Ventricular Contraction Abnormalities in Dilated Cardiomyopathy: Effect of Biventricular Pacing to Correct Interventricular Dyssynchrony

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OBJECTIVE
To measure ventricular contractile synchrony in patients with dilated cardiomyopathy (DCM) and to evaluate the effects of biventricular pacing on contractile synchrony and ejection fraction.

BACKGROUND
Dilated cardiomyopathy is characterized by abnormal ventricular activation and contraction. Biventricular pacing may promote a more coordinated ventricular contraction pattern in these patients. We hypothesized that biventricular pacing would improve synchrony of right ventricular and left ventricular (RV/LV) contraction, resulting in improved ventricular ejection fraction.

METHODS
Thirteen patients with DCM and intraventricular conduction delay underwent multiple gated equilibrium blood pool scintigraphy. Phase image analysis was applied to the scintigraphic data and mean phase angles computed for the RV and LV. Phase measures of interventricular (RV/LV) synchrony were computed in sinus rhythm and during atrial sensed biventricular pacing (BiV).

RESULTS
The degree of interventricular dyssynchrony present in normal sinus rhythm correlated with LV ejection fraction \((r = -0.69, p < 0.01)\). During BiV, interventricular contractile synchrony improved overall from \(27.5 \pm 23.1^\circ\) to \(14.1 \pm 13^\circ\) \((p = 0.01)\). The degree of interventricular dyssynchrony present in sinus rhythm correlated with the magnitude of improvement in synchrony during BiV \((r = 0.83, p < 0.001)\). Left ventricular ejection fraction increased in all thirteen patients during BiV, from \(17.2 \pm 7.9\%\) to \(22.5 \pm 8.3\%\) \((p < 0.0001)\) and correlated significantly with improvement in RV/LV synchrony during BiV \((r = 0.86, p < 0.001)\).

CONCLUSIONS
Dilated cardiomyopathy with intraventricular conduction delay is associated with significant interventricular dyssynchrony. Improvements in interventricular synchrony during biventricular pacing correlate with acute improvements in LV ejection fraction. (J Am Coll Cardiol 2000;35:1221–7) © 2000 by the American College of Cardiology

Dilated cardiomyopathy (DCM) is characterized by structural abnormalities of ventricular myocardium, affecting both ventricular activation and mechanical contraction (1–3). The electrical activation of ventricular segments may be delayed consequent to pathological involvement of the ventricular conduction system or due to inhomogeneous spread of excitation wavefronts across scarred tissue (4,5). In patients with left bundle branch block (LBBB) and no structural heart disease, a decreased left ventricular (LV) ejection fraction (EF) has been observed in association with marked interventricular asynchrony (6).

Preliminary data, not yet supported by controlled clinical trials, have demonstrated acute improvements in hemodynamic status during atrial synchronized biventricular pacing (BiV) in patients with dilated heart failure (7–12). These salutary effects may be achieved through enhanced synchrony of ventricular contraction. While previous investigations have focused on the effect of pacing site to improve acute hemodynamic parameters, pacing effects on ventricular contractile synchrony have not been characterized. We hypothesized that BiV would improve synchrony of right ventricular (RV) and LV contraction, contributing to improved ventricular EF.

Multigated equilibrium blood pool scintigraphy was used to measure ventricular contractile synchrony in patients with DCM and intraventricular conduction delay (IVCD). Phase imaging (13–15), a parametric method applied to blood
pool scintigrams, provided for the quantitative and qualitative analysis of ventricular contractile synchrony and was used to measure changes in synchrony during BiV.

Ventricular EF, computed from the identical scintigraphic data, was used to analyze the relationship between ventricular contractile synchrony and EF, both in sinus rhythm and during BiV.

