Reduction of Mitral Regurgitation by Biventricular Pacing with Intraventricular Timing Optimization in Patients without a Standard Indication: A Potential New Indication for Cardiac Resynchronization Therapy

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ABSTRACT. Biventricular (BiV) pacing is a well-established heart-failure therapy for patients with impaired left ventricular (LV) systolic function and ventricular dyssynchrony, as indicated by a prolonged QRS duration. This study tested the hypothesis that BiV pacing could reduce the degree of mitral regurgitation (MR) in patients with functional MR and a normal QRS duration, regardless of LV systolic function. Fourteen patients (8 females) were enrolled who had moderate-to-severe functional MR, an LV ejection fraction of 35±13% (range, 25–60%), and a normal QRS duration (<120 ms). These patients had class I or II indication for implantation of an implantable cardioverter-defibrillator (10 patients) or a pacemaker (4 patients). After successful lead placement, an external pacemaker was programmed in a random sequence to pacing off (baseline), right ventricular (RV) only, LV only, simultaneous BiV pacing, and sequential BiV pacing. The atrioventricular delay was programmed to maximize the transmitral velocity–time integral. The interventricular delay was varied from -12, 20, 40, and 60 ms during sequential BiV pacing. The atrioventricular delay was programmed to maximize the transmitral velocity–time integral. The interventricular delay was varied from -12, 20, 40, and 60 ms during sequential BiV pacing. All pacing sequences were delivered for 1 min, and the severity of MR was determined by transthoracic echocardiography. Compared with baseline, BiV pacing with optimal VV delay reduced the MR/left atrial area ratio from 55±16 to 32±15% (p=0.001) and the effective regurgitant orifice area from 85±45 to 54±28 mm² (p=0.001). Simultaneous BiV, RV only, or LV only pacing did not significantly alter these parameters. BiV pacing with optimal VV timing can acutely reduce the severity of functional MR in patients with a normal QRS duration and no standard indication for cardiac resynchronization therapy.

KEYWORDS. biventricular pacing, cardiac resynchronization therapy, interventricular delay, mitral regurgitation, QRS duration.

Michelle M. Fedewa discloses that she is an employee of Medtronic, Inc. This study was supported by a research grant (#784) from Medtronic, Inc., Minneapolis, MN.
Introduction

Cardiac resynchronization therapy (CRT), or biventricular (Biv) pacing, has emerged as a proven and well-accepted treatment for heart failure (HF) patients with ventricular dyssynchrony, as indicated by a prolonged QRS duration and impaired systolic function. Multiple studies have shown that Biv pacing improves left ventricular (LV) systolic and diastolic function, decreases LV diameter, improves functional status and quality of life, and decreases morbidity and mortality. In addition, recent studies have demonstrated that CRT in some patients causes a substantial acute and chronic reduction of the severity of mitral regurgitation (MR). Possible mechanisms by which Biv pacing can reduce MR include improved atrioventricular timing and LV reverse remodeling.

MR is a common and significant clinical problem that is associated with an increased incidence of HF, atrial arrhythmias, and sudden death. It has also been shown that moderate-to-severe MR decreases survival independent of HF etiology. Although surgical intervention has been shown to significantly improve outcomes in patients with MR, only a small fraction of patients actually receive this type of intervention, presumably due to a significant operative risk of the surgical procedure. Furthermore, there are few alternatives for those who are not good surgical candidates due to other comorbidities. The development of new, less invasive therapies could serve as an attractive alternative to surgical intervention. The effect of Biv pacing in patients with functional MR and a normal QRS duration has not been explored. Dyssynchrony indices, as assessed by tissue Doppler imaging, have not proven useful in the selection of HF patients with a normal QRS duration that might respond to CRT. However, it is possible that a subgroup of patients with functional MR might benefit from CRT. We hypothesized that Biv pacing could significantly reduce the severity of MR in HF patients with a normal QRS duration, regardless of left ventricular systolic function.

Methods

Patients

This study included patients with moderate-to-severe or severe functional MR documented by standard echocardiographic measures based on recommendations of the American Society of Echocardiography and normal QRS duration (<120 ms) undergoing implantation of a clinically indicated pacemaker or implantable cardioverter-defibrillator (ICD). Patients included were those considered not candidates for surgery or surgery was declined. Patients were excluded if the cause of their MR was primary (structural damage of the leaflets of the mitral valve) or if they presented with any of the following conditions: significant aortic stenosis, previous valve replacement or repair, uncontrolled hypertension, an indication for CRT, or currently receiving intravenous inotropes or vasodilators. LV systolic function was not a factor in the inclusion criteria of this protocol. Patients with atrial fibrillation were included if their underlying ventricular rate was 50–90 bpm. The study protocol was approved by the institutional ethics committee, and all patients gave written informed consent.

