Clinical progress after randomized on/off pacemaker treatment for hypertrophic obstructive cardiomyopathy


Background The therapeutic options for hypertrophic obstructive cardiomyopathy (HOCM) classically include medical treatment with beta-blockers and calcium antagonists or myectomy–myotomy as a surgical possibility for refractory cases. The observation that pacemaker activation of the heart in HOCM reduces the subaortic gradient is well known but less well investigated.

Methods Eighty-three patients (33 female and 50 male) mean age 53 (18–82) years, with symptoms refractory to drug treatment and a resting gradient above 30 mmHg, who responded favourably to temporary pacing, were included in this prospective study and had a pacemaker (DDD) implanted. After an initial double-blind crossover phase of 6 months, patients were reinvestigated at 12 months and followed for a mean of 36 months.

Results As observed during a screening investigation, the obstruction was significantly reduced from 72 ± 35 mmHg to 29 ± 24 mmHg (P<0.01) when the pacemaker was on, while no major effect was seen during the sham phase. The effect was persistent at 1 year with a remaining resting gradient of 28 ± 24 mmHg. In parallel, we documented an improvement in functional capacity, according to the NYHA classification and by quality of life analysis, and a significant improvement in dyspnoea and angina. Exercise on treadmill improved only in patients with reduced initial tolerance (<8 min). During the mean follow-up of 36 months, 65 patients remained on pacing alone, with eight patients having additional AV-node ablation and five patients finally having surgery.

Conclusion This controlled multicentre study shows that pacemaker treatment is an option for HOCM patients; it is inoffensive and does not exclude alternative methods, but satisfies 79% of patients beyond 3 years. (Europace 1999; 1: 77–84)

Key Words: pacemaker, hypertrophic cardiomyopathy, randomized trial, quality of life, dual chamber pacing.

Introduction

Hypertrophic cardiomyopathy is a complex disease requiring a complex treatment. It is usually a familial cardiac disorder, recognised to be heterogeneous in expression with diverse clinical manifestations and outcome. This structural and functional abnormality of the myocardium is the phenotype of many genetic disorders of encoding proteins in the sarcomere. The diagnostic characteristic is a thickened and non-dilated left ventricle in the absence of an associated condition that could explain the hypertrophy[1]. Echocardiography is the main diagnostic tool for identification of the hypertrophy and will allow distinction between diffuse, apical and septal predilections of the muscular malformation[2]. The prevalence of hypertrophic cardiomyopathy in the general population is estimated to be as high as 0.2%, and about 25% of these might present with septal hypertrophy leading to dynamic obstruction of the left ventricular outflow tract[3]. As many patients have additional malformations of the mitral valve apparatus with enlargement of leaflets or anomalous insertion of a papillary muscle, the systolic movements of this valve may be modified by the disorder. An anterior displacement can further contribute to the dynamic
subaortic obstruction and coincident mitral incompetence. The clinical finding is a harsh systolic ejection murmur accentuated by the Valsalva manoeuvre. The symptoms, mainly dyspnoea, chest pain, dizziness and palpitations are of multifactorial cause and may partially be explained by the anatomical abnormalities.

Dyspnoea is a consequence of diminished compliance of the left ventricle and mitral incompetence, which both lead to raised left atrial and pulmonary venous pressures. The dynamic character of the disease explains the often paroxysmal appearance of this symptom. Chest pain which may present as either typical or atypical of angina pectoris, reflects increased oxygen consumption of the thickened myocardium but it is also a consequence of changes in the intramyocardial and small vessels.

Impaired consciousness, palpitations, syncope and sudden death may reflect the haemodynamic consequence of severe obstruction, inadequate autonomic balance stemming from inappropriate peripheral arteriolar and venular tone, or arrhythmias such as atrial fibrillation and ventricular tachycardia.

