Long-term Results of Dual-Chamber (DDD) Pacing in Obstructive Hypertrophic Cardiomyopathy

Evidence for Progressive Symptomatic and Hemodynamic Improvement and Reduction of Left Ventricular Hypertrophy

Lameh Fananapazir, MD, FRCP; Neal D. Epstein, MD; Rodolfo V. Curiel, MD; Julio A. Panza, MD; Dorothy Tripodi, RN; Dorothea McAreavey, MD, MRCP

Background  We previously reported that 6 to 12 weeks of dual-chamber (DDD) pacing results in clinical and hemodynamic improvement in obstructive hypertrophic cardiomyopathy (HCM). This study examines the long-term results of DDD pacing in obstructive HCM.

Methods and Results  DDD devices were implanted in 84 patients (mean age, 49 ± 16 years) with obstructive HCM and severe drug-refractory symptoms. At a mean follow-up of 2.3 ± 0.8 years (maximum, 3.5 years), the New York Heart Association (NYHA) functional class had improved significantly (1.6 ± 0.6 versus 3.2 ± 0.5, P < .0001). Symptoms were eliminated in 28 patients (33%), improved in 47 patients (56%), but remained unchanged in 7 patients (8%). Two patients died suddenly (97% cumulative 3-year survival rate). In 74 patients with significant left ventricular outflow tract (LVOT) obstruction at rest, the LVOT gradients were significantly reduced at follow-up (27 ± 31 versus 96 ± 41 mm Hg, P < .00001). Symptoms and provokable LVOT gradients were also reduced in all 10 patients without significant resting but with provokable LVOT obstruction. Persistence of the LVOT obstruction and symptoms was attributed to inability to preexcite the interventricular septum (n = 8) and onset of atrial fibrillation (n = 7). Fifty patients had two cardiac catheterization evaluations, 3 ± 1 and 16 ± 4 months after implantation of a pacemaker. In this subgroup, the NYHA functional class improved from 3.2 ± 0.5 at baseline to 1.8 ± 0.7 at the initial evaluation (P < .0001), but with a further significant improvement at the second evaluation: 1.4 ± 0.6, P < .001. This symptomatic improvement was associated with progressive reduction of LVOT gradient at the two evaluations: baseline, 100 ± 47 mm Hg; first evaluation, 41 ± 36 mm Hg (P < .0001); and second evaluation, 29 ± 34 mm Hg (P < .01). Despite the presence of left bundle branch block, DDD pacing reduced LVOT obstruction significantly in 15 patients (LVOT gradient, baseline 89 ± 56 mm Hg versus 18 ± 26 mm Hg at follow-up, P < .0001). There was a weak but significant correlation between the reduction in LVOT gradients accomplished by AV pacing before implantation of DDD device and the eventual reduction in LVOT gradients recorded at the follow-up evaluation (r = .38, P = .0017). Echocardiography demonstrated significant thinning of the anterior septum and distal anterior LV wall in the absence of deterioration of LV systolic function.

Conclusions  (1) Although most of the improvement of symptoms and hemodynamic indexes occurs during the first few months of DDD pacing, further changes are often observed a year later; (2) DDD pacing is associated with an excellent prognosis in a subgroup of severely disabled patients, many of whom present with syncope or presyncope; (3) baseline pacing studies are not essential to identify patients who may benefit from pacing; (4) preexciting left bundle branch block is compatible with severe LVOT obstruction, and DDD pacing is also beneficial in this subgroup; (5) DDD pacing reduces both resting and provokable LVOT obstruction; (6) additional therapy, for example, radiofrequency ablation of the AV node, may be necessary in some patients either to preexcite the interventricular septum or to control atrial fibrillation; and (7) although LV hypertrophy has been considered a primary feature of HCM, pacing appears to reverse LV wall thickness in a significant subset of adult HCM patients. (Circulation. 1994;90:2731-2742.)

