Tissue Doppler Echocardiographic Evidence of Reverse Remodeling and Improved Synchronicity by Simultaneously Delaying Regional Contraction After Biventricular Pacing Therapy in Heart Failure

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Background—Biventricular pacing has been proposed to improve symptoms and exercise capacity in patients with advanced heart failure and wide electrocardiographic wave complexes. This study investigated the effect of biventricular pacing on reverse remodeling and the underlying mechanisms.

Methods and Results—Twenty-five patients with NYHA class III to IV heart failure and electrocardiographic wave complex duration >140 ms receiving biventricular pacing therapy were assessed serially up to 3 months after pacing and when pacing was withheld for 4 weeks. Tissue Doppler echocardiography was performed using a 6-basal, 6-mid segmental model to assess the time to peak sustained systolic contraction (TS). There was significant improvement of ejection fraction, dP/dt, and myocardial performance index; decrease in mitral regurgitation, left ventricular (LV) end-diastolic (205±68 versus 168±67 mL, P<0.01) and end-systolic volume (162±54 versus 122±42 mL, P<0.01); and improved 6-minute hall-walk distance and quality of life score after pacing for 3 months. The mechanisms of benefits were as follows: (1) improved LV synchrony, as evident by homogeneous delay of TS to a timing close to the latest (usually the lateral) segment abolishing the intersegmental difference in TS and decreasing the standard deviation of TS within the left ventricle (37.7±10.9 versus 29.3±8.3 ms, P<0.05); (2) improved interventricular synchrony; and (3) shortened isovolumic contraction time (122±57 versus 82±36 ms, P<0.05) but increased diastolic filling time. These benefits are pacing dependent, because withholding the pacing resulted in varying speeds in the loss of cardiac improvements.

Conclusions—Biventricular pacing reverses LV remodeling and improves cardiac function. Improvement of LV mechanical synchrony seems to be the predominant mechanism. (Circulation. 2002;105:438-445.)

Key Words: pacing ■ heart failure ■ echocardiography ■ pacemakers
function and synchronicity both before and after pacing therapy.12
The aims of the present study were to assess the effect of biventricular pacing on LV reverse remodeling and echocardiographic parameters of cardiac function; to demonstrate the potential mechanisms of benefits objectively by echocardiography and TDI, which included the improvement of intraventricular and interventricular synchrony and possibly other mechanisms; and to confirm if continuous pacing is necessary for the reverse remodeling and other benefits.

Methods

Patients
Twenty-five consecutive patients (mean age, 65±12 years; 18 males) with New York Heart Association (NYHA) class III (n=11) or IV (n=14) heart failure, LV ejection fraction <40%, and electrocardiographic evidence of prolonged electrocardiographic wave complex (QRS) of >140 ms received biventricular pacing therapy. The etiologies of heart failure were idiopathic dilated cardiomyopathy in 11, ischemic heart disease in 9, hypertensive cardiomyopathy in 3, alcoholic cardiomyopathy in 1, and chemotherapy-induced cardiomyopathy in 1 patient. Pharmacological management included diuretics in all patients, angiotensin-converting enzyme inhibitors in 21, angiotensin receptor antagonists in 4, β-blockers in 17, spironolactone in 12, and digoxin in 4 patients. Serial investigations were performed before pacemaker implantation as well as 1 week, 1 month, and 3 months after biventricular pacing was instituted. The pacemakers were then changed to sensing mode (ODO), and the investigations were repeated immediately 1 week and 4 weeks afterward. Studies included echocardiography, 6-minute hall-walk test, and Minnesota Living with Heart Failure Questionnaire for quality of life assessment. The study protocol was approved by the Ethics Committee, and written informed consent was obtained from all patients.

