You are invited to take part in a hypertension (high blood pressure) study. Whether or not you take part is your choice. If you don’t want to take part, you don’t have to give a reason, and it won’t affect the care you receive. If you do want to take part now, but change your mind later, you can pull out of the study at any time.

This Participant Information Sheet will help you decide if you’d like to take part. It sets out why we are doing the study, what your participation would involve, what the benefits and risks to you might be, and what would happen after the study ends. We will go through this information with you and answer any questions you may have. You do not have to decide today whether or not you will participate in this study. Before you decide you may want to talk about the study with other people, such as family, whānau, friends, or healthcare providers. Feel free to do this.

If you agree to take part in this study, you will be asked to sign the Consent Form on the last page of this document. You will be given a copy of both the Participant Information Sheet and the Consent Form to keep. This document is 10 pages long, including the Consent Form. Please make sure you have read and understood all the pages.

**WHAT IS THE PURPOSE OF THE STUDY?**

Hypertension is a common condition that increases the risk of a number of serious health conditions, such as stroke and heart failure. In most patients with hypertension the underlying cause is unclear. Also, blood pressure often stays high despite drug treatment. However, there is now new evidence that specialised receptors in the body that respond to changes in blood gas levels (i.e., chemoreceptors), are over-active in hypertension. This leads to worsening symptoms, reduced quality of life and poor outcomes. There are currently no treatments available that are non-invasive and free from harsh side effects, despite the potential clinical benefit of targeting these chemoreceptors. The purpose of the present study is to investigate new ideas about what causes high blood pressure to help the design of new treatments that are more targeted to the cause.

In this study we want to find to find out if short-term supplementation of vitamin B6 (pyridoxine) reduces the activity of these chemoreceptors, thus lowering blood pressure.

This study is funded by the University of Auckland. It is being conducted by A/Prof. James P Fisher (Lead Investigator, University of Auckland), Prof. Julian Paton (University of Auckland), Dr. Matt Dawes (University of Auckland and Auckland District Health Board), Dr. Ana Luiza Carrari Sayegh (Postdoctoral Research Fellow, University of Auckland), Dr. Mickey Fan...
This study [20/NTA/29] has been reviewed and approved by the Health and Disability Ethics Committee on 6 August 2020 for 3 years. This study has also been approved by the Auckland District Health Board Research Review Committee and by the Waitematā and the Auckland District Health Boards Māori Research Committee.

**WHAT WILL MY PARTICIPATION IN THE STUDY INVOLVE?**

We are inviting two groups of people to participate in this study:

- People with **high blood pressure** (untreated systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg).
- People with normal blood pressure (systolic blood pressure ≤120 mmHg or diastolic blood pressure ≤80 mmHg).

For safety and scientific reasons you are ineligible to participate in this study if you are:
- younger than 18 years old,
- are pregnant,
- are a smoker,
- have a body mass index <18 or >35 kg/m² (weight in kilograms divided by height in metres squared), or have another significant medical condition (e.g. heart failure, lung disease). An investigator will carefully check the inclusion/exclusion criteria with you and answer any queries.

Studies will be undertaken at the **Human Cardiovascular Physiology Laboratory, Level 7, Respiratory Physiology Department, Auckland City Hospital**. Participation involves one short Screening/ familiarisation visit (~45 min) and two experimental visits (~4 hours each). The general procedure of participating is as follows:

Once you have read this form, an investigator will contact you to make sure that your questions have been answered and check that you understand what is involved and the inclusion/exclusion criteria. They will then schedule a screening/familiarisation visit with you.

**Screening/ familiarisation visit**

At the screening/ familiarisation visit (~45 min) an investigator will explain again the nature of the procedures, answer any remaining questions and ask you to complete the Consent Form below. You will be asked to complete a General Health Questionnaire. Then, providing you meet the study inclusion/exclusion criteria, you will be enrolled into the study. Body weight and height will be measured, and then you will be familiarised with the study procedures.

**Experimental visit**

The two experimental visits will last ~4 hours each and be separated by 1 week. They will be scheduled for the morning. Prior to the study visit the following pre-study stipulations apply:

- No food intake for 2 hours prior to the study.
- No caffeine (e.g., coffee, coke, red bull) for 12 hours before the study.
- No alcohol on the day before the study and the day of the study.
- No exercise after 8:00 pm the evening before the study and no exercise on the day of the study.
• No ‘over the counter’ (e.g. paracetamol) or cardioactive medications (beta-blocker, ACE inhibitor, angiotensin receptor blockers, calcium antagonists, diuretics, alpha blockers) on the morning of the study. This can be discussed with a study investigator prior to your appointment. Please bring these medications [if you need to,] to your study appointment so you can take your usual medication immediately after the research tests (by late morning).

