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Multi-centre MRI study of the heart microstructure in healthy volunteers

Submission date
30/04/2025

Recruitment status
Not yet recruiting

Registration date
12/05/2025

Overall study status
Ongoing

Last Edited
20/06/2025

Condition category
Circulatory System

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Cardiac diffusion tensor imaging (cDTI) is an emerging magnetic resonance imaging (MRI) based technique for examining the microstructure of the heart. The cardiac function and microstructure are highly interconnected. The adult heart comprises more than a billion heart muscle cells that are intricately connected and that contract in a highly coordinated manner to support the beating of the heart. Changes to the heart microstructure are an important feature in conditions such as heart attack or myocardial infarction (MI) and hypertrophic cardiomyopathy (HCM), where the heart muscle wall thickens. For example, an increase in collagen and scar following changes in microstructure following MI, and cell disarray in HCM, which can be assessed with cDTI. The microscopic displacement of water molecules due to diffusion is heavily influenced by the presence of cells and by the properties of these cells such as size, shape, orientation, integrity and so forth. Thus, by encoding the water diffusion information in the MRI image, one can evaluate the cardiac microstructure. In cDTI, several diffusion directions are encoded and then diffusion tensors (a mathematical model that can be pictured in 3D as an American football in shape) are fitted. From the diffusion tensor, several quantitative values can be derived such as the mean diffusivity (MD) that describes the average apparent diffusion, the fractional anisotropy (FA) that describes how pointed the tensor is, and the helix angle (HA) and sheetlet angle (E2A) that reflect the orientations of the heart muscle cells and their arrangement in sheetlets.
The links between the diffusion tensor and cardiac microstructure have been verified in numerous preclinical ex vivo and in vivo studies. Early clinical studies have reported diffusion parameters in the pathologic heart. In particular, higher myocardial MD and lower FA have been reported in pathologies such as MI, HCM and aortic stenosis (AS). Similarly, differences in HA and E2A angles have been reported in conditions such as MI, HCM, AS and dilated cardiomyopathy (DCM). This is thought to be related to the underlying changes in the cardiac microstructure.
The field of cardiac diffusion MRI remains technologically challenging due to a number of factors such as motion from the heart beating and breathing, distorted images and long scan times. Nonetheless, the field has been rapidly expanding over the past years, with publications in cDTI more than doubling over the decade up to 2020, and whole-heart cDTI within clinically feasible scan times looks increasingly likely to be achievable within the foreseeable future.
The study aims to:
1. Evaluate variation in cDTI data due to differences in (i) site/operator/scanner, (ii) subject, (iii)

acquisition and (iv) post-processing methods.
2. Identify the greatest sources of variation and inform strategies for optimisation, standardisation and harmonisation of cDTI.
3. Inform power calculations and data interpretation in future larger studies, in particular, where different sites/methods are used.

Who can participate?
Healthy volunteers aged 18 to 65 years old with a body mass index (BMI) of 18.5 to 29.9 kg/m2. For the travelling volunteer study: Ability to travel independently between sites and to have all scans done within 2 months from first scan; possession of valid documentation (e.g. passport and visa) to travel between sites with validity extending to at least 8 months following first MRI scan, and with a passport no older than 10 years at the time of the last scan.

What does the study involve?
Non-travelling healthy volunteers will be identified, approached and recruited by non-travelling volunteer sites in accordance with site-specific ethics for sites outside the UK. Non-travelling volunteers will only be consented under the respective site-specific ethics. These are non-NHS sites and non-HRA-relevant.
Travelling volunteers will be recruited and consented by the study team at Royal Brompton Hospital to travel to multiple sites for a single MRI scan at each site. Potential volunteers who express interest in participating will be sent the participant information sheet (PIS) and research volunteer checklist. Before consent/scan, volunteers who wish to participate in the study will be asked to complete and return the research volunteer checklist for the study team to assess eligibility. Participants who meet eligibility requirements and are interested in participation will be invited to provide written consent. Consent will also be sought for the sharing and storing of personal information for study oversight, scan scheduling, safety monitoring, booking travel and reimbursement.
Volunteers will be invited to undergo a single MRI examination at each site. Before each scan, the participant's height and weight will be measured. A site-specific MRI screening questionnaire shall be completed to help ensure safety in the MRI scanner. The MRI scan will typically last between 60 to 90 minutes. Surface electrodes (stickers) will be placed on the chest to monitor heart beat during the scan.

