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Comparing the role of the carotid body in human heart failure

Submission date
25/02/2019

Recruitment status
Suspended

Registration date
02/05/2019

Overall study status
Completed

Last Edited
24/04/2020

Condition category
Circulatory System

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

Plain English summary of protocol

Background and study aims
Heart failure occurs when the heart's pumping efficiency is reduced. In half of patients with heart failure there are no symptoms at rest but when they start exercising they become very breathless and weak. This condition is called heart failure with preserved ejection fraction (HFpEF) and there is no cure or treatment to reduce symptoms and improve pumping efficiency on exertion. Small organs called carotid bodies located close to the main arteries carrying blood to the brain appear to become abnormally active and can cause breathlessness and muscle weakness. The aim of this study is to test the levels of activity of the carotid bodies in patients with HFpEF compared patients with HFrEF and healthy volunteers. The study will also test whether reducing this abnormal activity will help this specific group of heart failure patients to feel less breathless and weak during exercise and so be able to exercise for longer.

Who can participate?
Patients aged 18-90 with heart failure with preserved ejection fraction (HFpEF) or reduced ejection fraction (HFrEF), and healthy volunteers

What does the study involve?
There are three visits on separate days. The key parts of the study are:
1. Having blood pressure, heart rate, height, weight and oxygen levels measured
2. Two short (less than 15 minutes) cycling tests on different days
3. Doing an ECG (heart tracing)
4. Having a cannula inserted into a vein and blood samples taken
5. Measuring breathing and blood pressure response to different gas mixtures and to a drug (dopamine) given into a vein
6. Measuring nerve activity in the leg with a tiny, acupuncture-like electrode
7. After this, wearing a 24-hour blood pressure monitor

What are the possible benefits and risks of participating?
Participants get a heart tracing, full blood pressure screen, blood tests and bike test, which may be of some benefit from a health check-up point of view. Taking part in this study will help researchers understand more about the science underlying heart failure and why exercise is so difficult in this condition. They want to learn more about ways to test for carotid body activity,

and develop ways to identify patients who might benefit from treatments to target overactive carotid bodies.
Venous cannulation may cause some discomfort and local bruising. There is a very small chance of a clot forming and infection. The risk is small as the cannula will not remain in long. During respiratory (breathing) monitoring a mask will be fitted to measure what participants are breathing in and out. They are given different gases to breathe. This may make them feel a little breathless and increase their breathing for few minutes. They may feel a little light-headed for a short time. Dopamine will be given at a very low dose and no side effects are expected. Participants will be monitored closely at all times. If there are any problems the drug will be stopped and wear off very quickly (within a couple of minutes). This is used commonly in medical practice and is safe at this dose. The dose of dopamine used is lower than the routine dose in hospital care. The risk is therefore low. The side effects seen at higher doses include: feeling and being sick, chest pain, heart racing/thumping, fast heart rate, temporary narrowing (squeezing) of blood vessels, low blood pressure, breathlessness, and headache. Very rarely, patients develop slow heart rate, high blood pressure, injury if the drug leaks into soft tissue, big pupils, and abnormal heart rhythms. Given the lower dose that is used, no side effects are expected. This technique has been used in several other studies without any problems. When measuring nerve activity a tiny needle is inserted into a nerve that runs close to the skin near the knee. A second needle is placed into the skin surface nearby. Once a good nerve recording is found, the needles stay in the leg for about 1 hour. A slight bruised feeling or tingling may be felt while the tiny needle is placed into the nerve. This feeling normally disappears quickly. There should be no long-term side effects. Rarely patients experience a deep temporary ache or change in feeling. These symptoms can develop a few days after the nerve activity was measured and can last for 3 – 7 days. Participants should contact the researchers should they develop any problems after the study visit. For the bike exercise test participants cycle for less than 10 minutes. A doctor will be with them at all times and if they feel unwell, the test can be stopped at any time. There are no risks with wrist blood flow measurement as it is simply placing a probe on the wrist.