**METHODS**

**Patients.** Thirteen consecutive patients were enrolled between July 1997 and April 1998. Patients were screened for enrollment if they had chronic biventricular pacemakers, referral for electrophysiology testing or had recent open heart surgery with placement of epicardial pacing wires. Enrollment criteria included DCM, LV ejection fraction <35%, symptomatic heart failure (New York Heart Association [NYHA] functional class II–III) and sinus rhythm. Informed consent was obtained for each patient in accordance with the Committee On Human Research at UCSF. A permanent biventricular pacemaker was implanted in the six consecutive patients as part of a multicenter clinical trial (VIGOR, CHF Trial, Guidant, St. Paul, Minnesota). The remaining seven patients underwent acute BiV in the electrophysiology laboratory. In five patients BiV was performed using RV endocardial and coronary sinus (CS) branch vein pacing of the LV. The protocol was performed before EP testing for evaluation of syncope or near syncope. The remaining two patients underwent BiV postoperatively (coronary artery bypass grafting and aortic valve replacement) using epicardial pacing wires placed at the time of surgery.

No patient had more than mild to moderate mitral regurgitation measured by echocardiogram performed within three months before study enrollment. The clinical characteristics of the patient group are shown in Table 1.

**Pacing protocol.** In the six patients with permanent biventricular pacemakers, simultaneous BiV was performed using a custom made biventricular pacemaker (VIGOR CHF Model 1240, Guidant, St. Paul, Minnesota) with endocardial right atrial and RV leads and an epicardial LV lead. After baseline data were acquired in normal sinus rhythm (NSR), pacemakers were reprogrammed to the atrial sensed biventricular paced (VDD) mode. The atrioventricular (AV) delay was programmed to 120 ms. This AV delay was chosen to ensure complete biventricular capture and is within the optimal range identified for BiV in patients with DCM and bundle branch block (11,12). Patients were paced or nonpaced for a minimum of 3 to 5 min before image acquisition.

For the seven patients undergoing BiV during electrophysiologic study, bipolar electrograms were recorded using

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**Abbreviations and Acronyms**

AV = atrioventricular

BiV = atrial synchronized biventricular pacing

CS = coronary sinus

DCM = dilated cardiomyopathy

EDC = end-diastolic counts

EF = ejection fraction

ESC = end-systolic counts

IVCD = nonspecific intraventricular conduction delay

LBBB = left bundle branch block

LV = left ventricle or ventricular

NYHA = New York Heart Association functional class

RBBB = right bundle branch block

RV = right ventricle or ventricular

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**Table 1. Patient Characteristics**

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AVR = aortic valve replacement; BBB = bundle branch block; ETOH = alcohol related cardiomyopathy; IDC = idiopathic dilated cardiomyopathy; ISCH = ischemic cardiomyopathy; IVCD = nonspecific intraventricular conduction delay; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association functional class; RVEF = right ventricular ejection fraction.
a digital recording system (Pruka Engineering, Houston, Texas) with signals filtered at 30–500 Hz. Bipolar pacing was performed at twice diastolic threshold using a Bloom stimulator (Bloom Ltd., Reading, Pennsylvania), programmed to dual chamber pacing at 5–10 beats above the intrinsic sinus rate. Right and left ventricular pacing was achieved by pacing simultaneously from the distal electrode pair of the RV and from the LV epicardial catheter (CS branch vein or epicardial wire).

For all patients, loading conditions were held constant and complete biventricular capture was documented on 12-lead ECG at threshold testing and continuously during scintigraphic image acquisition.

**Lead placement.** Lead placement was documented fluoroscopically at the time of image acquisition in all patients. The RV lead position was apical in all 13 patients. The LV lead position was within two cm of the LV apex in 10 of the 13 patients. In subjects undergoing LV pacing using a CS branch vein, the LV lead was placed midway between the base and apex at the lateral LV wall in three patients and at the true LV apex in two patients.

