Cardiac Resynchronization Therapy Restores Optimal Atrioventricular Mechanical Timing in Heart Failure Patients With Ventricular Conduction Delay

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OBJECTIVES

We characterized the relationship between systolic ventricular function and left ventricular (LV) end-diastolic pressure (LVEDP) in patients with heart failure (HF) and baseline asynchrony during ventricular stimulation.

BACKGROUND

The role of preload in the systolic performance improvement that can be obtained in HF patients with LV stimulation is uncertain.

METHODS

We measured the maximum rate of increase of LV pressure, LVEDP, aortic pulse pressure (PP) and the atrioventricular mechanical latency (AVL) between left atrial systole and LV pressure onset in 39 patients with HF. Two subgroups were identified: “responder” if PP improved, or “nonresponder.”

RESULTS

Maximum hemodynamic improvement occurred at an atrioventricular (AV) delay that did not decrease LVEDP. Left ventricular and biventricular (BV) stimulation increased systolic hemodynamics significantly, despite no significant increase in LVEDP. All parameters decreased when the LVEDP was decreased by shorter AV delay. Left ventricular and BV stimulation provided better hemodynamics than right ventricular (RV) stimulation. For the nonresponder subgroup, systolic hemodynamics only worsened during AV delay shortening. For the responder subgroup, optimum PP was achieved when AVL was near zero.

CONCLUSIONS

Restoration of optimal left atrial-ventricular mechanical timing partly contributes to the hemodynamic improvements observed in this patient subgroup. However, preload alone cannot explain the differences seen between RV and BV stimulation and the contradictory PP decreases even at maximal preload in the nonresponder subgroup. These results may be explained by a site-dependent mechanism such as the degree of ventricular synchrony. Caution should be taken in these patients when optimizing AV delays using echocardiography techniques that focus on LV inflow. (J Am Coll Cardiol 2002;39:1163–9) © 2002 by the American College of Cardiology Foundation

Both ventricular stimulation site (1–3) and the atrioventricular (AV) delay (3) influence improvements of systolic function during cardiac resynchronization therapy (CRT). The mechanical AV delay affects systolic performance by modulating preload (4). Furthermore, the mechanical AV delay is prolonged with respect to the electrical AV delay in patients with heart failure (HF), and the prolongation is highly variable across individuals (5). Nevertheless, little data have been published on the role that AV delay and preload play in the improvements seen with CRT. Furthermore, despite the usage of inflow-based AV delay optimization techniques (6,7), no studies have tested whether systolic function is optimized by these techniques and, in particular, whether they might negatively impact patients that do not exhibit hemodynamic increases with CRT.

To address these issues and the relative importance of preload and resynchronization as mechanisms of action of CRT, we evaluated the relationship among aortic pulse pressure (PP), the maximum rate of left ventricular (LV) pressure increase (dP/dt\text{max}) and LV end-diastolic pressure (LVEDP) as a function of the programmed electrical AV delay in the patients enrolled in the Pacing Therapies for Congestive Heart Failure (PATH-CHF) study (8). We tested the hypothesis that, in the subgroup of patients that respond positively to CRT, the maximum increases in PP are obtained when the AV delay maximizes LV preload, as evaluated by LVEDP.

METHODS

Patient population. Thirty-nine of 42 patients enrolled in the PATH-CHF study, who had technically valid data, represent the study population. The PATH-CHF study was a multicenter prospective randomized crossover sequential study to evaluate the effects of CRT and stimulation site on...
Acute and chronic hemodynamic function in patients with New York Heart Association functional class III to IV HF and ventricular conduction delay. The complete PATH-CHF study inclusion and exclusion criteria as well as the study design and endpoints have been presented elsewhere (8,9). The ethical committees at all participating centers and the competent authorities of their respective countries approved the protocol. All patients provided written informed consent before participating in the study.

