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The role of the carotid chemoreflex in long-COVID

Submission date
03/03/2025

Recruitment status
Recruiting

Registration date
03/03/2025

Overall study status
Ongoing

Last Edited
01/04/2025

Condition category
Infections and Infestations

[_] 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
Long-COVID is a condition in which people continue to have health problems for many months or years after a COVID-19 infection. It is a big health and economic problem in the UK, affecting nearly 2 million people and costing £8 billion each year. Of these, 71% reported having symptoms for >1 year, 51% >2 years, and 31% for at least 3 years, a prevalence which is worryingly similar to that of March 2023, indicating that incidence is not declining over time. Many people with long-COVID experience ongoing breathing difficulties. They have a pattern of erratic breathing at rest, and during exercise, despite their lung function being normal. It is not currently known why this occurs, but there is increasing evidence that this is due to disruption of the control of breathing, coordinated by the brain and nervous system, rather than a specific lung problem. A key part of this breathing control system is the carotid chemoreflex. This is driven by small organs in the neck called the carotid bodies, which monitor the chemical status of the blood, sending signals into the brain causing breathing and circulatory adjustments. Thus, the carotid chemoreflex controls breathing and feelings of breathlessness. When someone is infected with the COVID-19 virus, the virus enters the carotid bodies and disrupts their normal function, which may explain why some patients with long-COVID are breathless at rest and during exercise. Our recent research shows that the carotid chemoreflex is more sensitive in people with long-COVID, without other health problems.
The aim of this study is to determine whether temporary inactivation of the carotid bodies improves breathing at rest and during exercise in people with long-COVID. We will monitor whether hyperventilation at rest is reduced, and breathing efficiency during exercise is improved when the carotid bodies are inactivated. This study will determine whether the carotid body is a target for future therapeutic treatment for patients with long-COVID and unexplained breathing difficulties.

Who can participate?
All participants must be 18-75 years old. For the long-COVID group, participants must have a diagnosis of long-COVID and breathlessness that affects their daily lives. For the control group, the participants must have had COVID but symptoms lasted less than 4 weeks, and no breathlessness.

What does the study involve?
Three study visits at the Clinical Research Facility, Bristol. Visit 1 is a screening visit and will involve five questionnaires, a 12-lead ECG, lung function tests, urine dipstick and pregnancy tests, height, weight, office blood pressure measurements and a blood sample. Participants will also be sent home with a 24-hour blood pressure monitor. Visits 2 and 3 will be identical, except participants will receive a different infusion (dopamine and saline) each day. The dopamine and saline infusion conditions will be randomised in order. Resting ventilation assessments and hypoxic ventilatory response testing will be completed. A ramped exercise tolerance test will also be performed. Ventilation, blood pressure, oxygen saturation and heart rate will be continuously recorded throughout the visits.

What are the possible benefits and risks of participating?
Benefits: You will get a heart tracing, full blood pressure screen and blood tests, which may be of some benefit from a health check-up point of view; however, these tests should not be relied upon for the identification of undiagnosed medical conditions. Taking part in this study will help us understand more about the science underlying long-COVID, and how the carotid body is involved in it. We want to learn more about the mechanisms of long-COVID, to help identify a treatment to improve some of the symptoms that people with long-COVID experience. Side effects: Venous cannulation: This may cause some discomfort and local bruising. There is a very small chance of a clot forming and infection. The risk is very small as the cannula will not remain in long.
Respiratory (breathing) monitoring: A mask will be fitted that allows us to measure what you are breathing in and out. There are no risks to breathing room air at rest. Dopamine infusion: We will give you a very low dose of dopamine (a drug) which we expect will not give any side effects. We will monitor you closely at all times and if there are any problems with the drug, we will stop the infusion which will stop any problems quickly (within a couple of minutes). This is used commonly in medical practice and is safe at this dose. Dopamine also exists naturally in your body and is a vital chemical messenger in your brain. The dose of dopamine we will use is lower than the routine dose in hospital care. The risk therefore is low. Dopamine is used in the UK for treating cardiogenic shock during a heart attack or during heart surgery because it improves blood flow. The side effects seen at higher doses include feeling and being sick, chest pain, heart racing, fast heart rate, temporary narrowing of blood vessels, low blood pressure, breathlessness, and headache. Very rarely, patients develop a slow heart rate, high blood pressure, injury if the drug leaks into soft tissue, big pupils and abnormal heart rhythms. Given the low dose we are using, we do not expect any side effects. We have used this technique in several other studies, without any problems. Hypoxic ventilatory response testing: Breathing nitrogen can cause some short-lived dizziness or light-headedness. The nitrogen can be immediately switched off and clears from the breathing circuit in seconds. Oxygen levels return to normal quickly after the nitrogen is switched off, and additional oxygen can be given if needed. Bike exercise test: we will ask you to cycle for up to 12 minutes. A research nurse and researcher will be with you at all times, and if you feel unwell, the test can be stopped at any time. The inherent side effects of exhaustive exercise may be experienced.

