DDD pacing in hypertrophic cardiomyopathy: a multicentre clinical experience

Alistair K B Slade, Nicolas Sadoul, Leonard Shapiro, Lidia Chojnowska, Jean-Phillippe Simon, Richard C Saumarez, Bernard Dodinot, A John Camm, William J McKenna, Etienne Aliot

Abstract

Background—DDD pacing has been advocated as an effective treatment for drug refractory obstructive hypertrophic cardiomyopathy. This study reports the outcome of pacing in 56 patients with refractory symptoms referred to four tertiary centres.

Methods—Core data on symptoms, drug burden, and left ventricular outflow tract gradient were recorded. Patients underwent a temporary pacing study with optimisation of the atrioventricular (AV) delay for greatest gradient reduction without haemodynamic compromise. Patients were assessed after implantation in terms of changes in symptoms, drug load, and outflow tract gradient.

Results—56 patients underwent pacing assessment. The mean (SD) left ventricular outflow tract gradient before pacing was 78 (31) mm Hg. At temporary study the mean (SD) left ventricular outflow tract gradient was 38 (24) mm Hg with a median (range) optimised sensed AV delay of 65 (25–125) ms. Fifty three patients were implanted and followed up for a mean (SD) of 11 (11) months. The median (range) programmed sensed AV delay was 60 (31–200) ms. Left ventricular outflow tract gradient at follow up was 36 (25) mm Hg. Forty four patients had improved functional class. Although a correlation ($r = 0.69$) was shown between acute and chronic left ventricular outflow tract gradient reduction, there was no correlation between magnitude of gradient reduction and functional improvement, and no appreciable change in pharmacological burden.

Conclusion—This series confirms symptomatic improvement after DDD pacing in hypertrophic cardiomyopathy. There remains, however, a discrepancy between perceived symptomatic benefit and modest objective improvement. Furthermore, the optimal outcome has been achieved only with continued pharmacological treatment. Current methods of temporary evaluation do not predict functional outcome which seems to be independent of the magnitude of gradient reduction.

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Management of patients with symptomatic obstructive hypertrophic cardiomyopathy remains problematic. Symptoms of chest pain, exertional dyspnoea, syncope, and palpitation may all require therapeutic intervention.¹ Current pharmacological treatment with β adrenergic blockers, calcium channel blockers, particularly verapamil, or disopyramide may be helpful but are often ineffective or poorly tolerated.^{2,3}

Surgery in the form of transaortic septal myectomy⁴ or mitral valve replacement⁵ still carries significant mortality and associated morbidity may be significant. There is thus a need for other therapeutic strategies in this highly symptomatic group of patients.

Dual chamber pacing with a short atrioventricular delay has been the subject of increasing interest as a therapeutic option.⁶⁻⁸ We report our experience of acute haemodynamic evaluation of dual chamber pacing in patients with drug refractory obstructive hypertrophic cardiomyopathy and subsequent outcome at follow up.

Patients and methods

STUDY POPULATION

The study population consisted of 56 consecutive patients with hypertrophic cardiomyopathy referred to tertiary referral centres for management of drug refractory symptoms. The distribution of patient recruitment was as follows: Nancy $n = 24$, London $n = 15$, Warsaw $n = 11$, and Cambridge $n = 6$.

Hypertrophic cardiomyopathy was diagnosed on the basis of typical clinical, echocardiographic, and haemodynamic features. All patients had a left ventricular outflow tract gradient greater than 30 mm Hg at rest ($n = 54$) or a gradient less than 30 mm Hg at rest but with a consistently provokable gradient > 30 mm Hg ($n = 2$). Detailed quantitative wall thickness data were available for 51 patients. The mean diameter of the interventricular septum was 23.4 (7.7) mm, and the mean free wall was 15.5 (4.2) mm. Morphological classification, using the Maron classification,⁹ was available for 43 patients: one had type 1 hypertrophy, nine type 2 hypertrophy, and 33 type 3 hypertrophy. This implies that most patients had some hypertrophy of the free wall of the left ventricle, although the data suggest considerable asymmetry in its distribution.