Study design

This was a non-randomized, acute, prospective, observational study. Patients meeting eligibility requirements underwent implantation of right atrial (RA) pacing and right ventricular (RV) pacing or defibrillator leads depending upon the indicated device. Using standard techniques, screw-in steroid eluting leads (Medtronic Inc., Minneapolis, MN) were implanted in the right atrium (for patients in sinus rhythm) and in the RV mid-septum. A unipolar (Medtronic Model 4193) or a bipolar (Medtronic Model 4194) LV lead was placed in the lateral or posterolateral vein of the coronary sinus venous system. All leads were temporarily connected to a Medtronic InSync III Model 8042 BiV pacemaker. When patients were in sinus rhythm, the device was programmed DDD with a lower rate of 50 bpm to promote intrinsic atrial activity. The atrioventricular delay was programmed at the setting which resulted in the maximal transmitral velocity–time integral (VTI) as assessed by echocardiography. When patients were in atrial fibrillation, the device was programmed to VVI with a lower rate of 5–10 bpm above the intrinsic rate.

The primary endpoint was the severity of MR. Echocardiography measurements were performed while the device was programmed to pacing off (baseline), RV only, LV only, simultaneous BiV, and sequential BiV pacing. To avoid bias resulting from a carryover effect as the pacing configuration was changed, the order of pacing mode was randomized using an envelope-based method. During simultaneous BiV pacing, the interventricular (VV) delay was set to a nominal value of 0 ms. During sequential BiV pacing, VV delays of ±12, 20, 40, and 60 ms were programmed in a sequential order. Pacing with each programmed setting was maintained for a minimum period of 1 min before changing the pacemaker programming. Since the pacemaker programming was changed without an intervening period of no pacing, the same baseline period (no pacing) was used to compare all of the different pacing modes and VV intervals. A Medtronic programmer (model 9790) was used for all acute programming.

During the implant procedure, all patients underwent echocardiography in the supine position to quantify MR. An Acuson Sequoia system was used for all echocardiographic measurements. A single sonographer performed all echocardiography measurements and was blinded to the programming of the device during assessment. The degree of MR was assessed using the ratio of the mitral regurgitant jet area to left atrial area (MR/LA) and the effective regurgitant orifice (ERO) area (i.e. regurgitant...
volume/VTI of the regurgitant jet). The apical four-chamber view was used to determine the MR/LA area ratio. For sequential BiV pacing, the VV delay that produced the greatest MR reduction (using the MR/LA area ratio and ERO area separately) was compared with the baseline value. The left ventricular outflow tract (LVOT) VTI was measured using pulsed Doppler echocardiography.

**Statistical analysis**

All values were expressed as the mean ± standard deviation or the number of patients (percentage). Comparisons of echocardiographic parameters between baseline and pacing were performed using a Student’s paired t-test. A p-value < 0.05 was considered significant.

**Results**

Between March 2006 and June 2008, 14 consecutive patients (6 males, 8 females) were enrolled in the study. The average patient age was 70 ± 9 years. Two patients had moderate-to-severe functional MR; the remaining 12 patients had severe functional MR. The QRS duration was 103 ± 14 ms, and the LVEF was 35 ± 13%. Five patients suffered from ischemic heart disease, five patients had non-ischemic cardiomyopathy and four patients had normal left ventricular size and systolic function. Additional baseline clinical characteristics are summarized in Tables 1 and 2.

The leads were successfully inserted in the intended sites in all patients. The LV lead was placed in a lateral vein in 11 patients, posterolateral vein in one patient, and a high lateral vein in two patients. Two patients presented with chronic atrial fibrillation and did not receive RA leads. There were no complications associated with the procedure.

The MR/LA area ratio was adequately obtained in 13/14 patients using the apical four-chamber view. Poor echocardiographic windows limited the evaluation in the other patient. For BiV pacing with the best VV delay, MR was reduced in 12 out of 13 patients. The MR/LA area ratio was 55 ± 16% at baseline and decreased to 32 ± 15% with BiV pacing as shown in Figure 1 (p = 0.001). This represented a significant mean absolute MR reduction of 21%. There was only one patient who did not show a measurable reduction in the degree of MR with BiV pacing, and it appeared to cause a slight worsening in this patient. However, the ERO area fell from 121 to 21%. There was only one patient who did not show a measurable reduction in the degree of MR with BiV pacing as shown in Figure 2. The MR/LA area ratios with simultaneous BiV, RV only, and LV only pacing were 43 ± 19, 48 ± 21, and 51 ± 19%, respectively; and these changes were not significantly different from baseline (55 ± 16%).