**Radionuclide techniques.** Erythrocyte labeling was performed using technetium-99m pertechnetate (16). Multigated equilibrium blood pool scintigrams were acquired at rest in the “best-septal” left anterior oblique projection to provide optimal RV/LV blood pool discrimination. A portable scintigraphic scanner (Elscint Ltd., Haifa, Israel) was used for imaging in the electrophysiology laboratory. The ECG was monitored continuously to ensure R wave gating of the QRS complex. Scintigraphy was performed at equilibrium for 5 min and for at least 6 million total counts, using 24 frames per cardiac cycle. Scintigrams were acquired for each patient in sinus rhythm and during BiV. Scintigrams were smoothed off-line, and RV/LV regions of interest were acquired at end-diastole and end-systole for the respective ventricle. Regions of interest were drawn automatically by the computer (Microdelta, Siemens Inc., Hoffman Estates, Illinois) with adjustments of border definition performed by an observer blinded to the state of conduction. Regions were then redrawn manually by a second observer, also blinded to the state of conduction, for computation of interobserver variability. After correction for background counts, LV and RV EFs were computed using the formula:

$$EF = \frac{EDC}{ESC}$$

where EDC is end-diastolic counts and ESC is end-systolic counts. Ejection fractions computed using this technique have demonstrated extremely low intra- and interobserver variability and have been highly reproducible when computer determined (17).

**Nuclear phase imaging.** Phase images were generated from the scintigraphic data using a commercially available computer program (Microdelta, Siemans Inc., Hoffman Estates, Illinois). The identical scintigraphic data used to generate RV and LV EFs were digitally processed to display the “phase” for each pixel overlaying the equilibrium blood pool and gated to the ECG R wave. The phase program assigns a phase angle (Ø) to each pixel of the phase image, derived from the first Fourier harmonic of the time versus radioactivity curve (a parallel of the ventricular volume curve) fitted to the cardiac cycle (13). The phase angle (Ø) corresponds to the relative sequence and pattern of ventricular contraction during the cardiac cycle.

Color encoded phase images with corresponding histograms were generated for each patient in NSR and during BiV. Scintigrams were intensity coded for amplitude, a parameter related to stroke volume, setting background pixels to black (zero amplitude) and providing clear edges to ventricular regions of interest. Pixels overlying cardiac regions below amplitude threshold, corresponding with low stroke volume, were also set to black. Phase images were generated for cardiac regions above amplitude threshold using a continuous rainbow color wheel, corresponding to phase angles from 0° to 360°. To avoid discontinuities of the phase angle display, the entire scale was shifted 180°, placing ventricular ejection at the center of the histogram display.

Mean phase angles were computed for RV and LV blood pools as the arithmetic mean phase angle Ø for all pixels in the ventricular region of interest (14,15). Interventricular contractile synchrony was measured as the absolute difference in RV and LV mean phase angles, delta Ø (RV-LV). Intraventricular contractile synchrony was measured as the standard deviation of the mean phase angle for the RV and LV blood pools (SD RVØ, SD LVØ) and was computed for each patient in NSR and during BiV.

**Electrocardiography.** Surface 12-lead electrocardiograms were acquired in NSR and during BiV. The QRS duration was measured from the first intrinsic deflection of the QRS complex to the terminal isoelectric component of the complex in NSR and from the first evoked QRS intrinsic deflection to the terminal isoelectric component during BiV. QRS measures were recorded from the surface lead demonstrating the greatest QRS duration.

**Statistics.** Statistical analysis was performed using the Student t test for paired/unpaired data, as appropriate. Linear regression analysis was performed using Pearson correlation coefficients. Interobserver variability in the measurement of LVEF was assessed as percent agreement.

**RESULTS**

The effects of BiV for each patient are summarized in Table 2. The effect of BiV on measured parameters is illustrated in Figure 1.

**Interventricular (RV/LV) contractile synchrony.** Interventricular contractile synchrony, measured as delta Ø (RV-LV), was significantly impaired in each of the eight
patients with manifest bundle branch block during sinus rhythm. A lesser degree of contractile dyssynchrony was observed in the five patients with IVCD (QRS ≤ 120 ms).

