ejection fraction was 0.28±0.07, with coronary artery disease present in all patients except 1. Baseline ECG revealed a wide spectrum of intraventricular conduction delay with a mean QRS duration of 123±31 ms. Six of 13 patients had a QRS duration of >120 ms, and 4 of these 6 patients had

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Ejection Fraction</th>
<th>PR, ms</th>
<th>QRS, ms</th>
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<td>98</td>
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<td>2</td>
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<td>0.35</td>
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<tr>
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<td>5</td>
<td>75</td>
<td>0.35</td>
<td>177</td>
<td>124 (LBBB)</td>
</tr>
<tr>
<td>6</td>
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<td>0.20</td>
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<td>127</td>
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<tr>
<td>7</td>
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<td>0.35</td>
<td>204</td>
<td>182 (LBBB)</td>
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<td>8</td>
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<tr>
<td>13</td>
<td>74</td>
<td>0.25</td>
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<td>108</td>
</tr>
</tbody>
</table>

Mean±SD 66±8 0.28±0.07 182±33 123±31

LBBB indicates left bundle-branch block.

Figure 1. Sample tracings of original signals of an integrated sympathetic neurogram, arterial BP, and CVP during RA-RV, RA-LV, and RA-BV pacing.
left bundle-branch block. A summary of patient characteristics and the ECG measurements is provided in the Table.

**Hemodynamic Changes During RV, LV, and BV Pacing**

Figure 1 illustrates a sample tracing of arterial BP, CVP, and the integrated neurogram for SNA during each pacing mode. Arterial BPs were slightly higher during both LV and BV pacing compared with RV pacing. The average hemodynamic data for all patients (n=13) during each pacing mode are summarized in Figure 2. Both LV (151±7/85±3 mm Hg) and BV (151±6/85±3 mm Hg) pacing resulted in arterial BPs that were greater (P<0.05) than during RV pacing (146±7/82±3 mm Hg). There were no differences in CVP among all pacing modes (P=0.27).

**Sympathetic Activity During RV, LV, and BV Pacing**

The normal pulse synchrony of SNA bursts was maintained under all conditions (Figure 1). The average data during each pacing mode are summarized in Figure 3. The sympathetic neural responses were a mirror image of the arterial BP responses. SNA was significantly less (P<0.02) during both LV (606±35 U) and BV (582±41 U) pacing compared with RV pacing (685±32 U) (P<0.02). However, BV pacing was not significantly less than LV pacing (P=0.56).

**Correlation Between QRS Duration and Hemodynamic/Sympathetic Neural Responses**

The patient population demonstrated a wide range of QRS durations (from 94 to 188 ms). Although the mean data for the patient group as a whole did not differ between LV and BV pacing, on inspection of individual data, there appeared to be some possible differences between LV and BV pacing when patients with a narrow QRS were compared with those with a wide QRS. Therefore, each hemodynamic variable and SNA were correlated against QRS duration to determine whether differences between LV and BV pacing may exist in some patients. Figure 4 illustrates the linear regression analysis between QRS duration and the difference between LV and BV pacing for mean BP (top) and SNA (bottom). Similar results were obtained for systolic and diastolic BPs.
For each variable, there was a trend toward narrow QRS durations with a lower mean BP and higher SNA during LV pacing compared with during BV pacing; however, the correlation coefficient values (range 0.42 to 0.49) were not statistically significant ($P=0.08$ to 0.14).

**Discussion**

The main findings of the present study are that (1) BV pacing results in improved hemodynamics and a decrease in sympathetic activity compared with RV pacing in patients with LV dysfunction regardless of the QRS duration and (2) the same benefits can be achieved with LV pacing alone. To the best of our knowledge, this is the first study to show that acute BV or LV pacing results in a decrease in sympathetic activity compared with RV pacing in patients with depressed ejection fraction. Increased sympathetic activity has been shown to be a negative prognostic factor in patients with congestive heart failure; therefore, if our present findings persist with long-term pacing, BV or LV pacing should be considered in patients with a depressed ejection fraction and an indication for chronic pacing.

**Dual Chamber Pacing as a Treatment of Congestive Heart Failure**

The usefulness of physiological dual chamber pacing with a short AV delay in patients with congestive heart failure was tested more than a decade ago. Brecker et al$^9$ demonstrated that in selected patients with shortened diastolic filling times, AV synchronous pacing with a short AV delay improved cardiac output and exercise duration. Pacing in these patients was associated with an increase in diastolic filling time and a reduction in presystolic mitral or tricuspid regurgitation, or both. Similarly, Nishimura et al$^10$ showed that DDD pacing could significantly improve cardiac performance in patients with a long PR interval and evidence of AV dysynchrony in the left heart. These results, however, were soon challenged by other studies that showed no improvement or even a decrease in cardiac performance with DDD pacing. Innes et al$^1$ tested the effect of AV synchronous pacing with an AV delay of 60 and 100 ms in 12 patients with stable heart failure. Pacing increased diastolic filling time but reduced the stroke volume and cardiac index. Linde et al$^2$ studied the long-term effect of AV synchronous pacing in 10 patients with NYHA class III or IV heart failure. Despite optimization of the AV delay with Doppler echocardiographic measurements, consistent improvement in stroke volume and cardiac output was observed in only 1 patient. The interest in conventional short AV delay DDD pacing in patients with heart failure waned as the result of a double-blinded randomized study that showed no immediate improvement in hemodynamics and no long-term change in ejection fraction or NYHA functional class.$^{11}$ With failure of conventional DDD pacing to show consistent improvement in hemodynamics in these patients, the interest has shifted to BV pacing.