While the prognosis in most asymptomatic patients seems good, symptoms reflect a threatening situation or important disability and require treatment. In order to reduce the hyperdynamic contraction of the left ventricle, beta-blockers, calcium antagonists and disopyramide have been prescribed with success. No scientific evaluation of the benefit of these treatments has, however, been made. For patients with severe symptomatic arrhythmias, amiodarone and an ICD implantation have been recommended, but neither has been submitted to a clinical trial which might prove the reduction in mortality. As the septal hypertrophy and systolic anterior movement of the mitral valve cause mechanical obstruction of left ventricular outflow, myotomy and myectomy as well as mitral valve replacement have been proposed for extremely severe and symptomatic cases, with acceptable (0–2%) operative mortality and favourable long-term outcome.

Recently, transcorynary alcohol ablation of the interventricular septum to create a localized infarct and septal shrinking was proposed for severely symptomatic patients with hypertrophic obstructive cardiomyopathy. Just as with any of the hitherto proposed treatments that offer no ability to cure the disease, our therapeutic goal must be to improve symptoms and to attempt reduction of obstruction, as this is the only objective parameter that may possibly indicate how treatment is influencing the phenotype of the disease.

Pacing has been recognised for over 20 years to reduce left ventricular outflow tract (LVOT) pressure gradient in patients with hypertrophic obstructive cardiomyopathy (HOCM). For pacing to be successful, dual chamber pacing is necessary in order to maintain the highly important atrial contribution to ventricular filling. It is obligatory to pace the ventricles from the right ventricular apex in order to affect the contraction pattern of the septum. There are several single centre reports published showing reduction of subaortic gradients and relief of symptoms. Two randomized blinded cross-over studies show more or less impressive improvement of quality of life and reduction of LVOT gradient. First Nishimura et al. sought to evaluate the clinical benefit of short optimized AV delay dual chamber pacing for HOCM in 21 consecutive patients, but could not show general superiority of this treatment. The European multicentre study, encompassing 83 patients for evaluation of pacemaker treatment in HOCM (PIC Study), documented with the cross-over phase that dual chamber pacing was safe, improved symptoms and reduced gradient. The observations made in these patients and their evolution up to December 1997, a 36 months-plus follow up, are the background of this paper.

Methods

The study was based on the guidelines of the European Standard EN 540, the European norm for Clinical Evaluation of Medical Devices, which includes compliance with the Declaration of Helsinki. All 12 participating centres received approval of the study protocol by their local ethical committees and all patients enrolled in the study gave their consent in writing. The study was designed to have a double-blind randomized cross-over first part, and open treatment in the second. Data management and randomization were centralized, data audit was performed during and at the end of the study and supervised by the study committee. Review and validation of case report forms, quality of life questionnaires, Holter tapes, echo tapes and Doppler results as well as cardiopulmonary exercise test data were performed in core laboratories selected before the onset of the study. Patients could be enrolled if they fulfilled the following inclusion criteria: a typical subaortic muscular obstruction with septal thickness of more than 14 mm, and a LVOT pressure gradient at rest, of at least 30 mmHg as measured by echo-Doppler, of at least 14 mm, and a LVOT pressure gradient at rest, of at least 30 mmHg as measured by echo-Doppler or catheter during ongoing medication. Patients above 18 years of age were eligible for the study if symptoms were either refractory to or intolerant of drug treatment, they were in NYHA class II or III, or, during cardiopulmonary exercise testing, the VO2 max was below 85% of the age-predicted value. Patients were excluded if they had chronic atrial fibrillation, or had a conventional indication for pacing. Further exclusion criteria were systemic hypertension refractory to treatment, a recent myocardial infarction or symptomatic coronary artery disease. Patients who met the enrolment criteria were stratified into group A or B according to the results from a temporary pacing procedure in which the haemodynamic effects of short AV delay dual chamber pacing were evaluated. If temporary short AV delay dual chamber pacing decreased the gradient by at least 30% patients were stratified into group A. If the decrease by temporary pacing was less than 30%, patients were stratified into group B. If temporary pacing induced
a negative haemodynamic effect, patients were not implanted with a permanent pacemaker. Both patient groups then followed the same protocol.

