ISRCTN13479086 https://doi.org/10.1186/ISRCTN13479086

Investigating how high blood pressure develops differently in men and women

Submission date
03/05/2019

Recruitment status
No longer recruiting

Registration date
28/06/2019

Overall study status
Completed

Last Edited
09/04/2021

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
Individual risk of developing high blood pressure (hypertension) depends on both age and sex. Young women are less likely to develop hypertension than young men. Previous research suggests that this may be because the nervous system regulates blood pressure differently in men and women. It is thought that in premenopausal women, female sex hormones make it harder for the nerves that control blood pressure (the sympathetic nerves) to raise blood pressure. As a result, most young women are protected against hypertension by their hormones. However, despite this protection, a number of young women do develop hypertension, the cause of which is unknown. The sympathetic nerves may be affected by female sex hormones differently in these women. Furthermore, the risk of women developing hypertension increases after the menopause. This may be because the sympathetic nerves find it easier to raise blood pressure when levels of female sex hormones are lower. This study aims to investigate why some premenopausal women develop hypertension and why risk of hypertension increases after the menopause, by measuring how active the sympathetic nerves are using a technique called microneurography.

Who can participate?
People with high and normal blood pressure across four different groups: premenopausal women, younger men, postmenopausal women and older men.

What does the study involve?
Sympathetic nerve activity is recorded at rest and during brief periods of handgrip exercise. Additionally, in younger women and men, sympathetic nerve activity is recorded during an infusion of the beta-blocker drug propranolol. The study involves one visit to the Clinical Research and Imaging Centre (Bristol), lasting about 5 hours for younger participants and 3 hours for older participants.

What are the possible benefits and risks of participating?
There is no therapeutic benefit to taking part in the study. However, this study is observational research and participants with hypertension may benefit from taking part by knowing more about their disease. The risk associated with conducting screening procedures is identification of incidental findings. Should abnormalities in ECG, blood pressure monitoring, urine analysis or

pregnancy testing be identified, the participant will be informed, as they may be unable to participate in the rest of the study. With the participant's permission, their GP will be informed of the findings in writing and the participant will be encouraged to see their GP about the results.
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, the researchers use sterile, single-use electrodes and a 'no-touch' technique after they have sterilised the skin.
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.
There are no known risks associated with handgrip exercise, or use of ultrasound to measure either blood flow to the arm (vascular ultrasound) or blood pumped by the heart (echocardiography).
During the study a Research Nurse or Doctor will take a blood sample, which will be tested for levels of sex steroid hormones. Participants may experience mild discomfort during venepuncture and/or mild swelling at the site.
Propranolol has side effects including:
Uncommon (1 to 10 patients in 1000):
1. Especially at start of treatment: Tiredness, vertigo, dazedness, confusion, nervousness, sweating, headache, sleep disorders, depressive mood, nightmares, hallucinations, false sensations (paraesthesia), feeling of cold in the limbs.
2. Transient gastrointestinal symptoms (diarrhoea, constipation, nausea, vomiting)
3. Allergic skin reactions (redness, itching, exanthema) and hair loss
4. Increased fall in blood pressure, severe slowing of heart rate (bradycardia), convulsive, short-term loss of consciousness (syncope), heart pounding (palpitations), atrio-ventricular conduction disorders or increase in heart muscle weakness (heart failure).
Rare (1 to 10 patients in 10,000):
1. A clinical picture similar to that of myasthenia gravis (pathological muscle weakness or tiredness)
2. Dry mouth
3. Inflammation of connective eye tissue (conjunctivitis), reduced tear flow (look for this in wearers of contact lenses)
4. Small areas of bleeding in the skin and mucus membranes (purpura) or reduction in the thrombocyte count (thrombocytopenia)
5. Occurrence of previously undetectable sugar disease (latent diabetes mellitus) or worsening of already existing sugar disease.
Very rare (fewer than 1 patient in 10,000):
1. Increase in existing myasthenia gravis
2. Outbreak of psoriasis vulgaris, increase in symptoms of the disease, scaly skin-like (psoriasiform) skin rashes
3. Increase in seizures in pain occurring convulsively in the region of the heart (angina pectoris), increase in the symptoms of peripheral blood flow disorders, including intermittent limping (intermittent claudication) and spasms of the arteries in the fingers (Raynaud's syndrome)
4. In long-term treatment, joint diseases (arthropathy), in which one joint (monoarthritis) or several (polyarthritis) may be affected
5. Libido and potency disorders
6. Elevation of liver enzymes (GOT, GPT) in the blood
7. In severe kidney function disorders: worsening of kidney function. Kidney function should be appropriately monitored during treatment with Dociton.
Frequency unknown:
1. Hypoglycaemia including hypoglycaemic seizures
Additionally, there is a risk of allergic reaction to the propranolol.

Propranolol will be given by a cannula. This is a small, flexible tube inserted with a needle into a vein in the arm by a Research Nurse or Doctor. Participants may experience mild discomfort during fitting of the cannula.

Where is the study run from?
1. University of Bristol (UK)
2. University Hospitals Bristol NHS Foundation Trust (UK)
3. NHS Bristol, North Somerset and South Gloucestershire CCG (UK)

When is the study starting and how long is it expected to run for?
August 2017 to April 2022

Who is funding the study?
British Heart Foundation (UK)

Who is the main contact?
Zoe Adams
zoe.adams@bristol.ac.uk

Contact information

Type(s)
Scientific

Contact name
Miss Zoe Adams

Contact details
Clinical Research and Imaging Centre
University of Bristol
60 St Michael's Hill
Bristol
United Kingdom
BS2 8DX
+44 (0)117 342 1513
zoe.adams@bristol.ac.uk

Type(s)
Scientific

Contact name
Dr Emma Hart

Contact details
G28 Biomedical Sciences Building
University of Bristol
University Walk
Bristol
United Kingdom

BS8 1TD
+44 (0)117 3311472
emma.hart@bristol.ac.uk

Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
40105

Study information

Scientific Title
Sex differences in the role of sympathetic nerve activity in the development of hypertension in humans

Study objectives
This study aims to investigate the role of sympathetic nerve activity in the development of hypertension in some premenopausal women, as well as in some postmenopausal women.

The main objectives are:
1. To assess whether premenopausal women with high blood pressure have greater levels of sympathetic nerve activity and sympathetic vascular transduction (measure of how well signals from sympathetic nerves are able to cause narrowing of blood vessels) compared to women of a similar age with normal blood pressure.
2. To assess whether postmenopausal women with high blood pressure have greater levels of sympathetic nerve activity and sympathetic vascular transduction compared to women of similar age with normal blood pressure, and to men of a similar age with high blood pressure.

Secondary objectives are:
1. To assess whether the role of certain blood vessel receptors (vascular beta-adrenergic receptors) in affecting regulation of blood pressure by the sympathetic nerves is different in premenopausal women with high blood pressure compared to those with normal blood pressure.
2. To assess whether A) level of sympathetic nerve activity and B) sympathetic vascular transduction (ability of signals from sympathetic nerves to cause narrowing of blood vessels) affect changes in blood flow that occur during/after handgrip exercise in premenopausal women with high blood pressure.

Hypotheses of primary objectives:
1. Null: There is no difference in the level of sympathetic nerve activity and sympathetic vascular transduction (the ability of signals from sympathetic nerves to cause narrowing of blood vessels) between premenopausal women with high blood pressure and premenopausal women with normal blood pressure. Alternative: There is a difference in the level of sympathetic nerve

activity and sympathetic vascular transduction between premenopausal women with high blood pressure and premenopausal women with normal blood pressure.
2. Null: There is no difference in the level of sympathetic nerve activity and sympathetic vascular transduction between postmenopausal women with high blood pressure and postmenopausal women with normal blood pressure. Alternative: There is a difference in the level of sympathetic nerve activity and sympathetic vascular transduction
between postmenopausal women with high blood pressure and postmenopausal women with normal blood pressure.