**Effect of BV Pacing Versus RV Pacing on Hemodynamics**

The mechanisms via which BV pacing is thought to improve cardiac function include the following: (1) a decrease in mitral regurgitation, (2) an increase in filling time, (3) optimization of left-sided mechanical AV delay, and (4) normalization of ventricular electrical activation. In patients with mild to moderate congestive heart failure, BV pacing has been shown to acutely improve global systolic ventricular function, presumably by improving coordination of segmental ventricular contraction.$^{12}$ In patients with intraventricular conduction delay, it is suggested that BV pacing restores the normal activation pattern, resulting in a decrease in mitral regurgitation and an improvement in effective preload.$^{13}$ Although some studies have considered the effect of BV pacing in patients with depressed ejection fraction, comparison between BV pacing and RV pacing has been assessed in only a few studies.$^{5,6,12,14}$ Cazeau et al$^5$ compared the hemodynamic effects of BV pacing with those of RV pacing in 8 patients with widened QRS and end-stage heart failure. Regardless of the AV delay, BV pacing was superior to RV pacing, resulting in a higher cardiac output and a decrease in pulmonary capillary wedge pressure and mean V-wave amplitude. Leclercq et al$^6$ assessed the acute hemodynamic effects of BV pacing in 18 patients with severe congestive heart failure and major intraventricular conduction delay (QRS $170\pm37$ ms). With AAI pacing used as a reference, this acute hemodynamic study demonstrated that BV DDD pacing significantly improved cardiac index compared with intrinsic conduction and single-site RV DDD pacing.

Our findings are consistent with those of these previous studies. Compared with RV pacing, BV pacing resulted in a significantly higher arterial BP with no significant change in CVP. This improvement was seen regardless of the presence or absence of intraventricular conduction delay. Thus, BV pacing was consistently superior to RV pacing.

**Effect on Hemodynamics of BV Pacing Versus LV Pacing**

With the superiority of BV pacing compared with RV pacing, the question emerged of whether the same hemodynamic improvement can be observed with LV pacing alone. Few studies have addressed this question by comparing the effect of LV pacing alone with that of BV pacing or baseline sinus rhythm in patients with severe heart failure.$^{8,12,14,15}$ Blanc et al$^8$ compared the acute hemodynamic changes associated with (1) RV apex or RV outflow tract pacing, (2) LV pacing, or (3) RV apex and LV pacing combined. Twenty-three patients with NYHA class III or IV, pulmonary capillary wedge pressure of $>15$ mm Hg, and either first-degree AV block or bundle-branch block (or both) were enrolled. Pacing from different ventricular sites was performed in either VDD mode (AVI 100 ms) or VVI mode in patients with atrial fibrillation. BV pacing resulted in higher systolic BP, lower pulmonary capillary wedge pressure, and lower V-wave amplitude than either baseline or RV pacing. Interestingly, the results with LV pacing alone were similar to those obtained with BV pacing. Kass et al$^{15}$ measured aortic and LV pressures in 18 patients with heart failure during VDD pacing at varying sites and AV delays. LV and BV pacing enhanced systolic BPs in patients with LV dysfunction and intraventricular conduction delay. In addition, the authors
demonstrated that these changes were primarily the result of a direct improvement in LV systolic function with minimal changes in diastolic filling pressures or relaxation. Recently, Auricchio et al.4 showed that BV and LV pacing increased maximum LV pressure and pulse pressure more than RV pacing in patients with congestive heart failure and wide surface QRS. Furthermore, these changes were more significant with LV pacing than with BV pacing.

Our results are similar to those of these previous studies. In patients with depressed ejection fraction and intraventricular conduction delay, LV pacing resulted in hemodynamic changes similar to those obtained with BV pacing. In addition, we found that patients without intraventricular conduction delay are also likely to benefit from LV pacing alone. We do not find this surprising because the beneficial effects of LV-based pacing are not limited to normalization of ventricular electrical activation but also include an increase in filling time, optimization of left-side mechanical atrioventricular delay, and a decrease in mitral regurgitation. However, our findings suggest that the beneficial effect of LV pacing alone tended to decrease as the QRS duration decreased, suggesting that patients with a wider QRS duration are more likely to benefit equally from LV and BV pacing, whereas those with a narrow QRS duration may benefit more from BV pacing.

