Sequential Versus Simultaneous Biventricular Resynchronization for Severe Heart Failure
Evaluation by Tissue Doppler Imaging

Peter Sogaard, MD, DMSc; Henrik Egeblad, MD, DMSc; Anders K. Pedersen, MD, DMSc; Won Yong Kim, MD, PhD; Bent Ø. Kristensen, MD, DMSc; Peter S. Hansen, MD, DMSc; Peter T. Mortensen, MD

**Background**—Cardiac resynchronization therapy (CRT) by means of simultaneous biventricular pacing improves left ventricular systolic performance and synchrony in patients with heart failure and bundle-branch block. We used tissue tracking and 3D echocardiography to evaluate the impact of sequential CRT with individualized interventricular delay programming.

**Methods and Results**—Twenty consecutive patients with severe heart failure and left bundle-branch block were included. Tissue tracking and 3D echocardiography were carried out before and on the day after pacemaker implantation. Eleven different interventricular delays were examined in each patient. Patients were reexamined after 3 months. Simultaneous CRT immediately reduced the extent of myocardium displaying delayed longitudinal contraction (DLC) from 48.6±16% to 23.2±13% (P<0.01) and increased left ventricular ejection fraction percentage (LVEF%) from 22.4±6% to 29.7±5% (P<0.01). However, optimum sequential CRT caused a further reduction in the extent of DLC from 23.2±13% to 11.1±7.2% (P<0.01), with a simultaneous increase in LVEF% (from 29.7±5% to 33.9±6%, P<0.01). Three months of optimum sequential CRT further improved LVEF% (from 33.6±6% to 38.6±7.2%, P<0.01). Tissue tracking detected the segments with DLC, and their location determined optimum interventricular delay programming. Compared with simultaneous CRT, sequential CRT increased diastolic filling time by 7±2.5%.

**Conclusions**—Compared with simultaneous CRT, sequential CRT significantly improves left ventricular systolic and diastolic performance. Tissue tracking can be used to select optimum interventricular delay during CRT. (Circulation. 2002;106:2078-2084.)

**Key Words:** imaging ■ echocardiography ■ heart failure ■ bundle-branch block ■ pacing

CARDIAC RESYNCHRONIZATION THERAPY (CRT) WITH SIMULTANEOUS RIGHT VENTRICULAR (RV) AND LEFT VENTRICULAR (LV) STIMULATION IS A PROMISING THERAPEUTIC OPTION IN PATIENTS WITH SEVERE HEART FAILURE (HF) AND LEFT BUNDLE-BRANCH BLOCK (LBBB).1 We and others have previously reported on the use of tissue Doppler imaging with tissue tracking (TT) for the detection and quantification of LV systolic performance2–4 and LV asynchrony.3,4 We found that the extent of myocardium with delayed longitudinal contraction (DLC) predicted the improvement in LV systolic performance and reversion of LV remodeling during short- and long-term CRT.3,4 Our observations indicate that DLCs represent mechanical LV asynchrony and thus a contractile reserve, which can be recruited by means of CRT.4 However, in patients with HF and LBBB, the location of myocardium displaying DLCs may vary. Recent development in pacemaker technology enables separate activation of the ventricular leads. In the present study, we hypothesize that individually tailored preactivation of myocardium displaying DLCs would further improve the overall response to CRT.

**Methods**

**Patient Population**

Twenty-one consecutive patients referred for implantation of a biventricular pacemaker were included in the present study after oral and written informed consent. The study was approved by the local ethics committee and was conducted according to the Helsinki declaration.

All patients were in sinus rhythm and had LBBB with a QRS duration >130 ms. Patients were in New York Heart Association (NYHA) class III or IV despite contemporary medical treatment for HF (Table).

