Detecting aneurysmal instability by linking imaging and genetics

Published: 19-12-2023
Last updated: 30-11-2024

Primary Objective: Identify markers that distinguish between high and low rupture risk IAs.Secondary Objective(s): • Gain insight in the hemodynamic and cellular processes underlying IA rupture risk.• Determine the interrelatedness of hemodynamic...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Aneurysms and artery dissections
Study type	Observational invasive

Summary

ID

NL-OMON53244

Source
ToetsingOnline

Brief title
DETAILING

Condition

- Aneurysms and artery dissections

Synonym
'cerebral aneurysm', 'Intracranial aneurysm'

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Genetics, Intracranial aneurysm, MRI, Subarachnoid haemorrhage

Outcome measures

Primary outcome

Main parameters in this study are:

1. Genetic parameters: gene expression (transcripts per million) of all genes specific to each arterial cell-type (detectable cell-types expected are vascular endothelial cells, vascular smooth muscle cells, vascular fibroblasts).

2. Aneurysm hemodynamic parameters 4D MR flow parameters a. mean flux (ml), b. stroke volume (ml per s), c. derived biomechanical parameters including pulsatility index, arterial distensibility (mm Hg-1), wall shear stress (Pa) and oscillatory shear index. These will be determined both in the aneurysm and in the feeding arteries.

3. Aneurysm configuration parameters: aneurysm size (length, width (mm), aneurysm volume (ml) and aneurysm irregularity (more complex geometric definitions as surface area, eccentricity, compactness, shape index and curvedness).

Main outcome measurements are: IA size, IA rupture risk assessment by the PHASES score.1

Secondary outcome

Not applicable

Study description

Background summary

Rupture of an intracranial aneurysm (IA) causes aneurysmal subarachnoid hemorrhage (ASAH), a severe form of stroke accounting for the highest patient-related costs across stroke-types, and for comparable life years lost to ischemic stroke. Upon detection of an IA, invasive surgical or endovascular intervention (clipping or coiling) can prevent rupture. However, interventions come with risk of complications and predicting which IAs are prone to rupture - and thus for which IAs intervention has favorable benefit-to-risk ratio - remains challenging. As a result, only a minority of IAs is treated, leaving many patients at risk of rupture.

The best surrogate for IA rupture is aneurysmal instability (growth and/or shape change), but this requires long follow-up with intervals of typically five years during which rupture may occur. Having an unruptured IA without knowing whether it may someday rupture causes a psychological burden in these patients. To allow fast prediction of rupture, single time-point aneurysmal and patient characteristics that correlate with rupture can be used to assess rupture risk. However, their predictive relevance has been debated as most ASAHs are the result of rupture of aneurysms with estimated low rupture risk (i.e. low PHASES score, the most commonly used rupture risk prediction).

Hemodynamic characteristics play a role in aneurysmal instability and rupture. Small changes in aneurysm shape can have significant impact on flow, and wall shear stress (WSS) can in turn cause vascular remodeling and IA destabilization Low pulsatility, blood flow instability, and aberrant WSS contribute to IA destabilizing and/or rupture. A recent UMCU study showed that 4D flow MRI on 7 Tesla can be used for accurate quantification of wall shear stress, flow, velocity, and pulsatility index in human IAs in vivo. However, these measurements rely on the application of additional magnetic field gradients and typically suffer from long acquisition times and low signal-to-noise ratio. Building on UMCU*s expertise in gradient hardware, we will boost MRI flow measurements by using a novel strong-gradient head insert coil (funded by Health Holland) which significantly improves the efficiency of translational motion (diffusion or flow) encoding. Having only been applied to diffusion MRI, this first use of strong gradients for flow MRI should lead to previously unattainable signal-to-noise levels, accurate quantification of slow-flow velocities, and short acquisition times.

Cellular changes occur prior to IA formation and during periods of aneurysmal instability. A dynamic process of vascular remodeling and inflammation leads to thinning and disruption of vascular layers, thereby destabilizing the vascular wall. Smooth muscle cells and endothelial cells have distinct roles in aneurysmal stability, complicating the detection of cellular markers and

necessitating a cell-type specific approach. Recently, single-nucleus RNA sequencing has become available to detect gene expression changes on a cellular level. It was shown that this technique can detect expression differences in arterial tissue that cell-types can be distinguished in IAs. We will use single-nucleus RNA sequencing to obtain expression patterns per cell-type.

Cellular and hemodynamic characteristics are intrinsically interrelated: Arterial geometry affects gene expression in vascular endothelial cells, including actin cytoskeletal organization, and inflammation. Pulsatility is associated with endothelial cell stress and with the expression of adhesion molecules. Here, we will tackle technical limitations in imaging and genomics to achieve unprecedented characterization of aneurysmal rupture risk.

We hypothesize that the joint analysis of hemodynamic and cellular markers can characterize IA rupture risk with precision that cannot be achieved by studying either component separately.

This project will develop single time-point markers of IA rupture risk, with the goal to detect IAs at high risk of rupture earlier and reduce burden of ASAH. To achieve this goal, we will be the first study to include markers of both 1) hemodynamic processes (from imaging) and 2) cellular characteristics (from biopsy and blood) in the same IA. By retrospective correlation with aneurysmal stability from existing longitudinal data, we aim to 1) gain better understanding of the interplay between hemodynamic and cellular processes underlying rupture risk, and 2) identify markers that can maximally discriminate between high and low rupture risk IAs. Identifying non-invasive markers from imaging and blood help pave the way to our long-term goal of prospective and early prediction of ASAH.

Study objective

Primary Objective:
Identify markers that distinguish between high and low rupture risk IAs.

Secondary Objective(s):
• Gain insight in the hemodynamic and cellular processes underlying IA rupture risk.
• Determine the interrelatedness of hemodynamic and cellular markers in IA.
• Test if cellular markers that explain differences in surrogate markers for rupture risk of IA can be detected in blood.

Study design

This study is a cross-sectional cohort study. The population consists of all patients of age 18 years or older with an unruptured IA who need surgical clipping to treat the IA and who are admitted to the UMC Utrecht. Within this

population we will study which genetic and hemodynamic parameters explain differences in surrogate markers for rupture risk (being IA size, and PHASES score).

The duration of the study is 3 years.

Study burden and risks

Participating will cost the patients time (one hour in total). The risk associated with the study are minimal. Undergoing an MRI scan is safe. the intracranial aneurysm biopsy will be taken after placing a clip and confirmation by the neurosurgeon that the aneurysm has been completely blocked off from the circulation. The neurosurgeon decides during surgery whether taking a biopsy is safe.

Contacts

Public
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584CX
NL
Scientific
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584CX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Elderly (65 years and older)

Inclusion criteria

Have an unruptured intracranial aneurysm
Need surgical clipping to treat the intracranial aneurysm
Age 18 years or older

Exclusion criteria

Unable to undergo a scan in the 7 Tesla MRI machine

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	19-03-2024
Enrollment:	16
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO

Date:	19-12-2023

Application type:	First submission
Review commission:	METC NedMec

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	NL84018.041.23