Assessment of Permanent Dual-Chamber Pacing as a Treatment for Drug-Refractory Symptomatic Patients With Obstructive Hypertrophic Cardiomyopathy
A Randomized, Double-Blind, Crossover Study (M-PATHY)

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Background—Dual-chamber pacing (DDD) has been proposed as a treatment alternative to surgery for severely symptomatic patients with obstructive hypertrophic cardiomyopathy (HCM), based largely on uncontrolled studies.

Methods and Results—This prospective, multicenter trial assessed pacing in 48 symptomatic HCM patients with $\geq 50$ mm Hg basal gradient, refractory to drug therapy. Patients were randomized to 3 months each of DDD pacing and pacing backup (AAI-30) in a double-blind, crossover study design, followed by an uncontrolled and unblinded 6-month pacing trial. With randomization, no significant differences were evident between pacing and no pacing for subjective or objective measures of symptoms or exercise capacity, including NYHA functional class, quality of life score, treadmill exercise time or peak oxygen consumption. After 6 additional months of unblinded pacing, functional class and quality of life score were improved compared with baseline ($P<0.01$), but peak oxygen consumption was unchanged. Outflow gradient decreased 40%, $82 \pm 32$ mm Hg to $48 \pm 32$ mm Hg ($P<0.001$), and was reduced in 57% of patients but showed no change or an increase in 43%. At 12 months, 6 individual patients (12%) showed improved functional capacity; each was 65 to 75 years of age. Left ventricular wall thicknesses in the overall study group showed no remodeling between baseline ($22 \pm 5$ mm) and 12 months ($21 \pm 5$ mm; $P=\text{NS}$).

Conclusions—(1) Pacing cannot be regarded as a primary treatment for obstructive HCM; (2) with randomization, perceived symptomatic improvement was most consistent with a substantial placebo effect; (3) longer, uncontrolled pacing periods were associated with some subjective benefit but unaccompanied by objective improvement in cardiovascular performance and should be interpreted cautiously; (4) modest reduction in outflow gradient was achieved in most patients; and (5) a small subset (12%) $\geq 65$ years of age showed a clinical response, suggesting that DDD pacing could be a therapeutic option for some elderly patients. (Circulation. 1999;99:2927-2933.)

Key Words: cardiomyopathy ■ pacing ■ surgery ■ hypertrophic cardiomyopathy ■ placebo

Severely symptomatic patients refractory to drug therapy with marked obstruction to left ventricular (LV) outflow constitute a small but important subset of patients with hypertrophic cardiomyopathy (HCM). For almost 40 years, the ventricular septal myotomy-myectomy operation has been the standard therapeutic option for these patients and has provided substantial symptomatic benefit with relief of outflow obstruction associated with low operative mortality. However, there are relatively few surgical centers sufficiently experienced with these operative techniques and as a result, many patients may not have ready access to this treatment option. In addition, some patients, such as the elderly, may not be ideal operative candidates. Consequently, the search for therapeutic alternatives to surgery is justified.

Permanent dual-chamber (DDD) pacing has been proposed as an adjunct treatment to reduce symptoms in markedly symptomatic patients with obstructive HCM. Whereas several early observational and uncontrolled studies have suggested that atrial-synchronous ventricular pacing may importantly reduce outflow gradient and symptoms, other more recent investigations have yielded less uniform and more mixed results, including some skepticism. The present randomized controlled trial was undertaken to resolve the uncertainties surrounding the utility and efficacy of DDD pacing in patients with obstructive HCM.
Methods

Patient Selection and Entry Criteria
Over a 21-month period (January 1995 to September 1996), 48 patients with obstructive HCM were enrolled into M-PATHY (Multicenter Study of Pacing Therapy for Hypertrophic Cardiomyopathy) from 14 centers in the United States, Canada, and United Kingdom. Ages ranged from 22 to 83 years (mean 53 ± 17); 26 (54%) were female. Each study patient fulfilled the following entry criteria:

1. Unequivocal diagnosis of HCM, on the basis of 2-dimensional echocardiographic demonstration of a hypertrophied (wall thickness ≥15 mm) and nondilated LV in the absence of another cardiac or systemic disease capable of producing the magnitude of hypertrophy present; 21% 9 patients had mild associated systemic hypertension, and 6 had documented coronary artery disease.

