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An observational study of brain blood vessel function in cerebral small vessel disease

Submission date
06/05/2016

Recruitment status
No longer recruiting

Registration date
23/05/2016

Overall study status
Completed

Last Edited
09/06/2025

Condition category
Circulatory System

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Stroke and dementia are among the most pressing health issues in Europe, affecting a large proportion of the population. Cerebral small vessel disease (SVD) is a major cause these conditions, accounting for more than 30% of strokes and at least 40% of dementia cases. It is thought to happen because of damage to the lining of the tiny blood vessels in the brain that prevent them from working properly, causing damage to brain tissue. Progress in understanding the mechanisms behind SVD has been slow, and there are currently no proven effective treatments. Investigate@SVDs is part of a coordinated programme (SVDs@target – funded through the European Union's Horizon 2020 research and innovation programme) designed to try and undertand the key mechanisms of different SVDs and how they contribute to individual SVDs. The aim of this project is to assess factors that drive brain microvascular dysfunction in different types of SVD.

Who can participate?
Adults who are able to have an MRI scan and have had a stroke due to SVD, have SVD associated cognitive impairment or have a genetic variant of SVD.

What does the study involve?
Participants visit the hospital at the start of the week to answer some questions about their health and have their blood pressure taken. A blood test is also taken and sent to a local laboratory to measure cells and chemicals in the blood that indicate if there is any inflammation. Then a blood pressure cuff is put around their arm which they will wear for a week while doing their usual activities, to continuously measure blood pressure. The recordings are sent anonymously via a mobile phone signal to a central computer for analysis. At the end of that week, participants attend another hospital visit to have a magnetic resonance brain scan to test the blood vessel leakiness and function. The scan lasts about two hours altogether, with a break in the middle. For the first part of the scan, the participant wears a face mask connected to some tubing. During the scan, for three minute intervals participants alternatively breath carbon dioxide mixed with air, and air alone (the carbon dioxide stimulates the brain blood vessels to open up and this can be detected on the scan). In the second part of the scan, after a break, participants have a small plastic tube placed into the vein at the elbow. After the next scan starts magnetic dye will be injected into the arm vein, which circulates to the brain with the

blood and the amount that leaks out of the blood vessels is measured by the scanner. After this scan has finished, the stiffness of the main blood vessels in the neck and arm are measured while the patient is lying on a couch. This is performed using a small camera that sits on the skin over the blood vessel and takes a few minutes.
What are the possible benefits and risks of participating?
There is no direct benefit of taking part in the study. Risks of participating are low as all scanning methods used are well established and all participants will be screened carefully for things that mean they shouldn't have the scans before they start. There is a small risks of pain and bruising during and after blood testing.

Where is the study run from?
1. Centre for Clinical Brain Sciences, Edinburgh (UK)
2. Ludwig-Maximilians University (Germany)
3. Maastricht University Medical Centre (Netherlands)

When is the study starting and how long is it expected to run for?
June 2017 to June 2019

Who is funding the study?
European Union Horizon 2020 (Belgium)

Who is the main contact?
Professor Joanna Wardlaw
joanna.wardlaw@ed.ac.uk

Contact information

Type(s)
Scientific

Contact name
Prof Joanna Wardlaw

ORCID ID
https://orcid.org/0000-0002-9812-6642

Contact details
Centre for Clinical Brain Sciences
Chancellor's Building
Little France Crescent
Edinburgh
United Kingdom
H16 4SB
+44 (0)131 332 2943
joanna.wardlaw@ed.ac.uk

Additional identifiers

Protocol serial number
1.0

Study information

Scientific Title
Imaging NeuroVascular, Endothelial and STructural Integrity in prepAration to TrEat Small Vessel Diseases

Acronym
INVESTIGATE@SVDs

Study objectives
1. Greater blood brain barrier permeability will be associated with more reduced CVR
2. It will be possible to have increased BBB permeability without decreased CVR as this should occur at an earlier point in the pathogenesis of SVD
3. Increased enlarged perivascular spaces on structural imaging will correlate with reduced microvascular function
4. More variable blood pressure will worsen BBB permeability and CVR, and this effect will be greater than the effect of hypertension alone

Ethics approval required
Old ethics approval format

Ethics approval(s)
South East Scotland Research Ethics Committee 01, ref: 16/SS/012

Study design
Cross sectional study

Primary study design
Observational

Study type(s)
Diagnostic

Health condition(s) or problem(s) studied
Sporadic small vessel disease - stroke, cognitive impairment

Interventions
After answering some questions about their health, the subjects will have a blood pressure cuff put on their arm to wear for a week while doing their usual activities. This measures blood pressure continuously by day and night. At the end of that week, the subjects will come for a magnetic resonance brain scan to test the blood vessel leakiness and function. The scan lasts about two hours altogether with a break in the middle. The blood pressure measurement cuff is removed. During the scan, the subject will lie in the scanner. For the first part, they will wear a face mask connected to some tubing. Some images of the brain to show size and shape will be taken. Then the subject will breath carbon dioxide mixed with air through the mask for three minutes, then air, then the carbon dioxide+air, then air. The carbon dioxide stimulates the brain blood vessels to open up and this can be detected on the scan. After the first part of the scan, the mask will be removed and the subject can have a break. Then they go back in the scanner and a small plastic tube is put into the vein at the elbow, like for a blood test. After the next scan starts, some magnetic dye will be injected into the arm vein while the scan continues. The dye

goes to the brain in the circulation and the amount that leaks out of the blood vessels over the next 20 minutes can be measured with the scanner. After this scan has finished, the subject will come out of the scanner and lie on a couch to have a measurement of the stiffness of the main blood vessels in the neck and arm. This is performed using a small camera that sits on the skin over the blood vessel. This takes a few minutes. Then the subject leaves and the study is finished.

