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

PARTICIPANT INFORMATION SHEET

Chief Investigator: Dr. Angus Nightingale, School of Physiology, Pharmacology & Neuroscience, Faculty of Biomedical Sciences, University of Bristol, Bristol, BS8 1TD. Email: Angus.Nightingale@bristol.ac.uk

Academic clinical fellow: Dr Ahmed El-Medany, School of Physiology, Pharmacology & Neuroscience, Faculty of Biomedical Sciences, University of Bristol, Bristol, BS8 1TD.
Email: Ahmed.El-Medany@bristol.ac.uk Phone: 0117 331 1971

Please contact Ahmed El-Medany if you have any questions about this study.

For any complaints please contact: PSCT@uhbw.nhs.uk or research-governance@bristol.ac.uk

You are being invited to take part in a research study at the University of Bristol, which is looking at the longer-term effects of COVID-19 on the body's ability to control breathing and cardiovascular functions in men and women. This information sheet explains why the study is being done and what happens during the study. If you are interested in taking part in this study, it is important that you read this sheet so that you fully understand what taking part involves. Feel free to discuss this information with your family, friends and GP. You can, of course, also contact us if you have any questions about the study.

1. Why is this study being done?

Around 4 million individuals have tested positive for COVID-19 in the United Kingdom (UK) up to February 2021. Some people who have recovered from the immediate effects of COVID-19 describe ongoing symptoms including poor exercise tolerance, fatigue, chest pain, inappropriate increases in heart rate when standing, and dizziness, which are common symptoms of 'Post-COVID-19 Syndrome' (sometimes termed *long* COVID-19). These symptoms typically last for more than 12 weeks and can be severely debilitating. Currently, we do not know why people develop post COVID-19 syndrome; understanding the causes underlying it could help us develop new therapies to help people recover. Following COVID-19 infection, evidence shows that multiple systems in the body

may drive post COVID-19 syndrome; including the brain and poor function of parts of the nervous system that control heart rate and blood pressure.

The carotid body, a small organ in the carotid arteries (blood vessels in your neck – where your pulse can be found), monitors oxygen levels in the blood and keeps tight control over breathing, heart rate, and blood pressure. This organ has a high amount of an enzyme by which coronavirus enters the cells and causes infection. The carotid body is also sensitive to inflammation, which is triggered by local infection. It is possible that infection of the carotid body by coronavirus, and the inflammation that happens after the infection, drives ongoing symptoms such as breathlessness, inappropriate increases in heart rate, and dizziness in people experiencing post COVID-19 syndrome.

The aim the study is investigate whether the carotid body is involved in the development of post COVID-19 syndrome in men and women.

2. What will taking part involve?

One telephone consultation, and **two study visits** to the research laboratory situated in University Hospital Bristol's Clinical Research Facility (located in St Michaels Hospital in Bristol – full address is on page 7).

The duration of the **first study visit will be up to 3 hours**, and the **second study visit will be up to 2 hours and 15 minutes**.

a) **Telephone consultation:** we will ask you screening questions with regards to any recent positive test results for, or symptoms of, COVID-19, recent travel outside the UK, and whether you have been in contact with someone who has recently tested positive for COVID-19.

b) **Study visit one (up to 3 hours):** You will be asked to attend a visit to our laboratory in the Clinical Research Facility. The first part of the visit involves screening. This is where we go through your medical history and complete some screening tests to make sure you are safely able to take part in the study. All participants will complete the screening part of the visit. The in the second part of the study will involve an assessment of the nerve signals that control your blood pressure, using a technique called microneurography, whilst at rest and whilst carrying out hand-grip exercises. We will also ask you to complete an exercise test on a bike (10 mins)

c) **Study visit two (up to 2 hours and 15 mins):** This is where we will assess how your carotid body controls your breathing, heart rate and blood pressure at rest and during exercise. The participant pathway on page 7 shows what happens during each study visit.

