The CRYSTAL study: CMR of intraventricular flow analysis and genetic phenotyping in Hypertrophic Cardiomyopathy (HCM): a roadmap for surgical myectomy

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The primary objective of this study is to assess wall shear stress in the left ventricle outflow tract using 4D flow CMR in healthy controls, asymptomatic HCM and before and after surgical myectomy in patients with HOCM,

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Myocardial disorders
Study type	Observational non invasive

Summary

ID

NL-OMON53188

Source
ToetsingOnline

Brief title
CRYSTAL

Condition

- Myocardial disorders
- Cardiac and vascular disorders congenital
- Cardiac therapeutic procedures

Synonym
(obstructive) hypertrophic cardiomyopathy, Thickened heart muscle

Research involving

Human

Sponsors and support

Primary sponsor: Cardiothoracale chirurgie
Source(s) of monetary or material Support: Ministerie van OC&W,Netherlands Heart Institute

Intervention

Keyword: 4D-flow CMR, Hypertrofic cardiomypathy (HCM) Omics, Surgical myectomy

Outcome measures

Primary outcome

Primary outcome: wall shear stress in HOCM patients (preoperative and at 6 months follow-up), HCM patients and controls.

Secondary outcome

First secondary outcome: Omics in HOCM patients

Omics (Tomo-seq and/or nanopore and/or other omics technique) will yield gene expression information for approximately 10.000 genes, for ±200 positions along ±2 cm tissue samples of patients with HCM. The raw output thus is a 10.000 x 200 gene expression table (genes x position) for each sample for each patient.

Second secondary outcome: Hemodynamic parameters in HOCM patients, HCM patients and controls.

Kinetics (kinetic energy, energy loss, LV myocardial deformation (by myocardial strain analysis)) and blood flow (helicity and vorticity of blood flow will be obtained to characterize LV flow).

Study description

Background summary

Hypertrophic Cardiomyopathy (HCM) is an inherited myocardial disease characterised by left ventricular hypertrophy (LVH), which carries an increased risk of life-threatening arrhythmias and sudden cardiac death. Presentation and phenotype of HCM also varies during lifetime, with specific differences between children and adults with HCM. HCM is associated with left ventricular outflow tract obstruction (LVOTO) due to interventricular septum hypertrophy, so called hypertrophic obstructive cardiomyopathy (HOCM). Currently, echocardiography is the gold standard for the assessment of HCM and most often used to guide surgical intervention for HOCM, but is hampered with reduced acoustic window. Meanwhile, cardiac magnetic resonance (CMR) is a comprehensive and non-invasive imaging modality capable of providing information on cardiac morphology, function, flow, perfusion and tissue characterization of patients with HCM. Despite the use of both imaging modalities for preoperative planning of surgical myectomy, it can still be challenging for the surgeon to correctly identify the extent and location of LVOT tissue that needs to be surgically removed in case of symptomatic LVOTO. Too conservative excision may lead to recurrence of LVOTO, whereas too aggressive excision may negatively affect cardiac function after surgery.
Recently, four-dimensional (4D) flow CMR has been shown to provide reliable qualitative and quantitative evaluation of the blood flow within the entire heart. Several 4D flow CMR studies demonstrated abnormal blood flow patterns and disturbed kinetics in the LV of HCM patients, specifically in the LVOT. 4D flow CMR may therefore be of additive value to characterize the location and extent of LVOT obstruction in HOCM, and thereby be of additive value for planning of surgical myectomy, in a complementary role to routine CMR and echocardiography.
Secondly, it is currently unknown whether or which molecular mechanisms underlie the local remodelling in the LVOT observed in HOCM patients, in response to local wall tension. In other words, it is unclear to which extent local gene expression in HCM patients may be related to (abnormalities in) local flow dynamics, myocardial deformation, and myocardial tissue characteristics of the LVOT. Based on recent advancements in RNA sequencing it is possible to obtain local HCM gene expression profiles with a high spatial resolution. Determination of the relationship between local flow patterns, myocardial deformation and myocardial tissue characterization in the LVOT, and how this influences HCM gene expression, could help to improve our understanding of HCM pathogenesis.
All parameters gained from the CRYSTAL study will add valuable non-invasive hemodynamic diagnostic parameters for the evaluation of HCM patients (children and adults), specifically for timing and planning of myectomy, and post-operative evaluation.

Study objective

The primary objective of this study is to assess wall shear stress in the left ventricle outflow tract using 4D flow CMR in healthy controls, asymptomatic HCM and before and after surgical myectomy in patients with HOCM,

Study design

Descriptive study and explorarory

Study burden and risks

HOCM patients undergoing surgical myectomy
o Participating in this study places minimal burden on the participants, as all clinical investigations are non-invasive and do not involve radiation exposure, which aligns with standard clinical practice.
o We will reassess the examinations, if any variables are missing from the examinations report. This process does not add any extra burden since the examinations have already been conducted. Additionally, the evaluation will be performed using approved products from UMC Utrecht, thereby introducing minimal additional risks.

Adults with HCM not undergoing surgical myectomy
o All patients will undergo standard of care examinations according to the UMC Utrecht hospital, including routine CMR and non-invasive 4D flow imaging, echocardiography, cardiopulmonary exercise testing and ECG.
o We will reassess the examinations, if any variables are missing from the examinations report. This process does not add any extra burden since the examinations have already been conducted. Additionally, the evaluation will be performed using approved products from UMC Utrecht, thereby introducing minimal additional risks.

Healthy adults without HCM
o Participation in this study has limited burden and risks for patients as it entails, questions for baseline characteristic, CMR with additional 4D flow measurements. A total of 60 minutes of CMR scan time will be the maximum.
o Participating in this study places minimal burden on the participants, as all clinical investigations are non-invasive and do not involve radiation exposure.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

HOCM patients undergoing surgical myectomy
o HOCM diagnosis according to the 2020 AHA/ACC Guideline for the Diagnosis and Treatment of patients With Hypertrophic Cardiomyopathy (2). Patients with resting or provoked gradients > 50 mm Hg generally considered to be the threshold for surgical myectomy in those patients with drug-refractory symptoms (2).
o Patients undergoing surgical myectomy in UMC Utrecht. Heart team (consisting of one cardiologist and one cardiothoracic surgeon) determine if surgical myectomy is required.
o Basal and midventricular HCM.
o No concomitant surgery. The following procedures are not considered as concomitant surgery: MAZE procedure, Left Atrial Appendage (LAA) resection, device implementation (Pacemaker or ICD).
o Patients > 18 years at the moment of the myectomy procedure
o Participation in UNRAVEL Biobank.
o Willing to comply with the study procedures and written informed consent.

Adults with HCM

o HCM diagnosis according to the 2020 AHA/ACC Guideline for the Diagnosis and Treatment of patients With Hypertrophic Cardiomyopathy (2). Imaging (2D echocardiography or CMR) showing a maximal end-diastolic wall thickness of > 15 mm basal or midventricular, in the absence of another cause of hypertrophy. Limited hypertrophy (13-14 mm) can be diagnostic when present in family members of a patient with HCM or in conjunction with a positive genetic test.
o Patients > 18 years, if possible aged matched HCM control subjects with respect to surgical myectomy patients.
o Participation in UNRAVEL Biobank.
o Willing to comply with the study procedures and written informed consent.

Healthy adult controls
o Patients > 18 years.
o Willing to comply with the study procedures and written informed consent.

Exclusion criteria

o General contra-indications to CMR.
o Aortic valve stenosis grade > 2.
o Intrinsic mitral valve (rheumatic, degenerative, infective, and mitral annulus calcification).
o Apical HCM.
o The coexistence of other forms of congenital heart disease.
o Prior cardiac surgery, stroke, percutaneous coronary intervention or previous alcohol septal ablation therapy.
o Concomitant surgery in group undergoing surgical myectomy. The following procedures are not considered as concomitant surgery: MAZE procedure, Left Atrial Appendage (LAA) resection, device implementation (Pacemaker or ICD).

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	23-11-2023
Enrollment:	40
Type:	Actual

Ethics review

Approved WMO

Date:	10-08-2023
Application type:	First submission
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL84587.041.23