A reproducibility study of novel noninvasive multimodal imaging techniques in atherosclerosis in healthy and cardiovascular diseased subjects

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Primary Objectives:A. To assess the reproducibility and variability (interscan, intra- and interreader) of novel (DCE-)MRI techniques to measure vessel wall dimensions, wall shear stress and vessel wall permeability in healthy and cardiovascular...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Arteriosclerosis, stenosis, vascular insufficiency and necrosis
Study type	Observational invasive

Summary

ID

NL-OMON41660

Source
ToetsingOnline

Brief title
VISUALIZE

Condition

- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
Atherosclerosis, cardiovascular disease

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Atherosclerosis, Imaging, MRI, PET/CT

Outcome measures

Primary outcome

-Intraclass correlation coefficient and coefficient of variation of the interscan, interreader and intrareader measurements of vessel wall dimensions (total wall volume, mean wall area, mean wall thickness, normalized walll index), wall shear stress and vessel wall permeability (k-trans and area under the curve) by (DCE-)MRI.

-Intraclass correlation coefficient of the interscan, interreader and intrareader measurements of vessel wall inflammation (TBR) by 18F-FDG PET/CT.

Secondary outcome

-Difference between vessel wall dimensions (total wall volume, mean wall area, mean wall thickness, normalized walll index measured by MRI), wall shear stress (measured by MRI), vessel wall permeability (k-trans, area under the curve measured by DCE-MRI) and vessel wall inflammation (TBR measured by 18F-FDG PET/CT) between healthy young and healthy older and cardiovascular subjects.

-Pearson*s correlation between vessel wall inflammation as measured by 18F-FDG

-PET/CT (TBR), MRI (wall shear stress), DCE-MRI (k-trans, AUC) and laboratory markers of systemic inflammation (CRP, LpPLA2).

Study description

Background summary

Atherosclerosis is the main cause of cardiovascular disease. It is a progressive disease, characterized by the formation of plaques in the vessel wall. After a long asymptomatic period, patients with atherosclerosis can present with symptoms of impaired blood flow due to stenosis (e.g. stable angina pectoris, claudicatio intermittens) or with acute complications due to plaque rupture (e.g. myocardial infarction, ischemic stroke). Vascular imaging techniques, like ultrasonography, magnetic resonance imaging (MRI) and positron-emission tomography / computed tomography (PET/CT) scans, enable detection of atherosclerosis before clinical symptoms occur. These techniques can further be used in clinical decision making by risk stratification and as a surrogate parameter for cardiovascular disease in therapeutic trials.

Ultrasonographic measurement of the intima-media thickness (IMT) is the most extensively validated modality in vascular imaging. Carotid IMT can predict future cardiovascular events and can be used as an end-point in clinical studies evaluating cardiovascular therapy. Furthermore, stenosis grade can be assessed by ultrasonography and is used to select patients eligible for carotid or femoral surgery.

However, stenosis grade and IMT have shown to be insufficient, not telling the whole story in atherosclerosis. Not only the degree of stenosis, but also the activity and vulnerability of the plaque drive progression and complications of atherosclerosis. Novel vascular imaging techniques, including MRI and 18-fluorodeoxyglucose (18F-FDG) PET/CT scan, do enable us to image these important plaque characteristics.

MRI can provide high-resolution images of the carotid artery, aorta and the femoral artery. MRI enables accurate analysis of the vessel wall dimensions and specific structures in the atherosclerotic plaque, like lipid-rich necrotic core, intra-plaque hemorrhage, loose matrix and the fibrous cap can be identified. Endothelial shear stress, an important determinant in endothelial permeability and influx of lipids and immune cells, promoting atherosclerosis, can also be measured by MRI. Dynamic contrast enhanced MRI (DCE-MRI) makes it possible to image vessel wall permeability, i.e. neovascularisation, in the atherosclerotic plaque, reflecting inflammatory activity.

18fluor-fluorodeoxyglucose PET/CT (FDG-PET/CT) is a nuclear imaging technique which measures metabolic activity by labelling glucose with a PET tracer (18-fluor). Since atherosclerosis is now classified as an inflammatory disease, and inflammation has high metabolic needs, FDG-PET/CT of the vessel wall was proposed as a read-out for atherosclerotic plaque inflammation. Indeed, FDG uptake in the vessel wall, expressed as the target (vessel wall) to background (blood pool) ratio (TBR), is associated with the number of macrophages in atherosclerotic lesions. and seems capable of visualizing

atherosclerotic plaque inflammation.

For implementation of vascular imaging techniques as an endpoint in clinical translational research and clinical practise, they should be accurate and reproducible. Reproducibility studies of MRI techniques to measure vessel wall dimensions and wall shear stress have been performed and show good reproducibility. However, new MRI scanners enable improved MRI techniques of the vessel wall, including faster scans, higher spatial resolution scans and three-dimensional MRI scans. In this study we will test the reproducibility of these new MRI techniques to measure vessel wall dimensions and wall shear stress.

