Left Ventricular or Biventricular Pacing Improves Cardiac Function at Diminished Energy Cost in Patients With Dilated Cardiomyopathy and Left Bundle-Branch Block

Gregory S. Nelson, PhD; Ronald D. Berger, MD, PhD; Barry J. Fetics, MSE; Maurice Talbot, RN; Julio C. Spinelli, PhD; Joshua M. Hare, MD; David A. Kass, MD

Background—Left ventricular or biventricular pacing/stimulation can acutely improve systolic function in patients with dilated cardiomyopathy (DCM) and intraventricular conduction delay by resynchronizing contraction. Most heart failure therapies directly enhancing systolic function do so while concomitantly increasing myocardial oxygen consumption (MVO₂). We hypothesized that pacing/stimulation, in contrast, incurs systolic benefits without raising energy demand.

Methods and Results—Ten DCM patients with left bundle-branch block (ejection fraction 20% delay as manifested by a QRS duration >140 ms) underwent cardiac catheterization to measure ventricular and aortic pressure, coronary blood flow, arterial–coronary sinus oxygen difference (ΔAVO₂), and MVO₂. Data were measured under sinus rhythm or with left ventricular or biventricular pacing/stimulation at the same heart rate. These results were then contrasted to intravenous dobutamine (n=7) titrated to match systolic changes during LV pacing. Systolic function rose quickly and substantially from LV pacing (18±4% rise in arterial pulse pressure, which correlates with cardiac output, and 43±6% increase in dP/dt max; both P<0.01). However, ΔAVO₂ and MVO₂ declined −4±2% and −8±6.5%, respectively (both P<0.05). Similar results were obtained with biventricular activation. In contrast, dobutamine raised dP/dt max 37±6%, accompanied by a 22±11% rise in per-beat MVO₂ (P<0.05 versus pacing).

Conclusions—Ventricular resynchronization by left ventricular or biventricular pacing/stimulation in DCM patients with left bundle-branch block acutely enhances systolic function while modestly lowering energy cost. This should prove valuable for treating DCM patients with basal dyssynchrony. (Circulation. 2000;102:3053-3059.)

Key Words: heart failure ■ bundle-branch block ■ pacing ■ oxygen

Congestive heart failure remains a major and growing public health problem despite recent therapy development. Major advances have been accomplished by antagonizing deleterious neurohormonal pathways and hemodynamic loads. However, a therapeutic avenue that has generally failed to improve patient longevity involves positive inotropic agents to enhance systolic function. Such drugs typically force an already inefficient and failing heart to further increase its energy expenditure, likely contributing to the adverse impact of these drugs.

The growing weariness against therapies that enhance systolic function at the expense of greater energy demand has raised concerns about a novel electrophysiological treatment for patients with dilated cardiomyopathy (DCM) and coordinate contraction due to intraventricular conduction delay (notably, left bundle-branch block [LBBB]). Conduction delay as manifested by a QRS duration >140 ms is common in DCM patients and is associated with reduced systolic performance, mechanical inefficiency, and worsened clinical outcome. In affected patients, left ventricular (LV) or biventricular (BiV) pacing/stimulation can be used to prematurely activate the region of the heart that is otherwise activated late in an effort to improve mechanical synchrony. The magnitude of acute systolic improvement from pacing/stimulation can be considerable; yet inasmuch as this principally stems from enhanced synchrony rather than altered myocyte function, one might predict less associated change in metabolic demand.

Accordingly, we tested the hypothesis that acutely enhanced systolic function with LV or BiV pacing/stimulation is achieved with minimal change in cardiac oxygen consumption. Patients with combined DCM and LBBB were studied, and results with pacing stimulation were compared with results with inotropic therapy with dobutamine, matching the systolic augmentation achieved by each intervention. We demonstrate that pacing/stimulation therapy rapidly improves systolic function while modestly reducing myocardial energy requirements. The latter is opposite the result observed with
dobutamine, even after correcting for concomitant changes in heart rate.

Methods

Study Group

Ten patients with DCM and LB_BB were studied. All patients provided informed consent, and the protocol was approved by the Joint Committee on Clinical Investigation of the Johns Hopkins Medical Institutions. Chronic heart failure medications were maintained at the time of study (digoxin, an ACE inhibitor, diuretics, and, in 5 patients, a β-blocker). All patients had an ejection fraction <35% (mean 19.7 ± 2.6%), LB_BB with QRS duration ≥140 ms (mean 179.1 ± 32.8 ms), PR interval ≥160 ms (mean 196.5 ± 13.6 ms), normal sinus rhythm (NSR), <20% vessel stenosis within the proximal left coronary circulation, and evidence of contractile improvement (≥15% increase in maximal rate of pressure rise [dP/dt max]) from LV pacing/stimulation. The latter was included so that changes in energetic demand would be particularly relevant. Only 1 patient was excluded from analysis on the basis of this last criterion. Hemodynamic data from these patients were included in a larger recently reported study.22

Most patients were in New York Heart Association class III (2 were in class IV). Eight patients had normal coronary anatomy and idiopathic DCM. One patient had >60% lesions in the right coronary, left anterior descending coronary, and circumflex marginal arteries but fully patent bypass grafts to the left anterior descending and right coronary arteries and no clinical history of documented infarction. Another had >90% lesions in the right coronary and left anterior descending coronary arterial diagonal branch and an infero-posterior infarction. All patients had ≤1+ mitral regurgitation, assessed by contrast ventriculography at the time of study. The mean age was 57.2 ± 3.5 years, and the resting heart rate was 88.1 ± 4.6 bpm. Males and females were equally represented.

Catheterization Protocol

Patients were sedated with midazolam (1 to 3 mg) and fentanyl (50 to 100 μg), and sedation was maintained as required throughout the procedure. A combined dual-sensor pressure-volume catheter (Millar 550-768) was advanced to the LV apex to measure simultaneous proximal aortic and ventricular pressures and LV cavity volume (Sigma V, Cardiodynamics).12 Because of markedly dilated and lateral cardiac vein, midway between the base and apex, LV (or BiV) stimulation was achieved by sensing intrinsic atrial activation and using a shortened atrioventricular (AV) delay to preexcite the left ventricle (VDD mode). The longest AV delay that still produced minimal change in cardiac end-diastolic volumes from LV VDD pacing,12 so changes in dP/dt max provided a specific measure of systolic response. Arterial pulse pressure (PP) served as a less noisy surrogate for cardiac output.12 The time constant of pressure relaxation was derived by use of 3-term monoeponential and logistic growth models,23 with the latter providing more stable assessments in failing hearts.26 The product of mean coronary flow and ΔAVO 2 indexed relative changes in MVO 2 (hemoglobin content was constant).

Statistical analysis was performed by use of commercial software (Systat 8.0). Comparisons of data measured during NSR versus pacing/stimulation or between predobutamine and postdobutamine infusion were performed by use of a Wilcoxon nonparametric test. Comparisons between these interventions were performed by a Kruskal-Wallis test. Other tests are identified in the text where appropriate. Unless otherwise noted, all data are reported as mean±SEM.

