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Measuring the blood vessel density in patients with heart failure or reduced cognitive function of vascular origin: CRUCIAL

Submission date
05/02/2020

Recruitment status
No longer recruiting

Registration date
12/02/2020

Overall study status
Completed

Last Edited
07/08/2025

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
The development of cognitive impairment and heart failure is linked to the presence of comorbidities. Comorbidities are other diseases like hypertension, aging, diabetes, and obesity.

Your capillary vessels are your smallest blood vessels. Decreases in the capillary density within a tissue is called microvascular rarefaction and this is a common feature of these comorbidities.

CRUCIAL proposes that microvascular rarefaction is an important marker of vascular cognitive impairment and heart failure. We will develop methods to assess capillary vessel density in a clinical setting to be used for identifying patients with vascular cognitive impairment and heart failure.

Who can participate?
We will be recruiting patients diagnosed with vascular cognitive impairment (Maastricht only), with diastolic heart failure (Pamplona only) and with aortic stenosis (London only). A fourth group will consist of participants who were recruited as children and have been followed several times over the last decades. They are now elderly. There is no new recruitment for this fourth group.

What does the study involve?
We will perform an MRI scan of the heart and brain of all patients using techniques that are sensitive to changes in the capillary vessel density. We will also collect a blood sample to try and identify circulating markers. We will use a camera to take a video under the tongue. This camera can image the capillaries at that location and we will see if the capillary density under the tongue relates to what is happening in the heart and brain. Lastly, we will do a type of eye test called an angio-OCT and investigate if we can detect changes in the heart and/or brain by looking at the blood vessels in the eye. These tests will take place over one day.

What are the possible benefits and risks of participating?
Participants will receive some MRI tests that are above their normal standard of care. Patients

with aortic stenosis and diastolic heart failure will receive a brain MRI scan and cognitive test. Patients with vascular cognitive impairment will receive a cardiac MRI and ECG.

The negatives are that the patients will have to spend longer in the MRI scanner than they would for a disease diagnosis only. For the vascular cognitive impairment patients, they will receive an additional injection of MRI contrast agent than they would normally receive.

Where is the study run from?
St Bartholemew's Hospital (UK), Academisch Ziekenhuis Maastricht (Netherlands) and Clínica Universidad de Navarra (Spain)

When is the study starting and how long is it expected to run for?
January 2020 to May 2024

Who is funding the study?
The European Commission (Belgium)

Who is the main contact?
Prof. Elizabeth Jones
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Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
848109

Study information

Scientific Title
Microvascular rarefaction in vascular cognitive impairment and heart failure: CRUCIAL

Acronym
CRUCIAL

Study objectives
Microvascular rarefaction is a major common pathway in the progression of vascular cognitive impairment (VCI) and cardiac disease including heart failure with preserved ejection fraction (HFpEF). We hypothesize that microvascular rarefaction in co-morbidities can be detected in the heart and brain using advanced MRI techniques, but may also be possible using other novel non-invasive biomarkers.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 17/07/2020, Medisch Ethische Toetsingscommissie (METC) Maastricht UMC (Maastricht UMC+ T.a.v. METC azM/UM, P. Debyelaan 25, Postbus 5800, 6202 AZ Maastricht, The Netherlands), ref: NL72696.068.20 / METC 20-018
2. Approved 24/02/2020, Comité de Ética de la Investigación de la Universidad de Navarra (no address provided; +34 82 2714; ceic@unav.es), ref: 2019.210
3. Approval pending, UK Health Research Authority (Level 3, Block B, Whitefriars, Bristol Research Ethics Committee Centre, BS1 2NT, UK; +44 (0)2071048046; centralbristol.rec@hra.nhs.uk), ref: none provided

Primary study design
Observational

Study design
Multi-centre observational cohort study

Study type(s)
Diagnostic

Health condition(s) or problem(s) studied
Microvascular dysfunction in the heart and brain, cerebral microvascular dysfunction, cardiac microvascular dysfunction, heart failure and vascular cognitive impairment

Interventions
Four cohorts of participants will be recruited from the three trial participating centres. Participant cohorts have either clinical HFpEF or asymptomatic cardiac structural and/or functional alterations, vascular cognitive impairment or are part of a control population of elderly patients.

1. 75 participants will be recruited to the MAASTRICHT cohort which will be composed of patients with presumed VCI due to cerebral small vessel disease (cSVD)
2. 60 to 70 participants will be recruited to the PAMPLONA-HFpEF cohort which will include HFpEF patients of hypertensive or valvular origin at different stages, patients with cardiac structural and/or functional alterations (stage B), and patients with clinical signs and symptoms of HF (stage C)
3. 60 participants will be recruited to the RELIEF-AS II cohort which will be composed of elderly patients with severe aortic stenosis who will undergo surgery for aortic valve replacement

4. The UCL BIRTH cohort will be participants from a longitudinal study of healthy aging and the influences of comorbidities. In the latest sweep participants will undergo cardiac and brain MRI, as well as a non-invasive assessment of the microvasculature by retinal OCT and GlycoCheck

Patients from all cohorts already routinely undergo echocardiography as part of the diagnosis. In order to ensure comparable data, we have harmonized our procedures.

