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Pacing for drug-refractory or drug-intolerant hypertrophic cardiomyopathy (Review)

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[Intervention Review]

Pacing for drug-refractory or drug-intolerant hypertrophic cardiomyopathy

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ABSTRACT

Background

Hypertrophic cardiomyopathy (HCM) is a genetic disease with an autosomal-dominant inheritance for which negative inotropes are the most widely used initial therapies. Observational studies and small randomised trials have suggested symptomatic and functional benefits using pacing and several theories have been put forward to explain why. Pacing, although not the primary treatment for HCM, could be beneficial to patients with relative or absolute contraindications to surgery or alcohol ablation. Several randomised controlled trials comparing pacing to other therapeutic modalities have been conducted but no Cochrane-style systematic review has been done.

Objectives

To assess the effects of pacing in drug-refractory or drug-intolerant hypertrophic cardiomyopathy patients.

Search methods

We searched the following on the 14/4/2010: CENTRAL (The Cochrane Library 2010, Issue 1), MEDLINE OVID (from 1950 onwards), EMBASE OVID (from1980 onwards), Web of Science with Conference Proceedings (from 1970 onwards). No language restrictions were applied.

Selection criteria

Randomised controlled trials of either parallel or crossover design that assess the beneficial and harmful effects of pacing for hypertrophic cardiomyopathy were included. When crossover studies were identified, we considered data only from the first phase.

Data collection and analysis

Data from included studies were extracted onto a pre-formed data extraction paper by two authors independently. Data was then entered into Review Manager 5.1 for analysis. Risk of bias was assessed using the guidance provided in the Cochrane Handbook. For dichotomous data, relative risk was calculated; and for continuous data, the mean differences were calculated. Where appropriate data were available, meta-analysis was performed. Where meta-analysis was not possible, a narrative synthesis was written. A QUROUM flow chart was provided to show the flow of papers.

Main results

Five studies (reported in 10 papers) were identified. However, three of the five studies provided un-usable data. Thus the data from only two studies (reported in seven papers) with 105 participants were included for this review. There was insufficient data to compare results on all-cause mortality, cost effectiveness, exercise capacity, Quality of life and Peak O2 consumption.

When comparing active pacing versus placebo pacing on exercise capacity, one study showed that exercise time decreased from (13.1 ± 4.4) minutes to (12.6 ± 4.3) minutes in the placebo group and increased from (12.1 ± 5.6) minutes to (12.9 ± 4.2) minutes in the treatment group (MD 0.30; 95% CI -1.54 to 2.14). Statistically significant data from the same study showed that left ventricular outflow tract obstruction decreased from (71 ± 32) mm Hg to (52 ± 34) mm Hg in the placebo group and from (70 ± 24) mm Hg to (33 ± 27) mm Hg in the active pacing group (MD -19.00; 95% CI -32.29 to -5.71). This study was also able to show that New York Heart Association (NYHA) functional class decreased from (2.5 ± 0.5) to (2.2 ± 0.6) in the inactive pacing group and decreased from (2.6 ± 0.5) to (1.7 ± 0.7) in the placebo group (MD -0.50; 95% CI -0.78 to -0.22).

When comparing active pacing versus trancoronary ablation of septal hypertrophy (TASH), data from one study showed that NYHA functional class decreased from (3.2 ± 0.7) to (1.5 ± 0.5) in the TASH group and decreased from (3.0 ± 0.1) to (1.9 ± 0.6) in the pacemaker group. This study also showed that LV wall thickness remained unchanged in the active pacing group compared to reduction from (22 ± 4) mm to (17 ± 3) mm in the TASH group (MD 0.60; 95% CI -5.65 to 6.85) and that LV outflow tract obstruction decreased from (80 ± 35.5) mm Hg in the TASH group to (49.3 ± 37.7) mm Hg in the pacemaker group.

Authors' conclusions

Trials published to date lack information on clinically relevant end-points. Existing data is derived from small trials at high risk of bias, which concentrate on physiological measures. Their results are inconclusive. Further large and high quality trials with more appropriate outcomes are warranted.

PLAIN LANGUAGE SUMMARY

Pacing for drug-refractory or drug-intolerant Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a genetic disease with an autosomal-dominant inheritance, which can cause obstruction in the left ventricle outflow tract. This obstruction can lead to a variety of symptoms like dyspnoea, chest pain, syncope and palpitations. The prevalence of HCM in the general population, as determined from echocardiographic studies in the United States, Japan, and China, has ranged from 0.16 to 0.29 percent. Treatment options for HCM ranges from drugs to surgery with each having its own limitations. Active cardiac pacing was suggested as a treatment option in some trials. We conducted this review to assess the available evidence on the effects of active pacing in drug-refractory or drug-intolerant HCM patients. Five studies (reported in 10 papers) were found to be relevant. However, three of the five studies provided un-usable data. Thus data from only two studies (reported in seven papers) with 105 participants was included for this review. There was insufficient data to compare results on all-cause mortality, cost effectiveness, exercise capacity, Quality of life and Peak O2 consumption. There was no difference in exercise capacity when comparing active pacing versus placebo pacing. However left ventricular outflow tract obstruction decreased significantly in the active pacing group compared to placebo. New York Heart Association functional class increased in the active pacing group compared to the placebo group and this was also observed when comparing active pacing versus trancoronary ablation of septal hypertrophy. Interpretation of these data needs to be cautious because existing data is derived from small trials at high risk of bias, which concentrate on physiological measures. Their results are inconclusive. Further large and high quality trials with more appropriate outcomes are warranted.

BACKGROUND

Description of the condition

Hypertrophic cardiomyopathy (HCM) is a genetic disease with an autosomal-dominant inheritance (Maron 1987a; Richardson 1996) resulting in sarcomere dysfunction (Watkins 1995). The prevalence of HCM in the general population, as determined from echocardiographic studies in the United States, Japan, and China, has ranged from 0.16 to 0.29 percent (Maron 1995; Maron 1999c; Hada 1987; Zou 2004). These observations suggest that HCM is present in approximately one in 350 to 625 individuals. HCM has been classified into three categories, based on the presence or absence of an intracavitary pressure gradient within a hypertrophied left ventricle (Maron 1987a; Richardson 1996):

- non-obstructive HCM, with no pressure gradient and thus no symptoms;
- obstructive HCM, which is characterised by resting pressure gradient; and
- latent HCM, which simulates obstructive HCM but is provoked only by manoeuvres.

Obstruction occurs when the anterior displacement of the anterior mitral leaflet through systole results in apposition of the hypertrophied papillary muscle and the hypertrophied left ventricle (LV) wall at the level of the mid-left ventricle, producing two distinct left ventricle chambers (Falicov 1977; Fighali 1987). This mitral valve-septal contact is responsible for the subaortic pressure gradient and the mitral regurgitation (Maron 1987b; Panza 1992a; Panza 1992b; Pollick 1982). Systolic anterior motion (SAM) of the mitral valve is the most important determinant of the severity of left ventricle outflow obstruction (LVOT).

HCM can present in infancy and childhood, but more typically develops during the pubertal growth spurt (Maron 1986), and is often diagnosed during family screening (Maron 1999 a), although late onset disease may be also seen. A small proportion of patients with HCM eventually progress to an end stage characterised by reduced systolic performance and, in severe cases, left ventricular dilation and wall thinning (Harris 2006; Kubo 2007; Spirito 1987), owing mostly to myocardial ischemias due to microvascular dysfunction (Olivotto 2006). Typical symptoms include dyspnoea, chest pain, syncope and palpitations. The presence of severe symptoms in patients with HCM (defined as New York Heart Association (NYHA) class III or IV) (Table 1) is associated with worse outcomes (Autore 2005; Maron 1999 a; Maron 2003; Takagi 1999). The major causes of death in HCM are sudden cardiac death, heart failure, and stroke (Maron 2000; Elliotte 2006). Factors that increase the likelihood of HCM-related death include an embolic stroke, basal outflow obstruction > 30 mmHg and marked left ventricular hypertrophy > 25 mm.

Studies conducted in England (McKenna 1981; McKenna 1984; McKenna 1988) and in Italy (Romeo 1990) on symptomatic patients demonstrated that the annual mortality rate of HCM was approximately 2% in adults and 4% to 6% in children and adolescents.