Results

Mechanoenergetics of Pacing/Stimulation

Figure 1 displays example data for the cardiac effects of LV pacing/stimulation therapy. Peak aortic and ventricular pressures, aortic PP, and dP/dt max all increased within 2 beats after the onset of pacing (Figure 1A), and these changes persisted virtually unchanged after 2 minutes of stimulation. Pressure-volume loops (Figure 1B) displayed an increase in loop area and width (stroke work and volume, respectively) and a decline in end-systolic volume with pacing. End-diastolic volume and corresponding end-diastolic pressure were unchanged. Despite the improved systolic function, myocardial oxygen consumption (MVO 2) declined because of a slight fall in coronary flow and transcardiac oxygen gradient (Figure 1C). Group data are provided in the Table, with individual and mean responses displayed in Figure 2. Both dP/dt max and aortic PP increased (42.8 ± 5.7% and 17.5 ± 3.7%, respectively; both P < 0.05), whereas heart rate, LV end-diastolic pressure, and isovolumic relaxation decay time did not significantly change. Despite the systolic improvement, ΔAVO 2 declined by −4.4 ± 1.6%, and MVO 2 fell by −7.9 ± 6.5% (both P < 0.05). The decline in MVO 2 was observed in all but 1 patient, in whom dP/dt max rose by nearly 80% and PP rose by nearly 40%, twice the group average. Excluding this patient yielded a larger decline in MVO 2 (−14 ± 3%, P < 0.01) and coronary flow (−9 ± 3%, P < 0.02). Similar mechanical and energetic changes were observed with BiV (right ventricular apex–LV free wall) pacing (Figure 2). BiV pacing/stimulation increased dP/dt max by 38.6 ± 10.2% and PP by 19.6 ± 5.0%, whereas ΔAVO 2 declined −5.8 ± 1.2%, and MVO 2 declined −12.7 ± 3.3% (all P < 0.05).
LV Pacing Compared With Dobutamine

Mechanoenergetic responses to dobutamine infusion are reported on the right side of the Table. Unlike LV pacing/stimulation, dobutamine increased MV˙ O 2 along with systolic function in each patient (n = 7). Baseline and intervention-enhanced dP/dtmax was similar for both interventions by study design (dobutamine increased dP/dt max 36.9 ± 5.7%; however, dobutamine raised MV ˙ O 2 42.1 ± 13.3% (P < 0.005 versus pacing/resynchronization therapy). Two of the patients had received β-blockers as part of chronic therapy, but as the dobutamine dose was titrated to match responses with LV pacing/stimulation, the percent ΔMV ˙ O 2 was similar with (38.3 ± 19.1%) or without (43.6 ± 18.2%) β-blockade. Last, in the 3 patients with interpretable LV volume signals, chamber efficiency was calculated from the stroke work/MV ˙ O 2 ratio. Efficiency increased by 100.1 ± 32.8% with LV pacing versus 33.5 ± 24.2% with dobutamine.

One potential source for the disparity in MV ˙ O 2 change between pacing/stimulation and dobutamine was an increase in heart rate that only accompanied dobutamine infusion. Figure 3 displays results for per-beat MV ˙ O 2 in both groups. Even after adjusting for heart rate, dobutamine significantly increased MV ˙ O 2 by 21.5 ± 11.0% versus a decline with pacing of −2.5 ± 6.7% (P = 0.025).

Discussion

Both LV free wall and BiV pacing/stimulation can enhance ventricular systolic performance in patients with DCM and LBBB, an effect thought to be due to improving contraction synchrony.10,12,13 The patients most likely to benefit are those with the greatest basal dyssynchrony, often reflected by a wide QRS duration.12,22,27 Because functional improvement can be substantial, analogous to that from 15 to 20 μg · kg⁻¹ · min⁻¹ IV dobutamine, this raises...
concerns about a potential energy cost. The present study provides important new data showing that systolic improvement from pacing resynchronization occurs without increasing energy consumption by the heart. Rather, we observed a modest yet significant decline in energy use. Improved mechanoenergetics is rapid, without changing the heart rate or arterial and/or venous loading. This supports a novel aspect of this therapy that may contribute to chronic benefits in DCM patients.

Mechanism of Improved Mechanoenergetics by Resynchronization Pacing

There is growing support for the hypothesis that the failing heart has among its primary lesions adverse mechanoenerget-

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**Table: Hemodynamic, Contractile, and Energetic Responses to LV Electrical Stimulation (VDD Pacing With LV Lateral Wall Preexcitation and Intravenous Dobutamine)**

<table>
<thead>
<tr>
<th></th>
<th>NSR</th>
<th>LV Stimulation</th>
<th>P</th>
<th>Re-Con</th>
<th>Dobutamine</th>
<th>P</th>
<th>P (Pacing vs Dobutamine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, bpm</td>
<td>88.1±4.6</td>
<td>85.8±4.5</td>
<td>0.08</td>
<td>86.1±6.2</td>
<td>100.2±6.5</td>
<td>0.018</td>
<td>0.001</td>
</tr>
<tr>
<td>LVEDP, mm Hg</td>
<td>31.2±3.5</td>
<td>32.4±3.3</td>
<td>0.44</td>
<td>31.3±3.4</td>
<td>28.1±3.8</td>
<td>0.028</td>
<td>0.064</td>
</tr>
<tr>
<td>TauF, ms</td>
<td>13.7±0.11</td>
<td>176.2±37.0</td>
<td>0.52</td>
<td>140.3±7.8</td>
<td>86.3±5.5</td>
<td>0.018</td>
<td>0.023</td>
</tr>
<tr>
<td>TauL, ms</td>
<td>39.8±3.8</td>
<td>48.6±6.6</td>
<td>0.21</td>
<td>42.7±2.9</td>
<td>30.0±1.7</td>
<td>0.018</td>
<td>0.017</td>
</tr>
<tr>
<td>dP/dt_{max}, mm Hg/s</td>
<td>587.3±22.6</td>
<td>842.1±50.4</td>
<td>0.005</td>
<td>574.7±31.2</td>
<td>797.9±45.7</td>
<td>0.018</td>
<td>0.696</td>
</tr>
<tr>
<td>PP, mm Hg</td>
<td>35.4±3.7</td>
<td>41.4±4.3</td>
<td>0.008</td>
<td>32.6±4.5</td>
<td>41.1±3.8</td>
<td>0.018</td>
<td>0.186</td>
</tr>
<tr>
<td>ΔAVO₂, % saturation/100</td>
<td>0.699±0.036</td>
<td>0.668±0.037</td>
<td>0.022</td>
<td>0.723±0.035</td>
<td>0.647±0.043</td>
<td>0.028</td>
<td>0.064</td>
</tr>
<tr>
<td>Mean Qcor, cm/s</td>
<td>23.8±2.4</td>
<td>22.5±2.1</td>
<td>0.14</td>
<td>21.7±2.6</td>
<td>33.6±3.7</td>
<td>0.018</td>
<td>0.001</td>
</tr>
<tr>
<td>MVO₂, DAVO₂ x Qcor</td>
<td>16.8±2.0</td>
<td>15.0±1.7</td>
<td>0.047</td>
<td>15.5±1.8</td>
<td>21.5±2.5</td>
<td>0.018</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Re-Con indicates recontrol (NSR); HR, heart rate; LVEDP, LV end-diastolic pressure; TauF, time constant of relaxation (exponential model); TauL, time constant of relaxation (logistic model); and Qcor, proximal left main coronary flow velocity.

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**Figure 2.** A, Individual patient changes in mechanical and energetic parameters comparing baseline control (Con) with LV free wall VDD pacing (LVpace) or with BiV pacing (BiVpace). In both instances, systolic function improved as MVO₂ declined. B, Summary data displaying percent changes induced by LV free wall (top) or BiV stimulation (bottom).
Cardiac inefficiency in the setting of LBBB can occur from several aspects of dysynchronous contraction. First, the early activated portion is already engaged in systolic stiffening when the opposing nonstimulated wall remains distensible, wasting energy. The resulting internal transfer of work from one side of the heart to the other reduces chamber efficiency. The present results indicate that with resynchronization pacing, the net load rebalancing can lead to a modest yet significant decline in oxygen utilization, which is likely related to lowering wall stress in the late activated lateral wall.

It is important to stress that the improved efficiency from resynchronization pacing is unlikely to be due to alterations in intrinsic myocyte function. Rather, the net effect is observed at the chamber level because of the enhancement of the effectiveness of the work performed by different regions of the wall. This process is analogous to that of a poorly timed automotive engine; each piston continues to burn fuel, but when timing is suboptimal, there is reduced effective compression and engine power, wasted work, and lower fuel economy.