2. Presence of severe refractory symptoms, as evidenced by moderate-to-severe functional disability resulting from exertional dyspnea or chest pain sufficient to support a desire for alternative treatment modalities, following administration (in standard dosages) of both a β-blocker and verapamil independently.2,21 Thirty-seven (77%) patients were in NYHA functional class III/IV and 11 (23%) were in advanced class II.

3. Peak instantaneous LV outflow tract gradient ≥50 mm Hg under basal conditions, estimated by continuous wave Doppler.22

Entry exclusions included chronic atrial fibrillation (AF), left bundle branch block, end-stage phase of HCM, prior septal myotomy-myectomy operation,1,9 systemic disease that would preclude completion of the protocol, and contraindications to (or established indications for) permanent pacing. The study was approved by institutional review boards of each participating institution, and informed consent was obtained from all participants.

Study Design
Cardiac catheterization and temporary pacing were performed to select the most appropriate atrioventricular (A-V) delay for long-term pacing (see below). Thereafter, each patient had implantation of a commercially available Medtronic Elite II or Thera DDD pacemaker. The right ventricular pacing lead was positioned in the apex in a standard fashion under fluoroscopic guidance.24 Rate response was programmed off in order to study the consequences of pacing without the confounding effects of correcting relative bradycardia.

The first 6 months of the study protocol used a randomized, crossover, double-blind design. Study patients were randomized to either 3 months of DDD pacing or pacing backup mode (AAI at 30bpm) and then crossed over to the alternative mode for the subsequent 3-month period. After 6 months, all patients were offered 6 additional months of pacing which was performed in an uncontrolled and unblinded fashion. Therefore, patients completing the 12-month protocol experienced 9 months of pacing (Figure 1). Clinical evaluation was performed at 4 intervals: baseline, after 3 months of either DDD pacing or AAI-30 mode, at 6 months after the alternative mode, and at 12 months after 6 additional months of pacing. This evaluation consisted of history, physical examination, patient-generated quality of life (QoL) questionnaire,23 noninvasive testing with 2-dimensional echocardiography and Doppler, treadmill exercise test with measurement of peak oxygen consumption VO₂, and 12-lead ECG. Complete ventricular capture and preexcitation was documented at the 4 interval check points and in most instances was substantiated by 24-hour ambulatory ECG (Holter).

Blinding
This randomized crossover study design was conducted in a double-blind fashion. Neither patients nor investigators at each participating center had knowledge of the pacing mode to which patients were assigned. For exercise testing, blinding of observers was performed by having one individual monitor the ECG while a physician supervised and encouraged symptom-limited maximum effort. Echocardiograms were recorded without an ECG to ensure interpreters were blinded to the pacing mode. Unavoidably, staff responsible for pacemaker programming or monitoring the ECG during exercise testing were aware of the pacing mode. Exercise tests and echocardiograms were analyzed in core labs, blinded to pacing mode and other clinical information.

Echocardiography
LV wall thickness at end-diastole was measured from the M-mode and 2-dimensional echocardiogram and with the magnitude and distribution of hypertrophy characterized in 4 segments of the LV.21 Peak instantaneous LV outflow gradient under basal conditions was measured with continuous wave Doppler, by assessing the waveform with the greatest flow-velocity conforming in shape and timing to that characteristic of obstructive HCM.22 LV filling was assessed by transmirtal flow-velocity,26 with the pulsed Doppler sample volume in the mitral orifice near the leaflet tips. Mitral regurgitation was estimated with color-flow imaging by measuring the maximal regurgitant jet area in cross-sectional planes.27

Quality of Life
The patients’ subjective perception of their QoL was measured with the Minnesota Living with Heart Failure Questionnaire,22 designed to evaluate impact of heart failure symptoms on daily activities. The questionnaire consists of 21 questions and has been validated for reliability and reproducibility.25

Exercise Testing
Cardiopulmonary exercise testing was performed using the Chronotropic Assessment Exercise Protocol28 with simultaneous and continuous measurement of oxygen consumption.

Cardiac Catheterization and Temporary Pacing
Peak systolic LV outflow gradient was recorded by simultaneous measurement of LV and femoral artery pressures with pacing leads in the right atrial appendage and right ventricular apex.24 Optimal sensed A-V delay was selected as the longest interval which captured the ventricle and induced greatest reduction in outflow gradient without compromising hemodynamics (ie, decreasing blood pressure ≥30 mm Hg), after testing a range of A-V intervals. Once the most appropriate A-V interval was established, subsequent arbitrary ma-
Manipulation was discouraged. Programmed A-V delay for the study group was 85 ± 35 ms.

**Drug Therapy**

At entry into the study, patients remained on their cardioactive medications: beta-blockers (65%), calcium channel blockers (principally verapamil) (46%), disopyramide (23%), and diuretic agents (27%), alone or in combination. During the second 6 months of the protocol, reduction or withdrawal of cardioactive drugs was permitted to evaluate the pure effects of pacing; at 12 months, only 3 study patients were no longer taking drugs.

**Statistical Analyses**

ANOVA for a 2-period crossover design was used to compare pacing to no pacing for several clinical parameters in the randomized portion of the study. Twelve-month results were compared with baseline using paired t tests.

Linear regression analysis and χ² tests were applied, where appropriate, to test relationships between variables and differences between subgroups. All P ≤ 0.05 were regarded as statistically significant. The study was designed to have ≥80% power to detect clinically significant differences in the primary end-points.

**Results**

**Protocol Outcome**

Of the 48 patients originally enrolled in this study, 4 did not participate in the crossover study phase (2 because of noncompliance, one who became pacemaker dependent, and one who refused to crossover to AAI mode from DDD at 3 months and elected ventricular septal myotomy-myectomy); the remaining 44 patients constitute the study group (Figure 2). Twelve of these 44 patients failed to conform to the complete protocol design: (1) 8 elected, in concert with and/or at the discretion of their cardiologist, for early and unscheduled crossover from AAI to DDD pacing mode, on the basis of a perception of increased symptoms; (2) one elected to leave the study after randomization to have surgical treatment; (3) one refused further DDD pacing at 6 months and remained in AAI; (4) one reprogrammed from DDD to AAI at 9 months because of AF; and (5) one, age 67, died suddenly 8 months and 2 weeks into the protocol (2 weeks after cardioversion for new onset AF; Figure 2).

**Symptoms and Functional Capacity**

**Randomized Phase**

No significant differences were evident with regard to NYHA functional class, QoL score, treadmill exercise time, or peak \( \dot{V} \)O₂ after 3 months of DDD pacing and AAI-30 (no pacing) in the randomized arm, and at 12 months following 6 additional months of pacing in the uncontrolled arm. Top, NYHA functional class (FC). Bottom, quality of life (QoL) score. Lower scores indicate less symptoms. Each bar for the randomized study arm represents combined data from all patients regardless of the treatment order for DDD pacing and no pacing.

**Uncontrolled Phase**

NYHA functional class and QoL scores at 12 months were significantly improved compared with baseline but did not differ from the shorter 3-month period of pacing in the randomized arm (Figures 3 and 4). These comparisons were no different if patients were in the DDD or the AAI modes during the initial 3 month period.

**Figure 2.** Flow chart describing evolution of the study showing deviations from the protocol such as unscheduled crossovers, withdrawals, and death. VS M-M indicates ventricular septal myotomy-myectomy, * defined as participating in at least a portion of both DDD and AAI modes during randomization. † Seven patients began the study in (and completed 3 months of) pacing but during the subsequent AAI mode were programmed back to DDD. One other patient began the study in the AAI mode but was reprogrammed to DDD pacing after only 2 months.

