Subacute and Chronic Effects of DDD Pacing on Left Ventricular Diastolic Function in Patients With Non-Obstructive Hypertrophic Cardiomyopathy

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The present study examined the ability of dual-chamber (DDD) pacing to improve symptoms and exercise tolerance in patients with non-obstructive hypertrophic cardiomyopathy (HNCM). Seven patients with HNCM who had failed to benefit from pharmacotherapy participated in the study. The New York Heart Association (NYHA) functional class status and exercise tolerance, which was determined by the treadmill exercise test, were recorded and an echocardiographic observation was performed before, and 1 week, 3 months and 1 year after the implantation of a permanent DDD pacemaker. The atrioventricular delay (AVd) was determined by measuring the point of peak rapid filling velocity and maximum cardiac output (CO). Two patients were not implanted with a permanent pacemaker because their CO and blood pressure decreased or because palpitation occurred during temporary pacing. The ratio between early and late peaks of flow velocity (1.56, 1.21, 0.95, and 0.86 before implantation and 1 week, 3 months and 1 year after implantation, respectively); deceleration time (ms: 263.2, 217.6, 204.6, 187.0); peak filling rate (ml/s: 146.2, 204.0, 233.2, 243.6); NYHA functional class status (2.0, 1.8, 1.6, 1.4); and exercise tolerance (s: 203, 264, 403, 480) were significantly improved after implantation. However, left ventricular dimension, percent fractional shortening, ejection fraction, acceleration time and the isovolumic relaxation time were not changed significantly. In conclusion, DDD pacing improved symptoms and the NYHA functional class status, which is associated with improvement of left ventricular diastolic function. It is proposed that DDD pacing would be useful in patients not only with obstructive but also non-obstructive hypertrophic cardiomyopathy refractory to medical treatment, depending on the careful selection of subjects. (Jpn Circ J 2001; 65: 283–288)

Key Words: DDD pacing; Doppler echocardiography; Long-term observation; Non-obstructive hypertrophic cardiomyopathy

In obstructive hypertrophic cardiomyopathy (HOCM), negative inotropic agents such as ß-blockers, calcium antagonists1, disopyramide2 and cibenzoline3 have been used to ameliorate the symptoms and outflow obstruction of the left ventricle (LV). Surgical therapies, such as myectomy4 and mitral valve replacement5, have also been carried out in patients with HOCM that is refractory to medical treatment. Recently, infusion of ethanol into the septal branches of the left anterior descending coronary artery to specifically induce necrosis of the hypertrophied septum has been reported as an ameliorative measure for HOCM6.

Conversely, it has been reported that dual-chamber (DDD) pacing results in clinical and hemodynamic improvement in patients with HOCM. The mechanism by which the subaortic pressure gradient is decreased is uncertain but may be related to decreased septal motion,9 late activation at the base of the septum with right ventricular apical pacing,10 or decreased LV contractility.9

There have been several reports pertaining to the symptoms and hemodynamic effects of DDD pacemakers in patients with non-obstructive hypertrophic cardiomyopathy (HNCM).11 Cannon and colleagues reported that DDD pacing in patients with HNCM was associated with an improvement in symptoms and exercise tolerance.12 However, there is a lack of objective evidence concerning symptomatic or hemodynamic improvement. It has also been reported that improvement of LV diastolic function may be one of the important objectives in treating HNCM patients. Therefore, we investigated the subacute and long-term changes in the diastolic function of the LV in patients with HNCM after they received a DDD pacemaker. In addition, we examined the relationships among the improvement of subjective symptoms and exercise tolerance and the alterations in the diastolic function of the LV in these patients.

Methods

Subjects

The subjects consisted of 7 patients with HNCM who had failed to benefit from pharmacotherapy and showed New York Heart Association (NYHA) functional class status of III or IV. No patient enrolled in the study had any family history of hypertrophic cardiomyopathy (HCM). The diagnosis of HCM was based on an echocardiographic demonstration of a non-dilated, hypertrophied LV in the absence of any other cardiac or systemic cause of LV hypertrophy.13 These patients showed no resting LV outflow gradient and no gradient ≥20 mmHg just after terminating the treadmill.
exercise test, as estimated by Doppler echocardiography.

