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Understanding how long COVID-19 impacts breathing, heart rate, and blood pressure control

Submission date
17/11/2021

Recruitment status
No longer recruiting

Registration date
27/01/2022

Overall study status
Completed

Last Edited
27/03/2024

Condition category
Infections and Infestations

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Around 4 million individuals have tested positive for COVID-19 in the UK up to February 2021. Those who have recovered from the acute effects of COVID-19 often describe ongoing symptoms including decreased exercise tolerance, fatigue, chest pain, and dizziness, typical of an emerging syndrome known as 'Post-COVID-19 Syndrome'. 'Post COVID-19 Syndrome' is emerging as a prevalent syndrome, encompassing a plethora of debilitating symptoms (including breathlessness, chest pain, palpitation, and orthostatic intolerance) which can last for weeks or more following mild to moderate illness. There is increasing evidence pointing to an ongoing, multi-system disorder involving the brain and dysfunctional neural control systems following COVID-19 infection. The carotid body, a small organ in the carotid arteries, monitors oxygen levels in the blood and keeps tight control over breathing, heart rate, and blood pressure. This organ has a high distribution of angiotensin-converting enzyme, the enzyme by which coronavirus enters cells. The carotid body is also sensitive to inflammation, which is triggered by local infection. It is possible this inflammation drives symptoms such as breathlessness, inappropriate increases in heart rate, and dizziness. The aim of this study is to investigate the longer-term effects of COVID-19 on breathing and cardiovascular (heart) functions in men and women.

Who can participate?
Patients aged 18-80 years old with previous COVID-19 infection with symptoms less than 4 weeks in duration or with a formal diagnosis of Post-COVID-19
Syndrome, without major illness

What does the study involve?
The study involves one telephone consultation and two visits to the Clinical Research Facility (CRF), Bristol. The duration of the first CRF visit will be up to 3 hours, and the second CRF visit will be up to 2 hours and 15 minutes. During the telephone consultation, the researchers will ask screening questions with regards to any recent positive test results for, or symptoms of, COVID-19, recent travel outside the UK, and whether participants have been in contact with someone who has recently tested positive for COVID-19. The first part of the visit involves screening. This

is where the researchers go through the participants' medical history and complete some screening tests to make sure they are safely able to take part in the study. The researchers will also carry out an assessment of the nerve signals that control the dilatation of the blood vessels using a technique called microneurography whilst carrying out hand-grip exercises. Office blood pressure will be measured twice on each arm with an automated blood pressure cuff, followed by two further readings from the arm with higher blood pressure, two minutes apart. An average of the final two readings will be used. Ambulatory blood pressure monitoring will be used to measure blood pressure over 24 hours. Participants will be issued an ambulatory blood pressure monitor after the screening visit. Participants will be asked to keep a blood pressure diary to record waking/sleeping times, which will be used to calculate daytime ambulatory blood pressure. Activities completed during blood pressure readings will also be noted. 12-lead electrocardiography (ECG) will be performed to exclude obvious cardiovascular disease (assessed by a Doctor). A urine pregnancy test will be performed for premenopausal women. The researchers will take a blood sample to test for levels of inflammation and catecholamine hormones. Microneurography is a technique used to measure the activity of the nerves that control blood pressure (the sympathetic nerves). The researchers use two small electrodes, similar to acupuncture needles. One is inserted into a nerve in the lower leg called the peroneal nerve. The other is placed into the surface of the skin nearby the nerve and acts as a reference. It may take up to an hour to position the electrodes correctly. The researchers will record sympathetic nerve activity at rest and whilst performing some handgrip exercise. Handgrip exercise involves squeezing a hand-held device at 40% of maximal voluntary contraction (the contraction generated with maximum effort). To work out 40%, participants first squeeze the device with maximum effort three times. The handgrip procedure will show how the changes in nerve activity and blood flow to the arm seen during exercise differ between men and women, younger and older people, and people with high or normal blood pressure. The researchers will measure the blood flowing to the arm using an ultrasound probe (see below). Throughout the study, heart rate is recorded using three ECG stickers. Blood pressure will be measured by a small cuff that inflates around the end of a finger. Breathing will be monitored by a belt placed around the chest (at the diaphragm). The researchers will measure the ability of receptors in the carotid artery to adapt to changes in oxygen levels and blood flow (chemoreflex testing). Throughout the test, they will monitor heart rate and rhythm, oxygen levels, and blood pressure. Participants will initially breathe room air then switch to pure pharmaceutical grade nitrogen gas for 10-45 seconds. This will be repeated around 5-8 times to achieve short-lived falls in oxygen level and assess how the body increases its breathing rate to compensate. Some of the study procedures (ECG, blood pressure monitoring, urine sample testing, and blood sample testing) could identify abnormal results. If abnormal results are found in ECG or urine participants may be unable to take part in the rest of the study. Participants will be informed of any abnormalities in urine or ECG during the study visit. 24-hour blood pressure monitoring and testing of the blood sample take place after the study visit. If abnormal results are found in the blood pressure or blood sample, participants will be informed. However, the testing of blood samples will take place at the end of the study. Therefore, the researchers may not know the results of this test for 2-3 years after participating. The researchers will also inform the participant's GP of any abnormal results if they have given permission for this.