Hypotheses of secondary objectives:
1. Null: There is no difference in the level of sympathetic vascular transduction during block of the beta-adrenergic receptors (propranolol infusion) between premenopausal women with high blood pressure and premenopausal women with normal blood pressure. Alternative: There is a difference in the level of sympathetic vascular transduction
during block of the beta-adrenergic receptors (propranolol infusion) between premenopausal women with high blood pressure and premenopausal women with normal blood pressure.
2. Null: A) There is no difference in the vasodilator response (widening of blood vessels) to handgrip exercise between premenopausal women with high blood pressure and postmenopausal women; B) There is a difference in the vasodilator response to handgrip exercise in premenopausal women with high blood pressure before and during
block of beta-adrenergic receptors (propranolol infusion). Alternative: A) There is a difference in the vasodilator response (widening of blood vessels) to handgrip exercise between premenopausal women with high blood pressure and postmenopausal women; B) There is no difference in the vasodilator response to handgrip exercise in
premenopausal women with high blood pressure before and after block of beta-adrenergic receptors (propranolol infusion).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 29/11/2018, Southwest - Frenchay Research Ethics Committee (Level 3, Block B, Whitefriars, Lewins Mead, Bristol BS1 2NT; Tel: +44 (0)207 1048 045; Email: nrescommittee.southwest-frenchay@nhs.net), ref: 18/SW/0237

Study design
Observational; Design type: Case-controlled study

Primary study design
Observational

Secondary study design
Case-control 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
Hypertension

Interventions
Participants with high blood pressure will be recruited from the Hypertension Clinic at the Bristol Heart Institute. We will also apply for the study to be included in the NIHR Clincial Research Network Portfolio for the West of England, so that participants in all groups may be recrutied via GPs through the primary care research network in the West of England. Participants with normal blood pressure, as well as postmenopausal women/older men with high blood pressure, will be recruited via posters and leaflets displayed around the University of Bristol and public spaces in the local community (e.g. local shops, cafes, community centres and GP reception areas); study adverts placed in community/University newsletters; study adverts emailed through University Faculty email; and information on the CRIC Bristol Website. Permission will be gained before posters/leaflets are left in public spaces and before adverts are emailed through University email. The study will also be publicised at blood pressure awareness events run by our group. Individuals in all participant groups that have previously taken part in mechanistic studies within our research group may be invited to take part.

Study duration: Participants will complete one study visit at CRIC Bristol, lasting approximately 5 hours for premenopausal women and younger men, and 3 hours for postmenopausal women and older men.

The following study schedule applies to all participants:
Pre-visit:
1. In the hypertension clinic participants will be given a leaflet containing the contact details of study staff.
2. If an individual expresses interest in taking part in the study, a screening telephone conversation will be arranged, during which study staff will ask about key exclusion criteria. A study visit date will then be arranged.

Study visit:
1. Explanation of study, opportunity to ask questions, informed consent received (20-30 min).
2. Screening procedures: medical history questionnaire; Office blood pressure and heart rate measurements; 12-lead electrocardiogram (ECG); Urine dipstick and pregnancy test for premenopausal women; Height and weight measurements (30-40 min). Participants will squeeze a hand-held handgrip dynamometer with maximal effort three times to provide a value of maximal voluntary contraction (used to calculate 40% for later handgrip exercise).
3. Venous blood sample obtained for testing of levels of sex steroid/catecholamine hormones (10 min). For premenopausal women and younger men only a cannula will also be fitted (inserted into a vein in the arm) (5-10 min).
4. Physiological monitoring equipment (3-lead ECG for heart rate, Finapres finger cuff for blood pressure and respiratory belt to monitor breathing) are set up (10 min).
5. Echocardiography: An ultrasound probe will be placed to the chest to measure the volume of blood pumped by the heart at each beat (15 min).
6. Microneurography: electrodes will be put into place (one into the peroneal nerve at the fibular head and one into the surface of the skin nearby). The position of the electrodes will be adjusted in order to record the nerve signals of interest (muscle sympathetic nerve activity). It can take up to one hour to search for a suitable site. Resting nerve activity will then be recorded for 10