Key Words  • pacing • cardiomyopathy

It has been proposed that atrial synchronized ventricular pacing may be an effective alternative to cardiac surgery.1-7 Right ventricular pacing causes the interventricular septum to move paradoxically. This increases the left ventricular outflow tract (LVOT) dimensions and thus reduces the LVOT blood velocities, which in turn results in less systolic anterior motion of the mitral valve and mitral regurgitation. We recently reported on the short-term beneficial results of chronic dual-chamber (DDD) pacing in obstructive hypertrophic cardiomyopathy (HCM) associated with severe drug-refractory symptoms.8 Six to 12 weeks of DDD pacing in 44 patients was associated with significant improvement of symptoms and reduction in LVOT obstruction.8

It is not established, however, whether the initial favorable results of DDD pacing are maintained long-term, particularly because HCM is a progressive myopathy. There are also many other issues that need to be resolved before DDD pacing gains general acceptance for treatment of obstructive HCM. HCM has markedly
heterogeneous clinical presentations. The role of DDD pacing therefore needs to be established in certain subgroups of HCM patients, for example, in patients who do not have LVOT obstruction at rest but who develop severe obstruction to LV outflow in response to exercise or changes in posture. The role of DDD pacing also needs to be established in another important subgroup consisting of HCM patients with preexisting left bundle branch block (LBBB) and hence, abnormal interventricular septal activation. A critical question is also whether the effects of temporary AV sequential pacing on the LV outflow obstruction should be studied in all patients before implantation of the permanent DDD device. This study attempts to address these issues in a large number of patients with obstructive HCM and severe drug-refractory symptoms.

### Methods

#### Patients

The study population consisted of 84 consecutive patients with obstructive HCM and severe symptoms refractory to drug therapy who were referred to the National Institutes of Health between May 1990 and August 1993 for consideration of an alternative therapy, such as surgical cure. Informed consent was obtained in accordance with a study protocol (90-H-224) approved by the Review Board of the National Heart, Lung, and Blood Institute. The short-term results of DDD pacing were reported previously in 44 of the patients.\(^8\) The clinical characteristics of the 84 patients are detailed in Table 1. Two patients had systolic hypertension. Eighty-one patients were either in New York Heart Association (NYHA) functional class III or IV. The remaining 3 patients were in NYHA functional class II but were included because of recurrent syncope. Five patients had previously undergone LV septal myotomy and myectomy. All patients had failed to benefit or had developed untoward side effects to adequate doses of verapamil (240 to 360 mg/d) and a β-blocker. In addition, the negative inotropic antiarrhythmic drug disopyramide had been tried unsuccessfully in 9 patients.

Baseline investigations included history and physical examination; 12-lead ECG; symptom-limited multistage Bruce protocol treadmill exercise tests; chest radiograph; 48-hour Holter monitoring; M-mode, two-dimensional, and Doppler echocardiography; right and left heart catheterization; and coronary angiography. All cardiovascular drugs were discontinued at least 5 half-lives before evaluation except for diuretics, which were omitted on the day of cardiac catheterization.

### Echocardiography

Echocardiographic studies were performed with a Hewlett-Packard (Sonos 1000) real-time, phase array, 90° ultrasonic scanner with a 2.5-MHz transducer. The magnitude and distribution of LV hypertrophy were assessed in a number of standard cross-sectional planes. Diastolic wall thickness was measured directly from the television monitor with calipers at both the mitral valve and papillary muscles. M-mode echocardiograms were derived from the two-dimensional image under direct anatomic visualization. In the short axis, the LV wall was divided into four segments both at the mitral valve level (basal anterior septum, basal posterior septum, basal anterior free wall, and basal posterior free wall) and at the level of the papillary muscle (distal anterior septum, distal posterior septum, distal anterior free wall, and distal posterior free wall). Changes in LV segmental wall thickness and motion were assessed by two independent observers who were unaware of the clinical findings or other results of the study. Paradoxical septal motion was defined as motion of the interventricular septum toward the right ventricle during systole determined by M-mode echocardiography. The severity of systolic anterior motion was graded as follows: 0, absent; 1+, present with minimum distance between mitral valve and ventricular septum during systole >10 mm; 2+, without mitral-septal contact but with a distance of <10 mm between mitral valve and septum during systole; 3+, brief mitral-septal contact (<30% of the time between closure and opening of the mitral valve); 4+, prolonged apposition of mitral valve with septum (>30% of the time between closure and opening of the mitral valve).

Continuous-wave Doppler examination estimated the magnitude of the LVOT gradient using a 1.9-MHz nonimaging transducer.\(^9\) Particular care was taken to separate the LVOT signal from that of mitral regurgitation.\(^11\) The presence and severity of mitral regurgitation was assessed by color flow Doppler according to previously validated criteria.\(^12\)

### Cardiac Catheterization

Right heart pressures and cardiac output were measured with a thermodilution Swan-Ganz catheter. The LVOT gradient was recorded using the side arm of a Cordis 8F sheath and a 7F Cordis end-hole catheter placed in the LV. The right femoral and ascending aortic pressures were compared and agreed within 5 mm Hg. All patients had significant LVOT obstruction, defined as a subvalvular gradient of >30 mm Hg at rest or >55 mm Hg after provocation (amyl nitrite inhalation, Valsalva maneuver, or isoproterenol infusion).