Synchrony improvement, defined as a reduction in delta Ø (RV-LV) during BiV, was observed in each of the eight patients with overt bundle branch block and in one patient with an IVCD of 120 ms. For the group overall, interventricular dyssynchrony improved from 27.5 ± 23.1° to 14.1 ± 13.0° (p < 0.01). Three patients with IVCD demonstrated a small increase in interventricular dyssynchrony during BiV (range 1° to 8°), and one patient with IVCD experienced no net change. The four patients showing no improvement of interventricular contractile synchrony during BiV had the lowest dyssynchrony measures during sinus rhythm (range 2° to 10°) and each had a QRS duration of <120 ms. The relationship between QRS duration and degree of interventricular dyssynchrony present in sinus rhythm was significant (r = 0.66, p < 0.05).

A significant positive correlation was observed (r = 0.83, p < 0.001) between the degree of interventricular dyssynchrony in sinus rhythm and the degree of improvement of interventricular synchrony during BiV.

A small increase in mean QRS duration was noted during BiV compared with sinus rhythm (155.8 ± 48.2 ms NSR vs. 175.5 ± 41.4 ms BiV, p < 0.03). Only 3 of 13 patients demonstrated pacing induced reductions in QRS duration.

**Intraventricular contractile synchrony.** Intraventricular contractile synchrony measured as the standard deviation of the mean phase angle (SD LVØ, SD RVØ; Table 2, Fig. 1) varied significantly from patient to patient during sinus rhythm. A significant correlation was observed between intraventricular (LV) dyssynchrony and depressed LVEF (r = −0.73, p < 0.01).

During BiV, intraventricular contractile dyssynchrony increased overall for the LV but not the RV. This increase of intraventricular dyssynchrony showed no significant correlation with changes in QRS duration or with changes in RV or LV EF.

**Phase image analysis.** Figure 2, A to D, illustrates the abnormal ventricular contraction patterns present in four patients with DCM and ventricular conduction delay. In sinus rhythm, delayed LV contraction is observed with LBBB (Fig. 2, A and B), and delayed RV contraction is observed with right bundle branch block (RBBB) (Fig. 2C). The patient with IVCD (Fig. 2D) has a less remarkable degree of RV/LV dyssynchrony. Significant intraventricular dyssynchrony, characterized by inhomogenous phase, was observed in each of the four patients.

Patients with complete bundle branch block achieved a greater degree improvement of interventricular synchrony, illustrated as a decrease in the difference between RV and LV mean phase angles.

**Radionuclide EFs.** Acute improvements in LVEF were observed in each of the 13 patients during BiV (Table 2, Fig. 1). Left ventricular EF improved overall from 17.2 ± 7.9% to 22.5 ± 8.3% (p < 0.0001), corresponding with a mean relative improvement of 36%. Mean interobserver variability for LVEF was <5%, in accord with previously published accounts for multigated blood pool EFs acquired at rest (17). Observers agreed within 0 to 3 LVEF percentage points for all remeasured regions.

Acute improvements in RVEF were observed in 11 of the

### Table 2. Changes With Biventricular Pacing

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<th>RVEF (%)</th>
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**BBB** = bundle branch block - left (L), right (R) or IVCD (intraventricular conduction delay); BiV = atrial sensed biventricular pacing; CS = biventricular pacing using coronary sinus branch vein; E = epicardial biventricular pacing; NSR = normal sinus rhythm; P = permanent biventricular pacemaker; LVEF = left ventricular ejection fraction; RVEF = right ventricular ejection fraction; ΔØ (RV-LV) = difference in RV and LV mean phase angles; SD LVØ = standard deviation of LV mean phase angle; SD RVØ = standard deviation of RV mean phase angle.
improvement of interventricular synchrony and percent improvement in RVEF during BiV ($r = 0.48$, $p = \text{NS}$). Nonetheless, 11 of 13 patients demonstrated improvements in RVEF during BiV.