minutes.
7. Handgrip exercise: The participant will squeeze a hand-held device at 40% of their maximal voluntary contraction for 2 minutes. Blood flow to the forearm will be monitored before, during and for up to 5 minutes after handgrip exercise using ultrasound (probe held over the brachial artery in the upper arm).
This is the end of the study for postmenopausal women and older men - the electrodes and other equipment are removed. For premenopausal women and younger men, the study schedule continues as follows:
8. An infusion of the beta-blocker drug propranolol is started (0.15 mg/kg bolus administered manually over 10 minutes, then 0.004 mg/kg/min maintenance infusion administered by infusion pump for ~30 min).
9. Muscle sympathetic nerve activity is recorded for 5 minutes.
10. Handgrip exercise with ultrasound is repeated (same procedure as above).
11. Echocardiography is repeated (same procedure as above).
This is the end of the study for premenopausal women and younger men - the electrodes, cannula and other equipment are removed.
After the study: All participants are issued with an ambulatory blood pressure monitor to wear at home for 24 hours.
Premenopausal women and younger men wait at CRIC for one hour to check for side effects of propranolol.

Intervention Type
Other

Primary outcome measure
1. Level of sympathetic nerve activity measured using microneurography at baseline
2. Level of sympathetic vascular transduction measured using microneurography & vascular ultrasound at baseline

Secondary outcome measures
1. The change in sympathetic vascular transduction measured using microneurography & vascular ultrasound at baseline and during block of beta-adrenergic receptors (during propranolol infusion)
2. The vasodilator response (increase in blood flow) to handgrip exercise measured using vascular ultrasound at baseline

Overall study start date
11/08/2017

Completion date
30/04/2022

Eligibility

Key inclusion criteria
1. Aged 18-75 years
2. Hypertensive patients: Office blood pressure ≥ 140/90 mmHg and daytime ambulatory blood pressure ≥135/85 mmHg
3. Normotensive participants: Office blood pressure < 140/90 mmHg and daytime ambulatory

blood pressure < 135/85 mmHg
4. Postmenopausal women: No period for at least 12 months and not using hormonal contraception (NICE, 2015)

Participant type(s)
Mixed

Age group
Adult

Lower age limit
18 Years

Upper age limit
75 Years

Sex
Both

Target number of participants
Planned Sample Size: 148; UK Sample Size: 148

Key exclusion criteria
1. Secondary causes of hypertension
2. Body mass index > = 30 kg/m2
3. Oophorectomy (removal of ovaries) prior to onset of natural menopause
4. Pregnancy/breastfeeding women
5. Taking hormone replacement therapy
6. Taking nitrate, steroid, anti-coagulant or immunosuppressant medication or medication as part of a clinical trial
7. Major illness e.g. cancer, inflammatory disease (including vasculitis) or receiving palliative care
8. Diagnosed cardiovascular (including arrhythmia), respiratory (including asthma), psychiatric, renal or ophthalmic disease
9. Congenital or acquired neurological conditions (including dementia), language disorders, repeated or chronic pain conditions (excluding menstrual pain and minor sporadic headaches)
10. Diabetes
11. Symptoms of febrile illness less than a week before experiment
12. Excessive alcohol consumption (> 28 units/week) or use of illicit drugs
13. Needle phobia
14. Inability to understand instructions given in English
15. Mild, moderate or severe persistent asthma (due to potential broncho effects of a systemic beta-blocker)

For premenopausal women and younger men only (relating to the propranolol infusion):
1. Individuals with any of the conditions listed in the instructions for use document of Dociton solution of injection (propranolol hydrochloride) in which Dociton must not be used:
1.1. Hypersensitivity to propranolol/beta-blockers or other ingredients in Dociton
1.2. Heart muscle weakness
1.3. Shock
1.4. Grade II or III AV block
1.5. Sick sinus syndrome