At the baseline study, after measurement of right and left heart pressures and cardiac outputs during normal sinus rhythm, the hemodynamic indexes were remeasured during right atrial (RA) and AV sequential (AV delay of 120 milliseconds) pacing modes at a heart rate of 120 beats per minute. At the follow-up study, the hemodynamic indexes were recorded during sinus rhythm and DDD pacing and in addition, during RA and AV sequential pacing modes at a heart rate of 120 beats per minute by external programming of the pacemaker device.

Fifty patients had two or more catheterization evaluations, 3±1 and 16±4 months after implantation of the permanent DDD pacing device.

### Table 1. Clinical Characteristics of Patients With Obstructive Hypertrophic Cardiomyopathy Who Received a Dual-Chamber (DDD) Permanent Pacing Device for Severe Drug-Refactory Symptoms

<table>
<thead>
<tr>
<th>No.</th>
<th>84</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>49±16 (range, 11-77)</td>
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<tr>
<td>Male sex, No.</td>
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<td>NYHA functional class, mean±SD</td>
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<table>
<thead>
<tr>
<th>Symptoms, n (%)</th>
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<tbody>
<tr>
<td>Chest pain</td>
</tr>
<tr>
<td>Dyspnea</td>
</tr>
<tr>
<td>Palpitations</td>
</tr>
<tr>
<td>Syncope</td>
</tr>
<tr>
<td>Presyncope</td>
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</table>

<table>
<thead>
<tr>
<th>LVOT gradient, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥30 mm Hg at rest</td>
</tr>
<tr>
<td>&lt;30 mm Hg at rest; ≥55 mm Hg with provocation</td>
</tr>
<tr>
<td>LBBB, n (%)</td>
</tr>
<tr>
<td>Prior LVMM, n (%)</td>
</tr>
</tbody>
</table>

NYHA indicates New York Heart Association; LVOT, left ventricular outflow tract; LBBB, left bundle branch block; and LVMM, left ventricular septal myotomy and myectomy (Morrow procedure).

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Fifty patients had two or more catheterization evaluations, 3±1 and 16±4 months after implantation of the permanent DDD pacing device.
Radiofrequency Ablation of the AV Node

To control ventricular rate without using drugs and to ensure ventricular preexcitation, patients who developed paroxysmal or chronic atrial fibrillation were treated with radiofrequency ablation of the AV node, and their pacemakers were programmed to DDI/DDIR or VVIR modes, respectively. A 7F steerable catheter with a 4-mm distal pole (Mansfield-Webster, Bard, or EPT) was positioned across the tricuspid valve. Attempts were made to perform ablation near the site at which the distal bipolar pair of electrodes recorded relatively large right atrial electrograms and a sharp His-bundle deflection. A Radionics RFG-3C radiofrequency current generator (Radionics Inc) provided the energy source. Radiofrequency energy was delivered for up to 60 seconds at 50 to 75 W between the distal electrode and a patch electrode (Bard Dispersive Electrode) positioned between the scapulae. Acceptable ablation end points were slowing of the ventricular response to <70 beats per minute during atrial fibrillation or onset of complete heart block.

Implantation of Permanent Dual-Chamber Pacing Systems

DDD permanent pacemakers were implanted in all 84 patients by standard techniques (ventricular lead was positioned at right ventricular apex). The pulse generators were Medtronic 7074 in 39 patients, 7070 in 16, 7075 in 2, and 7071, 7076, and 7108 in 1 patient each; Pacesetter 2020 in 8 and 2022 in 15 patients; and CPI 1224 in 1 patient. The lower rate was programmed to 70 beats per minute and the upper rate to 150 to 170 beats per minute. The programmed AV delay was the longest interval that permitted ventricular preexcitation (maximum widening of the QRS complex) during the exercise tests.

Follow-up Evaluation

Patients were scheduled for in-hospital follow-up evaluations at 2 to 3 months and >1 year after DDD pacemaker implantation. Repeat investigations included history and physical examination, 12-lead ECG, chest radiograph, echocardiogram, treadmill exercise tests, and right and left heart catheterization. Follow-up data were obtained during DDD pacing and with the pacemaker switched off during normal sinus rhythm. Long-term follow-up also included clinical assessment at intervals of 6 or 12 months and telephone follow-up with patients, relatives, and physicians.

