

## Dual-Chamber Pacing for Hypertrophic Cardiomyopathy: A Randomized, Double-Blind, Crossover Trial

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**Objectives.** In a double-blind, randomized, crossover trial we sought to evaluate the effect of dual-chamber pacing in patients with severe symptoms of hypertrophic obstructive cardiomyopathy.

**Background.** Recently, several cohort trials showed that implantation of a dual-chamber pacemaker in patients with severely symptomatic hypertrophic obstructive cardiomyopathy can relieve symptoms and decrease the severity of the left ventricular outflow tract gradient. However, the outcome of dual-chamber pacing has not been compared with that of standard therapy in a randomized, double-blind trial.

**Methods.** Twenty-one patients with severely symptomatic hypertrophic obstructive cardiomyopathy were entered into this trial after baseline studies consisting of Minnesota quality-of-life assessment, two-dimensional and Doppler echocardiography and cardiopulmonary exercise tests. Nineteen patients completed the protocol and underwent double-blind randomization to either DDD pacing for 3 months followed by backup AAI pacing for 3 months, or the same study arms in reverse order.

**Results.** Left ventricular outflow tract gradient decreased significantly to  $55 \pm 38$  mm Hg after DDD pacing compared with the baseline gradient of  $76 \pm 61$  mm Hg ( $p < 0.05$ ) and the gradient

of  $83 \pm 59$  mm Hg after AAI pacing ( $p < 0.05$ ). Quality-of-life score and exercise duration were significantly improved from the baseline state after the DDD arm but were not significantly different between the DDD arm and the backup AAI arm. Peak oxygen consumption did not significantly differ among the three periods. Overall, 63% of patients had symptomatic improvement during the DDD arm, but 42% also had symptomatic improvement during the AAI backup arm. In addition, 31% had no change and 5% had deterioration of symptoms during the DDD pacing arm.

**Conclusions.** Dual-chamber pacing may relieve symptoms and decrease gradient in patients with hypertrophic obstructive cardiomyopathy. In some patients, however, symptoms do not change or even become worse with dual-chamber pacing. Subjective symptomatic improvement can also occur from implantation of the pacemaker without its hemodynamic benefit, suggesting the role of a placebo effect. Long-term follow-up of a large number of patients in randomized trials is necessary before dual-chamber pacing can be recommended for all patients with severely symptomatic hypertrophic obstructive cardiomyopathy.

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Dual-chamber pacing has recently been proposed as an alternative to surgical myectomy for patients with severely symptomatic hypertrophic obstructive cardiomyopathy unresponsive to medical therapy (1-3). Several institutions have shown that implantation of a dual-chamber pacemaker can reduce the severity of left ventricular outflow tract gradient and relieve symptoms in both short- and intermediate-term follow-up periods (1-3). The mechanism for improvement is unclear but may be related to both a short-term effect of gradient reduction by dyssynchronous contraction of the septum caused by pacing the right ventricular apex and a more long-term effect of ventricular remodeling (1). On the basis of these studies, it

has been proposed that dual-chamber pacing be performed in all patients unresponsive to medical therapy before surgical myectomy is considered (2).

All previous studies have consisted of cohorts in which pacemakers were implanted and the patients were followed up serially after the implantation. Two end points of the previous studies were the labile left ventricular outflow gradient and subjective symptomatic improvement, both of which can be affected by factors other than direct hemodynamic improvement. The purpose of this double-blind, randomized, crossover trial was to evaluate objectively the effect of dual-chamber pacing in patients with severely symptomatic hypertrophic obstructive cardiomyopathy in whom medical therapy had failed.

### Methods

**Patient entry criteria.** The study group consisted of patients with hypertrophic obstructive cardiomyopathy who came

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to our institution between November 1993 and January 1995 with severe symptoms unresponsive to medical therapy. All patients had the diagnosis of hypertrophic cardiomyopathy established by conventional two-dimensional echocardiographic criteria (2,4,5). For inclusion in this study, we required a rest left ventricular outflow tract gradient  $>30$  mm Hg at the time of cardiac catheterization. For patients with a rest gradient  $<50$  mm Hg, a provoked gradient  $>50$  mm Hg was required for entry into the study. All patients had to be in normal sinus rhythm at the time of entry into the study and active enough to perform symptom-limited treadmill exertion tests. Patients who were excluded included those with significant concomitant valvular heart disease of aortic stenosis, aortic regurgitation or mitral stenosis; those with mitral regurgitation thought to be caused by a primary valvular abnormality; and those with significant coronary artery disease (diameter of stenosis  $>70\%$  by visual estimation of a major epicardial artery). The study was approved by the institutional review board of the Mayo Clinic, and written informed consent was obtained from all participants.

