Level of agreement in the assessment of carotid plaque composition between multi-contrast and multi-sequence MRI

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Primary Objective:1. The primary objective is to investigate the level of agreement between scoring the presence of IPH on MR images acquired with MP-RAGE (conventional sequence) with scoring IPH on the multicontrast sequences. The level of...

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

Summary

ID

NL-OMON49184

Source
ToetsingOnline

Brief title
Multi-contrast versus multi-sequence carotid MRI

Condition

- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
atherosclerosis, stroke

Research involving
Human

Sponsors and support

Primary sponsor: Imaging
Source(s) of monetary or material Support: European Union□s Horizon 2020 research and innovation programme under the Marie Sk□odowska-Curie grant agreement No 722609

Intervention

Keyword: atherosclerosis, carotid artery, MRI, multi-contrast

Outcome measures

Primary outcome

Main study parameter

• The primary objective is to investigate the level of agreement between scoring presence of IPH on MR images acquired with MP-RAGE (conventional sequence) with scoring IPH on the multicontrast sequences. The level of agreement will be assessed by calculating Cohen*s *.

Secondary outcome

Secondary study parameters

• To investigate the level of agreement between scoring the presence of a LRNC, calcifications, a thin or rupture fibrous cap, and ulcerations on the multicontrast images versus the conventional multisequence MR images.

• To study the correlation between the vessel wall and luminal volume and volumes of calcifications, LRNC and IPH as delineated on the multicontrast sequences versus the conventional multisequence MRI protocol.

• To study the correlation between the presence/volume of calcifications, LRNC, thin or ruptured fibrous cap, ulcerations and IPH as quantified using the multicontrast MRI sequences and histology.

Study description

Background summary

Complications of cardiovascular disease, such as stroke, continue to be the leading cause of death and long-term disability in the western societies. Despite significant advances over the past 20 years in treating cardiovascular disease, the incidence of its complications is still high and there remains an unexpectedly high number of apparently healthy individuals who die from sudden cardiovascular events without prior symptoms.
Stroke as a major cardiovascular complication- is in two-thirds of the cases related to rupture of an atherosclerotic plaque, the so-called *vulnerable plaque* of an extracranial artery (usually carotid artery). Subsequently, the ruptured plaque develops superficial thrombosis and sheds debris into the cerebral vasculature.

Although occasionally heralded by transient ischemic events, the majority of strokes occur without prior prodromal symptoms. Up until now, indications for carotid endarterectomy in have been based largely on the severity of stenosis and symptomatology. However, the degree of luminal stenosis seems not to be the solely factor that matters. In recent years, the plaque composition on MRI, including intraplaque haemorrhage (IPH), a large lipid-rich necrotic core (LRNC), and thin or ruptured fibrous cap has emerged as an important determinant of ischemic events alongside the degree of luminal narrowing.

These characteristics of plaque vulnerability can be visualised using MRI because of its superior soft tissue contrast. A meta-analysis by Gupta et al. found that IPH, LRNC and thin or ruptured fibrous cap as determined by MRI, demonstrated a hazard ratio of 4.59 (95% confidence interval (CI), 2.91-7.24), 3.00 (95% CI, 1.51-5.95), and 5.93 (95% CI, 2.65-13.20) respectively, for future stroke or transient ischemic attack. A more recent meta-analysis by Schindler et al. showed that the presence of IPH in carotid plaques is an independent risk predictor for ipsilateral ischemic stroke in both symptomatic and asymptomatic patients that is stronger than any known clinical risk factor.

Despite the advantages of MRI in determining plaque vulnerability, it is not yet used in daily clinical practice. One of the reasons is long MRI scan times. To visualize different vulnerable plaque components, multiple MRI sequences need to be acquired. This can accumulate to a scan time of around 30-40 minutes. To tackle this problem, recently multicontrast sequences have been developed which acquire multiple contrasts in a single sequence, reducing the total scan time significantly to less than 6 minutes. Another advantage is that because these multiple contrasts are acquired simultaneously, they are co-registered to each other, unlike conventional multi-sequence MRI which acquires images with different contrasts sequentially and suffers from misregistration errors between different contrast images.

In the present study, we will validate two multicontrast sequences namely Multicontrast ATherosclerosis Characterization (MATCH) and Bright*blood and black*blOOd phase SensiTive (BOOST) inversion recovery sequence. Patients with

a carotid plaque of >= 2 mm in thickness based on ultrasound or CTA will be scanned with the two multicontrast sequences under investigation followed by the conventional MRI sequences. Different plaque components will be delineated independently on the conventional and on the multicontrast images by trained observers using dedicated software to calculate the volume of the various plaque components, the vessel wall and the lumen. In those patients that need to undergo carotid endarterectomy in standard clinical care, the carotid endarterectomy specimen will be collected and processed under supervision of the pathology research laboratory. The volumetric data on plaque composition obtained from the imaging will be compared histological quantification of plaque composition.