The mean symptom duration before assessment for pacing was 7.0 (5.5) years. The table gives the presence and severity of the cardinal

Department of
Cardiological
Sciences, St George's
Hospital Medical
School, London
A K B Slade
R C Saumarez
A J Camm
W J McKenna

Department of
Cardiology, University
of Nancy, France
N Sadoul
J-P Simon
B Dodinot
E Aliot

Regional Cardiac
Centre, Papworth,
Cambridge
L Shapiro

Department of
General Cardiology,
National Institute of
Cardiology, Warsaw,
Poland
L Chojnowska

Correspondence to:
Dr A K B Slade, Department
of Cardiological Sciences, St
George's Hospital Medical
School, Cranmer Terrace,
London SW17 0RE.

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Characteristics of patients at baseline

	No
Total study population	56
Sex (M:F)	34/22
Mean (SD) (range) age (years)	48 (18) (16–79)
Mean (SD) (range) symptom duration (years)	7.0 (5.5) (1–30)
NYHA functional class	
I	1 (2)
II	12 (21)
III	42 (75)
IV	1 (2)
Angina class	
I	15 (27)
II	22 (39)
III	19 (34)
IV	0
Presyncope	15 (27)
Syncope	22 (39)
Palpitations	19 (34)
Drug treatment	
β Blockers	35 (63)
Calcium channel antagonists	22 (39)
Both β blockers and calcium channel antagonists	7 (13)
Disopyramide	2 (4)
Amiodarone	14 (25)
Prior myectomy	1 (2)

Values in parentheses are percentages.
NYHA, New York Heart Association.

symptoms associated with hypertrophic cardiomyopathy. One patient in New York Heart Association (NYHA) functional class I was referred for pacing because of isolated recurrent syncope.

The table also lists the baseline drug treatment for the study population. In addition, 14 patients were receiving amiodarone at a dosage of 200 mg or less daily for suppression of non-sustained ventricular tachycardia or paroxysmal atrial fibrillation. All patients were in sinus rhythm at the time of referral, although two had paroxysmal atrial arrhythmia. One patient had undergone septal myectomy in 1983. Sixteen of the 24 patients from Nancy have been previously reported but are included here with longer follow up.¹⁰

TEMPORARY PACING STUDY

Fifty two patients underwent temporary evaluation of dual chamber pacing before implantation. Under local anaesthesia temporary pacing wires were inserted through the right internal jugular, subclavian or femoral veins, positioned under fluoroscopic control in the right atrial appendage and at the right ventricular apex, and connected to an external temporary dual chamber pacemaker which allowed programming of sensed atrioventricular (AV) delays to 0 ms. The studies were performed in DDD mode with the lower rate set below sinus rate to allow P wave tracking. Patients were assessed haemodynamically at a series of AV intervals from baseline PR interval to the shortest sensed AV delay not associated with haemodynamic deterioration, defined as a reduction in mean aortic pressure or cardiac output of ≥ 10%. Assessment of outflow tract gradient was performed by either cardiac catheterisation or continuous wave Doppler echocardiography. Assessment by catheterisation consisted of a fluid filled 6 French gauge pigtail catheter sited at the left ventricular apex with central arterial pressure transduced from the side arm of an 8 French gauge valved introducer in the femoral artery. A positive study was defined as a reduction in

outflow tract gradient of greater than 30% in the absence of haemodynamic deterioration. The optimal AV delay was invariably associated with maximal broadening of the QRS complex indicating maximal pre-excitation of the right ventricular apex.

EXERCISE TESTING

A subset of 12 patients (St George’s Hospital) additionally underwent baseline treadmill exercise testing (Marquette MAX-1, Marquette Electronics, Milwaukee, Wisconsin) with simultaneous respiratory gas analysis (Marquette MGA 1100 Mass Spectrometer, Marquette Gas Analysis, St Louis, Missouri). This subgroup of patients undergoing metabolic exercise testing had a mean oxygen consumption of 50% of their age predicted maximum indicating severe functional limitation.