**Initial evaluation.** All patients were initially interviewed and examined by one of two cardiologists (R.A.N., A.J.T.). Symptoms were subjectively assessed by the New York Heart Association functional classification. A Minnesota quality-of-life form was used for a more objective measurement of the patients' functional capacity.

After the initial examination, comprehensive two-dimensional and Doppler echocardiographic assessments were performed. The peak instantaneous left ventricular outflow tract gradient was measured by continuous wave Doppler echocardiography (6-8). Mitral inflow velocity was measured by the method previously described (9-12). The degree of mitral regurgitation was assessed by color flow imaging.

A symptom-limited maximal treadmill exertion test was done with a standard Mayo protocol and simultaneous analysis of respiratory gases. Starting at 2.5 metabolic equivalents (METs) for the first 2 min, the work load was increased by 2 METs every 2 min thereafter. Expired gas analysis was performed using a Medical Graphics CPX cart. Maximal oxygen consumption was defined as the highest 16-breath average obtained during exercise.

Short-term hemodynamic catheterization was performed to determine the immediate response of the left ventricular outflow tract gradient to dual-chamber pacing using high fidelity manometer-tipped catheter pressures and a transseptal approach to avoid catheter entrapment (13). The details of this study have been previously described (14). Simultaneous mitral inflow velocity curves were measured by pulsed wave Doppler echocardiography. Left atrial pressure, left ventricular pressure, aortic pressure, pulmonary artery pressure and cardiac output were measured in normal sinus rhythm and during atrial synchronous pacing at varying atrioventricular intervals (14,15). The optimal atrioventricular interval was documented as that producing the lowest left ventricular outflow tract gradient without a significant decrease in aortic pressure or increase in left atrial pressure (2,14). In all patients, complete

right ventricular pre-excitation, as assessed by the QRS morphology, was required to achieve the optimal hemodynamic benefit.

**Study design.** On completion of the baseline tests, a permanent dual-chamber pacemaker was implanted. After 1 day, to assure proper functioning of the pacemaker, the patients were randomized in a double-blind, crossover fashion. In one arm, the pacemaker was set at a backup AAI at a rate of 30 beats/min so that it would not be activated. In the other arm, the pacemaker was set at a DDD mode, and the optimal atrioventricular delay defined by the catheterization procedure was used. Electrocardiographic monitoring at rest and during light exercise was performed during DDD pacing to assure that complete ventricular pre-excitation was present. The mitral flow velocity curves during DDD pacing at the optimal atrioventricular delay were similar to those obtained during the temporary catheterization study when atrial synchronous pacing was performed at the same atrioventricular delay, indicating similar mechanical atrial-ventricular synchrony.

The patients were then asked to perform telephone transmissions at monthly intervals. These transmissions were reviewed to assure that the pacemaker was continuing to function normally. So that the additive effect of dual-chamber pacing could be determined, all patients continued to take the same medications they were taking at presentation. Patients were told to call their physician if their symptoms became worse.

The patients returned for follow-up examination at 2- to 3-month intervals. The examination was repeated by an observer who had no knowledge of the pacemaker setting. A repeat subjective assessment of percent functional capacity was made. The patients were asked whether their symptoms were less severe, worse or unchanged. Another Minnesota quality-of-life form was filled out. The comprehensive two-dimensional and Doppler echocardiographic examinations and the cardiopulmonary treadmill test were repeated. After the repeat tests, the patients had their pacemakers programmed to the opposite arm of the study. After another 2 to 3 months, the above evaluation protocol was repeated.