Before you give your consent to participate

- After reading this information sheet, if you are interested in taking part please contact Ahmed El-Medany (details at end of sheet).
- We will then contact you to check your eligibility to take part. This will either be by email or over the phone. A member of the Research Team will call you and complete a brief pre-screening questionnaire with you. We will also be able to answer any questions you have about the study.
- If you are eligible to take part according to the pre-screening questionnaire, and you would like to take part, we will then arrange a time for you to come in for the study visit.
- When you arrive for the study visit, we will first explain the study to you and answer any questions you have.
- If you then decide you would like to take part in the study, we will ask you to sign a consent form.
- **Taking part in the study is completely voluntary and you can withdraw at any point, without giving a reason.**
- If you do decide to take part, you will be given a study ID number, which will be used to anonymously label your information.
- During consent, we will also ask for your permission to contact your GP to inform them about any abnormal results we find during the screening tests. This is optional and you are welcome to decline this. This will not affect your participation in the study.

Screening completed during study visit one:

After consent, we will then complete the following screening tests to ensure you are able to participate in the study. The screening tests may show that you are not eligible to participate in the study, in which case we will not be able to include you in this study and your involvement will end.

- Full, detailed medical history
- Height and weight measurements.
- 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 (ABPM) will be used to measure blood pressure over 24 hours. These are monitors that you wear for 24 hours, but you can freely move about and do normal daily activities. Participants will be issued with a 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 blood pressure levels. Activities completed during blood pressure readings will also be noted. This is to rule out any undiagnosed hypertension.
- 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.

Note: These screening tests and the Doctor's analysis of the ECG are for the purposes of the study only and should not be relied upon for the identification of undiagnosed medical conditions.

Experimental procedures

After the screening tests, we will then complete the following experimental procedures.

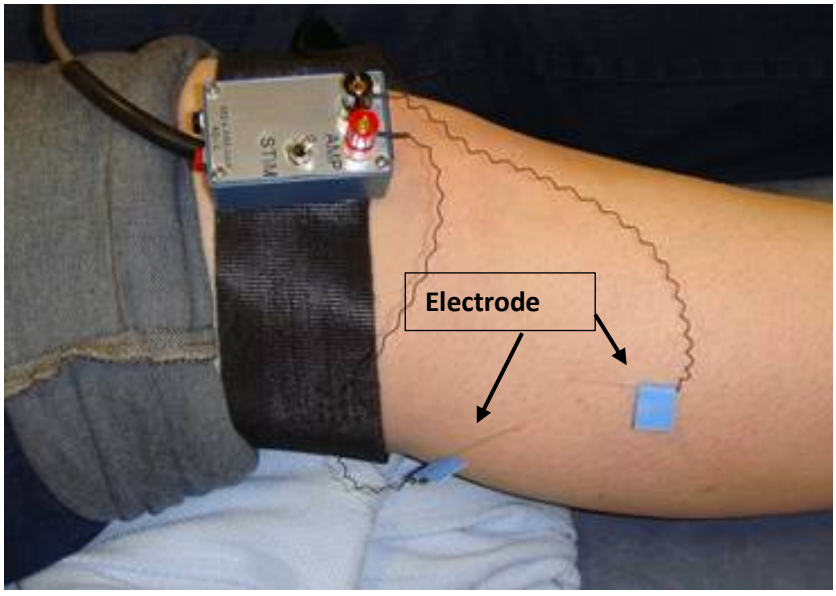
For everyone:

- Blood sample

We will take a blood sample to test for levels of inflammation and catecholamine hormones. Your blood sample will be tested at the Department for Clinical Biochemistry at the Bristol Royal Infirmary. After testing, the sample will be disposed of in accordance with the Human Tissue Authority Code of Practice. We will take 20 mL of blood in total (approximately 4 table spoons).

