Henry Wellcome Laboratories for Integrative Neuroscience & Endocrinology
Dorothy Hodgkin Building
Whitson Street
Bristol BS1 3NY, U.K.

A pilot study of U-RHYTHM technology to investigate 24-hour catecholamine measurements

U-RHYTHM and catecholamines: A pilot study

Why have I been contacted?

We are seeking patients who are interested in taking part in a study investigating hormones and blood pressure.

You have been invited because you have had a recent diagnosis of phaeochromocytoma or paraganglioma and have either responded to an advertisement about our research, or have been referred by a member of your clinical team (doctors and other health professionals involved with your care).

You are invited to take part in a research study

Before you decide, it is important for you to understand why the research is being done and what it will involve.

Please take time to read the following information carefully and discuss it with friends, relatives, or your GP if you wish.

Please ask us if there is anything that is not clear or if you would like more information.

Take time to decide whether you wish to take part and remember that your participation is voluntary.

What is the purpose of this research study?

We want to learn more about how phaechromocytoma/paraganglioma are diagnosed and treated. These tumours can produce high levels of **catecholamine hormones** that can cause life threatening high blood pressure, sometimes leading to strokes and heart attacks. However, in many cases, it can be quite difficult to make the diagnosis, which can be confused with other causes of high blood pressure, for example.

The current standard of care for people suspected of having phaechromocytoma is to measure catecholamines in a blood sample, and/or in a sample of urine. In this study, we are testing a new method called **U-RHYTHM microdialysis** that will allow us to measure daily rhythms of catecholamines without having to take blood samples or disturb sleep. This study

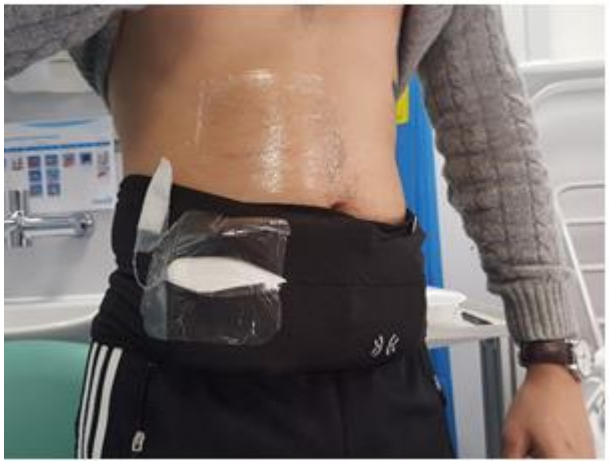
is a pilot trial because catecholamines have never been measured like this in humans before. We would like to use U-RHYTHM microdialysis in a group of people with phaeochromocytoma/paraganglioma to see how these rhythms are different from 'healthy' people who have normal blood pressure. We hope this will eventually lead to a better understanding of phaeochromocytoma/paraganglioma diagnosis and treatment.

What is U-RHYTHM microdialysis?

Microdialysis is a way of measuring hormones in the body without needing to take any blood. A very narrow sampling tube (less than the width of a pin head) with tiny holes ("pores") allows only very small molecules like hormones, to pass. In this study the tube is placed just beneath the skin of the stomach. For most people this is either not painful or only very briefly uncomfortable, so we don't use pain relief routinely. However, we can make the area numb with local anaesthetic if you would like it. Once the tube is in place, it cannot be seen or felt. A small pump is used to pump a sterile salty water solution very slowly through the tube (less than 1 teaspoon is pumped over 24 hours). Because of the way microdialysis works, there is no fluid 'lost' from your body during the sampling process.

Next, the sampling tube is connected to a sample collector, called U-RHYTHM. The U-RHYTHM devices stores samples collected from the sampling tube. The pump and U-RHYTHM are both kept in a stretchy belt, which is worn around the waist. Together, everything weighs less than a tin of baked beans. You can see a picture of the system below.

The sampling tube and pump are fully approved for use in humans (CE marked). The U-RHYTHM collector is a research device developed by our team. It does not have CE marking. However, it has already been successfully used in hundreds of healthy volunteers and patients and we know it is safe and well tolerated. The device stores hormone samples only – safety valves prevent any flow of liquid back toward the body.



The U-RHYTHM microdialysis automatic sample collection system.

