Predictors of Systolic Augmentation From Left Ventricular Preexcitation in Patients With Dilated Cardiomyopathy and Intraventricular Conduction Delay

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Background—VDD pacing can enhance systolic function in patients with dilated cardiomyopathy and discordant contraction; however, identification of patients likely to benefit is unclear. We tested predictors of systolic responsiveness on the basis of global parameters as well as directly assessed mechanical dysynchrony.

Methods and Results—Twenty-two DCM patients with conduction delay were studied by cardiac catheterization with a dual-sensor micromanometer to measure LV and aortic pressures during sinus rhythm and LV free-wall pacing. Pacing enhanced isovolumetric (dP/dtmax) and ejection-phase (pulse pressure, PP) systolic function by 35±21% and 16.4±11%, respectively, and these changes correlated directly (r=0.7, P<0.001). %ΔdP/dtmax was weakly predicted by baseline QRS (r=0.6, P<0.02), more strongly by baseline dP/dtmax (r=0.7, P=0.001), and best by bidiscriminate analysis combining baseline dP/dtmax ≤700 mm Hg/s and QRS ≥155 ms to predict %ΔdP/dtmax ≥25% and %ΔPP ≥10% (P<0.0005, χ²), with no false-positives. Benefit could not be predicted by %ΔQRS. To test whether basal mechanical dysynchrony predicted responsiveness to LV pacing, circumferential strains were determined at 80 sites throughout the LV by tagged MRI in 8 DCM patients and 7 additional control subjects. Strain variance at time of maximal shortening indexed dysynchrony, averaging 28.0±7.1% in normal subjects versus 201.4±84.3% in DCM patients (P=0.001). Mechanical dysynchrony also correlated directly with %ΔdP/dtmax (r=0.85, P=0.008).

Conclusions—These results show that although mechanical dysynchrony is a key predictor for pacing efficacy in DCM patients with conduction delay, combining information about QRS and basal dP/dtmax provides an excellent tool to identify maximal responders. (Circulation. 2000;101:2703-2709.)

Key Words: heart failure ■ bundle-branch block ■ pacing ■ magnetic resonance imaging ■ mechanics

Left ventricular (LV) or biventricular preexcitation by dual-chamber (VDD) pacing with a shortened atrioventricular interval substantially improves systolic function in some patients with dilated cardiomyopathy (DCM) and conduction delay.1-5 By providing early stimulation to the otherwise late-activated region, pacing probably improves contractile coordination to enhance ejection. However, the therapy involves an implantable device, making it important to identify patients most likely to benefit.6 Because the therapy targets chamber-level mechanoelectrical abnormalities, it seems plausible that easily assessed features of a failing heart may help identify responders. If so, this would contrast with current pharmacological therapy, which is broadly applied to DCM patients, usually without specific knowledge of the individual substrate that might favor one therapy over another.

To date, the principal approach for identifying pacing candidates has been QRS prolongation on a surface ECG. Recent studies have reported a weak but significant positive correlation between basal QRS width and systolic response to pacing.4,5 This was obtained by combining patients with narrow and wide QRS complexes, however, leaving unresolved whether quantitative correlations persist among subjects with conduction delay. QRS duration also correlates inversely with basal contractile function, as indexed by the maximal rate of pressure rise (dP/dtmax),7,8 suggesting that the latter may provide another predictor of pacing response. Finally, QRS duration and dP/dtmax are indirect markers of the presumed primary abnormality, mechanical dyssynchrony, so direct measures of dyssynchrony might better predict benefit.

Accordingly, the goal of this study was to evaluate the utility of several easily obtained measures of global baseline chamber function for predicting systolic response to optimal-site VDD pacing. We also developed a novel metric to directly quantify mechanical dyssynchrony from tagged MRI.
(TMRI) analysis to directly test the relation between wall dyssynchrony and systolic improvement induced by LV pacing.

Methods

Study Group

Twenty-two patients with DCM (NYHA class III to IV) provided informed consent and underwent cardiac catheterization to determine systolic influences from optimal single-site ventricular pacing. Mechanical data from a subset of these patients (n=15) were used to analyze predictors of mechanical response to LV free-wall pacing. Patient DCM21 was excluded from this analysis because he had a right bundle-branch block (RBBB), and DCM22 because of a large anterolateral infarction with akinesis.