What are the possible benefits and risks of participating?
The results of this study will be of immediate benefit to the NHS by identifying a new mechanism that contributes to ongoing symptoms when recovering from COVID-19. Understanding what drives some of the symptoms in Post-COVID-19 Syndrome will help guide future treatments for COVID-19. Further work could include testing the efficacy of exercise interventions and breathing control techniques in these populations. Further benefits to patients include increasing confidence that exercising is safe when recovering from COVID-19 and that it has beneficial effects, as well as raising awareness of the benefits of early monitoring

of oxygen levels in people who have COVID-19 to determine whether low oxygen levels are more likely in people with an altered sense of taste or smell.
During the study, a Research Nurse or Doctor will take a blood sample, which will be tested for levels of inflammation and catecholamine levels. Participants may experience mild discomfort and/or mild swelling at the site. Microneurography sometimes causes numbness or tingling (paraesthesia) in the lower leg for 3-7 days after the procedure is completed. However, this is reported to occur in less than 10% of cases. To minimise the risk of infection, the researchers use sterile, single-use electrodes and a 'no-touch' technique after they have sterilised the skin. There are no known risks associated with handgrip exercise or the use of ultrasound to measure either blood flow to the arm (vascular ultrasound) or blood pumped by the heart (echocardiography). Repeated blood pressure measurements may lead to mild discomfort and numbness in the arm or finger. There are no known risks associated with monitoring heart rate or breathing. During the chemoreflex 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 saturation levels return to normal quickly after the nitrogen is switched off, and supplemental oxygen can be given if needed.

Where is the study run from?
Clinical Research Facility, Bristol (UK)

When is the study starting and how long is it expected to run for?
March 2021 to March 2023

Who is funding the study?
1. The University of Bristol (UK)
2. Above & Beyond (UK)
3. Elizabeth Blackwell Institute (UK)

Who is the main contact?
Dr Ahmed El-Medany
Ahmed.El-Medany@bristol.ac.uk

Contact information

Type(s)
Scientific

Contact name
Dr Angus Nightingale

Contact details
Bristol Heart Institute
Bristol Royal Infirmary
University Hospitals Bristol and Weston NHS Foundation Trust
Upper Maudlin Street
Bristol
United Kingdom
BS2 8HW
+44 (0)1173426572
angus.nightingale@bristol.ac.uk

Type(s)
Public

Contact name
Dr Ahmed El-Medany

ORCID ID
http://orcid.org/0000-0003-4419-6693

Contact details
School of Physiology, Pharmacology & Neuroscience
Faculty of Biomedical Sciences
University of Bristol
Bristol
United Kingdom
BS8 1TD
+44 (0)1173311971
Ahmed.El-Medany@bristol.ac.uk

Type(s)
Public

Contact name
Dr Emma Hart

Contact details
School of Physiology, Pharmacology & Neuroscience
Faculty of Biomedical Sciences
University of Bristol
Bristol
United Kingdom
BS8 1TD
+44 (0)1173311971
Emma.Hart@bristol.ac.uk

Additional identifiers

EudraCT/CTIS number

IRAS number
296727

ClinicalTrials.gov number

Secondary identifying numbers
IRAS 296727

Study information

Scientific Title

Assessment of chemoreflex control of respiratory and cardiovascular systems in Post-COVID-19 syndrome