The "U-RHYTHM" sample collector (top right box) and pump (top left box) are carried in a stretchy band around the waist (lower panel).

The sampling tube is just below the skin, on the lower part of the stomach, and cannot be seen in this picture.

body.

Do I have to take part?

Taking part is voluntary – it is up to you to decide. If you do decide to take part, we will ask you to sign a consent form and give you a copy of this information sheet and the consent form to keep. If you change your mind, you can withdraw at any time, even after the study has started. If you decide not to take part you do not have to give a reason, nobody will be upset.

Where do I come for the study visits?

The study will be carried out at the Medical Surgical Research Unit (MSRU), which is part of the Bristol Royal Infirmary hospital, in central Bristol. We will provide further details of how to get there and can reimburse you for your travel costs. If you live further away and or travelling to the study unit is difficult, we may be able to arrange local hotel accommodation.

What will happen to me?

This study consists of several study visits: A **screening** visit to check if you can participate in the study, followed by further **study** visits. The first set of 3 study visits occurs **before** any planned surgical treatment. If you consent for the **post-operative** part of the study, you would attend for another set of 3 study visits. We will write to your GP to let them know you are participating, provided you give us permission.

What happens first?

We will talk to you by phone and/or email with some general questions. This may include asking about any symptoms of or recent infection with COVID-19. We will then arrange the screening visit.

Screening visit

We will discuss with you all aspects of the study. If you would still like to be involved informed consent will be taken. Once you have consented, the researcher will take your medical history to make sure that you are fit enough to take part in the study. Other information including your date of birth, smoking status, height and weight will also be recorded, as these may affect the way your body produces hormones.

Who can take part in the study?

- Males and females, aged 16 or older
- A diagnosis of hormone secreting phaeochromocytoma/paraganglioma. If you give consent to participate, we will check your hospital records to confirm this.

Reasons you might not be able to take part

- If you are pregnant or breastfeeding
- If you have used illicit drugs recently, or intravenous drugs in the past

- If you are taking certain medications that could significantly interfere with the measurements in our study

Sampling set-up visit

You will come to our research facility at a time that suits you. We will place a glucose sensor on your arm or tummy. It is approximately the size of a £2 coin. This will measure your sugar levels for the rest of the study. The sensor is waterproof and is not painful. You will also be given a ring and/or a wristwatch to monitor your sleep, and movements, and may also record your skin temperature. These measurements occur automatically. We may provide you with a phone or tablet to download the information from the devices. Finally, we will give you some diaries to write down your sleep, food, and activity at different times during the study.