Selection of the brand and type of the pacemaker generator could be determined by the individual investigator. However, the pacemaker had to be a DDD device with separately programmable paced and sensed AV delays (AVD) and with very short AVDs available. After pacemaker implantation, the AV delay was optimized by echo-Doppler criteria. The optimal AV delay was defined as that which induced the lowest LVOT gradient without lowering the aortic pressure or the diastolic mitral flow. Patients were randomized into one of the two arms of the study with the defined sequence of therapy mentioned. Short AV delay dual chamber pacing was defined as on (ON) whereas the opposite pacing mode, atrial inhibited pacing at a rate of 30 beats \( \cdot \min^{-1} \), was defined as pacemaker off (OFF).

Patients were reassessed according to the flow sheet (see Fig. 1) with the possibility of early cross-over to the alternate study period in the event of symptoms. Medication had to be kept unchanged during the cross-over phase. After 6 months the patients were asked for the preferred study period and their pacemakers were programmed accordingly. The study ended by a mandatory 12 month visit and further tracking of the cases was requested for this report.

Holter recordings were performed in each phase to confirm appropriate functioning of the pacemaker and complete ventricular capture in DDD mode. The recordings were analysed in a central laboratory and no information was given to the investigator immediately. Exercise testing followed a symptom-limited modified Bruce protocol with measurement of spirometric and metabolic data whenever possible.

Symptomatology was evaluated according to the NYHA classification for the functional status. In addition, a specific quality of life assessment questionnaire was employed. Details of this QOL questionnaire have been described elsewhere\cite{21}. It has been specially designed and validated for pacemaker patients as well as for ischaemic heart disease. Translations of the questionnaire into the various European languages spoken by patients in this study were validated against the original. The patients completed the QOL form after instruction by a nurse otherwise not involved in the study and not informed of the status of the patient.

**Statistical methods**

The key analysis of the cross-over phase was the intra-patient comparison, performed according to the Hills–Armitage procedure. The patient status in pacemaker OFF was compared with the status of the same patient in pacemaker ON using paired tests as published earlier\cite{20}, while 1 year data were compared with screening, pacemaker OFF and ON periods. Evaluation over time was realised by comparing the results of the different follow-up examinations in chronological order. The long-term therapeutic effect was tested by comparing the 1 year results with the baseline screening and pacemaker OFF data. All statistical tests used have been adapted to the type of variable analysed: for discrete variables a Chi-square or a Fisher exact test was used as appropriate, for continuous variables the Student’s t- or Wilcoxon test was used. A \( P \)-value of less than 0·05 was considered statistically significant.
Table 1  Baseline patient data in all 83 patients (mean ± SD)

<p>| | | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>52·90</td>
<td>14·87</td>
</tr>
<tr>
<td>Gender (F/M)</td>
<td>33/50</td>
<td></td>
</tr>
<tr>
<td>LVOT gradient, no IPG (mmHg)</td>
<td>70·69</td>
<td>28·56</td>
</tr>
<tr>
<td>LVOT gradient, PM-Test (mmHg)</td>
<td>40·58</td>
<td>29·65</td>
</tr>
<tr>
<td>LVOT grad. 1 year, N=76 (mmHg)</td>
<td>27·67</td>
<td>23·72</td>
</tr>
<tr>
<td>Optimal AV delay (ms)</td>
<td>74·79</td>
<td>26·87</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>2·55</td>
<td>0·50</td>
</tr>
<tr>
<td>Dyspnoea grade</td>
<td>2·46</td>
<td>0·69</td>
</tr>
<tr>
<td>Angina grade</td>
<td>1·41</td>
<td>1·01</td>
</tr>
<tr>
<td>Angina y/(y+n)</td>
<td>0·57</td>
<td>47</td>
</tr>
<tr>
<td>Syncope y/(y+n)</td>
<td>0·13</td>
<td>11</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>70·14</td>
<td>10·62</td>
</tr>
<tr>
<td>LV diameter diastolic (mm)</td>
<td>44·18</td>
<td>6·90</td>
</tr>
<tr>
<td>Septal thickness (mm)</td>
<td>20·64</td>
<td>5·25</td>
</tr>
</tbody>
</table>

