Assessment of myocardial function, endothelial function and perFUSION in early and advanced disease stages of Hypertrophic CardioMyopathy: FUSION-HCM

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In different stages of HCM, to measure the: - Myocardial perfusion- Myocardial function- Volume parameters of the heart- Fibrosis- Function of the small vessels (endothelial (dys)function)- Diastolic function and strain of the heart

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

Summary

ID

NL-OMON56339

Source
ToetsingOnline

Brief title
FUSION-HCM

Condition

- Myocardial disorders
- Cardiac and vascular disorders congenital

Synonym
Enlarged heart muscle disease

Research involving
Human

Sponsors and support

Primary sponsor: Amsterdam UMC
Source(s) of monetary or material Support: NWO VICI Jolanda van der Velden

Intervention

Keyword: Cardiomyopathy, Endothelial, Hypertrophic, Perfusion

Outcome measures

Primary outcome

- Myocardial perfusion

- Endothelial (dysf)function

Secondary outcome

- Fibrosis

- Diastolic function

- Strain

- Volume parameters

- Myocardial efficienty in advanced HCM patients (wall thickness>=15mm) who have

participated in previous studies.

Study description

Background summary

Hypertrophic cardiomyopathy (HCM) is a genetic disorder characterized by asymmetric hypertrophy of the heart in absence of loading conditions like hypertension or valve disease. The genetic mutation underlying HCM sets in motion a cascade of functional and metabolic changes ultimately leading to disease. In addition to energy deficiency, studies have also shown reduced cardiac perfusion, diastolic dysfunction, and microvascular dysfunction, even before the onset of hypertrophy. We propose that mutation-induced energy deficiency triggers metabolic and mitochondrial changes causing diastolic dysfunction, and hypoperfusion of the heart before hypertrophy occurs. Whether

these genetic mutation directly causes microvascular remodeling and thereby microvascular dysfunction or it is a consequence of diastolic dysfunction and thereby reduced cardiac perfusion, has not been elucidated. The causality and sequence of these cardiovascular changes need to be defined to develop targeted preventive therapies.
A comparison will be made between mutation carriers without signs of cardiac hypertrophy (septal thickness <12 mm), mutation carriers with a mild phenotype (asymmetric septal thickness >=12 until <15mm) and patients with advanced HCM (>=15mm). As the thick filament mutations represent the majority of all HCM cases, we will include 25 individuals with a MYBPC3 mutation or a MYH7 mutation per disease stage (minimal age 18 years). Imaging studies will also be performed in healthy control individuals to define the normal (healthy) cardiac characteristics.
As the pathomechanism of HCM is thought to be a cascade of changes, all measures of cardiac perfusion, endothelial (dys)function, and cardiac function will be measured in the different stages of disease as described above.

Study objective

In different stages of HCM, to measure the:
- Myocardial perfusion
- Myocardial function
- Volume parameters of the heart
- Fibrosis
- Function of the small vessels (endothelial (dys)function)
- Diastolic function and strain of the heart

Study design

Observational with invasive measurements.

Study burden and risks

Participants will have to come to the hospital for two separate days, one day for 6 hours and the second day for 2 hours. They have to lie still for long periods in scanners, intravenous lines will be inserted which can be painful and unpleasant. Adverse reactions to dotarem are rare. The side effects of adenosine can be unpleasant. There is always a doctor present to terminate the test if this is considered necessary. The radiation exposure of the PET/CT scan is 1.8-4.8 mSv, which falls in category IIb and is associated with low risk.
Performing this research in this population is justified because this research will thoroughly examine the sequence of events leading to HCM and aims to find ways to better predict progression of disease in mutation carriers and/or find targets for preventative therapy. This study with capacitated adults will yield a tremendous amount of knowledge about the sequence of events driving HCM. This study is the first to do extensive measurements of function and perfusion of

the heart, and endothelial (dys)function in different stages of HCM. The implications of this study involve predictvie and prognostic strategies for HCM which currently do not exist. Additionally, findings of this study may lead to new therapeutic targets for HCM or verification of therapeutic strategies that are currently being researched. Because we compare different techniques in this study, we also gain knowledge about the usage of less invasive/burdensome/expensive methods to predict the onset of disease. FO rthis study it is essential to involve both MYBPC3 and MYH7 mutation carriers because these two groups form the vast majority of HCM-causing mutations. The risk can be considered negligible because the Amsterdam UMC has much experience with the procedures performed in this study and specialists (cardiologists, nuclear radiologists) are involved in all aspects of the study. All procedures except the Laser Speckle Contrast Analysis and Oxygenation-Sensitve Cardiac Magnetic Resonance Imaging (a novel sequence during the MRI scan) are routinely performed in the Amsterdam UMC for clinical and/or research purposes.

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

MYBPC3 mutation carrier
MYH7 mutation carrier
Genotype-negative first degree relative of a MYBPC3 or MYH7 mutation carrier

Exclusion criteria

>=70 years old
Insulin-dependent diabetes mellitus
Pregnancy
Smoking
Claustrophobia
Pacemaker/ICD
Renal insufficiency <30 GFR
Hypertension (systolic >140mmHg or diastolic >90mmHg)
For the genotype negative group, no phenotype group, and mild phenotype group: the use of blood pressure medication (diuretics, beta-blockers, ACE-inhibitors, angiotensin II receptor blockers, calcium channel blockers, alpha blockers)
For the HCM phenotype group: when it is unsafe to withhold from blood pressure medication (as specified above) for two days, as assessed by their own cardiologist
Left ventricular outflow tract gradient > 50mmHg
Aortic valve disease
Left bundle branch block
(History of) Obstructive coronary artery disease
Chronic atrial fibrillation
Hormone replacement therapy
Second or third-degree AV-block, sick-sinussyndrome, prolonged QT-interval
Asthma and other obstructive pulmonary diseases
Previous adverse reaction to adenosine or dotarem

Study design

Design

Study type:	Observational invasive
Intervention model:	Other

Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	05-09-2024
Enrollment:	100
Type:	Actual

Ethics review

Approved WMO

Date:	24-11-2023
Application type:	First submission
Review commission:	METC Amsterdam UMC

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	NL83573.018.23