**Figure 3.** Two subjective clinical measures of functional capacity at 4 intervals during the study protocol: baseline, after 3 months each of DDD pacing and AAI-30 (no pacing) in the randomized arm, and at 12 months following 6 additional months of pacing in the uncontrolled arm. Top, NYHA functional class (FC). Bottom, quality of life (QoL) score. Lower scores indicate less symptoms. Each bar for the randomized study arm represents combined data from all patients regardless of the treatment order for DDD pacing and no pacing.
On the basis of blinded echocardiographic measurements, maximum LV wall thickness (usually anterior ventricular septum) did not differ significantly between baseline (22.5 ± 0.5 mm), AAI (23.7 ± 4 mm), 3 months of DDD pacing (21.4 ± 4 mm), and after 6 additional months of pacing (21.7 ± 5 mm) (Figure 6). No individual patient showed change in wall thickness ≥3 mm at 12 months.

LV Wall Thickness

On the basis of blinded echocardiographic measurements, maximum LV wall thickness (usually anterior ventricular septum) did not differ significantly between baseline (22.5 ± 0.5 mm), AAI (23.7 ± 4 mm), 3 months of DDD pacing (21.4 ± 4 mm), and after 6 additional months of pacing (21.7 ± 5 mm) (Figure 6). No individual patient showed change in wall thickness ≥3 mm at 12 months.

LV Diastolic and Systolic Function Parameters

There were no identifiable differences in peak passive filling flow-velocity (E) and peak flow-velocity associated with atrial contraction (A), between the pacing and nonpacing modes. E to A ratios were: baseline (1.2 ± 0.6), after AAI (1.2 ± 0.7), after randomized pacing (1.2 ± 0.6), and at 12 months (1.1 ± 0.5). Percent fractional shortening, end-diastolic dimension, and mitral regurgitation jet area did not differ at 12 months (46 ± 9%, 45 ± 6 mm, and 6.9 cm², respectively) compared with baseline (43 ± 10%, 44 ± 7 mm, and 6.3 cm²).

Sensed A-V Delay

Programmed sensed A-V interval showed no correlation with the change in outflow gradient between baseline and 12 months (r = −0.08; P = NS); similarly, no relation was evident between duration of A-V delay and peak VO₂ (r = 0.004; P = NS).

Individual Patient Analysis

A retrospectively established definition was used to identify individual patients who may have benefited clinically from pacemaker treatment. Six patients (12% of the 48) showed some clinical response by virtue of a subjectively perceived improvement of one NYHA functional class (from III to II or I), as well as a ≥10 point increase in QoL score, and ≥10% increase in treadmill exercise time and peak VO₂; none of these patients had crossed over early from AAI to DDD (Figure 2). Drug therapy had been discontinued over the last 6 months of the study in 2 of the responders.

The 6 responders were 69 ± 4 years of age (range, 65 to 75), compared with 51 ± 16 years for other patients who completed the study at 12 months (P < 0.001). Of the 25 study patients <65, none were responders; of the 15 patients ≥65 years of age, 6 (40%) were responders (P = 0.001). At 12 months, in the responders, exercise time was 9.7 ± 3.4 minutes and VO₂ was 15.9 ± 1.3 mL · min⁻¹ · kg⁻¹, similar to other patients (11.0 ± 3.7 minutes and 16.9 ± 4.4 mL · min⁻¹ · kg⁻¹, respectively; P = NS); however, patients with clinical response had significantly lower peak VO₂ at entry (12.4 ± 1.7 mL · min⁻¹ · kg⁻¹) compared with others (17.1 ± 5.5 mL · min⁻¹ · kg⁻¹; P < 0.0005).

Figure 4. Two objective measures of functional capacity and cardiovascular function at 4 intervals during the protocol. Top, Treadmill exercise time. Bottom, peak oxygen consumption (VO₂).