FOLLOW UP

Patients were completely re-evaluated after a minimum of 1 month with subjective assessment of symptomatic and functional status and objective assessment of drug burden and outflow tract gradient. The subset of patients who had undergone metabolic treadmill exercise testing underwent repeat evaluation.

STATISTICAL ANALYSIS

Normally distributed data are presented as mean (one SD). Non-parametric data (AV intervals) are presented as median together with the range. Paired data were compared using Wilcoxon’s sign rank test. Contingency tables are evaluated with the χ^2 test and Fisher’s exact test. A two tailed p value of < 0.05 was considered significant.

Results

TEMPORARY PACING STUDY

Fifty two patients underwent a temporary pacing study. The mean (range) left ventricular outflow tract pressure gradient before implant was 78 (31) (30–195) mm Hg which reduced at temporary study to a mean of 38 (24) mm Hg giving a mean reduction of 49%. The median (range) optimised sensed AV delay was 65 (25–125) ms.

Four patients did not undergo temporary study before pacemaker implantation: two because of a small resting but a consistently large provokable gradient, one because of the development of complete heart block between angiography and the temporary study, and one because of intermittent second degree heart block and associated syncope. Three patients were not implanted as a result of the temporary study: two because of failure to demonstrate haemodynamic improvement and one because the mechanism of syncope was not thought to be the result of a small left ventricular outflow tract gradient which reduced at study.

PACEMAKER IMPLANTATION

Patients who responded at temporary study were implanted with dual chamber pacemak-

Figure 1 Change in New York Heart Association (NYHA) functional class at follow up after DDD pacing.

Figure 2 Change in anginal symptoms at follow up after DDD pacing.

ers using conventional implant techniques with leads sited in the right atrial appendage and the right ventricular apex with particular attention given to the precise apical siting of the ventricular lead. The pacemaker generators utilised were: ELA Chorus (seven), Chorus 2 (four), Chorus RM (nine), Biotronik Gemnos (nine), Physios 01 (eight), Diplos (one), Medtronic Minuet (six), Elite (four), Thera-DR (one), Siemens-Pacesetter Synergyst II (one), Paragon (one), Teletronics Reflex (one), and Intermedics Relay (one). The median (range) sensed AV delay was 60 (31–200) ms. The initial pacing mode of choice was DDD which was successfully instituted in 49 patients. DDDR was programmed initially in three patients because of intermittent atrial arrhythmias which were electively treated with His bundle ablation before pacemaker implantation and DDIR was programmed in another one because of paroxysmal atrial arrhythmias.

FOLLOW UP

Patients were followed up for a mean (SD) (range) period of 11 (11) (1–70) months. Three patients died. The one patient with NYHA class IV status before pacing died suddenly within a few days of implant. Two patients who were not implanted died suddenly 4 and 5 months after temporary pacing failed to show any benefit.

There was a significant improvement in functional class with 23 patients achieving NYHA class I. Nine patients (17%) showed no improvement or one had worsening functional status (fig 1). Angina was improved to class I status in 39 patients (75%) of the study population but 10 (19%) with symptomatic angina showed no improvement (fig 2). Syncope was present in 22 patients before implant with presyncope/dizziness in a further 15. At follow up three patients had sustained syncope, one of whom had not experienced syncope before pacing. Two patients described presyncope at follow up: one had previously described syncope, the other continued to experience presyncope.

In the subset of patients who underwent metabolic exercise testing there was a small but significant ($P < 0.02$) improvement in maximum oxygen uptake from 18.7 (3.8) ml/kg/min to 20.8 (4.6) ml/kg/min.

