Comparison of Dual-Chamber Pacing Versus Septal Myectomy for the Treatment of Patients With Hypertrophic Obstructive Cardiomyopathy

A Comparison of Objective Hemodynamic and Exercise End Points

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OBJECTIVES

The purpose of this study was to compare the treatment effects of septal myectomy with dual-chamber pacing in patients with hypertrophic obstructive cardiomyopathy (HOCM).

BACKGROUND

The optimal treatment for symptomatic patients with drug-refractory HOCM is unknown. Both dual-chamber pacing and surgical myectomy may result in subjective symptom improvement. However, no direct comparisons with objective end points have been reported.

METHODS

Thirty-nine patients with symptomatic HOCM were analyzed in this concurrent cohort study. Twenty patients underwent surgical myectomy, and 19 received dual-chamber pacemakers based on patient preference. These patients had prospective baseline and follow-up evaluations including physician assessment, echocardiography and standardized metabolic treadmill exercise testing.

RESULTS

Baseline symptom status, left ventricular outflow tract gradients, exercise times and maximal oxygen consumption peak were similar between the two groups. Left ventricular outflow gradient was reduced from $76 \pm 57$ to $9 \pm 17$ mm Hg ($p = 0.0001$) after myectomy, and from $77 \pm 61$ to $55 \pm 39$ mm Hg ($p = 0.07$) after pacing ($p = 0.02$ for comparison with myectomy). Ninety percent of myectomy patients experienced symptomatic improvement as compared with 47% in the pacing group. Exercise duration increased significantly from $6.6 \pm 2.8$ to $8.7 \pm 3.0$ min ($p = 0.0003$) after myectomy compared with a change from $6.4 \pm 2.1$ to $7.0 \pm 2.2$ min ($p = \text{NS}$) in the pacing group. Maximal oxygen consumption increased from $19.4 \pm 6.4$ to $22.2 \pm 6.5$ ml/kg/min after myectomy ($p = 0.004$), whereas the pacing group did not experience any significant change ($19.6 \pm 6.5$ vs. $20.1 \pm 6.5$ ml/kg/min, $p = \text{NS}$).

CONCLUSIONS

Surgical myectomy and dual-chamber pacing improve subjective measures of functional status in patients with symptomatic HOCM. In this nonrandomized study, myectomy offered greater reduction in left ventricular outflow tract gradients and larger improvements in objective measures of patient symptoms and functional status when compared with dual-chamber pacing. (J Am Coll Cardiol 1999;34:191–6) © 1999 by the American College of Cardiology

The treatment of patients with hypertrophic obstructive cardiomyopathy (HOCM) refractory to medical therapy is controversial. Surgical myectomy, when performed in experienced centers, has been shown to be safe and efficacious in relieving the left ventricular outflow obstruction and improving symptoms (1–6). Implantation of a dual-chamber pacemaker may also provide hemodynamic and symptomatic improvement in selected patients (7–10). Although implantation of a dual-chamber pacing device is less invasive than septal myectomy, it has been suggested that its results may not be as beneficial as initially proposed (10–12).

The clinical decision regarding the optimal therapy of this subset of patients should be based on multiple factors including age, lifestyle and risk of surgery. Knowledge of the outcome of these two treatment modalities is required, including objective measures of functional status. The purpose of this nonrandomized cohort study is to directly compare the subjective and objective outcomes of these two treatment modalities, performed at a single center, in patients with symptomatic HOCM.
Abbreviations and Acronyms
HOCM = hypertrophic obstructive cardiomyopathy
NYHA = New York Heart Association
VO2 peak = maximal oxygen consumption