Where is the study run from?
University of Bristol (UK)

When is the study starting and how long is it expected to run for?
August 2024 to January 2027

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

Who is the main contact?
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Contact information

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Public, Scientific, Principal Investigator

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
348370

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
ID: 2989729, CPMS 65060

Study information

Scientific Title
Understanding the mechanistic role of the carotid chemoreflex in patients with long-COVID and unexplained breathing difficulties

Study objectives
The mechanistic hypothesis is that the carotid chemoreflex is persistently hyperactive at rest and during exercise, driving hyperventilation and persistent breathlessness in long-COVID patients.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 28/01/2025, London - Fulham Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)115 8839435; fulham.rec@hra.nhs.uk), ref: 24/LO/0917

Study design
Randomized cross-over trial

Primary study design
Interventional

Secondary study design
Randomised cross over trial

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

Study type(s)
Other

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
Long-COVID

Interventions
The mechanistic hypothesis is that the carotid chemoreflex is persistently hyperactive at rest and during exercise, driving hyperventilation and persistent breathlessness in long-COVID patients. To investigate this, the researchers will assess whether intravenous low-dose dopamine infusion, to inhibit the carotid chemoreflex at rest and during exercise, reduces hyperventilation in non-hospitalised patients with long-COVID. Participants will undergo testing in two conditions to assess carotid body chemosensitivity at rest (semi-supine position). Both conditions will be administered in the presence of a registered nurse or medical doctor. The dopamine and saline infusion conditions will be randomised in order (e.g. given on visit 2 or visit

3 – simple randomisation using sealedenvelope.com). Prior to infusion, participants will be asked to breathe room air for 5 minutes to assess the normal level of ventilation.

Intravenous dopamine infusion to inhibit the carotid body: participants will be given an intravenous infusion of dopamine (2 µg/kg/min) which will be maintained throughout the study visit (maximum dopamine exposure time will be 1.5 hours). Dopamine will be supplied by the Pharmacy Stores department at University Hospitals Bristol and Weston NHS Foundation Trust, and subsequently stored at the Clinical Research Facility.

Intravenous 0.9% saline infusion as vehicle control: participants will be given an intravenous infusion of 0.9% sterile saline throughout the study visit (maximum saline exposure time 1.5 hours).

Intervention Type
Other

Primary outcome measure
Chemoreflex sensitivity calculated by the increase in minute ventilation divided by the SpO2%; this is termed the hypoxic ventilatory response or HVR and is expressed as L/min/SpO2%

Secondary outcome measures
1. Hypoxic blood pressure measured using a Finapres, continuous beat-to-beat blood pressure throughout infusion
2. Heart rate during hypoxia measured using a 3-lead ECG continuously throughout infusion
3. Resting minute ventilation and breathing frequency measured via a face mask and gas analyser and will be measured continuously (breath-by-breath) throughout infusion
4. Minute ventilation, respiratory rate and oxygen consumption (VO2) measured using a face mask and gas analyser continuously (breath-by-breath) throughout exercise
5. Dyspnoea score measured using the Borg scale 1-10 every 2 minutes throughout exercise
6. Heart rate measured using a 12-lead ECG continuously throughout exercise
7. Blood pressure measured using a blood pressure cuff every minute throughout exercise

