Long-term benefits of pacing in obstructive hypertrophic cardiomyopathy

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INTRODUCTION
Hypertrophic cardiomyopathy (HCM), the most common inherited cardiac disorder, is defined by unexplained left ventricular hypertrophy. HCM is associated with a range of clinical expressions, including severe limitation, premature sudden death and asymptomatic survival to advanced age.1 A subset of people have left ventricular (LV) outflow tract obstruction (LVOTO), where systolic anterior motion of the mitral valve results in mitral regurgitation and mitral-septal contact that impedes LV ejection. Approximately 25% have obstruction evident at rest and many others have obstruction provoked by exercise. Although not all patients with obstruction are symptomatic, many are limited by chest pain, breathlessness, dizziness and syncope; LVOTO is an important therapeutic target.

Initial treatment with negative inotropes such as β blockers, verapamil and disopyramide often fails to control symptoms or is associated with intolerable side effects.1 Surgical left ventricular myectomy (LVM) was adopted as the first effective treatment for symptom relief;2–5 with short atrioventricular (AV) delay pacing6 and alcohol septal ablation (ASA)7 subsequently developed as less invasive options.

Following observations of a potentially beneficial haemodynamic effect of pacing, placebo-controlled studies in the late 1990s divided expert opinion and pacing failed to gain widespread acceptance.5–7 Re-examination of the role of pacing in HCM is desirable for several reasons. First, the efficacy of ASA and LVM remain untested by randomised trial. Second, the randomised trials of pacing therapy have important limitations. Third, new device technology introduces novel treatment opportunities. Fourth, some patients are unsuitable for either ASA or LVM. Finally, recent data have demonstrated long-term symptomatic benefit from pacing in as many as 80% of patients.8–10

RATIONALE FOR DUAL CHAMBER PACING
In obstructive HCM, right ventricular (RV) pacing reduces LVOTO acutely and chronically. The history of the development of DDD pacing for this indication and its likely mechanisms of action have been expertly summarised elsewhere.11 Briefly, ventricular pacing changes the activation pattern of myocardial depolarisation, bypassing intrinsic AV nodal conduction by initiating ventricular depolarisation at the RV apex. The resulting ventricular systolic contraction, associated with a shorter PR interval and left bundle branch block, reduces the severity of LVOTO by causing paradoxical movement of the septum away from the systolic anterior motion of the mitral valve. Reduced LV inotropy may also contribute. Apical RV lead placement and carefully chosen paced AV delays are critical for successful treatment.

Concerns that long-term DDD pacing in heart failure is associated with progressive LV systolic impairment, others regarding impaired LV filling resulting from short AV delay pacing, equivocal randomised trial data of pacing in HCM and the simultaneous development of ASA reduced enthusiasm for pacing as an LVOTO reduction strategy.12–14

OUTCOMES FOLLOWING DDD PACING FOR OBSTRUCTIVE HCM
Early non-randomised studies reported that DDD pacing significantly reduced LVOTO and improved symptoms.12,13 Although RV apical pacing undoubtedly reduces LVOTO, the short AV delay needed to by pass intrinsic AV conduction can impede active atrial transport and stiff, hypertrophied ventricles are particularly dependent on atrial systolic function for adequate filling. In this context, short-term randomised trials were designed to assess changes in objective measures of functional status following pacing.

SHORT-TERM PACING
Pacing In Cardiomyopathy (PIC) study
The European PIC study included 12 centres, recruiting 85 patients.6 Patients were randomised to a 3-month crossover between DDD and placebo (AAI) pacing, and optimal AV delays were chosen with Doppler guidance. DDD pacing improved symptoms of dyspnoea, chest pain and functional class, and acute gradient reduction did not predict longer-term response. DDD pacing resulted in an LVOTO reduction of 51%, a reduction reversed after 3 months of AAI pacing. In patients initially randomised to AAI, 28% reported an improvement in symptoms suggesting a placebo effect. However in those initially randomised to DDD, one-third of the patients presented prematurely to clinic with worsening symptoms after crossover to AAI. After completion of both crossover phases, 98% of blinded patients declared a preference for DDD pacing.

M-PATHY (Multicenter PAcing THerepy for HCM)
This study, enrolling 48 patients with obstructive HCM and severe symptoms, was similar in design to PIC.5 In the 32 patients completing the study, there was no improvement in quality-of-life score or peak oxygen consumption during exercise testing (oxygen consumption) after 3 months of active pacing despite a 40% LVOTO reduction. After 6 months of unblinded DDD pacing in a second phase of the study, there were significant improvements in quality of life and exercise duration, but not in peak oxygen consumption. Subgroup analyses identified that more elderly patients (>65 years) were likely to have symptomatic and objective exercise improvement following pacing. In the third and smallest study, the Mayo Clinic Study, the study protocol, investigators and conclusions were similar to those of M-PATHY.

Concerns about these trials have included the following
1. Exclusion bias: Nearly a fifth of the M-PATHY cohort chose unscheduled crossover to DDD pacing or refused AAI pacing, citing symptomatic benefit; they were excluded from the final analysis.

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2. Crossover bias: The trials incorporated crossover after 3 months of AAI or DDD pacing. LVOTO reduction following DDD is progressive over several months, and may persist for a time after pacing stops.\(^5\) \(^12\) \(^14\) Crossover effects from delayed and persisting efficacy may have obscured treatment benefits.

