Improved Left Ventricular Mechanics From Acute VDD Pacing in Patients With Dilated Cardiomyopathy and Ventricular Conduction Delay

David A. Kass, MD; Chen-Huan Chen, MD; Cecilia Curry, MSE; Maurice Talbot, RN; Ronald Berger, MD; Barry Fetics, MSE; Erez Nevo, MD, ScD

Background—Ventricular pacing can improve hemodynamics in heart failure patients, but direct effects on left ventricular (LV) function from varying pacing site and atrioventricular (AV) delay remain unknown. We hypothesized that the magnitude and location of basal intraventricular conduction delay critically influences pacing responses and that single-site pacing in the delay-activated region yields similar or better responses to biventricular pacing.

Methods and Results—Aortic and LV pressures were measured in 18 heart failure patients (mean±SD: LV ejection fraction, 19±7%; LV end-diastolic pressure, 25±8 mm Hg; QRS duration, 157±36 ms). Data under normal sinus rhythm were compared with ventricular pacing (VDD) at varying sites and AV delays (randomized order). Right ventricular (RV) apical or midseptal pacing had negligible contractile/systolic effects. However, LV free-wall pacing raised dP/dt max by 23.7±19.0% and pulse-pressure by 18.0±18.4% (P<0.01). Biventricular pacing yielded less change (11±12.8±9.3% in dP/dt max, P<0.05 versus LV). Pressure-volume analysis performed in 11 patients consistently revealed minimal changes with RV pacing but increased stroke work and lower end-systolic volumes with LV pacing. Optimal AV intervals averaged 125±49 ms, and within this range, AV delay had less influence on LV function than pacing site. Basal QRS duration positively correlated with %ΔdP/dt max (P<0.005), but pacing efficacy was not associated with QRS narrowing. Conduction delay pattern generally predicted pacing sites with most effect.

Conclusions—VDD pacing acutely enhances contractile function in heart failure patients with intraventricular conduction delay. Single-site pacing at the site of greatest delay achieves similar or greater benefits to biventricular pacing in such patients. These data clarify pacing-effect mechanisms and should help in candidate identification for future studies. (Circulation. 1999;99:1567-1573.)

Key Words: mechanics • ventricles • pacing • conduction • heart failure

Dual-chamber (VDD) pacing with ventricular preexcitation is a novel therapy for patients with dilated cardiomyopathy (DCM) currently undergoing clinical trials throughout the United States and Europe. Initial research focused on the utility of shortening atrioventricular (AV) conduction to optimize chamber filling and limit mitral regurgitation and used standard right ventricular apical (RVA) pacing.1–5 However, subsequent clinical trials raised doubts about the general efficacy of this approach.6–8 Attention then shifted to RV septal (RVS) pacing9 and multisite pacing as methods to restore contractile synchrony in subjects with baseline intraventricular conduction delay.10,11 Recently, Blanc and colleagues12 compared RV, left ventricular (LV), and biventricular (BiV) pacing modes in DCM patients and reported that LV free-wall (LVFW) pacing acutely enhanced femoral systolic pressure while lowering pulmonary wedge pressure. Interestingly, responses from single LV sites were similar to BiV pacing (LVFW+RVA). The mechanisms for these results remain unclear, because improved chamber loading, reduced mitral regurgitation,3,5 and enhanced contractile function each could explain the observations. To date, no study has directly assessed effects of varying VDD pacing site on LV systolic and diastolic function or the added influence of varying AV delay. Furthermore, the dependence of RV or LV pacing efficacy on basal QRS morphology is unknown.

To address these issues, we conducted an acute catheterization study of VDD pacing effects in patients with DCM, varying both site and AV interval and evaluating their effects on LV mechanics. The following hypotheses were tested: (1) single-site pacing in the region of delayed activation in DCM patients with underlying conduction delay achieves a response as good as or better than BiV pacing; (2) baseline QRS-interval prolongation correlates with the magnitude of
systolic mechanical response; and (3) pacing site has a greater impact on the response than AV delay unless this delay is unusually short.