Statistical Analysis

Data are expressed as mean±1 SD. Only paired data were compared by Student’s t test and Wilcoxon’s signed rank tests. Contingency tables were evaluated by χ² and Fisher’s exact tests. Cumulative survival was determined by product-limit survival analysis using sudden death as time variable. Spearman’s test was used to examine the correlation between LVOT gradient changes induced during baseline pacing studies and the changes in LVOT gradient observed after chronic DDD pacing. A value of P<.05 was considered significant. A Bonferroni correction was used to adjust for multiple comparisons (ie, repeated measurements on left ventricular wall dimensions).13

Results

Pacemaker Programmed Indexes

The initial programmed pacing mode was DDD in 68 patients (81%), DD多吃 in 14 patients (17%), and DD多吃 in 2 patients (2%) (due to history of paroxysmal atrial fibrillation). At the last follow-up evaluation, 52 patients, or 62%, were in DDD mode. Several patients were programmed to DDDR mode (23 patients, or 27%) to ensure septal preexcitation (reduce fused beats at rest or during exercise) or to improve chronotropic response to exercise. The pacing device was programmed to VVIR in 7 patients because of development of chronic atrial fibrillation and to DD多吃 in 2 patients because of paroxysmal atrial fibrillation.

The most common initial programmed AV delays were 120 (n=36) and 125 (n=37) milliseconds. However, some patients required shorter AV delays of 80 (n=1), 100 (n=7), and 110 (n=1) milliseconds to ensure septal preexcitation. In two patients, satisfactory septal electrical activation was achieved at the longer AV delays of 130 and 150 milliseconds. At follow-up evaluations, the AV delay was shortened in 8 patients (10%) to ensure greater interventricular septal preexcitation. However, in 15 patients (18%), the AV delay was increased after radiofrequency ablation of the AV node (n=8) or because of prolongation of intra-atrial conduction (abnormally prolonged P wave) in association with a long PR interval (n=7). Hence, the final programmed AV delays to ensure preexcitation were 75 milliseconds in 1 patient, 100 in 9 patients, 110 in 3 patients, 120 in 20 patients, 125 in 25 patients, 130 in 4 patients, 140 in 3 patients, 150 in 8 patients, and 180 in 2 patients.

Symptomatic Outcome and Prognosis

The NYHA functional class improved significantly (1.55±0.61 versus 3.16±0.45, P<.00001) after 2.3±0.75 years (maximum, 3.5 years) of DDD pacing. The overall experience with DDD pacing and symptomatic improvement are summarized in Figs 1 and 2, respectively. Notably, symptoms were abolished in 28 patients (33.3%), reduced in 47 (56%), and unchanged in 7 (8.3%). Four of the latter 7 patients underwent LV septal myotomy and myectomy (Fig 1). Two patients died suddenly 10 months and 16 months, respectively, after implantation of DDD pacemaker: a 3-year cumulative survival rate of 97%. In both patients, symptoms and LVOT obstruction had improved before sudden death.

Thirty-five patients (42%) had 1 to 8 episodes of syncope before pacing. In contrast, during the follow-up period only 5 patients (6%) had syncope.

The reduction in symptoms was accompanied by a significant improvement in treadmill exercise performance: the exercise duration increased from 319±161 seconds at baseline to 429±170 seconds, or a 35%
increase, at the last follow-up evaluation ($P < .00001$). At the baseline study, exercise induced syncope in 1 patient and lightheadedness in an additional 15 patients. However, despite the increased exercise duration, only 5 patients complained of lightheadedness during DDD pacing at the follow-up evaluation ($P < .02$). The systolic and diastolic pressures and heart rate–blood pressure products achieved at maximal exercise at the baseline and follow-up studies were similar.

Of the 75 patients in whom symptoms were improved or eliminated and who had failed multiple drug therapies before DDD pacing, 29 (39%) were not receiving any cardiac drugs at the last follow-up. Sixteen patients were on drugs solely to control paroxysmal atrial arrhythmias. Sixteen patients were on mild diuretics. β-Blockers and calcium channel antagonists were administered for hypertension or migraine in 3 patients and for residual cardiac symptoms in 13 patients.