On the pre-operative study day

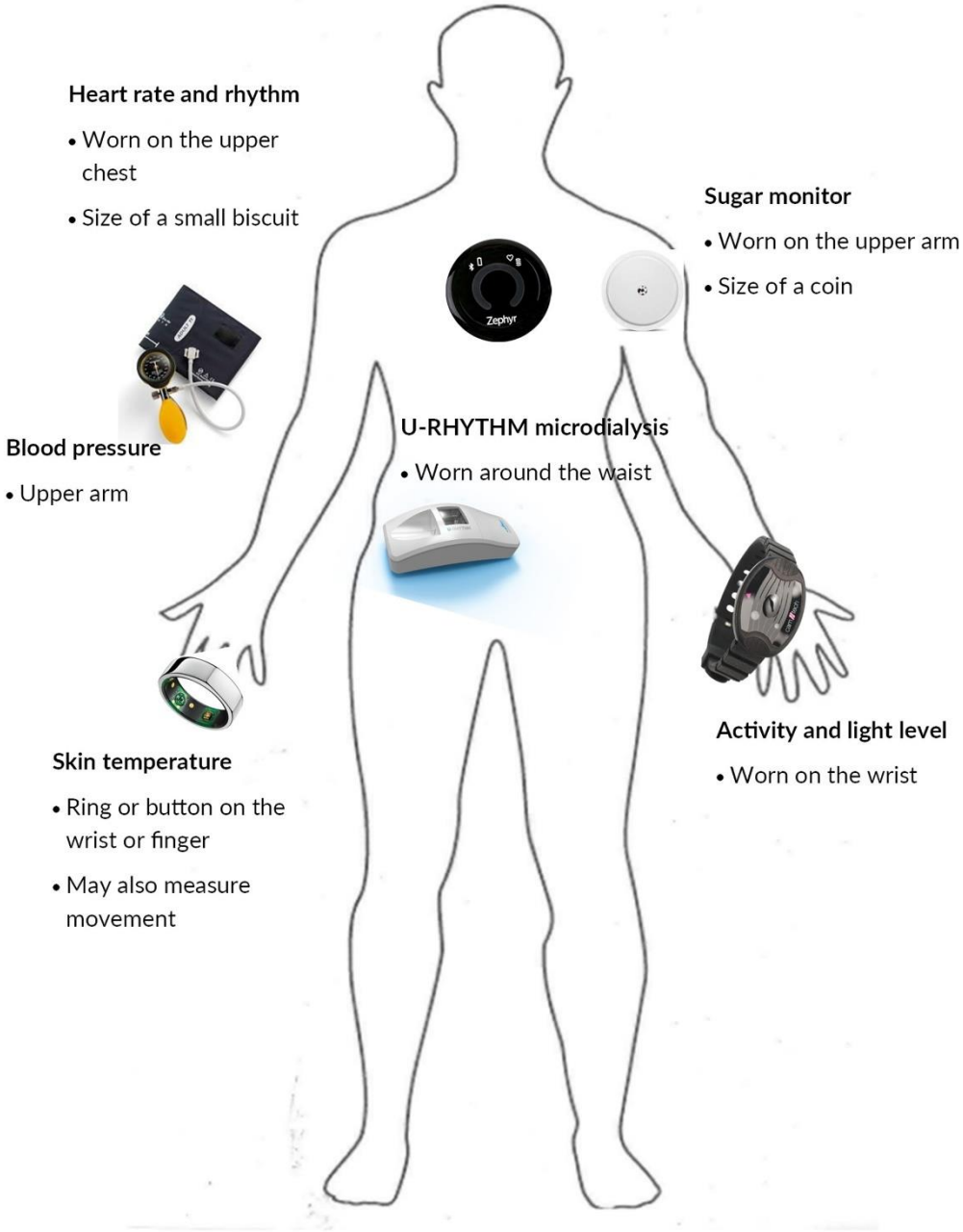
This visit will take about 1 hour and occurs 1 week after the "Sampling set-up visit". You will arrive at the research unit at a pre-arranged convenient time in the morning. Women of child-bearing age may be asked to perform a pregnancy test as pregnancy may affect the results of the study. You will also be asked to provide a urine sample to test for drugs of abuse (e.g. marijuana, opiates) as hormone levels can also be affected by different types of drugs and medications. We will take a fasting blood sample from a vein in your arm to check baseline hormone levels and then we will give you breakfast. We will give you a special bottle to collect urine in for the next 24 hours.

Next, we will connect the U-RHYTHM microdialysis sampling system. If you have a lot of hair growth around your belly button, we may need to shave this hair first to make sure we can safely and easily place the microdialysis sampling tube. The device will sample automatically without you having to do anything. We will place an arm cuff attached to a small machine that will automatically measure blood pressure. We may place 1-2 more small skin thermometers on your wrist and abdomen. We will place a monitor that records your heart rate and rhythm (ECG) to the front part of your chest, just below the collarbone, using sticky pads. The device is about the size of a biscuit. Once everything is set up you will be able to leave the research facility.

We will contact you, usually by phone to text message, about 12 hours later, to check everything is working properly.

During this part of the study (approximately 27 hours), you will not be able to have a shower/bath and we also ask that you do not participate in any sport. Apart from that you will be free to carry on your normal activities as you would on any other day.

Wearable devices in this study



At the end of the pre-operative study

The next day, usually between midday and 4pm, you will return to the Research Unit. We will remove all the devices and take your completed diaries. Finally, we will ask you to complete a questionnaire asking how you felt about using the U-RHYTHM microdialysis system.

Post-operative study visits

If you and your doctors decide you need an operation to remove your phaeochromocytoma/paraganglioma, we would like to contact you to arrange a further sampling study, usually within 3 months after the operation date. You do not have to consent to this, but if you agreed, the process would be the same as the pre-operative study (a call to confirm that you were still willing and eligible, followed by 3 sampling visits as described above).

Support

Throughout the study period, a researcher will be available to contact via telephone.