METHODS

Patients. This study is part of an ongoing, prospective analysis of patients presenting to the Hypertrophic Cardiomyopathy Clinic at our institution. The patients in this report were seen by one of two investigators (R.A.N., A.J.T.) between May 1993 and August 1997. The diagnosis of HOCM in all patients was established by the standard two-dimensional echocardiographic feature of hypertrophy of the myocardium in the absence of identifiable etiology. All patients had disproportionate septal hypertrophy, either diffusely or localized to the basal septum. During systole, there was projection of the septum into the left ventricular outflow tract with systolic anterior motion of the mitral valve in all patients. Patients with concomitant midventricular obstruction, anomalous insertion of the papillary muscle or localized apical hypertrophy were excluded from this report. The maximum left ventricular outflow tract gradient was determined using standard Doppler echocardiography. Patients who were considered candidates for therapeutic modalities to decrease dynamic left ventricular outflow obstruction were those with 1) a resting left ventricular outflow tract gradient of >50 mm Hg or 2) a provoked gradient of >50 mm Hg for those patients with resting gradients 30 to 50 mm Hg (13–15). The subset of patients in this study consisted of those with left ventricular outflow obstruction who were severely symptomatic despite optimal medical therapy with beta-adrenergic antagonists, calcium channel inhibitors, or both. The decision to proceed with septal myectomy or dual-chamber pacing was based on patient decision after outlining the benefits and risks of each therapeutic modality. The surgical group represents a subset of the 89 isolated surgical myectomies (i.e., no bypass grafts or concomitant valvular surgery) performed between May 1993 and August 1997. Only these 20 patients had the appropriate preoperative and postoperative exercise testing and are included in this report. The pacing group consisted of 19 patients referred between November 1993 and January 1995. The results of a randomized crossover trial of pacing mode were included in a previous report (10). Patients were excluded if there was concomitant cardiac disease such as primary valvular pathology or coronary artery disease.

Initial evaluation. All patients were interviewed and examined by an experienced cardiologist. Symptomatology was assessed by the New York Heart Association (NYHA) classification. After the initial examination, comprehensive two-dimensional and Doppler echocardiography was performed to assess ventricular morphology, dynamic left ventricular outflow obstruction (peak instantaneous gradient), systolic anterior motion of the mitral apparatus and severity of mitral regurgitation.

Exercise testing. The symptom-limited maximal treadmill exercise test was performed according to a standard Mayo protocol with simultaneous respiratory gas analysis. The exercise protocol consists of an initial stage of 2.5 metabolic equivalents for the first 2 min with increases by 2 metabolic equivalents every 2 min. Expired gas analysis was performed using a Medical Graphics CPX cart. The maximal exercise oxygen consumption (VO2 peak) was defined as the highest 16-breath average during the test. Standard age, gender and activity level algorithms were used to predict VO2 peak for each patient. These are expressed as % predicted = 100 × (observed value/predicted value).

Surgery. Standard cardiopulmonary bypass and myocardial preservation techniques were used. After aortotomy, excision of the septum was initiated with two parallel longitudinal incisions: one beneath the nadir of the right aortic cusp and the second beneath the commissure separating the right and left cusps. The incisions were joined superiorly and a mass of muscle was excised to the level of the papillary muscles. Additional myocardium was removed between the initial excision and the lateral attachment of the anterior mitral leaflet. The left ventricular outflow tract was inspected and palpated for completeness of the resection, before the closure of the aortotomy.

Pacing protocol. All patients underwent hemodynamic catheterization to assess the immediate response to dual-chamber pacing. This protocol has been previously described (10). In brief, catheterization of the aorta, left ventricle (via transseptal technique) and right heart chambers was performed simultaneously with Doppler echocardiography. The optimal atrioventricular interval was defined as that producing the lowest left ventricular outflow tract gradient without compromise of aortic or left atrial pressures (8,9). By protocol, the tested intervals were 60, 100, 140, 180, 200 and 240 ms. Patients then underwent placement of dual-chambered permanent pacemakers.

Follow-up. All patients in this study returned to the Hypertrophic Cardiomyopathy Clinic for follow-up including repeat clinical evaluation, echocardiography and metabolic treadmill testing. The mean length of follow-up after myectomy was 415 days. For patients who underwent the pacing protocol, patients were prospectively studied after 2 to 3 months of continuous dual-chamber pacing.

Statistics. Data are expressed as mean ± SD. Repeated measures analysis of variance was used to test for differences in continuous variables between the two treatment groups. New York Heart Association functional classification was analyzed as a continuous variable as above and as an ordinal variable using the Wilcoxon rank-sum test. Multivariate linear regression was used to assess variable independence.
with respect to change in exercise variables. Significance was defined as p < 0.05.