**Experimental protocol**
You will be asked to lie on your back in supine position on a bed. A small blood sample (~20 ml) will be taken from a vein on the back of your hand or the forearm. After the blood sample, you will be provided with either an oral vitamin B6 supplement or placebo tablet. These will be prepared by Auckland Pharmacy Clinical Trials Department, Auckland District Hospital. After a two-hour rest period will then be observed to allow the blood level of vitamin B6 to increase. Another small blood sample will then be taken.

Your left leg will then be supported in a slightly elevated position and lower limb vein diameter (left leg) non-invasively monitored. A wide cuff will be placed around your left thigh. By inflating this cuff (60 mmHg, 5 minutes) and then slowly deflating it (over 1 minute) we can assess how compliant your veins are. The cuff is inflated to a light pressure and will not feel as tight as a standard blood pressure measurement made with a cuff around the upper arm.

Non-invasive equipment will then be attached for the measurement of your heart rate, blood pressure, brain blood flow and breathing. All measures are described in detail below. We will then assess your “peripheral” and “central” chemoreceptor sensitivity using two short (~5-10 minutes) trials where you will breath in different gas mixtures. We will stimulate your peripheral chemoreceptors using a low oxygen gas mixture, and your central chemoreceptors using a high carbon dioxide and high oxygen gas mixture. After each trial you will be asked to rate your breathing sensation using a simple 0-10 scale.
Measurements
Throughout the experimental procedures described in the paragraph above we will continuously monitor your breathing and cardiovascular system. An ultrasound examination of a vein in your lower leg will be made using a probe placed lightly on the skin with the help of a gel. This is like the scan used with pregnant women. Your heart rate will be measured using an electrocardiogram by placing sticky electrode patches on your chest. Your blood pressure will be monitored by a small blood pressure cuff around the finger, and another around your upper arm. Breathing will be monitored with a lightweight mask covering your mouth and nose, or a mouthpiece with a nose clip. A lightly placed finger-clip will monitor your blood oxygen saturation. Blood flow of the large arteries in your brain will be measured using two probes placed lightly on your temples with the help of an adjustable headband and gel.

WHAT ARE THE POSSIBLE BENEFITS AND RISKS OF THIS STUDY?

Benefits: You may notice a reduction in your high blood pressure during this study. However, this is not guaranteed. We will be happy to talk to you about the data collected (e.g., your heart rate, blood pressure). The information we will gather from all the people taking part in this study will help us understand what causes high blood pressure and how best to treat it in the future.

Risks and discomforts: The risks associated with this study are low. The research team are experienced with all the procedures used. To further minimise the risk associated with this investigation studies will be undertaken in a clinical research laboratory at Auckland City Hospital. Medically trained personnel will be in close proximity, along with crash cart facilities, in the unlikely event that they are required. In addition, your heart rate, blood pressure, breathing and blood oxygen levels will be very carefully monitored throughout the study. The experiment will be stopped at your request or if the investigator thinks that it is in your best interests.

With-holding morning medications. Cardiovascular medicines are given to provide protection over years/decades and therefore the delay in medicines in this study (of 3-4 hours) will be extremely unlikely to cause harm over that time frame. As stated above, please bring your usual medications to your study appointment so you can take them immediately after the research tests (by late morning).

Hypoxia and hypercapnia are used to stimulate the peripheral and central chemoreceptors, and may produce feelings of breathlessness, light-headedness or dizziness. The risk of this is low, and further minimised by being applied for a short period of time (5 minutes), but if this does occur, symptoms rapidly reverse (in a few seconds) by breathing normal room air again. Remember you are lying down so there is no risk of falling. Before the test begins, you will receive instructions to remove the mouthpiece if symptoms develop. You will also be carefully monitored by an investigator, who can also quickly switch you to room air breathing if required. In the unlikely event that it is needed, oxygen can be administered.

Vitamin B6 acute supplementation has no reported risks. Higher doses (1-6 grams) for longer durations (12-40 months) have been linked to sensory neuropathy (includes pins and needles, tingling, numbness). However, this has not been reported with one-off doses as used in the current study. Nevertheless, you should inform the study team if you experience nausea, headache and drowsiness, or in the unlikely event that you experience numbness or tingling of the fingers or toes.
Detection of Abnormalities: The measures made are for research purposes and are not a medical exam or diagnostic test. There is a small possibility that we may incidentally find an abnormality that is clinically significant, such as a heart rhythm abnormality. In the event of this, you will be informed and will be advised to consult your general practitioner. If you do not wish to know about this type of finding, please do not participate.

COVID-19: This study will not be conducted while New Zealand is at Alert Levels 3 and 4. The study will proceed at Alert Levels 1 and 2, undertaking and adhering to institutional guidance from the University of Auckland regarding practices to minimise the risk of transmission. This will include the researchers wearing personal protective equipment and maintaining appropriate physical distance when able. All equipment is always sterilised between participants, and surfaces disinfected. If you feel unwell on the day of your scheduled testing, have been in close contact with a confirmed or probable case of COVID-19, or have returned from overseas in the 14 days prior to your scheduled testing, please do not come in for assessment.