**Statistics.** Data were expressed as mean value  $\pm$  SD. For comparison of the measured variables among baseline, DDD mode and backup AAI mode, a repeated measures analysis of variance was used if the data approximated a gaussian distribution. If the data did not sufficiently approximate a gaussian distribution, Friedman's procedure was used (for the changes in left ventricular outflow gradient). For variables in which there was a difference among the three periods, a pairwise comparison among the three time points was made with a Student-Newman-Keuls test when repeated measures analysis of variance was performed or with a Bonferroni adjustment when Friedman's procedure was performed to adjust for the problem of multiple comparisons. To assess the possibility of a carryover effect after DDD pacing, a procedure based on totals of the treatment arms was used (16). The Pearson and Spearman correlation coefficients were used to assess the association of clinical and catheterization variables with symp-

**Table 1.** Follow-Up Data

	Baseline	Pacing Mode	
		DDD	AAI
HR (beats/min)	62.7 ± 5.8	65.9 ± 10.8	68.1 ± 11.9
SBP (mm Hg)	136 ± 22	136 ± 19	126 ± 19
LVO gradient (mm Hg)	76.7 ± 61	54.9 ± 38*†	83.4 ± 59
QOL score	55.1 ± 23.7	41.6 ± 25.9*	48.4 ± 23.2
NYHA class	2.9 ± 0.4	2.4 ± 0.7	2.6 ± 0.7
Exercise duration (min)	5.7 ± 2.7	6.9 ± 2.2*	6.3 ± 2.3
VO <sub>2</sub> max (ml/kg per min)	19.4 ± 6.7	20.0 ± 6.5	19.8 ± 6.1

\*p < 0.05 compared with baseline. †p < 0.05 compared with AAI. Data are presented as mean value ± SD. AAI = atrial paced, atrial sensed, inhibited; DDD = dual-chamber paced, dual-chamber sensed, triggered inhibited; HR = heart rate; LVO = left ventricular outflow; NYHA = New York Heart Association; QOL = quality of life; SBP = systolic blood pressure; VO<sub>2</sub> = maximal oxygen consumption.

tomatic response. Statistical significance was set a priori at p < 0.05.

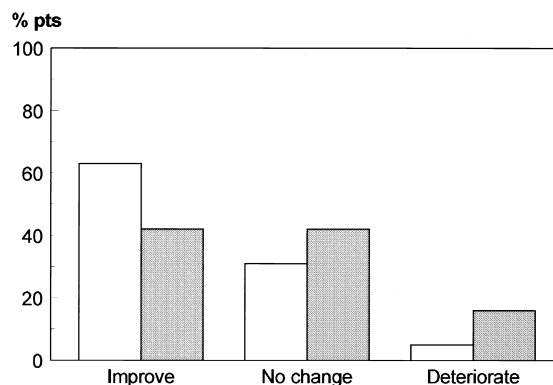
## Results

**Patient group.** Twenty-one patients were entered into the study protocol. One patient had continued severe limiting symptoms after implantation of the pacemaker, despite placement in the DDD arm. He subsequently underwent surgical myectomy and was excluded from the study. Another patient did not return for follow-up. Nineteen patients completed both arms of the study and formed the basis of this analysis.

Of the 19 patients, 10 were men and 9 women, with a mean age of 58 years (range 35 to 74). Eight of the patients had a family history of hypertrophic cardiomyopathy. Concurrent medications included beta-adrenergic blocking agents in 16 and calcium channel blocking agents in 10. Eight patients were taking a combination of beta-blockers and calcium channel blockers. The dosage range of beta-blockers was equivalent to 100 to 480 mg of propranolol, and the dosage range of calcium channel blockers was equivalent to 240 to 480 mg of verapamil. The medication dosage was held constant throughout the protocol. One patient had a myectomy but had recurrent symptoms and documented outflow tract gradient. Two patients had concomitant aortic valve disease but only mild stenosis (gradient <20 mm Hg and normal output). All patients were in normal sinus rhythm and had a PR interval of 168 ± 25 ms (range 120 to 200).

**Baseline measurements.** All patients had symptoms that significantly limited their normal daily activity. Of the 19 patients, 1 was in functional class IV, 16 were in class III and 2 were in class II. The major symptom was dyspnea, which was present in all patients. Twelve patients had exertional angina and four had exertional presyncope. None of the patients had experienced a complete syncopal event, and none had an out-of-hospital arrest. The mean Minnesota quality-of-life score was 55.1 ± 23.7.

The mean septal thickness on two-dimensional echocardi-



**Figure 1.** Subjective symptomatic response after each of the two pacing arms. Shown are the percentages of patients (pts) who experienced improvement, no change or deterioration from the baseline state. **Open columns** = continuous DDD pacing; **gray columns** = AAI, backup mode with the atrial rate set at 30 beats/min.