RESULTS

Baseline characteristics. There were 20 patients in the surgical group (14 men, six women) with a mean age of 42 ± 14 years. At the time of the procedure, medications included beta-adrenergic blocking agents in 16, calcium channel blocking agents in 9, disopyramide in 4 and amiodarone in 3 patients. Seven patients were on two or more of the above agents. Chronic atrial fibrillation was present in one patient; two others had intermittent atrial fibrillation. Five patients in the myectomy group had undergone prior permanent pacemaker implantation for the treatment of HOCM, but continued to have significant symptoms and a residual gradient despite the pacemaker. None of these five patients had experienced subjective sustained improvement after the pacemaker implantation.

There were 19 patients in the pacing group (10 men, 9 women) with a mean age of 59 ± 13 years (p = 0.0002 for the difference in age between the groups). The medication distributions and dosages were similar. One patient in the pacing group had undergone myectomy 5 years earlier and had redeveloped symptoms 1 year before presentation.

Baseline assessment. All patients had significant functional limitations in their daily activity. In the surgical group, there were 5 patients in class II, 14 in class III and 1 in class IV. This is similar to the distribution in the pacing group (class II = 2, class III = 16, class IV = 1; Table 1, Fig. 1).

Baseline left ventricular outflow gradient (76 ± 57 vs. 77 ± 61 mm Hg, p = NS), exercise times (6.6 ± 2.8 vs. 6.4 ± 2.1 min, p = NS), % predicted exercise times (54 ± 19 vs. 56 ± 24%, p = NS) and VO2 peak (19.4 ± 6.5 vs. 19.6 ± 6.5 ml/kg/min, p = NS) were similar between the surgical and pacing groups, respectively.

Posttreatment assessment. There were no deaths in either group during the follow-up period. Left ventricular outflow gradient was reduced from 76 ± 57 mm Hg to 9 ± 17 mm Hg (p = 0.0001, comparison of pretreatment with posttreatment) in the surgical group as compared with a reduction from 77 ± 61 mm Hg to 55 ± 39 mm Hg (p = 0.07) in the pacing group (Fig. 2). The change in gradient after therapy was significantly different between the two groups (p = 0.03). Eighteen (90%) of the surgical patients had residual gradients of less than 20 mm Hg, whereas 5 (26%) of the pacing patients had posttreatment gradients of less than 20 mm Hg.

All of the myectomy patients were in functional class I–II at the time of follow-up. Nearly half (n = 9) of the pacing patients remained in class III–IV, with 10 patients experiencing no symptomatic improvement. New York Heart

Table 1. Pre- and Post-treatment Data for Patients with Drug Refractory HOCM

<table>
<thead>
<tr>
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<th>Myectomy (n = 20)</th>
<th>DDD Pacing (n = 19)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>42 ± 14</td>
<td>59 ± 13*</td>
</tr>
<tr>
<td>LVOT gradient (mm Hg)</td>
<td>76 ± 57</td>
<td>9 ± 17†</td>
</tr>
<tr>
<td>NYHA class</td>
<td>2.8 ± 0.6</td>
<td>1.3 ± 0.5†</td>
</tr>
<tr>
<td>Exercise time (min)</td>
<td>6.6 ± 2.8</td>
<td>8.7 ± 3.0†</td>
</tr>
<tr>
<td>% predicted</td>
<td>54 ± 19</td>
<td>74 ± 24†</td>
</tr>
<tr>
<td>VO2 peak (ml/kg/min)</td>
<td>19.4 ± 6.5</td>
<td>22.2 ± 6.5†</td>
</tr>
<tr>
<td>% predicted</td>
<td>52 ± 15</td>
<td>61 ± 14†</td>
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*p < 0.05 for comparison between groups.
†p < 0.05 for comparison within groups.
DDD = dual-chamber; LVOT = left ventricular outflow tract; NYHA = New York Heart Association; VO2 peak = peak oxygen consumption.

Figure 1. Change in New York Heart Association (NYHA) classification from baseline to follow-up for patients undergoing surgical septal myectomy or dual-chamber (DDD) pacing.
Association functional class improved from 2.8 ± 0.6 to 1.3 ± 0.5 (p < 0.0001) after myectomy and from 2.9 ± 0.4 to 2.4 ± 0.7 (p = 0.002) after dual-chamber pacing. The improvement in functional class after therapy was significantly better in the myectomy group (p = 0.0006). The stated p values are consistent when tested as continuous or ordinal data.