The mean range left ventricular outflow tract gradient before implant was 78 (31) (30–195) mm Hg and at follow up was 36 (25) mm Hg giving a reduction of 54%. There

was correlation ($r = 0.69$, $P < 0.0001$) between the values of gradient reduction with temporary pacing and the chronic reduction at follow up (fig 3).

There was no significant difference, however, in the absolute value of gradient reduction (43 (27) mm Hg *v* 35 (17) mm Hg, $P = \text{NS}$) nor is the percentage change in gradient (54 (24) mm Hg *v* 56 (22) mm Hg, $P = \text{NS}$) between those who had improved functional class and the nine whose functional class remained unchanged. There were no significant differences in age (48 (17) years responders *v* 48 (18) years non-responders, $P = \text{NS}$) and symptom duration (7.4 (5.8) years responders *v* 5.4 (4.8) years non-responders, $P = \text{NS}$) between the two groups. The programmed AV delay of the group that failed to change functional class was not significantly different from that of the study group (median 60 ms *v* 65 ms, $P = \text{NS}$).

CONCOMITANT PHARMACOLOGICAL TREATMENT

There was no significant change in the overall drug burden after pacemaker implantation. Thirteen patients were introduced to β blocking agents or had their dosage increased, while seven were able to reduce or discontinue β blocking agents. Seven patients were introduced to calcium channel blockers or received an increase in dosage, whereas 13 had their dosage reduced or discontinued. Atrio-ventricular nodal blocking agents were specifically introduced in two patients in an attempt to slow native atrioventricular conduction and improve complete capture of the right ventricular apex. Both patients taking disopyramide discontinued the drug: one because of drug intolerance and one after septal myectomy because of failure of DDD pacing in combination with verapamil and disopyramide.

Three patients required His bundle ablation and reprogramming of their pacing systems for established (two) and paroxysmal (one) atrial fibrillation.

Discussion

SYMPTOMATIC IMPROVEMENT/GRADIENT REDUCTION

The role of cardiac pacing in the reduction of the left ventricular outflow tract gradient in hypertrophic cardiomyopathy was first reported serendipitously more than 25 years ago.¹¹ At the same time it had been noticed anecdotally that patients who developed left bundle branch block after septal myectomy had a better functional outcome. Sporadic reports^{6 12 13} over the years have culminated in the recent intense interest in the role of DDD pacing in obstructive hypertrophic cardiomyopathy following the simultaneous publication in 1992 of two major series from Lausanne⁷ and the National Institutes of Health.⁸

Our study confirms that dual chamber pacing with non-physiological shortened AV delays improves subjective symptoms in about 80% of patients with drug refractory hypertrophic cardiomyopathy. This symptomatic

Figure 3 Correlation between acute gradient reduction at temporary study and chronic reduction at follow up after DDD pacing. LVOT, left ventricular outflow tract.

improvement was associated with a decrease in the systolic gradient, the magnitude of which is in keeping with previously reported studies. Objective evidence of functional improvement is presented which suggests at best a mixed response with small improvements in maximal oxygen capacity.

The apparent reduction in the frequency of syncope may be misleading. Syncope is experienced in about 15% of a referral population of patients with hypertrophic cardiomyopathy often following exertion or emotional stress.¹⁴ It is a bad prognostic feature and associated with the risk of sudden death, especially in the young.¹⁵ It is important to note that the follow up is much shorter than the duration of symptoms before implant and that given the fluctuating nature of symptoms in hypertrophic cardiomyopathy a longer follow up period is required before a definitive comment can be made regarding reduction in syncopal burden. Ominously, one patient developed syncope after pacemaker implantation and subsequently underwent myectomy.

TEMPORARY STUDY

This study demonstrates a reasonable correlation between the values for gradient reduction at acute study and those at follow up. However, there was no significant difference in the absolute value of gradient reduction nor percentage change in gradient between those who had improved functional class and those whose functional class remained unchanged. The role of a temporary study has previously been questioned.¹⁶ This study shows a stronger correlation between magnitude of left ventricular outflow tract gradient reduction at acute study and that at chronic follow up but is the first to comment on the predictive value of a temporary study in terms of functional outcome rather than gradient reduction alone, which seems to carry little predictive value. Alternative physiological measures such as acute assessment of exercise capacity might provide complementary information that might refine the predictive accuracy of a temporary study.¹⁷ Whether those who show no immediate change in haemodynamics at temporary study will benefit from long-term pacing remains unanswered, although ongoing prospective, blinded, randomised crossover studies of DDD pacing are including such patients.

Another problem of the temporary study is the use of haemodynamic data to guide implantation. While the left ventricular outflow tract gradient can be determined non-invasively by Doppler echocardiography, cardiac output is not so reliably obtained. At follow up more reliance is consigned to the QRS duration. Any sign of fusion on the electrocardiogram suggesting incomplete activation of the ventricles from the right ventricular apex should lead to: (i) shortening of the AV delay to regain complete ventricular capture; (ii) additional AV nodal blocking agents and/or; (iii) consideration of radiofrequency ablation of the AV node which allows programming of normal AV delays.

EXERCISE TESTING

The improvement in symptoms reported here, as in previous studies, is mainly based on subjective assessment of patients symptoms and such subjective point assessment of symptoms may be unreliable, particularly in a disease in which daily fluctuation in symptoms is common. The placebo effect of pacemaker implantation may also contribute to subjective improvement. Assessment with maximal symptom limited exercise testing with respiratory gas analysis offers an objective basis for assessment of medical intervention in hypertrophic cardiomyopathy.¹⁸

CONCOMITANT PHARMACOLOGICAL TREATMENT

The improvement in symptoms in this study was not obtained with pacing treatment alone and occurred with pacing in conjunction with medical treatment such as β blockers or calcium antagonists. The drug burden was unchanged and some patients have been given increased doses of AV nodal blocking agents specifically to facilitate complete ventricular capture.

The largest previously reported series of patients paced for hypertrophic cardiomyopathy were all initially free from medication⁸ but after more prolonged follow up a significant proportion received drugs again.¹⁶ Other reported experiences have continued drug treatment unchanged with one recent study also demonstrating the specific use of AV nodal blocking agents to prolong native conduction through the AV node and facilitate complete ventricular capture.¹⁹

IMPORTANCE OF ATRIOVENTRICULAR INTERVAL PROGRAMMING

The temporary study data reveal a wide range of AV delays giving optimal haemodynamic values. This correlates with the AV delays required to produce complete right ventricular pre-excitation—the crucial requirement for success of this treatment. The variability of these values presumably reflects the variability in native conduction and in the use of AV nodal blocking drugs. In our study, the median value of the programmed sensed AV delay was 60 ms. This value is in agreement with that in European studies^{7 19 20} but is significantly shorter than the AV delays described by Fananapazir *et al*⁸ who reported their initial experience with DDD pacing in 44 patients free of medications for the study period. All, except five patients had AV delays of 100 ms or more. Their recently expanded series of 84 patients gives a similar distribution of AV delays with all but two patients programmed initially with an AV delay of 100 ms or greater.¹⁶

In our joint experience, such AV delay values in the presence of normal AV conduction produce at best only partial right ventricular capture, are not associated with maximal reduction in the left ventricular outflow tract gradient, and are unlikely to induce clinical improvement.

The choice of generator was dictated by the

programmable features available, individual patients specific requirements, and the spectrum of devices available in any one centre. The major criterion for selection was the ability to programme very short AV delays as our temporary studies showed haemodynamic benefit with sensed AV delays as low as 30 ms.

There are important haemodynamic differences between sensed and paced atrial events²¹ with equivalent left atrial-left ventricular relations when the paced AV delay is significantly longer than the sensed AV delay.²² The implication is that while paced AV delays of 100–125 ms may produce complete right ventricular pre-excitation the equivalent sensed AV delays are usually 50–100 ms shorter, highlighting the need for pacemakers with ultra-short AV delays.

MECHANISMS OF IMPROVEMENT

Symptomatic improvement after DDD pacing in patients with obstructive hypertrophic cardiomyopathy is thought to be related to the decrease in left ventricular outflow tract gradient. The mechanism of obstruction is still not perfectly understood but the most favoured mechanism postulates that blood passing at increased velocity through the narrowed left ventricular outflow tract creates Venturi forces causing systolic anterior motion of the mitral valve and impaired closure leading to outflow tract obstruction and a variable degree of mitral regurgitation.²³

The most commonly accepted mechanism of gradient reduction after pacing in hypertrophic cardiomyopathy remains inversion of the ventricular contraction sequence as a consequence of right ventricular apical activation mimicking left bundle branch block leading to: (i) widening of the left ventricular outflow tract; (ii) a decrease in the Venturi effect; and (iii) a decrease in systolic anterior motion of the mitral valve. To maintain efficacy it is paramount that the ventricles are permanently and completely activated from the right ventricular apical pacing site.

Apical pre-excitation of the right ventricle which mimics left bundle branch block is probably not the only explanation for gradient reduction as pacing has been reported to decrease the outflow tract gradient and give symptomatic relief in patients with pre-existing left bundle branch block.¹⁶ However, the pattern of ventricular activation in patients with left bundle branch block does not exactly mimic the pattern induced by pacing with right ventricular apical capture.²⁴ Another explanation is that gradient reduction occurs as a consequence of reduced systolic function with chronic chamber dilatation as a potentially deleterious long-term effect.²⁵

Speculation on the mechanism of benefit has focused on the left ventricular outflow tract gradient and its reduction with pacing. Hypertrophic cardiomyopathy is a condition in which diastolic function is abnormal and may be an important cause of symptoms. Previous work on the effect of short AV delay pacing on diastolic function has drawn different conclusions. Acute studies with cardiac

catheterisation or Doppler echocardiography have demonstrated worsened diastolic parameters,^{26,27} whereas work using nuclear medicine techniques have demonstrated some improvements in filling parameters²⁸ and cited these as a possible mechanism of benefit. The numbers studied to date are small and further information will come from ongoing randomised crossover trials of DDD pacing.

ROLE OF SURGERY

Surgical myectomy has been considered to be the definitive treatment for obstructive hypertrophic cardiomyopathy.⁴ The operation is effective at reducing left ventricular outflow tract gradients acutely and chronically and is associated with improved symptoms, exercise capacity, and objective evidence of improved myocardial perfusion. Early series suggested mortality of greater than 5% but improved cardiac surgical techniques have improved operative mortality to 1–2%.²⁹ Mitral valve replacement (with a low profile prosthetic valve) has been advocated by some as an alternative surgical option but results have been less impressive.⁵

Myectomy produces a greater reduction in left ventricular outflow tract gradient than pacing (87%³⁰ v 50%^{7,8}). It is considered that myectomy is unlikely to be successful unless the residual gradient is small. It is unclear whether the larger residual gradient after successful DDD pacing is important. Nevertheless, it seems appropriate to pursue evaluation of dual chamber pacing as a low risk therapeutic intervention in patients with symptomatic hypertrophic cardiomyopathy.

LIMITATIONS OF STUDY

This study adds to the published anecdotal experience of pacing in patients with hypertrophic cardiomyopathy, although the multi-centre nature of the experience brings with it varying clinical practice. Specifically, the choice of pharmacological approach and pacemaker prescription were determined by local factors.

The true role of DDD pacing in the management of obstructive hypertrophic cardiomyopathy requires properly designed randomised controlled studies with detailed characterisation of the trial population and objective assessment of benefit. Such studies are under way in Europe and America and will undoubtedly advance our knowledge of the mechanism of benefit of DDD pacing in hypertrophic cardiomyopathy, provide greater objective evidence of such benefit, and aid identification of those patients most likely to benefit from DDD pacing.

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