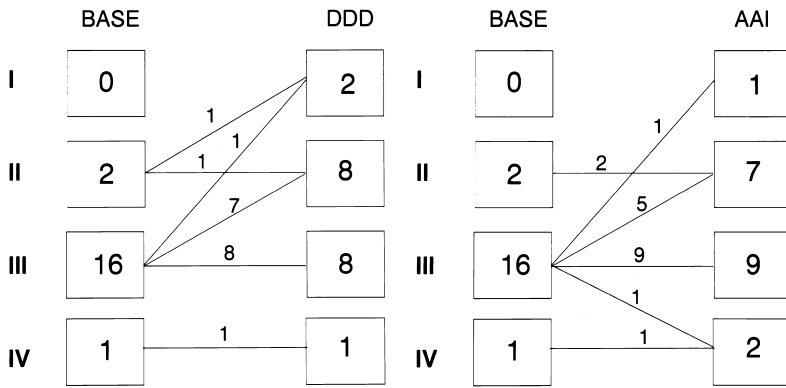
ography was 2.2 cm (range 1.6 to 3.3). Systolic anterior motion of the mitral valve was seen in all patients. The mean left ventricular outflow tract gradient by Doppler echocardiography at the time of outpatient echocardiography was 76 ± 61 mm Hg (range 12 to 250). The degree of mitral regurgitation was mild in 10 patients, moderate in 6 and severe in 1.

The mean exercise duration in the baseline state was 5.7 ± 2.7 min. Maximal oxygen consumption achieved at peak exercise was 19.4 ± 6.7 ml/kg body weight per min. The indication for stopping the exercise test was fatigue or shortness of breath in all patients. No symptomatic supraventricular or ventricular arrhythmias occurred during the exercise test.

**Acute cardiac catheterization.** The average gradient at catheterization was 87 ± 54 mm Hg (range 30 to 220). Five patients had a rest gradient between 30 and 50 mm Hg. All five of these patients had an increase in gradient to >100 mm Hg during isoproterenol infusion. The mean left atrial pressure was 19 ± 9 mm Hg (range 3 to 36), and the mean left ventricular end-diastolic pressure was 27 ± 8 mm Hg (range 14 to 44). The optimal atrioventricular delay during dual-chamber pacing was found to be the longest atrioventricular interval possible before native anterograde conduction: 60 ms in 15 patients, 100 ms in 2 and 120 ms in 2. The average decrease in gradient with dual-chamber pacing was 33 ± 29 mm Hg (range 0 to 105). Thirteen patients had and six did not have a decrease in the left ventricular outflow tract gradient with temporary dual-chamber pacing.

**Follow-up data (Table 1).** Eleven patients were randomized to the AAI backup mode as the initial arm and eight to the DDD pacing mode. No significant difference in heart rate or blood pressure occurred at any of the three periods. There was no significant evidence of a carryover effect due to the order of the pacing modes when the end points of percent functional capacity, Minnesota quality-of-life score, left ventricular outflow gradient, exercise duration and maximal oxygen consumption were compared.

Figure 1 illustrates the symptomatic improvement per-



**Figure 2.** Change in New York Heart Association classification (I-IV) of patients (arabic numerals) from baseline (BASE) to DDD pacing for 3 months (left) or backup AAI pacing for 3 months (right).

ceived by each patient during the follow-up periods. Sixty-three percent of patients in the DDD-paced mode and 42% in the backup unpaced mode (AAI) had symptomatic improvement over the baseline state. With DDD pacing, 31% of patients felt that symptoms were unchanged and 6% felt that symptomatic status had deteriorated. The final functional classifications at baseline and in the two different pacing modes are shown in Figure 2. There were no significant differences in the average functional classification among the three periods.