Results

Patient characteristics are summarized in Table 1. A total of 83 patients were screened and included over a period of 24 months. The inclusion rate of three to four patients per month was quite stable but no log of additional patients screened or paced for HOCM was kept. The 12 participating centres in eight European countries contributed each between one and 15 cases. Of the whole study population, one patient died in hospital due to perforation of the right ventricle that caused tamponade and irreversible shock, following the temporary pacing protocol. Seventy-nine patients were investigated 12 months after permanent pacemaker implantation and 82 patients were tracked after a mean follow-up period of 36 months (22 to 46 months). Drug treatment consisted of beta-blockers (n=42 average dose propranolol=150 mg . day⁻¹); 39 were on calcium antagonists at an average dose of verapamil of 240 mg; 12 patients received amiodarone at an average dose of 200 mg . day⁻¹ and three were on disopyramide 300 mg . day⁻¹; diuretics were given to 10 and ACE inhibitors to three patients. The results revealed the randomization for the cross-over phase was without bias as the two patient groups were comparable in all standard parameters. Eighteen patients, classified as group B, were significantly younger than Group A, but the resting gradient was comparable. Figure 1 shows the flow diagram of all patients. During the cross-over phase, switching the pacemaker off was recognised by 14 of 42 patients as an important deterioration in their status and motivated them to seek an early consultation at the study centre. Such events were not seen when the change was from pacemaker OFF to ON. After this blinded cross-over study period, 76 patients preferred the period when their pacemakers were programmed to ON while four chose OFF, one of whom later changing back to ON. Two patients were not satisfied with pacing and underwent surgery during the initial period of the cross-over study. Importantly, the overall level of symptoms improved to a comparable extent by having the pacemaker programmed ON, irrespective of the randomization order and to an equal extent in group A and B patients. This benefit persisted at the 1 year reassessment for most parameters and remained significantly above the baseline values. However, due to unsatisfactory control of symptoms three further patients underwent surgery for HOCM and seven patients AV node ablation to allow optimization of atrioventricular synchrony. At 36 months, 75% of patients still remain satisfied with this treatment while 25% have required additional treatment.

Evolution of the LVOT gradient, as measured by echo-Doppler is shown in Fig 2. There was a spontaneous slight but significant reduction of the LVOT gradient after implantation of the pacemaker, even during the period the pacemaker was programmed to OFF. This observation was pronounced in group A where the initial value of 72 ± 35 mmHg fell to 52 ± 34 mmHg, but was not seen in group B. With 3 months of ON however a clinically important and significant further reduction of the obstruction (25 ± 20 mmHg) was documented for group A, in group B it was 45 ± 28 mmHg. At 1 year the favourable haemodynamic effect on the measured gradient persisted, with a residual gradient of 28 ± 21 mmHg for both groups. Apart from this haemodynamic effect, serial echocardiographic measurements did not reveal significant morphological changes. A systolic anterior movement (SAM) documented in 62 patients before pacing, completely disappeared in 12 patients after 1 year of pacing. The global ejection fraction was 70 ± 11% at entry in the study and 68 ± 12% at 1 year (ns).

Exercise test results for the group as a whole showed no change in total duration, with 12·9 ± 5·0 min and 13·3 ± 4·1 min after 1 year. In contrast, pacing ON increased the exercise duration by 21% in patients with a reduced exercise tolerance at baseline of less than 8 min (P<0·05). Maximal heart rate was identical, with 119 ± 27 beats . min⁻¹ during pacing ON vs 121 ± 22 beats . min⁻¹ during pacing OFF, reflecting 74% of the predicted maximum (influenced by oral medication). Systolic pressure at maximal workload was 143 ± 26 mmHg at baseline and 146 ± 24 mmHg on pacing after 1 year. During exercise, no patient suffered a significant pressure fall or arrhythmia and the reason for stopping, in the majority, was general exhaustion. On Holter, full ventricular capture during the active pacing period was over 98% while atrial pacing occurred in <2% during the off-phase.

