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

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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% to 40%, QRS duration 179 ± 3 ms, mean ± SEM) 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 discoordinate 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

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Methods

Study Group
Ten patients with DCM and LBBB 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%), LBBB with QRS duration ≥140 ms (mean 179.1±31.4 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.12

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 inferoposterior 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 depressed hearts, volume signals were interpretable (beyond noise range) in only 3 studies; however, data from these patients were consistent with prior results in a similar study.12

A bipolar electrode catheter was placed in the right atrium to sense the sinus rate. A pacing wire (Cardima, 01-043013) was advanced through a flexible sheath (Arrow, CL07680) introduced into the coronary sinus. The wire was usually placed in a lateral or anterolateral cardiac vein, midway between the base and apex,12 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 full preexcitation (106.0±11.6 ms, mean±SD) was determined and used for the present study. BiV stimulation was also tested (n=5) by simultaneously activating the LV free wall and right ventricular apex.

An intracoronary Doppler catheter (Cardiometrics) was placed in the proximal left main coronary artery to monitor coronary flow, digitizing the analog-output signal for analysis. In 4 studies, vessel diameters before and during LV pacing/stimulation were determined by contrast imaging, and no changes were detected. Thus, flow velocity was presumed to be proportional to volume flow. The arterial–coronary sinus oxygen saturation difference (∆AVO2) was determined by hemoximeter.

Hemodynamic data and blood samples were obtained under NSR and after 2 minutes of steady-state pacing/stimulation. This time period was based on studies showing that transient changes in coronary flow and cardiac oxygen consumption in response to acute mechanical changes stabilize within 60 to 90 seconds.23,24 Both conditions were alternated twice (after repeat baseline measurements), and results were averaged. Last, after reestablishing NSR, dobutamine (10 to 25 μg·kg⁻¹·min⁻¹ IV) was titrated to match dP/dt max changes observed with LV pacing, and mechanoenergetic measurements were repeated.

Data Analysis
Hemodynamic data were sampled at 200 Hz, and results reflect values derived from an average of at least 15 sequential cycles. dP/dt was calculated in real time by use of a digital filter12 from which its maximal value, dP/dt max, was determined. Prior studies have reported 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 ∆AVO2 indexed relative changes in MVO2 (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 (MVO2) 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 delay time did not significantly change. Despite the improved systolic improvement, ∆AVO2 declined by −4.4±1.6%, and MVO2 fell by −7.9±6.5% (both P<0.05). The decline in MVO2 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 MVO2 (−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 ∆AVO2 declined −5.8±1.2%, and MVO2 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 $\dot{V}O_2$ along with systolic function in each patient ($n=7$). Baseline and intervention-enhanced $\frac{dP}{dt_{\text{max}}}$ was similar for both interventions by study design (dobutamine increased $\frac{dP}{dt_{\text{max}}}$ by 36.9 ± 5.7%); however, dobutamine raised $\dot{V}O_2$ by 42.1 ± 13.3% ($P<0.005$ versus pacing/resynchronization therapy). Two of the patients had received $\beta$-blockers as part of chronic therapy, but as the dobutamine dose was titrated to match responses with LV pacing/stimulation, the percent $\Delta\dot{V}O_2$ was similar with (38.3 ± 19.1%) or without (43.6 ± 18.2%) $\beta$-blockade. Last, in the 3 patients with interpretable LV volume signals, chamber efficiency was calculated from the stroke work/$\dot{V}O_2$ 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 $\dot{V}O_2$ change between pacing/stimulation and dobutamine was an increase in heart rate that only accompanied dobutamine infusion. Figure 3 displays results for per-beat $\dot{V}O_2$ in both groups. Even after adjusting for heart rate, dobutamine significantly increased $\dot{V}O_2$ by 21.5 ± 11.0% versus a decline with pacing of $-5.4\pm6.7\%$ ($P=0.025$).

**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. The patients most likely to benefit are those with the greatest basal dyssynchrony, often reflected by a wide QRS duration. Because functional improvement can be substantial, analogous to that from 15 to 20 $\mu$g·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 mechanoenergetic-
ders the heart inefficient.\textsuperscript{19} Activation, which depresses systolic pump function and ren-
sulting internal transfer of work from one side of the heart
as the latter enters relaxation, again wasting energy. The
last, the late region can stretch the early activated region
while the early activated portion is already engaged in systolic stiffen-
ing. \textsuperscript{16,18,31} Second, the late-stimulated work as the shortening of one region is largely converted to
the opposing nonstimulated wall remains distensible, wasting
energy. The effectiveness of the work performed by different regions
observed at the chamber level because of the enhancement of
intrinsic myocyte function. Rather, the net effect is
inasmuch as restoring chamber volume to baseline largely
negates improved efficiency.\textsuperscript{36} Similar issues apply to other
agents displaying inhibitory action against phosphodiesterase-
III.\textsuperscript{37,38} Even calcium sensitizers, which can acutely benefit
mechanoenergetics, have not typically reduced MVO\textsubscript{2}.\textsuperscript{36}

The only other therapy shown to chronically reduce MVO\textsubscript{2}
yet improve systolic function is \textbeta-blockade, as elegantly
demonstrated by Eichhorn and colleagues.\textsuperscript{39,40} Unlike resyn-
chronization pacing, however, a component of the MVO\textsubscript{2}
decline relates to slower heart rates and requires chronic
exposure. Resynchronization pacing may in fact facilitate the
use of \textbeta-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 inhibi-
tors. 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 re-
sponses in intact hearts and compatible with many prior
studies in this regard.\textsuperscript{23,24} Furthermore, 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 complex-
ity of the study often required 2 to 3 hours of instrumen-
tation 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 infu-
sion; 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. How-
ever, this administration route (versus intracoronary) can
lower systemic vascular resistance and thus LV load,\textsuperscript{41}
thereby diminishing MVO\textsubscript{2}. Although cardiac output was not
directly measured with dobutamine, it likely increased be-
cause of the higher PP, and because systolic pressure was
unaltered (108 versus114 mm Hg, \( P = 0.2 \)), systemic resis-
tance likely declined. Despite this, we observed a significant

**Comparison With Other Heart Failure Therapy**

To our knowledge, an intervention that substantially im-
proves systolic function without altering heart rate or reduc-
ing vascular load and that is accompanied by even a modest
decline in MVO\textsubscript{2} is rather unique. Sympathomimetic agents
such as dobutamine or isoproterenol elevate heart rate and
thus MVO\textsubscript{2}, but they also increase per-beat MVO\textsubscript{2}.\textsuperscript{32-34}
Vasodilators such as nitroprusside lower MVO\textsubscript{2} both per
minute and per beat, but this is largely attributable to their
unloading effects to reduce stress and workload.\textsuperscript{35} Inhibitors of
phosphodiesterase-III, such as enoximone, elevate cAMP to
combine vasodilating and inotropic effects. The net decline in
per-beat MVO\textsubscript{2} is mostly dependent on the vasodilation,
inasmuch as restoring chamber volume to baseline largely
negates improved efficiency.\textsuperscript{36} Similar issues apply to other
agents displaying inhibitory action against phosphodiesterase-
III.\textsuperscript{37,38} Even calcium sensitizers, which can acutely benefit
mechanoenergetics, have not typically reduced MVO\textsubscript{2}.\textsuperscript{36}
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 thermodilution 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,30 NO-mediated mitochondrial respiration,31 oxidative stress,31,43 and coronary flow reserve from endothelial dysfunction.44 Thus, although therapies that improve systolic function yet increase energy demand often alleviate symptoms in the short term, chronic treatment has consistently proven disappointing.3,4 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.

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