What are the possible benefits and risks of participating?
This study is done solely for research purposes and participants will not benefit from taking part. Their participation may, however, benefit future care. The scans will be for research purposes only and cannot be used for clinical diagnosis.
MRI is safe and no ionising radiation (energy that can potentially cause damage to cells) is used for this scan. There are no known risks from the technique. Some people may experience claustrophobia (fear of confined spaces). The MRI staff will do all that they can to make participants feel comfortable during the scan. Participants may withdraw from the study at any time. For travelling volunteers, there is a small risk associated with travel. Participants are asked to highlight any concerns they may have about such travel. Travel and accommodation will be arranged through reputable vendors, and participants will be kept updated on any travel advisories at the time.

Where is the study run from?
This is an international multi-centre initiative, initiated by the Society of Cardiovascular Magnetic Resonance Cardiac Diffusion Special Interest Group. The Project Management Committee responsible for taking decisions on the study has members based in Switzerland, the UK and the USA.

When is the study starting and how long is it expected to run for?
July 2024 to August 2029

Who is funding the study?
Investigator initiated and funded

Who is the main contact?
Dr Irvin Teh, i.teh@leeds.ac.uk

Study website
https://scmr.site-ym.com/forums/posts.aspx?group=196088&topic=1809160

Contact information

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Scientific, Principal Investigator

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
343837

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
Nil known

Study information

Scientific Title
Multi-centre investigation of cardiac diffusion tensor imaging (DTI) in healthy volunteers by SCMR Cardiac Diffusion Special Interest Group NETwork

Acronym
SIGNET

Study objectives
There exists a wide range of reported diffusion tensor imaging (DTI) metrics in the literature, including reports that are potentially artifactual, which have been previously highlighted. This will be influenced by the subject cohort, e.g. health vs disease. Other potential sources of variation include differences in sites/operators/scanners, acquisition and post-processing methods. This variation needs to be better understood to support clinical validation of the technique.

Early work has evaluated reproducibility in a ten-site study in isotropic phantoms and in a two-site study in healthy volunteers. In this study, we propose a broad multi-centre collaborative effort to evaluate inter-site variation due to differences in (i) site/operator/scanner, (ii) acquisition and (iii) post-processing methods. The results will guide the interpretation of the cardiac diffusion MRI literature, and help to refine strategies for standardisation and harmonisation of protocols. We propose in the first instance to study healthy volunteers to establish a baseline of variation due to technical (non-pathology related) factors.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 31/07/2024, University of Leeds School of Medicine Research Ethics Committee (SoMREC) (Worsley Building, University of Leeds, Leeds, LS2 9JT, United Kingdom; -; FMHUniEthics@leeds.ac.uk), ref: MREC 23-027

Study design
Multi-centre prospective observational study

Primary study design
Observational

Secondary study design
Cross sectional study

Study setting(s)
Hospital, University/medical school/dental school

Study type(s)
Diagnostic

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet.

Health condition(s) or problem(s) studied
Evaluation of cardiac microstructure with cardiac DTI

Interventions
Single MRI scan for non-travelling volunteers
Single MRI scan for travelling volunteers at each site, over multiple sites

Non-travelling healthy volunteers will be identified, approached and recruited by non-travelling volunteer sites in accordance with site-specific ethics for sites outside the UK. Non-travelling volunteers will only be consented under the respective site-specific ethics. These are non-NHS sites and non-HRA-relevant.

Travelling volunteers will be recruited and consented by the study team at Royal Brompton Hospital to travel to multiple sites for a single MRI scan at each site. Potential volunteers who express interest in participating will be sent the participant information sheet (PIS) and research volunteer checklist. Prior to consent/scan, volunteers who wish to participate in the study will be asked to complete and return the research volunteer checklist for the study team to assess eligibility. Participants who meet eligibility requirements and are interested in participation will be invited to provide written consent. Consent will also be sought for the sharing and storing of personal information for study oversight, scan scheduling, safety monitoring, booking travel and reimbursement.

Volunteers will be invited to undergo a single MRI examination at each site. Prior to each scan, participants' height and weight will be measured. A site-specific MRI screening questionnaire shall be completed to help ensure safety in the MRI scanner. The MRI scan will typically last between 60 to 90 minutes. Surface electrodes (stickers) will be placed on the chest to monitor heartbeat during the scan.

Intervention Type
Other

Primary outcome measure
Cardiac DTI data including mean diffusivity, fractional anisotropy, helix angle and E2 angle. For non-travelling volunteers, these will be acquired at baseline. For travelling volunteers, these will be acquired at all travelling volunteer sites within 2 months of baseline.