1.6. Sino-atrial block
1.7. Bradycardia (resting pulse < 50 beats/min)
1.8. Hypotension
1.9. Acidosis
1.10. Taking MAO inhibitors
1.11. Late stage peripheral blood flow disorders
1.12. tendency towards bronchial spasm e.g. bronchial asthma.
2. Individuals with any condition listed in the instructions for use document in which Dociton should be used with caution:
2.1. Grade I AV block
2.2. Diabetes mellitus
2.3. Lengthy strict fasting and severe physical stress
2.4. Phaeochomocytoma
2.5. Impaired liver or kidney function
2.6. Individual/family history of psoriasis
2.7. History of severe hypersensitivity reaction or receiving treatment to weaken allergic reactivity).
3. Individuals taking/recently taken any medication listed in the instructions for use document as being affected by Dociton or affecting Dociton:
3.1. Insulin/oral antidiabetics
3.2. Other blood pressure-lowering medications, nitroglycerin, diuretics, vasodilators, tricyclic antidepressants, phenothiazines, barbituates
3.3. Calcium antagonists of the nifedipine type
3.4. Calcium antagonists of the verapamil or diltiazem type
3.5. Antiarrhythmics, e.g. disopyramine or others
3.6. Cardiac glycosides
3.7. Reserpine
3.8. Alpha-methyldopa
3.9. Guanfacine, clonidine
3.10. Adrenaline, noradrenaline
3.11. Monoamine oxidase inhibitors
3.12. Indometacin
3.13. Narcotics
3.14. Peripheral muscle relaxants e.g. suxamethonium, tubocurarine
3.15. Cimetidine
3.16. Also quinidine and/or propafenone, rifamycin, theophylline, warfarin, thioridazine, nifedipine, nisoldipine, nicardipine, isradipine, lacidipine (possible interactions with propranolol affecting breakdown of active substances of both))

Date of first enrolment
22/02/2019

Date of final enrolment
28/02/2021

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
University of Bristol
Clinical Research and Imaging Centre
60 St Michael's Hill
Bristol
United Kingdom
BS2 8DX

Study participating centre
University Hospitals Bristol NHS Foundation Trust
Marlborough Street
Bristol
United Kingdom
BS1 3NU

Study participating centre
NHS Bristol, North Somerset and South Gloucestershire CCG
South Plaza
Marlborough Street
Bristol
United Kingdom
BS1 3NX

Sponsor information

Organisation
University of Bristol

Sponsor details
Research Governance Team
Trinity Street
College Green
One Cathedral Square
Bristol
England
United Kingdom
BS1 5DD
+44 (0)117 4284091
research-governance@bristol.ac.uk

Sponsor type

University/education

ROR
https://ror.org/0524sp257

Funder(s)

Funder type
Charity

Funder Name
British Heart Foundation; Grant Codes: FS/17/38/32935

Alternative Name(s)
the_bhf, The British Heart Foundation, BHF

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
1. Peer-reviewed scientific journals
2. Conference presentation
3. Results of the study may be presented at public science events

Intention to publish date
30/04/2023

Individual participant data (IPD) sharing plan
Personalised study data will be maintained at the University of Bristol in paper and/or electronic format. Both paper and electronic records will be kept in a locked cupboard in a locked room in a department with security-limited access. Access to the records is restricted to researchers working on the study. Password protection will be used for electronic data and, for the purposes of data analysis, anonymised data will be held on an encrypted flash drive, to be locked as above when not in use. No identifiable data will be stored on laptop computers or portable electronic devices. Analysis will take place by the study team led by Dr Emma Hart and collaborators (using anonymised data). Data will be collected and retained in accordance with the Data Protection Act 1998. Study documents (paper and electronic) will be retained in a secure location during

and after the trial has finished. 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. The Chief Investigator, Dr Emma Hart, 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. Personal data will be stored for 15 years at the University of Bristol in electronic and hard copy. Access will be controlled by Dr Emma Hart who will continue to act as custodian.

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