The MATCH sequence acquires three different contrasts (hyper T1 weighted (T1w) black blood, grey blood and T2 weighted (T2w) black blood). In a study with 53 patients, MATCH showed results comparable to a conventional multicontrast protocol (Time of flight (TOF), T1w, T2w) in quantitative measures of luminal area, outer wall area, mean area of LRNC and loose matrix, while MATCH showed a larger mean area of IPH and calcifications. The performance of MATCH was not compared to a hyper T1w sequence such as a three-dimensional magnetization-prepared rapid acquisition gradient echo (MP-RAGE). MP-RAGE is more sensitive and specific to IPH detection and the use of such a sequence was recently recommended in a white paper with consensus recommendations by experts [14]. In the same study , using carotid endarterectomy specimens from 13 patients as a reference, MATCH performed as well as the conventional sequences (TOF, T1w, T2w) in detecting IPH, LRNC, loose matrix, and calcifications with an acquisition time of only 2 * minutes. MATCH still needs to be validated with multi-sequence MRI including a hyper T1w sequence and with histology in larger studies.

BOOST is another multicontrast sequence initially developed for coronary plaque imaging. The BOOST sequence to be used in the present study has been optimised for carotid artery imaging and acquires bright and black blood images with a single sequence. The feasibility of thrombus visualization with BOOST was shown in an ex-vivo pig heart, but a validation study with conventional multi-sequence MRI and histology still needs to be performed

Study objective

Primary Objective:

1. The primary objective is to investigate the level of agreement between scoring the presence of IPH on MR images acquired with MP-RAGE (conventional sequence) with scoring IPH on the multicontrast sequences. The level of agreement will be assessed by calculating Cohen*s kappa.

Secondary Objectives:

1. To investigate the level of agreement between scoring the presence of an LRNC, calcifications, a thin or rupture fibrous cap, and ulcerations on the multicontrast images versus the conventional multisequence MR images.
2. To study the correlation between the vessel wall and luminal volume and volumes of calcifications, LRNC and IPH as delineated on the multicontrast sequences versus the conventional multisequence MRI protocol.
3. To study the correlation between the presence/volume of calcifications, LRNC, thin or ruptured fibrous cap, ulcerations and IPH as quantified using the multicontrast MRI sequences and histology.

Study design

A cross-sectional validation study will be performed.

Study burden and risks

Due to the strong magnetic field and the narrow bore of an MRI scanner, patients with contra-indications for MRI cannot be scanned. Patients with contra-indications for MRI, such as pacemakers, vessel clips, or metal splinters in the eye will be excluded from the study. Claustrophobic patients are also excluded from the study. An MRI exam is safe and therefore adds no additional risk for the patient. The patients need to invest time for the MRI examination.

Patients with a renal clearance higher or equal to 30 ml/min/1.73 m2 will receive a gadolinium-based contrast agent during the MRI examination. Patients with a renal clearance of less than 30 ml/min/1.73 m2 will be scanned without the contrast agent. The side effects of the MRI contrast agent (Gadovist) are rare, amongst others nausea (0.25%), vomiting (0.05%), urticaria (0.04%), feeling of warmth, tachycardia, wheals (for each 0.03%), dizziness, itching, vasodilatation, itchy throat (for each 0.02%) and cough, dyspnoea, flushing, hives, generalized itching, oral dryness, facial redness, sensation of heat, skin disorder and aggravated nausea (for each, 0.01%) [3]. Out of 14299 patients, two serious adverse drug reactions (ADRs) occurred (0.01%), which were considered by the treating physician to be probably associated with the administration of Gadovist; one patient had a severe anaphylactic reaction and the other presented with itching and swelling in the throat. In most cases, side effects occur immediately after contrast injection, and therefore patients will remain in the hospital for 30 minutes after injection. The administration of the contrast agents is relatively safe and side effects are rare.

There are no treatment benefits to the patients; however, they will obtain the satisfaction of advancing knowledge that may help others. If the multicontrast sequences perform as well or better than the conventional sequences, multicontrast sequences could replace the conventional sequences. This would make the use of carotid plaque imaging with MRI more convenient and it will

help towards clinical translation.
MRI contrast agent and the insertion of a peripheral venous catheter are both associated with very rare or minor adverse events.
In conclusion, the inconvenience this study will bring to included patients is acceptable compared to the effects of the hoped diagnostic role of these sequences in patients with carotid artery disease.

Contacts

Public
Selecteer

P. Debyelaan 25 25
Maastricht 6229 HX
NL
Scientific
Selecteer

P. Debyelaan 25 25
Maastricht 6229 HX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

• Patients with a carotid plaque >= 2 mm thick based on ultrasound or CTA
• Age: 18 years or older (no maximum age)
• Informed consent by signing informed consent form regarding this study

Exclusion criteria

• Patients with carotid plaque <= 2 mm in size based on ultrasound or CTA
• Standard contra-indications for MRI (electronic implants like pacemakers or other electronic implants, metallic eye fragments, vascular clips, claustrophobia, etc.)
• Severe co-morbidity, dementia or pregnancy

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	08-04-2021
Enrollment:	40
Type:	Actual

Ethics review

Approved WMO

Date:	02-12-2020
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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
ClinicalTrials.gov	NCT04569006
CCMO	NL73156.068.20