All cohorts will undergo ECG measurements. This is a standard-of-care procedure for HFpEF patients but not for VCI. Also, all participants will have 30 mL blood samples taken and a uniform neuropsychological assessment designed to cover global cognitive function. A concise battery (30 min) of cognitive tests will be used for the HFpEF cohort whereas the VCI cohort will undergo a more extensive set of tests as part of diagnosis (before joining the study).

The study aims to use MRI to detect microvascular dysfunction in the heart and brain. The study will also explore other non-invasive methods (Glycocheck machine, circulating biomarkers, OCT-angiography). All participants will undergo a Glycocheck measurement, which involves placing a camera under the tongue and acquiring images for 5 mins, and angioOCT, which involves a retinal scan that lasts around 1 min. All participants will also undergo cardiac and brain MRI.

The MAASTRICHT cohort will be injected with a contrast agent in the morning and undergo a 90 min scan. In the afternoon, they will receive a second gadolinium contrast agent injection and undergo a 35 min cardiac scan. The total dose of gadolinium will be kept below 0.3 mmol/kg.

The PAMPLONA-HFpEF cohort and RELIEF-AS II cohort will undergo a 30 min brain MRI scan in the morning, without contrast. In the afternoon, they will undergo gadolinium-enhanced MRI cardiac imaging that lasts 45-50 mins and includes an adenosine stress perfusion test unless counter-indicated because the participant is at higher risk of complication (atrioventricular block, severe asthma/COPD or significantly impaired systolic function LVEF <40%).

The UCL BIRTH cohort will undergo gadolinium-enhanced MRI cardiac imaging that lasts 45-50 mins and includes an adenosine stress perfusion test unless counter-indicated because the patient is at higher risk of complication (atrioventricular block, severe asthma/COPD or significantly impaired systolic function LVEF <40%). On a second day, they will return and receive the brain MRI scan, including a gadolinium contrast agent. This scan will last 60 mins.

The MAASTRICHT cohort, PAMPLONA-HFpEF cohort, and RELIEFAS II cohort will have all tests done in one day. The UCL BIRTH cohort will have cardiac and brain MRIs on separate days and thus testing will be done over 2 days.

Intervention Type
Mixed

Primary outcome(s)
First clinical confirmation of microvascular function measurements using state-of-the-art MRI measurements at baseline in a large patient cohort

Key secondary outcome(s)
1. Identification of microvascular rarefaction as a predictive disease measurement in diastolic heart failure (HFpEF) and/or vascular cognitive impairment from MRI measurements at baseline
2. Development of alternate non-invasive measurements of microvascular rarefaction or dysfunction using Glycocheck machine, circulating biomarkers and OCT-angiography measurements at baseline

Completion date
31/12/2024

Eligibility

Key inclusion criteria
The MAASTRICHT cohort
1. Cognitive complaints
2. Signs of cerebral small vessel disease on brain MRI defined as at least Fazekas grade > 1
3. < 26 on the Montreal Cognitive Assessment
4. Aged 60 to 80 years
The PAMPLONA-HFpEF cohort
1. Clinical symptoms of HFpEF of hypertensive or valvular origin (classified according to the current guidelines of the European Society of Cardiology, or ESC)
2. Structural and/or functional alterations such as left ventricular hypertrophy, left atrial dilation, and diastolic dysfunction but clinical symptoms not yet developed
3. Aged 45-85 years
The RELIEF-AS II cohort
1. Severe aortic stenosis
2. Suitable for aortic valve replacement surgery
3. 50 to 85 years
The UCL BIRTH cohort
1. Aged 60-80 years

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Senior

Lower age limit
60 Years

Upper age limit
80 Years

Sex
All

Total final enrolment
471

Key exclusion criteria
1. Pregnancy and/or lactation
2. eGFR <30ml/min
3. Magnetic resonance incompatible devices

4. Inability to complete the study
The MAASTRICHT cohort
1. Non-vascular cause for the cognitive deficit. Clinical evidence of neurodegenerative disease(s) such as Alzheimer’s Disease, frontotemporal dementia, Lewy Body disease, or hypokinetic rigid syndrome
2. Lack of independence in daily living and/or a clinical dementia rating ≤1.0
3. Lack of capacity to consent to participate
The PAMPLONA-HFpEF cohort
1. Severe bone or metabolic disease
2. Active neoplasia
3. Flow-limiting coronary artery disease >50% stenosis or prior myocardial infarction
4. LVEF <50%.
The RELIEF-AS II cohort
1. Flow-limiting coronary artery disease >50% stenosis

Date of first enrolment
01/09/2020

Date of final enrolment
31/08/2024

Locations

Countries of recruitment
United Kingdom

England

Netherlands

Spain

Study participating centre
St Bartholomew's Hospital
West Smithfield
London
United Kingdom
EC1A 7BE

Study participating centre
Academisch Ziekenhuis Maastricht
P. Debyelaan 25
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Netherlands
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Study participating centre
Clínica Universidad de Navarra
Av. de Pío XII 36
Pamplona, Navarra
Spain
31008

Sponsor information

Organisation
European Commission

ROR
https://ror.org/00k4n6c32

Funder(s)

Funder type
Government

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 and/or analyzed during the current study during this study will be included in the subsequent results publication

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		31/07/2025	07/08/2025	Yes	No
Protocol article		16/01/2023	03/05/2023	Yes	No
Other unpublished results	Case–control study methods investigation of microvascular architecture	06/11/2024	28/02/2025	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes