Left Ventricular Pacing Minimizes Diastolic Ventricular Interaction, Allowing Improved Preload-Dependent Systolic Performance

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Background—Left ventricular (LV) pacing improves hemodynamics in patients with heart failure. We hypothesized that at least part of this benefit occurs by minimization of external constraint to LV filling from ventricular interaction.

Methods and Results—We present median values (interquartile ranges) for 13 heart failure patients with LV pacing systems implanted for New York Heart Association class III/IV limitation. We used the conductance catheter method to measure LV pressure and volume simultaneously. External constraint was measured from the end-diastolic pressure-volume relation recorded during inferior vena caval occlusion, during LV pacing, and while pacing was suspended. External constraint to LV filling was reduced by 3.0 (4.6 to 0.6) mm Hg from 4.8 (0.6 to 7.5) mm Hg (P<0.01) in response to LV pacing; effective filling pressure (LV end-diastolic pressure minus external constraint) increased by 4.0 (2.2 to 5.8) mm Hg from 17.7 (13.3 to 22.6; P<0.01), LV end-diastolic volume increased by 10 (3 to 11) mL from 238 (169 to 295) mL (P=0.01), whereas LV end-systolic volume did not change significantly (−1 [−2 to 3] mL from 180 [124 to 236] mL, P=0.97), which resulted in an increase in stroke volume of 11 (5 to 13) mL from 49 (38 to 59) mL (P<0.01). LV stroke work increased by 720 (550 to 1180) mL·mm Hg from 3400 (2110 to 4480) mL·mm Hg (P=0.01), and maximum dP/dt increased by 120 (2 to 161) mm Hg/s from 635 (521 to 767) mm Hg/s (P=0.03).

Conclusions—This study suggests a potentially important mechanism by which LV pacing may produce hemodynamic benefit. LV pacing minimizes external constraint to LV filling, resulting in an increase in effective filling pressure; the consequent increase in LV end-diastolic volume increases stroke volume via the Starling mechanism. (Circulation. 2004;110:2395-2400.)

Key Words: heart failure □ diastole □ cardiac output □ hemodynamics □ pacing

Recently, biventricular pacing has been shown to significantly reduce morbidity and rehospitalization in congestive heart failure (CHF) patients with prolonged QRS durations who remain severely symptomatic despite optimal medical therapy.1,2 Such patients frequently have marked mechanical dyssynchrony that is improved by biventricular pacing,3,4 which augments left ventricular (LV) contractile function.5,6 Short atrioventricular delay pacing may also reduce presystolic mitral regurgitation.7 In several acute hemodynamic and echocardiographic studies, however, LV pacing has been shown to produce greater or equal improvements in parameters than biventricular pacing8–11 despite increasing rather than decreasing QRS duration.8 Furthermore, the acute hemodynamic benefit of LV pacing was predicted by higher pulmonary capillary wedge pressure but not by QRS duration.12 Even patients with a high pulmonary capillary wedge pressure and a normal QRS duration derived acute hemodynamic benefit.13

We hypothesized that at least part of the acute hemodynamic benefit from LV pacing may be due to reduced external constraint to LV filling. In previous work, we demonstrated that in CHF patients with high pulmonary capillary wedge pressure, LV filling was markedly impeded by external constraint from the right ventricle (RV) via the shared interventricular septum (direct diastolic ventricular interaction)14 and from the stretched pericardium (pericardial constraint). Lower-body negative pressure reduced RV volume but increased LV volume and stroke volume. We concluded that this was because the reduction in external constraint from the RV and the pericardium was greater than the fall in LV end-diastolic pressure (LVEDP), resulting in an increase in the effective filling pressure.15 LV pacing induces a phase shift such that LV contraction and filling both occur before they do in the RV.6,16,17 Because pericardial stretch (and therefore pericardial pressure) depends on total cardiac volume, a smaller RV volume during LV filling would result in...
less constraint to LV filling, a greater LV end-diastolic volume, and (by the Frank Starling mechanism) greater LV stroke work (LVSW).

Methods

We recruited 23 consecutive patients (21 males) who had permanent LV pacing systems implanted at our institution for severe heart failure (New York Heart Association III/IV) despite maximum tolerated medical therapy. All patients underwent a detailed clinical assessment before implantation that included transthoracic echocardiography and cardiac catheterization as part of a specialized heart failure clinic. As a consequence of our acute pacing data in patients with normal QRS duration,13,18 it is our institutional policy to implant LV pacing systems into patients with normal QRS duration in conjunction with an elevated pulmonary capillary wedge pressure/external constraint.

The study population therefore includes a broad range of QRS durations (Table 1; complete range 80 to 182 ms). Optimal AV delay was set, using the Doppler transmitral flow profile, as the shortest AV delay that did not truncate the atrial flow wave. This project was conducted with approval from the Local Research Ethics Committee, and all subjects gave written informed consent. The procedures followed were in accordance with our institutional guidelines. Subjects underwent catheterization of the LV, without sedation, by a standard over-the-wire pigtail catheter technique. A left ventriculogram was recorded to aid catheter positioning and to calibrate LV end-diastolic volume (LVEDV). A long 7.5F sheath (Fast-Cath, Daig Corporation) was fed into the LV cavity over the pigtail catheter. The pigtail catheter was then removed, leaving the long sheath in the LV apex, which allowed the combined micromanometer/dual-field conductance catheter (CA-71103-PL catheter, CD Leycom; SPC-570 catheter, Millar Instruments) to be fed into the LV apex. The conductance catheter method provides a continuous online beat-by-beat measurement of LV volume.20 The conductance catheter calibration has been described elsewhere.21 To avoid the risk of displacing the coronary sinus pacing wire, we applied a modified parallel conductance calibration via a right atrial injection to avoid catheterization of the RV.

Hemodynamic measurements were performed during LV pacing (VDD mode) and while pacing was suspended. The interventions were applied in random order, each with a run-in (stabilization) period of 5 minutes. All data were acquired during an unforced end-expiratory breath hold. From each acquisition run, the derivatives of pressure and volume were calculated as the mean of 10 to 15 consecutive beats free from atrial or ventricular ectopic activity. Pressure-volume analysis was also performed during an inferior vena cava (IVC) occlusion, which reduced central blood volume and RV pressure acutely, achieved with a 40-mm IVC occlusion balloon catheter (Meditec, Boston Scientific International). Data were acquired with a CFL-512 system (CD Leycom), which allows further offline analysis (CircLab, Leiden University, the Netherlands). We defined end diastole as the initial point of rapid increase in LV pressure after the a wave. The end-systolic point was defined as the point in the cardiac cycle when \( \frac{P(t)}{\text{V}(t)} \) was maximal. \( P(t) \) and \( V(t) \) are the instantaneous LV pressure and volume, respectively; \( V_d \) represents the hypothetical LV volume at zero pressure and was determined by an iterative approach.23

Immediately after IVC occlusion, in those cases in which significant external constraint was present, LVEDV increased despite a reduction in LVEDP (Figure 1, beats 1 to 6). After this initial increase in LVEDV, further reductions in LVEDV were accompanied by reductions in LVEDV (Figure 1, beat 6 onward). Assuming that these latter points represented the transmural LVEDV-LVEDV relation, we fitted these points using a quadratic equation and defined the degree of external constraint as the pressure difference between the control point (beat 1) and the regression line (Figure 1, vertical arrow).

Statistical Analysis

To avoid making any assumptions about the distribution of these paired data, the baseline variables have been described by their median (interquartile range). The effect of LV pacing has been described by the median (interquartile range) of the within-subject differences and compared with baseline by a Wilcoxon signed rank sum test.

Results

The study protocol was performed without complication in all subjects. We were unable to achieve a stable apical conductance-catheter position in 4 of the patients, whereas the signal-to-noise ratio for volume was too low in 3 other subjects. It was not possible to use LV pacing data from 3 of the remaining 16 patients because of technical difficulties with the pacemaker programming. In summary, complete paced and unpaced data were available for 13 patients. Table 1 shows the baseline characteristics of these 13 patients. Table 2 summarizes the effects of LV pacing across the group. LVEDP did not change significantly. External constraint was significantly reduced by LV pacing. The effective filling pressure (LVEDP minus external constraint) increased with LV pacing. Figure 2 presents data for each individual case. Cases 2, 5, 10, and 13 had minimal or no measurable external constraint at baseline (Figure 3A); in these patients, the effective filling pressure and the LVEDP were therefore

<table>
<thead>
<tr>
<th>TABLE 1. Characteristics of Study Population</th>
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<td>Number</td>
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<tr>
<td>Age, y</td>
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<tr>
<td>Male gender</td>
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<tr>
<td>Etiology, IHD/DCM</td>
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<td>ACE/ARB use</td>
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<td>QRS duration, ms</td>
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<td>NYHA class</td>
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<td>LVEF, %</td>
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IHD indicates ischemic heart disease; DCM, dilated cardiomyopathy; ARB, angiotensin II receptor blocker; NYHA, New York Heart Association; and LVEF, LV ejection fraction.

Figure 1. Example of end-diastolic pressure-volume relation during IVC occlusion of patient with significant external constraint. Number markers represent successive beats after IVC occlusion (see text).
equal and overlie each other. The remaining cases showed a rise in the effective filling pressure with LV pacing, associated with an increase in LVEDV (Figure 2). External constraint was observed in cases with QRS duration <130 ms and patients with QRS duration <130 ms (Figure 3A). Cases 2, 5 (QRS duration <130 ms), and 10 (QRS duration >130 ms) had no measurable external constraint at baseline. Within the range of 0 to 8 mm Hg, the greater the external constraint, the greater the magnitude of its reduction by LV pacing (Figures 3A and 4). Above 8 mm Hg of external constraint, LV pacing appeared less effective at reducing external constraint.

As shown in Table 2, LVSW increased for the group as a whole with LV pacing; however, in 3 cases (2, 5, and 8), there was either no significant increase in LVSW or a decrease in LVSW was observed (Figure 3B). Two of these cases (2 and 5) had no measurable external constraint and had a QRS duration <130 ms.

The end-systolic pressure-volume relation was constructed for each case. The slope of the relation was calculated as an index of systolic contractile function. The end-systolic pressure-volume relation slope was available in both the unpaced state and during LV pacing in 8 patients. For the 8 highly heterogeneous available data sets, no statistical difference was demonstrated between the unpaced state and LV pacing (Table 2; Figure 3C).

When we plotted absolute change in LVSW against absolute change in LVEDV (Figure 5A), the majority of cases (including all of the cases with QRS duration >130 ms) could be described by a reasonably tight linear relationship, in keeping with the Frank-Starling mechanism. The main outliers from this relationship were cases 10 and 13, which had minimal or no measurable external constraint and a QRS duration >130 ms at baseline (Figure 3A). These 2 cases had the most convincing improvement in systolic contractile function (Figure 3C). Finally, when we plotted absolute change in LVSW against absolute change in LV end-systolic volume (Figure 5B), the majority of the cases were clustered around the zero LV end-systolic volume change line. However, cases 10 and 13 appear to have experienced a rise in LVSW associated with a reduction in LV end-systolic volume, which implies a predominantly systolic contractile benefit.

### Discussion

This study has shown that LV pacing reduces external constraint to LV filling, effectively recruiting LV preload despite a similar LVEDP. Static equilibrium analysis has been used to quantify the external constraint to LV filling. With this technique, external constraint is quantified as the difference in LVEDP before and after removal of the pericardium while a constant LVEDV is maintained. This technique can only be used when the chest is open. However, in the present study, we applied a modified approach by continuously measuring LV pressure and volume during occlu-

<table>
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<th>Table 2. Effects of LV Pacing</th>
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<td><strong>Baseline</strong></td>
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<td>Heart rate, bpm</td>
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<td>LVEDP, mm Hg</td>
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<td>External constraint, mm Hg</td>
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<td>Effective filling pressure, mm Hg</td>
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<td>LVEDV, mL</td>
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<td>Stroke volume, mL</td>
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<td>Stroke work, mL · mm Hg</td>
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<tr>
<td>dP/dt max, mm Hg/s</td>
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<tr>
<td>ESPVR slope</td>
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<tr>
<td>τ, ms</td>
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<td>LVESP, mm Hg</td>
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LVESV indicates LV end-systolic volume; ESPVR, end-systolic pressure-volume relation; and LVESP, LV end-systolic pressure.

Values are medians (interquartile range).

**Figure 2.** LVEDP versus LVEDV (closed symbols) before LV pacing (beginning of arrow) and after LV pacing (end of arrow) for each individual case. Cases with QRS duration >130 ms are represented by circles and cases with QRS duration >130 ms by squares. Also plotted is effective filling pressure (LVEDP minus external constraint) against LVEDV (open symbols) before LV pacing (beginning of arrow) and after LV pacing (end of arrow) for each individual case. Numbers represent case number. Note cases 2, 5, 10, and 13 had minimal or no measurable external constraint at baseline, and so effective filling pressure and LVEDP were equal and overlie each other.
sion of the IVC to acutely reduce RV volume and pressure.\textsuperscript{26} This acute reduction in RV volume removes external constraint to LV filling from the RV and pericardium. During this intervention, LVEDP was progressively reduced over several beats. For each beat, the relation between LVEDP and LVEDV was assessed. In the absence of external constraint, IVC occlusion gradually reduces both LVEDP and LVEDV, with the values progressing downward and leftward along a single end-diastolic pressure-volume relation. In contrast, in severe heart failure, when marked external constraint is present, LVEDV initially (for a few beats) increases as LVEDP falls. Only after the external constraint has been removed do the pressure-volume values move down and to the left (Figure 1). This initial increase in LVEDV is consistent with the recent observations of Kroeker et al\textsuperscript{27} that an acute reduction in right atrial volume was accompanied by an immediate, transmural pressure–mediated increase in LVEDV, when pericardial pressure exceeded 5 mm Hg.

In the present study, we confirm our hypothesis that at least part of the acute hemodynamic benefit of LV pacing is due to reduction of external constraint to LV filling. In the absence of external constraint, the measured LVEDP approximates the effective filling pressure of the LV. In contrast, in a variety of acute experimental models associated with RV pressure and volume overload, the pericardium becomes stretched. The pericardium exhibits an exponential stress-strain relationship: in health, pericardial pressure is thought to be almost zero, but when stretched above its unstressed volume, pericardial pressure rises exponentially.\textsuperscript{28} RV end-diastolic pressure and pericardial pressure are usually very similar.\textsuperscript{29–32} Increases in pericardial pressure with pericardial stretch are associated with comparable increases in RV end-diastolic pressure.\textsuperscript{30–32} In these situations, the intracavitary LVEDP may markedly overestimate the effective filling pressure of the LV, which is determined by subtracting the external constraint (by the RV and pericardium) from the LVEDP. In animal studies, pericardial pressure was approximately zero when LVEDP was <9 mm Hg but above

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure1}
\caption{Figure 1. LV pacing versus external constraint (A), LVSW (B), and end-systolic pressure-volume relation (ESPVR; C). Number labels represent case numbers. Circles connected by solid lines represent patients with QRS duration <130 ms. Squares connected by broken lines represent patients with QRS duration >130 ms.}
\end{figure}

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure2}
\caption{Figure 4. Amount by which measured external constraint was reduced by LV pacing versus measured baseline external constraint for each subject. Note 3 cases had no measurable external constraint and occupy zero point. Circles represent patients with QRS duration <130 ms, and squares represent patients with QRS duration >130 ms. Case numbers can be derived by cross-referencing measured baseline external constraint with Figure 3A.}
\end{figure}