Methods

Study Group

Eighteen patients with DCM (NYHA class III to IV) provided informed consent and underwent cardiac catheterization. The protocol was approved by the Joint Committee on Clinical Investigation of the Johns Hopkins Medical Institutions. Patients were in normal sinus rhythm (NSR), all but 1 with an AV interval >150 ms, and none with prior indications or need for pacing. Most had minimal or mild (+1) mitral regurgitation. Patients maintained chronic medications to the time of study (generally digoxin, an ACE inhibitor, and diuretics, with carvedilol in 1 patient, patient 18). They were studied under mild sedation (midazolam 1 to 3 mg, fentanyl 50 to 100 mg). Table 1 provides clinical characteristics. Most patients (13 of 18) had nonischemic DCM with an LBBB conduction delay pattern (11 of 18). Two had right bundle-branch block (RBBB), 1 bifascicular block (RBBB+ left anterior hemiblock), and none, no block.

Table 1. Clinical Characteristics of Patient Study Group

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<th>Age, y</th>
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<th>PR, ms</th>
<th>QRS, ms</th>
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Mean 53.8 18.9 84.2 204.1 156.8
SD 11.4 6.6 13.6 69.2 35.8

EF indicates ejection fraction; HR, sinus rhythm heart rate; PR, atrioventricular delay; QRS, mean duration measured from 2 or 3 identical leads recorded in each patient; IDC, idiopathic dilated cardiomyopathy; ICM, ischemic cardiomyopathy; IVCD, intraventricular conduction defect; Bifas, bifascicular block (RBBB+ left anterior hemiblock); and none, no block.

Catheterization Protocol

A combined 6F dual pressure-volume (PV) catheter (Millar 550-768) was advanced through a 90-cm flexible long sheath (Arrow CL-07690) and placed so that the pigtail tip lay at the distal LV apex. The sheath was continuously flushed with heparin/saline. The catheter provided simultaneous proximal aortic and ventricular cavity micromanometer pressures and chamber volume. Pressure offset was calibrated to an external zero pressure at study conclusion. Time-varying cavity volumes were derived from the conductance catheter as previously described.13,14 A steerable electrode catheter was positioned at the RVA or mid to upper RVS and a second catheter in the right atrium for atrial sensing. A flexible sheath fitted with a steerable electrode catheter was positioned in the coronary sinus. The steerable catheter was removed and replaced with a 1.4F high-torque guidewire which was then advanced to a lateral marginal vein or anterior cardiac vein, and a 3F quadrupolar catheter ( Elecath 204-12723) was advanced over the wire to this site for LV epicardial pacing. Pacing was generally achieved in a position midway between the base and apex.

Pacing in VDD mode was initiated at the RVA (n=17), RVS (n=15), LVFW (n=11), or combined RVS (or RVA) and LVFW (BiV; n=10). Not every site was studied in all 19 patients. At each site, 3 or 4 different AV intervals were studied. Each AV interval differed by 25 to 30 ms, with the longest delay being 20 to 70 ms shorter than the intrinsic AV interval, ensuring inclusion of an interval near 120 ms in each patient. Data were recorded after 2 minutes at steady state for each condition, and the order of pacing site and AV interval was randomized. Pacing was then suspended for 1 to 2 minutes, and repeat NSR data were obtained before the pacing intervention was changed. Multiple NSR data provided assessment of physiological variance for each parameter (expressed by coefficient of variation = SD/mean×100). Hemodynamic changes with pacing were assessed relative to the immediately preceding NSR data.

Data Analysis

In 7 studies, the volume catheter signal was uninterpretable (ie, isovolumic) because of low signal-to-noise ratios. Thus, the primary analysis in all patients was based on the micromanometer data. In addition to aortic systolic pressure, pulse pressure (PP) was used as a surrogate for changes in cardiac output. At a constant heart rate and vascular load, PP directly correlates with cardiac output.15 To directly test the validity of this assumption, data from all subjects in
whom both PP and PV-loop data were obtained at ≳2 VDD pacing sites with varying responses (5 patients, n = 15 observations) were subjected to multiple regression, including terms for between-subject differences. The result was highly significant, with an overall regression of $r = 0.88$ ($P = 0.008$) and mean slope of 5.1 ± 1.6 (ie, ~5% change in cardiac output for each 1% change in PP).