Description of the intervention

A pacemaker is an electronic surgically implanted device that maintains regular heart rate by modifying cardiac output when it senses abnormal intracardiac potentials. It consists mainly of two parts: the pulse generator and the pacing lead(s). The pulse generator controls the pacing system and interprets the signals it receives back from the beating heart, while the pacing leads are thin, specially insulated wires that carry electrical impulses to the heart and return signals back from it to the pulse generator. A pacemaker usually requires little power and runs for several years by lithium batteries (Furman 1977; Levine 2002; Mond 1983).

Two types of pacemakers are currently available: single-chamber pacemakers sense and pace either in the atrium or the ventricle, while dual chamber pacemakers (DDD) can sense and pace in both chambers (Hauser 1983). The atrial or ventricular output can be either inhibited or triggered in response to a sensed signal. Rate responsive pacemakers have one or more sensors that detect physical activity and adjust the pacing rate accordingly, which is necessary in patients with chronotropic incompetence (Bush 1994; Clarke 1991).

In 1987, the North American Society of Pacing and Electrophysiology (NASPE) and the British Pacing and Electrophysiology Group (BPEG) set up the NASPE/BPEG Generic Pacemaker Code (NBG Code), which they developed to describe different pacing modes (Bernstein 1987). Due to recent developments in technology this code has been updated (Bernstein 2002); see Table 2 for details. See Table 3 for a Glossary of Terms.

Pacemakers are not without adverse events. Reported complications are paroxysmal atrial fibrillation, infection, local irritation and electrode displacement (Gao 2007; Kappenberger 1997).

How the intervention might work

Several theories have been put forward to explain how dual-chamber pacing with short atrioventricular (AV) delay reduces systolic anterior motion and subsequent left ventricle outflow obstruction:

1. Pre-excitation of the right ventricle alters the dynamics and timing of ventricular contraction, ensuring left ventricle apical activation prior to septal activation (Betocchi 2002; Pak 1998). This may help by decreasing the excursion of the septal wall into the left ventricle outflow obstruction. The paradoxical (delayed) activation of the inter-ventricular septum during dual-chamber pacing could limit outflow tract narrowing by decreasing the projection of the ventricular septum into the outflow tract and its dynamic obstruction (Pak 1998).
2. The negative inotropic effect may play a role by decreasing the ejection acceleration and decreasing early forces on the mitral valve (Sherrid 1998).
3. Pacing activation of the right ventricular apex could produce early activation of the papillary muscles and chordae which could limit mitral valve leaflet excursion. Premature apical tensing of the mitral apparatus - thus early tensing of the chordal apparatus of the mitral valve - may possibly reduce systolic anterior motion by mitigating excess slack.

Why it is important to do this review

Many treatments are now available for HCM including drug therapy, septal ablation and septal myotomy. Unfortunately the evidence on the effectiveness of these interventions is limited. Furthermore,

there are no systematic reviews evaluating the beneficial and harmful effect of pacing in HCM. Also, there is data which indicates how many patients with HCM get implanted with pacemakers.

Negative inotropes, including beta blockers (Fananapazir 1992; Thompson 1980), calcium channel blockers (Bonow 1985b; Rosing 1985), and disopyramide (Sherrid 2005) are the most widely used initial therapies, although the data supporting their use come from uncontrolled studies. Unfortunately there are little randomised controlled trials on the efficacy of any of these therapies. As a result, treatment strategies are based upon observational studies and clinical experience (Fifer 2008).

Septal ablation consists of infarction and thinning of the proximal interventricular septum via an infusion of ethanol through an angioplasty catheter. This procedure, however, can be complicated by complete heart block, electrocardiogram changes, right bundle branch block and ventricular arrhythmias (Boltwood 2004).

Septal myotomy, in which an extensive part of the cardiac septal muscle has to be excised to achieve clinical progress, is in the same instance a risk factor for ventricular septal deficit (Maron 2004; Siegman 1989; ten Berg 1994).

Due to the fact that many patients will continue having symptoms or develop complications despite maximal therapy, and because only limited data is available on the efficacy of the above mentioned interventions, alternative interventions have been sought in order to improve the patient's symptoms and probably the clinical endpoint.

Observational studies and small randomised trials have suggested symptomatic and functional benefits from pacing (Gadler 1997; Kappenberger 1997). The 2008 American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) guidelines recommended use of a pacemaker in patients with HCM for sinus node dysfunction or AV block (Epstein 2008). Permanent pacing may be considered in medically refractory symptomatic patients with HCM and significant resting or provoked left ventricular outflow tract obstruction.

Pacing, although not the primary treatment for HCM, could be beneficial to patients with relative or absolute contraindications to surgery or alcohol ablation, usually because of septum/mitral valve anatomy or co-morbidities. This review is important because it summarises the best available evidence on the benefit and harm of pacing for drug-refractory and drug-intolerant HCM.

OBJECTIVES

To assess the available evidence on the effects of pacing in drug-refractory or drug-intolerant HCM patients.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomised controlled trials (RCTs) of either parallel group or crossover design that had assessed the beneficial and harmful effects of pacing for hypertrophic cardiomyopathy. We placed no restrictions on blinding, publication status, conference proceedings, or language. We excluded quasi-randomised and observational studies.

Types of participants

We included children (defined as <18 years old) or adults (≥18 years old) of either sex with drug-refractory or drug-intolerant HCM, with or without other heart co-morbidities.

Types of interventions

Considering at least three month treatment duration and irrespective of follow-up period, we compared dual-chamber pacing (DDD), dual-chamber pacing with rate modulation (DDD-R), or VDD with appropriate programming to:

- placebo (minimum rate backup pacing AAI and VVI);
- myotomy;
- septal ablation (non surgical septal reduction therapy with or without alcohol ablation); or
- another type of pacing (DDD, DDD-R or VDD).

Types of outcome measures

Primary outcomes

Our primary outcomes were:

- all-cause mortality;
- exercise capacity;
- symptoms improvement as measured by improvement of: New York Heart Association functional class and/or exercise capacity (as measured by exercise duration or walking distance or both);
- quality of life, as measured according to a recognised scale.

When different scales for measuring quality of life were used in different studies, we reported the number of statistically significant differences in quality of life as improved, not improved or worsened as reported by each trialist. Where several studies had used the same scale, we summarised the results together.

Secondary outcomes

Our secondary outcomes were:

- left ventricle outflow obstruction gradient;
- NYHA functional classification;
- left ventricular wall thickness;
- peak oxygen consumption;
- complications related to the device implantation; and
- cost-effectiveness.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, 2010, Issue 1), MEDLINE 1950 to April 2010, EMBASE 1980 to April 2010, and Science Citation Index Expanded (1970 to April 2010). (Royle 2003) The search strategies used can be found in Appendix 1. No language or date restrictions were applied.

Searching other resources

We checked the bibliographic references of identified randomised clinical trials and meta-analyses to find randomised clinical trials not identified by the electronic searches. We then approached the principal authors of the identified randomised clinical trials and enquired about any other randomised clinical trials they might know of. We looked for unpublished or ongoing studies by searching the metaRegister of controlled trials (including International Standard Randomised Controlled Trial Number Register (ISRCTN) and the National Institutes of Health (NIH) - randomised trial records) at http://www.controlled-trials.com/.

Data collection and analysis

We performed the review and meta-analyses following the recommendations of The Cochrane Collaboration (Higgins 2008). We performed the analyses using Review Manager 5.1 (RevMan 2011).

Selection of studies

We listed the identified trials and two authors (HA and KC) independently assessed their fulfilment of the inclusion criteria. We listed the excluded trials with the reason for exclusion. Disagreements were resolved by discussion. We summarised the flow of papers through the search and selection process using a QUOROM flow chart.

Data extraction and management

Two authors (MQ and HA) extracted data independently and resolved disagreements by discussion. A standardised data collection form was used to extract data on methods, participants, interventions, and outcomes. If more than one publication on a single randomised clinical trial was identified, the most appropriate data was extracted.

Assessment of risk of bias in included studies

We assessed methodological quality according to the level of confidence that the design and report of a published trial restricted bias in the intervention comparison (Moher 1998). In assessing the risk of bias we used The Cochrane Collaboration's tool for assessing risk of bias as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008).

Measures of treatment effect

Dichotomous data

We calculated the relative risks with 95% confidence intervals (CI).

Continuous data

We calculated the mean differences with 95% CI.

In case the overall results were statistically significant by the random-effects model, we calculated relative risk reduction (RRR), the number needed to treat (NNT) and the number needed to harm (NNH) if possible.

Unit of analysis issues

When we retrieved crossover studies in the search, we took only the first arm into consideration. This should reduce the possibility of a carryover effect of pacing on left ventricular wall thickness (Fananapazir 1994).

Dealing with missing data

We performed all analyses on an intention-to-treat basis, using the last reported observed response ('carry forward'), and including all participants, irrespective of compliance or follow up. In addition, we performed 'a worst scenario' analysis, considering all participants with missing data as treatment failures.

Assessment of heterogeneity

We aimed to assess statistical heterogeneity using a Chi^2 test and used the I^2 test to quantify inconsistency across included studies (Higgins 2003, Higgins 2008) and by examining the graphical presentations ('forest plot') (Egger 1997). We would use the random-effects model to avoid the risk that the variability between the studies may be exclusively because of a random sampling variation around a fixed effect. Using the random-effects model is also recommended by Clinical Evidence (Clinical Evidence).

Assessment of reporting biases

We tried to locate the protocol for each included randomised controlled trial (RCT). If the protocol was available, we compared its outcomes with those in the published RCT report. If it was not available, we compared the outcomes listed in the methods section of the report with the actual reported results.We had aimed to use a funnel plot (Egger 1997) of all included trials to check the presence of publication bias.

Data synthesis

We aimed to undertake meta-analysis where there were sufficient data of suitable type, using RevMan 5.1 (RevMan 2011). In the event that there were too few clinically homogeneous trials for us to be able to perform a meta-analysis, we presented a narrative synthesis. When we could not find relevant RCTs, we used non-RCT studies in the discussion section.

Subgroup analysis and investigation of heterogeneity

We aimed to perform subgroup analyses according to whether participants are:

- asymptomatic or symptomatic; and
- children or adults.

Sensitivity analysis

We aimed to conduct sensitivity analyses to compare:

- RCTs lasting three months with those lasting for more than three months;
- low-quality and high-quality studies.

RESULTS

Description of studies

Results of the search

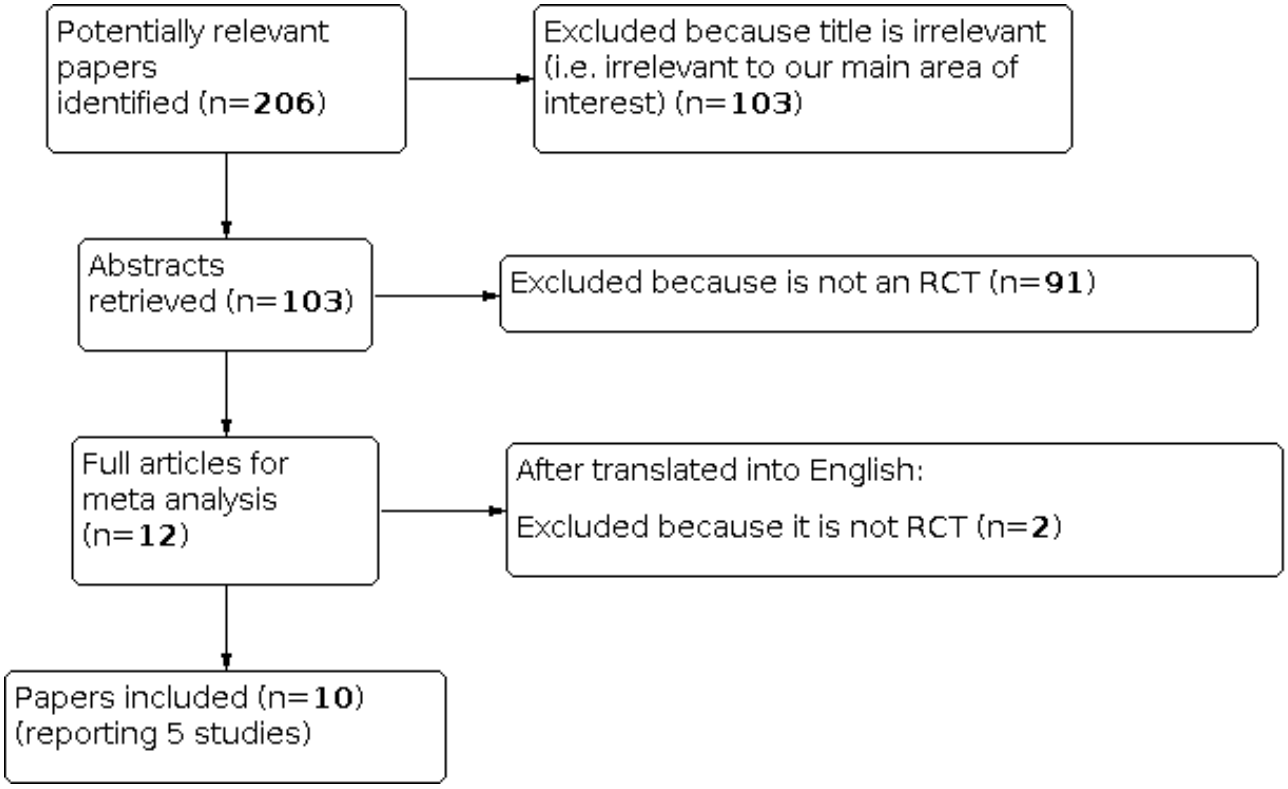
A total of 206 papers were originally retrieved by searching the databases, of which 103 papers were judged to be clearly irrelevant. The abstracts of the remaining 103 papers were retrieved and of these, 91 were excluded as they did not meet one or more of the inclusion criteria. We extracted data of the 12 remaining papers. Six of those paper were originally in English, one in French, one in Czech, one in Chinese and three in German. Both the French

paper (Gras 1995b) and the Czech paper (Krejci 2006) were excluded because they were not randomised. Eventually, we had 10 papers reporting five included studies; six of the 10 papers were reported the same study (Kappenberger 1997) including two that were exactly the same but with different German-to-English translated titles on different databases (Medline and Embase).

In the five included studies, 184 participants were recruited. Apart from (Gao 2007) which did not specify neither the male proportion nor the mean age, the male proportion in the other four studies was 59.6% and the range of mean age is (53-69). Three studies were conducted in the USA (Maron 1999b; Mickelsen 2004; Nishimura 1997), one in Switzerland (Kappenberger 1997) and one in China (Gao 2007). Maron 1999b was funded in part by a grant from Medtronic, Inc. No information about funding were provided in the rest. Wash-out periods were not determined in all four cross-over studies (Kappenberger 1997; Maron 1999b; Mickelsen 2004; Nishimura 1997).

Please refer to the QUOROM flow chart (Figure 1).

Figure 1. QUOROM flow chart.



See (Characteristics of included studies), and (Characteristics of excluded studies).

Included studies

Gao 2007 is a Chinese RCT (with an English abstract) of parallel design that recruited 23 participants aged > 60 years old. The Chinese full text was translated. It is the only study in this review that compared active pacing versus trancoronary ablation of septal hypertrophy.

Kappenberger 1997 is a multicenter RCT of cross-over design done in Switzerland that recruited 82 patients. The study group classified patients into Group A when the acute study showed a peak gradient reduction of >30% after acute pacing was introduced or Group B if there was less or no gradient modification. Although it was mentioned in the study that patients were fully assessed after each phase of the study, data regarding the first phase was not provided. We contacted the authors in order to obtain the data but with no success. Luckily, the same group published another paper (Linde 1999) using the same patient group and considering only the first arm data in their analyses. Data on left ventricular outflow tract obstruction, exercise capacity and NYHA functional classification were taken from Linde 1999. Another paper (Kappenberger 1997b) was a meeting abstract for the same study published in different journal and was referenced to it. The other three papers (Meisel 1999, Miesel 2000a and Meisel 2000) referenced to Kappenberger 1997 were all in German and results in all these exactly match Kappenberger 1997. Meisel 2000 was cited twice for the same paper; one was in English and the other was the German translation and were found in different databases (Medline vs. Embase), where as Meisel 1999 was published in supplement 2 of the same journal a year before.

Maron 1999b conducted the M-PATHY study that was a multicenter randomised, double-blind, crossover study with 44 patients. The first six months of the study protocol used a randomised, crossover, double-blind design where patients were randomised to either three months of DDD pacing or placebo pacing (AAI at 30bpm). Patients were crossed over to the alternative mode for the subsequent three month period. After six months, all patients were paced for six months in an uncontrolled and unblinded fashion. Clinical evaluation was performed at four intervals: baseline, after

three months of either DDD pacing or AAI-30 mode, at six months after the alternative mode, and at 12 months after six additional months of pacing. Although they evaluated their patients at the 4 aforementioned intervals, complete data was not provided in the full text. We contacted the author and the sponsoring company and they expressed that the data for the first arm is not obtainable at the time. This is unfortunate as this is one of the most important studies in this area and yet we can not analyse its data.