Catheterization Protocol

Patients were mildly sedated (midazolam 1 to 3 mg, fentanyl 50 to 100 mg). Catheters included a dual-sensor micromanometer (Millar 550-768) to measure simultaneous proximal aortic and LV pressures, an atrial sensing electrode, and a quadrupolar pacing electrode (Cardima, model 01-043013) advanced through a flexible sheath (Arrow, CL07680/CL07665) placed within the coronary sinus. In patients with LBBB, optimal response was achieved by pacing in a midlateral or anterolateral coronary vein. In the patient with RBBB, optimal effects were achieved by pacing the mid-right ventricular (RV) septum.

MR Tagging Protocol

The methods of noninvasive myocardial motion and circumferential strain analysis by TMRI have been described previously. Images were acquired on a GE Sigma 1.5-T scanner, with tags placed on the myocardium by saturating the proton spins in evenly spaced planes, taking images perpendicular to the tag planes. Two orthogonal short-axis views and a single long-axis view were obtained, with 11 slices in each short-axis view and tags oriented in a cartesian grid. The first long-axis slice bisected the septum and lateral wall, with each subsequent slice being rotated around the long axis by 20°.

Data Analysis

Invasive LV and aortic pressures were measured at rest and after 2 minutes of sustained VDD-mode pacing. LV pressure was digitally differentiated with a moving 5-point weighted slope, from which dP/dtmax was determined. Previous studies have found minimal change in LV loading with acute VDD pacing, so dP/dtmax provided an accurate measure of systolic response.

Pulse pressure (PP) was determined as a surrogate for changes in cardiac output. PP is more stable, with an excellent signal-to-noise ratio compared with flow assessments. Although PP does not always directly reflect mean flow, it did so in the present study because VDD pacing did not alter heart rate, ventricular preload, or arterial load. We have previously reported a strong direct correlation between PP and output in this setting, with a 1%ΔPP corresponding to a 4% to 5% change in cardiac output.

TMRI tags and contours were delineated with custom-made semiautomated software. Tagged points from the images yielded 3D strain tensors during systole, from which local strain and global strain maps were derived. The displacements were field-fitted in prolate spheroidal coordinates to calculate 3D Lagrangian strain tensors by the method of O’Dell et al. Circumferential strain (Ecc) was calculated on a mesh grid of 3 radial, 8 longitudinal, and 24 circumferential sampling points. Because midwall fibers are predominantly circumferential, Ecc represented fiber shortening or lengthening. Strain maps for the whole heart were generated first and then synthesized into a dyssynchrony index. The time of maximal negative Ecc (shortening) was determined for the whole ventricle. Strains at all sites were then assessed at this time (yielding Ecc*), and the coefficient of variation of these strains (CVEcc) indexed dyssynchrony: CVEcc = 100%×(SD Ecc*/mean Ecc*).

Statistical correlations between variables were tested by least-squares linear regression. Comparisons between normal sinus rhythm and pacing results were performed with a paired t test, and comparisons of TMRI data between DCM patients and normal volunteers were made by unpaired t test. Other tests are identified in the text where appropriate. Data are reported as mean±SD.

Results

Hemodynamic Response to Pacing

Hemodynamic and contractile responses to LV free-wall pacing are provided in Table 2. dP/dtmax increased +35.5±20.8% (n=20, P<0.0005), PP +16.4±11.2% (n=18, P<0.0005), and systolic pressure +6.4±4.4%
Combining basal QRS and dP/dt max enhanced the predictive accuracy for identifying responsive patients. Patients with a basal QRS duration of ≥155 ms and basal dP/dt max ≤700 mm Hg/s consistently yielded the greatest improvements with pacing (%ΔdP/dt max ≥25%). Both baseline dP/dt max ≤700 mm Hg/s and basal QRS ≥155 ms were significantly associated with a %ΔdP/dt max ≥25% (n = 20, P<0.0005 and P = 0.004, respectively). Combining both criteria (Figure 3) yielded no false-positives or false-negatives for predicting a ≥25% rise in dP/dt max (P<0.0005 by χ²) and 2 false-negatives for predicting a ≥10% rise in PP (P = 0.001 by χ²). PP was not recorded in 2 patients with %ΔdP/dt max ≥25%; however, on the basis of the regression relating %ΔPP and %ΔdP/dt max (see above), the predicted %ΔPP was ≥16% in each case.

