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Characterising disease mechanisms in coronary microvascular disease

Submission date 22/01/2021	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [X] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 28/01/2021	**Overall study status** Completed	
Last Edited 19/02/2025	**Condition category** Circulatory System	

Plain English summary of protocol

Current plain English summary as of 22/05/2023:
Background and study aims
Angina is the term used to describe chest pain that is caused by an imbalance between the supply and demand of blood to the heart muscle. The coronary circulation supplies the heart muscle with its blood supply and is made up of large arteries (visible on a special x-ray test called an angiogram) and small arteries (the microvasculature, not visible on an angiogram). Up to 30% of patients with angina have no detectable narrowings in their large arteries but have disease of the small arteries; this is known as coronary microvascular disease (CMD). CMD is associated with poor quality of life, adverse clinical outcomes and an increased cost to the healthcare and social system. It is now possible to assess the small arteries using special techniques during an angiogram. Using these techniques, our group has shown that there may be two distinct subtypes of CMD. Patients with either subtype suffer from an inability to dilate their small arteries in response to stress; this leads to a supply:demand mismatch, leading to angina. However, they have distinct differences in their disease mechanisms and may respond in a disparate manner to different anti-anginal therapy. In this study, we will test the utility of disease characterisation in predicting response to common antianginal therapy in patients with angina and small vessel disease; therefore, assessing the clinical translation of our catheter lab based measurements.

Who can participate?
All adult patients attending for diagnostic coronary angiography for stable angina at St. Thomas' Hospital who are found to have unobstructed coronary arteries.

What does the study involve?
The protocol will consist of four visits. On the day of the first visit, patients will be requested to undergo a treadmill exercise tolerance test (ETT). We will insert a venous cannula into one of the veins in their arms, through which we will withdraw a small sample of blood to be analysed before and 2 hours after the ETT. The blood tests will be analysed to look for markers of reduced blood supply to the heart before and after exercise. During their visit, patients will be requested to fill out a questionnaire pertaining to their angina symptom burden and quality of life. Their pedometer data will be noted. Patients will then be given a commonly used anti-anginal agent (either amlodipine or ranolazine) and requested to take the medication for four

weeks. After 4 weeks, patients will be requested to return for the second visit. They will undergo a repeat ETT, pre-exertion and post-exertion (2 hours post-exertion) blood tests and are requested to fill out a questionnaire as before. Their pedometer data will be noted. They will be given the other commonly used anti-anginal agent (if they were given amlodipine for the first 4 weeks, then they will be given ranolazine, and vice versa) and requested to take the medication for four weeks (after a 1-week washout period). After 4 weeks of taking the medication, they will be requested to return for the third visit. Patients will undergo the final ETT, pre-exertion and post-exertion (2 hours post-exertion) blood tests and requested to fill out a questionnaire as before. Their pedometer data will be noted. Finally, patients will be requested to stop the study medication and return for a final visit 4 weeks later. This will mark the end of the study.

What are the possible benefits and risks of participating?
Benefits: The coronary angiogram with small blood vessel assessment will help provide clarity into patients' diagnosis, which may allow for a more targeted therapeutic approach. The treadmill test and pedometer analysis provide useful information about patients' exercise capacity, and the blood tests may give information on whether there is evidence of reduced blood supply to the heart during exertion.
Risks: Radiation exposure: The placing of the special angioplasty wire for research measurements will lengthen the screening time by up to 5 minutes with resultant small additional ionizing radiation exposure to form images of your body.

Where is the study run from?
St. Thomas’ Hospital (UK)

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

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
Dr Aish Sinha, aish.1.sinha@kcl.ac.uk

Previous plain English summary:
Background and study aims
Angina is the term used to describe chest pain that is caused by an imbalance between the supply and demand of blood to the heart muscle. The coronary circulation supplies the heart muscle with its blood supply and is made up of large arteries (visible on a special x-ray test called an angiogram) and small arteries (the microvasculature, not visible on an angiogram). Up to 30% of patients with angina have no detectable narrowings in their large arteries but have disease of the small arteries; this is known as coronary microvascular disease (CMD). CMD is associated with poor quality of life, adverse clinical outcomes and an increased cost to the healthcare and social system. It is now possible to assess the small arteries using special techniques during an angiogram. Using these techniques, our group has shown that there may be two distinct subtypes of CMD. Patients with either subtype suffer from an inability to dilate their small arteries in response to stress; this leads to a supply:demand mismatch, leading to angina. However, they have distinct differences in their disease mechanisms.

In this study, we will investigate the disease mechanisms underlying the different CMD subtypes using coronary angiogram with special small vessel assessment. We will test our hypothesis of whether one of the CMD subtypes have an inability to augment their blood flow due to dysfunction of enzymes that normally lead to dilation of small arteries. We will also test the

utility of our disease characterisation in predicting response to common antianginal therapy in patients with angina and small vessel disease; therefore, assessing the clinical translation of our catheter lab based measurements.

This study will provide a better understanding of the mechanisms that lead to CMD. This knowledge can be used to develop novel therapeutic targets in the future.

Who can participate?
All adult patients attending for diagnostic coronary angiography for stable angina at St. Thomas' Hospital who are found to have unobstructed coronary arteries.

What does the study involve?
Catheter laboratory protocol: At present, as part of the normal care, patients will be scheduled to have a coronary angiogram with the possibility of pressure recordings made within narrowed arteries (using an angioplasty pressure wire) to help decide the best treatment option (options include stents, medicines, operation). If the large arteries look normal, then they will undergo measurements of the small arteries as part of standard of clinical care. Participants of this study will undergo further assessment of the small arteries in response to the infusion of a safe substance called S-methyl-L-thiocitrulline (SMTC).
Exercise protocol: The exercise protocol will consist of three visits. Four weeks prior to the first visit, patients will be given a pedometer device and requested to wear it so that their daily level of activity can be analysed. On the day of the first visit, patients will be requested to undergo a treadmill exercise tolerance test (ETT). We will insert a venous cannula in to one of the veins in their arms, through which we will withdraw a small sample of blood to be analysed before and two hours after the ETT. The blood tests will be analysed to look for markers of reduced blood supply to the heart before and after exercise. During their visit, patients will be requested to fill out a questionnaire pertaining to their angina symptom burden and quality of life. Their pedometer data will be downloaded and their device reset to factory settings and returned back to them. Patients will then be given a commonly used anti-anginal agent (either Amlodipine or Ranolazine) and requested to take the medication for four weeks. After four weeks, patients will be requested to return for the second visit. They will undergo a repeat ETT, pre-exertion and post-exertion (2 hours post-exertion) blood tests and requested to fill out a questionnaire as before. Their pedometer data will be downloaded and their device reset to factory settings and returned back to them. They will be given the other commonly used anti-anginal agent (if they were given Amlodipine for the first four weeks, then they will be given Ranolazine, and vice versa) and requested to take the medication for four weeks. After four weeks of taking the medication, they will be requested to return for the third visit. Patients will undergo the final ETT, pre-exertion and post-exertion (2 hours post-exertion) blood tests and requested to fill out a questionnaire as before. Their pedometer data will be downloaded. This will mark the end of the study.

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Who is the main contact?
Dr Aish Sinha, aish.1.sinha@kcl.ac.uk

Contact information

Type(s)
Scientific

Contact name
Dr Aish Sinha

Contact details
The Rayne Institute
St. Thomas' Hospital
Westminster Bridge Road
London
United Kingdom
SE1 7EH
+44 (0)7828295640
Aish.1.sinha@kcl.ac.uk

Type(s)
Scientific

Contact name
Prof Divaka Perera

Contact details
St. Thomas' Hospital
Westminster Bridge Road
London
United Kingdom
SE1 7EH
+44 (0)2071881048
divaka.perera@kcl.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
288132

Protocol serial number
CPMS 47795, IRAS 288132

Study information

Scientific Title
Characterising disease mechanisms in patients with coronary microvascular disease

Acronym
ChaMP-CMD

Study objectives
Current study hypothesis as of 22/05/2023:
1a. Patients with angina with non-obstructive coronary arteries (ANOCA) and coronary microvascular disease (CMD, defined by a CFR <2.5) will have a greater improvement in their exercise capacity in response to Amlodipine, compared to patients with ANOCA and normal microvascular function (controls, defined by a CFR ≥2.5).
1b. Patients with ANOCA and coronary microvascular disease (CMD, defined by a CFR<2.5) will have a greater improvement in their exercise capacity in response to ranolazine, compared to patients with ANOCA and normal microvascular function (controls, defined by a CFR ≥2.5).
2a. Endotyping CMD will allow the selection of more specific therapies than identifying CMD alone. It is hypothesised that patients with functional coronary microvascular disease (fCMD, defined by a CFR <2.5 and hMR <2.5 mmHg/cm/s) will have a greater improvement in their exercise capacity in response to ranolazine compared to amlodipine.
2b. Patients with structural coronary microvascular disease (sCMD, defined by a CFR <2.5 and hMR ≥2.5 mmHg/cm/s) will have a greater improvement in their exercise capacity in response to amlodipine compared to ranolazine.

Previous study hypothesis:
1. Resting coronary blood flow (CBF) in patients with functional coronary microvascular disease (CMD) is elevated due to an upregulation of neuronal nitric oxide synthase (NOS). Intracoronary S-methyl-l-thiocitrulline (SMTC), an nNOS inhibitor, will attenuate the resting CBF in these patients by 16% or more compared to patients with structural CMD
2. Our novel disease characterisation will predict clinical response to commonly used antianginal therapy. Ranolazine and Amlodipine will improve exercise duration by 30 seconds or more, compared to baseline, in patients with functional and structural CMD, respectively, as compared to exercise duration in the other subtype.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 17/12/2020, London - Bromley Research Ethics Committee (Health Research Authority, Skipton House, 80 London Road, London, SE1 6LH, UK; +44 (0)207 104 8063; bromley.rec@hra.nhs.uk), ref: 20/LO/1294

Study design

Prospective randomised phenotype-blinded crossover trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Coronary microvascular disease

Interventions
Current interventions as of 22/05/2023:
Patients will be recruited from the catheter laboratory protocol or if they have already had invasive coronary physiology assessment previously. On their first visit of the exercise protocol, patients will undergo treadmill exercise tolerance test (ETT), venepuncture for blood sampling before and after the ETT, complete a validated angina questionnaire (Seattle Angina Questionnaire [SAQ]) and have their pedometer data analysed. Patients will then be requested to take 4 weeks of either amlodipine or ranolazine. After 4 weeks, patients will return for the second exercise protocol visit and undergo the same investigations as above (ETT, pre-exertion and post-exertion blood sampling, angina questionnaire and pedometer data analysis). After this, patients will be requested to cross over to the other drug (either amlodipine or ranolazine) for 4 weeks (after 1 week washout period). After 4 weeks, patients will return for the third exercise protocol visit to have the same assessments carried out as before. Patients will then be requested to stop their study medications and return for the final visit 4 weeks later. This will mark the end of the exercise protocol and the study.

Previous interventions:
Our study has two protocols. The catheter lab protocol aims to characterise disease mechanisms in the subtypes of CMD and the exercise protocol aims to test the utility of our novel disease characterisation in predicting response to commonly prescribed anti-anginal therapy.

Catheter Lab Protocol (as part of routine care with additional research measurements) (visit #1):
The catheter lab protocol will involve consenting patients already listed for a coronary angiogram (invasive procedure commonly used to assess the arteries supplying the heart using contrast dye and special xrays). Patients who are found to have visually normal or borderline coronary artery disease will undergo further testing in the form of pressure wire testing. A special wire, termed the Combowire, will be placed in the left anterior descending (LAD) vessel to allow simultaneous pressure and flow measurements, without further manipulation during the protocol. Measurements will be taken following infusions of each of the following substances: adenosine, acetylcholine and S-methyl-Lthiocitrulline
(SMTC). The measures of pressure and flow will allow calculation of fractional flow reserve (FFR), coronary flow reserve (CFR), hyperaemic microvascular resistance (hMR) and acetylcholine flow reserve (AChFR). FFR measures the significance of large vessel narrowing, with a value of <0.80 typically suggesting functionally significant disease in the large arteries; this group will not be included in the research protocol and will be treated as per the current clinical guidelines. In patients with an FFR≥0.80, CFR≤2.5 is a means of identifying patients with small vessel disease. Patients with CFR≤2.5 will be subdivided into two subtypes according to their hMR. The differential blood flow response to SMTC between the two subtypes will be assessed. These measurements will all take place in one setting. It is important to mention that measurements of FFR, CFR, hMR and AChFR form part of standard of care for patients with angina and

unobstructed large arteries. The research component here is the infusion of SMTC and the measurements made in response to it.