Ventricular micromanometer pressures yielded peak-systolic and end-diastolic pressure (EDP). EDP equaled the pressure when dP/dt exceeded 10% of dP/dt$_{max}$. Pressure was digitally differentiated by use of a running 5-point weighted slope, and peak and minimal values were determined. These values were also normalized to instantaneous pressure (eg, dP/dt$_{max}$/IP) to minimize load effects.

Two relaxation time constants were determined from pressure data between dP/dt$_{min}$ and the point at which pressure was EDP + 5 mm Hg: $t_r$ based on a monoexponential decay and $t_l$ based on a logistic decay. Neither fit forced pressure decay to zero. In patients with interpretable conductance-volume data, LV PV loops were derived and used to assess loop area (stroke work) and steady-state end-diastolic and systolic volumes.

Statistical analysis was performed with commercial software using repeated-measures ANOVA with posthypothesis testing of pacing-site differences by Tukey’s test. Other tests are identified in the text where appropriate. All data are presented as mean ± SD.

Results

Baseline Data

Resting cardiac index was 2.0 ± 0.41 L·min$^{-1}$·m$^{-2}$ at a mean heart rate of 82.1 ± 12.3 bpm. Contractile function indexed by dP/dt$_{max}$ was depressed, at 760.1 ± 241.2 mm Hg/s (typical value in normal individuals is 1700 ± 300 mm Hg/s), and diastolic function was abnormal, as evidenced by an elevated LVEDP: 24.8 ± 7.8 mm Hg and prolonged isovolumic relaxation: $t_r$, 171 ± 118 ms (versus 46 ± 3 in normals) and $t_l$, 46.3 ± 17.3 ms (versus 21 ± 1 in normals).

Ventricular Responses to VDD Pacing

Individual results for dP/dt$_{max}$, arterial PP, and peak-systolic pressure for each pacing site are shown in Figure 1, and percent changes for these and other parameters are given in Table 2. Data are at optimized AV interval for each patient, which on average was 125 ± 48.7 ms.

Although RVA and RVS pacing had negligible effects on these parameters, all 3 rose significantly and consistently with LVFW and BiV pacing. For LVFW pacing, dP/dt$_{max}$ increased 23.7 ± 19% (an absolute change of 147.2 ± 109.5 mm Hg/s), peak-systolic pressure rose 5.7 ± 4.4%, and PP increased 18 ± 18.4%. These changes were significantly greater than with RVA pacing ($P < 0.005$) and generally higher than RVS pacing. BiV pacing induced quantitatively smaller responses than LVFW pacing ($P < 0.05$ for dP/dt$_{max}$ by paired t test). Heart rate was not directly altered by VDD-mode pacing, with heart rate for NSR and VDD pacing being similar regardless of pacing site.
Ventricular Mechanics of VDD Pacing in DCM

Table 2. Summary Hemodynamic Responses (Percent Change) With Varying Pacing Site(s) at Optimal AV Delay

<table>
<thead>
<tr>
<th></th>
<th>RVA (n=17)</th>
<th>RVS (n=15)</th>
<th>LVFW (n=11)</th>
<th>BiV (n=10)</th>
<th>ANOVA</th>
<th>CoV</th>
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<tbody>
<tr>
<td>HR</td>
<td>0.04±4.0</td>
<td>−0.76±3.1</td>
<td>−1.2±3.1</td>
<td>−0.09±3.5</td>
<td>NS</td>
<td>3.7</td>
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<tr>
<td>LVEDP</td>
<td>2.4±2.0</td>
<td>−8.7±29.0</td>
<td>+6.5±16.6</td>
<td>−2.1±16.2</td>
<td>NS</td>
<td>11.1</td>
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<td>LVESP</td>
<td>1.2±6.8</td>
<td>1.01±3.2</td>
<td>5.7±4.4†</td>
<td>3.2±3.5</td>
<td>0.001</td>
<td>3.1</td>
</tr>
<tr>
<td>dP/dtmax</td>
<td>2.8±12.7</td>
<td>5.7±10.3</td>
<td>23.8±19.1†</td>
<td>12.8±9.3</td>
<td>0.001</td>
<td>2.8</td>
</tr>
<tr>
<td>dP/dtmax/IP</td>
<td>1.2±14.6</td>
<td>4.2±13.3</td>
<td>22.1±19.1‡§</td>
<td>12.1±12.8</td>
<td>0.017</td>
<td>6.1</td>
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<tr>
<td>dP/dtmin</td>
<td>−18.1±8.4</td>
<td>−4.1±11.4</td>
<td>−1.7±9.1</td>
<td>−4.2±7.3</td>
<td>0.079</td>
<td>5.1</td>
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<tr>
<td>dP/dtmin/IP</td>
<td>−4.7±13.3</td>
<td>−1.7±16.9</td>
<td>+3.4±12.2</td>
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<tr>
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<td>+9.2±41.9</td>
<td>+11.7±52.7</td>
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<td>14.7</td>
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<tr>
<td>PP</td>
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<td>18.0±18.4*</td>
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</tr>
<tr>
<td>QRS</td>
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<td>11.9±24.2</td>
<td>3.0±25.8</td>
<td>NS</td>
<td>...</td>
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</table>