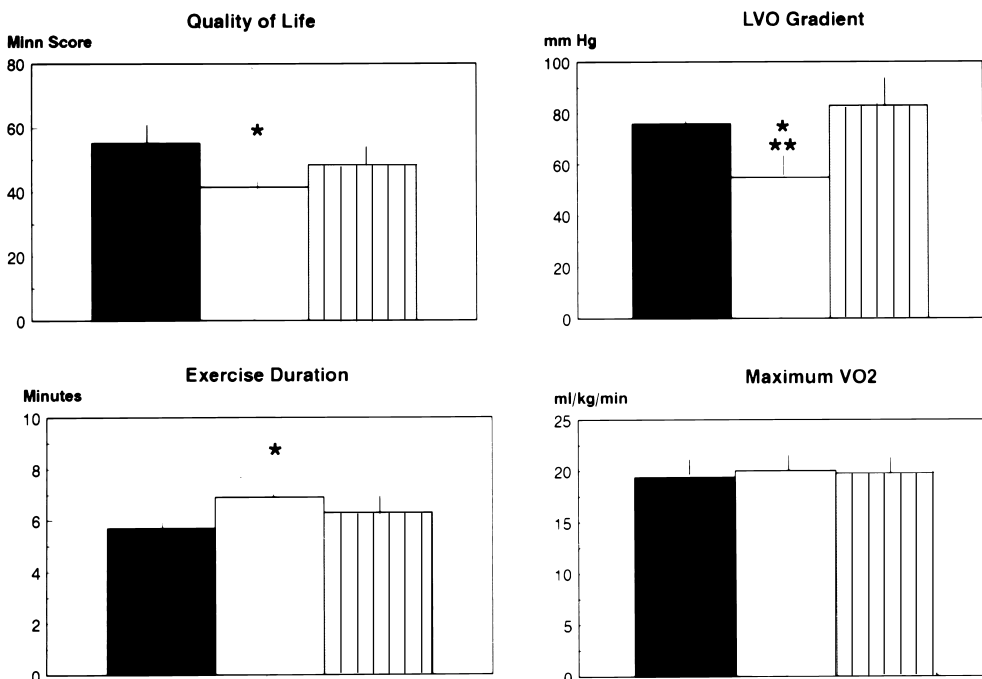
The Minnesota quality-of-life score was significantly lower

during DDD pacing than in the baseline state ( $41.6 \pm 25.9$  vs.  $55.1 \pm 23.7$ ;  $p < 0.05$ ). A lower score means fewer symptoms or limitation of activity. There was no significant difference in the score during backup AAI pacing compared with the baseline state. However, the score was not significantly different when DDD pacing was compared with backup AAI pacing (Fig. 3).

Left ventricular outflow tract gradient during the DDD pacing mode was significantly reduced from the baseline value—from  $76 \pm 61$  to  $55 \pm 38$  mm Hg ( $p < 0.05$ ) (Fig. 4). The gradient in the AAI backup mode ( $83 \pm 59$  mm Hg) was essentially unchanged from that in the baseline state ( $76 \pm 61$  mm Hg), but there was a high variability between the two periods. The mean difference between the gradient in the baseline state and that in the backup AAI mode was  $-11 \pm 41$  mm Hg (Fig. 4).

Exercise duration was significantly improved in the DDD arm from that at baseline—from  $5.7 \pm 2.7$  to  $6.9 \pm 2.2$  min

**Figure 3.** Changes in the objective measurements of symptoms, exercise testing and gradient at three periods. **Top left,** Minnesota quality-of-life score. **Top right,** Left ventricular outflow (LVO) gradient. **Bottom left,** Duration of exercise on treadmill testing. **Bottom right,** Maximal oxygen consumption ( $\dot{V}O_2$ ) achieved during exercise testing. **Solid bars** = baseline; **open bars** = DDD pacing; **striped bars** = AAI pacing. Mean  $\pm$  SD bars are shown. \* $p < 0.05$  compared with baseline. \*\* $p < 0.05$  compared with AAI pacing.



( $p < 0.05$ ). There was no significant difference in the exercise time between the AAI arm and the baseline state. However, exercise duration in the DDD pacing arm was not significantly different from that in the AAI backup mode. Maximal oxygen consumption achieved in either the DDD mode or the AAI mode was not significantly changed from the baseline value (Fig. 3). During exercise in the DDD pacing arm, anterograde native atrioventricular conduction developed in two patients at the maximal heart rate. The remaining 17 patients had complete ventricular pre-excitation throughout the exercise test.

**Association with symptomatic improvement during DDD pacing.** The baseline clinical and catheterization variables were examined to determine if any were associated with clinical subjective improvement during DDD pacing. Younger age was associated with a higher perceived functional capacity during DDD pacing ( $r = -0.46$ ,  $p = 0.045$ ). The mean baseline left ventricular outflow gradient was higher in the patients who had symptomatic improvement than in those who did not ( $107 \pm 52$  vs.  $51 \pm 36$  mm Hg;  $p = 0.02$ ). There was no significant association between symptomatic improvement and gender, left atrial pressure or drop in gradient during temporary pacing.

## Discussion

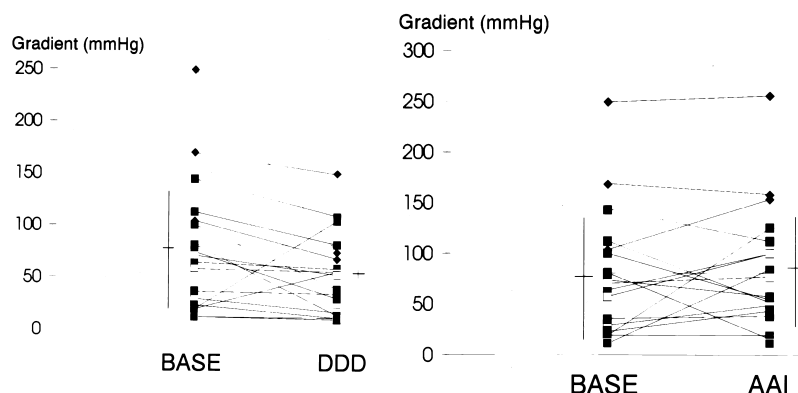
The demonstration that implantation of a dual-chamber pacemaker relieves symptoms and reduces left ventricular outflow tract gradient in patients with severe symptomatic hypertrophic cardiomyopathy has been met with great enthusiasm (1–3). However, the experience to date with dual-chamber pacing has been limited to cohort trials from single institutions. Before widespread application of a therapeutic modality can be recommended, the true effect of the therapy must be documented prospectively in a comparison with conventional therapy without the influence of possibly confounding factors (17).

**Effect of dual-chamber pacing on symptoms.** In the study herein, the short-term effect of dual-chamber pacing was evaluated in a blind, randomized manner. The reason for the backup AAI mode was to account for any “placebo” effect that may occur whenever a treatment is instituted (18–20). Al-

though 63% of the patients had symptomatic improvement in the DDD pacing mode, it is interesting that 42% of the patients also reported symptomatic improvement when the pacemaker was effectively off. The administration of any treatment has both physiologic and psychological effects on the patient, and these are interrelated (18–20). These placebo effects can be potent, and because they act synergistically with active treatment effects to influence patient outcome, they may erroneously lead to improper interpretations of the results of a treatment. For example, the Minnesota quality-of-life score was statistically better after DDD pacing than during the baseline state. After the permanent pacemaker had been placed, however, there was no statistically significant difference in the quality-of-life score between the DDD mode and the AAI backup mode. It may be more appropriate to evaluate the true results of a technique by comparing them with those of a similar placebo rather than with the baseline data (18).

More than 30% of patients had no symptomatic improvement (and 5% had symptomatic deterioration) during this short follow-up period. This percentage is higher than any reported in other studies, in which more than 90% of patients experienced symptomatic improvement (1,2). Several differences in study design may contribute to this difference. One is that administration of all medications was continued in the current study after implantation of the permanent pacemaker. The reason for continuing the medication was to determine the *additive* effect of pacemaker therapy over conventional medical therapy rather than to evaluate the isolated effect of pacing the right ventricle. In patients with a dynamic outflow tract gradient, any therapy to reduce the degree of obstruction may be less effective if negative inotropic agents are present. It is also possible that discontinuation alone of medications associated with a high incidence of side effects may result in subjective symptomatic improvement. The length of follow-up was short in the current study, so that any long-term consequences, such as remodeling effects on the left ventricle, were not taken into consideration. Thus, the results of this study need to be compared with those of the initial short-term follow-up studies (2) and should not be extrapolated for comparison with results of the recently published longer term follow-up studies (1,3).

**Figure 4.** Doppler-derived left ventricular outflow tract gradients in 19 patients. **Left,** Baseline (BASE) and continuous DDD pacing are compared. There is a significant decrease in the gradient during DDD pacing ( $p < 0.05$ ). **Right,** Baseline and backup AAI pacing are compared. There is no significant difference between the two periods.



In the initial short-term follow-up of 1.5 to 3 months, symptomatic improvement was present in 95% of patients after pacemaker implantation (2).

**Effect of dual-chamber pacing on exercise testing and gradient.** The objective measurements of exercise tolerance were of interest. There was a statistically significant increase in exercise duration during the DDD mode over that in the baseline state. As with the quality-of-life score, however, exercise duration in the DDD mode was no greater than that in the backup AAI mode. This finding raises the possibility of a "training" effect of repetitive treadmill tests, which must be taken into consideration when the results of therapy on exercise duration are evaluated. No statistically different change in maximal oxygen consumption was achieved during either DDD pacing or the backup AAI mode in comparison with the baseline value.