Figure 5. Peak instantaneous left ventricular (LV) outflow gradient measured under basal conditions with continuous wave Doppler at 4 intervals during the protocol. *P < 0.001 versus AAI and baseline.

LV Outflow Tract Gradient

Peak instantaneous outflow tract gradient (resulting from mitral valve systolic anterior motion) for the 40 study patients in DDD at 12 months was 82 ± 33 mm Hg at baseline and was decreased after 3 months of pacing and at 12 months to the same degree (48 ± 32 mm Hg; P < 0.001), representing a change of 40% (Figure 5). When change in gradient was assessed at 12 months with respect to individual patients, 23 (57%) showed a decrease of ≥30 mm Hg (including 8 patients to a gradient <20 mm Hg); 17 patients (43%), however, showed no or only a small gradient decrease <30 mm Hg, or even an increase.

Percent change in outflow gradient with pacing at 12 months (compared with baseline) showed no significant relationship with the maximum change in gradient during temporary pacing (r = 0.08). Therefore, subaortic gradient change with temporary pacing was not predictive of the long-term pacing effect. Of note, no relationship was evident between change in gradient and the QoL score or peak VO₂ (r = 0.143 and −0.082, respectively; P = NS).
Five of the 6 responders showed reduction in outflow gradient of 35 to 40 mm Hg (the other decreased only 10 mm Hg). Maximum wall thicknesses were moderate (17 to 23 mm); hypertrophy involved anterior and posterior septum in 5 patients and was more diffuse in the other. Several parameters measured at baseline were not significantly different in responders and nonresponders: PR interval on ECG (163±23 versus 183±38 ms), LV end-diastolic dimension (47±3 versus 43±6 mm), and sensed A-V delay (82±13 versus 85±38 ms).

Adverse Events
Seventeen patients (35%) experienced 22 clinically adverse events. Eight were pocket site infections, generator migration, lead dislodgement, fracture or malfunction, or pacemaker dependence. The other 14 events included sudden cardiac death (n=1), AF (n=3), syncope or progressive heart failure (n=9), and myocardial infarction (n=1); only 6 adverse events occurred during pacing. Annual mortality for the study group was 2.3%.

Discussion
The fundamental utility of any new treatment modality for severely symptomatic patients with HCM rests with its demonstrable effect on the primary end-points of disabling symptoms (exertional dyspnea and chest pain) and exercise capacity.1–3 Several earlier studies, largely observational and uncontrolled in design, have reported subjective improvement in functional capacity with short-term pacing but have offered little or no substantiation by objective measures of exercise testing such as exercise time or peak VO₂.12–14 We believe that exercise testing data are critical to assessing symptomatic and functional capacity. It is possible that some of these early departures to favorable clinical effects of pacing because the unscheduled AAI to DDD crossovers were not accompanied by improvement in other subjective or objective measures of functional capacity. Therefore, there was no evidence that the longer periods of pacing assessed at 12 months produced any subjective symptomatic benefit beyond that reported after 3 months of pacing in the randomized arm. Of note, 8 patients chose to make unscheduled crossovers from nonpacing mode back to DDD pacing (after 3 prior months of pacing in 7), usually resulting from a perception of worsening symptoms. However, it was not possible to attribute these protocol departures to favorable clinical effects of pacing because the unscheduled AAI to DDD crossovers were not accompanied by improvement in other subjective or objective measures of functional capacity. The other 14 patients were assessed individually to determine whether a subset showing a symptomatic response to pacing could be identified. This required establishing, retrospectively, a demanding arbitrary definition of clinical improvement in several testing modalities. With this approach, 6 of our patients (about 10%) were identified as having subjectively and objectively measured symptomatic and functional benefit that was probably attributable to the pacing intervention.

Of note, each of these 6 patients was ≥65 years old and as a group were older than the other study patients without evidence of clinical response. Therefore, DDD pacing could represent a therapeutic option for some elderly HCM patients, particularly those who reject (or are not optimal candidates for) operation, or do not have access to experienced surgical treatment for this disease. Indeed, it is perhaps not unexpected that in a disease as diverse as HCM,1–3,10,21,23 an intervention such as DDD pacing would produce a highly variable clinical response.

