Validation of MRI measurements in myocardial biopsies

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

Summary

ID

NL-OMON47680

Source
ToetsingOnline

Brief title
Validation of MRI measurements in myocardial biopsies

Condition

- Myocardial disorders

Synonym
Cardiac muscle disease, cardiomyopathy

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: NIH

Intervention

Keyword: energy metabolism, fibrosis, MRI, myocardium

Outcome measures

Primary outcome

The main study parameters are:

1. Pre-contrast and post-contrast T1 times as quantified by a MOLLI sequence. Extracellular matrix volume fraction as calculated from myocardial and blood pool pre-contrast and post-contrast T1 and haematocrit.

2. Myocardial creatine content based on 1H-MRS, relative to the total water signal.

3. Myocardial TG content based on 1H-MRS, relative to the total water signal

4. Histological quantification of collagen volume fraction in myocardial biopsies

5. Biochemical quantification of myocardial creatine and triglyceride content.

Secondary outcome

1. Standard cardiac parameters obtained during a routine cardiac MRI protocol, including left and right ventricular end-diastolic and end-systolic volumes, stroke volumes, ejection fractions, left ventricular wall thickness and mass.

2. Routine measurements of plasma glucose, insulin, HbA1c, cholesterol, and lipids will be obtained from blood samples obtained at the time of MRI.

3. MicroRNA levels as measured in myocardial tissue and peripheral blood.

Study description

Background summary

This research protocol aims to validate two novel magnetic resonance imaging (MRI) techniques to visualize cardiac muscle properties against histology obtained in myocardial biopsy material. MRI is the gold standard imaging modality for patients with dysfunction of the cardiac muscle, called cardiomyopathy. In many patients, the exact cause of cardiomyopathy cannot be diagnosed because current imaging modalities have important limitations. One of these limitations is the fact that mild and diffuse myocardial fibrosis cannot be visualized, even though this is an important hallmark of cardiomyopathy. A second limitation is the fact that myocardial metabolism and myocardial triglyceride (TG, i.e. fat) depositions cannot be quantified noninvasively. Potential solutions for these limitations are a novel MRI technique called T1 mapping to quantify diffuse myocardial fibrosis, and a 1H-MR spectroscopy protocol (1H-MRS) to visualize myocardial metabolism and quantify myocardial TG content, respectively. However, these novel MRI protocol have not been validated properly against histology.
Patients who have a clinical indication for open heart surgery and are on the waiting list for the operation will be asked to participate in this research protocol. We will enroll (a) patients with severe aortic valve stenosis who are on the waiting list for surgical aortic valve replacement, and (b) patients with hypertrophic cardiomyopathy (HCM) with left ventricular outflow tract obstruction who are on the waiting list for surgical septal myectomy according to Morrow. Patients from both categories will be asked to undergo an MRI scan while on the waiting list. The research MRI acquisition procedures will be similar to routine MRI procedures and all safety precautions will be in place. The MRI protocol will consist of ECG triggered sequences for T1 mapping (MOLLI sequence) and for 1H-MRS measurements of tissue creatine (Cr) and TG content (PRESS and STEAM sequences, respectively). The research protocol requires one contrast bolus administration. In addition, patients with severe aortic valve stenosis undergoing aortic valve replacement will be asked permission for myocardial biopsies to be taken during surgery. The risk of this procedure is negligible. In patients with HCM undergoing Morrow septal myectomy, surgical excision of part of the basal septal myocardium is the indication for surgery. In this patient category, we will request patients* permission for the use of the excised myocardium. Myocardial biopsy samples will be used for quantification of histologically documented diffuse myocardial fibrosis, which will be correlated with extracellular matrix volume fraction as calculated based on pre- and post-contrast T1 times of the myocardium measured during the pre-surgery MRI. Myocardial biopsy material will also be used to quantify myocardial Cr and TG concentrations with biochemical assays. Results will be used to verify measurements obtained during the pre-surgery MRI.
In addition to MRI parameters, microRNAs (miRNAs) hold great promise as a new class of circulating biomarkers in peripheral blood. This unique study protocol which will acquire myocardial tissue biopsies will also be used as a platform to validate the miRNA-signatures in peripheral blood against

miRNA-signatures in myocardial biopsy tissue. Together with the miRNA-signature in peripheral blood obtained 6 months post-surgery, this will provide us with new insights into the function of identified miRNAs and improve their prognostic and in the future possibly even therapeutic value.
We expect to observe statistically significant correlations between noninvasive MRI-measured extracellular matrix volume and histologically proven diffuse myocardial fibrosis, between noninvasively 1H-MRS quantified tissue TG content and biochemically determined TG concentrations, and between 1H-MRS of tissue Cr content and biochemically determined Cr concentrations.