Biventricular Pacemaker or Implantable Cardioverter Defibrillator Implantation
Atriosynchronized biventricular pacemaker was implanted as previously described.1,10 The LV pacing lead was inserted by transvenous approach through the coronary sinus into the lateral or posterolateral cardiac vein. Nineteen patients received an Attain system (model 2187 in 14, model 4189 in 2, and model 4191 in 3 patients [side-wire lead]) (Medtronic Inc) and 6 received the Easytrak over-the-lead (model 4512, Guidant Inc). The biventricular devices used were InSync (model 8040, Medtronic Inc) in 19, Contak TR (model 1241, Guidant Inc) in 4, and biventricular cardioverter defibrillator (model 1823, Guidant Inc) in 2 patients. The atrioventricular interval was optimized by Doppler echocardiography.13

Echocardiography
Standard echocardiography, including Doppler studies, was performed (System 5, Vingmed-General Electric). The LV dimensions and ejection fraction were measured by two-dimension guided M-mode method. Change in LV volume was assessed by Simpson’s equation using the apical 4-chamber view. LV diastolic function and cardiac output were assessed by pulse-wave Doppler echocardiography.14 The rate of pressure rise in systole (dP/dt) was estimated from the continuous-wave Doppler mitral regurgitation velocity curve.15 Myocardial performance index (MPI) was also calculated.16 The severity of mitral regurgitation was assessed by the percentage jet area relative to the left atrial size in the apical 4-chamber view. At least 3 consecutive beats of sinus rhythm were measured, and the average value was taken.

TDI was performed using apical views for the long-axis motion of the ventricles as previously described.12,17,18 Two-dimension echocardiography with TDI-color imaging was performed with a 2.5- or 3.5-MHz phase-array transducer. Gain settings, filters, and pulse repetition frequency were adjusted to optimize color saturation, and sector size and depth were optimized for the highest possible frame rate. At least 3 consecutive beats were stored, and the images were digitized and computer analyzed offline (EchoPac 6.3.6, Vingmed-General Electric). Myocardial pulse-Doppler velocity profile signals were reconstructed offline from the TDI color images that provided regional myocardial velocity curves.15 From the apical 4-chamber, 2-chamber, and long-axis views, a 6-basal and 6-mid segmental model was obtained in the LV, namely the septal, lateral, anteroseptal, posterior, anterior, and inferior segments at both basal and mid levels.12 The peak myocardial sustained systolic velocity (Smax) and the time to peak Smax (T1/2) were measured. For the Ts, the beginning of

### Table 1. Serial Changes in Echocardiographic and Clinical Parameters After Biventricular Pacing in 25 Patients With Heart Failure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>1 Week</th>
<th>1 Month</th>
<th>3 Months</th>
<th>Off, Immediate</th>
<th>Off 1 Week</th>
<th>Off 4 Weeks</th>
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<td>3.3±0.5</td>
<td>2.9±0.6†</td>
<td>2.7±0.6†</td>
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<td>2.9±0.5§</td>
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<td>29±19*</td>
<td>24±19‡</td>
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<td>26±20*</td>
<td>26±23*</td>
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<td>6-minute hall walk, meter</td>
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<td>361±94*</td>
<td>377±76*</td>
<td>...</td>
<td>373±89*</td>
<td>362±84*</td>
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<tr>
<td>Fractional shortening, %</td>
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<td>14.1±6.8*</td>
<td>15.5±7.1*</td>
<td>16.4±7.2†</td>
<td>13.2±6.3‡§</td>
<td>12.9±2.9§</td>
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<td>Ejection fraction, %</td>
<td>27.9±10.2</td>
<td>33.5±13.1*</td>
<td>38.3±14.1*</td>
<td>40.0±14.7‡</td>
<td>33.6±13.2‡§</td>
<td>33.1±13.9‡§</td>
<td>29.8±11.6‡§</td>
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<td>Cardiac output, L/min</td>
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<td>3.0±0.5§</td>
<td>2.8±0.4†</td>
<td>2.6±0.6</td>
<td>2.5±0.5‡</td>
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<tr>
<td>LVD systole, cm</td>
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<td>5.9±1.2</td>
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<td>6.5±1.2</td>
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<td>LVV systole, mL</td>
<td>162±54</td>
<td>153±48</td>
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<td>122±42‡</td>
<td>118±46‡</td>
<td>131±59‡</td>
<td>148±64‡</td>
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<td>LVV diastole, mL</td>
<td>205±68</td>
<td>195±63</td>
<td>181±65*</td>
<td>168±67‡</td>
<td>162±72‡</td>
<td>175±65‡</td>
<td>189±70‡</td>
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<td>Mitrail regurgitation, % area</td>
<td>36±19</td>
<td>21±17*</td>
<td>18±16†</td>
<td>18±15‡</td>
<td>28±16‡</td>
<td>28±17‡</td>
<td>30±19‡</td>
</tr>
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</table>

LVD indicates left ventricular diameter; LVV, left ventricular volume; and MPI, myocardial performance index.