**Comparison With Other Heart Failure Therapy**

To our knowledge, an intervention that substantially improves systolic function without altering heart rate or reducing vascular load and that is accompanied by even a modest decline in MVO₂ is rather unique. Sympathomimetic agents such as dobutamine or isooproterenol elevate heart rate and thus MVO₂, but they also increase per-beat MVO₂. Vasodilators such as nitroprusside lower MVO₂ both per minute and per beat, but this is largely attributable to their unloading effects to reduce stress and workload. Inhibitors of phosphodiesterase-III, such as enoximone, elevate cAMP to combine vasodilating and inotropic effects. The net decline in per-beat MVO₂ is mostly dependent on the vasodilation, inasmuch as restoring chamber volume to baseline largely negates improved efficiency. Similar issues apply to other agents displaying inhibitory action against phosphodiesterase-III. Even calcium sensitizers, which can acutely benefit mechanoenergetics, have not typically reduced MVO₂.

The only other therapy shown to chronically reduce MVO₂ yet improve systolic function is β-blockade, as elegantly demonstrated by Eichhorn and colleagues. Unlike resynchronization pacing, however, a component of the MVO₂ decline relates to slower heart rates and requires chronic exposure. Resynchronization pacing may in fact facilitate the use of β-blockers in particularly ill or less tolerant patients as well as provide a modest energetic reserve to improve tolerance to other inotropic agents, such as phosphodiesterase-III inhibitors. This clearly requires further testing.

**Study Limitations**

The present protocol was designed to test the acute mechanoenergetic effects of LV and BiV pacing/stimulation. Although the time point for analysis was brief, it was sufficient to define steady-state mechanoenergetic responses in intact hearts and compatible with many prior studies in this regard. Moreover, given the stability of the mechanical pacing response, it is unlikely that energetic changes would suddenly deviate from those observed in this earlier time frame. The technical complexity of the study often required 2 to 3 hours of instrumentation before collecting data. Given that results were measured in duplicate, different pacing-site combinations were used, and it was necessary to revert to NSR for recontrol each time, we purposely selected a time period established as sufficient for steady-state responses, yet not so long that it compromised completing the protocol. It remains unknown whether the rapidly improved efficiency that we observed is chronically sustained. This will require future serial studies, and proof of overall chronic efficacy is the subject of several current multicenter trials.

We compared pacing with intravenous dobutamine infusion; the latter was chosen to mirror the typical setting in which this agent is used as well as to minimize manipulation of the coronary catheter fitted with a Doppler probe. However, this administration route (versus intracoronary) can lower systemic vascular resistance and thus LV load, thereby diminishing MVO₂. Although cardiac output was not directly measured with dobutamine, it likely increased because of the higher PP, and because systolic pressure was unaltered (108 versus 114 mm Hg, P = 0.2), systemic resistance likely declined. Despite this, we observed a significant
rise in per-beat MVO₂ with dobutamine, and this would likely have been greater without any peripheral load change. The need for coronary sinus instrumentation to place the LV pacing wire precluded the use of a thermomission catheter to measure total coronary sinus flow. Proximal left main coronary flow was used as a surrogate, but this did not reflect total coronary flow. Thus, energetic parameters were best interpreted in relative (baseline versus pacing) rather than absolute terms.

Last, the present study was conducted in patients with primarily nonischemic DCM, minimal mitral regurgitation, and a documented systolic response to pacing. For the most part, these features reflected our referral base of patients with a wide QRS duration, sinus rhythm, and DCM. Nonetheless, these are not characteristics of many heart failure patients, and some caution is advised in generalizing these findings to the broader DCM population.

Summary

The mechanisms underlying energy limitations in heart failure are still being elucidated but are presently thought to include abnormalities of creatine kinase shuttling, NO-mediated mitochondrial respiration, oxidative stress, and coronary flow reserve from endothelial dysfunction. Thus, although therapies that improve systolic function yet increase energy demand often alleviate symptoms in the short term, chronic treatment has consistently proven disappointing. Resynchronization therapy by LV or BiV pacing/stimulation is a novel approach whereby the timing rather than intrinsic muscle contraction is enhanced to improve systolic function. By rapidly achieving this gain yet modestly lowering energy demand, this therapy has promising potential to benefit the failing heart.

Acknowledgments

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References


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