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Pacemaker therapy for drug-refractory symptoms in mid-cavity hypertrophic cardiomyopathy

Submission date 03/01/2018	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 11/01/2018	**Overall study status** Completed	
Last Edited 07/11/2024	**Condition category** Circulatory System	

Plain English summary of protocol

Background and study aims
Hypertrophic cardiomyopathy (HCM) is the most common familial heart disease, affecting one in five hundred of the general population. It involves abnormal thickening of the heart in absence of other reasonable causes such as heart valve disease, and the various patterns of thickening mean blood flow within the heart is often abnormal. Obstruction to blood flow out into the main artery (the aorta) is often present at a level below that of the aortic valve, and this can place extra strain upon the heart muscle. This extra strain means patients frequently suffer from symptoms such as shortness of breath and chest pain, poor exercise tolerance, or dizzy spells. Around 60% of HCM patients will have obstruction to blood flow at the base of the heart, at the level of the mitral valve, and there are several invasive therapies to consider as treatment if treatment with medicine is failing to reduce symptoms. However, in a smaller group of around one in ten HCM patients, obstruction to blood flow occurs in a different area, within the middle of the left heart. These patients provide a challenge for management, as they are less suitable for invasive treatment options. Using a pacemaker to excite the heart in patients with obstruction within the middle of the heart has been demonstrated to reduce the obstruction and importantly improve patient symptoms. The aims of this study are to find out how effective cardiac pacing is at reducing obstruction in the middle of the heart, and to see whether this leads to an improvement in symptoms.

Who can participate?
Patients aged over 18 undergoing implantation of a pacemaker

What does the study involve?
Participants undergo an assessment and pacemaker implantation. They are randomly allocated to have the pacemaker set up to pace all the time (active pacing) or back-up pacing only (very little pacing) for 24±2 weeks. At 24±2 weeks their symptoms and physical performance are assessed at a visit to the hospital and they then have the pacemaker switched to the other setting for another 24±2 weeks (either active pacing or back-up pacing depending on which they had first). Participants are assessed again at 48±2 weeks.

What are the possible benefits and risks of participating?
It cannot be guaranteed that a patient's symptoms will improve as part of this study. However, patients with the condition have very few treatment options available to them if medication doesn't ease their symptoms. Early tests of using a pacemaker for the condition have been very encouraging, so this study may lead to larger studies that change how patients are treated all over the world with the specific heart condition. Significant side effects are not expected as part of the study. If patients feel unwell for any reason they can get in contact with the research team. If any unexpected health-related findings are discovered as part of this study, they will be shared appropriately with the patient and the clinical team responsible for their care.

Where is the study run from?
St Bartholomew's Hospital (UK)

When is the study starting and how long is it expected to run for?
June 2017 to May 2022 (updated 10/05/2021, previously: May 2021)

Who is funding the study?
National Institute for Health Research (UK)

Who is the main contact?
Dr Saidi Mohiddin

Contact information

Type(s)
Scientific

Contact name
Dr Saidi Mohiddin

ORCID ID
http://orcid.org/0000-0002-1031-4084

Contact details
Barts Heart Centre
No 1 St Martins Le Grand
London
United Kingdom
EC1A 4AS

Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number
NCT03450252

Secondary identifying numbers

36358

Study information

Scientific Title
Distal ventricular pacing and intraventricular gradient reduction for symptomatic relief in drug-refractory hypertrophic cardiomyopathy patients with mid-cavity obstruction

Study objectives
Hypertrophic cardiomyopathy (HCM) is the most common familial heart disease, affecting one in five hundred of the general population. Characterised by abnormal thickening of the heart in absence of other reasonable causes such as heart valve disease, the various patterns of thickening mean blood flow within the heart is often abnormal. Obstruction to blood flow out into the main artery, the aorta, is often present at a level below that of the aortic valve, and this can place extra strain upon the heart muscle.

This extra strain means patients frequently suffer from debilitating symptoms such as shortness of breath and chest pain, poor exercise tolerance, or dizzy spells. Around 60% of HCM patients will have obstruction to blood flow at the base of the heart, at the level of the mitral valve, and there are several invasive therapies to consider as treatment if treatment with medicine is failing to reduce symptoms. However, in a smaller group of around one in ten HCM patients, obstruction to blood flow occurs in a different area, within the middle of the left heart. These patients provide a challenge for management, as they are less suitable for invasive treatment options.

Using a pacemaker to excite the heart in patients with obstruction within the middle of the heart has been demonstrated to reduce the obstruction and importantly improve patient symptoms, and this is supported by our pilot data. The research questions to be addressed are: How effective is cardiac pacing at reducing obstruction in the middle of the heart? The second question is does this lead to symptomatic benefit for the patient?

Ethics approval required
Old ethics approval format

Ethics approval(s)
London Harrow Research Ethics Committee, 06/12/2017, ref: 17/LO/1725

Study design
Randomised; Interventional; Design type: Treatment, Complex Intervention

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
Hospital

Study type(s)

Treatment

Participant information sheet
See additional files

Health condition(s) or problem(s) studied
Hypertrophic cardiomyopathy

Interventions
Patients will be identified in outpatient cardiomyopathy clinics, with initial screening and eligibility assessment made by a researcher. A trained member of the research team will take informed consent in the cardiac department at Barts Heart Centre. Recruited subjects will then attend for baseline assessment by a researcher and performance testing over one encounter.

A member of the research team shall direct the participant to fill out the Kansas City Cardiomyopathy questionnaire and the SF36 questionnaire in a private office without interruption. The six-minute walk test shall be performed in the cardiac department by a member of the cardiac physiology team, as per standard care. Cardiac Magnetic Resonance Imaging (MRI) will be done in the imaging department at Barts Heart Centre, performed by the imaging team and reviewed by a consultant cardiologist. Cardiopulmonary exercise testing with simultaneous echocardiography (stress echo) shall take place in the cardiac department and be performed by a member of the cardiac physiology team along with members of the research team as necessary. A small blood sample (~5 mL) shall be taken in the cardiac department at each study visit for analysis of the protein brain natriuretic peptide. The sample shall be taken from venous cannulation performed by a trained individual.

There is a further attendance for device implantation and invasive haemodynamic pacing study. A trial randomisation service (such as https://www.sealedenvelope.com or www.randomize.net) will be used to assign participants to one of the cross over arms initially. One group will have the pacemaker set up to pace all the time (active pacing), and one group will be set up for back-up pacing only (very little pacing) for 24±2 weeks. The pacemaker implant shall be performed in the catheter labs of Barts Heart Centre, by a consultant cardiologist. Adjustments to pacemaker settings shall occur at the visits to the cardiac department at Barts Heart Centre. They shall be performed by a member of the cardiac physiologist team who is qualified to do so. At 24±2 weeks the patients' symptoms and physical performance will be assessed at a visit to the hospital and they will then have the pacemaker switched to the other setting for another 24±2 weeks (either active pacing or back-up pacing depending on which they had first). Patients will then be assessed again at 48±2 weeks. The length of each treatment phase is longer than previous pacemaker studies at 24 weeks in order to account for any wash-out periods, which have historically been a criticism of cross-over trial designs.

Intervention Type
Device

Phase
Phase II/III

Drug/device/biological/vaccine name(s)
Not provided at time of registration

Primary outcome measure

Direct measurement of obstructive gradient (mmHg) via intracardiac catheter during pacemaker implant; Timepoint(s): During implant

Secondary outcome measures
The feasibility of performing a cross-over study and the associated performance tests and symptomatic assessments in this patient population. The statistical information collected will be used to design a much larger research trial of patient benefit.

Overall study start date
01/06/2017

Completion date
31/05/2022

Eligibility

Key inclusion criteria
1. Male or female, >18 years
2. Referred for PPM +/- ICD implantation for either primary prevention of sudden cardiac death or other indications such as heart block or obstructive physiology
3. HCM patients with a mid-cavity gradient of ≥30 mmHg demonstrated by echocardiography and morphology confirmed by cardiac MRI. Gradient confirmed by cardiac catheterisation
4. All patients should be taking maximum tolerated doses of beta blockers or verapamil with or without disopyramide
5. Symptoms refractory to optimum medical therapy as above, for example breathlessness, chest pain, dizziness, or syncope

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 25; UK Sample Size: 25

Key exclusion criteria
1. Patients with multi-level obstruction, i.e. across the mid-cavity and outflow tract
2. Patients with moderate or severe valvular stenosis or regurgitation due to primary valvular disease
3. Patients with untreated symptomatic coronary disease
4. Patients in atrial fibrillation at the time of implantation
5. Pregnancy
6. Renal failure with eGFR < 20mL/min

7. Any patient not suitable in the clinicians opinion
8. Any patient who is for whatever reason is not expected for more than one year
9. Patients unable to provide informed consent

Date of first enrolment
01/02/2018

Date of final enrolment
31/03/2022

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
St Bartholomew's Hospital
Barts Heart Centre
London
United Kingdom
EC1A 7BE

Sponsor information

Organisation
Queen Mary University of London

Sponsor details
c/o Dr Sally Burtles
Director of Research Services & Business Development (JRMO)
QM Innovation Centre, 5 Walden Street
Whitechapel
London
England
United Kingdom
E1 2EF

Sponsor type
University/education

ROR
https://ror.org/026zzn846

Funder(s)

Funder type
Government

Funder Name
NIHR Trainees Co-ordinating Centre (TCC); Grant Codes: ICA-CDRF- 2016-02- 068

Results and Publications

Publication and dissemination plan
Project results will be submitted for publication in peer-reviewed journals (e.g. European Heart Journal, Journal of the American College of Cardiology), irrespective of outcome, within 12 months of completion.

Intention to publish date
31/05/2023

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version V6	01/12/2017	11/01/2018	No	Yes
Protocol file	version V9	09/11/2017	11/01/2018	No	No
HRA research summary			28/06/2023	No	No