Secondary outcome measures
Signal-to-noise ratio and potential non-compliance of scans with the protocol collected during each scan

Overall study start date

31/07/2024

Completion date
31/08/2029

Eligibility

Key inclusion criteria
1. Healthy volunteer
2. Male or female; sites shall aim to recruit equal numbers, i.e. male (n = 6) / female (n = 6)
3. Age 18 to 65 years old
4. Body mass index (BMI) 18.5 to 29.9 kg/m2
5. For travelling volunteer study: Ability to travel independently between sites, and to have all scans done within 2 months from first scan; possession of valid documentation (e.g. passport and visa) to travel between sites with validity extending to at least 8 months following first MRI scan, and with passport no older than 10 years at time of last scan.

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
18 Years

Upper age limit
65 Years

Sex
Both

Target number of participants
Non-travelling volunteer sites: 12 per site, with provision for up to additional 4 subjects per site as contingency. Travelling volunteer sites: 12 in total, with provision for up to additional 4 subjects in total as contingency. Total final enrolment shall be 12 × (N+1) where N = number of non-travelling volunteer sites, with provision for up to 4 × (N+1) as contingency. Example: Assuming N = 20 non-travelling volunteer sites and 0 volunteers needed for contingency, then total final enrolment will be (20+1)*12 = 252.

Key exclusion criteria
1. Safety or clinical concerns precluding participation
2. Any history of health conditions that may affect the heart (e.g. hypertension, diabetes, arrhythmias, angina, myocardial, valve and vessel disease)
3. Pregnancy or breastfeeding, including suspected pregnancy
4. Claustrophobia that limits/prevents participants from remaining in the MRI scanner
5. Inability to lie flat on the scanner table
6. Physical frailty
7. Contraindications to MRI (some pacemakers, intraorbital debris, intraauricular implants, intracranial clips, etc)

8. Those who could be considered to have a particularly dependent relationship with an investigator, e.g. members of staff or students
9. Involvement with the research apart from volunteering
10. Any relevant health conditions precluding safe travel between sites within 2 2-month time frame (For travelling volunteer study)

Date of first enrolment
01/09/2025

Date of final enrolment
31/05/2026

Locations

Countries of recruitment
Belgium

Denmark

England

France

Japan

Poland

Switzerland

United Kingdom

United States of America

Wales

Study participating centre
Aarhus University Hospital
Aarhus
Denmark
8200

Study participating centre
Barts Health
London
United Kingdom
E1 1BB

Study participating centre
Beth Israel Deaconess Medical Center
Boston
United States of America
MA 02215

Study participating centre
Boston Children's Hospital
Boston
United States of America
MA 02115

Study participating centre
Brussels University Hospital
Brussels
Belgium
1090 Jette

Study participating centre
Cardiff University Brain Research Imaging Centre
Cardiff
United Kingdom
CF24 4HQ

Study participating centre
Cleveland Clinic
Cleveland
United States of America
OH 44195

Study participating centre
Copenhagen University
Copenhagen
Denmark
1172 København

Study participating centre

CREATIS-Lyon
Lyon
France
69100 Villeurbanne

Study participating centre
Emory University
Atlanta
United States of America
GA 30322

Study participating centre
ETH Zurich
Zurich
Switzerland
8092 Zürich

Study participating centre
Geneva University Hospital
Geneva
Switzerland
1205 Genève

Study participating centre
Hokkaido University Hospital
Hokkaido
Japan
060-8648

Study participating centre
Live Healthy Imaging
Houston
United States of America
TX 77401

Study participating centre

Medical University of Gdansk
Gdansk
Poland
80-210

Study participating centre
Massachusetts General Hospital
Boston
United States of America
MA 02114

Study participating centre
National Heart, Lung, and Blood Institute - Medstar Washington Hospital
Bethesda
United States of America
MD 20892

Study participating centre
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Study participating centre

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Sponsor type
University/education

Website
https://www.leeds.ac.uk/

ROR
https://ror.org/024mrxd33

Funder(s)

Funder type
Other

Funder Name
Investigator initiated and funded

Results and Publications

Publication and dissemination plan
Planned publication in peer-reviewed journals and conferences.

Intention to publish date
31/12/2026

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a publicly available repository.

Anonymised research data will be made available by UoL to the research community for the current study and future research as governed by the Collaboration Agreement.

Access to publicly available data by third parties will be governed by an agreement with an End User / Data Sharing Agreement.

IPD sharing plan summary
Stored in publicly available repository