**Hemodynamic Results in Patients With Resting LVOT Obstruction**

At the baseline study, 74 patients had significant LVOT obstruction (LVOT gradient of ≥30 mm Hg) in the absence of any provocation maneuvers. In this subset of patients, DDD pacing reduced resting LVOT gradients dramatically: from 96±41 mm Hg at baseline to 29±34 mm Hg at last follow-up evaluation (1.2±0.5 years after implantation of DDD device; $P < .00001$). Notably, at the last follow-up evaluation, LVOT obstruction was eliminated or insignificant in 48 patients (65%), reduced in 20 patients (27%), but remained unchanged in 6 patients (8%). The heart rates, however, were similar on the two occasions.

Five of the 74 patients had a history of prior LV septal myotomy and myectomy. In this subset, DDD pacing reduced the LVOT gradient from 77±50 to 5±5 mm Hg, $P = .03$.

**Relation of Acute Pacing Studies to Hemodynamic Findings After Chronic Dual-Chamber Pacing**

To determine the ability of acute pacing studies, performed before implantation of a pacemaker, to identify patients who would benefit from DDD pacing therapy, we studied, in 65 patients, the relation between changes in LVOT gradient induced by pacing at the baseline study and alterations in LVOT gradient after chronic DDD pacing. The long-term effect of chronic DDD pacing on LVOT obstruction was significantly more pronounced than the effect of acute AV pacing: Chronic DDD pacing reduced the LVOT gradient by 67±47 mm Hg compared with baseline values recorded in sinus rhythm ($P < .0001$), but at the baseline study, a change from right atrial pacing at 120 beats per minute to AV pacing at 120 beats per minute reduced the LVOT gradient by 31±34 mm Hg (Fig 3).

There was significant correlation ($r = .38, P < .0017$) between changes in LVOT gradients induced by AV pacing recorded at the baseline cardiac catheterization and the eventual reduction in LVOT gradients noted at the follow-up study (Fig 3). There were, however, notable disparities: For example, in one patient, AV pacing reduced LVOT gradient by only 20 mm Hg, but chronic DDD pacing reduced the LVOT gradient by 245 mm Hg. In contrast, in another patient, acute AV pacing reduced the LVOT gradient by about 140 mm Hg, but chronic DDD pacing reduced the LVOT gradient by only 87 mm Hg.

**Evidence for Progressive Symptomatic and Hemodynamic Improvement: Results of DDD Pacing in Patients Who Were Evaluated on Two Separate Occasions**

Although there was marked symptomatic improvement after about 3±1 months of DDD pacing, many patients reported further significant relief of symptoms after a longer period (16±4 months) of follow-up (Fig 2).

Fifty patients had two cardiac catheterization evaluations. Most of the reduction in LVOT gradient occurred within 3 months of implantation of the permanent DDD device. However, there was a further significant decrease in LVOT gradient after a further 1 year of DDD pacing (Fig 4). Fig 5 illustrates the progressive reduction in LVOT gradient in such a patient. The reduction in LVOT obstruction was not accompanied by a significant change in LV filling pressures or cardiac output (Fig 4).
Hemodynamic Adaptation to Chronic Dual-Chamber Pacing

Progressive hemodynamic improvement was also demonstrated in sinus rhythm at the two follow-up cardiac catheterization studies, when DDD pacing was discontinued: The LVOT gradient and LV systolic pressure were reduced, and the arterial pulse pressure increased significantly at the first evaluation, with further significant changes in these hemodynamic indexes recorded at the second evaluation (Fig 6). Additionally, there was evidence of progressive significant reduction in LV end-diastolic pressure (Fig 6). The hemodynamic changes, however, were not accompanied by significant alterations in heart rate or cardiac output.

Results of Pacing in Patients With Provokable LVOT Obstruction but Without Resting LVOT Obstruction

Ten patients did not have evidence of significant resting LVOT obstruction (LVOT gradient, 13±11 mm Hg) but developed marked LVOT obstruction after isoproterenol infusion (132±60 mm Hg). In all 10 patients, DDD pacing reduced the provoked LVOT gradients significantly (Fig 7).

Results of DDD Pacing in Patients With LBBB

Fifteen patients had LBBB before DDD pacing. These patients had evidence of severe LVOT obstruction despite the abnormal septal electrical activation finding (Fig 8). Furthermore, DDD pacing (right ventricular apical electrical activation) was also effective in reducing LVOT obstruction without increasing LV filling pressures and reducing cardiac output in this subgroup of patients (Fig 8).