Treadmill exercise duration improved by 32% from 6.6 ± 2.8 to 8.7 ± 3.0 min (p = 0.0003) in the myectomy group compared with an improvement of 9% from 6.4 ± 2.1 to 7.0 ± 2.2 min (p = NS) in the pacing group (Fig. 3). The difference in improvement between the two treatment groups was statistically significant (p = 0.05). The postmyectomy VO2 peak increased from 19.4 ± 6.5 to 22.2 ± 6.5 ml/kg/min (p < 0.004), whereas the pacing group had an insignificant change from 19.6 ± 6.5 to 20.1 ± 6.5 ml/kg/min. Improvement in VO2 peak was greater in the surgical group compared with the pacing group (p = 0.04, Fig. 4). On the basis of predicted percentage values for VO2 peak, the myectomy patients had a more significant baseline impairment (52 ± 15% vs. 70 ± 15%, p = 0.0005), and showed more improvement posttreatment (9 ± 12% vs. 1 ± 12%, p = 0.04). There were no differences before or after treatment with respect to the peak exercise respiratory exchange ratio or ventilatory anaerobic threshold between the two groups.

Subset analysis. There were nine patients in the pacing group who experienced improvement in symptoms. In these 9 patients, the exercise time increased from 7.3 to 7.7 min and peak VO2 increased from 22.2 to 23.2 ml/kg/min. The magnitude of the increase in objective functional capacity in these 9 patients was less than observed in the myectomy group (increase in exercise time 0.9 ± 2.1 min, increase in peak VO2 1.0 ± 3.0 vs. 2.9 ± 3.9 ml/kg/min). There were only four patients in our pacing group who increased exercise time by >2 min. These patients could not be distinguished from the remainder of the pacing patients using pretreatment data.

DISCUSSION

The pathophysiology producing symptoms in HOCM is complex and includes left ventricular outflow obstruction, diastolic dysfunction, mitral regurgitation and arrhythmias (16–20). The goal of therapy has been directed against the outflow obstruction. Reduction of the left ventricular outflow obstruction may subsequently influence the diastolic filling characteristics of the left ventricle through changes in loading conditions and decreasing severity of mitral regurgitation, if the mitral regurgitation is secondary to distortion of the mitral apparatus from systolic anterior motion. Despite initial concerns regarding the efficacy of decreasing (or eliminating) the outflow obstruction by surgical means (21–23), surgical myectomy has been shown to produce excellent relief in symptomatic patients with HOCM (1–4,24–26).

Implantation of a dual-chamber pacemaker has been shown to decrease the severity of left ventricular outflow obstruction and improve symptoms (7,8). It is a less invasive
technique that is more widely available to the cardiology community. The initial enthusiasm for permanent pacing as a treatment panacea has been tempered by more modest results in recent studies (10,11).

In clinical decision making, it is necessary to have an objective comparison of the results of the two therapeutic modalities. Controlled randomized trials are the standard by which outcomes may be compared but may not be possible in uncommon diseases such as HOCM. Thus, the results of prospectively gathered data in cohort series must be made available.

Effects on left ventricular outflow gradient. In the present study, both surgical myectomy and dual-chamber pacing resulted in overall reductions in left ventricular outflow tract gradient, with a greater reduction in gradient after myectomy. This is not unexpected, because the anatomic dimensions of the outflow tract are altered by the operation. Improvements in the diastolic filling properties of the left ventricle may be best achieved by near abolishment of the outflow obstruction with consequent changes in contraction load on the left ventricle (17). This near abolishment of the gradient was achieved in 90% of patients undergoing myectomy versus only 26% of patients in the pacing group. Our results are similar to previously reported hemodynamic results (1,2,27,28).

Subjective status. A higher percentage of patients experienced subjective symptomatic improvement after myectomy as compared with pacing (90% vs. 47%). There are many limitations to the subjective NYHA classification, but it provides a semiquantitative assessment of a patient’s lifestyle. A possible “placebo effect” must always be taken into consideration in the subjective evaluation of any therapeutic modality (7,9,10). Nonetheless, symptom improvement is the goal of therapy in these patients. In this study, myectomy resulted in 100% of patients in class I–II versus 53% in the pacing group. The accuracy of the NYHA class is reflected in the postmyectomy patients: class I patients exercised 8.9 min vs. 8.1 min for the class II patients. Likewise, the VO2 peak was nearly 24 ml/kg/min in class I patients versus 19.9 ml/kg/min in class II patients.