Intervention Type
Other

Primary outcome(s)
Blood brain barrier leakiness is measured during the magnetic resonance scan from the gadolinium contrast agent uptake in the brain over 20 minutes after intravenous injection. The resulting contrast-time curve is modelled statistically to calculate contrast retention (leak) in different areas of the brain.

Key secondary outcome(s))
1. Cerebrovascular reactivity to inhaled carbon dioxide is measured once prior to blood brain barrier leakiness
2. Blood pressure (systolic, diastolic, mean blood pressure, pulse pressure, and variability in blood pressure) is measured continuously for seven days prior to blood brain barrier leakiness scanning
3. Vascular stiffness is measured immediately after blood-brain barrier leakiness scanning using pulse wave velocity

Completion date
30/05/2020

Eligibility

Key inclusion criteria
1. Age 18 years or older
2. Able to undergo MRI
3. Capacity to give written informed consent
4. Symptomatic SVD defined as:
4.1. A history of clinical lacunar stroke syndrome in the last 5 years with a recent small subcortical infarct visible on MRI scan or CT scan* compatible with the clinical syndrome.
OR
4.2. A diagnosis of CADASIL established by molecular genetic testing of the NOTCH3 gene (presence of an archetypical, cysteine-affecting mutation) or the presence of granular osmiophilic material (GOM) in ultrastructural, electron microscopy analysis of skin biopsy

*On MRI, a recent infarct is defined as a DWI lesion on the acute MRI scan. On CT, recent infarct is defined as a novel lacune on CT within 3 weeks after the event that was not visible on the admission CT.
or cognitive impairment defined as visiting a memory clinic and a clinical dementia rating [CDR] score of ≥ 0.5, and capacity to consent with confluent deep white matter hyperintensities (WMH) on MRI (defined on the Fazekas scale as deep WMH score ≥ 2)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
78

Key exclusion criteria
1. Inclusion criteria are not met
2. Unwillingness or inability to give written consent
3. Pregnant or breastfeeding women, women of childbearing age not taking contraception.
4. Acceptable contraception in women of childbearing age is a “highly effective” contraceptive measure as defined by the Clinical Trials Facilitation Group (http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf) and includes combined (oestrogen and progesterone containing) or progesterone-only contraception associated with inhibition of ovulation, or intrauterine device or bilateral tubal occlusion
5. Contraindications to MRI (pacemaker, aneurysm clip, cochlear implant etc.)
6. Contraindications to gadolinium contrast agent used for MRI
7. Other major neurological or psychiatric conditions affecting the brain and interfering with the study design (e.g. multiple sclerosis)
8. In case of clinical lacunar stroke syndrome other causes of stroke such as:
8.1. ≥50% luminal stenosis (NASCET) in large arteries supplying the area of ischaemia
8.2. Major-risk cardioembolic source of embolism (permanent or paroxysmal atrial fibrillation, sustained atrial flutter, intracardiac thrombus, prosthetic cardiac valve, atrial myxoma or other cardiac tumours, mitral stenosis, recent (<4 weeks) myocardial infarction, left ventricular ejection fraction less than 30%, valvular vegetations, or infective endocarditis)
8.3. Other specific causes of stroke identified (e.g. arteritis, dissection, migraine/vasospasm, drug misuse)
9. Other stroke risk factor requiring immediate intervention that would preclude involvement in the study
10. Renal impairment (eGFR <30 ml/min)

Date of first enrolment
30/04/2018

Date of final enrolment
31/07/2019

Locations

Countries of recruitment

United Kingdom

Scotland

Germany

Netherlands

Study participating centre
Centre for Clinical Brain Sciences
Chancellor's Building
Little France Crescent
Edinburgh
United Kingdom
EH16 4SB

Study participating centre
Ludwig-Maximilians Universitaet
Institute for Stroke and Dementia Research
Feodor-Lynen-Strasse 17
Munich
Germany
81377

Study participating centre
Maastricht University Medical Centre
Dept of Neurology
Maastricht University Medical Center
PO Box 5800
Maastricht
Netherlands
6202 AZ

Sponsor information

Organisation
Academic and Clinical Central Office for Research and Development (ACCORD)

ROR
https://ror.org/01x6s1m65

Funder(s)

Funder type
Research organisation

Funder Name
Horizon 2020

Alternative Name(s)
EU Framework Programme for Research and Innovation, Horizon 2020 - Research and Innovation Framework Programme, European Union Framework Programme for Research and Innovation

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analyzed during the current study are/will be available upon request from Joanna Wardlaw and the University of Edinburgh. The data will not be available until the primary analysis is complete and published.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		26/06/2021	16/08/2022	Yes	No
Abstract results		01/09/2021	05/06/2024	No	No
Basic results		25/06/2021	25/06/2021	No	No
Other publications		09/12/2024	09/06/2025	Yes	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes