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Hypertrophic cardiomyopathy

Late benefits of dual-chamber pacing in obstructive hypertrophic cardiomyopathy: a 10-year follow-up study

Enrique Galve, Antonia Sambola, Germán Saldaña, Iván Quispe, Elsa Nieto, Anna Diaz, Arturo Evangelista, Jaume Candell-Riera

ABSTRACT

Objective To examine the mid-term and long-term outcomes in patients with obstructive hypertrophic cardiomyopathy (HCM) submitted to pacing.

Design Prospective, observational study.

Setting Single, non-referral centre.

Patients and intervention Fifty patients (62±11 years) with HCM refractory to medical treatment, all in New York Heart Association (NYHA) class III or IV, and with a rest gradient >50 mm Hg underwent a dual-chamber pacemaker implantation. Patients were followed-up for up to 10 years (mean 5.0±2.9, range 0.6–10.1).

Results During the first year of follow-up, rest gradients decreased (baseline 86±29 mm Hg; 3 months 55±37; 1 year 41±26; p=0.0001). NYHA class improved, as well as exercise tolerance (baseline 281±112 m; 3 months 334±106 m; 1 year 348±78 m; p<0.0001). The physical and mental components of the quality of life instrument SF-36 also improved. Left ventricular wall thickness remained unchanged, while ejection fraction decreased (baseline 76±10%; 3 months 74±8%; 1 year 66±13%; p=0.002). During the long-term follow-up, an additional reduction in obstruction was found (final rest gradient 28±24 mm Hg, p<0.02). Those patients who did not improve to NYHA class I or II and continued to have obstruction were given other treatments (six, alcohol ablation; three, surgical myectomy).

Conclusions Pacing in HCM results in a significant reduction in obstruction, improvement of symptoms and exercise capacity that is progressive and may be achieved after a long period of time. In this series, only 18% of cases needed a more aggressive treatment to relieve residual obstruction and obtain a satisfactory symptomatic status. In conclusion, these results emphasise the need for new controlled studies of pacing with a longer follow-up.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a genetic condition characterised by the presence of otherwise unexplained ventricular hypertrophy, that may be associated with left ventricular outflow tract (LVOT) obstruction. The importance of the obstruction has been a subject of debate over decades1; about 25% of patients have an LVOT resting gradient, and exercise can induce obstruction in two-thirds of those patients with apparently non-obstructive types.2 LVOT obstruction is a powerful predictor of adverse prognosis.3 Several ways can be used to treat patients with obstructive HCM who remain refractory to medical treatment. Traditionally, surgical myectomy has been the ‘gold standard’, being safe and efficacious, but has the disadvantage that good results are mostly achieved at experienced centres.4–8 Over the past decade alcohol septal ablation has been developed as an alternative to open heart surgery. This percutaneous technique produces a localised infarction of the septal myocardium by alcohol injection into the appropriate septal artery, which reduces LVOT obstruction.9,10 Dual-chamber pacing has been reported as another therapeutic option, often criticised because of poor results. However, studies with pacing have been short in duration.11–13

METHODS

From a series of 326 patients with HCM seen at our centre, we prospectively included in this study 50 consecutive subjects (62±11 years old, range 26–81) with the obstructive variant that fulfilled the following inclusion criteria: (a) unequivocal diagnosis of HCM on the basis of two-dimensional echocardiographic demonstration of a left ventricular hypertrophied wall thickness ≥15 mm, in the absence of another cardiac or systemic disease able to produce the magnitude of hypertrophy present; (b) important functional limitation (New York Heart Association (NYHA) class III or IV) despite maximal tolerated drug treatment (generally including β blockers, verapamil and/or disopyramide) and (c) a resting LVOT gradient ≥50 mm Hg. Patients with only a provocative gradient (without a gradient at rest) were not included. None of our patients had been operated on, submitted to pacemaker implantation or alcohol septal ablation before inclusion. The baseline characteristics of patients are summarised in table 1. The local institutional review committee approved the study. All patients gave their written informed consent to participate.

Pacing protocol

All patients underwent a permanent DDD or VDD pacemaker implantation. The ventricular lead was placed at the apex of the right ventricle. The optimal atrioventricular (AV) interval was defined as that obtaining a complete ventricular capture both at rest and during exercise. A Holter recording was used to check the maximal capture during daily activities. The optimal AV intervals had to be done in 11 cases (22%), always under...
Doppler control to obtain the better atrial contribution to ventricular filling. In three cases an ablation of the AV junction was necessary to obtain an adequate capture.