The left ventricular outflow tract gradient definitely decreased in the DDD pacing arm compared with the results in either the baseline or the AAI backup arm, supporting the findings of previous studies. The gradient may continue to decrease with time if a remodeling effect occurs (1). However, the left ventricular outflow tract gradient is known to be highly variable and dynamic and perhaps should not be used as a single, solid end point of therapy in patients with hypertrophic obstructive cardiomyopathy (4,13). This characteristic is reflected in the wide variation in the measured gradient from the baseline state to the backup AAI mode, with differences >100 mm Hg without intervention.

The residual gradient in most patients was still substantial with dual-chamber pacing. In addition, factors other than just the outflow tract gradient need to be evaluated to determine the efficacy of pacing on the pathophysiologic mechanisms in patients with hypertrophic obstructive cardiomyopathy. A complex interplay of many other interrelated processes, including diastolic dysfunction, mitral regurgitation and arrhythmias, contributes to symptoms in these patients (4,13,21). The effect of long-term dual-chamber pacing on these other processes in patients with hypertrophic cardiomyopathy remains to be elucidated.

**Study limitations.** The number of patients in the study was small, and larger numbers may be required to show statistically significant differences. As in any crossover trial, a carryover effect may be present in patients randomized to the placebo arm after the true intervention arm. Fananapazir et al. (1,2) showed that the left ventricular outflow tract gradient continues to decrease even after the pacemaker has temporarily been turned off, suggesting a remodeling process of the left ventricle. This carryover effect cannot be ruled out in this study as the reason for the mild trend toward improvement in the entire group during the AAI backup mode. However, 11 of the 19 patients were randomized to the AAI mode first, and the results from these 11 patients were no different from those in the remaining 8 patients who were randomized to a DDD pacing mode during the initial arm of the study.

Caution must be applied when examining the associations

of baseline characteristics with symptomatic improvement. The number of patients was small, and type 1 statistical errors could be present. The relations shown were poor and may not be clinically useful unless these associations can also be shown in multicenter studies of a larger number of patients.

The relatively short duration (2 to 3 months) in the DDD mode may not have allowed sufficient time for significant improvement in maximal oxygen consumption because of increased physical activity secondary to improved symptomatic status. The short duration of follow-up may not have allowed for the full hemodynamic effect of DDD pacing to occur, as there may be a remodeling process with time (1). Further symptomatic and hemodynamic improvement has been shown with continued pacing for over 2 years compared with the initial results of pacing for 1.5 to 3 months (1).

**Clinical implications.** The results of this study should not be interpreted as indicating that dual-chamber pacing is not beneficial in patients with severely symptomatic hypertrophic obstructive cardiomyopathy. A number of patients in this study achieved both symptomatic and hemodynamic improvement from dual-chamber pacing. A statistically significant improvement in exercise duration, quality-of-life score and left ventricular outflow tract gradient was achieved during dual-chamber pacing compared with baseline values. Also, further improvement in both symptoms and hemodynamic data may occur with time, because a late remodeling effect of pacing the right ventricle can result (1). The placebo effect alone is time-limited and would not account for the long-term improvement shown in previous studies.

For advocates of routine implantation of permanent pacemakers in all patients with symptomatic hypertrophic cardiomyopathy, however, this study should provide some reservation. A subset of patients will not have a beneficial response to this therapy, and patients must be made aware of this potential outcome. In addition, at selected institutions surgical myectomy can now be performed at low risk with a high rate of success in abolishing gradient and improving symptoms (22-27). The excellent long-term outcome after surgical myectomy has been documented (28). Thus, surgical intervention should still be considered a therapeutic option in selected patients.

Many questions have not been answered by this small, preliminary, single-center study (17). More patients need to be studied in this manner to attempt to determine predictors of whether improvement will occur with dual-chamber pacing. Longer follow-up is also required to see the extent of further improvement from the proposed remodeling process of long-term dual-chamber pacing as well as any potential detrimental effects. Several multicenter randomized trials that may answer these questions are in progress. Until the results of these trials become available, however, physicians should be aware of the limitations of routine implantation of permanent pacemakers and the role the placebo effect may play, as well as be cognizant of other options available for patients with severely symptomatic hypertrophic obstructive cardiomyopathy.

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