Where is the study run from?
1. University of Bristol (UK)
2. University Hospitals Bristol NHS Foundation Trust (UK)
3. NHS Bristol, North Somerset & South Gloucestershire CCG (UK)

When is the study starting and how long is it expected to run for?
January 2018 to April 2021

Who is funding the study?
British Heart Foundation (UK)

Who is the main contact?
Dr Katrina Hope
katrina.hope@bristol.ac.uk

Study website
http://www.uhbristol.nhs.uk/hypertension

Contact information

Type(s)
Scientific

Contact name
Dr Katrina Hope

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
40286

Study information

Scientific Title
Comparing the mechanistic role of the carotid bodies in human heart failure with and without preserved ejection heart failure

Study objectives
The null hypotheses to be tested are:
1. There is no significant difference in CB chemosensitivity and tonicity between patients with HFpEF, patients with HFrEF and age-matched healthy controls.
2. Inactivating the carotid bodies in patients with HFpEF will result in no significant change in (i) an exaggerated chemoreflex mediated hyperventilatory response to hypoxia, (ii) raised basal sympathetic nerve discharge and, (iii) depressed arterial baroreflex function and (iv) exercise intolerance.

Ethics approval required
Old ethics approval format

Ethics approval(s)

Approved 04/12/2018, South West - Central Bristol Research Ethics Committee (Whitefriars, Level 3, Block B, Lewin's Mead, Bristol, BS1 2NT, Tel: +44 (0)2071048028; Email: nrescommittee.southwest-bristol@nhs.net). ref:
18/SW/0241

Study design
Observational; Design type: Case-controlled study

Primary study design
Observational

Secondary study design
Case-control study

Study setting(s)
Hospital

Study type(s)
Treatment

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

Health condition(s) or problem(s) studied
Heart failure

Interventions
1. Carotid body chemosensitivity testing: brief, intermittent lowering of inhaled oxygen levels to test hypoxic ventilatory response at rest.
2. Muscle Sympathetic Nerve Activity measurement: insertion of acupuncture needle-sized electrodes into common peroneal nerve to directly measure nerve activity.
3. Exercise tolerance testing with and without carotid body inhibition: VO2 peak test with an intravenous infusion of dopamine or saline as vehicle control.
Total of 3 visits within 2 months.

Intervention Type
Other

Primary outcome measure
1. CB chemosensitivity and tonicity and levels of sympathetic activity in HFrEF & HFpEF patients compared to healthy controls at rest:
1.1. Hypoxic ventilatory response (HVR) in litre/minute/%SpO2
1.2. Change in minute ventilation during dopamine infusion (l/min)
1.3. Muscle sympathetic nerve activity (burst frequency, usually quantified as bursts per 100 heartbeats) at baseline
2. Change in exercise tolerance and perceived rate of exertion in HFpEF patients as a result of dopamine administration vs saline during VO2 Peak Test:
2.1. BORG score at peak
2.2. VO2 peak measurement, overall VE/VCO2 slope

Secondary outcome measures
Differences between healthy controls, HFrEF & HFpEF groups at rest during carotid body chemosensitivity testing:
1. BP responses to hypoxia
2. BP response to dopamine and hypoxia (small subset of participants)
3. HR responses to hypoxia
4. HR responses to dopamine and hypoxia (small subset of participants)
5. Inflammatory markers
6. Pulse Wave Analysis

Overall study start date
01/01/2018

Completion date
30/04/2021

Eligibility

Key inclusion criteria
All participants:
1. Aged 18-90 years

HFrEF participants:
As per the European Society of Cardiology (ESC) guidelines:
1. Signs and symptoms of heart failure AND
2. Raised natriuretic peptides AND
3. Evidence of reduced ejection fraction (EF < 40%)

HFpEF participants:
As per the European Society of Cardiology (ESC) guidelines:
1. Signs and symptoms of heart failure AND
2. Raised natriuretic peptides (e.g. NTproBNP) AND
3. Evidence of preserved ejection fraction (EF > 50%) AND
4. Objective evidence of cardiac functional and structural alterations