Acronym
ARC C-19

Study objectives
Post COVID-19 syndrome is emerging as a prevalent syndrome, encompassing a plethora of debilitating symptoms (including breathlessness, chest pain, palpitation, and orthostatic intolerance) which can last for weeks or more following mild to moderate illness. Whilst this is partially due to direct lung injury, increasing evidence points to an ongoing, multi-system disorder involving the brain and the carotid body. The carotid body, a small organ in the carotid arteries, monitors oxygen levels in the blood and keeps tight control over breathing, heart rate, and blood pressure. This organ has a high distribution of angiotensin-converting enzyme 2, the enzyme by which coronavirus enters cells. The carotid body is also sensitive to inflammation, which is triggered by local infection. It is possible this inflammation drives symptoms such as breathlessness, inappropriate increases in heart rate, and dizziness. The aim of this study is to investigate the longer-term effects of COVID-19 on autonomic and peripheral chemoreflex control of respiratory and cardiovascular systems. This will be achieved by recruiting patients from two populations both of whom have had acute COVID-19: Firstly, a group with Post-COVID-19 Syndrome and secondly a matched control group with COVID-19 symptoms lasting no longer than 4 weeks as per NICE guidelines. The researchers will assess carotid body chemosensitivity at rest and during submaximal exercise. They will also assess autonomic function at rest and during exercise. These data will provide an insight into whether the carotid body is involved in post-COVID-19 syndrome and whether it is linked to autonomic dysfunction. The carotid body could be targeted to help treat post-COVID-19 syndrome.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 05/10/2021, Hampshire Research Ethics Committee (2 The Square, Temple Quay, Temple Quay House, BS1 6PN, UK; hampshireb.rec@hra.nhs.uk), ref: 21/SC/0260

Study design
Single-center observational longitudinal case-control study

Primary study design
Observational

Secondary study design
Case-control study

Study setting(s)
Hospital

Study type(s)
Quality of life

Participant information sheet

Health condition(s) or problem(s) studied
Post-COVID-19 syndrome

Interventions
The researchers will measure the hypoxic ventilatory response at rest and during moderate dynamic exercise. They will measure sympathetic nerve activity via microneurography, which is a direct measure of the sympathetic nerve activity at 1) rest and 2) during isometric handgrip exercise. They will measure C-reactive protein (CRP) and Interleukin-6 (IL-6) at rest and following peak exercise. They will examine whether this correlates with the increase in sympathetic nerve activity measured.

Intervention Type
Not Specified

Primary outcome measure
1. Level of muscle sympathetic nerve activity at rest is measured using microneurography at baseline
2. Level of MSNA during exercise is measured using microneurography following 6-12 minutes of ramped bike exercise tolerance testing
3. Hypoxic ventilatory response at rest will be calculated using spirometry, and ear oxygen saturation monitoring at baseline
4. Hypoxic ventilatory response during exercise will be calculated using spirometry, and ear oxygen saturation monitoring following 2 minutes of cycle ergometry at 30-40% VO2 peak and inhalation of medical grade nitrogen gas for 10-45 seconds
5. Change in the inflammatory biomarker IL-6 from rest to peak exercise will be measured using venous blood sampling at baseline and following 6-12 minutes of ramped exercise bike testing

Secondary outcome measures
1. Spontaneous sympathetic baroreflex sensitivity will be measured using microneurography at baseline and following 6-12 minutes of ramped bike exercise tolerance testing
2. Spontaneous parasympathetic baroreflex sensitivity will be measured using 3-lead electrocardiogram (ECG) recording at baseline
3. 24-hour ambulatory blood pressure and office blood pressure will be measured using a 24-hour blood pressure cuff and office blood pressure cuff, respectively, continuously and at baseline, respectively
4. Beat-to-beat blood pressure variability at rest will be measured using a beat-to-beat finger blood pressure recording at baseline
5. Change in blood pressure (BP) in response to handgrip exercise will be measured using an office blood pressure cuff following 2 minutes of handgrip exercise
6. Sympathetic-respiratory coupling at rest will be measured using microneurography and a respiratory belt at baseline
7. Maximal oxygen uptake (VO2 peak) will be measured using a 12-lead ECG and spirometry following 3 minutes of pre-exercise baseline rest
8. Ventilatory efficiency (VE/VCO2) slope will be calculated from minute ventilation (VE) measurements at rest and VCO2 measurements following 2 minutes of ramped bike exercise tolerance testing
9. Rating of perceived exertion will be measured using the Borg scale after 6-12 minutes of ramped bike exercise tolerance testing
10. Change in heart rate from peak exercise to recovery will be measured using 3-lead ECG recording within the first 2 mins of stopping exercise
11. Blood pressure response to hypoxia at rest will be measured using an office blood pressure