The clinical evolution is shown in Fig 3. Of those 73 patients who were still on pacing after 36 months, 32 (45%) patients were classified in NYHA functional class II, and 41 (54%) class I. Activating the pacemaker was felt as an improvement and after 1 year, this remained almost unchanged, although 14 improved further while 13 considered they had sustained some loss of benefit. The overall improvement under pacing ON (DDD), at 1 and 3 years compared with baseline remains significant and has been maintained. This observation is further substantiated by the answers given in the quality of life questionnaires, the results of which are summarized in
Fig. 4. The ability for cognitive and sexual functioning were not modified, but pacing induced significant quality of life improvements in the other investigated parameters and this remains stable after 1 year.

Interestingly, patients had few cardiovascular complications, embolic events or severe cardiac decompensation. Of those patients continuing on pacing, no persistent atrial fibrillation has been observed. While syncopal episodes were reported by 10 patients before entering the study, during the whole observation only four syncopal events were reported and no deaths occurred.

Discussion

This paper shows that dual chamber pacing improves symptoms in patients with hypertrophic obstructive cardiomyopathy with a left ventricular outflow tract gradient at rest of at least 30 mmHg, who are symptomatic despite maximal conventional drug treatment. Furthermore, the LV gradient was reduced at acute haemodynamic testing. This effect persists beyond 1 year and remains satisfactory over 3 years without any further intervention in 65 of 83 patients.

Simultaneously, short AV delay dual chamber pacemaker treatment reduces the left ventricular outflow tract obstruction acutely as well as long-term. These observations have to be validated in comparison with so-called established therapies for HOCM[22]. The benefit of beta-blockers[8], Ca-antagonists[9] and, more recently, class 1 antiarrhythmics[10] are well accepted but none of these drugs has ever been evaluated in a study of scientific rigor as should be mandatory today.

Of course pacing influences ventricular contraction in many different ways. In HOCM not only is inverted septal activation of importance, but also the redistribution of wall stress, probably leading to modification of coronary flow, as documented in animal experiments and human studies[24–26]. The subjective improvement and objective gradient reduction, in this study, are associated with an apparent contradiction in that there was no improvement in exercise tolerance and that no structural changes could be documented. It seems...
**Figure 3** The functional classes according NYHA classification. Note that the improvement from baseline to pacemaker off (OFF) reflects a placebo effect, which, however, is not significant. Active pacing (ON) gives a significant improvement, for the group as a whole as well as for individuals, which persists long-term. 

<table>
<thead>
<tr>
<th>Time</th>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
<th>Class IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>10%</td>
<td>45%</td>
<td>3%</td>
<td>45%</td>
</tr>
<tr>
<td>OFF</td>
<td>I [10%]</td>
<td>II [49%]</td>
<td>III [40%]</td>
<td>IV [1%]</td>
</tr>
<tr>
<td>ON</td>
<td>44%</td>
<td>48%</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>48%</td>
<td>42%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>36 mths</td>
<td>54%</td>
<td>42%</td>
<td>3%</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 4** Selected features of quality of life, as assessed by repeated questioning of the patient. The improvement is expressed against the baseline (0 axis) according to the interpretation of symptoms on a 0–10 scale. ■ = active (blind pacing period); □ = at 12 months.
probable that the basic problem of the myofibrillar disarray cannot be influenced by pacing. Unlike drugs, however, pacing reduces contractility and provokes asynchronous contraction, thereby modifying wall stress and myocardial oxygen consumption. Although not the essence of HOCM, the gradient is therefore a parameter upon which we can judge the value of a therapeutic intervention and in the short-term the only one we have. Some improvement might be explained by the fact that under pacemaker protection, drug treatment can be intensified. However, this was reported for only a few cases and in the open phase of this study. Radiofrequency ablation of the AV node in order to optimize the AV interval was offered as a supplementary intervention to eight patients and resulted in satisfactory relief of symptoms in all of them. This procedure might be considered if full ventricular capture is not possible without loss of atrial filling[27]. Of the five patients who finally underwent surgical myectomy, three improved further, one remained symptomatic and in one no further information is available.