Overall study start date
21/08/2024

Completion date
05/01/2027

Eligibility

Key inclusion criteria
All participants:
1. 18-75 years old
2. Self-reported positive PCR or antibody test before vaccination

Long-COVID patients only:
1. Breathlessness affecting their daily lives measured by the Modified Yorkshire COVID-19 Rehabilitation Scale (used in long-COVID clinics)

Age and sex-matched controls only:
1. Asymptomatic or symptoms lasting less than 4 weeks after COVID-19 infection

2. Must not have breathlessness affecting their daily life (checked on screening call and by questionnaire during lab screening)

Participant type(s)
Healthy volunteer, Patient, All

Age group
Adult

Lower age limit
18 Years

Upper age limit
75 Years

Sex
Both

Target number of participants
54

Key exclusion criteria
1. Body mass index ≥30 kg/m2
2. Diagnosed with severe asthma or uncontrolled asthma
3. Pregnancy/breastfeeding women
4. Ongoing requirement for oxygen therapy
5. Taking antihypertensive, nitrate, steroid or immunosuppressant medication or medication
6. Major illness e.g., cancer, inflammatory disease (including vasculitis) or receiving palliative care
7. History of organ transplantation or are candidates for organ transplantation at the time of screening
8. History of Chronic Fatigue Syndrome prior to COVID-19 infection
9. Diagnosed cardiovascular disease (including current non-benign arrhythmia, chronic heart failure)
10. History of major psychiatric disorder including bipolar disorders, schizophrenia, schizoaffective disorder, major depression
11. Diagnosis of structural lung disease (such as COPD or pulmonary fibrosis)
12. Diagnosed renal disease
13. Congenital or acquired neurological conditions (including dementia), language disorders, repeated or chronic pain conditions (excluding menstrual pain and minor sporadic headaches)
14. Diabetes mellitus
15. Symptoms of febrile illness 2 weeks before experiment
16. Lower respiratory tract symptoms at time of screening visit
17. Excessive alcohol consumption (>28 units/week) or use of illicit drugs
18. History of tobacco smoking within the last 12 months
19. Inability to understand instructions given in English
20. Surgery under general anaesthesia within 3 months
21. History of stroke
22. Heart transplant
23. Coronary revascularisation

24. Haemodialysis or peritoneal dialysis
25. Participating in another study for an investigational medicinal product
26. Known allergy to dopamine

Date of first enrolment
24/02/2025

Date of final enrolment
05/01/2027

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
University Hospitals Bristol and Weston - Clinical Research Facility
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University of Bristol

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Sponsor type
University/education

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ROR
https://ror.org/0524sp257

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council

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

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
1. Project webpage: included on Dr Hart's group website hosted by UHBW NHS Trust. This will summarise the project motivation, aims, and methods in lay terms. It will offer a link for those interested in participating. The webpage will feature updates on project events, progress, relevant publications, and links to external resources. Promotion will be done via social media and targeted newsletters. Impact measurement: number of views, number of people recruited via website. Timeline: Duration of project +2 years.
2. Workshop for patients, carers, and healthcare workers: A half-day workshop focusing on the management of long-COVID, breathing
difficulties and breathlessness. The aim will be to communicate findings and create a roadmap of what should happen next in collaboration with patients (beyond those included in the study) and health carers. Impact measurement: Number of delegates, feedback from forms, project plan. Timeline: Q4 in year 3 of the project.
3. Public talks: Pint-of-Science in Year 2 of the project. Impact measurement: Number in audience, feedback from forms.
4. Dissemination to the scientific community: via conference presentations (national; Physiological Society annual conference and international;
European Respiratory Society), as well as via open-access peer-reviewed manuscripts. We will

use pre-print servers where possible and share publications via social media to build maximal engagement and knowledge exchange. Impact measurement: Number of downloads/views. Timeline: Conferences at start year 2 and end year 3. Publications at start year 3 and end year 3

Intention to publish date

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 - https://data.bris.ac.uk/data/
Raw data will not be publicly available.
Data will be available once analysed and published.
Patient data will all be anonymised and consent will be obtained.

IPD sharing plan summary

Stored in publicly available repository, Available on request