ANOVA indicates P values for overall effect of pacing site on hemodynamic change; CoV, coefficient of variation for NSR data; HR, heart rate; LVESP, LV end-systolic pressure; dP/dtmax and dP/dtmin, peak and minimal first derivative of pressure; dP/dtmax/IP and dP/dtmin/IP, peak and minimal first derivative of pressure normalized to instantaneous LV pressure at each point; τ<sub>1</sub>, isovolumic relaxation time constant (logistic); and τ<sub>2</sub>, isovolumic relaxation time constant (monoexponential). Data for PP were not obtained in 2 of the patients for which other parameters were recorded (ie, n=15 for RVA, n=13 for RVS, etc.).

*P<0.005 vs RVA; †P<0.005 vs RVS; ‡P<0.02 vs RVA; §P<0.05 vs RVA.

(85.2±14 versus 85.1±13 bpm for RVA; 80.2±11.3 versus 79.6±11.6 bpm for RVS; 81.1±11.9 versus 80.1±12.1 bpm for LVFW; and 81.1±12.7 versus 80.9±12.1 bpm for BiV).

In contrast to systole, VDD pacing had little effect on diastolic function (EDP, peak negative dP/dt, and relaxation time constants). If anything, relaxation was slightly faster with right heart pacing (P<0.01 combining both RVA and RVS data), whereas it tended to prolong with LVFW pacing (P<0.0001 versus right heart responses by Mann-Whitney U test).

Figure 2 displays steady-state PV loops from a patient with a baseline LBBB. Neither RVA nor RVS pacing induced changes in the resting PV loop, consistent with the hemodynamics shown in Table 2. However, LVFW pacing reduced end-systolic volume and increased loop width (stroke volume) and area (stroke work). BiV pacing also enhanced stroke work and stroke volume but less so than LVFW pacing. As previously noted, percent changes in cardiac output (or stroke volume) correlated with simultaneous changes in PP. For the subject in Figure 2, the correlation r value was 0.98 (P=0.005). Loop data with RVA (n=11) or RVS (n=9) pacing revealed enhanced stroke work or stroke volume in only 4 instances. In contrast, systolic improvement was observed in 8 of 10 PV-loop cases (5 studies) with LV or BiV pacing (P=0.002, χ²). In patients with resting QRS prolongation, LVFW+BiV pacing increased stroke work by 45±43% (P=0.04) and stroke volume by 40±40%.

Figure 2. PV loops from a patient with baseline LBBB as a function of varying pacing site. Data again are shown for optimal AV interval at each site. Solid line indicates NSR-control; dashed line, VDD pacing. There was negligible effect from RVA or RVS pacing. However, LV pacing produced loops with greater area (stroke work) and width (stroke volume) and a reduced systolic volume. The latter is consistent with increased contractile function and thus with elevation of dP/dtmax. These results were similar in subset of patients in which data were measurable.
Influence of Basal QRS Duration and Changes in QRS Duration With Pacing

To test whether LV systolic response to VDD pacing depended on underlying conduction delay, basal QRS duration was plotted against the %\(\Delta\)dP/dt\(_{\text{max}}\) induced by VDD pacing in each patient. Because RVA pacing yielded minimal or negative changes in dP/dt\(_{\text{max}}\) in most patients, we first performed the analysis excluding this site. Data were fit by multiple regression with pacing site as a categorical variable and QRS duration as a continuous variable and revealed dependence of contractile response on QRS duration (\(P=0.005\), multiple regression \(r=0.65\)) even accounting for pacing site (Figure 3). This was also significant (\(P<0.05\)) if RVA pacing was included.