Exercise protocol (visit #2-4):
For the exercise protocol, patients will be recruited from the catheter laboratory protocol or if they have already been characterised with CMD previously. Patients will be issued with a pedometer four weeks prior to their first visit of the exercise protocol and requested to wear it. On their first visit of the exercise protocol, patients will undergo treadmill exercise tolerance test (ETT), venepuncture for blood sampling before and after the ETT, complete a validated angina questionnaire (Seattle Angina Questionnaire, SAQ) and have their pedometer data analysed. Patients will then be requested to take 4 weeks of either Amlodipine or Ranolazine, which are both commonly used empirical anti-anginal
drugs in patients with CMD. After four weeks, patients will return for the second exercise protocol visit and undergo the same investigations as above (ETT, pre-exertion and post-exertion blood sampling, angina questionnaire and pedometer data analysis). After this, patients will be requested to crossover to the other drug (either Amlodipine or Ranolazine) for four weeks. After four weeks, patients will return for the third exercise protocol visit to have the same assessments carried out as before. This will mark the end of the exercise protocol and the study.

Patients who have already been characterised with CMD in the catheter laboratory previously can participate in the exercise protocol without having to repeat a coronary angiogram. These patients will receive a separate patient information sheet and consent form. Both of these are attached with the application.

We may utilise data from clinically indicated cardiac MRI scans for research purposes.

Intervention Type
Other

Primary outcome(s)
Current primary outcome measure as of 22/05/2023:
Change in exercise time (in seconds) compared with baseline, measured using an exercise treadmill test at visit 2, visit 3 and visit 4

Previous primary outcome measure:
1. Coronary blood flow will be measured during the coronary angiogram on visit 1
2. Exercise ability will be measured as exercise duration on a treadmill on visits 3 and 4

Key secondary outcome(s))
Current secondary outcome measures as of 22/05/2023:
Change in angina-specific quality of life compared with baseline, measured using the Seattle Angina Questionnaire (SAQ) Summary Score at visit 2, visit 3 and visit 4

Previous secondary outcome measures:
Measured at visits 3 and 4:
1. Health-related quality of life measured using The Seattle Angina Questionnaire
2. Step count measured on a pedometer
3. Cardiac biomarkers (high sensitivity troponin T) measured using blood test

Completion date

03/01/2024

Eligibility

Key inclusion criteria
1. All adult patients attending for diagnostic coronary angiography for stable angina at St. Thomas' Hospital who are found to have unobstructed coronary arteries (epicardial coronary artery stenosis < 30% and/or pressure wire negative stenosis).
2. Tertiary referrals for invasive microvascular assessment of patients with angina and established unobstructed coronary arteries.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Total final enrolment
87

Key exclusion criteria
Current exclusion criteria as of 22/05/2023:
1. Patients who are unable or unwilling to consent
2. Contraindications to adenosine
3. Contraindications to amlodipine and/or ranolazine
4. Patients who are already taking the study medications for clinical reasons and are unable to stop them
5. Presence of more than moderate valve disease
6. Previous percutaneous coronary intervention or bypass surgery
7. Known structural heart disease (e.g. cardiomyopathy or congenital heart disease)
8. Pregnant or breastfeeding females
9. Patients who are unable to exercise on a treadmill or those who can exercise for >540 seconds in the absence of any revealed cardiac symptoms on baseline exercise test

Previous exclusion criteria:
1. Patients who are unable or unwilling to consent
2. Contraindications to adenosine or acetylcholine (for the catheter laboratory protocol), or amlodipine or ranolazine (for the exercise protocol)
3. Presence of more than moderate valve disease
4. Previous stenting or bypass surgery
5. Heart failure with reduced ejection fraction (LVEF< 50%), cardiomyopathy or congenital heart disease
6. Pregnant or breastfeeding females

7. Patients who are unable to exercise on a treadmill or those who have a good exercise capacity at baseline (>540seconds in men and >480seconds in women) will be excluded from the exercise protocol

Date of first enrolment
16/03/2021

Date of final enrolment
16/09/2023

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
St Thomas' Hospital
Guy's and St Thomas' NHS Foundation Trust
Westminster Bridge Road
London
United Kingdom
SE1 7EH

Sponsor information

Organisation
King's College London

ROR
https://ror.org/0220mzb33

Organisation
Guy's and St Thomas' NHS Foundation Trust

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council; Grant Codes: MR/T029390/1

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, Medical Research Committee and Advisory Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
All data generated or analysed during this study will be included in the subsequent results publication.

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		02/01/2024	19/02/2025	Yes	No
HRA research summary			28/06/2023	No	No
Protocol file	version 6.0	29/09/2022	22/05/2023	No	No
Statistical Analysis Plan	version 1.0	26/03/2023	22/05/2023	No	No