The question must arise as to whether a placebo effect might bias these observations. It is a fact that the simple implantation but not activation of the pacemaker brought some benefit to the patients. This effect was of the order of 30% compared with the benefit when pacing was active, a value generally observed in drug treatments.

To our knowledge, this is the first study that has been able to evaluate this component of an invasive therapy. Placebo effects are thought to fade after a short time, as we also observed, but the symptomatic benefit, according to the quality of life questionnaire at 12 months after implantation, proved a long-lasting effect independent of that of the early placebo. This treatment alone was apparently still satisfactory for 79% of patients over the whole tracking period.

Although long-term results from an uncontrolled study of the effects of dual chamber pacing in patients with hypertrophic obstructive cardiomyopathy has been published, this, to our knowledge, is the first randomized controlled multicentre study on this subject. In the preliminary phase of this study a randomized and blinded assignment to pacing OFF or ON was the first step. It proved the superiority of active pacing vs a sham intervention both short-and long-term[50]. This result is even more impressive as it was obtained using a multicentre design. A small single-centre study has recently failed to demonstrate symptomatic benefit by dual chamber pacing[19]. There are several possible explanations for this. Firstly, the study material was small. Secondly, pacemakers were implanted even if acute testing failed to show a beneficial influence on haemodynamics. Moreover, there was no information as to the totality of ventricular capture, a prerequisite for successful pacing. Finally, the quality of life questionnaire used was developed for patients with heart failure rather than for patients with pacemakers. Our more selective approach in a larger population may account for this difference.

Our study results emphasize the importance of gradient reduction in HOCM. Clearly the symptoms in HOCM are multifactorial and include left ventricular diastolic dysfunction, impaired coronary vasodilatory reserve and myocardial ischaemia. The contribution of these factors to symptoms vary among patients and a direct one-to-one correlation with any particular pathophysiological mechanism is usually not evident, not even with the subaortic gradient[2]. However, the perceived benefit of surgery on symptoms is reported to be largely the consequence of a reduction of the outflow gradient[2], as also shown in this study. As we included only patients with prominent gradients we cannot argue how pacing might act in non-obstructive forms. We can, however, conclude, in accordance with careful previous observations in HOCM patients[18], that the amount of the initial gradient reduction is not predictive of the symptomatic response to pacing. Although no clear correlation exists and despite some contrasting opinions[23], we still believe that a complete lack of gradient reduction or haemodynamic deterioration during temporary dual chamber pacing does not justify pacemaker implantation today. On repeating Doppler measurements during the various phases of this study, we observed important spontaneous alterations of the resting gradients, reflecting the variability of this disease. With regard to the symptomatic benefit, our results compare well with retrospective analyses of surgical series[13] resulting in similar symptomatic improvement although of a lesser magnitude.

The outcome of the first series of non-surgical septal reduction has recently been published[28]. Although a gradient reduction of a similar magnitude to that achieved by pacing is obtained by provoking septal infarction, the intervention may be hazardous. It creates irreversible damage leading to complete AV block in some and longer hospitalizations than in paced patients. Long-term results are not yet known, and the important remodelling after septal ablation might, with time, lead to dilatation of the left ventricle. We feel that pacing offers an intermediate solution which is clinically effective, causes little or no irreversible damage and does not preclude further more aggressive therapies should they be needed.

**Conclusion**

This controlled, multicentre study has documented a long-lasting symptomatic benefit of pacemaker treatment for HOCM which occurred in parallel with a reduction in the LV outflow gradient. This new therapeutic option was offered to patients who were symptomatic despite beta-blockers, calcium antagonists and disopyramide treatment. In persistent refractory cases, a surgical approach, or similar radical procedure is still an option, but as an alternative to irreversible types of therapy, pacing may offer the HOCM patient relief of symptoms over a relatively long term.
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