In order to rule out ischemic heart disease, we performed selective coronary arteriography (CAG). Each of the 7 patients selected for inclusion in the study were shown angiographically to have normal coronary function and/or showed no significant defect with adenosine triphosphate stressed thallium-201 cardiac scintigraphy. The subjects consisted of 6 men and 1 woman with a mean age of 64.4±5.2 years (mean±SD). The clinical characteristics of these 7 patients are described in Table 1.

**Atrioventricular Delay Determination**

The right side of the heart was catheterized via the right femoral route under local anesthesia. The heart was stimulated with 2 intracardiac electrodes, one each at the right atrium and at the apex of the right ventricle. For determining the optimal atrioventricular delay (AVd), the atrium and ventricle were stimulated with an external dual-chamber pulse generator (Medtronic 5345, Medtronic Japan, Kawasaki, Japan). The AVd was increased from 60 ms to 140 ms at intervals of 20 ms during 3 min of constantly observing LV inflow and cardiac output (CO) using Doppler15,16 and M-mode17 echocardiography, respectively. Echocardiography was performed with a Toshiba SSH-160A (Toshiba, Tokyo, Japan) system with a 3.5 MHz transducer for 2-dimensional and M-mode examinations and a 2.5 MHz transducer for continuous Doppler measurements. The interventricular septum and posterior wall thickness, as well as the end-diastolic and end-systolic diameters of the LV, were measured according to the criteria recommended by the American Society of Echocardiography18 Continuous-wave Doppler recordings of the LV inflow were made throughout the temporary dual pacing with a standard apical 4-chamber window. These measurements were performed at the end of every AVd. Finally, a DDD permanent pacemaker (Medtronic 7086, Medtronic Japan, Kawasaki, Japan) was implanted with informed consent after the optimal AVd was determined to be 100 ms in 4 patients and 80 ms in 1 patient. This was the point of peak rapid filling velocity (E; ms) and the point where CO was at its maximum. All pulse generators were programmed to DDD mode with an upper rate limit of 160 beats/min. DDD pacing occurred at a heart rate of <60 beats/min, with P wave-synchronized pacing at a heart rate of >60 beats/min up to the upper rate limit. In 2 patients who were not implanted with the permanent pacemaker, one showed decreases in CO and blood pressure and the other showed palpitation and chest oppression during temporary pacing. The changes of AVd, E and CO before and after temporary pacing in those 5 patients who were able to receive the permanent pacemaker are shown in Table 2.

**Follow-up Examination**

The NYHA functional class status and Doppler and M-mode echocardiography were recorded at baseline and after follow-up periods of 1 week (1W), 3 months (3M) and 1 year (1Y) after implanting the DDD pacemaker. We measured the acceleration time (AcT; ms), percent fraction shortening (%FS; %) and ejection fraction (EF; %) as indices of the LV contractile function, and we measured A/E (A: atrial contraction at LV end diastole), peak rapid filling velocity (E; ms), deceleration time (DcT; ms), and peak filling rate (PFR; ml/s) as indices of the LV diastolic function. Symptom-limited treadmill exercise tests were performed at the baseline study and at 1W, 3M and 1Y after implantation using the modified Bruce protocol19 with blood pressure (mmHg) and exercise duration (s) also measured. There was no change in the pharmacological treatment during any of these periods.