**Implantation Technique**

Three transvenous pacing leads were inserted, one in the right atrium and another on the high interventricular septum or in the RV outflow tract. In addition, a coronary sinus lead (Medtronic 2187 or 10512) was positioned on the LV free wall through a coronary sinus

Received June 12, 2002; revision received August 7, 2002; accepted August 7, 2002.

From the Department of Cardiology, Aarhus University Hospital, Skejby Sygehus, Aarhus, Denmark.

Correspondence to Peter Sogaard, MD, DMSc, Department of Cardiology, Aarhus University Hospital, Skejby Sygehus, Brendstrupgaardstræde, DK 8200 Aarhus N, Denmark. E-mail psogaard@dadhnet.dk

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Circulation is available at http://www.circulationaha.org

DOI: 10.1161/01.CIR.0000034512.90874.8E

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The RV and LV pacing leads were positioned to ensure that the sensed local intracardiac activation was measured early for the RV lead and late for the LV lead according to the QRS complex on the surface ECG. The pacing leads were connected to a dual-chamber biventricular pacemaker (In-Sync III, Medtronic) with programmable interventricular delay. The pacemaker was programmed in the DDD mode, and adjustment of the atrioventricular delay was performed during simultaneous pacing. According to Ritter et al., the longest possible AV filling time, without truncation of the A wave, was chosen by means of pulsed Doppler analysis of the transmitral flow. In these patients, the average AV delay was 106.5 ± 26.6 ms.

**ECHO Protocol**

We have previously reported in detail on the tissue Doppler imaging techniques and 3D echocardiography (ECHO) in the setting of biventricular pacing as well as on observer variability. Intraobserver variability for measurement of LV volumes and LV ejection fraction percentage (LVEF%) is 3% to 5%. 3D ECHO volumes are accurate and reproducible compared with magnetic resonance imaging; consequently, the number of patients required in a 2D ECHO study should be at least 4 times higher to achieve the same statistical power on volume measurements. In brief, 3D ECHO and tissue Doppler recordings were performed on the day before and after implantation of the pacemaker. Measurements were repeated after 3 months. During the first postimplantation evaluation, the ECHO examinations were carried out during

**Demographics and Clinical Variables**

<table>
<thead>
<tr>
<th>Age, y</th>
<th>66 ± 8</th>
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</thead>
<tbody>
<tr>
<td>Sex (male/female), n</td>
<td>17/3</td>
</tr>
<tr>
<td>IHD/non-IHD, n</td>
<td>11/9</td>
</tr>
<tr>
<td>Previous AMI, n</td>
<td>11</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>176 ± 25</td>
</tr>
<tr>
<td>PR interval, ms</td>
<td>186 ± 36</td>
</tr>
<tr>
<td>ACE inhibitor, n (%)</td>
<td>20 (100)</td>
</tr>
<tr>
<td>Diuretics, n (%)</td>
<td>20 (100)</td>
</tr>
<tr>
<td>β-Blocker, n (%)</td>
<td>20 (100)</td>
</tr>
<tr>
<td>Aldosterone antagonist, n (%)</td>
<td>20 (100)</td>
</tr>
<tr>
<td>Digoxin, n (%)</td>
<td>15 (75)</td>
</tr>
</tbody>
</table>

Values are given as mean ± SD or number of patients (percentage). IHD indicates ischemic heart disease; and AMI, acute myocardial infarction.