**Complications.** None of the study patients experienced complications related to lead placement, BiV or radionuclide image acquisition.

**DISCUSSION**

**Contraction abnormality in DCM.** The results of this study support the hypothesis that DCM with ventricular conduction delay is associated with significant ventricular contraction abnormalities during sinus rhythm. Analysis of nuclear phase images and histograms suggests that these contraction abnormalities exist as multiple levels of dyssynchrony. At one level is intraventricular dyssynchrony, represented on phase images as inhomogenous phase or discontinuous progression of phase angles between adjacent ventricular segments. For this diverse group of patients, the mean standard deviation of the LV phase angle was 32.8°. These findings are consistent with the observations of Frais et al. (15) in which the mean standard deviation of the LV phase angle for 18 patients with DCM was 27.3°, compared with a mean of 8.9° in 16 patients with normal hearts. That this measure did not improve with BiV is an important observation. Biventricular pacing, by changing the orientation of the activation/contraction wavefront, may not be expected to overcome conduction delay related to fixed scar in the myopathic ventricle.

A second level of dyssynchrony, interventricular dyssynchrony, is represented on phase images as an asymmetric RV/LV phase pattern. Dyssynchrony at this level is related to the site of bundle branch block and demonstrates greatest significance at QRS duration $>120$ ms. For this group of patients with DCM, the mean difference in RV and LV phase measured in sinus rhythm was 27.5°, a value greater than that reported by Frais et al. (14) for patients with isolated RBBB or LBBB ($\pm 21.8°$). That cardiomyopathy may contribute to interventricular dyssynchrony is supported by the observation in this study that the patients with the lowest LVEF, also demonstrate the greatest interventricular dyssynchrony.

**BiV improves interventricular synchrony.** The ability of BiV to correct interventricular dyssynchrony was demonstrated in this study. The magnitude of improvement in interventricular synchrony during BiV correlated significantly with improvements in LVEF. Changes in LVEF with pacing exceeded the measured interobserver variability. These data suggest that interventricular dyssynchrony is a correctable parameter contributing to LV dysfunction. That patients with lesser degrees of interventricular dyssynchrony (QRS $<120$ ms) also demonstrated improved LVEF during BiV suggests that additional mechanisms related to BiV may contribute to EF improvement.
Phase image analysis has provided a window onto the mechanisms by which BiV may affect myocardial performance. In patients with bundle branch block, the ‘preexcitation’ of a critical bulk of late contracting ventricular myocardium may act to shorten the delay in RV and LV emptying. The simultaneous activation of the LV and RV may contribute to improved ventricular septal coordination, a parameter associated with depressed ventricular EF in patients

Figure 2. Resynchronizing effects of biventricular pacing. Phase images acquired in four patients with DCM and varying patterns of IVCD. Contraction sequence, from early to late: green, azure, navy, violet, orange, yellow. Histograms illustrate dispersion of phase angles during ventricular ejection, plotted as phase angle (x axis) versus number of pixels (y axis). Vertical bars represent the arithmetic mean phase angle, Ø, computed for RV and LV blood pools. (A) Patient with DCM and LBBB. (Left) Abnormal phase pattern in sinus rhythm with right to left (azure to navy) ventricular contraction sequence. Left ventricular apex and septum contract with extreme delay, in phase with atrial systole (orange segment at top of figure). Histogram illustrates abnormal dispersion of phase angles spanning the cardiac cycle, with ΔØ of 75°. (Right) Characteristic apex to base contraction sequence during BiV. Phase pattern is more symmetrical across interventricular septum. Despite close proximity to pacing stimulus sites (green), the LV apex (yellow) fails to contract in sequence. A decrease in phase angle occurs with pacing. (B) Patient with DCM and LBBB. (Left) Dysynchronous RV and LV phase pattern in sinus rhythm. The bulk of the RV (green) contracts before onset of LV contraction (azure). Histogram illustrates bimodal distribution of phase angles for the RV and LV, with ΔØ of 28°. (Right) During BiV, ventricular activation originates simultaneously at the LV and RV apices (green), followed by RV outflow tract (azure) and LV base (azure, navy). A more symmetrical RV and LV phase pattern is observed with restoration of early septal contraction (green). Histogram illustrates a decrease in ΔØ to 0°, representing a 28° correction of baseline interventricular dyssynchrony. (C) Patient with DCM and RBBB. (Left) Dysynchronous RV and LV phase pattern in sinus rhythm. Ventricular activation originates at LV septum and base (azure), followed by bulk of RV (navy) and LV lateral wall (navy). Histogram illustrates disparity in RV and LV phase during sinus rhythm with ΔØ of 28°. (Right) During BiV, ventricular contraction originates at the RV apex and LV apical-septum (azure) in proximity to pacing stimulus sites. The RV and LV basal and midsegments (navy) contract in sequence with minimal delay. A more symmetrical phase pattern is observed across the interventricular septum. Ventricular contraction proceeds from apex to base, representing a 26° correction of baseline interventricular dyssynchrony. (D) Patient with DCM and IVCD. (Left) Diffuse and inhomogeneous contraction pattern in sinus rhythm. Ventricular activation originates at LV base and RV apex (green); eccentric contraction pattern, culminating at LV apex and RV base (azure/navy). Histogram illustrates gross dispersion of RV and LV phase angles with ΔØ of 15°. (Right) During BiV, intraventricular contraction abnormalities persist. The LV base and RV apex remain early (azure); the LV free wall and RV base contract with delay (navy/violet). Histograms demonstrate an 8° correction of interventricular dyssynchrony. BiV = atrial sensed biventricular pacing; DCM = dilated cardiomyopathy; IVCD = nonspecific intraventricular conduction delay; LBBB = left bundle branch block; LV = left ventricular; RBBB = right bundle branch block; RV = right ventricular.
with LBBB or during single ventricle (RV) pacing (6,18,19). These and other hemodynamic alterations may influence the proportionality between LV end-diastolic and stroke volumes, despite persistent heterogeneity of the LV contraction pattern.

**Study limitations.** This study documented the acute changes in ventricular synchrony and EF consequent to BiV. Extrapolation of these data to predict the clinical effects of chronic pacing is not appropriate.

Hemodynamic indexes, which can influence EF, such as intracardiac pressure and volume were not measured in this study. Pacing was performed in the VDD mode in six patients, during which time the sinus rate did not vary significantly from the nonpaced mode. Atrial pacing was performed just above the sinus rate in those patients with temporary pacing, and this may have influenced EF. Loading conditions were held constant, but an arterial line was not in place to measure beat-to-beat changes in blood pressure. The effects of BiV on AV valve regurgitation were not measured in this study and may have contributed to EF improvements. However, no patient in the study had more than mild to moderate mitral regurgitation. An AV delay of 100 to 120 ms was programmed to achieve complete biventricular capture and may have contributed to the observed improvements in EF. However, recent studies of pacing in heart failure have demonstrated a greater relative contribution of ventricular pacing site to improvements in LV performance than achieved through AV delay optimization (11,12). Further studies evaluating these parameters during chronic BiV are warranted.

Left ventricular lead placement varied somewhat between patients, and lead placement variations may have important effects on the degree of benefit obtained from BiV.

**Clinical impact and conclusions.** Despite advances in the medical management of congestive heart failure, a significant number of patients with LV systolic dysfunction progress to severe and medically refractory symptoms (20). Preliminary studies have suggested a possible role for chronic BiV in the management of patients with advanced heart failure and bundle branch block (7,8). The data presented here suggest that BiV, by correcting interventricular contractile dysynchrony, may in part contribute to improved ventricular function. The results of ongoing clinical trials of chronic BiV will determine if ventricular resynchronization improves clinical measures of heart failure severity.

**References:**