Acute data collection. The acute test procedure and data collection have been previously described (3). Briefly, under general anesthesia, permanent pacing leads were inserted (Sweet-Tip, Guidant Corp. CRM, St. Paul, Minnesota) in the right atrial appendage and right ventricle (RV), and an epicardial screw-in lead was attached to the LV via a limited thoracotomy. Patients were instrumented for acute study by placing two 8F dual transducer Millar micromanometer catheters (Millar Instruments, Houston, Texas) for measuring aortic, RV and LV pressures. Each patient was tested in univentricular (RV and LV) and biventricular (BV) configurations, using five AV delays, that divided the intrinsic AV interval into five equal duration segments ranging from 0% to 86% of this interval. Each site/AV delay combination was repeated five times in random order. Data were digitized (16-bit resolution, 500 Hz sampling rate, TEAC, Montebello, California) for offline analysis.

Hemodynamic parameters and responses to CRT. Aortic diastolic and systolic pressures, PP, LVEDP and dP/dt_max were extracted using custom software (Guidant Corp.). Aortic pulse pressure was defined as the difference between aortic systolic and diastolic pressure; LVEDP was measured as the LV pressure at the beginning of LV mechanical contraction. Absolute values and changes from baseline were evaluated.

Patients for whom there was an increase in PP with respect to their intrinsic baseline by more than 5% for any stimulation mode and AV delay combination were placed in a responder subgroup. The remaining patients were placed in a nonresponder subgroup.

Atrial and ventricular electrical/mechanical events. Figure 1 illustrates the electrical and mechanical events and the timing intervals measured. Right atrial electrical activation is designated as right atrium (RA). The peak of a small change in LV pressure before ventricular systole reflects LA systole (A_p) as seen in the LV (10). Thus, the RA-A_p interval is a complex electromechanical delay comprising the time elapsed from RA to the mechanical activation of the left atrium, which, in turn, creates a pressure increase in the LV. The start of LV contraction is marked as L_s. During intrinsic rhythm, RA-L_s represents the electromechanical AV delay. The interval between left atrial systole and the beginning of the LV contraction is defined as the AV mechanical latency (AVL). During intrinsic beats, AVL reflects the lag between the end of left atrial contraction, as seen in the LV, and the beginning of LV contraction. A positive AVL (meaning left atrium precedes LV) indicates that the left atrium contributes to the LV filling process; a negative value, which can occur when the ventricle is paced
with a sufficiently short AV delay, indicates ventricular contraction preceding the peak of atrial filling.

**Timing measurements.** The intrinsic timing of Ls was determined directly from an intrinsic LV pressure curve as the first point (before the peak of systole) having a slope $\geq 0.1 \text{ dP/dt}_{\text{max}}$. As illustrated in Figure 1, for each paced beat, the last intrinsic pressure curve of each sequence was aligned with each of the corresponding five paced ven- tricular pressure curves at a fiducial point coinciding with RA. Then, the Ls point for that paced beat was determined from the difference of the two pressure curves using the slope technique described for an intrinsic beat.

The Ls points, their corresponding LVEDP, PP and dP/dt_{max} from all the paced beats with a same stimulation mode and AV delay were averaged. The timing of intrinsic Ls and Ap were averaged from the first set of 15 intrinsic beats. Only beats with intrinsic AV intervals within $\pm 1$ SD of the group mean were included in the analysis. The Ap timing was assumed to remain unchanged during the duration of the procedure and to remain unaffected by atrial synchronous ventricular stimulation.

**Statistics.** A two-tailed unpaired t test was used to evaluate the differences in baseline data between responder and nonresponder subgroups. A two-tailed paired t test was used to test the significance of changes in PP and dP/dt_{max} from all the paced beats with a same stimulation mode and AV delay. To account for multiple comparisons, a p value of 0.05 was considered significant. Results are expressed as the mean $\pm$ SD in the text and mean $\pm$ SE in the plots.

## RESULTS

Table 1 contains the demographic data for the study population. Most patients had left bundle branch block. During the acute testing, all patients except one (who required DDD pacing due to bradycardia) were paced in VDD mode. Of 39 patients, 27 were in the responder subgroup and 12 in the nonresponder subgroup. Nonresponder patients had a shorter QRS duration and larger dP/dt_{max} than the responders (Table 1).