What are the potential side effects and risks of taking part?

Risk related to COVID-19

The University has strict guidelines around the conduct of research during the COVID-19 pandemic and we will continue if it is safe to do so. If we are advised that we must halt the study due to COVID-19, we will let you know immediately and you will still receive compensation.

We will need to ask you about COVID-19 symptoms at each study visit. If you become unwell during the study, you must tell us as soon as you can so we can help arrange for you to get tested if appropriate. You must wear a face mask during every study visit. Due to the nature of the study, there are times in which it will not be possible to maintain physical distance. Researchers will wear personal protective equipment including gloves, visors, and aprons during these times.

The remaining risk of participating in this study is very small

The microdialysis system is very safe and has been used in over 600 participants without any significant side effects. Like any other procedure there is a small risk of discomfort during insertion of the microdialysis sampling tube. There is theoretically a small risk of infection and allergic reaction. This risk is considered to be extremely low as we use an aseptic (clean) method, and the tube is made from low allergy material. If infection or allergy is suspected, we will immediately remove the probe and stop the study. About 2 in every 100 people report minor bruising or slight discomfort at the site where the sampling tube is placed in the skin.

Taking a blood sample from the vein can be slightly uncomfortable, and occasionally can cause minor bruising or bleeding at the site. Very occasionally people can faint while having a blood test – we will ask you about this before the test.

The continuous glucose monitoring system (CGMS) is very safe and we do not believe it will cause anything other than possible very minor discomfort at the time that the sensor is placed on the skin. CGMS systems are used as part of routine medical care for people with diabetes.

We don't believe that there will be any risk associated with the chest-worn heart monitor, watch, ring, or other wearable devices.

Unexpected abnormal blood tests or other results

If during the study your blood results or other tests reveal an abnormality, we will arrange a meeting with you to explain these results. We will ask you if you wish for this information to be sent to your GP and if appropriate, we may recommend an appointment with your GP or other appropriate person or service.

If, at any time during the study, new information becomes available that could affect your participation, the researchers will talk to you about this and discuss whether you want to continue in the study.

Will I receive any reimbursement for my time?

Yes. We realise that this study requires a lot of commitment on your behalf. We can provide a fee as compensation for inconvenience, travel expense, and potential time away from work.

The payment will be up to £250 if you complete the entire study. If you attend the screening appointment but are not eligible to participate, we will offer you £20 in compensation for your time.

What will happen to my samples?

Urine collected for pregnancy and illicit drug testing will not be kept (the sample will be discarded immediately after testing).

Your blood sample will be split into 2 parts. One part will be tested at the Bristol Royal Infirmary NHS laboratory, and no left-over sample is retained. The rest of the blood sample, a sample of urine from the 24-hour collection, and your U-RHYTHM samples will be stored in a freezer within the University of Bristol and then sent away to our collaborators for analysis. All samples will be labelled with a study code that contains no personal identifying information.

Residual parts of these samples may be kept for up to 5 years in case analyses need to be repeated or if additional results are required to successfully complete the study. The samples could be used in future ethically approved research studies if you give consent.

If you decide to withdraw from the study, you can ask for your samples to be destroyed even if they have not already been analysed, or for any information obtained from analysing your samples to be destroyed.

What happens to the other data collected during the study?

We will need to use information from you and from your medical records for this research project. This information will include your NHS number, name and contact details which will be held by the research site. People will use this information to do the research or to check your records to make sure that the research is being done properly.

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

With your permission, we will write to your GP to let them know that you have participated in our research. We won't share any of the results or any other details with your GP unless you ask us to.

We will collect information in both paper and electronic form

Information about your participation will be recorded on paper Clinical Record Forms (CRFs). These do not contain any personal identifying information. CRFs forms are stored securely in a locked office within the University of Bristol.

Results and other data collected from these forms may be transferred to password-protected electronic forms hosted on secure servers by the University of Bristol.

Data from all wearable devices will be stored securely

Information about your sleep and activity is stored in the memory of the devices. This data will be downloaded and stored in anonymised form in a secure location on a password protected computer, hosted by the University of Bristol. No personal identifying information will be stored on the watch or within the data stored on the computer.