Initial studies with permanent DDD pacing in obstructive HCM have emphasized the sometimes impressive reduction in the dynamic LV outflow gradient, although there is considerable variability in the magnitude and consistency of this response.11–14,16 In the present study, basal outflow gradient at 12 months (after 9 months of pacing) showed a modest but significant decrease of ≈40% from baseline;
nevertheless, the basal gradient remained within the operative range for the study group (ie, ≈50 mm Hg).1–9 This reduction in outflow gradient with DDD pacing exceeded that previously reported in another double-blind randomized study (ie, 25%),10,11 but was less than that in other studies (ie, 43% to 72%).11–14

The gradient response to pacing in the present investigation was also variable and unpredictable among individual patients. Furthermore, the partial gradient reduction we observed with pacing is more modest than occurs with surgery (myotomy-myectomy or mitral valve replacement) in which obstruction at rest is usually abolished or substantially reduced (to <20 mm Hg) and normal intraventricular pressures are restored.1–9 Finally, we found no correlation between reduction in outflow gradient and symptom relief or exercise performance.13

We could not confirm prior claims that long-term pacing in HCM produces LV remodeling with wall thinning.14 Our echocardiographic measurements of LV wall thickness (which were made without knowledge of pacing modality) showed no differences throughout the study period and no convincing examples of wall thinning in any patient. This observation is reassuring because the only model of wall thickness regression documented in HCM is the unfavorable end-stage phase23 for which heart transplantation is the only effective therapeutic option.1,3,23

Defining the precise mechanism by which pacing may decrease gradient (or improve symptoms in some patients) is beyond the scope of this study. However, other investigators have suggested pacing may influence myocardial perfusion10 and asynchronous ventricular septal activation,12,13,16 produce paradoxical septal motion12,14 or a negative inotropic effect,31 decrease mitral valve systolic anterior motion,12,14 or increase end-systolic volume.31

We conclude on the basis on this randomized controlled study that DDD pacing cannot be regarded as a primary treatment option for severely symptomatic, drug-refractory patients with obstructive HCM. Current standard treatment dictates1–3 that this small but important subgroup of patients should first be considered candidates for the myotomy-myectomy operation. Nevertheless, expert surgery for this disease is not always readily available, and some patients may not be satisfactory operative candidates,1,7 particularly those of advanced age.10 In these instances, surgical alternatives such as DDD pacing (or possibly alcohol septal ablation) can be considered. We also wish to leave open the option of pacing selected patients on a trial basis before surgery to judge individual responses to this intervention (such as those of elderly patients).

Appendix

Participating Centers and Investigators
University of Alabama at Birmingham Medical Center (Drs Neal Kay and Andrew Epstein); Minneapolis Heart Institute, Minn (Dr Adrian Almquist, Susan Casey, RN, and Dr Barry Maron); Cleveland Clinic Foundation, Ohio (Drs Harry Lever and Bruce Wilcoff); St. George’s Hospital Medical School, London, UK (Drs William McKenna and Allister Slade); Texas Heart Institute, Houston (Dr Zvonimir Krajer); Toronto Hospital, Toronto, Canada (Drs Harry Rakowski and E. Douglas Wigle); The Mayo Clinic, Rochester, Minn (Drs Rick Nishimura, John Symanski, Margaret Lloyd and Jamil Tajik); Veterans Administration Medical Center, Dallas, Tex (Dr Paul Grayburn); Beth Israel Hospital, Boston, Mass (Drs Mark Josephson and Beverly Loret); Bowman-Gray School of Medicine, Winston-Salem, NC (Dr George Crossley); Medical College of Virginia, Richmond (Dr David Gilligan); Genesis Medical Center, Davenport, Iowa (Dr Michael Giudici); Montefiore Medical Center, Bronx, NY (Dr Jay Gross); University of Pittsburgh School of Medicine, Pa (Dr James Shaver).

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