**Preload dependence of the hemodynamic changes.** For the group of all patients, the maximum increases in PP and dP/dt_{max} occurred at 43% of the intrinsic AV interval (Fig. 2). At this AV delay, PP and dP/dt_{max} increases were significant for LV and BV stimulation and significantly larger than the increases seen for RV stimulation, while LVEDP did not change with LV or BV stimulation but significantly increased with RV stimulation (Table 2). Shortening the AV delay (from 43% to 0%) decreased PP, dP/dt_{max} and LVEDP (Table 2). The LVEDP decrease had a significantly larger impact on PP than on dP/dt_{max} ($p \leq 0.01$), for LV ($-9\%$ vs. $-6\%$), RV ($-7\%$ vs. $-4\%$) and BV ($-10\%$ vs. $-5\%$) stimulation.

**Responders.** The responder subgroup (Fig. 2, Table 2), showed the same changes as the group of all patients, but, due to its definition, the increases were larger. Also in this subgroup, PP decreased about twice as much as dP/dt_{max} ($p < 0.001$), when the AV delay was decreased from 43% to 0%.

**Nonresponders.** The nonresponder subgroup showed a monotonic decrease in PP and dP/dt_{max} when the AV delay was shortened. This decrease occurred with no significant decrease in LVEDP until AV delays were shorter than 43% of the intrinsic AV interval (Table 2). At middle AV delays, PP and dP/dt_{max} were significantly worse for RV stimulation compared with LV and BV stimulation. The percentage decreases in PP and dP/dt_{max} were similar for short AV delays.

**AV time lag measurements.** A measurable atrial peak (Fig. 1) was present in the LV pressure in 29/39 patients (19 responders and 10 nonresponders). The size of the atrial peak ranged between 0.5 mm Hg and 6.0 mm Hg. The intrinsic AVL varied from 33 ms to 140 ms, lasting on the average 65 $\pm$ 24 ms. The LV stimulation that resulted in the largest increase in PP in the responder subgroup occurred when AVL was in the range of 25 ms ($p < 0.0001$ vs. chance alone) (Fig. 3). For values of AVL outside of this range, the PP changed rapidly, declining symmetrically to near or below baseline (Fig. 3). For the nonresponder subgroup, however, the largest PP consistently occurred at the longest AV delay irrespective of the value of AVL (Fig. 3). A similar relationship between AVL and PP was observed for BV and RV stimulation modes.

The correspondence for all stimulation modes of the
maximum PP increase in the responder subgroup with a nearly zero AVL is quantified in Figure 4A. The RA–Ls was linearly correlated with the RA–Ap ($r^2 = 0.7$, slope = 1.1, intercept $= -28$ ms), indicating that at optimum AV delay AVL is small. The average AVL for maximum PP increase was $3 \pm 17$ ms for LV stimulation, $-3 \pm 15$ ms for BV stimulation and $-3 \pm 22$ ms for RV stimulation (p = NS). The relationship between RA–Ap and RA–Ls was weaker ($r^2 = 0.2$) when $dP/dt_{\text{max}}$ was maximized (Fig. 4B).

**DISCUSSION**

This study suggests that there are at least two electromechanical determinants of the PP and $dP/dt_{\text{max}}$ changes: 1) the active contribution of the left atrial systole to LV filling and 2) the improvement of contractile function due to resynchronization of inter/intraventricular contractions by LV or BV pre-excitation (11). The fact that for all stimulation modes the maximum $dP/dt_{\text{max}}$ and PP were obtained at an AV delay that preserved the baseline values of LVEDP suggests that preload plays a significant role in determining the point at which the optimum acute hemodynamic impact of CRT is achieved. This role is further supported by the behavior observed in the responder subgroup, where PP is consistently the optimum when AVL is near zero independently of the pacing site or site combination. It is likely that improved cooperative ventricular contraction amplifies the PP and $dP/dt_{\text{max}}$ increases in responder patients, since both the optimum PP and $dP/dt_{\text{max}}$ are significantly larger than intrinsic for both LV and BV stimulation, which, in turn, are larger than RV stimulation, even though all three types

**Figure 2.** The average aortic pulse pressure (PP), maximum rate of increase of left ventricular pressure ($dP/dt_{\text{max}}$) and left ventricular (LV) end-diastolic pressure (LVEDP) obtained during LV (left) and right ventricular (RV) (right) stimulation at each tested atrioventricular (AV) delay and at baseline (i.e., 100%) for the population, the responder subgroup and the nonresponder subgroup. Actual AV delays were normalized to baseline intrinsic AV interval (AVI) to simultaneously represent both the effect of short AVIs and pre-excitation present in the individual patients.
Table 2. Impact of AV Delay Changes on Hemodynamics for the Population, the Responder Subgroup and Nonresponders

<table>
<thead>
<tr>
<th>Site of Stimulation</th>
<th>All Patients</th>
<th>Responders</th>
<th>Nonresponders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PP (mm Hg)</td>
<td>dP/dt\text{max} (mm Hg/s)</td>
<td>LVEDP (mm Hg)</td>
</tr>
<tr>
<td>Changes from intrinsic to 43% AVI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV</td>
<td>2.7 ± 4.1</td>
<td>85 ± 83</td>
<td>0.4 ± 2.5</td>
</tr>
<tr>
<td>RV</td>
<td>0.5 ± 2.6</td>
<td>15 ± 66</td>
<td>0.7 ± 1.5*</td>
</tr>
<tr>
<td>BV</td>
<td>2.8 ± 3.8</td>
<td>77 ± 81</td>
<td>-0.1 ± 2.9</td>
</tr>
<tr>
<td>Changes from 43% AVI to 0% AVI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV</td>
<td>-3.4 ± 2.1</td>
<td>-39 ± 37</td>
<td>-4.5 ± 4.0†</td>
</tr>
<tr>
<td>RV</td>
<td>-2.9 ± 2.5§</td>
<td>-26 ± 35</td>
<td>-4.9 ± 3.3‡</td>
</tr>
<tr>
<td>BV</td>
<td>-4.1 ± 2.9</td>
<td>-32 ± 37</td>
<td>-4.5 ± 4.0†</td>
</tr>
</tbody>
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*p < 0.01; †p < 0.001 for the change; §p < 0.01; ‡p < 0.001 between RV and biventricular stimulation; |p < 0.01; ¶p < 0.001 between RV and LV stimulation.

AV = atrioventricular; AVI = atrioventricular intrinsic; BV = both right and left ventricles (biventricular stimulation); dP/dt\text{max} = maximum rate of increase of left ventricular pressure; LV = left ventricle; LVEDP = left ventricular end-diastolic pressure; PP = aortic pulse pressure; RV = right ventricle.

Figure 3. (A) Relationship between aortic pulse pressure (PP) and atrioventricular mechanical latency (AVL) during left ventricle (LV) stimulation in the responder subgroup. Measurements are shown for all 19 patients with measurable and stable presystolic peaks. Pulse pressure changes are normalized to the maximum PP increases in each patient. Note that the AVL was calculated not only at five individual paced atrioventricular (AV) delays but also at the interpolated optimal AV delay for PP. The interpolation was based on a fourth order polynomial fit to the response curve. (B) Distribution of AVL values that corresponded to maximum increase in PP during LV stimulation in A. Each bin represents a 10 ms range of AVL values, and the number under each bin is the center value of that bin. (C) Same as A for 10 nonresponder patients. (D) Same as B for the nonresponder subgroup.
of stimulation equivalently advance the start of LV contraction and achieve a near-zero AVL. The observation that the AV delay that optimizes \( \frac{dP}{dt_{\text{max}}} \) is associated with a poor correlation between R-L S and R-AP (Fig. 4B) and that the sensitivity of \( \frac{dP}{dt_{\text{max}}} \) to decreases in LVEDP is less than for PP suggests that \( \frac{dP}{dt_{\text{max}}} \) may be more associated with a contractile function mechanism, such as the degree of intraventricular synchronization, which is less preload-dependent.

The roles of preload and ventricular synchrony in CRT. Stimulating the delayed LV alone or biventricularly appears necessary to maximally resynchronize ventricular contractions, increasing cooperative contractile function and output (3). Right ventricular stimulation is less effective at pre-exciting the delayed LV, minimally improving contractile function. The small PP increases during RV stimulation despite a larger LVEDP are consistent with this hypothesis. Thus, most of the PP increases with RV stimulation might be explained by the LVEDP increases, whereas the incremental increases in PP with LV and BV stimulation are likely due to better ventricular synchronization.