**Mechanical Dyssynchrony as a Predictor of Pacing Response**

Figure 4 displays TMRI strain maps for a control subject (A) and a DCM patient (B) from base to apex (top to bottom) and septum to lateral wall (left to right). The time of maximal negative Ecc is denoted by an asterisk on each plot. Contrac-
tion was synchronous in the normal heart, with nearly all strains negative (shortening), with similar amplitude and phase. In contrast, the DCM heart with LBBB displayed heterogeneity of strain magnitude and temporal pattern. There was marked phase delay between early septal and late lateral shortening, with reciprocal stretch of the anteroseptal territory (positive strain) during the latter. Near-akinetic transition regions (posterior wall) were observed in this patient with normal coronary arteries and idiopathic disease.

Table 3 summarizes these results. Ecc* was $-18.6\pm2.9\%$ in normal subjects, versus $-5.3\pm2.1\%$ in DCM hearts ($P=0.001$), consistent with DCM cardiodepression. Strain variance was low in normal subjects: CV Ecc* = $28.0\pm7.1\%$, versus $201.4\pm84.3\%$ in the DCM with LBBB ($P=0.001$). Thus, dyssynchrony in DCM subjects was nearly an order of magnitude greater than in control subjects. As displayed in Figure 5, mechanical dyssynchrony was well correlated with $\%\Delta dP/dt_{\text{max}}$: $\%\Delta dP/dt_{\text{max}} = 0.18 \times \text{CV Ecc}^* - 8.8$ ($n=8$, $r=0.85$, $P=0.008$).

Discussion

In normal or hypertrophied hearts, ventricular preexcitation induces discoordination, and the extent of dyssynchrony correlates with depression of ejection- and isovolumic-phase systolic indexes. This dysfunction can be offset by concomitant stimulation of the opposing wall to restore synchrony, and improvement depends on the extent of dyssynchrony generated by the first lead.17,18 Such observations have suggested that patients with DCM and basal discoordination might benefit from LV or biventricular VDD pacing, and this was recently confirmed.2–5 However, the response magnitude varies, highlighting the importance of identifying responsive individuals.6

The present study is the first to systematically test potential markers of clinical response to pacing. We demonstrated that mechanical dyssynchrony is a good predictor of systolic improvement, but recognizing that MRI analysis is not widely available and is also labor-intensive, global surrogate markers were sought. Here we found that a bidiscriminate approach that uses both basal QRS duration ($\geq 155$ ms) and $dP/dt_{\text{max}}$ ($\geq 700$ mm Hg/s) provides a fairly robust prediction of patients likely to display at least a 25% rise in $dP/dt_{\text{max}}$ and 10% rise in arterial PP. The latter correlates directly with cardiac output in this setting and would be associated with a 40% to 50% rise in output.4 Although we measured baseline $dP/dt_{\text{max}}$ invasively, this parameter can be assessed with

Figure 2. A, Baseline contractile function indexed by $dP/dt_{\text{max}}$ was inversely correlated with its subsequent change during LV pacing: $\%\Delta dP/dt_{\text{max}} = 0.08 \times dP/dt_{\text{max BASE}} + 91.3$. B, Analogous results were obtained from regression of absolute change in $dP/dt_{\text{max}}$ and its change with LV pacing: $\Delta dP/dt_{\text{max}} = -1.4 \times dP/dt_{\text{max BASE}} + 484.7$.

Figure 3. Based on results shown in Figures 1A and 2A, threshold criteria were derived to provide improved prediction of robust responders. Patients with baseline QRS $\geq 155$ ms and/or baseline $dP/dt_{\text{max}}$ $\geq 700$ mm Hg/s yielded greatest improvement with pacing ($\%\Delta dP/dt_{\text{max}} \geq 25\%$ and $\%\Delta \text{PP} \geq 10\%$). Combining both criteria yielded no false-positives or false-negatives for predicting a $\geq 25\%$ rise in $dP/dt_{\text{max}}$ ($P=0.0005$ by $\chi^2$) and 2 false-negatives for predicting a $\geq 10\%$ rise in PP ($P=0.001$ by $\chi^2$). In 2 patients with $\%\Delta dP/dt_{\text{max}} \geq 25\%$, PP was not recorded; however, based on correlation between $\%\Delta dP/dt_{\text{max}}$ and $\%\Delta \text{PP}$, both would be predicted to demonstrate a rise of $\approx 16\%$. 

Figure 3.
Doppler cardiography, as validated by several previous studies. Baseline dP/dt max values in the present study group were remarkably low despite the absence of bradycardia or systolic hypotension. Many previous studies of DCM in which patients with conduction delay were not targeted have reported consistent values for dP/dt max of ~900 mm/s, 30% higher than in the present study but similar to values during pacing. Yet, the functional status, ejection fraction, etc, of the present patient group was indistinguishable from those in these previous studies. It is unlikely that the presence of only minor mitral regurgitation in the present study explained this difference, because MR would be expected to exacerbate dilation and basal depression. Thus, the major difference appears to lie in the discoordination, suggesting that dP/dt max is particularly sensitive to this behavior.

Figure 4. Representative strain maps derived by TMRI for representative control (A) and DCM (B) hearts are shown. These plots display simultaneous strains at multiple regions from base to apex (top to bottom) and septum to lateral wall (left to right). Time of maximal negative circumferential strain is denoted by asterisk shown on each strain plot for each location. Contraction is synchronous in normal heart, with nearly all strains being negative (ie, shortening) with similar amplitude and phase. In contrast, DCM heart displays marked regional variability in magnitude and temporal strain pattern. In this subject with LBBB, septal region shortened early, and lateral wall shortened much later, resulting in stretch of anterosetal territory (positive strain). Near-akinetic transition regions (ie, posterior wall) are also observed in this patient with normal coronary arteries and idiopathic cardiomyopathy.
The TMRI method uniquely provides detailed quantitative 3D analysis of regional myocardial dyssynchrony with adequate sensitivity even in DCM hearts. However, the analysis is complex and unlikely to be implemented in the general clinical arena. Alternative imaging methods, such as contrast echocardiography, 24 3D echo imaging, 25 or cine modes on standard MRI systems, may prove useful in this regard. On the basis of the present data, such evaluations may further improve targeting of pacing therapy. However, our results already demonstrate that the basal QRS and dP/dtmax criteria provide sufficient discrimination to define robust responders with virtually no false-positives.

The correlation between short-term responsiveness to pacing and long-term clinical outcome remains unknown. Although it may turn out that having an excellent immediate hemodynamic response is ultimately counterproductive or that no response does not preclude long-term benefit, both seem unlikely. PP and dP/dtmax provide direct evidence of the magnitude by which resynchronization assists systolic function in a given patient; therefore, as with a pharmacological agent, one would expect at least a binary discrimination between having some response and long-term benefit. Alonso et al 26 recently reported that QRS narrowing with pacing was more often observed in patients displaying long-term benefit, yet the present data found no immediate relation between such narrowing and mechanical response. This intriguing disparity remains to be resolved by more data and prospective analyses.

**Study Design Limitations**

We did not perform invasive catheterization in normal volunteers to test whether LV or biventricular pacing improves or worsens systolic function in individuals with narrow-complex QRS. Studying normal patients invasively poses potential risks and no possible benefit and thus was not feasible. However, analogous data have been reported in animal studies, and these consistently demonstrate that single-site (LV or RV) pacing of a heart with normal conduction (narrow QRS) produces a significant decline in dP/dtmax and other markers of systolic function. 14,15,17,18,27

We also limited our analysis to DCM patients with widened QRS complexes, and it remains possible that some individuals with more narrow complexes might also benefit. Previous studies have reported regional wall motion abnormalities, heterogeneous wall stress, and myocardial perfusion in DCM patients with normal-appearing epicardial vessels 28,29 although none reported QRS durations to test correlations with these phenomena. Certainly, surface ECG–based estimates may underestimate the temporal spread of depolarization if early and late portions have relatively low voltages. However, there is evidence that the pacing-responsive population with a narrow QRS duration is small. Auricchio et al 5 reported correlations between QRS and mechanical response to pacing and found little effect in individuals with a duration <155 ms. These data have been further extended to 74 patients (A. Auricchio and C. Stellbrink, personal communication), and only 3% of patients with a QRS <155 ms had a positive pacing response as defined in our study (ie, both %ΔdP/dtmax ≥25% and %ΔPP ≥10%). Even after the threshold for a positive response had been lowered to a 5% rise in each variable, the false-negative rate was only 12%. This indicates that although some patients have substantial enough mechanical dyssynchrony to benefit from pacing therapy yet have a narrow QRS complex, this population is small.