The ERO area was adequately measured in 13/14 patients. For BiV pacing with the best VV delay setting, there was a 31% reduction of ERO area from 85 ± 45 mm² at baseline to 54 ± 28 mm² with pacing as shown in Figure 3 (p = 0.001). In one patient, the ERO area increased with sequential BiV pacing. However, this patient had a reduction in the MR/LA area ratio from 74% at baseline to 40% with BiV pacing. The ERO areas with simultaneous BiV, RV only and LV only pacing were 72 ± 29, 69 ± 30, and 81 ± 50 mm², respectively; and these changes were not significantly different from baseline (85 ± 45 mm²).

The LVOT VTI was successfully measured in all 14 patients. There were no significant changes in LVOT VTI from baseline observed with BiV pacing as shown in Figure 4. Furthermore, the LVOT VTI with simultaneous BiV, RV only, and LV only pacing were also not significantly different from baseline.

**Discussion**

This pilot, single-center, prospective study demonstrated that BiV pacing with VV delay timing manipulation (optimization) can acutely reduce the degree of functional MR in patients who do not meet current criteria for implantation of a CRT device. We noticed a significant reduction of the MR/LA area ratio and of the ERO area in the majority of the patients. To our knowledge, this is the first study to assess the effect of BiV pacing with VV timing manipulation on functional MR in patients with a narrow QRS, regardless of the status of LV systolic function. Since functional MR is a common condition associated with significant morbidity and mortality,15,16,21–23 it is possible
that BiV pacing with optimal VV delay could be an important new therapy for the treatment of functional MR.

Previous studies in patients with a standard indication for implantation of a CRT device demonstrated that there was an acute reduction in the degree of MR in some patients.7–9,11 Although the mechanisms of this effect are not well understood, one mechanism that has been proposed is resynchronization or better coordination of the contractility of the papillary muscle and/or the adjacent myocardial tissues leading to improvement of the coaptation of the mitral valve leaflets.9,24,25 In addition, an increase of the maximal rate of rise of LV systolic pressure (LV dP/dtmax) as a result of BiV pacing can translate into increased transmitral closing forces and a reduction of ERO area.11,24,26 These mechanisms may or may not apply to our patients. The patients enrolled in previous CRT trials were New York Heart Association class III with a LVEF ≤35%, a prolonged QRS duration (>120 ms), and were thought to have ventricular dyssynchrony. However, our patients were clearly different since they had a narrow QRS complex (<120 ms), and not all of them had decreased LV systolic function.

The physiology of mitral valve function is complex. The effectiveness of mitral valve closure depends on the interaction of several anatomical and dynamic factors. Anatomically, the status of the mitral valve annulus, leaflets, chordae tendinae, papillary muscles, left atrium, and LV size and function play important roles in mitral valve function. In the case of a dilated heart, as was present in 10 of our patients, functional MR could be the result of dilation of the mitral annulus that leads to an increased distance between the papillary muscles and between the papillary muscles and mitral valve annulus.27,28 In addition, undetected dyssynchrony of the papillary muscle and/or adjacent myocardium could lead to functional MR.29–31 In the case of the patients with normal LV size and function, the potential mechanisms for the development of functional MR are less well understood. In these patients, geometrical distortion of the LV cavity may not play an important mechanistic role. Perhaps, dyssynchrony of the papillary muscles and/or adjacent myocardium, or abnormalities of coaptation of the leaflets themselves could have been responsible for inefficient valve closure. In this study, all patients had a normal QRS duration, which does not exclude the presence of cardiac dyssynchrony. It is possible that our patients had inter- or intraventricular dyssynchrony despite a normal QRS duration.

Previous studies showed that CRT with simultaneous BiV may reduce MR in some patients with cardiac dyssynchrony and a prolonged QRS duration. However, programming VV timing to a nominal setting of “0” was not the optimal VV timing (greatest MR reduction) in 79% of out patients. This observation stresses the importance of manipulating VV timing to obtain maximal