cuff at baseline
12. Blood pressure response to hypoxia during exercise will be measured using an automated brachial arm blood pressure cuff throughout cycle ergometry
13. Heart rate response to hypoxia at rest will be measured using 12-lead ECG monitoring at baseline
14. Heart rate response to hypoxia during exercise 12-lead ECG monitoring throughout 6-12 minutes of cycle ergometry and following inhalation of medical grade nitrogen gas for 10-45 seconds
15. Capillary blood lactate at rest will be measured using a capillary blood sample at baseline
16. Capillary blood lactate at end of moderate exercise will be measured using a capillary blood sample following 2 minutes of ramped exercise bike testing, and at the end of the cycle ergometry intermittent hypoxia protocol at around 33 minutes
17. Change in other inflammatory biomarkers, including C-reactive protein (CRP) from rest to peak exercise will be measured using venous blood sampling at baseline and following 6-12 minutes of ramped exercise bike testing
18. Change in catecholamines from rest to peak exercise will be measured using venous blood sampling at baseline and following 6-12 minutes of ramped exercise bike testing

Overall study start date
01/03/2021

Completion date
31/03/2023

Eligibility

Key inclusion criteria
All participants:
Aged 18-80 years

Post-COVID-19 Syndrome participants:
As per NICE guidelines https://www.nice.org.uk/guidance/ng188

Age and sex-matched controls@
1. Positive SARS-CoV-2 antibody test before vaccination, or a positive COVID-19 PCR antigen swab test
2. Asymptomatic or symptoms <4 weeks after COVID-19 infection

Participant type(s)
Mixed

Age group
Mixed

Lower age limit
18 Years

Upper age limit
80 Years

Sex

Both

Target number of participants
54

Total final enrolment
28

Key exclusion criteria
All participants:
1. Body mass index ≥35 kg/m²
2. Pregnancy/breastfeeding women
3. Ongoing requirement of oxygen therapy
4. Taking antihypertensive, nitrate, steroid or immunosuppressant medication or medication
5. Major illness e.g., cancer, inflammatory disease (including vasculitis) or receiving palliative care
6. History of organ transplantation or are candidates for organ transplantation at the time of screening
7. History of Chronic Fatigue Syndrome prior to COVID-19 infection
8. Diagnosed cardiovascular disease (including current non-benign arrhythmia, chronic heart failure)
9. History of major psychiatric disorder including bipolar disorders, schizophrenia, schizoaffective disorder, major depression.
10. Diagnosis of structural lung disease (such as COPD or pulmonary fibrosis)
11. Diagnosed renal disease
12. Congenital or acquired neurological conditions (including dementia), language disorders, repeated or chronic pain conditions (excluding menstrual pain and minor sporadic headaches)
13. Diabetes Mellitus
14. Symptoms of febrile illness 2 weeks before experiment
15. Excessive alcohol consumption (>28 units/week) or use of illicit drugs
16. History of smoking within 2 months
17. Inability to understand instructions given in English
18. Surgery under general anaesthesia within 3 months
19. History of stroke
20. Heart transplant
21. Coronary revascularisation
22. Haemodialysis or peritoneal dialysis
23. Participating in another study for an investigational medicinal product

Controls:
Symptoms lasting >4 weeks following acute, confirmed, COVID-19 infection

Date of first enrolment
01/11/2021

Date of final enrolment
28/02/2023

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Bristol Royal Infirmary
Marlborough Street
Bristol
United Kingdom
BS2 8HW

Study participating centre
UHBW Clinical Research Facility (Bristol)
60 St Michael's Hill
Bristol
United Kingdom
BS2 8DX

Sponsor information

Organisation
University of Bristol

Sponsor details
Research & Enterprise Division (RED)
1 Cathedral Square
Bristol
England
United Kingdom
BS1 5DD
+44 (0)1173940177
research-governance@bristol.ac.uk

Sponsor type
University/education

Website
http://bristol.ac.uk

ROR
https://ror.org/0524sp257

Funder(s)

Funder type
Charity

Funder Name
Above & Beyond

Funder Name
Elizabeth Blackwell Institute

Results and Publications

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

Intention to publish date
01/06/2023

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from the chief investigators, Dr Angus Nightingale (Angus.Nightingale@bristol.ac.uk).

Personal data will be stored for 15 years at the University of Bristol in electronic and hard copy. Access will be controlled by Dr Angus Nightingale who will continue to act as custodian. Dr Angus Nightingale 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. 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 the date is 15 years after the last patient last visit.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 2	09/09/2021	15/12/2021	No	Yes
Protocol file	version 1	06/07/2021	15/12/2021	No	No
HRA research summary			28/06/2023	No	No
Results article		19/02/2024	27/03/2024	Yes	No