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Improving symptoms and exercise responses in patients heart failure with iron deficiency

Submission date
27/01/2020

Recruitment status
Suspended

Registration date
28/02/2020

Overall study status
Completed

Last Edited
20/04/2020

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
Chronic heart failure is a common condition where the pumping function of the heart is reduced. Many other body systems are affected after the start of this illness. These effects contribute to the symptoms experienced in the condition. Researchers are interested in the relationship between iron deficiency, found in roughly half of chronic heart failure patients, and the activity of the autonomic nervous system. This nervous system controls blood pressure, heart rate and the body's response to exertion. It is overactive in chronic heart failure. This overactivity worsens chronic heart failure. Iron is crucial in effective muscle function. Iron deficiency may be causing changes within the muscle leading to increased activity of the sensors within muscle that influence the autonomic nervous system. Treatment of iron deficiency in chronic heart failure is a recommended treatment. It can improve symptoms and reduce admissions, but researchers are unsure of the mechanism whereby this is achieved. This study will assess a possible cause. The aim of this study is to treat a group of iron-deficient heart failure patients with intravenous iron and assess whether treatment leads to a beneficial reduction in autonomic nervous system activity. They will be compared with chronic heart failure patients with normal iron levels.

Who can participate?
Patients aged 18 and over with chronic heart failure and reduced ejection fraction seen in cardiac clinics in Bristol

What does the study involve?
Iron-deficient participants visit the research unit before and after treatment of low iron levels with intravenous iron. Assessments will include measuring physical observations during gentle exercise and recording the activity of peripheral nerves. These observations can be used to assess the autonomic nervous system and find out whether activity changes after treatment.

What are the possible benefits and risks of participating?
Benefits include the opportunity for an exercise test and engagement with the heart failure research team. Risks include short-lasting discomfort from nerve function testing.

Where is the study run from?
Clinical Research and Imaging Centre in Bristol (UK)

When is the study starting and how long is it expected to run for?
August 2018 to August 2020

Who is funding the study?
1. Pharmacosmos A/S
2. British Society for Heart Failure (UK)
3. Above & Beyond – fundraising for Bristol city centre hospitals (UK)

Who is the main contact?
Dr Angus Nightingale
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
252618

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 42211, IRAS 252618

Study information

Scientific Title

Novel mechanisms of autonomic dysfunction in chronic heart failure – effects of iron replacement therapy on skeletal muscle metaboreflex and contribution to sympathetic nerve activation

Acronym
ADMIRAL-HF

Study objectives
Does the treatment of iron deficiency in patients with chronic heart failure lead to a change in the levels of activity of the autonomic nervous system as assessed by direct recordings of the activity of nerves?

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 28/06/2019, South West – Frenchay REC (HRA Centre, Level 3, Block B, Whitefriars, Lewins Mead, Bristol, BS1 2NT, UK; +44 (0)207 104 8360, +44 (0)207 104 8041; nrescommittee.southwest-frenchay@nhs.net), REC ref: 19/SW/0098

Study design
Non-randomised; Both; Design type: Treatment, Screening, Drug, Case-controlled study

Primary study design
Interventional

Secondary study design
Non randomised 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
Chronic heart failure

Interventions
Two groups of participants will be recruited:
1. Participants with chronic heart failure and an ejection fraction of less than 40% who are iron deficient as defined by the European Society of Cardiology
2. Participants with chronic heart failure and an ejection fraction of less than 40% who are not iron deficient

Participants from both groups will attend for study visits at the Clinical Research and Imaging Centre (CRIC) involving clinical assessment and assessments of the autonomic system at baseline. In addition, the iron-deficient group will attend the Bristol Royal Infirmary for treatment with intravenous iron and they will be reassessed post this therapy. The visits are as follows:

1. Confirmation of suitability for recruitment into the study, informed consent, medical history and medication review, physical observations and blood tests which shall be stored. If the participant has not had a recent ECG this will be performed on this visit. The impact of heart failure of participant quality of life will be assessed by use of a validated questionnaire. This visit shall take approximately two hours.

2. This will involve two components. Firstly, there will be an assessment of the activity of the autonomic nervous system by muscle sympathetic nerve activity (MSNA). This will involve the placement of microelectrodes into the common peroneal nerve to record activity. This is a well-established technique for measuring the activity of sympathetic nerves (sympathetic nerves represent one component of the autonomic nervous system). Next participants will perform handgrip exercise. After completion of a short period of exercise, a blood pressure cuff shall be inflated around the recently active arm. (This is necessary to trap metabolites which have built up post-exercise and activate the metaboreflex). Observations of heart rate, blood pressure and respiratory rate will be recorded. The participant will also be asked to perform a short exercise test on an exercise bike. Their ability to exercise and the efficiency of their exercise shall be assessed by looking at their oxygen usage. This cardiopulmonary function testing involves the use of a sealed mask over their nose and mouth. This visit will take approximately four hours.

3. After the second visit, the group with iron deficiency shall attend the hospital for treatment with intravenous iron.

4. All patients who have been treated with iron shall have the investigations performed in visit two repeated. Participants will have blood tests repeated and stored. A symptom-based questionnaire will be repeated.

Intervention Type
Supplement

Primary outcome measure
Muscle sympathetic nerve activity assessed by microneurography before and after treatment with intravenous iron therapy

Secondary outcome measures
1. Levels of activity of the autonomic nervous system assessed by measured activity of physical observations such as heart rate, blood pressure, respiratory rate and cardiopulmonary function testing post exercise before and after treatment with intravenous iron therapy
2. Blood markers of inflammation before and after treatment with intravenous iron therapy

Overall study start date
01/08/2018

Completion date
01/08/2020

Eligibility

Key inclusion criteria
1. Adults aged 18 and over
2. Diagnosis of chronic heart failure with reduced ejection fraction (HFrEF)
3. New York Heart Association (NYHA) class II and III symptoms
4. Able to attend for assessments
5. On stable, optimal treatment for heart failure. This includes stable pharmacological therapy and device therapy
6. Willingness to receive intravenous iron replacement therapy (if indicated)

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 48; UK Sample Size: 48

Key exclusion criteria
1. Unable to provide informed consent
2. Inability to participate in physical assessments for reasons other than HFrEF (e.g. musculoskeletal impairment, neurological disorder)
3. Severe COPD
4. Long term oxygen therapy
5. Uninvestigated anaemia
6. Active malignancy
7. Active bleeding source
8. Awaiting gastrointestinal investigations
9. Diagnosis of additional disease likely to significantly worsen over the following 12 months
10. Patients with diagnosis of heart failure with preserved ejection fraction or isolated right ventricular impairment
11. Previous allergic reaction to any intravenous iron preparation
12. NHYA class I and IV heart failure
13. Atrial fibrillation or frequent ectopy
14. Presence of cardiac device (pacemaker, implantable cardiac device, cardiac resynchronisation therapy) with frequent need for atrial pacing
15. Anticipated changes in heart failure treatment over the next 3 months
16. Taking immunosuppressive therapy
17. Known autoimmune or inflammatory disorders
18. Diagnosis of ongoing primary muscle or neurological disorder

Date of first enrolment

13/09/2019

Date of final enrolment
01/05/2020

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
University Hospitals Bristol NHS Foundation Trust
Marlborough Street
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Sponsor information

Organisation
University of Bristol

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Sponsor type
Hospital/treatment centre

Website
http://bristol.ac.uk/

ROR
https://ror.org/0524sp257

Funder(s)

Funder type
Industry

Funder Name
Pharmacosmos A/S

Funder Name
British Society for Heart Failure

Alternative Name(s)
BSH

Funding Body Type
Private sector organisation

Funding Body Subtype
Associations and societies (private and public)

Location
United Kingdom

Funder Name
Above & Beyond

Results and Publications

Publication and dissemination plan
1. Peer-reviewed scientific journals
2. Internal report
3. Conference presentation
4. Publication on website
5. Other publication

Intention to publish date
01/08/2021

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study 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?
HRA research summary			28/06/2023	No	No