Mickelsen 2004 conducted a study of 11 patients that was different than the other included studies we have in our review in that they analysed the aortic flow in the descending aorta using Doppler, after they implanted the pacemaker in patients with medical refractory symptoms thought to be secondary to hypertrophic obstructive cardiomyopathy. Patients in this cross-over RCT underwent three different types of pacing: placebo pacing (AAI set to 30 bpm), active DDD pacing with an AVinterval at 30 ms (DDD30), and active DDD pacing with the AV interval "optimised" using aortic Doppler echocardiography (DDDop). The optimisation means to select the AV interval that generated the maximal R-N interval (QRS to notch) interval, where the notch is a sign of any sudden change in velocities which denotes obstruction. As per our protocol and in the case of a cross-over design we considered only the first arm of the study. This study, however, did not present data separately, although they had done separate analysis after the first phase was completed. We contacted the author and unfortunately we have not heard from him yet.

Nishimura 1997 conducted an RCT with cross-over design that recruited 21 patients and evaluated active pacing versus inactive pacing for patients with hypertrophic cardiomyopathy with severe symptoms unresponsive to medical therapy. After the cross-over design was done there was no long follow up reported. Data about the first arm of this cross over study was not given, and even after contacting the author we have not received any response. .

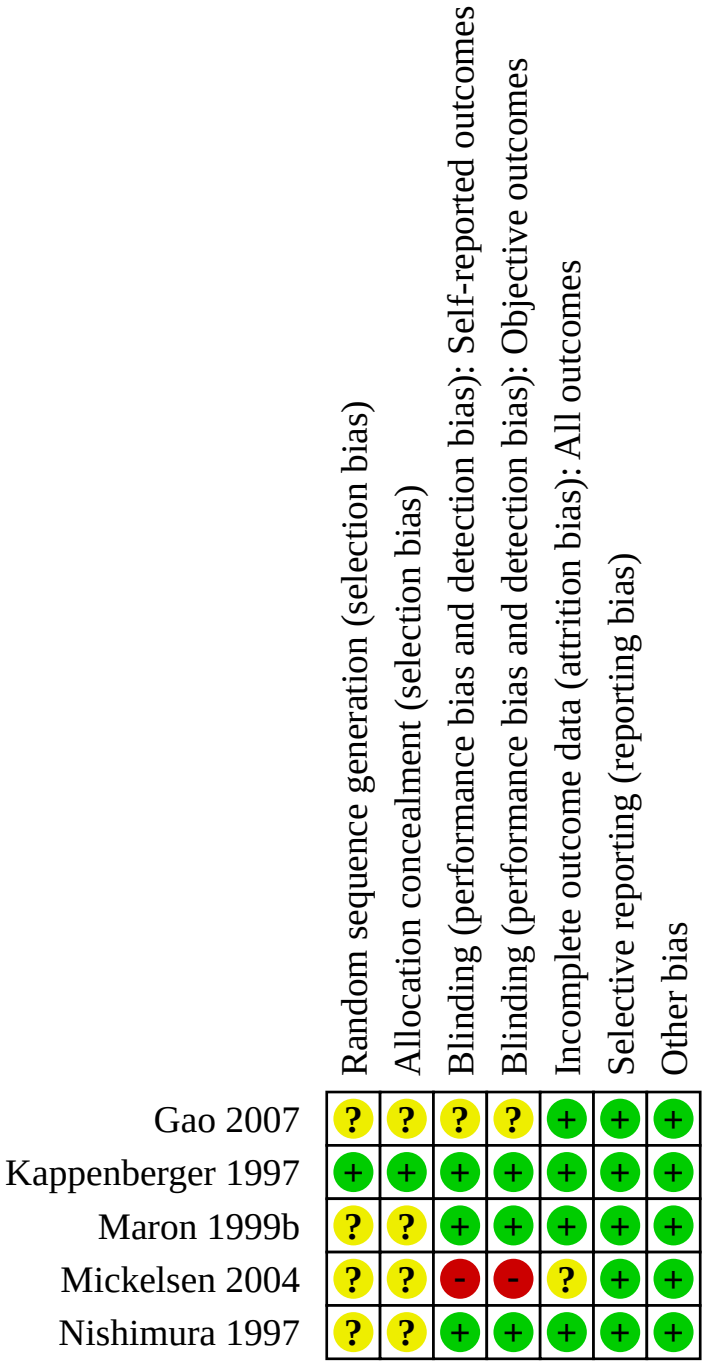
Excluded studies

Out of 206 papers identified in the search, 103 papers were excluded early in the selection process because the title was irrelevant to our main area of interest. Ninety-three papers of the remaining 103 were not randomised controlled trials. See (Characteristics of excluded studies).

Risk of bias in included studies

After assessing each of the five included studies individually by two of the authors, it was found that the methodological quality of the included studies in this review is inconsistent. Please see the characteristics of included studies tables (Characteristics of included studies). We used the 'Risk of bias graph' figure, which illustrates the proportion of studies with each of the judgements ('Low risk', 'High risk', 'Unclear risk' of bias) for each entry in the tool. Please refer to (Figure 2).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

All the five included studies were conducted using a random sequence generation, however, the methods for this aim were unclear in four of them (Gao 2007; Maron 1999b; Mickelsen 2004; Nishimura 1997) and therefore the risk of selection bias was unable to be determined. Kappenberger 1997 did mention using

central randomisation to define the sequence generation and that allocation was concealed.

Blinding

Three of the included studies (Kappenberger 1997, Maron 1999b, Nishimura 1997) conducted a double-blinded study and therefore they were classified as low risk for having performance or detection bias. One of the studies, Mickelsen 2004, conducted a single blinded study and Gao 2007, did not give any information regarding whether blinding was considered or not.

Incomplete outcome data

Fortunately, incomplete outcome data were completely reported in four of the five included studies, and therefore would be considered as low-risk studies for attrition bias:

In Gao 2007: it was noted that two patients dropped out from the treatment group and that was clearly reported.

In Kappenberger 1997: Of the 83 participants, 81 completed the first phase of the cross over and two dropped out; three of the placebo group patients were shifted to the second arm earlier than the first 12-week period. Data from all drop-outs were clearly reported.

In Maron 1999b: Of the 44 participants, 12 failed to complete the protocol design; three in the second phase which is beyond the inclusion criteria of our review (taking only the first arm) and nine in the first phase (one after randomisation and eight reprogrammed early from placebo to treatment group). These incomplete data were clearly reported.

In Nishimura 1997: Of the 21 participants, One patient was excluded from the study in the first phase (from the treatment group) due to his severe symptoms and underwent myotomy. Another did not show for follow up. All these data were reported clearly.

Only in one study, Mickelsen 2004, there were no information regarding the incomplete outcome data and therefore its bias risk will be considered unclear.

Selective reporting

There was no selective reporting of outcomes, time-points or subgroup analyses in three of the five included studies (Gao 2007; Kappenberger 1997; Maron 1999b).

Other potential sources of bias

In Kappenberger 1997 the p value of most of the parameters in the inactive pacing group were not specified making it hard to know if the effect was statically significant or not.

In Gao 2007 we noticed that the numbers about the outcomes from the table provided in the study differs significantly from the numbers provided in the English abstract.

Effects of interventions

All-cause mortality

The description of all-cause mortality was insufficient in all trials. None of the trials included has reported mortality among participants.

Exercise capacity

Only Kappenberger 1997 reported on exercise capacity; no data could be extracted from the other included trials on this outcome as the data from the two cross-over phases was combined and we could not take the data regarding the first phase only. The authors were contacted to retrieve the data on the first phase only, but no additional data was provided.

Kappenberger 1997 reported on exercise capacity; exercise time has decreased from (13.1 ± 4.4) minutes to (12.6 ± 4.3) minutes. It was increased significantly from (12.1 ± 5.6) minutes to (12.9 ± 4.2) minutes at the end of the first phase in the treatment group (MD 0.30; 95% CI -1.55 to 2.15).