Echocardiographic Evidence of Reduction of LVOT Obstruction and Regression of Left Ventricular Wall Thickness After Chronic DDD Pacing

Baseline and follow-up echocardiograms of sufficient quality for comparison were available in 48 patients. At the level of mitral valve septal coaptation, DDD pacing caused clear-cut paradoxical interventricular septal motion in 21 patients (44%). In most of the remaining patients, DDD pacing induced less prominent alterations in septal motion, often eliminating or reducing the inward systolic movement of the interventricular septum. These findings were associated with significant reduction of systolic anterior motion, LVOT blood velocities, and mitral regurgitation (Table 2).

Chronic DDD pacing did not significantly alter LV diastolic dimension. However, largely as the conse-
Fig 6. Graphs documenting marked hemodynamic improvement recorded during normal sinus rhythm at the first follow-up cardiac catheterization study (NSR) and at the second cardiac catheterization (NSR2) compared with values recorded before implantation of the dual-chamber (DDD) pacing device (NSR). PCW indicates mean pulmonary arterial capillary wedge pressure; MPA, mean pulmonary arterial pressure; CO, cardiac output; LVEDP, left ventricular end-diastolic pressure; LV, left ventricular systolic pressure; LVOT gradient, left ventricular outflow tract gradient; and AoS, systemic arterial systolic pressure.

Notably, chronic DDD pacing reduced LV wall thickness by ≥4 mm (maximum, 17 mm) in 11 patients (23%) (Figs 9 and 10). LV wall thinning was most prominent in basal anterior and distal anterior septal segments (Table 2). The reduction in LVOT gradient in the 11 patients with significant regression of LV hypertrophy was not significantly different from that of the remaining 37 patients (62±46 versus 58±39 mm Hg).

Fig 7. Graphs showing the changes in hemodynamic indexes due to dual-chamber (DDD) pacing in 10 symptomatic patients with hypertrophic cardiomyopathy who did not have significant left ventricular outflow tract (LVOT) obstruction at rest (LVOT gradient <30 mm Hg) but who developed significant LVOT obstruction with provocation maneuvers (LVOT gradient ≥55 mm Hg). The provoked LVOT gradients at the baseline and follow-up studies were measured at the same increased heart rate during isoproterenol infusion. PCW indicates mean pulmonary arterial capillary wedge pressure; MPA, mean pulmonary arterial pressure; LVEDP, left ventricular end-diastolic pressure; CO, cardiac output; Pulse pressure, systemic arterial pulse pressure; and NSR, normal sinus rhythm.
Discussion

Our long-term evaluation of DDD pacing in obstructive HCM confirms that this novel therapy is highly effective in relieving severe symptoms refractory to drug therapy. Angina, dyspnea, palpitations, and symptoms of impaired consciousness are eliminated or decreased in 89% of the patients. This symptomatic improvement is associated with significant reduction in LVOT obstruction, reduction in pharmacotherapy, and improvement in exercise performance. Notably, our study demonstrates that the symptomatic and hemodynamic benefits recorded early after implantation of DDD pacemaker often become more pronounced with the passage of time. At present it is unclear why in some patients LVOT obstruction is eliminated almost immediately, but in others, maximal results are observed only after more than a year of DDD pacing.

An important limitation of this study is that the severity of LVOT obstruction in HCM may vary markedly in the same patient under different conditions. To study the effects of DDD pacing on LVOT obstruction, therefore, requires that a large number of well-characterized patients with obstructive HCM be studied under standardized conditions. The patients in this study were of two types: The largest subgroup consisted of patients in whom prior echocardiographic and cardiac catheterization studies had invariably demonstrated significant

![Fig 8. Tracing demonstrating the effect of improved interventricular septal preexcitation on left ventricular outflow tract (LVOT) obstruction in a patient with left bundle branch block in whom DDD pacing had only partially improved symptoms.](image)

TABLE 2. Echocardiographic Findings in Patients With Obstructive Hypertrophic Cardiomyopathy Before and After Chronic Dual-Chamber (DDD) Pacing

<table>
<thead>
<tr>
<th>Baseline (NSR)</th>
<th>Follow-up</th>
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<tr>
<td></td>
<td>DDD</td>
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<tr>
<td><strong>LV chamber size and function</strong></td>
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<tr>
<td>LV diastolic dimension, mm</td>
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<tr>
<td>LV systolic dimension, mm</td>
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<tr>
<td>LV fractional shortening, %</td>
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<td>Left atrial systolic dimension, mm</td>
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<td><strong>Indexes of LVOT obstruction</strong></td>
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<tr>
<td>Severity of SAM (I-IV)</td>
<td>3.58±0.87</td>
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<tr>
<td>Severity of mitral regurgitation (I-IV)</td>
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<tr>
<td>CW Doppler LVOT velocity, m/s</td>
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<tr>
<td>Estimated LVOT gradient, mm Hg</td>
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<tr>
<td><strong>LV wall thickness, mm</strong></td>
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<tr>
<td>Basal anterior septum</td>
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<td>17.4±5.0</td>
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<td>Distal posterior free wall</td>
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</table>

NSR indicates normal sinus rhythm; DDD, dual-chamber pacing; LV, left ventricle; LVOT, left ventricular outflow tract; SAM, systolic anterior motion of the mitral valve; CW, continuous-wave; basal refers to level of mitral valve; and distal refers to level of papillary muscles.