Participant type(s)
Mixed

Age group
Adult

Lower age limit
18 Years

Upper age limit
90 Years

Sex
Both

Target number of participants
Planned Sample Size: 55; UK Sample Size: 55

Key exclusion criteria
All participants:
1. Requirement for oxygen therapy to maintain oxygen saturation
2. Oxygen saturations at rest < 92%
3. Chronic obstructive pulmonary disease (COPD) and known structural lung disease
4. Current smoker (within the last 2 months)
5. Acute coronary syndrome, coronary revascularisation or unstable angina in last 6 months
6. HF related hospitalisation in the last 1 month.
7. Transient ischaemic attack or stroke in the last 6 months
8. Surgery under general anaesthesia in the last 3 months
9. Change in regular medications within the last 1 month
10. Clinically significant neurological disorder, including peripheral neuropathy
11. Type 1 Diabetes Mellitus
12. Heart transplant
13. Haemodialysis or peritoneal dialysis
14. Pregnancy, breast feeding or recent unprotected intercourse
15. Palliative care/chemotherapy
16. Recreational drug use and/or intravenous drug use
17. Alcohol intake > 28 units/week
18. Febrile illness/clinically significant infection within two weeks of participation
19. Contraindications to dopamine administration:
19.1. Known phaeochromocytoma
19.2. Known hyperthyroidism
19.3. Known uncontrolled atrial or ventricular tachyarrhythmias
19.4. Known hypersensitivity to dopamine or any of the excipients
19.5. Participants on the following medications:
19.5.1. Monoamine oxidase I inhibitors
19.5.2. Phenytoin
19.5.3. Ergot alkaloids
19.5.4. Tricyclic antidepressants
19.5.5. Guanethidine

Healthy controls:
1. No history of hypertension

Date of first enrolment
01/08/2018

Date of final enrolment
01/08/2020

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
University of Bristol
Clinical Research & Imaging Centre
60 St Michael's Hill
Bristol
United Kingdom
BS2 8DX

Study participating centre
University Hospitals Bristol NHS Foundation Trust
Marlborough St
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BS1 3NU

Study participating centre
NHS Bristol, North Somerset & South Gloucestershire CCG
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Sponsor information

Organisation
University of Bristol

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Sponsor type
University/education

ROR
https://ror.org/0524sp257

Funder(s)

Funder type
Charity

Funder Name
British Heart Foundation; Grant Codes: 32917

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

Funding Body Type
Private sector organisation

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

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal.

Intention to publish date
31/12/2021

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a non-publically available repository.
Personalised study data will be maintained at the University of Bristol in paper and/or electronic format. Both paper and electronic records are kept in a locked cupboard in a locked room in a department with security-limited access. Access to the records is restricted to researchers working on the study. Password protection will be used for electronic data and, for the purposes of data analysis, anonymised data will be held on an encrypted flash drive, to be locked as above when not in use. No identifiable data will be stored on laptop computers or portable electronic devices. Analysis will take place by the study team led by Dr Emma Hart and collaborators (using anonymised data). Data will be collected and retained in accordance with the Data Protection Act 1998. Study documents (paper and electronic) will be retained in a secure location during and after the trial has finished. All source documents will be retained for a period of fifteen years following the end of the study. Where trial-related information is documented in the

medical records, those records will be identified by a ‘Do not destroy before dd/mm/yyyy’ label where date is 15 years after the last patient last visit.
The Chief Investigator, Dr Katrina Hope, will have control of and act as custodian of the data on behalf of the University of Bristol and University Hospitals Bristol NHS Foundation Trust.
Personal data will be stored for 15 years at the University of Bristol in electronic and hard copy. Access will be controlled by Dr Nightingale who will continue to act as custodian.
The Chief Investigator will allow monitors persons responsible for the audit, representatives of the Ethics Committee and of the Regulatory Authorities to have direct access to source data /documents. This is reflected in the Participant Information Sheet (PIS) and consent form. The study will be monitored and audited in accordance with the sponsor and NHS Trust policy. All trial related documents will be made available on request for monitoring and audit by University of Bristol, UH Bristol and the relevant Research Ethics Committee.

IPD sharing plan summary

Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No