Anonymised information about your sugar levels, heart rate, temperature and other parameters are also recorded within electronic device memory. During and after the sampling sessions are complete, this information will be downloaded from the device either directly to study computers or stored anonymously and securely on an internet server. Information is encrypted at the time of transfer from the device.

Your data is secure and confidential

The University of Bristol is the sponsor for this study based in the United Kingdom. We will be using information from you and/or your medical records 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. Researchers at the University will keep identifiable information about you for 5 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 the personal data of research participants, and how the University ensures information is handled appropriately, at these webpages:

http://www.bristol.ac.uk/secretary/data-protection/policy/research-participant-fair-processing-notice/

http://www.bristol.ac.uk/secretary/information-governance/

Our researchers will keep your name, NHS number (where applicable) and contact details confidential and will not pass this information to any third parties or those unconnected to the study. Occasionally the University of Bristol may arrange for regulatory organisations to review your medical and research records to check the accuracy of the research study. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details.

Future research

If you have consented, the information about your health and care may be provided to researchers running other research studies in the same organisation and in other organisations. These organisations may be universities, the NHS, or companies involved in health and care research in this country or abroad.

Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research. This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of health and care research and cannot be used to contact you or to affect your care. It will not be used to make decisions about future services available to you, such as insurance.

What are my responsibilities?

We would like you to let us know of any changes in your health or any medication you may take. You need to complete the study tasks and attend your appointments as per the agreed time.

How will I benefit from participating?

You will not benefit directly from taking part in this research study and your participation is voluntary. However, we hope the information from this research will eventually lead to better treatment of high blood pressure.

How will the results of this research be used?

The results of this study will be published in scientific journals and presented at medical meetings. A meeting of all research participants may be arranged to discuss our findings, and

we will offer to share the results with you on completion of the study. Information will also posted on our project website at https://biorhythm.blogs.bristol.ac.uk/.

Who is organising and funding the research?

The Henry Wellcome Laboratories for Integrative Neuroscience (part of the University of Bristol) is carrying out the research in collaboration with clinical colleagues at University Hospitals Bristol Weston NHS Foundation Trust. The research is sponsored by the University of Bristol and is being funded by the Wellcome Trust

It has full approval from the NHS Research Ethics Board. Funding pays the salaries of some of the research staff and other direct costs of doing the research. Researchers are not receiving any payments other than their usual salaries.

What do I do now?

Thank you for considering taking part in this study. If, after reading this information, you would like more information or decide that you would like to take part, please contact one of the study researchers.

Contact details

Email

microdialysis@bristol.ac.uk

Call and speak to one of the study researchers

Dr. Thomas Upton	0117 455 1408
Prof. Stafford Lightman	0117 331 3167

If you would like more information

You can find out more about how we use your information by visiting www.hra.nhs.uk/information-about-patients/, speaking to one of our research team, or contacting the Data Protection Officer at University of Bristol by email data-protection@bristol.ac.uk or phone 0117 45 56325

If you would like to discuss the science behind the study with an independent person, please phone Prof. Lightman's secretary on 0117 331 3167.

You can also find out more information about U-RHYTHM microdialysis at www.u-rhythm.co.uk, and at the ULTRADIAN study website www.ultradian.net

Patient Advice and Liaison Service (PALS)

The Patient Advice and Liaison Service (PALS) offers confidential advice, support and information on health-related matters. They provide a point of contact for patients, their families, and their carers.

PALS provides help in many ways. For example, it can:

- help you with health-related questions
- help resolve concerns or problems when you're using the NHS
- tell you how to get more involved in your own healthcare

You can contact PALS at the Bristol Royal Infirmary by

Email: PSCT@uhbw.nhs.uk

Telephone: 0117 342 1050

If you have concerns

The Research Governance team at the University of Bristol is an independent contact if you wish to make a complaint or voice any concerns about this study.

Email: research-governance@bristol.ac.uk

Call: (0117) 42 84051

Write to: Research and Enterprise Development (RED),

University of Bristol,

1 Cathedral Square,

Bristol BS1 5DD

The University of Bristol, as the study Sponsor, operates a Clinical Trial protection scheme, which operates in respect of the University's legal liabilities for any injury arising specifically as a consequence of your participation in the study. Additionally, the standard provision of the NHS Indemnity Scheme will operate in respect of the provision of clinical treatment.