The alteration of cooperative contractile function also explains the PP and \( \frac{dP}{dt_{\text{max}}} \) decreases despite maintained preload in nonresponder patients. We hypothesize that this subgroup has relatively little ventricular asynchrony so that any pre-excitation tends to desynchronize the ventricles. In fact, the nonresponder patients had higher baseline hemodynamic function than responder patients, most notably a significantly higher \( \frac{dP}{dt_{\text{max}}} \) associated with a shorter QRS duration. It is well known that RV stimulation worsens LV systolic function compared with normal activation (12), with the results being less detrimental for LV or BV (13).

Alternatively, nonresponders may have baseline asynchrony, but the stimulation electrode placements are ineffective for restoring ventricular synchrony (14). By either explanation, CRT stimulation at long AV delays would be expected to have the least impact and may even be beneficial, while stimulation at short AV delays may desynchronize the ventricles worsening contractile function and decreasing PP. This hypothesis would explain why the maximum PP and \( \frac{dP}{dt_{\text{max}}} \) are observed at the longest AV delays in nonresponder patients, despite suboptimal AVL values.

AV mechanical lag and end-diastolic pressure as preload determinants. In a normal heart, atrial and ventricular systole are temporally coordinated to optimize blood transfer (10). For HF patients with prolonged AV conduction and diastolic mitral regurgitation, filling may be compromised (15). Although LVEDP is a good surrogate for preload, it does not take into account the dynamics of AV coordination, which is an important determinant of the efficiency of the LV contraction. The AVL individually measures AV coordination and takes into account any LV pressure decreases between the peak of LA systole and the start of LV contraction. Such pressure drops may be created by diastolic mitral regurgitation (15,16).

Clinical implications. Pulse pressure and \( \frac{dP}{dt_{\text{max}}} \) are indexes used to assess the LV systolic function because of their correlation with stroke volume and global contractile function, respectively, under the experimental conditions used in our study (2,4). Nevertheless, care should be taken when using these relationships because of their dependence on preload and arterial impedance. Inflow-based Doppler echocardiography techniques are gaining popularity as a method for optimizing the AV delay for CRT (6,7).
Basicallly, the method uses Doppler mitral flow velocity recordings to optimize the left AV mechanical timing such that filling time is maximized by starting the LV contraction at the end of the A-wave. However, an AVL of zero would correspond to the time of peak velocity in the A-wave and not to the end of the A-wave, suggesting that the optimum AV delay for responder patients may be shorter than currently believed. In contrast, for nonresponder patients, for whom a zero AVL is associated with PP and dP/dtmax decreases, the optimum AV delay is longer than the AV delay obtained using the inflow Doppler technique. Because this and other preload optimization methods will not account for the apparent nonpreload determinants of PP, they should be used with discretion. If a patient can be identified as responder type, optimizing by preload methods would seem safe. However, nonresponder patients should probably not be optimized by preload alone. For these patients, it may be better to optimize ventricular resynchronization rather than preload. The degree of resynchronization may be assessed by dP/dtmax (17).

Study limitations. Because only the peak of atrial contraction could be estimated from the presystolic component, the ventricular contraction may alter the shape or size of the presystolic component, making the determination of the atrial event less accurate. All these measurements were performed with the patients anesthetized, supine and at rest. Varying degrees of mitral regurgitation could have affected the results.

Conclusions. For HF patients with conduction defects, CRT with an appropriate AV delay can increase PP and dP/dtmax by restoring optimal AV mechanical timing and inter/intraventricular mechanical synchrony. The largest PP and dP/dtmax occurs at an AV delay that does not decrease LVEDP. The optimal PP for the responder subgroup patients occurs when the peak of left atrial systole coincides with the start of LV contraction. Changes in preload alone cannot explain the changes in PP observed with CRT, strongly supporting the presence of a second mechanism, probably related to the ability of LV and BV stimulation to improve the synchrony of the ventricular contraction (11,17).

The nonpreload mechanism appears to be the dominant PP and dP/dtmax determinant in the nonresponder subgroup. Thus, caution should be taken when optimizing AV delays using a method that only maximizes preload.

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