**Study design**

In the first 13 patients a preliminary study was performed: patients underwent temporary AV sequential pacing with different AV delays under Doppler-echocardiographic control to obtain information about the response and the best AV delay.14 This acute study was discontinued because of progressive knowledge that gradient reduction and symptomatic improvement could not be predicted by the assessment of temporary DDD pacing.15

The initial design was contemplated only at one-year follow-up with clinical and complementary examinations performed at baseline, three months and at one year. Later on, the follow-up was open and based only on clinical needs. This explains the disparity between the frequent evaluations during the first year and the long-term follow-up.

**Echocardiography**

An echocardiographic-Doppler study was performed to obtain the peak instantaneous LVOT gradient under resting conditions, and after provocative manoeuvres (Valsalva and/or nitroglycerin). Mitral regurgitation was evaluated by semiquantitative analysis based on visual assessment after integrating pulsed, continuous and colour Doppler data collected at various angles and classified in five grades: grade 0=absent; grade I=trace; grade II=mild; grade III=moderate; grade IV=severe.16 17 The left ventricular (LV) ejection fraction was obtained by the Simpson method. LV wall thickness was measured from the M mode. Cardiologists blinded to the results of the study obtained all the echocardiographic recordings.

**Walking test**

The walk test was performed in an indoor corridor 25 m long, according to the recommendations of Guyatt et al,18 and the total distance walked during 6 min was recorded.

**Quality-of-life instruments**

Patients’ subjective perception of their quality of life was evaluated by the Short Form-36 Health Survey (SF-36), a generic health-related quality-of-life questionnaire,19 that has a validated Spanish version.20

**Follow-up**

Patients were closely monitored during the first year after implantation. During this period of time all subjects were submitted three times (before implantation, at 3 months and at 1 year) to a clinical evaluation, echocardiographic study, 6-min walking test and quality-of-life tests. After the first year of follow-up, patients were visited twice a year (or more often if clinically necessary) for pacemaker and clinical evaluations only. Echocardiography was performed annually. Mean follow-up time was 5.0±2.9 years (range 0.6–10.1).

**Statistical analysis**

Descriptive analysis was performed using mean±SD and range for continuous variables, and absolute and relative frequencies for categorical variables. Analysis of variance for repeated measurements was used to compare the influence of the pacemaker for the continuous variables, and $\chi^2$ test for categorical variables. In all figures and tables $p$ values refer to all measurements throughout the follow-up time. A two-tailed value of $p<0.05$ was considered significant. Statistical analysis was performed using the statistical package SPSS 11.0.

**RESULTS**

**NYHA functional class**

All patients were by definition in class III–IV at baseline. At 3 months, 25% of patients were in class III, while 68% were in class II and 7% were in class I. No patient was in class IV. This was statistically significant with respect to baseline ($p=0.0001$). At 1 year, the situation was similar, with only a 23% of patients in class III and no patients in class IV ($p=0.0001$ with respect to baseline). At the final follow-up, all patients were in class I or II, with the exception of four patients who were in class III and one in class IV ($p=0.0001$).

**6-Minute walking test**

Figure 1 depicts the evolution of walking distance in the 6-min corridor test. The distance increased progressively from baseline to 3 months and to 1 year ($p=0.0001$). The test was not performed at the final follow-up.

**Quality of life**

Figure 2 depicts the evolution of the SF-36 quality-of-life instrument during the first year. Both the physical ($p=0.0001$) and the mental ($p=0.02$) component increased progressively from baseline to 3 months to 1 year.

**LVOT gradient evolution**

Figure 3 depicts the rest subaortic gradient evolution, evaluated by Doppler imaging. From a baseline of 36±29 mm Hg, the LVOT gradient decreased to 55±37 mm Hg at 3 months, to 41±26 mm Hg at 1 year and finally, decreased to 28±24 mm Hg at the final follow-up ($p=0.0001$). The inducible LVOT gradient decreased by a similar degree: it was 114±53 mm Hg at baseline, 53±30 mm Hg at 3 months, 68±46 mm Hg at 1 year, and 38±24 mm Hg at the final follow-up ($p=0.05$).

**Mitral regurgitation**

Figure 4 depicts the evolution of mitral regurgitation during the study. At baseline, 47% of patients had moderate or severe mitral regurgitation. As the LVOT gradient decreased, the severity of mitral regurgitation decreased similarly to 53% at 3 months, to 30% at 1 year, and to 22% at the final follow-up ($p=0.001$).
Systolic function and LV dilatation

Table 2 depicts the evolution of the echocardiographic parameters. Neither the left ventricular end-diastolic diameter nor the left atrial diameter changed during the study period. The interventricular septum, the posterior wall thickness and the LV mass did not decrease (p = NS) after the pacemaker implantation. However, the left ventricular ejection fraction decreased after pacemaker implantation (p = 0.002), although the final ejection fraction was still within the normal range (65 ± 15%). Quantitative segmental evaluation was not performed, but the visual echocardiographic analysis showed that the decrease was due to hypokinesia-paradoxical movement of the interventricular septum due to the pacemaker activation.

Mortality, need for other treatments

Patients were followed-up as described above. After the first year of follow-up, patients who did not reach NYHA class I or II, and who continued to have persistent LVOT gradients, were submitted to other types of treatment (alcohol septal ablation or surgical myectomy, depending on the anatomy). During a follow-up of 5.0 ± 2.9 years (range 0.6–10.1), six patients (12%) needed alcohol septal ablation and three patients (6%) surgical myectomy. During the same period of time, six patients (12%) died, although none of them because of the procedures. Mortality was due to heart failure (three cases, although in two of them the gradient had decreased to 22 and 31 mm Hg respectively), stroke (one case) and two disease of extracardiac origin (one case of airway aspiration in Alzheimer’s, and another of sepsis). At the final follow-up, all patients who had received only pacing treatment were in NYHA class I–II, with the exception of five patients who were in class III–IV, but who could not undergo alcohol ablation or surgery owing to the absence of residual LVOT gradients. Atrial fibrillation of new onset developed in five subjects during the follow-up (in two cases it was only transient).

Comparison of responders and non-responders

Baseline data, including age, sex, NYHA class, LVOT gradient, degree of mitral regurgitation, echocardiographic parameters, 6-min walking distance and quality-of-life parameters were not significantly different among those who improved after pacing and those who did not improve (ie, needed invasive procedures or died during the follow-up).

Complications of the technique

Pacemaker implantation resulted in only two minor haematomas. Later one case of pocket infection occurred that could be resolved with explantation and contralateral insertion. There were no cases of lead dislodgement, fracture or pacemaker malfunction. No patient died or had other significant morbidity owing to the pacemaker procedures.

DISCUSSION

Treatment of HCM has two objectives: the prevention of sudden death, which in high-risk patients can only be achieved by implantable cardioverter-defibrillators, and the symptomatic benefit, that can be given, in addition to drugs, by pacing, alcohol ablation or surgery.

The observation that pacing in the apex of the right ventricle could reduce the outflow gradient in obstructive HCM was made by chance more than 30 years ago, although this modality of treatment expanded in the nineties, when symptom relief associated with LVOT gradient reduction was well documented in observational studies. Subsequently, two randomised, crossover studies have been performed that did not yield clear results. The PIC study involved 83 patients and found that those patients randomised to an active pacemaker had a modest reduction in the LVOT gradient (from 59 to 30 mm Hg) and a non-significant increment in the exercise time.

Figure 1 6-Min walking test. Functional capacity evaluated by means of the distance covered in the 6-min corridor test. The baseline scale indicates before pacemaker implantation, and 3 months and 12 months after active pacing.

Figure 2 SF-36 quality of life. Physical and mental components of the SF-36 quality-of-life instrument measured under basal conditions, and during the first year of follow-up after pacing.


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treatment in obstructive HCM, also with a long-term follow-up (up to 10 years): they found a statistically significant decline in LVOT gradient that was maintained and more apparent over time (baseline LVOT gradient 82±35 vs 42±53 at early vs 32±25 mm Hg at late follow-up).

Despite years of experience, the mechanisms whereby pacing with short AV delay reduce LVOT obstruction are not fully understood, particularly because there are no echocardiographic studies with sufficient follow-up. Acutely, pre-excitation of the right ventricular apex alters the dynamics and timing of the septal wall, which induces its paradoxical movement, avoids projection of the basal septum into the LVOT and thus decreases mitral valve apposition and, consequently, alleviates obstruction. However, it is well known that acute and chronic effects may differ substantially, and absence of gradient reduction initially may be associated with an important decrease later. This is probably due to a phenomenon of ventricular remodelling in relation to dysynchrony that can have a delay and be present in the long term. Our study does not have detailed segmental analyses to answer this question, but it is noteworthy that in the long term left ventricular ejection fractions decreased (although within normal limits), probably as part of the process of remodelling (see table 2).

Another point that has to be dealt with is the functional benefit. PIC11 and M-PATHY studies12 included patients in NYHA classes II to IV, while in our study we restricted the inclusion to classes III and IV. Although neither trial documented improvement in exercise tolerance, the PIC study showed that the subgroup of patients who had a baseline reduced exercise capacity (<10 min) obtained a statistically significant benefit. It can be inferred that in order to obtain a benefit, it is necessary to include patients with a reduced exercise capacity before pacing.

The mean age of patients in the PIC study11 and in the M-PATHY study12 was 53 years, while patients in our series were significantly older (62±11 years). Interestingly, in the M-PATHY study only those patients over 65 years had a significant clinical response (which was not present below this age).12 This might explain our better results and has to be emphasised since other voices have raised the possibility of treating specific patients with pacing, such as those of advanced age.29 For whom aggressive treatment by alcohol ablation or surgery is not desirable.

A 12% mortality during the follow-up in our study could be viewed as high, but if we consider the duration of the study (up to 10 years), the baseline age of the patients (62±11 years) and the severity of symptoms (all patients were initially in class III and IV), this figure could be expected. Annual mortality in HCM ranges from 1% in non-tertiary centres to 3–6% in tertiary centres, reflecting the differences in clinical status.29

Our study was initially designed to have a 1-year follow-up and this explains why the majority of tests and controls were restricted to this initial period of time. The most interesting

![Figure 3](image1.png) Changes in outflow gradient. Evolution of peak left ventricular outflow tract gradient (mm Hg), before pacemaker implantation (baseline), and during early and late follow-up after pacing. (from 12.3 to 15'). Similarly, the M-PATHY study12 involved 48 patients (although only 32 completed the study) and showed a small reduction in the LVOT gradient in those having an active pacemaker (from 82 to 48 mm Hg, p<0.001) but not associated with an increase in the functional capacity (from 9.2 to 10.8 min). Afterwards, a Mayo Clinic study13 (not randomised) compared a pacemaker with surgical septal myectomy and demonstrated the clear superiority of surgery, both in LVOT gradient results and in functional capacity, with respect pacing. After these studies, the ACC/AHA/HRS 200826 guidelines designated pacing as a class IIb indication in obstructive HCM, while surgery remained the designated pacing as a class IIb indication in obstructive HCM, while surgery remained the

![Figure 4](image2.png) Mitral regurgitation. Changes in mitral regurgitation grade from baseline before pacemaker implantation to 3 months and 12 months after pacing, and at final follow-up, expressed as percentages of the total number of patients.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Echocardiographic evolution parameters</th>
</tr>
</thead>
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<tr>
<td></td>
<td>Baseline</td>
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<tr>
<td></td>
<td>n=50</td>
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<tr>
<td>LVEDD (mm)</td>
<td>43±5</td>
</tr>
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<td>IVS thickness (mm)</td>
<td>21±4</td>
</tr>
<tr>
<td>PW thickness (mm)</td>
<td>15±5</td>
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<tr>
<td>LV mass (g)</td>
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<tr>
<td>LA (mm)</td>
<td>50±9</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>76±10</td>
</tr>
</tbody>
</table>

IVS, interventricular septum; LA, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; PW, posterior wall.
results, however, were found in the long-term follow-up, in that patients were managed without protocol restrictions, taking all decisions only from a clinical point of view. On the one hand, we observed that a long period of time is needed for a significant decrease in the LVOT gradient. On the other hand, pacing over the long term (in these relatively elderly patients) improves symptoms in the vast majority of subjects, since the need for alcohol ablation and/or surgery for clinical reasons and persistence of LVOT obstruction can be avoided in most cases. Thus in this study a strategy that started with pacing has shown that in the long term only a 18% of subjects needed to be submitted to a more invasive procedure (alcohol ablation and/or surgery). It should be remembered that the disadvantage of these invasive techniques is that, even in the best hands, mortality is not negligible—estimated as between 1% and 2%. Another point to be emphasised is that alcohol ablation induces right bundle branch in 62% of cases, while surgical myectomy induces left bundle branch block in about 93% of cases, and also that both techniques induce acute and not infrequently permanent AV block (some groups recognise that 40% of their patients receive a permanent pacemaker after alcohol ablation). Finally, alcohol septal ablation and surgical myectomy are techniques that can be performed with good results only in very specialised centres, while pacing is an easy procedure available everywhere; patients can be referred to more specialised centres for alcohol ablation and surgery after pacemaker implantation if no improvement occurs.

Limitations
This study has some limitations. First, it is observational and uncontrolled (a placebo effect of pacing cannot be excluded in data such as NYHA functional class, 6-min walking time and quality of life). Second, segmental ventricular analysis was not performed to determine if left ventricular remodelling was the main cause of LVOT gradient reduction.

SUMMARY
This study examines the long-term results of pacing in obstructive HCM, both in amelioration of symptoms and in LVOT gradient reduction, and emphasises that the process can be delayed over a certain period of time. Eighty-two per cent of patients in our series could be managed without other strategies. Considering these results, new randomised studies with pacing are warranted in HCM with a longer follow-up to determine the role of this technique. Since nowadays many patients with HCM are submitted to cardioverter-defibrillator implantation for primary prevention, those subjects with significant obstruction could be randomised to active/non-active pacing as a therapeutic trial.

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Conflicts of interests
None.

Ethics approval
This study was conducted with the approval of the Comité Etico Hospital Vall D’Hebron.

Patient consent
Obtained.

Provenance and peer review
Not commissioned; externally peer reviewed.

REFERENCES