![Figure 1. A, Top, TT images in apical 4-chamber, 2-chamber, and long-axis views in systole in patient with idiopathic dilated cardiomyopathy before implantation of biventricular pacemaker. Most of lateral wall, posterior wall, and distal parts of anterior wall are gray, indicating lack of systolic motion toward the apex (white arrows). Color-coded scaling at left side of each image indicates regional motion amplitude. Mechanical function of interventricular septum and inferior walls is abnormal, with greater motion amplitude in segments adjacent to apex (green arrows). Bottom, Extent of myocardium (colored segments) with DLC in diastole (mitral valve open). DLC is present in lateral, posterior, and inferior walls. Note that remaining part of LV is gray, indicating either no motion or motion toward base of heart (relaxation). B, Same patient and views as in panel A (systole). Top, Simultaneous CRT resulting in contraction of larger proportion of lateral wall. Improvement is also noted in posterior wall. In addition, each segment shows improved systolic shortening as seen from color coding. Moreover, abnormal distribution of myocardial motion in interventricular septum has been normalized. Bottom, Impact of sequential CRT with LV activated by 20 ms before RV. Compared with simultaneous CRT, sequential CRT yields further improvement in overall proportion of contracting myocardium in lateral and posterior walls. In addition, each segment shows further improvement in systolic shortening amplitude.](http://circ.ahajournals.org/doi/abs/10.1161/CIRCULATIONAHA.116.027691)
simultaneous CRT and at 5 different interventricular delay intervals
(12, 20, 40, 60, and 80 ms) with either LV lead preactivation or RV
lead preactivation. Thus, a total of 11 different interventricular
delays were examined, with an equilibrium period of 10 minutes
between each examination.

3D ECHO was performed during end-expiratory apnea within 1
breath-holding by using ECG-triggered coaxial rotation from the
apical window with 30° intervals between the scanning planes. The
resulting 6 digital cine loops were transferred to a computer for
offline analysis (Echo-Pac software, GE-Vingmed Ultrasound). In
each of the 6 views, endocardial borders were drawn manually in end
diastole and end systole for calculation of LV end-diastolic volume
(LVEDV), end-systolic volume (LVESV), and LVEF%.3,4,6–8

Tissue Doppler recordings were acquired as digital loops in
end-expiratory apnea during 1 heart beat in the apical 4-chamber,
2-chamber, and long-axis views. To avoid aliasing, the settings of the
ultrasound equipment and color-coded area were adjusted to obtain
the highest possible frame rate (mean 115 frames/s, range 100 to 135
frames/s). A TT image in systole was derived from the digital loops
in each of the apical views (Figures 1A and 2A, top). Another TT
image was recorded in diastole to visualize myocardium with DLC
(Figures 1A and 2A, bottom), and the number of segments with DLC
was registered. Strain rate analysis (Figure 3) was carried out in each
segment, and motion toward the apex in diastole was registered as
DLC if negative strain rate analysis documented that the motion
reflected true shortening.

The 16-segment LV model9 was applied to the TT images. From
the color-coded TT image, the motion amplitude toward the apex in
systole was recorded in each segment. The global systolic contract-
amplitude (GSCA) was calculated as the average shortening
amplitude of all 16 segments. Calculation of GSCA was performed
in the 11 different interventricular delay recordings at baseline and
after 3 months. Optimum interventricular delay programming of the
pacemaker was identified by maximum GSCA in each patient
(Figures 1B and 2B).

To minimize the variability of the measurements, all ECHO
recordings were performed and analyzed by the same author (P.S.).
A 6-minute hall walk was performed at baseline and after 3 months.

Statistical Analysis
Differences between ECHO variables at baseline and during CRT were
evaluated by a nonparametric ANOVA (Kruskal-Wallis). A paired t test
was used to evaluate changes in the 6-minute hall walk and NYHA class. A value of $P<0.05$ was considered statistically significant.

**Results**

One patient developed atrial fibrillation between pacemaker implantation and ECHO evaluation and was excluded from analysis. Clinical and demographic variables of the remaining 20 patients are given in the Table. Tissue Doppler analysis was feasible in all 16 segments in all patients. Similarly, 3D ECHO recordings were adequate for analysis in all 20 patients.