Study objective

The main objective of this study is to biochemically and histologically validate two novel MRI techniques to characterize myocardial properties that are expected to be useful for the diagnosis of various forms of cardiomyopathy. A second objective is to validate miRNA signatures in peripheral blood samples against myocardial miRNA content.

Study design

We will perform an MRI protocol on patients who have a clinical indication for open heart surgery and are on the waiting list for either surgical aortic valve replacement or surgical septal myectomy. We will employ a novel MRI sequence called T1 mapping to quantify the extent of diffuse myocardial fibrosis, and a 1H-MRS protocol to visualize myocardial creatine and triglyceride content. A total of 5 blood samples will be drawn at the time of the MRI. If patients have given signed informed consent, a myocardial biopsy will be taken during aortic valve replacement surgery. Patients undergoing surgical septal myectomy will be asked permission for the use of the routinely excised myocardium. At the routine outpatient visit 6 months post-surgery, an additional blood sample will be obtained. Myocardial parameters obtained using noninvasive pre-surgery MRI will be validated against biochemical assays and histology in the myocardial biopsies. Furthermore, miRNA profiling will be performed on both peripheral blood and myocardial tissue of these patients.

Study burden and risks

Patients on the waiting list for open heart surgery will be asked to undergo an MRI scan before the operation. Surgery will not be delayed for the research MRI protocol. The MRI is a noninvasive procedure, except for the insertion of an intravenous canula for contrast administration. The MRI protocol takes 60 min. The research MRI acquisition procedures will be similar to routine MRI procedures and all safety precautions will be in place. Patients with established contra-indications for MRI will not be recruited. When patients wish to stop the scanning procedure and get out of the scanner they can press a *panic button*, which is standard procedure for every MRI. Patients are also

able to talk to the researchers in the control room at any time during the experiment. Potential hazards from high-energy radiofrequency or gradient pulses are not any higher than in the manufacturer*s sequences. MRI does not require ionizing radiation, and gadolinium contrast is well tolerated with only very rare cases of gadolinium allergy ever reported in the literature. The intravenous canula will be used to draw blood for research purposes (5 tubes = 15.8 ml in total).

Patients undergoing surgical aortic valve replacement will be asked permission for myocardial biopsies to be taken during surgery. During surgery, myocardial biopsy specimens will be taken from the basal LV septum using a Tru-cut type biopsy needle. A total of 4 biopsies will be obtained. The size of each biopsy sample is <0.1 g, which is less than a thousandth of the total myocardial volume. Obtainment of LV septal biopsies in patients with aortic valve stenosis (and consequent left ventricular hypertrophy) is regarded safe, due to the concentric left ventricular hypertrophy that is present in these patients, due to extensive experience of operators, clear visibility of the interventricular septum after thoracotomy, and because the MRI will be used to guide the operator to the most optimal biopsy site. In addition, the size of the biopsies is small (3 x 3 x 3 mm). As a result, the risk for conduction abnormalities as a result of the biopsies is negligibly small. Patients undergoing surgical septal myectomy will be asked permission for the use of the myocardium that is excised routinely during this procedure. The risks of this type of surgery are inherent to the operation that is clinically indicated. At the routine outpatient clinic visit 6 months post-surgery, we will draw an additional blood sample (2 tubes of 2.7 ml = 5.4 ml).

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

(a) Patients with severe aortic valve stenosis who have a clinical indication for surgical aortic valve replacement according to the ESC guidelines, have been accepted for surgery, and have been placed on the waiting list (n=30).
(b) Patients with hypertrophic cardiomyopathy and left ventricular outflow tract obstruction who have a clinical indication for surgical septal myectomy according to the ESC guidelines, have been accepted for surgery, and have been placed on the waiting list (n=20).

Exclusion criteria

1. Under the age of 18.
2. Renal failure (estimated glomerular filtration rate < 30 ml/min).
3. Claustrophobia or another contra-indication for MRI.
4. Not able to provide written informed consent.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-04-2016
Enrollment:	50
Type:	Actual

Ethics review

Approved WMO

Date:	26-03-2015
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	NL52084.018.15