- Microneurography

This is a technique used to measure the activity of the nerves that control blood pressure (the sympathetic nerves). We use two small electrodes, similar to acupuncture needles (the tip of the electrode is the width of a human hair). One is inserted into a nerve in the lower leg called the peroneal nerve which runs down the side of your leg. 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. We will record your sympathetic nerve activity at rest and whilst you perform some handgrip exercise. Below is a picture of what the electrodes look like and where they are normal inserted.



- Handgrip exercise

Handgrip exercise involves squeezing a hand-held device. You will squeeze the device at 40% of your maximal voluntary contraction (the contraction generated with maximum effort). To work out 40%, we will ask you to first squeeze the device with maximum effort three times. The handgrip procedure will tell us how the changes in nerve activity, heart rate and blood pressure seen during exercise differ between people who have post COVID-19 syndrome and people who did not develop post COVID-19 syndrome after coronavirus infection.

- Physiological monitoring

Throughout the study we will record your heart rate 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).

- Exercise test on a stationary bike:

We will ask you to complete an exercise test which involves cycling on a stationary bike. This is to test your maximum exercise capability. The intensity of the exercise will increase every minute. You will be asked to exercise until you feel you cannot exercise anymore, and the test will be stopped. Usually, people exercise for about 10 minutes. You will be asked to wear a tight-fitting mask so we can monitor your breathing. We are doing this because post COVID syndrome affects exercise tolerance, and we want to measure whether this syndrome limits exercise capacity.

***On study day two**:*

- Carotid body testing (also called chemoreflex testing)

We will measure the ability of receptors (the carotid body) in the carotid arteries to adapt to changes in oxygen levels and blood flow. Throughout the test we will monitor your heart rate and rhythm, oxygen levels, and blood pressure. We will initially ask you to breath room air, then we will add nitrogen gas to the room air for 10-45 seconds. Nitrogen is a gas that is already present in room air. We are just adding some more to the air you breathe in, which reduces the amount of oxygen that you breathe in (only for very short periods of time). This will be repeated around 5-8 times, to achieve short-lived falls in your oxygen level and assess how your body increases your breathing rate to compensate. This will involve wearing a tight-fitting mask so we can monitor your breathing.

- Exercise and carotid body testing

After measuring the ability of your receptors (carotid bodies) in your neck to respond to changes in oxygen at rest, we will then test how well they can adapt during exercise. This is because your carotid bodies control your breathing response to exercise. You will be asked to exercise on a bike at an intensity which is 40% of your maximal exercise ability (which we tested on visit one). We will initially ask you to breath room air, then we will add nitrogen gas to the room air for 10-45 seconds. Nitrogen is a gas that is already present in room air. We are just adding some more to the air you breathe in, which reduces the amount of oxygen that you breathe in (only for very short periods of time). This will be repeated around 5-8 times, to achieve short-lived falls in your oxygen level and assess how your body increases your breathing rate to compensate. Again, this will involve wearing a tight-fitting mask so we can monitor your breathing

Note on incidental findings

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 you may be unable to take part in the rest of the study. We will inform you of any abnormalities in urine or ECG during the study visit. 24-hour blood pressure monitoring and testing of your blood sample takes place after the study visit. If abnormal results are found in your blood pressure or blood sample, we will contact you to inform you. We will also inform your GP of any abnormal results if you have given permission for this.

3. What do I need to do before the study visit?

There are several things we will ask you to do before you attend the appointment:

- Please wear or bring comfortable clothing. To make recordings from the nerve in your leg we will need one of your legs to be bare from mid-thigh down during the experiment. Therefore, you may wish to bring your own shorts or trousers that roll up comfortably.
- Please bring a suitable face covering, and wear this at all times whilst on the research site, unless you cannot wear one for a health or disability reason. We would ask that you please keep 2 metres apart from other people wherever possible.
- Pease report any new symptoms of cough, fever/high temperature, loss of taste and/or smell, shortness of breath, or contact with anyone who has had either a cough or fever, or tested positive for coronavirus, in the 14 days prior to your appointment.
- Please do not take painkillers such as aspirin, paracetamol, or ibuprofen for 24 hours before the study.
- However, <u>you should</u> take any medications that have been prescribed by your Doctor. Please let us know which medications you have taken on the day of the study.
- Please do not drink alcohol on the day of the study or the evening before the study.
- Please do not drink caffeine on the morning of the study.
- Please do not exercise on the day of the study or after 7pm the evening before the study.