**Location of DLC**

The present study population included 11 patients with ischemic cardiomyopathy caused by previous myocardial infarction and 9 patients with idiopathic dilated cardiomyopathy. In spite of comparable LBBB configuration, the locations of DLCs differed between the 2 groups of patients. In patients with idiopathic dilated cardiomyopathy, myocardium with DLC tended to be located in the lateral and posterior walls of the LV (Figure 1A, bottom). In contrast, DLC was more frequent in the septum and in the inferior wall in patients with ischemic cardiomyopathy (Figure 2A, bottom). However, 1 patient with idiopathic dilated cardiomyopathy showed DLC in the septum and the adjacent part of the inferior wall, and 1 patient with ischemic cardiomyopathy presented with DLC in the lateral and posterior walls (Figure 4A and 4B).

**Baseline Versus Simultaneous CRT**

Simultaneous CRT reduced the extent of segments at the LV base, displaying DLCs from $48.6\pm16\%$ to $23.2\pm13\%$ ($P<0.01$). In parallel, the GSCA index increased by $32.6\pm6\%$ ($P<0.01$). This was accompanied by an increase in LVEF% from $22.4\pm6\%$ to $29.7\pm5\%$ ($P<0.01$) (Figure 5), and LVEDV and LVESV were reduced by $9\pm5\%$ and $18\pm7\%$, respectively ($P<0.01$ for both) (Figure 5).

The diastolic filling time as measured by pulsed Doppler evaluation increased from $380\pm80$ ms at baseline to $430\pm88$ ms during simultaneous CRT with optimized AV delay ($P<0.01$).

**Simultaneous Versus Optimized Sequential CRT**

In all patients, the ECHO parameters improved further during sequential CRT. Preactivation of the LV lead was superior in 9 patients (exemplified in Figure 1B), whereas preactivation in the RV was superior in the remaining 11 patients (exemplified in Figure 2B). Compared with simultaneous CRT, optimum sequential CRT reduced the extent of segments with DLC at the LV base from $23.2\pm13\%$ to $11.1\pm7.2\%$ ($P<0.05$). GSCA was increased by $18\pm6\%$ ($P<0.01$), accompanied by an increase in LVEF% from $29.7\pm5\%$ to $33.6\pm6\%$ ($P<0.01$) (Figure 5). The LVEDV remained unchanged at optimum sequential CRT, whereas LVESV was further reduced ($9\pm4\%$) ($P<0.05$), as seen in Figure 5.
Without any further AV-delay optimization, the diastolic filling time increased from 430±88 ms during simultaneous CRT to 460±80 ms \((P<0.05)\) during optimum sequential CRT.

### Predictors of Optimum Sequential CRT

In the 9 patients with DLC of the posterolateral wall, optimum sequential CRT was obtained through LV lead preactivation. In contrast, RV lead preactivation resulted in the highest GSCA in the 11 patients with DLC in the septum and adjacent inferior wall.

Average GSCAs from all 11 different interventricular delays are presented in Figure 6, dividing patients into those showing optimum response from RV preactivation versus those showing optimum response from LV preactivation. Optimum RV and LV preactivation intervals were narrow, ranging between 12 and 20 ms. An increase in interventricular delay to \(\geq40\) ms caused a significant reduction in GSCA \((P<0.01)\), even though the lead to preactivate was chosen correctly. This timing of the interventricular delay also resulted in a poorer GSCA than obtained during simultaneous pacing \((P<0.01)\). Any preactivation of the lead opposite the
one showing optimum resynchronization caused a significant reduction in GSCA compared with simultaneous CRT ($P<0.01$).

**Three-Month Follow-Up**

All of the 20 patients were alive after 3 months. The NYHA class improved from $3.45±0.5$ at baseline to $1.9±0.45$ after 3 months. Similarly, the 6-minute hall walk improved from $222±100$ m at baseline to $401±110$ m after 3 months ($P<0.01$). During 3 months of follow-up, LVEDV and LVESV were significantly reduced (from $218±58$ to $194±59$ mL and from $145±47$ mL to $119±56$ mL, respectively; $P<0.01$ for both). LVEF% increased from $33.6±6\%$ to $38.6±7\%$ ($P<0.01$), as did GSCA (from $4.7±0.5$ to $5.5±0.6$ mm, $P<0.01$).

**Discussion**

The present study confirms our previous observations of an immediate beneficial effect of simultaneous CRT on LV volumes and systolic performance.$^{3,4,8}$ It is also in accordance with our earlier findings that this improvement appears in parallel with a reduction in the extent of myocardium displaying DLC with a negative strain rate, ie, segments showing contraction in diastole.$^{3,4}$

Despite similar QRS morphology, patients with HF and LBBB may present with a different location of mechanical asynchrony, which primarily seems to be related to the underlying etiology (Figure 4A and 4B). In the present study, individual tailoring of the interventricular delay with preactivation of regions showing mechanical asynchrony produced a further significant reduction in the extent of DLC, ie, improved recruitment of the contractile reserve. This was accompanied by a significant improvement in LVEF%. Thus, compared with simultaneous CRT, sequential CRT offers a potential to further improve LV systolic performance, and this additional benefit can easily be visualized and quantified by means of TT. The improvement in GSCA, as demonstrated by TT, is closely related to the improvement in LVEF as previously reported.$^{4}$

Surprisingly, the benefit of sequential CRT was present within a relatively short range of interventricular delays from RV preactivation by 20 ms to LV preactivation by 20 ms. Any further increase in interventricular delay or preactivation of regions not exhibiting DLCs resulted in increased mechanical asynchrony and compromised systolic performance, even when sequential CRT was compared with simultaneous CRT (Figure 6). These observations emphasize the importance of a preimplantation evaluation of the mechanical asynchrony in terms of the location of myocardium with DLCs. For that purpose, TT is an excellent “at a glance” method that is also very useful for customizing the pacemaker programming (Figures 1 and 2).

During short-term pacing, a further improvement in LV systolic performance and dimensions was noted. This is in accordance with our previous findings of reversed LV remodeling during 1 year of CRT$^{4}$ and in accordance with another short-term evaluation study.$^{10}$ In parallel, NYHA class improved significantly, and the 6-minute hall walk increased to a doubled walking distance, an improvement that exceeds recent reports.$^{1,10}$

AV delay adjustment is commonly performed by using pulsed Doppler evaluation of transmitral flow,$^{1,10}$ as described by Ritter et al.$^{5}$ Previous studies have emphasized the importance of a short AV delay during standard dual-chamber pacing in patients with HF to optimize the hemodynamic response.$^{11,12}$ However, in another study, the same benefit could not be documented.$^{13}$ At present, the importance of AV-delay programming during CRT has systematically been evaluated by dP/dt measurements in 1 study only.$^{14}$

Obviously, DLC not only diminishes the global LV systolic performance but also interferes with diastolic filling and causes abnormal LV wall stress in diastole. In the present study, establishment of simultaneous CRT together with AV-delay adjustment significantly prolonged the diastolic filling time. Sequential CRT with individually optimized interventricular delay caused an additional significant increase in diastolic filling time. This benefit appeared in parallel with a further reduction in the extent of segments displaying DLC, without any further adjustment of the AV delay or change in heart rate. Thus, the degree of diastolic filling abnormality seemed related to the degree of LV asynchrony. This indicates that proper correction of LV asynchrony can improve AV mechanics and diastolic LV performance.$^{15}$ Thus, optimized ventricular synchronization should probably be achieved in advance of AV-delay adjustment to prevent inappropriate AV-delay programming, which might reduce LV filling.$^{15}$

In conclusion, in patients with severe HF and LBBB, tailored sequential CRT, compared with simultaneous CRT, causes a further significant improvement in LV systolic and diastolic performance. Tissue Doppler imaging in terms of TT proved useful in predicting and optimizing interventricular delay programming during sequential biventricular pacing.

**References**

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Circulation. 2002;106:2078-2084
doi: 10.1161/01.CIR.0000034512.90874.8E

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