BE-STRONG HCM: Biomarkers, Exercise Stress Testing, and MRI to Obtain New InsiGhts in Hypertrophic CardioMyopathy

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1) To demonstrate an elevated troponin concentration before exercise and a rise of troponin after exercise in both pre-clinical HCM mutation carriers and HCM patients with the hypertrophic phenotype, 2) To evaluate the troponin rise in relation to...

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

Summary

ID

NL-OMON35538

Source
ToetsingOnline

Brief title
Troponin in hypertrophic cardiomyopathy and mutation carriers

Condition

- Myocardial disorders
- Chromosomal abnormalities, gene alterations and gene variants

Synonym
a thickened heart muscle based on genetic predisposition, Hypertrophic cardiomyopathy

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Exercise stress testing, Hypertrophic cardiomyopathy, Imaging, Troponin

Outcome measures

Primary outcome

Proportion of patients (pre-clinical HCM mutation carriers and clinical HCM patients) with 1) a baseline troponin concentration above the upper reference limit (the 99th percentile) of the high-sensitivity troponin assay that will be used, and 2) a troponin rise after exercise testing (more than or equal to 20% of the baseline concentration) using the same high sensitivity-troponin assay.

Secondary outcome

Pre-clinical HCM-group (genotype positive, no hypertrophy)

-The correlation between troponin (baseline concentration, rise after exercise) and MRI parameters (i.e. myocardial mass and function, number of segments with and volume (in mL) of LGE, presence of edema);

-The correlation between troponin (baseline, rise after exercise) and clinical follow-up (development of the hypertrophic phenotype, septum wall thickness >13mm).

Clinical HCM group (genotype positive or negative, with hypertrophy)

-The correlation between troponin (baseline concentration, rise after exercise) and MRI parameters (i.e. myocardial mass and function, number of

segments with and volume (in mL) of LGE, presence of edema);

-The correlation between troponin (baseline concentration, rise after exercise)

and: a) death due to all causes, cardiovascular death, and sudden cardiac death

at two and 5 year follow-up; b) admission to the hospital for cardiac reasons

(i.e. new episode of heart failure, arrhythmia, syncope) during two and five

year follow-up; c) event free survival at two and 5 year, defined as alive at

the time of telephone call and not admitted for any cardiac adverse event

during follow-up.

Study description

Background summary

Hypertrophic cardiomyopathy (HCM) is the most common inheritable heart disease, characterized by marked left ventricular hypertrophy (LVH) in the absence of a disease that can cause hypertrophy to such extent. The clinical course in patients with a full-blown hypertrophic phenotype is very heterogeneous, ranging from early sudden cardiac death to late onset heart failure. Current risk stratification to predict the outcome of individual HCM patients is still unsatisfactory. From studies on gene carriers with a proven causal mutation but without the hypertrophic phenotype, we know that the hypertrophy and subsequent clinical course may develop later in life. The pathophysiology of both the onset of hypertrophy in gene carriers and the development of disease in clinical HCM patients with hypertrophic hearts is incompletely understood. It is however recognized that ischemia plays a significant role. Interestingly, although playing an important role in ischemic heart disease cardiac troponin has received little attention in HCM patients. Against this background, we will study the release of cardiac troponin after stress testing in 1) mutation carriers without the hypertrophic phenotype (pre-clinical HCM) and in 2) patients with clinically overt HCM (clinical HCM).

Study objective

1) To demonstrate an elevated troponin concentration before exercise and a rise of troponin after exercise in both pre-clinical HCM mutation carriers and HCM patients with the hypertrophic phenotype, 2) To evaluate the troponin rise in relation to phenotypic characteristics, 3) To study the correlation between a

troponin rise and development of hypertrophy in pre-clinical mutation carriers and the association between adverse cardiac events at two and 5-year follow-up.

Study design

All eligible subjects either mutation carriers without hypertrophy or clinical HCM patients with hypertrophic hearts will undergo a baseline MRI, a bicycle exercise test and blood sampling to assess serum troponin levels. Six and 24 hours after the exercise test repeat blood samples will be drawn. Troponin rise of more than or equal to 20% will be called significant. Telephone follow-up will occur on day 730 (+ 7 days) and on day 1826 (+ 35 days). A troponin rise will be associated with the presence and extent of fibrosis and edema of the heart as assessed with MRI. In mutation carriers the development of the hypertrophic phenotype will be checked during follow-up. In patients with clinical HCM clinical endpoints such as sudden cardiac death, new episodes of heart failure and rhythm disturbances will be scored. The exercise induced troponin rise will be analysed in multivariable analysis to assess its association with the abovementioned outcome parameters.

Study burden and risks

Participants will have to pay 3 visits to the hospital at baseline and will be followed-up by telephone call after two and five years. The risks are limited to a potential allergic reaction to the MRI contrast agent Gadolinium (0-1%) and in highly rare instances nephrogenic systemic fibrosis (NSF) may develop (see references 80-82 in the study protocol). The MRI investigation in the present study is regarded safe in the HCM population we will study, bearing in mind the in- and exclusion criteria (i.e. patients with impaired renal function defined as a glomerular filtration rate below 30 mL/min/m2 will be excluded). The same is true for undergoing an exercise test, which in general is regarded as a safe test in HCM patients. Only in patients with HCM and a severe obstruction of the left ventricular outflow tract an exercise test may pose a risk. Therefore, these participants will be excluded.
Participation will take time and effort. To partly compensate for this, participants will receive reimbursements for travelling costs.
Participants will have no direct benefit. Hopefully our findings will enhance our knowledge and improve risk stratification in these patients in the future.

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

•Patients with an echocardiographically proven hypertrophic cardiomyopathy according to the ESC guidelines;
•Individuals with a HCM associated mutation without the clinical characteristics of hypertrophic cardiomyopathy (pre-clinical HCM patients);
•Age >= 18 years;
•Able to comply with the protocol;
•Written informed consent.

Exclusion criteria

•Known significant epicardial coronary artery disease;
•Patients with LVH in the clinical setting of other disorders that explain the myocardial hypertrophy (amyloidosis, MELAS, Anderson-Fabry, WPW etc.);
•Heart failure NYHA class III-IV;
•Patients with known hemodynamic instability or syncope during exercise due to left ventricular
outflow gradient or occurrence of ventricular arrhythmia;
•History of PTSMA (percutaneous transluminal septal myocardial ablation) or Morrow

myectomy;
•Patients not able to complete a bicycle test;
•Any contraindication to MR imaging (MR imaging is not obligatory for assessment of the primary objective, therefore relative exclusion criterion);
•Recent (within 30 days) admittance to the hospital for any cardiac reason (myocardial infarction, heart failure, cardiac arrhythmia, etc.);
•Severe renal insufficiency (eGFR < 30 ml/min);
•Any other condition which, in the opinion of the investigator, may pose a significant hazard to the subject if he or she participates in the present study.

Study design

Design

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

Primary purpose: Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-05-2012
Enrollment:	0
Type:	Actual

Ethics review

Approved WMO Date:	09-02-2012
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-08-2012
Application type:	Amendment

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-05-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	NL37776.091.11