*P<0.05 vs baseline.
†P<0.001 vs baseline.
‡P<0.01 vs baseline.
§P<0.01 vs biventricular pacing for 3 months.
||P<0.05 vs biventricular pacing for 3 months.
Figure 1. Changes in 6-minute hall-walk distance, Minnesota Living With Heart Failure quality of life score, LV end-diastolic (●) and end-systolic (★) volumes, ejection fraction, dP/dt, mitral regurgitation, isovolumic contraction time, and LV filling time before and after biventricular pacing as well as when pacing was suspended for 4 weeks. *Significant difference vs baseline. †Significant difference vs biventricular pacing for 3 months. See Tables 1 and 2 for probability value. The time axis scale is not in proportion.
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TABLE 2. Serial Changes in Doppler Echocardiographic Parameters After Biventricular Pacing in 25 Patients With Heart Failure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>1 Week</th>
<th>1 Month</th>
<th>3 Months</th>
<th>Off, Immediate</th>
<th>Off 1 Week</th>
<th>Off 4 Weeks</th>
</tr>
</thead>
<tbody>
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<td>Isovolumic contraction time, ms</td>
<td>122±57</td>
<td>93±42*</td>
<td>91±43*</td>
<td>82±36*</td>
<td>135±21†</td>
<td>141±34†</td>
<td>145±51†</td>
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<td>Ejection time, ms</td>
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<td>Isovolumic relaxation time, ms</td>
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<td>139±60</td>
<td>131±41</td>
<td>134±45</td>
<td>135±47</td>
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<tr>
<td>MV-E, ms</td>
<td>97±34</td>
<td>84±32*</td>
<td>83±32*</td>
<td>78±29†</td>
<td>85±33</td>
<td>87±36</td>
<td>89±40</td>
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<tr>
<td>MV-A, ms</td>
<td>86±32</td>
<td>74±36*</td>
<td>77±35</td>
<td>72±31*</td>
<td>79±30</td>
<td>87±33</td>
<td>82±27</td>
</tr>
<tr>
<td>MV-DT, ms</td>
<td>224±92</td>
<td>220±79</td>
<td>201±85</td>
<td>225±95</td>
<td>208±68</td>
<td>205±54</td>
<td>222±79</td>
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<tr>
<td>Left ventricular filling time, ms</td>
<td>328±96</td>
<td>440±100*</td>
<td>412±110*</td>
<td>429±89*</td>
<td>365±101†</td>
<td>353±92†</td>
<td>366±104†</td>
</tr>
</tbody>
</table>

MV-A indicates transmitral peak atrial filling velocity; MV-E, transmitral peak early diastolic filling velocity; and MV-DT, deceleration time of early diastolic filling.

*P<0.05 vs baseline.
†P<0.05 vs biventricular pacing for 3 months.
‡P<0.01 vs baseline.

Statistics
For the comparison of parametric variables at different time points of assessment or among myocardial segments, paired sample t test with Bonferroni correction was used. To assess systolic synchronicity, standard deviation of TS (T S-SD) of the 12 LV myocardial segments was used. The interobserver and intraobserver variabilities have been compared in 60 consecutive measurements and were 4.7% and 3.2%, respectively. Validation had been performed previously in physical models, animal models and human subjects, and TDI was found to be accurate to assess regional velocity and timing of cardiac events.

Results
All patients were successfully implanted and were receiving biventricular pacing at follow-up. The biventricular pacing threshold was 1.9±1.3 V at implantation and 3.2±2.3 V at 3 months at a pulse duration of 0.5 ms (P<0.05). The optimized atrioventricular interval was 92±22 ms. The QRS duration decreased from 162±30 to 142±20 ms (P=0.001). There was no change in heart failure medications, except in 2 patients who only tolerated β-blocker therapy after implantation with biventricular pacemakers. The 1- and 4-week investigations after cessation of biventricular pacing were not performed in 3 patients. One patient with severe class IV heart failure was inotropically dependent before pacemaker implantation was considered unsafe to stop the therapy. One patient who developed acute congestive heart failure within 1 day after pacing was suspended, and therapy was turned back on. One patient was admitted for pump failure after 3 months and died.

Clinical Assessment
The New York Heart Association functional class decreased by at least one class in all but 2 patients. One of the patients subsequently died of pump failure. None of the patients experienced worsening of symptoms. In 1 patient, pulsus alternans was resolved after biventricular pacing. There was also progressive improvement in quality of life score (P=0.001 at 3 months) after pacing, and the benefit was relatively maintained up to 4 weeks after pacing was stopped. The 6-minute hall walk distance was also increased early after pacing therapy, improved additionally by 3 months (all P<0.05) and was maintained after biventricular pacing was stopped (Table 1 and Figure 1).

Left Ventricular Function
The LV fractional shortening and ejection fraction improved progressively during biventricular pacing and were significantly higher than baseline values at 1 (P<0.05) and 3 months (P<0.001). When pacing was stopped, repeating echocardiogram immediately showed a decrease in these parameters, although they were still significantly higher than prepacing values. These parameters decreased additionally 4 weeks after biventricular pacing was stopped (P<0.01 versus 3 months). The change in cardiac output followed a similar pattern to that of ejection fraction. The LV end-diastolic and end-systolic volumes were significantly smaller than baseline after pacing therapy for 1 month (P<0.05) and reduced additionally by 3 months (P<0.01). There was no change in LV volume immediately when pacing was stopped, but it was enlarged progressively over the subsequent 4 weeks (P<0.05 versus 3 months). The LV end-systolic diameter was also reduced significantly 1 and 3 months after pacing therapy (both P<0.05). The mid-systolic mitral regurgitation reduced immediately after pacing (P<0.05) and was sustained throughout the pacing period. The benefit was maintained partially during the first week after pacing was suspended. The dP/dt increased progressively and was significant after 3 months of pacing (P<0.01). The benefit was lost gradually on cessation of pacing. The isovolumic contraction time was reduced only during the period of biventricular pacing. The MPI improved gradually over the 3-month period and began to return to baseline values as soon as pacing was stopped (Tables 1 and 2 and Figure 1).

For diastolic function (Table 2), 4 patients with initial total fusion of early diastolic and atrial filling changed to an abnormal relaxation pattern (reversed early and atrial filling velocity ratio and deceleration time >240 ms) after optimization of atrioventricular interval. The LV filling time was significantly increased after optimization of atrioventricular...
interval (P<0.05). Cessation of biventricular pacing was associated with immediate loss of such benefit. There was no change in isovolumic relaxation time, ejection time, and deceleration time attributable to biventricular pacing (Table 2 and Figure 1).

**Intraventricular Synchrony**

Using TDI, there was marked segmental variation in TS before pacing, being earliest in the basal anteroseptal segment and latest in the basal lateral segment (148±25 versus 216±52 ms, P<0.01). After biventricular pacing therapy, the difference in TS between the 2 regions was abolished (191±32 versus 213±44 ms, P=NS) (Figures 2 and 3). There was also marked regional variation in the TS among all the LV segments at baseline (ANOVA P<0.05), which was abolished after pacing therapy (ANOVA P=NS) (Figure 2).

As illustrated in Figure 2, all segments had TS delayed after biventricular pacing and were significant in the basal anteroseptal, basal posterior, basal anterior, midanteroseptal, and midlateral segments when compared with the corresponding values at baseline (all P<0.05). In some patients with left bundle branch block and paradoxical septum motion in systole, the TS was delayed before pacing. This was corrected by abolishing the abnormal septal motion together with delaying the wall contraction by pacing therapy (Figure 3). Therefore, biventricular pacing improved the synchronicity of the LV by delaying the TS in segments with initially early peak sustained systolic contraction so that all the regions of the LV had synchronized systolic contraction, albeit slightly and simultaneously delayed.

When the TS-SD was compared in the LV, it was significantly shorter after biventricular pacing for 3 months than baseline (37.7±10.9 versus 29.3±8.3 ms, P<0.05). When pacing was stopped and TDI was repeated immediately, the TS-SD was increased again (41.1±11.8 ms, P<0.01 versus 3 months) and remained abnormal 4 weeks after pacing was stopped (37.8±10.6 ms, P<0.05 versus 3 months). There was no significant change in the regional Sd or the amplitude of regional long-axis displacement before and after biventricular pacing therapy (Table 3).

**Interventricular Synchrony**

At baseline, the TS at the basal right ventricular segment was comparable to the basal septal segment (septal, 185±33 versus right ventricular, 182±37 ms; P=NS) but was significantly earlier than the basal lateral segment (216±52 ms, P<0.05). After biventricular pacing, the difference in TS between the 2 segments was abolished (right ventricular, 206±54 versus lateral, 214±64 ms; P=NS).

**Discussion**

This study documents the effectiveness of synchronous biventricular pacing to induce LV reverse remodeling in patients with advanced heart failure. There was also improvement of systolic function, reduction of mitral regurgitation, increase in diastolic filling time, and improvement of clinical status. Mechanistically, the benefits are attributable to an improvement in intraventricular and interventricular synchrony as well as to a shortening of isovolumic contraction time. The observed benefits were lost in various speeds when pacing was stopped.

**LV Reverse Remodeling After Biventricular Pacing**

Prevention of cardiac remodeling improves prognosis in heart failure.9 The present study confirms the previous observation that biventricular pacing can result in reverse remodeling,10,23 and the changes are associated with improvement in cardiac function. However, it was not known how LV volume might change if pacing was withdrawn. This study found that LV volume increased gradually over 4 weeks after cessation of biventricular pacing. In addition, other echocardiographic benefits were also lost with time. The improvement in diastolic filling time, isovolumic contraction time, and MPI, which were largely dependent on the control of atrioventricular internal, were lost immediately. The benefits on ejection fraction and cardiac output were lost gradually over 4 weeks. These observations provide strong evidence that pacing is the cause of LV remodeling. The present study additionally confirmed the previous observations that systolic function and clinical status were improved, as supported by the gain in ejection fraction, dP/dt, MPI, 6-minute hall-walk distance, and quality of life score.6,7,10 Furthermore, the improvements in quality of life score and walking distance were maintained for at least 4 weeks after pacing was suspended. This may indicate that the onset and offset of clinical benefits have a time lag, and a longer period of follow-up is needed before the loss of clinical benefit is observed.

**Cardiac Resynchronization by Biventricular Pacing**

Prolongation of QRS duration has been described in patients with heart failure and is an indicator of increased mortality.24 This is likely attributable to dyssynchronous LV systolic movement, as demonstrated by a tagged MRI study in patients with dilated cardiomyopathy.11 However, improvement of cardiac synchronicity has not been demonstrated.
objectively after pacing therapy. Using TDI, we demonstrated the presence of LV systolic dyssynchrony in patients before pacing therapy by the significant regional difference in TS and the marked increase in TS-SD among the 12 LV segments. The improvement of intraventricular synchronicity after biventricular pacing was reflected by the loss of regional difference in TS as well as the significant reduction in TS-SD. Interestingly, biventricular pacing improves LV synchronicity by homogeneously delaying those sites with early peak systolic contraction, in particular in the anteroseptal, septal, inferior, and posterior segments, causing all segments to contract late with respect to the QRS onset but simultaneously with respect to each other. Nonetheless, as illustrated in Figure 3, some patients actually had paradoxical septal motion so that sustained systolic contraction is earlier in the lateral wall. In this situation, biventricular pacing helps by abolishing the abnormal septal motion together with delaying the TS in the lateral wall so that synchronicity was successfully achieved. Therefore, biventricular pacing improves LV synchronicity not by early preexcitation of the lateral wall but by ensuring a delayed, yet synchronous, contraction. In the right ventricle, there was also delay in the TS to a magnitude similar to that of the septum during biventricular pacing, resulting in simultaneous peak contraction with the LV; ie, interventricular synchrony is also achieved. Because the segmental peak systolic velocities and the regional long-axis systolic displacement were not changed during biventricular pacing, this finding suggests that biventricular pacing has no direct inotropic effect on the failing heart. This is consistent with the recent finding that biventricular pacing did not increase the energy consumption of the heart; rather, it ensures improved ejection fraction through a more efficiently contracting ventricle.