Mechanical improvement with pacing was not associated with QRS narrowing. Rather, QRS duration tended to widen with pacing overall (+11.2±27%, combined data, \(n=50\), \(P<0.005\)), although variability for each site (Table 2) was too high to reach significance.

Influence of AV Interval

Figure 4 shows influences of AV interval with VDD pacing on chamber filling (LVEDP) and systolic function (dP/dt\(_{\text{max}}\)). RVA and RVS pacing site data are combined and contrasted to combined data with LVFW and BiV pacing. LVEDP and dP/dt\(_{\text{max}}\) declined very slightly as AV interval shortened to near 120 ms and fell more at shorter delays with greater preload decline (\(P<0.05\) and \(P<0.01\), respectively). Enhancement of dP/dt\(_{\text{max}}\) from LVFW or BiV over RV pacing was observed at AV intervals between 100 and 160 ms, with a maximum at 125 ms.

Conduction Delay Pattern and Long AV Intervals

Although mean data (Table 2) indicated that LVFW or BiV pacing was beneficial, RV pacing was not always ineffective. In both subjects with RBBB (patients 15 and 16), RVS pacing yielded changes greater than those from LVFW pacing and similar to BiV pacing. For example, dP/dt\(_{\text{max}}\) rose 18.3% and 15.9% with RVS pacing, versus 7.7% and 7.3% with LVFW. Interestingly, RVA pacing still lowered dP/dt\(_{\text{max}}\) in both patients (-10.8% and -5.7%). Similar patterns occurred with PP and systolic blood pressure. RVS pacing was also effective in 2 patients with very long AV intervals (ie, >300 ms, patients 12 and 13) despite an LBBB morphology. For example, in these patients, dP/dt\(_{\text{max}}\) rose by 19% with RVS pacing, although it still increased more with LVFW pacing (27.2%).

Discussion

The present data support recent findings showing that LVFW or BiV pacing in patients with DCM and underlying ventricular conduction delay enhances systolic pressures.\(^{10,12}\) We provide the first demonstration that these changes relate primarily to direct improvement of LV systolic function, with
minimal changes in diastolic filling pressures or relaxation. We further clarify the value of selecting an appropriate AV delay near 120 ms, although within this range, small differences in delay have far less influence than pacing site. Although a wider baseline QRS was associated with greater mechanical improvement by pacing, changes in the QRS with pacing did not predict efficacy. If anything, BiV pacing induced the smallest change in QRS width yet did not have the largest mechanical benefit. Last, and admittedly based on a small sample, patients with RBBB and those with very long AV delays may benefit from VDD pacing.

Mechanisms of VDD Pacing Effects

VDD pacing has 2 primary effects on the heart. The first relates to the AV interval, which influences the timing of atrial contraction relative to the preceding and subsequent QRS complexes. Shortening the interval can diminish mitral regurgitation, lengthen the time available for diastolic filling,1,3,5 and alter the filling pattern from one characterized principally by an early-filling wave to one with more physiologically balanced early and late (atrial) filling components.1,4 The latter pattern should also lower mean atrial pressures even if net filling is similar,17,18 possibly explaining declines in pulmonary wedge pressure.12

The second mechanism relates to changing contraction coordination. Acute single-site pacing in normal hearts induces discoordinate wall motion, reducing contractile function.19,20 The prematurely activated region shortens against little load with little net contribution to systole. The late-activated region encounters a more compliant early-stimulated wall and stretches this region during its systole, further reducing ejection efficiency. This results in higher end-systolic volume and rightward shift of the ventricular end-systolic pressure-volume relation.19,21

Patients with underlying RV or LV conduction delays are analogous to those having single-site pacing in the opposing ventricle. One may therefore predict that pacing the region with delayed activation with an appropriate AV delay might improve contractile synchrony and systolic function and lower end-systolic volumes. The present data support this hypothesis, because pacing the LVFW in patients with LBBB (or RVS in those with RBBB) significantly improved systolic function. In patients with PV-loop data, this was accompanied by an increase in stroke volume and stroke work, reduced end-systolic volume, and minimal change in end-diastolic volume. There was also a direct relation between the magnitude of conduction delay (QRS duration) and systolic contractile response to VDD, supporting the notion that the more dis synchronous the heart at baseline, the more likely it is that pacing benefits function.