Symptoms improvement:

As measured by improvement of the NYHA functional class and/or exercise capacity (as measured by exercise duration or walking distance or both); both Gao 2007 and Kappenberger 1997 reported on symptoms improvements per protocol; no data could be extracted from the other included trials on this outcome as the data from the two cross-over phases was combined and we could not take the data regarding the first phase only. The authors were contacted to retrieve the data on the first phase only, but no additional data was provided.

Gao 2007 reported that NYHA functional class improved from (3.2 ± 0.7) to (1.5 ± 0.5) and from (3.0 ± 0.1) to (1.9 ± 0.6) post transcoronary ablation of septal hypertrophy (TASH) and dual-chamber cardiac pacing (PM), respectively versus baseline.

Of note, this study also used a general symptomatic score which was decreased from (5.9 ± 1.6) to (1.8 ± 0.7) and from (4.5 ± 1.3) to (2.3 ± 1.6) post TASH and PM, respectively versus baseline.

Kappenberger 1997 reported that NYHA functional class has dropped from (2.5 ± 0.5) at the baseline to (2.2 ± 0.6) and from (2.6 ± 0.5) at the baseline to (1.7 ± 0.7) at the end of the first phase in the placebo versus the treatment group, respectively.

Quality of life

Only one trial (Kappenberger 1997) reported on quality of life; no data could be extracted from the other included trials on this outcome as the data from the two cross-over phases was combined and we could not take the data regarding the first phase only. The authors were contacted to retrieve the data on the first phase only, but no additional data was provided.

Kappenberger 1997 evaluated quality of life using the Karolinska questionnaire as per-protocol. General quality-of-life questions concerned physical functioning, such as the ability to be self autonomous, that is, walking a few hundred meters on level ground, and the capacity for more strenuous physical activity, such as lifting heavy objects; social, sexual, and cognitive functioning; alertness; sleep; self-perceived health; and emotional state. There were 16 questions on symptoms, and two questions regarding self-perceived health status. The results were added into averages. A percentage assessment for quality-of-life parameters was chosen in the presentation of results, because the scales differ for the various dimensions.

In the placebo group, there was a statistically significant improvement from the baseline in the following measures:

Alertness, Chest pain, Dyspnea, Dizziness, Palpitations, Cognitive functioning, Quality of sleep, Self-autonomy, Strenuous activity, Social functioning, Self-perceived restriction in health, Self-perceived health, Depression score. There were no significant percentage differences (6, 29, 20, 27, 35, 27, 28, 7, 3, 8, 16, 7, 19, respectively). However there was a statistically significant worsening from the base line in sexual functioning with a percentage difference of (-3).

In the treatment group, there was a statistically significant improvement from the baseline in the following measures: Alertness, Chest pain, Dyspnea, Dizziness, Palpitations, Quality of sleep, Self-autonomy, Strenuous activity, Sexual functioning, Social functioning, Self-perceived restriction in health, Self-perceived health, Depression score. There were no significant percentage differences (19, 43, 30, 35, 40, 15, 29, 17, 7, 18, 32, 18, 17, respectively). However there was a statistically significant worsening from the base line only in cognitive functioning with a percentage difference of (-7).

Left ventricle outflow obstruction gradient

Only two trials (Gao 2007 and Kappenberger 1997) reported on left ventricle outflow obstruction gradient per-protocol. None of the other included trials reported outcome on the first cross-over phase as per-protocol as the data from the two cross-over phases was combined. The author were contacted to retrieve the data on the first phase only, but no additional data was provided.

Gao 2007 reported that the decrease of left ventricular out flow pressure gradient was (80.0 ± 35.5) mmHg (1 mmHg =0.1333 kPa) and (49.3 ± 37.7) mmHg post transcoronary ablation of septal hypertrophy (TASH) and dual-chamber cardiac pacing (PM) treatments respectively versus baseline (MD -30.70; 95% CI -62.41 to 1.01).

Kappenberger 1997 reported that left ventricular outflow obstruction dropped from (71 ± 32) mmHg at the baseline to (52 ± 34) mmHg, and from (70 ± 24) mmHg at the baseline to (33 ± 27) mmHg at the end of the first phase in the placebo versus the treatment group, respectively; this difference was not significant (MD -19.00; 95% CI -32.39 to -5.61).

New York Heart Association Functional Classification

Only two trials (Gao 2007 and Kappenberger 1997) reported on NYHA functional classification per-protocol. None of the other included trials reported outcome on the first cross-over phase as per-protocol as the data from the two cross-over phases was combined. The authors were contacted to retrieve the data on the first phase only, but no additional data was provided.

Gao 2007, and as mentioned above in symptoms Improvement, reported that NYHA class was improved from (3.2 ± 0.7) to (1.5 ± 0.5) and from (3.0 ± 0.1) to (1.9 ± 0.6) post transcoronary ablation of septal hypertrophy (TASH) and dual-chamber cardiac pacing (PM), respectively versus baseline. Effect difference among the two treatment arms was not significant (MD -0.50; 95% CI -1.05 to 0.05).

Kappenberger 1997, and as mentioned above in symptoms Improvement, reported that NYHA functional class was dropped from (2.5 ± 0.5) at the baseline to (2.2 ± 0.6), and from (2.6 ± 0.5) at the baseline to (1.7 ± 0.7) at the end of the first phase in the placebo versus the treatment group, respectively. Active pacing significantly improved NYHA functional classification significantly compared with placebo pacing (MD -0.50; 95% CI -0.78 to -0.22).

Left ventricular wall thickness

Only one trial (Gao 2007) reported on left ventricular wall thickness per-protocol. Gao 2007 reported that interventricular wall thickness was significantly reduced post transcoronary ablation of septal hypertrophy (TASH) [(22 ± 4) mm versus (17 ± 3) mm] and remained unchanged in dual-chamber cardiac pacing (PM) group. Effect difference among the two treatment arms was not significant (MD 0.60; 95% CI -5.65 to 6.85).

Peak oxygen consumption

Only one trial (Kappenberger 1997) reported on Peak oxygen consumption per-protocol. None of the other included trials reported outcome on the first cross-over phase as per-protocol as the data from the two cross-over phases was combined. The authors were contacted to retrieve the data on the first phase only, but no additional data was provided.

Kappenberger 1997 reported that peak oxygen uptake, measured by ml/kg/min, decreased from (19.9 ± 5.7) to (18.2 ± 5.0) in the placebo group where increased from (17.1 ± 5.6) to (18.7 ± 5.5) in the treatment group, both at the end of the first phase .

Complications related to the device implantation

Only two trials (Gao 2007 and Kappenberger 1997) reported on complications related to the device implantation per-protocol. Gao 2007 reported three patients with paroxysmal atrial fibrillation (two patients in TASH group and one patient in PM group) developed chronic atrial fibrillation during the follow-up. Kappenberger 1997 mentioned that 30 reported adverse events were related to the pacemaker treatment: infection and local irritation (no=8) or electrode displacement (seven atrial and three ventricular). Despite these problems, correct pacemaker function was finally achieved in all patients. No other minor event was related to pacing; one patient was operated on during cross over phase for failure of therapy.

Cost effectiveness

None of the included trials considered cost effectiveness as one of the outcome measures.

DISCUSSION

Summary of main results

There was no significant difference between the five studies in terms of pacing mode and patient population. All studies enrolled adult patients (>18) who were diagnosed with HOCM that was refractory to medical treatment or were not tolerating the medical treatment. Four of the studies used the cross-over design (Kappenberger 1997; Maron 1999b; Mickelsen 2004; Nishimura 1997) and only Gao 2007 used the parallel design. The pacing mode used in the treatment group in all studies was DDD pacing and the inactive pacing was AAI pacing. Gao 2007 was the only study that compared DDD pacing to TASH. In general (except Gao 2007), all studies reported on exercise capacity and quality of life. All studies reported on NYHA functional class. We were unable to use data from 3 studies because the authors had not provided data in the first arm of the study (Maron 1999b; Mickelsen 2004; Nishimura 1997). Moreover, there was insufficient data to compare results on

all-cause mortality, cost effectiveness, quality of life and Peak O2 consumption. Thus, the data for this systematic review based on two small studies, one of which had high risk of bias.

The only study whose data can be used on the exercise capacity time was Kappenberger 1997 who reported that the exercise time has decreased from (13.1 ± 4.4) min to (12.6 ± 4.3) min in the placebo group and has increased from (12.1 ± 5.6) min to (12.9 ± 4.2) min in the treatment group (MD 0.30; 95% CI -1.55 to 2.15). Similarily, there was only one study (Gao 2007) whose data could be used on Left ventricular thickness which reported that the Left ventricular thickness remained unchanged in the active pacing group (MD 0.60; 95% CI -5.65 to 6.85). Kappenberger 1997 was able to identify worsening scores of sexual and cognitive functioning in the intervention groups compared with the placebo groups.

Overall completeness and applicability of evidence

The main limitation was the unavailability of the first phase data in three of the five included studies (Maron 1999b; Mickelsen 2004; Nishimura 1997). We attempted to obtain the data by writing to the authors, but none was forthcoming.Thus, we await these data in order to have more complete evidence. Meanwhile we cannot comment on the applicability of any evidence.

Quality of the evidence

Of the five included studies we used data from two studies (Gao 2007; Kappenberger 1997) one of which was a high-quality studies Kappenberger 1997. Between these two studies we have 105 patients.

Potential biases in the review process

The quantity and quality of available evidence limited our findings and interpretations. Only five trials total were included in this review, three of which provided unusable data due to restrictions in our protocol regarding the cross-over trials where we only took the first arm into consideration.

Only one of the five included studies reported on the method used in randomization and concealment (Kappenberger 1997), while all the other four only reported that the study was randomized with out specifying the method used; this can increase the selection bias in the included studies.

Moreover, none of the trials included in this review reported on patients mortality. One might argue that RCTs with longer follow-up periods are required to confirm a beneficial effect of active pacing in hypertrophic cardiomyopathy.

Agreements and disagreements with other studies or reviews

Guidelines regarding the management of HCM have been issued by the American College of Cardiology and the European Society of Cardiology (Clinical Practice Guideline 2003; Clinical Practice Guidline 2003b). It is recommended that pharmacologic therapy is the first-line approach to relief the symptoms of HOCM. Beta-blockers are generally the initial choice. In case of refractory symptoms despite maximal medical treatment or in case of drug-intolerant, other invasive therapies might be considered. These interventions consist of surgical septal myectomy, dual-chamber pacing, and catheter-based alcohol septal ablation. Surgical septal myotomy is usually considered to be the gold standard for treatment of HOCM. Dual-chamber pacing is limited to patients who have coexisting illnesses that are contraindications to other therapies or those who require pacing for bradycardia (Nishimura 2004b).The evidence collected in this review shows no convincing evidence to support or refute the use of active pacing in patients with hypertrophic cardiomyopathy.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence collected in this review shows no convincing evidence to support or refute the use of active pacing in patients with HCM. Though, active pacing may decrease both the left ventricular wall thickness and the left ventricular outflow obstruction the evidence is based on small trial numbers and is thus incomplete.

Implications for research

Adequately powered and long-term conducted RCTs with low risk of bias are needed to support or change the current results and knowledge of the effects active pacing in HCM. We advise authors who are conducting an RCT with a cross-over design to report the data after each phase so that data can be meaningfully interpreted. We feel that much data is missing in this area because only combined data from both phases were reported.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Gao 2007

Study characteristics	
Methods	RCT with parallel design
Participants	23 participants (15 as treatment group and 8 as a comparison group), Adults (> 18)
Interventions	Intervention: Transcoronary ablation of septal hypertrophy Control: Dual Chamber cardiac pacing
Outcomes	Ssymptoms improvement (NYHA classification, CCS classification) left ventricle outflow obstruction gradient (pressure gradient) New York Heart Association Functional Classification left ventricular wall thickness.
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Gao 2007 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Authors mentioned that the patients "were randomised."
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding (performance bias and detection bias) Self-reported outcomes	Unclear risk	No information given
Blinding (performance bias and detection bias) Objective outcomes	Unclear risk	No information given
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 drop-outs in the treatment group, clearly reported
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Low risk	No other bias could be found

Kappenberger 1997

Study characteristics	
Methods	RCT with crossover design
Participants	82 participants (41 as treatment group and 41 as a comparison group), Adults (> 18)
Interventions	intervention: DDD pacing Control: Placebo (AAI)
Outcomes	exercise capacity (walking) symptoms improvement (Clinical hx and quality of life questionnaire) quality of life (karolinska) left ventricle outflow obstruction gradient New York Heart Association Functional Classification complications related to the device implantation (irritation, infection, electrodes displacement)
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stratified by central randomisation

Kappenberger 1997 *(Continued)*

Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding (performance bias and detection bias) Self-reported outcomes	Low risk	Double blind
Blinding (performance bias and detection bias) Objective outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of the 83 patients, 82 completed the first phase of the cross over, however, three of the placebo patients were shifted to the second arm earlier than the first 12-week period. They were clearly reported
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Low risk	No other bias could be found

Maron 1999b

Study characteristics	
Methods	RCT with crossover design
Participants	44 participants (No info available on how many patients in the treatment and the comparison group), Adults (> 18)
Interventions	Intervention: DDD pacing Control: Placebo (AAI)
Outcomes	Left ventricle wall thickness exercise time (Chrono-tropic Assessment Exercise Protocol) quality of life (Minnesota Living with Heart Failure Questionnaire) oxygen consumption left ventricle outflow obstruction gradient New York Heart Association Functional Classification complications related to the device implantation (pocket site infections, generator migration,lead dislodgement, fracture or malfunction).
Notes	Its data is unusable for this review. Author was contacted and he could not provide us with the data needed.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The first 6 months of the study protocol used a randomised, crossover, double-blind design

Maron 1999b *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No information given
Blinding (performance bias and detection bias) Self-reported outcomes	Low risk	Double blind
Blinding (performance bias and detection bias) Objective outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	12 patient failed to complete the protocol design: 9 in the first phase (one after randomisation and 8 reprogrammed early from placebo to treatment group). Clearly reported
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Low risk	No other bias could be found

Mickelsen 2004

Study characteristics	
Methods	RCT with crossover design
Participants	11 participants (No info available on how many patients in the treatment and the comparison group), Adults (> 18)
Interventions	Intervention: DDDwith anAVinterval at 30 ms (DDD30), and DDD with the AV interval “optimised” using aortic Doppler echocardiography (DDDop) Control: Placebo (AAI)
Outcomes	Exercise time (treadmill) quality of life (SF-36) left ventricle outflow obstruction gradient.
Notes	Its data is unusable for this review. Author was contacted and there was no reply.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	randomised single-blinded crossover trial
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding (performance bias and detection bias) Self-reported outcomes	High risk	Single blinded

Mickelsen 2004 *(Continued)*

Blinding (performance bias and detection bias) Objective outcomes	High risk	Single blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information given the study
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Low risk	No other bias could be found

Nishimura 1997

Study characteristics	
Methods	RCT with crossover design
Participants	21 participants (9 as treatment group and 11 as a comparison group), Adults (> 18)
Interventions	Intervention: DDD pacing Control: Placebo (AAI)
Outcomes	Exercise capacity (treadmill) symptoms improvement (Subjective as improved, no change, deteriorate) quality of life (Minnesota) left ventricle outflow obstruction gradient New York Heart Association Functional Classification peak oxygen consumption.
Notes	Its data is unusable for this review. Author was contacted and there was no reply.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding (performance bias and detection bias) Self-reported outcomes	Low risk	Double blind
Blinding (performance bias and detection bias) Objective outcomes	Low risk	Double blind

Nishimura 1997 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	One patient was excluded from the study (from the treatment group) due to his severe symptoms and underwent myotomy Another did not show for follow-up
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Low risk	No other bias could be found

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Agarwal 2010	Irelevant title (title is not related to our main area of interest).
Aizawa 1993	Irelevant title (title is not related to our main area of interest).
Alam 2006	Irelevant title (title is not related to our main area of interest).
Alam 2009	Irelevant title (title is not related to our main area of interest).
Alfonso1996	Irelevant title (title is not related to our main area of interest).
Anderson 1983	Irelevant title (title is not related to our main area of interest).
Badie 2009	Irelevant title (title is not related to our main area of interest).
Begley 2001	not RCT, everyone got paced
Bellon 1995	Irelevant title (title is not related to our main area of interest).
Ben 2000	not RCT
Betocchi 1988	Irelevant title (title is not related to our main area of interest).
Betocchi 1996	Irelevant title (title is not related to our main area of interest).
Betocchi 2002	no randomisation
Bhatia 2004	not RCT
Binder 2008	not RCT
Birnie 2006	Irelevant title (title is not related to our main area of interest).
Bonow 1985	Irelevant title (title is not related to our main area of interest).
Braunschweig 2000	not RCT
Braunwald 1997	Irelevant title (title is not related to our main area of interest).
Brignole 1988	Irelevant title (title is not related to our main area of interest).

Study	Reason for exclusion
Brill 1985	Irelevant title (title is not related to our main area of interest).
Bryce 2001	not RCT
Can 2009	Irelevant title (title is not related to our main area of interest).
Cannon 1985	Irelevant title (title is not related to our main area of interest).
Cannon 1987 a	Irelevant title (title is not related to our main area of interest).
Cannon 1987 b	not RCT
Cannon 1990	Irelevant title (title is not related to our main area of interest).
Capezzuto 2000	not RCT
Cesario 2006	not RCT
Chen 2007	not RCT
Ciaramitaro 2006	Irelevant title (title is not related to our main area of interest).
Coats 2008	not RCT
Cregg 1999	Irelevant title (title is not related to our main area of interest).
da Fonseca 2007	Irelevant title (title is not related to our main area of interest).
Daley 1987	not RCT
Daubert 2004	not RCT
Deharo 2000	not RCT
Dimitrow 2000	no randomization
Dimitrow 2002	Irelevant title (title is not related to our main area of interest).
Dimitrow 2004	not randomized
Duarte 1999	not RCT
El 2007	Irelevant title (title is not related to our main area of interest).
El 2008	Irelevant title (title is not related to our main area of interest).
Faber 2007 a	Irelevant title (title is not related to our main area of interest).
Faber 2007 b	Irelevant title (title is not related to our main area of interest).
Fananapazir 1991	not randomised
Fananapazir 1998	not RCT
Fei 2001	not RCT

Study	Reason for exclusion
Ferguson 1997	not RCT
Fernandes 2005	Irelevant title (title is not related to our main area of interest).
Finsterer 2010	Irelevant title (title is not related to our main area of interest).
Frank 1978	not randomised
Frank 1983	Irelevant title (title is not related to our main area of interest).
Freedman 2001	not RCT
Gadler 1997	a follow up study, not RCT
Gadler 1999	not randomized
Gadler 1999b	not controlled
Gadler 2001	not RCT
Gietzen 2004	review
Gietzen 2005	review
Gilligan 2000	review
Goethals 1999	review
Gold 1999	Irelevant title (title is not related to our main area of interest).
Gold 2001	not RCT
Goodwin 1989	not RCT
Gras 1995	not RCT
Gras 1995b	cohort study
Gras 1995c	not RCT
Gregoratos 1999	not RCT
Hagege 2009	not RCT
Harrison 1976	Irelevant title (title is not related to our main area of interest).
Haruki 2010	a case report
Hauer 2001	not RCT
Hauer 2001b	not RCT
Hayes 1999	not RCT
Hayes 2004a	not RCT

Study	Reason for exclusion
Hayes 2004b	not RCT
Herold 1991	Irelevant title (title is not related to our main area of interest).
Hess 1982	Irelevant title (title is not related to our main area of interest).
Hilleman 2001	Irelevant title (title is not related to our main area of interest).
Honda 2005	not RCT
Itoh 1988	Irelevant title (title is not related to our main area of interest).
Izawa 1996	Irelevant title (title is not related to our main area of interest).
Izawa 1997	Irelevant title (title is not related to our main area of interest).
Jandik 1990	Irelevant title (title is not related to our main area of interest).
Jansson 1990	Irelevant title (title is not related to our main area of interest).
Jeserich 2001 a	Irelevant title (title is not related to our main area of interest).
Jeserich 2001 b	Irelevant title (title is not related to our main area of interest).
Juliard 1987	Irelevant title (title is not related to our main area of interest).
Kaik 1992	Irelevant title (title is not related to our main area of interest).
Kappenberger 1997c	not an RCT
Kappenberger 1999	f/u and not RCT
Kass 1999	Irelevant title (title is not related to our main area of interest).
Kido 2006	Irelevant title (title is not related to our main area of interest).
Kim 1987	Irelevant title (title is not related to our main area of interest).
Kovacic 2003	Irelevant title (title is not related to our main area of interest).
Krejci 2006	not randomised
Kuck 1987 a	not RCT
Kuck 1987 b	Irelevant title (title is not related to our main area of interest).
Kuck 1988	not RCT
Kuhn 1999	Irelevant title (title is not related to our main area of interest).
Kuhn 2000	Irelevant title (title is not related to our main area of interest).
Kuhn 2001	not RCT
Kukar 2006	not RCT

Study	Reason for exclusion
Kusumoto 2002	Irelevant title (title is not related to our main area of interest).
Kusumoto 2006	Irelevant title (title is not related to our main area of interest).
Lakkis 1998	not RCT
Lakkis 2000	not RCT
Lakkis 2001	not RCT
Landmark 1982	not RCT
Lerakis 1997	Irelevant title (title is not related to our main area of interest).
Lerakis 2001	not RCT
Lo 1987	Irelevant title (title is not related to our main area of interest).
Lopez 2002	not RCT
Losi 1998	not controlled
Maron 1995	not RCT
Maron 1998	not an RCT
Martin 1996	not RCT
McKenna 2009	not RCT
McNamara 1983	Irelevant title (title is not related to our main area of interest).
Megevand 2005	not RCT
Meisel 2001	not RCT
Merrill 2000	Irelevant title (title is not related to our main area of interest).
Milic 2005	Irelevant title (title is not related to our main area of interest).
Millaire 1995 a	Irelevant title (title is not related to our main area of interest).
Millaire 1995 b	Irelevant title (title is not related to our main area of interest).
Millaire 1998	Irelevant title (title is not related to our main area of interest).
Miyajima 1988	Irelevant title (title is not related to our main area of interest).
Mohiddin 2002	not an RCT
Mohiddin 2010	not RCT
Monakier 2004	Irelevant title (title is not related to our main area of interest).
Montijano Cabrera 2001	not RCT

Study	Reason for exclusion
Naccarelli 1982	Irelevant title (title is not related to our main area of interest).
Nagueh 2001	Irelevant title (title is not related to our main area of interest).
Nakatani 1996	Irelevant title (title is not related to our main area of interest).
Nandhakumar 2008	Irelevant title (title is not related to our main area of interest).
Nessler 1999	Irelevant title (title is not related to our main area of interest).
Niki 1999	Irelevant title (title is not related to our main area of interest).
Nishimura 1993	not RCT
Nishimura 1996	not RCT
Nishimura 1996b	not RCT
Nishimura 2004	not RCT
Nowinski 2005	no randomization
Ohtani 2003	case report
Oka 2007	Irelevant title (title is not related to our main area of interest).
Ommen 1999	not randomised, based on patient preference
Ovsyshcher 2004	Irelevant title (title is not related to our main area of interest).
Pace 1994	Irelevant title (title is not related to our main area of interest).
Pak 1998	not RCT
Park 1999	not RCT
Pasternac 1982	Irelevant title (title is not related to our main area of interest).
Paulus 1988	Irelevant title (title is not related to our main area of interest).
Posma 1996	not RCT
Ralph-Edwards 2005	Irelevant title (title is not related to our main area of interest).
Reith 2003	not RCT
Rousseau 1980	Irelevant title (title is not related to our main area of interest).
Ryden 2001	Irelevant title (title is not related to our main area of interest).
Saumarez 1992	not randomised
Saumarez 1995	Irelevant title (title is not related to our main area of interest).
Saumarez 2003	Irelevant title (title is not related to our main area of interest).

Study	Reason for exclusion
Saumarez 2008	not randomised
Schulte 1999	not RCT
Seggewiss 1998	Irelevant title (title is not related to our main area of interest).
Seggewiss 2003	not RCT
Seggewiss 2007	Irelevant title (title is not related to our main area of interest).
Shamim 2002	not RCT
Shefer 1987	Irelevant title (title is not related to our main area of interest).
Sherrid 2005	Irelevant title (title is not related to our main area of interest).
Silva 2008	no comparison group.
Slade 1996	not RCT
Slade 1996b	not RCT
Solomon 1999	not RCT
Somura 2001	Irelevant title (title is not related to our main area of interest).
Sorajja 2000	not RCT
Spirito 1997	not RCT
Spirito 1999	not RCT
Sud 2007	Irelevant title (title is not related to our main area of interest).
Syed 2004	Irelevant title (title is not related to our main area of interest).
Takechi 2003	Irelevant title (title is not related to our main area of interest).
Talreja 2004	Irelevant title (title is not related to our main area of interest).
Tascon 1995	Irelevant title (title is not related to our main area of interest).
Thompson 1980	Irelevant title (title is not related to our main area of interest).
Thompson 1983	Irelevant title (title is not related to our main area of interest).
Topaz 1989	Irelevant title (title is not related to our main area of interest).
Topilski 2006	not RCT
Trohman 2004	not RCT
Unno 2009	Irelevant title (title is not related to our main area of interest).
van der 2005	not a pacing study

Study	Reason for exclusion
Vazquez 2001	Irelevant title (title is not related to our main area of interest).
Venugopa 2007	Irelevant title (title is not related to our main area of interest).
Watson 1987	Irelevant title (title is not related to our main area of interest).
Weiner 1999	not RCT
Weiss 1976	Irelevant title (title is not related to our main area of interest).
Wexler 2009	Irelevant title (title is not related to our main area of interest).
Yamakado 1990	Irelevant title (title is not related to our main area of interest).
Zeng 2006	Irelevant title (title is not related to our main area of interest).