The reproducibility of FDG-PET/CT to measure vessel wall inflammation in patients with atherosclerotic disease was good in studies by Rudd et al. This group is the only so far that studied the reproducibility of FDG-PET/CT. Since FDG-PET/CT of the vessel wall is increasingly used as an endpoint in therapeutic trials and may be implemented in clinical practise, it is important to confirm the reproducibility of this technique by other research groups. In the present study, we will study the reproducibility of FDG-PET/CT of the vessel wall in subjects with cardiovascular disease and healthy volunteers. To the best of our knowledge, there are no prior studies on this topic in healthy volunteers.

Study objective

Primary Objectives:
A. To assess the reproducibility and variability (interscan, intra- and interreader) of novel (DCE-)MRI techniques to measure vessel wall dimensions, wall shear stress and vessel wall permeability in healthy and cardiovascular subjects.
B. To assess the reproducibility and variability (interscan, intra- and interreader) of 18 F-FDG-PET/CT scan to measure vessel wall inflammation in healthy and cardiovascular subjects.

Secondary Objective:
- To assess the correlation between the degree of arterial wall inflammation as measured by 18F-FDG -PET/CT and wall shear stress as measured by MRI and vessel wall permeability as measured by DCE-MRI.
- To assess the correlation between the degree of arterial wall inflammation as assessed with 18F-FDG -PET/CT and circulating markers of inflammation.
- To assess the difference in vessel wall dimensions, wall shear stress, vessel wall inflammation and vessel wall permeability between healthy young subjects, healthy older subjects and cardiovascular subjects.
- To compare the reproducibility and variation of different MRI techniques to measure vessel wall dimensions.

Study design

This study is designed as a single center, observational study. After screening for eligibility, all subjects will undergo cardiovascular risk assessment and laboratory testing. Thereafter, all subjects will undergo subsequently a MRI scan and 18F-FDG -PET/CT scan.

In a subset of subjects, vascular imaging will be repeated on the same day. The MRI scan will take 60 minutes. A repeat MRI scan of 60 minutes will be performed after 60 minutes of rest. After the administration of 18F-FDG and a resting period for its distribution, PET/CT scan of the carotid artery and aorta will be performed. This scan takes 20 minutes. In subjects undergoing a repeat 18F-FDG PET/CT scan, only the PET/CT scan will be repeated, not the injection of 18F-FDG, thereby limiting the extra radiation exposure. This scan again takes 20 minutes and will be performed after a resting period of 20 minutes.

Study burden and risks

The results of this study contribute to the quality of novel techniques in atherosclerotic imaging, thereby contributing to risk stratification in individual patients and testing of new anti-atherosclerotic treatment. Individual subjects will gain no direct benefit from this study. The risk of participating in this study is estimated to be low. Gadovist is routinely used as a contrast agent in magnetic resonance imaging. Protocols that describe what to do in case of contrast-induced hypersensitivity reactions are implemented at our department and drugs to treat these hypersensitivity reactions are readily available at the site of the MRI scan. MRI is a safe imaging technique without radiation exposure. The exposure to radiation related to 18F-FDG PET/CT scan is 7.5 mSv for all subjects. This is below the maximum permitted 10 mSV per year.

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

Group A: 20 subjects with cardiovascular disease.
-Aged 40 years or older
-Known with either
a)A history of cardiovascular disease, such as but not limited to transient ischemic attack (TIA), ischemic stroke, unstable angina pectoris, myocardial infarction or peripheral artery disease.
b)Cardiovascular risk factors, such as but not limited to hypertension, diabetes mellitus, hypercholesterolemia (LDL > 4.0 mmol/l), low HDL-cholesterol (<1.03 mmol/l), smoking, obesity (BMI > 27 kg/m2).;Group B: 20 young healthy volunteers
-Aged 40-55 years
-No history of cardiovascular disease
-No cardiovascular risk factors ;Group C: 20 older healthy volunteers
-Aged 55-75 years
-No history of cardiovascular disease
-No cardiovascular risk factors

Exclusion criteria

Exclusion criteria for all subjects;1. Known systemic disorders such as hepatic, renal, hematologic, and malignant diseases or any clinically significant medical condition that could interfere with the conduct of the study in the opinion of the investigator.
2. Standard contra-indications to MRI, 18F-FDG PET, and CT based on physicians experience and current practices (e.g. claustrophobia, metal in the body, as a result of e.g. osteosynthetic material, pacemaker implantation or artificial cardiac valves).
3. Inability or unwillingness to comply with the protocol requirements, or deemed by

investigator to be unfit for the study.;Exclusion criteria for group A: Cardiovascular patients;1. Changes in dose or frequency of doses of lipid-lowering drugs, antihypertensive drugs or antidiabetic drugs.in the last 6 weeks prior to baseline measurements.
2. Cardiovascular event in the last 3 months prior to baseline measurements.;Exclusion criteria for group B and C: Healthy volunteers;1. A history of cardiovascular disease
2. A known elevated risk for cardiovascular disease
3. Use of any cardiovascular medication, including but not limited to lipid-lowering therapy, antihypertensive drugs, antidiabetic drugs, platelet aggregation inhibitors and anticoagulants.

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:	Recruitment stopped
Start date (anticipated):	04-10-2013
Enrollment:	60
Type:	Actual

Ethics review

Approved WMO

Date:	04-07-2013
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	NL43143.018.13