**Sympathetic Activity in Congestive Heart Failure**

Sympathetic activity is increased in patients with congestive heart failure. This is evidenced by elevated levels of circulating norepinephrine levels16–18 and increases in adrenergic nerve outflow, as measured with microneurography.19 The cause of this increase is thought to be in part secondary to abnormal baroreflex control of adrenergic outflow from the central nervous system. Patients with heart failure have been shown to have a blunted HR response and a reflex increase in forearm vascular resistance during tilt-table testing.20,21 Although the increase in sympathetic activity may play a compensatory role early during the disease process, chronic adrenergic activation is recognized as a contributor to the vicious cycle that promotes progression of the disease through multiple effects, including increased afterload, exertion of a direct toxic effect on the failing myocardium, increased myocardial oxygen demand, and triggered ventricular arrhythmias. Indeed, elevated plasma norepinephrine levels have been shown to correlate with cardiac mortality rates and are a better prognostic predictor than ejection fraction.22 It is not clear, however, whether this is a cause of death or simply a marker of the underlying cardiac disease.

The adverse effect of adrenergic stimulation prompted the use of β-blocker therapy in patients with congestive heart failure. In the present study, we sought to compare the effects of single-site and multisite pacing on sympathetic outflow in patients with LV dysfunction. A reduction in sympathetic activity with a given pacing mode would provide an additional method of interrupting the deleterious cycle that is facilitated by increased sympathetic activity in patients with heart failure.

**Effect of Pacing on Sympathetic Activity**

Saxon et al.23 recently showed a decrease in serum norepinephrine levels after 12 weeks of BV pacing in patients with congestive heart failure and conduction delay. This decrease was noted only in 21 patients with baseline norepinephrine levels of >800 pg/mL. The authors explained these findings with the positive inotropic effect of BV pacing in these patients. To our knowledge, this is the only study that assessed the effect of chronic BV pacing on serum catecholamine levels in patients with congestive heart failure.

The purpose of the present study was to compare BV pacing with single-site pacing in patients with LV dysfunction. We did not, therefore, compare BV pacing with sinus rhythm. Our results indicate for the first time that acute BV and LV pacing reduces sympathetic activity compared with RV pacing in patients with LV dysfunction regardless of the QRS duration. Although not statistically significant, a comparison of the differences between BV and LV pacing and the QRS duration revealed a correlation with $r=0.42$. This correlation suggests that the narrower the QRS, the greater is the benefit of BV pacing relative to LV pacing. On the other hand, the wider the QRS, the smaller is the difference and the more likely patients are to benefit equally from LV and BV pacing. Nevertheless, these data suggest that there may be a modest advantage to BV pacing compared with LV pacing alone, particularly in patients with narrow QRS durations.

We believe the changes in SNA are the result of the changes in arterial BP. The decrease in SNA during LV and BV pacing compared with RV pacing occurred in the setting of an increase in arterial BP, suggesting an arterial baroreflex–mediated sympathoexcitation. Another possible mechanism for the decrease in sympathetic activity is a direct effect of pacing on the cardiopulmonary baroreceptors resulting in increased cardioinhibition and thus a decrease in peripheral sympathetic activity. We believe this is very unlikely because RA filling pressures were similar in all three pacing modes.

**Clinical Implications**

If the hemodynamic and autonomic changes noted with acute pacing prove to be present with chronic pacing, then LV-based pacing should be offered to patients with LV dysfunction and an indication for chronic pacing. In addition to the hemodynamic improvement, the decrease in sympathetic activity may have an impact on mortality rate in these patients. As previously discussed, elevated levels of serum norepinephrine levels have been shown to correlate with mortality rates in patients with congestive heart failure. Therefore, a decrease in sympathetic activity, which has been shown to correlate with serum norepinephrine levels, may result in improved survival rates. This hypothesis must be tested in prospective studies that assess the long-term benefits of LV-based pacing.

**Study Limitations**

This study has limitations. First, pacing was performed at a rate slightly faster than sinus rhythm, and therefore our findings may not be present during an atrium-sensed/ventricle-paced mode. We think this is unlikely, and we believe our method is a better one because it allowed a direct comparison between single-site and multisite pacing while avoiding the spontaneous variations in HR commonly seen during DDD or VDD pacing. Second, our results were obtained with an AV interval of 100 ms and may not be present.
with a shorter or longer AV delay. The duration of the AV interval during pacing has been shown to be an important variable that modulates the hemodynamic outcome. We chose an AV interval of 100 ms to avoid competition with intrinsic conduction, and we cannot exclude the possibility that a different PR interval may have yielded different results. Finally, it should be emphasized that the current findings are the result of acute pacing, and the same conclusions may not be true with chronic pacing. This study, however, provides the basis for an evaluation of the chronic effect of multisite pacing on sympathetic activity in patients with congestive heart failure.

References

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