3. Device complications: Complications related to device implantation were reported for 16% of M-PATHY patients, with PIC reporting similar rates. Effects on quality-of-life outcomes of these high complication rates are not examined.

4. Specialist expertise: The best published results following LVM and ASA are from the few experienced centres. M-PATHY incorporated 14 centres, an average of 5.4 patients per centre (seven in PIC). Pacing for LVOTO reduction requires expertise in the indication and in device programming.

5. Placebo effect: The randomised studies document a large placebo effect but demonstrate relative benefit of active over placebo pacing. The placebo effect of more invasive procedures may be greater,\(^15\) and its importance following ASA and LVM remain uncharacterised.

6. Symptoms or exercise: Symptom status and exercise impairment are multifactorial and somewhat independent. Impaired exercise performance is demonstrated in patients with HCM without LVOTO, and symptoms correlate poorly with exercise duration. Where symptoms define the study group, this is the meaningful outcome measure. Examining efficacy for improved exercise performance requires studies where exercise performance defines inclusion.

In summary, these placebo-controlled studies demonstrate a reduction in LVOTO magnitude, an improvement in symptoms and quality of life, but not in objective exercise parameters. At best, the trials appropriately attribute weak or no efficacy to pacing. At worst, a minimally invasive and helpful treatment is now less often considered as a treatment option.

LONGER-TERM DDD STUDIES

The few reports of long-term outcomes following DDD pacing are not randomised studies, and should be interpreted accordingly. The PIC study investigators report sustained symptom improvement in paced patients after the initial randomised double-blind crossover phase was completed (up to 3 years).\(^16\) \(^17\) Three long-term observational studies with broadly similar findings, have been published since PIC and M-PATHY.\(^3\) \(^4\) \(^8\) In each, a low complication rate is reported and there is scrupulous attention to device programming, including regular optimisation of AV delays. Their results include progressive symptom improvement and LVOTO reduction well beyond the first year of treatment, and fewer than 20% of patients require more aggressive treatment. Finally, death from heart failure and non-cardiac mortality were reported in some of the cohorts; sudden death is not.

The largest and most comprehensive of these studies is a single-centre report on 50 patients with an average of 5 years of follow-up (range 0.6–10.1 years), published in this issue of the journal (see page 352).\(^9\) Patients were older than in PIC and M-PATHY (62 years compared with 53 years), were more symptomatic (all in New York Heart Association (NYHA) class III or IV, PIC and M-PATHY also recruited NYHA II). Only patients with resting LVOTO >50 mm Hg were studied; LVOTO at baseline (86±29 mm Hg) was more severe than in PIC (59±56 mm Hg), but similar to M-PATHY (82±52 mm Hg). Continuous outpatient attention to pacing parameters was taken; Doppler, Holter and exercise studies guided programming for AV optimisation.

The authors describe impressive results; most patients were in NYHA class I or II by the final evaluation and 6 min walking test results improved by nearly 25% after 1 year. LVOTO continued to decline throughout the follow-up period; 86±29 mm Hg at baseline, 55±57 at 3 months, 41±26 at 1 year and 28±24 at the final assessment. Complications were infrequent with a single serious complication (pocket infection).

A reduction in ejection fraction was recorded (76±10 to 65±15%; p=0.002), but there was no change in LV cavity or left atrial sizes. Six (12%) patients died during follow-up; three with heart failure, one stroke and two from non-cardiac disease. It must be noted that the cohort comprised highly symptomatic and older patients with HCM, in whom the natural history of the disease includes atrial fibrillation and stroke, and progression to end-stage disease with congestive heart failure.\(^10\) Similar or even higher mortality rates are reported in the long-term outcomes following ASA\(^19\) and LVM.\(^20\) Nonetheless, concerns about the adverse effects of chronic pacing on cardiac remodelling remain.

CONCLUSIONS

Non-randomised cohort studies show that ASA and LVM reduce LVOTO, and may be effective at improving symptoms.\(^21\) \(^22\) Longer-term follow-up studies also suggest that the value of pacing in managing patients with obstructive HCM may have been understated; new data suggest that pacing continues to reduce symptom limitation and LVOTO well beyond the period of observation in earlier randomised studies.

Dual-chamber pacing should be considered in certain groups with drug-refractory symptoms and LVOTO. These include (a) people who are too frail to undergo more invasive treatment; (b) people with only modest left ventricular hypertrophy, or with unsuitable septal perforator anatomy; (c) those with conventional indications for pacing; (d) people at high risk of developing heart block following ASA or LVM, in whom a trial of pacing may be considered. Furthermore, pacing does not preclude escalation to ASA or LVM, and pacer-defibrillators introduce an opportunity for therapeutic trials of pacing, before an escalation to ASA or LVM, in patients also judged to be at risk of sudden death.

It must be remembered, however, that pacemaker implantation is an invasive procedure. The reported frequency of complications has been high, and younger patients will require multiple generator changes. Drug treatment remains the first-line treatment for symptomatic obstructive HCM, and if unsuccessful, then ASA, LVM and pacing are all viable treatment options. Each intervention is performed best in experienced centres, and pacing requires regular review for the optimisation of device programming.

FUTURE DIRECTIONS

Dual-chamber pacing, ASA and LVM could prove complementary; heterogeneous disease and patient factors may define niches, and/or a therapeutic approach with a cascade of invasiveness. The role of pacing for end-stage disease and mid-cavity obstructive HCM remain speculative; here, the use of LV and multi-site pacing may present additional treatment options, offering more subtle alterations of ventricular activation patterns.

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