Participant study pathway

Order of activities	Time taken (mins)
Pre-visit:	
1. **Invitation to study- letter given / sent to potential participants**	n/a
2. **Screening Telephone call - Relevant medical history taken**	~30
Visit 1: (total time of visit – up to 3 hours)	
3. Informed consent obtained	~15
4. Screening: electrocardiogram (measures heart rhythm)	~15
5. Screening: Urinary pregnancy test	~5
6. Screening: Height, weight, blood pressure measurement	~10
7. Handgrip familiarisation	~10
8. Measurement of nerve activity at rest and during handgrip exercise	~90
9. Break	~15-30
10. Exercise test on stationary bike (to maximum exercise capability)	~20
Leave with at home blood pressure monitor (called an ambulatory blood pressure monitor).	
Visit 2: (total time of visit – up to 2 hours and 15 mins)	
11. Carotid body testing at rest (changes in oxygen levels and measurement of breathing response)	~30
12. Break	~60
13. Carotid body testing during cycling exercise	~30

4. Where will the study take place?

This study will take place at the Clinical Research Facility, Bristol. The full address is:

Clinical Research Facility (CRF)
60 St Michael's Hill,
Bristol,
BS2 8DX
Tel (reception): 0117 331 1971
Google maps link: https://goo.gl/maps/7uPzXyyk4UiCXF6B9

5. Must I take part?

No. It is entirely your decision. If you are interested, please let us know by contacting us (details at the top and bottom of this sheet). Signing a consent form only happens

when you are completely happy that all your questions have been answered. You are also free to withdraw from the study at any time point, without having to give a reason.

6. What are the possible risks or side effects of taking part?

- Venepuncture for blood sample

During the study, a Research Nurse or Doctor will take a blood sample, which will be tested for levels of inflammation and catecholamine levels. You may experience mild discomfort during venepuncture and/or mild swelling at the site.

- Microneurography

Microneurography sometimes causes numbness or tingling (parathesia) 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, we use sterile, single-use electrodes and a 'no-touch' technique, after we have sterilised your skin.

- Handgrip exercise

There are no known risks associated with handgrip exercise .

- Physiological monitoring

Repeated blood pressure measurements may lead to mild discomfort and numbness in the arm or finger. There are no known risks associated with monitoring of heart rate or breathing.

- Carotid body 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. The face mask that is worn to monitor your breathing can cause some discomfort.

- Maximal exercise test

  The testing protocol involves exercise to exhaustion, therefore the inherent side effects of exhaustive exercise may be present including but not limited to: weakness, fatigue, vomiting, muscle soreness, and headache.

7. Who is able to take part in the study?

Men and women aged 18-80 years old who have previously tested positive for COVID-19, with a previous COVD-19 swab and/or antibody test, and with either: A) ongoing symptoms of breathlessness, dizziness, on inappropriate increased heart for over 12 weeks; or B) infective symptoms (cough, breathlessness, change in sense of smell or taste) for less than 4 weeks.

8. Who is not able to take part in the study?

For safety reasons, people with the following conditions/criteria are unable to take part in the study:

- Body mass index ≥35 kg/m^2

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

9. What are the possible benefits of taking part?

The results of this study will be of benefit to the NHS by identifying a novel 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 clarify its pathophysiology and guide future therapies 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 altered sense of taste or smell.

10. Will I receive any reimbursement for taking part in the study?

We will reimburse you for your travel to the Clinical Research Facility. Participants will receive a total reimbursement of up to £20 per study visit.