### Table 2: Intrinsic and paced QRS duration, VV off-set and left ventricular volumes

<table>
<thead>
<tr>
<th>Patient</th>
<th>Intrinsic QRS (ms)</th>
<th>Paced QRS Duration (ms)</th>
<th>VV off-set (ms)</th>
<th>LVESV (ml)</th>
<th>LVEDV (ml)</th>
<th>EF%</th>
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<tbody>
<tr>
<td>1</td>
<td>86</td>
<td>162</td>
<td>RV-LV 0</td>
<td>91</td>
<td>129</td>
<td>35%</td>
</tr>
<tr>
<td>2</td>
<td>88</td>
<td>118</td>
<td>LV-RV 60</td>
<td>65</td>
<td>107</td>
<td>25%</td>
</tr>
<tr>
<td>3</td>
<td>118</td>
<td>120</td>
<td>RV-LV 20</td>
<td>NA</td>
<td>NA</td>
<td>20%</td>
</tr>
<tr>
<td>4</td>
<td>90</td>
<td>130</td>
<td>LV-RV 12</td>
<td>NA</td>
<td>NA</td>
<td>30%</td>
</tr>
<tr>
<td>5</td>
<td>88</td>
<td>148</td>
<td>LV-RV 60</td>
<td>108</td>
<td>152</td>
<td>25%</td>
</tr>
<tr>
<td>6</td>
<td>117</td>
<td>115</td>
<td>RV-LV 0</td>
<td>47</td>
<td>64</td>
<td>50%</td>
</tr>
<tr>
<td>7</td>
<td>119</td>
<td>122</td>
<td>RV-LV 60</td>
<td>214</td>
<td>116</td>
<td>35%</td>
</tr>
<tr>
<td>8</td>
<td>96</td>
<td>118</td>
<td>LV-RV 20</td>
<td>95</td>
<td>131</td>
<td>30%</td>
</tr>
<tr>
<td>9</td>
<td>120</td>
<td>120</td>
<td>RV-LV 20</td>
<td>61</td>
<td>96</td>
<td>60%</td>
</tr>
<tr>
<td>10</td>
<td>106</td>
<td>108</td>
<td>LV-RV 12</td>
<td>138</td>
<td>179</td>
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</tr>
<tr>
<td>11</td>
<td>102</td>
<td>90</td>
<td>LV-RV 20</td>
<td>92</td>
<td>109</td>
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</tr>
<tr>
<td>12</td>
<td>86</td>
<td>122</td>
<td>LV-RV 40</td>
<td>83</td>
<td>138</td>
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</tr>
<tr>
<td>13</td>
<td>108</td>
<td>170</td>
<td>RV-LV 12</td>
<td>36</td>
<td>86</td>
<td>60%</td>
</tr>
<tr>
<td>14</td>
<td>118</td>
<td>182</td>
<td>RV-LV 0</td>
<td>41</td>
<td>90</td>
<td>50%</td>
</tr>
</tbody>
</table>

EF: ejection fraction; LV: left ventricular lead; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; RV: right ventricular lead.

![Figure 1: Ratio of the mitral regurgitant jet area to left atrial area (MR/LA) with no pacing (baseline) and biventricular pacing (optimal VV delay) in 12 out of 13 patients.](image-url)
Recent reports\textsuperscript{32–34} have suggested that LV pacing alone may have a beneficial impact on MR. In our study, while LV pacing alone reduced MR in some patients, the effect of LV only pacing on the entire group was not significant. RV pacing (mid-septum) alone had an overall neutral effect. The findings of this study suggest that the greatest reduction of functional MR is obtained by BiV pacing with VV timing manipulation, regardless of underlying LV geometry or function. Further studies to explore the mechanistic effects of BiV pacing on the complex physiology of a dysfunctional mitral valve in this group would be of interest.

The best VV delay when optimized using the MR/LA area to reduce MR did not correlate with the best VV delay when optimized using the EROA area to reduce MR. This discordance may be explained by the fact that these two methods of MR assessment are totally different in principle. However, in general, there was a significant acute reduction of the severity of MR with both of these methods. Although BiV pacing with optimal VV timing reduced the MR/LA area ratio and the EROA, it had a neutral effect on the LVOT VTI. A significant reduction in MR should have increased the VTI in the LVOT; however, the difficulty in obtaining an adequate angle to measure VTI in the supine position may have introduced significant error in the VTI measurement.

**Limitations**

This study has several potential limitations. It was difficult to perform the echocardiographic measurements in the catheterization laboratory with the patient in the supine position while maintaining sterile conditions. In addition, the methods used to assess MR could have been affected by the presence of eccentric jets or poor transthoracic windows. Furthermore, because of anatomical variations of the cardiac venous system, we were not able to pace at the exactly the same location on the LV lateral wall in each patient. In addition, we cannot exclude the presence of intraventricular dyssynchrony, since we did not assess this condition in our patients.

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**Figure 2:** Assessment of mitral regurgitation via two-chamber and four-chamber views. Sinus rhythm (no pacing) and biventricular pacing (optimal VV delay) are shown for the same patient.
Finally, the severity of MR was evaluated acutely in the present study without any long-term follow-up. Additional studies are needed to determine the long-term effect of BiV pacing with VV timing optimization on the severity of MR.

Conclusions

The findings of this study suggest that the greatest pacing-induced reduction of functional MR can be obtained with BiV pacing and VV timing manipulation regardless of the underlying LV geometry. In addition, BiV pacing and VV timing manipulation can acutely reduce the severity of functional MR in patients with a normal QRS duration and no standard indication for CRT. Moreover, MR was reduced in patients with both normal and impaired systolic function.

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