*P<.05, †P<.01, ‡P<.001 vs sinus rhythm at baseline; §P<.0001 vs DDD pacing at follow-up.
LVOT at rest. A much smaller subgroup comprised patients who consistently did not have evidence of LVOT obstruction at rest by noninvasive and invasive studies but in whom severe LVOT obstruction could readily be provoked by isoproterenol infusion. Both groups of patients with obstructive HCM derived benefit from DDD pacing.

A gratifying result was the reduction in symptoms of impaired consciousness. Syncope has been associated with a poor prognosis (about 4% to 6% annual mortality) in HCM. However, even though almost half of the patients in the present study presented with syncope or presyncope and most had severe congestive symptoms, only two sudden deaths occurred during the 2.5-year period of follow-up (about 1% annual mortality). This compares favorably with the probable 8% to 10% cumulative mortality had the patients been subjected to cardiac surgery. Given the satisfactory results in most patients who receive DDD pacemakers and the relative simplicity of this approach compared with cardiac surgery, it is most unlikely that it will ever be possible to compare the two modes of therapy through a randomized prospective study. We believe that cardiac surgery will be reserved for only a minority of patients who fail to respond to DDD pacing or who have independent mitral valve disease (severe mitral regurgitation due to mitral valve prolapse, or aberrant papillary muscle obstructing LV outflow).

We have also previously reported that when, after several weeks of pacing, the DDD device is switched off and recordings are made in normal sinus rhythm, the hemodynamic indexes and cardiac electrical properties are often noted to have changed profoundly. The present study confirms this finding and demonstrates that the adaptive hemodynamic changes recorded early after implantation of the pacemaker are exaggerated after a longer period of DDD pacing. A molecular basis for the adaptive cardiac changes is at present being investigated. Further studies are also necessary to establish whether the changes in hemodynamic indexes and cardiac electrical properties reduce the tendency to atrial and ventricular arrhythmias.

A finding of practical importance is that detailed invasive evaluation of the hemodynamic consequences of AV sequential pacing before implantation of DDD pacemaker poorly identifies patients with obstructive HCM, who are most likely to benefit from this novel therapy, and is therefore unnecessary. It is therefore even less likely that indirect studies of the effects of temporary AV sequential pacing on LVOT gradient, such as Doppler echocardiography, will assist in the selection of such patients. There are two major reasons...
for the poor correlation between acute and chronic consequences of pacing. First, small changes in cardiac output may have profound effects on LVOT gradient. Thus, if acute AV pacing augments the cardiac output at the baseline study, the LVOT gradient may not decrease or in some patients may even increase. Second, the adaptive hemodynamic changes in response to chronic DDD pacing undoubtedly contribute significantly to the success of this therapy. Failure to respond to DDD pacing was most often related to inability to preexcite the interventricular septum and thus to relieve the LVOT gradient because of relatively rapid AV node conduction. In a few patients, the problem was aggravated by the coexistence of slow intra-atrial conduction as shown by the markedly prolonged P waves on the surface 12-lead ECG. Programming of AV intervals that are too short in these patients, to ensure ventricular capture, may lead to simultaneous contraction of the LV and left atrial chambers. Left atrial contraction in the presence of a closed mitral valve will result in pulmonary congestion and diminished LV diastolic filling and hence aggravation of the LVOT obstruction. Radiofrequency ablation or modification of the AV node ensured maximal ventricular capture and the proper sequence of atrial and ventricular contraction. Although this procedure may render the patient dependent on the pacemaker, it can be justified if it results in relief of the LVOT obstruction and thus precludes the need for major cardiac surgery.