VDD pacing had no significant beneficial or detrimental effects on diastolic relaxation or the diastolic PV relation. The latter is not surprising, because pacing-induced discoordination or varying AV delay does not directly alter chamber compliance.19 However, discoordination prolongs relaxation,22 so it might seem paradoxical that LVFW pacing tended to lengthen relaxation despite systolic improvement, whereas relaxation shortened with RV pacing despite negligible systolic changes. However, abnormalities such as altered calcium cycling linked to reduced sarcoplasmic reticular proteins and function23,24 and β-adrenergic signaling25 also contribute potently to relaxation delay and are not directly altered by improved contractile synchrony. It is unlikely that altered systolic loading was important, in that the systolic pressure change with pacing was small and imposed throughout ejection (ie, Figure 2).

BiV Versus Single-Site Pacing

This is only the second study to directly compare BiV with single-site pacing in patients with DCM, and consistent with the report by Blanc et al.,12 single-site pacing was equal or superior to BiV pacing in patients with underlying LBBB-type conduction delay. One might expect that LV pacing would shift early activation to the left heart and not necessarily achieve mechanical asynchrony. However, it is likely that myocardial conduction emanating from LV epicardial pacing is slow compared with intrinsic conduction via the conducting fascicle, so mechanical forces remain synchronized even with early excitation. Some RV-LV stimulation delay may be important, given the often disproportionate rise in LV mass in DCM patients, and may help explain similar if not diminished mechanical responses with BiV pacing.

It remains possible that BiV pacing may improve on single-site pacing if there is an inability to control the timing between RV and LV activation, as with second- and third-degree heart block or atrial fibrillation. BiV pacing might also be useful in patients with profound first-degree AV block and a normal QRS complex. Single-site pacing would be anticipated to reduce systolic function and thereby offset benefits from improved chamber filling, whereas BiV would probably better maintain electrical and mechanical synchrony in such patients. Future developments in pacing technology should allow variable timing between RV and LV stimulation, so that this delay can be optimized in a given patient. Whether this will indeed enhance function beyond that from single-site pacing remains to be determined.

Methodological Considerations and Limitations

This is the first study to use LV epicardial pacing with a catheter introduced via the coronary sinus. This differs from the open-chest epicardial pacing used by Foster et al.10 or endocardial pacing used by Blanc et al.12 but is similar to methods currently being tested for long-term results.26 In the study by Blanc et al, nearly 25% of patients had atrial fibrillation, whereas we excluded these patients to facilitate contractile function analysis, because contractility varies with RR interval.23 We also excluded patients with preexisting pacemakers,26 because this could reflect different substrates. This does not mean that neither group may benefit from VDD pacing.

There were several technical limitations. Continuous-cardiac-output catheters were used to circumvent the need for repeated fluid boluses, but substantial variability persisted. We therefore used PP as a surrogate, assuming a constant arterial impedance and heart rate. The high correlation between percent changes in both parameters supports this assumption. In addition, the conductance (volume) catheter
method failed in 7 of 19 patients because of inadequate signal-to-noise ratio.

Finally, this short-term study may not reflect long-term responses. Long-term trials targeting optimal single-site pacing need to be performed and are under way at our and other institutions. Given the rise in dP/dt max with pacing and the poor outcomes often reported with long-term isotropic trials for DCM, one could raise concerns over pacing benefits. However, improving contractile coordination differs from interventions elevating intracellular calcium, such as adrenergic stimulation or phosphodiesterase III inhibition, and may not have the same energetic consequences. This hypothesis is currently being tested. The present data help rationalize ongoing and future long-term trials and assist in identifying the appropriate target group.

The present data, along with results of other recent studies, support the notion that VDD pacing in DCM patients and ventricular conduction delay may be therapeutically useful. In particular, the data help clarify the mechanism for such effects and define the patient group for which right or left heart pacing is most likely to be beneficial. There have been no single-site left heart chronic pacing multicenter trials to date, but our data suggest that such approaches deserve consideration, particularly in patients with LBBB. We await the results of such randomized clinical trials to determine whether VDD pacing will indeed be a useful addition to heart failure treatment.

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