Patients with normal hearts and conduction delay were not studied either; although such data would be interesting, it fell outside the focus of our study. Basal function in this group would most likely be similar to a normal heart into which an RV pacemaker was inserted to produce an LBBB pattern. Adding an LV free-wall pacemaker (ie, biventricular pacing) improves function, as reported experimentally. 17 We speculate that the major difference in this regard between DCM and normal hearts is that any improvement with recoordination

**Table 3. Quantification of Mechanical Dyssynchrony by TMRI: Comparison of Results in Patients With DCM Versus Normal Volunteers**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Ecc*, %</th>
<th>CV_Ecc*, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal1</td>
<td>23.7 ± 5.6</td>
<td>23.6</td>
</tr>
<tr>
<td>Normal2</td>
<td>14.3 ± 4.7</td>
<td>32.9</td>
</tr>
<tr>
<td>Normal3</td>
<td>20.0 ± 3.6</td>
<td>18.0</td>
</tr>
<tr>
<td>Normal4</td>
<td>16.8 ± 4.1</td>
<td>24.4</td>
</tr>
<tr>
<td>Normal5</td>
<td>18.3 ± 6.4</td>
<td>35.0</td>
</tr>
<tr>
<td>Normal6</td>
<td>17.4 ± 6.5</td>
<td>37.4</td>
</tr>
<tr>
<td>Normal7</td>
<td>19.5 ± 4.8</td>
<td>24.6</td>
</tr>
<tr>
<td>DCM5</td>
<td>2.0 ± 5.0</td>
<td>250.0</td>
</tr>
<tr>
<td>DCM6</td>
<td>7.6 ± 11.0</td>
<td>144.7</td>
</tr>
<tr>
<td>DCM7</td>
<td>6.6 ± 15.2</td>
<td>230.3</td>
</tr>
<tr>
<td>DCM8</td>
<td>2.5 ± 8.7</td>
<td>348.0</td>
</tr>
<tr>
<td>DCM9</td>
<td>4.3 ± 11.4</td>
<td>265.1</td>
</tr>
<tr>
<td>DCM20</td>
<td>7.3 ± 9.3</td>
<td>127.4</td>
</tr>
<tr>
<td>DCM21</td>
<td>5.2 ± 6.3</td>
<td>121.2</td>
</tr>
<tr>
<td>DCM22</td>
<td>6.5 ± 8.1</td>
<td>124.6</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>-18.6 ± 2.9</td>
<td>28.0 ± 7.1</td>
</tr>
<tr>
<td>DCM</td>
<td>-5.3 ± 2.1</td>
<td>201.4 ± 84.3</td>
</tr>
<tr>
<td>P</td>
<td>0.001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Figure 5.** Mechanical dyssynchrony assessed by coefficient of variation of strains at time of maximal shortening (CV_Ecc*) correlated with systolic improvement with LV pacing as assessed by %ΔdP/dtmax. %ΔdP/dtmax = 0.18 × CV_Ecc*−8.8 (r = 0.85, P = 0.008).
becomes more significant in the former as other functional mechanisms fail.

Conclusions

The concept of targeting heart failure therapy individually by prospectively identifying factors to predict clinical responsiveness is an attractive one. This is currently elusive for pharmacological therapy, although differences in patient response to treatment are common. Our growing understanding of molecular and biochemical signaling changes in heart failure may ultimately provide the needed insight. Device therapies by their nature generally demand targeting to specific patient groups. The present data demonstrate the ability to identify an optimal candidate group who display substantial acute functional responses to pacing, and such pretreatment predictions are relatively unique among heart failure therapies. These issues should become increasingly important as 3 major multicenter trials commence this year to study the effects of chronic pacing on exercise capacity, hospitalization, and mortality.

Acknowledgments

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