Atrial fibrillation is the most common supraventricular arrhythmia recorded in HCM.\textsuperscript{17,18} Sudden loss of atrial contribution, tachycardia, and irregular LV filling and emptying can have devastating hemodynamic consequences and precipitate sudden death.\textsuperscript{17-19} We have previously reported that radiofrequency ablation of the AV node coupled with rate-responsive pacing results in
satisfactory symptomatic and hemodynamic outcome in HCM patients with atrial fibrillation.20 Although the relief of LVOT obstruction and consequently, reduction of mitral regurgitation and of left atrial pressures may help prevent atrial arrhythmias, our study did not provide evidence to support this. Conversely, ventricular pacing with retrograde atrial activation due to inability to sense P waves satisfactorily could precipitate atrial fibrillation. However, there was no evidence of pacemaker malfunction, such as failure to sense P waves, in the patients who developed atrial fibrillation. The baseline left atrial dimensions in the patients were also not significantly different from those in patients who did not develop atrial fibrillation. Furthermore, the left atrial dimensions did not significantly change during follow-up. These findings suggest that the atrial fibrillation was the consequence of progression of atrial electrical disease that was not significantly affected by DDD pacing. In some patients, an attempt was made to maintain sinus rhythm by prescribing antiarrhythmic drugs. If this failed, then to prevent the dire clinical consequences of atrial fibrillation and to ensure satisfactory pacing, we performed radiofrequency modification/ablation of the AV node and programming of the pacemaker to mode switching (DDI) in patients with paroxysmal atrial fibrillation and rate-responsive ventricular demand (VVIR) pacing in patients with chronic atrial fibrillation.

This study also reveals another important consequence of chronic DDD pacing in obstructive HCM: The anterior basal and distal septal segments and posterior distal septal segment thinned significantly in 23% of the patients. In the remaining patients, the LV wall thickness was unchanged or the LV wall thinning was less prominent. Importantly, the reversal of the LV wall thickness was segmental and not global, was associated with amelioration of symptoms, and was not accompanied by diminution of LV function. When pacing was discontinued, the LV fractional shortening had not altered significantly, and the hemodynamic findings were improved: LV end-diastolic, pulmonary arterial, capillary wedge, and mean pulmonary arterial pressures had decreased, systemic arterial pressure had increased, and cardiac outputs were maintained. We have also reported that DDD pacing in obstructive HCM improves myocardial perfusion as demonstrated by exercise 201Tl scintigraphy.21 Recently, in studies involving small numbers of patients, Sadoul et al22 and Jeanrenaud et al23 also reported small decreases in LV mass with minor or no alteration of LV cavity dimensions and hence, of LV function.

It has been suggested that the decrease in LV hypertrophy may be due to the reduction of the LVOT obstruction. However, we have not found a correlation between the reduction in LVOT gradient and the change in LV wall dimensions. Furthermore, a similar thinning of the LV wall has not been observed in patients who have undergone successful LV septal myotomy and myectomy. Hence, the reversal of LV wall thickness may be a direct consequence of pacing and not secondary to the reduction of LVOT obstruction.

Recent animal studies have demonstrated that during LV contraction after activation of the specialized His-Purkinje system, there is homogeneity of myocardial fiber strain and stress.24 In contrast, asynchronous electrical activation during LV apical pacing in dogs has been shown to reduce fiber strain in areas of early electrical activation.25 The altered workload has been associated with a reduction in LV mass near the pacing site.26 In a further recent retrospective study, in patients with LBBB, M-mode echocardiographic examination showed LV wall thickness to be significantly less in the early activated septum than in the late activated posterior wall.27 The reduction in LV wall thickness in our patients was more impressive than that reported in animals and occurred both near the pacing site and distally (basal anterior septum). Therefore, an explanation for the changes in LV mass may be that right ventricular apex causes early activation of the anterior septum and more delayed electrical activation of the posterior septum, posterior LV free wall, and anterolateral LV free wall. This, in turn, causes important segmental differences in contractile work and hence changes in LV mass. The exciting finding of regression of LV hypertrophy in a subset of adult HCM patients has prompted us to prospectively investigate the distinct possibility that in children, DDD pacing may attenuate the LV hypertrophy and prevent LVOT obstruction from developing during the period of most rapid growth (puberty).

References
17. McAreavey D, Fananapazir L. Altered cardiac hemodynamic and electrical state in normal sinus rhythm following chronic dual chamber pacing for relief of left ventricular outflow obstruction in hypertrophic cardiomyopathy. *Am J Cardiol*. 1992;70:651-656.
Long-term results of dual-chamber (DDD) pacing in obstructive hypertrophic cardiomyopathy. Evidence for progressive symptomatic and hemodynamic improvement and reduction of left ventricular hypertrophy.

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