ISRCTN17374454 https://doi.org/10.1186/ISRCTN17374454

Exploring the link between coronary microvascular dysfunction and heart failure with preserved ejection fraction

Submission date 04/02/2025	**Recruitment status** Recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 06/03/2025	**Overall study status** Ongoing	
Last Edited 09/04/2025	**Condition category** Circulatory System	

Plain English summary of protocol

Background and study aims:
Heart failure is a burdensome condition characterised by the heart's inability to maintain adequate blood flow throughout the body and commonly manifests as profound exertional breathlessness. It is categorised by ejection fraction, a measure of how much blood is 'ejected' by the left ventricle when it contracts and is broadly split into heart failure with reduced ejection fraction (HFrEF) or preserved ejection fraction (HFpEF). There have been numerous innovations in the treatment of the latter that has markedly improved the quality of life and prognosis for sufferers; conversely, few treatments are effective in HFpEF. Whilst speculative, this may be due to contemporary trials employing a 'one-size-fits-all' approach to a complex and likely multi-faceted condition. One such facet may be coronary microvascular dysfunction (CMD), an under-diagnosed condition characterised by the inability of the small arteries of the heart to augment blood flow to demand. Prior research has identified that CMD is prevalent among HFpEF sufferers. However, it is unclear whether CMD is a causative factor or simply a by-product of the 'stiff' heart muscle observed in HFpEF. This study aims to elucidate the association between these two conditions by comparing how sufferers with HFpEF and CMD differ from those with sole HFpEF, of which we hypothesise that the difference will be distinct.

Who can participate?
Potential participants aged 18 to 85 years who have been clinically diagnosed with HFpEF and who will undergo an invasive coronary angiogram as part of their standard clinical care.

What does the study involve?
Participants with a high likelihood of HFpEF will be recruited into a multi-stage study taking place over approximately 9 weeks; they will undergo a detailed assessment of their hearts at rest and on exercise, both invasively in the cardiac catheter lab as well as non-invasively with a cardiac MRI scan. Differences in response to exercise and commonly prescribed angina treatment will be compared between participants with and without CMD.

What are the possible benefits and risks of participating?
In terms of benefits, participants will undergo a detailed physiological assessment both

invasively and non-invasively that will offer both themselves and their clinicians further insights into their condition. This study will ultimately aim to clarify whether CMD has implications for HFpEF sufferers and may pave the way for larger clinical trials, which will stand to benefit sufferers in the long term. In terms of risks, there will be additional radiation exposure during their coronary angiogram beyond what would be considered standard clinical care. Radiation exposure can precipitate immediate complications such as burns, or long-term complications such as the theoretical risk of causing cancer; however, this risk has been assessed by a medical physics expert and is felt to be low/comparable to the radiation dose used in standard clinical care.

Where is the study run from?
King's College London (UK)

Where is the study run from?
St Thomas' and King's College Hospital (UK)

When is the study starting and how long is it expected to run for?
October 2023 to October 2027

Who is the main contact?
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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
327243

Protocol serial number
CPMS 58427

Study information

Scientific Title
Elucidating the pathophysiological link between coronary microvascular dysfunction and heart failure with preserved ejection fraction

Acronym
CMD-HFpEF

Study objectives
Participants with coronary microvascular dysfunction (CMD) and heart failure with preserved ejection fraction (HFpEF) have distinct exercise pathophysiology, myocardial perfusion during stress and response to anti-ischaemic therapies versus those with HFpEF and normal microvascular function or those without HFpEF.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 28/02/2025, Hampstead Research Ethics Committee (Royal Free Hospital, London, NW3 2QG, United Kingdom; +44 (0)207 104 8284; hampstead.rec@hra.nhs.uk), ref: 25/LO/0146

Study design
Non-randomized interventional study

Primary study design
Interventional

Study type(s)
Diagnostic

Health condition(s) or problem(s) studied
Coronary microvascular dysfunction (CMD) and heart failure with preserved ejection fraction (HFpEF)

Interventions
This study comprises an invasive and non-invasive observational arm as well as a phenotype-blinded therapeutic arm.

In the observational arm, participants undergo invasive characterisation in the cardiac catheter lab and non-invasive characterisation via a cardiac MRI. In the cardiac catheter lab, participants will have pulmonary capillary wedge pressure and coronary physiology measured at both rest and exercise. The method of exercise employed will either be supervised ergometry via a bike attached to the end of the catheter lab table, or hand-grip using a grip dynanometer; the exercise will be supervised by a member of the research team.

In the phenotype-blinded therapeutic arm, participants and researchers are blinded to the characterisation performed in the aforementioned invasive and non-invasive studies. They will have a baseline 6-minute walk distance (6MWD) measured and then be administered 4 weeks worth of oral ranolazine, starting at 375 mg twice a day, then up-titrated up to a maximum 7of 50 mg twice a day from the second week onwards. They will undergo a repeat 6MWD and then be taken off ranolazine, with a repeat 6MWD to be measured following its cessation.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Ranolazine

Primary outcome(s)
Ratio between the normalised delta of pulmonary capillary wedge pressure and 'exercise flow reserve' (i.e. the ratio between filling pressures and changes in coronary blood flow on exercise), measured once during the study’s invasive assessment

Key secondary outcome(s))
6-minute walk distance (6MWD) on anti-ischaemic treatment versus baseline, measured in metres at baseline, post 4 weeks of ranolazine administration and post 4 weeks off of ranolazine

Completion date
31/10/2027

Eligibility

Key inclusion criteria
1. Indication for coronary angiography AND a
2. Clinical diagnosis of HFpEF

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
85 years

Sex
All

Key exclusion criteria
1. Severe valvular disease
2. Significant epicardial coronary stenoses
3. Congenital heart disease
4. Suspected infiltrative heart disease (echo or CMR)
5. Inability to perform ambulatory, hand grip or cycle ergometric exercises
6. Pregnancy
7. Concurrent enrolment in a CTIMP trial

Date of first enrolment
03/04/2025

Date of final enrolment
31/10/2027

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
St Thomas' Hospital
Westminster Bridge Road
London
United Kingdom
SE1 7EH

Study participating centre
King's College Hospital
Denmark Hill
London
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SE5 9RS

Sponsor information

Organisation
King's College London

ROR
https://ror.org/0220mzb33

Organisation
Guy's and St Thomas' NHS Foundation Trust

ROR
https://ror.org/00j161312

Funder(s)

Funder type
Charity

Funder Name
British Heart Foundation

Alternative Name(s)
The British Heart Foundation, the_bhf, BHF

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Stored in non-publicly available repository, Data sharing statement to be made available at a later date