ADDITIONAL TABLES

Table 1. Table: New York Heart Association Functional Classification

New York Heart Association-**Functional Class**	**Symptoms**
Class I	No limitation during ordinary activity
Class II	Slight limitation, as evidenced by shortness of breath nor fatigue or both during moderate exertion or stress
Class III	Marked limitation with minimal exertion that interferes with normal daily activity
Class IV	Inability to carry out any physical activity; patients typically have marked neurohumoral activation and muscle wasting

Table 2. Table: Revised NBG Code for Pacing Modes

Chamber being paced	Chamber being sensed	Response to sensing	Rate modulation	Multisite pacing
O = none	O = none	O = none	O = none	O = none
A = atrium	A = atrium	I = inhibited	R = rate modulation	A = atrium
V = ventricle	V = ventricle	T = triggered		V = ventricle
D = dual (A + V)	D = dual (A + V)	D = dual (T + I)		D = dual (A + V)
Manufacturer's designation only: S = single (A or V)	Manufacturer's designation only: S = single (A or V)			

Table 3. Table: Glossary

A	Atrium
AAI	Single-chamber atrial pacing; one lead is positioned in the atrium; pacing and sensing occurs in the atrium; atrial pacing is inhibited by sensed spontaneous atrial depolarisation; no rate modulation or multi-site pacing
AAIR	Single chamber atrial pacing as above but with rate modulation
AV synchrony	Normal sequence of atrial depolarisation and contraction followed by ventricular depolarisation and contraction; maintenance of this sequence results in optimal ventricular filling and cardiac output
BPEG	British Pacing and Electrophysiology Group
D	Dual (atrium and ventricle)
DDD	Dual-chamber pacing; use of two leads, one in the atrium and one in the ventricle; pacing and sensing occurs in both the atrium and the ventricle; in the absence of intrinsic activity, both chambers are paced at the programmed base rate; normally inhibited by atrial or ventricular sensing and with ventricular pacing triggered by atrial sensing; no rate modulation or multi-site pacing
DDDR	Dual chamber as above but with rate modulation
HCM	Hypertrophic cardiomyopathy
Inhibited	A type of pacemaker response in which the output pulse is suppressed (or inhibited) when an intrinsic event is sensed
NASPE	North American Society of Pacing and Electrophysiology
NBG Code	NASPE/BPEG Generic Code
Rate modulation	The ability of pacemakers to increase the pacing rate in response to physical activity or metabolic demand
Sensing	The detection of spontaneous cardiac depolarisation
Tracking	A dual-chamber pacing function in which atrial activity is sensed and results in a paced ventricular response after a predefined delay (the AV interval)
VDD	Ventricular pacing, triggered by atrial sensing, inhibited by ventricular sensing, with no atrial pacing
VVI	Single-chamber ventricular pacing; one lead is positioned in the ventricle; pacing and sensing occurs in the ventricle; ventricular pacing is inhibited by sensed spontaneous ventricular depolarisation; no rate modulation or multi-site pacing; loss of AV synchrony may occur with this pacing mode; may be referred to as 'non-physiological' pacing

APPENDICES

Appendix 1. Search strategies

Database searched: CENTRAL (*The Cochrane Library* 2010, Issue 1)

Date of search: 14/4/2010

#1 MeSH descriptor Cardiomyopathy, Hypertrophic explode all trees

#2 (cardiomyopath* in All Text near/3 hypertroph* in All Text)

#3 HCM in All Text

#4 HOCM in All Text

#5 (#1 or #2 or #3 or #4)

#6 MeSH descriptor Pacemaker, Artificial this term only

#7 MeSH descriptor Cardiac Pacing, Artificial this term only

#8 pacemaker* in All Text

#9 pacing in All Text

#10 pacer* in All Text

#11 (#6 or #7 or #8 or #9 or #10)

#12 (#5 and #11)

Database searched: MEDLINE OVID (1950 onwards)

Date of search: 14/4/2010

1. exp Cardiomyopathy, Hypertrophic/

2. (hypertrophic adj3 cardiomyopath*).tw.

3. hcm.tw.

4. hocm.tw.

5. 1 or 2 or 3 or 4

6. Cardiac Pacing, Artificial/

7. Pacemaker, Artificial/

8. pacemaker*.tw.

9. pacing.tw.

10. pacer*.tw.

11. 6 or 7 or 8 or 9 or 10

12. 5 and 11

13. randomized controlled trial.pt.

14. controlled clinical trial.pt.

15. randomized.ab.

16. placebo.ab.

17. drug therapy.fs.

18. randomly.ab.

19. trial.ab.

20. groups.ab.

21. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20

22. exp animals/ not humans.sh.

23. 21 not 22

24. 12 and 23

Database searched: EMBASE OVID (1980 onwards)

Date of search: 14/4/2010

1. exp hypertrophic cardiomyopathy/

2. (hypertrophic adj3 cardiomyopath*).tw.

3. hcm.tw.

4. hocm.tw.

5. 1 or 2 or 3 or 4

6. exp heart pacing/

7. artificial heart pacemaker/

8. pacemaker*.tw.

9. pacing.tw.

10. pacer*.tw.

11. 6 or 7 or 8 or 9 or 10

12. 5 and 11

13. random$.tw.

14. factorial$.tw.

15. crossover$.tw.

16. cross over$.tw.

17. cross-over$.tw.

18. placebo$.tw.

19. (doubl$ adj blind$).tw.

20. (singl$ adj blind$).tw.

21. assign$.tw.

22. allocat$.tw.

23. volunteer$.tw.

24. crossover procedure/

25. double blind procedure/

26. randomized controlled trial/

27. single blind procedure/

28. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27

29. (animal/ or nonhuman/) not human/

30. 28 not 29

31. 12 and 30

Database searched: ISI Web of Science – with Conference Proceedings (1970 onwards)

Date of search: 14/4/2010

#9 #8 AND #7 AND #3

#8 TS=(random* OR blind* OR placebo*)

#7 #6 OR #5 OR #4

#6 TS=pacer*

#5 TS=pacing

#4 TS=pacemaker*

#3 #2 OR #1

#2 TS=(hcm OR hocm)

#1 TS=(hypertrophic SAME cardiomyopath*)

WHAT'S NEW

Date	Event	Description
26 March 2021	Review declared as stable	This review was assessed in March 2021 as being not a clinical priority question and not an active area of research.

HISTORY

Protocol first published: Issue 5, 2010
Review first published: Issue 5, 2012

CONTRIBUTIONS OF AUTHORS

Mohammed Qintar: protocol development, trial identification, data extraction, data analysis, and drafting the review.

Abdulrahman Morad: protocol development and drafting the review.

Hazem Alhawasli: protocol development, trial identification, data extraction, data analysis, and drafting the review.

Khaled Shorbaji: protocol development, trial identification, data analysis, and drafting the review.

Belal M Firwana: data analysis, and drafting the review.

Adib Essali: protocol and review revision and providing consultation

Waleed Kadro: protocol and review revision and providing consultation.

All authors have contributed and approved to the final version of the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- The Psychiatry Centre, Teshreen Hospital, Damascus, Syrian Arab Republic

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

No subgroup or sensitivity analyses were performed.

INDEX TERMS

Medical Subject Headings (MeSH)

Cardiomyopathy, Hypertrophic [physiopathology] [*therapy]; Exercise Tolerance [physiology]; *Pacemaker, Artificial; Randomized Controlled Trials as Topic; Time Factors

MeSH check words

Adult; Humans