**Statistics**

Statistical analysis was performed using the one-way analysis of variance (ANOVA) followed by the Dunnet test for multiple comparison with the baseline control in paramet-

### Table 1  Clinical Characteristics

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>NYHA</th>
<th>IVST (mm)</th>
<th>PWT (mm)</th>
<th>PRI (ms)</th>
<th>Symptoms</th>
<th>Current medications**</th>
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<tbody>
<tr>
<td>1</td>
<td>66</td>
<td>M</td>
<td>III</td>
<td>23</td>
<td>16</td>
<td>160</td>
<td>CP, GF</td>
<td>Atenolol (50 mg), diltiazem (90 mg)</td>
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<tr>
<td>2</td>
<td>61</td>
<td>M</td>
<td>III</td>
<td>19</td>
<td>12</td>
<td>210</td>
<td>CP, DP, GF</td>
<td>Atenolol (50 mg), nitrindipine (10 mg)</td>
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<tr>
<td>3</td>
<td>73</td>
<td>M</td>
<td>III</td>
<td>25</td>
<td>14</td>
<td>150</td>
<td>DP, GF</td>
<td>Propranolol (30 mg), diltiazem (90 mg)</td>
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<td>68</td>
<td>M</td>
<td>III</td>
<td>21</td>
<td>13</td>
<td>190</td>
<td>CP, GF, PS</td>
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<td>57</td>
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<td>III</td>
<td>17</td>
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<td>160</td>
<td>DP, GF</td>
<td>Propranolol (30 mg), diltiazem (90 mg)</td>
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<tr>
<td>6</td>
<td>62</td>
<td>F</td>
<td>IV</td>
<td>22</td>
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<td>7</td>
<td>64</td>
<td>M</td>
<td>III</td>
<td>24</td>
<td>14</td>
<td>180</td>
<td>CP, DP, GF</td>
<td>Atenolol (50 mg), diltiazem (90 mg)</td>
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</table>

**Patients who were not implanted with pacemaker; **the dose shown is the daily dose.

### Table 2  Hemodynamic Changes Before and After Temporary Pacing

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>AVd (ms)</th>
<th>HR (beats/min)</th>
<th>E (m/s)</th>
<th>A/E</th>
<th>CO (L/min)</th>
<th>AVd (ms)</th>
<th>HR (beats/min)</th>
<th>E (m/s)</th>
<th>A/E</th>
<th>CO (L/min)</th>
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<td>0.47</td>
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<td>100</td>
<td>60</td>
<td>0.54</td>
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<td>52</td>
<td>0.70</td>
<td>1.52</td>
<td>4.1</td>
<td>100</td>
<td>60</td>
<td>0.78</td>
<td>1.43</td>
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<tr>
<td>3</td>
<td>104</td>
<td>50</td>
<td>0.63</td>
<td>1.47</td>
<td>3.5</td>
<td>80</td>
<td>60</td>
<td>0.66</td>
<td>1.38</td>
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<tr>
<td>4</td>
<td>145</td>
<td>55</td>
<td>0.82</td>
<td>1.29</td>
<td>4.3</td>
<td>100</td>
<td>60</td>
<td>0.84</td>
<td>1.24</td>
<td>4.1</td>
</tr>
<tr>
<td>5</td>
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<td>64</td>
<td>0.58</td>
<td>1.74</td>
<td>3.4</td>
<td>100</td>
<td>70</td>
<td>0.62</td>
<td>1.65</td>
<td>3.3</td>
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</table>

AVd, atrioventricular delay; HR, heart rate; E, peak rapid filling velocity; A/E, ratio between early and late peaks of flow velocity; CO, cardiac output.
ric data. For non-parametric data, Kruskal–Wallis one-way analysis of variance followed by Dunnett’s non-parametric test was performed for multiple comparison with the baseline control. Data are presented as mean±SD.

Results

Symptomatic Changes

The NYHA functional class of each patient improved significantly after the pacemaker was implanted, as shown in Fig.1. The treadmill exercise duration significantly increased progressively from baseline (202.8±71.5 s), to 1W (264.0±48.0), to 3M (403.0±55.5; p<0.01) and to 1Y (479.8±64.2; p<0.01) (Fig 2, left). The systolic blood pressure-heart rate (pressure-rate) product significantly increased progressively from baseline (21.3±2.7×10³ mmHg×beat/min), to 1W (25.6±1.8), to 3M (30.4±4.7; p<0.01) and to 1Y (32.9±4.9; p<0.01) (Fig 2, right).

Changes in Left Ventricular Systolic Function

The mean intraventricular septum thickness and mean LV posterior wall thickness at baseline were 21.6±2.8 mm and 13.0±1.9 mm, respectively. Fig 3 shows the short- and long-term changes in LV systolic functional parameters of %FS, EF and AcT after DDD pacemaker implantation. The %FS, EF and AcT just before DDD pacemaker implantation (baseline) were 50.4±2.6%, 83.5±3.0%, and 110.2±9.6 ms, respectively. During the follow-up period, there were no significant changes in these 3 parameters. The measured LV end-diastolic and end-systolic dimensions are shown in Fig 4. There were no changes in these parameters in the follow-up period.

Changes in Left Ventricular Diastolic Function

Fig 5 shows the short- and long-term changes in the LV diastolic functional parameters of A/E, E, DcT and PFR
The values at baseline were 1.56±0.20, 0.65±0.13 m/s, 263.2±38.3 m/s and 146.2±19.0 ml/s, respectively. The A/E, E, DcT and PFR improved significantly at 1W [1.21±0.20 (p<0.05), 0.79±0.10, 217.6±24.9 (p<0.05), 204.0±31.7 (p<0.05), respectively]; at 3M [0.95±0.17 (p<0.01), 0.88±0.11 (p<0.01), 204.6±17.9 (p<0.01), 233.2±28.6 (p<0.01)], and at 1Y [0.86±0.15 (p<0.01), 0.91±0.09 (p<0.01), 199.4±18.4 (p<0.01), 243.6±28.0 (p<0.01), respectively]. Conversely, no significant change in isovolumic relaxation time (IRT; ms) was found; it was 88.5±8.3 at baseline, 84.9±7.3 at 1W, 85.7±9.0 at 3M, and 90.3±7.9 at 1Y.

Fig 6 shows the changes in LV inflow as measured using Doppler echocardiography in patient 1, a 66-year-old man. There was a significant increase in E and improved A/E at 1 year.

Discussion

The present study was conducted to investigate the short- and long-term effects of DDD pacing in patients with HNCM refractory to medical treatment. Five of 7 patients had symptomatic and hemodynamic improvement associated with normalization of LV diastolic dysfunction. In patients with non-obstructive HCM, DDD pacing may be a useful strategy, depending on the careful selection of subjects.

In 1975, Hassenstein and coworkers first reported that temporary dual-chamber pacing improved the symptoms and the LV outflow tract (LVOT) pressure gradient in patients with HOCM. Moreover, the reduction of the LVOT pressure gradient obtained using DDD pacing has been reported to be the most important means of improving the symptoms of HOCM. McDonald and colleagues reported that the improvement of LV diastolic function might be another important aspect. In fact, they also reported that DDD pacing improved exercise tolerance, LV filling and symptoms in patients with HOCM; however, these were short-term results. Seidelin et al proposed that the improvement of symptoms and exercise tolerance achieved by the use of a DDD pacemaker might be related to normalization of LV diastolic dysfunction. Their report was a case report about only 1 patient, however, and they employed only the treadmill exercise test to evaluate the changes of LV diastolic function. The results of the present study indicate that the symptoms, exercise tolerance and LV diastolic dysfunction were significantly improved. Because of the small number of subjects, there was no significant correlation between the improvement in subjective symptoms and exercise tolerances, and LV diastolic dysfunction. However, 6 months
after starting dual-chamber pacing therapy, LV diastolic function worsened in all 5 patients and shortness of breath appeared in 2 of 5 patients when the program with dual-chamber pacing was stopped temporarily. Therefore, the improvement in subjective symptoms and exercise tolerances may be associated with an improvement in LV diastolic dysfunction.