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure3}
\caption{Figure 5. Change in LVSW versus change LVEDV (A) and change in LVSW against change in LV end-systolic volume (LVESV; B). Cases with QRS duration <130 ms are represented by circles, and cases with QRS duration >130 ms are represented by squares. Number labels (italics) represent case numbers.}
\end{figure}
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Capillary wedge pressure present in the majority of patients with LVEDP/pulmonary capillary wedge pressure >15 mm Hg.14,26 In patients with CHF, marked external constraint to LV filling was present in the majority of patients with LVEDP/pulmonary capillary wedge pressure >15 mm Hg.14,26

In accordance with our hypothesis, LV pacing significantly reduced this external constraint, presumably by causing a phase shift in LV filling relative to RV filling, as recently demonstrated in the LV pacing canine model,17 in which LV relaxation and filling occurred relatively early compared with RV relaxation and filling. If so, RV diastolic pressure and pericardial pressure are likely to be lower at any given LV diastolic volume. This is further supported by our pilot data,33 which show that LV pacing acutely reduces RV end-diastolic volume. The reduction in external constraint in the present study was associated with an increase in the effective filling pressure, and LVEDV was greater at any level of LVEDP. In accordance with the Frank-Starling mechanism, this resulted in an increase in LV stroke volume and LVSW.

In previous studies, it has been suggested that LV pacing and biventricular pacing may have minimal or no effect on diastolic mechanisms, on the basis of the observation that neither τ nor LVEDP changed.5,8,9 The present study confirms that LV pacing does not significantly affect τ or LVEDP across a group of patients, yet we have shown marked effects on diastolic function that are explainable by the reduction in external constraint to LV filling.

Within the range of 0 to 8 mm Hg, the greater the external constraint, the greater the magnitude of its reduction by LV pacing (Figure 4). Notably, however, LV pacing appeared less effective in reducing external constraint when it exceeded 8 mm Hg. A potential explanation for this observation would be that above a certain amount of external constraint, the phase shift in LV filling relative to RV filling (induced by LV pacing) becomes insufficient to prevent the development of significant constraint to LV filling in late diastole. However, the sample size was relatively small, and our observations could also reflect measurement error.

There was a significant increase in the maximum first derivative of LV pressure (dP/dt max; Table 2). However, dP/dt max reflects both the contractile state of the LV and the loading conditions under which the LV is functioning.34 Heart rate and LV end-systolic pressure were similar in the paced and unpaced states (Table 2). The observed increase in LV dP/dt max may be explained by an increase in LV preload via the mechanisms described earlier or by an increase in intrinsic LV contractile function, as exemplified by cases 10 and 13 (Figure 5A and 5B). In these cases, it is likely that the improvements observed are secondary to improvements in mechanical dysynchrony.5,8,9

Clinical Implications
Our study suggests a potentially important mechanism by which LV pacing may produce at least some of its hemodynamic benefit. Whether biventricular pacing may similarly reduce external constraint is uncertain. Because it would be expected to produce a lesser phase shift in the timing of ventricular filling, the benefit may not be as great.

Study Limitations
These studies were performed supine and at rest. The magnitude of ventricular interaction is variable; it is likely to decrease on adopting the upright posture as the RV volume decreases, and it is likely to increase on exercise, secondary to intestinal venoconstriction.35 Indeed, ventricular interaction may be an important mechanism contributing to stroke volume limitation and exercise intolerance in CHF.36 The present studies did not examine the effect of LV pacing on ventricular interaction during exercise.

Conclusions
LV pacing relieves the external constraint to LV filling, resulting in an increase in the effective filling pressure, which is associated with an increase in stroke volume. The extent to which this mechanism is responsible for the symptomatic benefits associated with this therapy requires further evaluation.

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References

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