Effects on objective exercise parameters. The comparison of the effect of treatment on the objective measures of exercise performance was interesting. Exercise duration showed more overall improvement in the surgical group as compared with the pacing group. Maximal oxygen consumption, which is a more specific indicator of cardiac performance than exercise time, and % predicted VO2 peak were measured. The surgical group experienced significantly better improvements in these measures of oxygen consumption than the pacing group. The postsurgical improvements in exercise duration and VO2 peak are similar to published results from the National Institutes of Health (1).

Two randomized crossover trials of dual-chamber pacing examined objective measures of exercise tolerance (28,29). Although the overall improvements in these objective parameters were modest, they retrospectively identified subsets of patients who achieved significant improvements in exercise time and VO2 peak. In our own pacing group there were only four patients with improvements in exercise time comparable to the surgical group. This small group of patients could not be identified on the basis of any preimplantation parameter.

Study limitations. There are multiple limitations of this nonrandomized cohort analysis of a small number of patients. This study was not “designed” as a prospective investigation but rather, was a retrospective analysis prompted by the controversies with respect to treatment modalities in these patients. This introduces the inherent deficiencies and potential bias of any retrospective analysis. Patients were assigned to treatment based on patient preference, and thus may not be comparable. There were significant differences in baseline age; the myectomy patients were younger than the pacing patients. However, the baseline symptomatic status, the baseline exercise duration and the baseline VO2 peak were similar between the two groups. There was also no difference in the severity of the left ventricular outflow tract obstruction between the pacing and surgical groups.

The two groups were not true concurrent cohorts, as the entry of patients into the pacing group ended before that of the surgical group. Patients who underwent dual-chamber pacing from 1995 to 1997 are part of a multicenter randomized trial, which has shown similar results to the initial pacing study (29).

This surgical group represents only a subset of the total myectomy population during the study period (n = 89), thus the applicability of the results to all patients undergoing surgical myectomy was not evaluated. However, many patients undergoing myectomy were not included in this study because the patients were felt to be too sick for preemptive exercise testing. Of these patients not included in this report who returned to the Hypertrophic Cardiomyopathy Clinic after surgical myectomy, 95% were NYHA class I–II. Thus, the inclusion of these patients would have strengthened the conclusions of the study.

The current data do not include the placebo effect on symptomatic improvement or the training effect on objective measures of exercise tolerance. Both of these factors may play significant roles in the analysis of the effect of intervention, as has been recently demonstrated in randomized crossover trials. The long duration of sustained improvement in the surgical group (mean follow-up 415 days) mitigates against a placebo effect. There was no difference in comparisons between the groups or comparing pretreatment and posttreatment data within groups in the respiratory exchange ratio, which measures the degree of effort or in anaerobic threshold that is subject to “training effects.” Follow-up was longer in the surgical group as compared with the pacing group. However, past studies have not
shown further symptomatic or hemodynamic improvement beyond the initial three months of dual-chamber pacing (28,30).

**Implications.** At the present time, there is not a single therapy that should be applied to all patients with severely symptomatic HOCM unresponsive to medical management. There are benefits and drawbacks to both surgical myectomy and dual-chamber pacing. Septal myectomy requires specialized tertiary referral centers and is more complex than implantation of a permanent pacemaker. However, surgical treatment of symptomatic HOCM results in greater improvements in outflow tract gradient reduction, NYHA symptom class, exercise time and VO2 peak compared with dual-chamber pacing.

There may, however, be a subset of patients who derive enough benefit from pacing to achieve a satisfactory way of life, thus avoiding or delaying the need for surgery. There are some patients who may wish to first undergo the less invasive route of pacemaker implantation, with the option of surgical myectomy later if there is no improvement. In addition, other therapeutic modalities have emerged for treatment of these patients, such as catheter-based septal ablation (31,32). Further investigation is required to be able to identify responders and compare results between the available treatments. These are the focus of ongoing randomized trials. Ultimately, the decision as to the best therapy must be individualized to each patient depending on age, anatomy, hemodynamics, way of life and risks of therapy.

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**REFERENCES**