11. What happens if I do not want to carry on with the study?

You are free to withdraw from the study at any time, without giving a reason. Identifiable data already collected, with consent, will be retained and used in the study. A decision to withdraw at any time, or a decision not to take part, will not affect your ongoing medical care in any way.

12. What if something goes wrong?

In the unlikely event that you are harmed in this study, there are no specific compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action, but you may have to pay for it. This study will be sponsored by the University of Bristol. The University has Public Liability insurance to cover the liability of the University to research participants. If you have any general complaints regarding the study, please contact Dr. Angus Nightingale. Contact details are listed at the start of this information sheet.

13. Will my identity be protected/what happens to my personal data?

The University of Bristol is the sponsor for this study based in the United Kingdom. We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. The University of Bristol will keep identifiable information about you for 15 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally identifiable information possible. You can find out more about how we use your information by contacting a member of the study team (Academic Clinical Fellow: Dr Ahmed El-Medany, Ahmed.El-Medany@bristol.ac.uk; Chief Investigator: Dr Angus Nightingale, Angus.Nightingale@bristol.ac.uk or research scientist: Dr Emma Hart; emma.hart@bristol.ac.uk).

This study is a collaboration between the University of Bristol and University Hospitals Bristol and Weston NHS Foundation Trust. The staff working on this study may be employed by either organisation or have dual contracts with both. Study staff will collect information from you and your medical records for this research study in accordance with our instructions.

The University of Bristol and University Hospitals Bristol and Weston NHS Foundation Trust will use your name, date of birth and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from University Hospitals Bristol and regulatory organisations may look at your medical and research records to check the accuracy of the research study. Study staff will pass these details

to University Hospitals Bristol along with the information collected from you and your medical records. The only people in University Hospitals Bristol and Weston NHS Foundation Trust who will have access to information that identifies you will be people who need to contact you, such as study staff, or those auditing the data collection process. The people who analyse the information collected in the study will be members of the study team who will have access to your name, date of birth and contact details.

The University of Bristol and University Hospitals Bristol and Weston NHS Foundation Trust will keep identifiable information about you from this study for 15 years after the study has finished.

Anonymised data collected in this study may be used in future research. Should this occur, the data will be shared anonymously with other researchers. If in the course of the research, results are found that could be important for your personal health, study staff will contact you and, with your permission, your GP who may subsequently require further information. Your blood sample will be analysed by both study staff and University Hospitals Bristol staff in the Department of Clinical Biochemistry. Staff in Clinical Biochemistry will only have access to your study ID, age and sex.

14. What happens to my blood sample?

Whole blood is not stored but serum/plasma, which contains hormones, is stored. We will only analyse the sample for inflammation and catecholamine levels. We do not look at DNA. Samples will be stored in a locked freezer at a University of Bristol or a NHS site, with an ID number, your sex, and your age on the sample. Samples will be discarded after testing.

15. What happens at the end of the study?

The full results of the study will not be known until the last participant has been tested. If you are interested in receiving a summary of the results, please contact Ahmed El-Medany (contact details are given at the head and base of this sheet).

16. Who is funding the study?

Above and Beyond (charity raising money for Bristol Hospitals) is funding this research study, along with contribution from the University of Bristol's Elizabeth Blackwell Institute for Research.

17. Who has reviewed the study?

This study has been reviewed by the University of Bristol Research Design Service. All research in the NHS is looked at by an independent group of people called a Research Ethics committee to protect your safety, rights, well-being and dignity. This study has been reviewed and given a favourable opinion by the NHS [insert name] Research Ethics Committee.

18. Insurance

Insurance/Indemnity will be provided by the Sponsor, University of Bristol.

19. What do I do now?

If you are interested in taking part in the study, or have any questions, please contact Ahmed El-Medany by email or phone (details below).

Thank you for reading this information sheet and for considering whether you would like to take part in the study.

Contact information

If you are interested in taking part in the study, or have any questions, please contact:

Ahmed El-Medany

Email: Ahmed.El-Medany@bristol.ac.uk

Phone: 0117 331 1971