**Other Mechanisms of Benefit by Biventricular Pacing**

One of the findings in this study was the shortening of isovolumic contraction time during biventricular pacing, without change in ejection time and isovolumic relaxation.
time. More precisely, this is actually the wasted presystolic time after atrial filling is completed but before mitral valve closure. With atrioventricular interval optimized by Doppler echocardiography, there was forced closure of the mitral valve immediately after atrial filling was completed, hence the presystolic time was abolished.13 As a result, diastolic filling time was increased and the fusion of early and late diastolic filling was reduced. The mid-systolic mitral regurgitation was also improved, probably as a result of improved synchronicity that reduced the distortion of mitral apparatus during contraction.

The proposed mechanisms of improvement in intraventricular synchrony, atrioventricular synchrony, and interventricular synchrony are summarized in Figure 4. As this study was conducted in a relatively short duration, the long-term benefits need to be prospectively assessed by additional studies. In addition, whether reverse remodeling induced by biventricular pacing therapy will improve the prognosis of heart failure, as is seen in pharmacological therapy, needs to be addressed by large-scale, multicenter studies.

**Acknowledgment**

The work was supported by a research grant from Medtronic, Inc.

**References**


**TABLE 3.** Comparison of Peak Regional Sustained Systolic Velocities (SM) and Maximal Regional Long-Axis Systolic Displacement (Disp) of the Heart Before and 3 Months After Biventricular Pacing

<p>| TABLE 3. Comparison of Peak Regional Sustained Systolic Velocities (SM) and Maximal Regional Long-Axis Systolic Displacement (Disp) of the Heart Before and 3 Months After Biventricular Pacing |</p>
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<th>BL</th>
<th>BP</th>
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<td>Disp, 3 months, mm</td>
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<td>7.3±3.5</td>
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<td>Tp, baseline, ms</td>
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<td>Tp, 3 months, ms</td>
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<td>201±44</td>
<td>213±44</td>
<td>203±51</td>
<td>210±57</td>
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</table>

*P<0.05 when comparing baseline with 3-month pacing for the same segment.

†P<0.05 when comparing baseline with 3-month pacing for the same segment.

‡P<0.05 when compared with the basal anteroseptal segment at baseline.

ANOVA P<0.05 when compared among all the segments at baseline.

ANOVA P=NS when compared among all the segments at 3-month pacing.

**Figure 4.** Proposed mechanisms of benefit of biventricular pacing. The major mechanism is by delaying the Tp in the left ventricular (LV) segments so that intraventricular synchrony is improved. As a result of improved synchrony, systole becomes more effective, and ejection fraction (EF), cardiac output (CO), and other parameters of cardiac function are improved. Left ventricular end-systolic volume (LVESV) is reduced. By synchronizing the contraction, mechanical mitral regurgitation (MR) attributable to distortion of mitral apparatus in the presence of dysynchrony and left atrial (LA) pressure is reduced. As a result, LV end-diastolic pressure and volume (LVEDV) are decreased. A second mechanism is the shortening of isovolumic contraction time (IVCT) after optimization of atrioventricular delay. The effective diastolic filling time is increased, which, in turn, increases the stroke volume. A less important mechanism is the improvement of interventricular synchrony between the left and right (RV) ventricles. This benefit may mediate through ventricular interdependence. This results in the gain in RV cardiac output and, hence, the LV filling is augmented. The end effect of reverse remodeling will additionally improve cardiac synchrony and decrease secondary mitral regurgitation, forming a positive feedback loop.


Tissue Doppler Echocardiographic Evidence of Reverse Remodeling and Improved Synchronicity by Simultaneously Delaying Regional Contraction After Biventricular Pacing Therapy in Heart Failure

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