For evaluating LV diastolic function, some investigators have suggested that the assessment of transmitral flow velocity with pulsed Doppler echocardiography provides a non-invasive and clinically useful technique. By use of this technique, we evaluated the improvement in LV diastolic function afforded by DDD pacemaker implantation in HNCM patients. The results of the present study demonstrate an improvement in symptoms accompanied by significant normalization of LV diastolic function. Certainly, there is a possibility that the normalization of A/E might have been pseudo-normalization as a result of the extreme increase in LV end-diastolic pressure. This does not seem to have been the case, however, given that the IRT exhibited no significant changes and both the symptoms and exercise tolerance improved significantly during the follow-up period.

In 1994, Cannon et al reported that permanent DDD pacing with discontinuation of prior medical therapy was associated with an improvement in symptoms and exercise tolerance in patients with HNCM. In their study, however, there was a lack of objective evidence of hemodynamic or myocardial perfusion improvement during exercise. There are several differences between the results of permanent DDD pacing that they reported and those found in the present study. Three factors may have contributed to these differences. First, in some patients studied by Cannon et al, prior medical therapy was discontinued; whereas in the present study the medical therapy continued unchanged. Second, methodological differences; for example, in their study, atrioventricular delay was programmed ‘to the longest delay that would allow maximal pre-excitation’, whereas in the present study it was ‘the point at which the peak rapid filling velocity and CO showed a maximum’. Finally, of the 12 patients in their study had NYHA class IV, but in the present study there were no patients with NYHA class IV at the time of implanting the permanent DDD pacemaker (the patient with NYHA class IV was not implanted with a permanent pacemaker).

The mechanism is, as yet, unclear. In patients with HNCM, atrial contractile dysfunction contributes closely to LV diastolic function. Dual-chamber pacing with short AVd increases the left atrial pressure and causes this higher driving pressure across the mitral valve in early diastole, supporting LV diastolic relaxation. The results of a previous study have been interpreted to indicate that dual-chamber pacing produces improved diastolic filling of the heart due to higher and faster early peak filling. Therefore, LV diastolic dysfunction and exercise tolerance may be improved by dual-chamber pacing.

**Study Limitations**

The present study has at least 3 important limitations. First, because the subjects had HNCM, the results do not apply directly to HOCM patients; however, Maron et al reported that patients with HNCM showed more severe alterations in the Doppler indices of diastolic function than did patients with obstruction. Therefore, normalization of LV diastolic dysfunction may be closely related to the improvement of subjective symptoms in HCM patients both with and without obstruction.

The second limitation is that we determined the AVd only by measuring LV inflow and CO using Doppler and M-mode echocardiography. In principle, to determine AVd, an accurate measurement of cardiac and pulmonary capillary wedge pressure is needed, but making this measurement in each patient using a thermodilution Swan–Ganz catheter is complicated because 3 different venous routes are needed. By using the Doppler and M-mode echocardiographic technique, we were able to demonstrate changes in diastolic function and CO in patients during different pacing modes and thus determine the optimum AVd.

The third limitation is the small number of subjects, and the fact that 2 patients were not implanted with the permanent pacemaker. The reason for this was because one patient developed palpitation and the other patient (patient 6 in Table 1) experienced decreased CO and blood pressure during temporary pacing, suggesting that severe myocardial damage may have occurred in the latter patient, whose NYHA class was IV. To implant a DDD pacemaker in HNCM patients, subjects must be selected carefully in cases with only refractory to medical treatment. Also, a thorough study of the effects of DDD pacing in HNCM patients requires a large number of well-characterized patients to be studied under various conditions.

**Conclusion**

DDD pacing improved symptoms and exercise tolerance, as well as LV diastolic dysfunction in patients with HNCM. These symptomatic and hemodynamic benefits were detectable early after implanting the DDD pacemaker, and became more pronounced over time. Therefore, after confirming the suitability of implanting a DDD pacemaker using Doppler echocardiography, pacemaker implantation may be a useful treatment not only for patients with HOCM but also with HNCM.

**References**

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