WHO PAYS FOR THE STUDY?

As a participant in this study you will not incur any costs. You will receive a $50 voucher for each experimental session attended, in recognition of your participation.

WHAT IF SOMETHING GOES WRONG?

If you were injured in this study, you would be eligible to apply for compensation from ACC just as you would be if you were injured in an accident at work or at home. This does not mean that your claim will automatically be accepted. You will have to lodge a claim with ACC, which may take some time to assess. If your claim is accepted, you will receive funding to assist in your recovery. If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won’t affect your cover.

WHAT ARE MY RIGHTS?

Your participation in this study is entirely voluntary. You are free to decline to participate, or to withdraw from the research at any practicable time, without experiencing any disadvantage. You have the right to access information collected about you as part of the study. You will be informed of any new information related to the study that becomes available during the study that may have an impact on your health. Your identity will be kept strictly confidential and you will not be identified in the publication of the research findings.

WHAT HAPPENS AFTER THE STUDY?

No study intervention (e.g., B6 or placebo) will be supplied beyond the duration of your participating in the study. During this study the research team will record information about you and your study participation. This includes the results of any study assessments (e.g., ECG, BP, respiration and blood vessel function). If needed, information from your hospital records and your GP may also be collected. You cannot take part in this study if you do not consent to the collection of this information.

Identifiable Information
Identifiable information is any data that could identify you (e.g. your name, date of birth, or address). The following groups may have access to your identifiable information:

- Research team (to complete study assessments)
- Laboratory staff, to process and report your blood sample test
- Sponsor study monitors, to make sure the study is being run properly and that the data collected is accurate.
- The sponsor and its representatives, if you make a compensation claim for study-related injury. Identifiable information is required in order to assess your claim.
- The sponsor, ethics committees, or government agencies from New Zealand, if the study or site is audited. Audits are done to make sure that participants are protected, the study is run properly, and the data collected is correct.
- Your usual doctor, if a study test gives an unexpected result that could be important for your health. This allows appropriate follow-up to be arranged.

De-identified (Coded) Information

To make sure your personal information is kept confidential, information that identifies you will not be included in any report generated by the research team or any study information sent to the sponsor. Instead, you will be identified by a code. The research team will keep a list linking your code with your name, so that you can be identified by your coded data if needed.

The following groups may have access to your coded information:

- The sponsor, for the purposes of this study.

The results of the study may be published or presented, but not in a form that would reasonably be expected to identify you.

Security and Storage of Your Information.

Your identifiable information is held at University of Auckland and/or Auckland DHB in a locked filing cabinet in a department with security-limited access, along with all paper records (e.g., health history forms) during the study. After the study it is transferred to a secure archiving site and stored for at least ten years, then destroyed. Your coded information will be entered into electronic case report forms stored in secure and password protected University of Auckland servers. Coded study information will be kept by the sponsor in secure, cloud-based storage indefinitely. All storage will comply with local and/or international data security guidelines.

Risks.

Although efforts will be made to protect your privacy, absolute confidentiality of your information cannot be guaranteed. Even with coded and anonymised information, there is no guarantee that you cannot be identified. The risk of people accessing and misusing your information (e.g. making it harder for you to get or keep a job or health insurance) is currently very small, but may increase in the future as people find new ways of tracing information.

Rights to Access Your Information.

You have the right to request access to your information held by the research team. You also have the right to request that any information you disagree with is corrected.

Please ask if you would like to access the results of your screening and safety tests during the study.
If you have any questions about the collection and use of information about you, you should ask the research team.

The full results of the studies being conducted will not be known until after the last participant has been tested and the data analysed (up to two years). The results will be reported in professional publications and meetings but will not be published in a form that identifies individual participants. If you are interested in receiving a summary of the results, please indicate as appropriate on the consent form below.

Rights to Withdraw Your Information.

You may withdraw your consent for the collection and use of your information at any time, by informing the research team.

If you withdraw your consent, your study participation will end and the study team will stop collecting information from you.

If you agree, information collected up until your withdrawal from the study will continue to be used and included in the study. You may ask for it to be deleted when you withdraw, unless you withdraw after the study analyses have been undertaken.

HDEC Auditing.

An approved auditor appointed by New Zealand Health and Disability Ethic Committees, or any relevant regulatory authority or their approved representative may review your medical records for the sole purpose of checking the accuracy of information recorded for the study, for auditing purposes.

WHAT WILL HAPPEN TO MY BLOOD SAMPLE?

Your donated blood sample will be processed and stored by the Auckland Regional Biobank. The sample will be measured for vitamin B6 and metabolites, markers of sympathetic nerve activity and standard biochemistry measures (e.g., glucose, cholesterol). There may be a small amount of these left over after this study has ended that can be destroyed using standard University of Auckland approved procedures. If you wish, your unused samples can be disposed of with a karakia (blessing) at the end of the study.

We understand that many Māori consider their blood to be tapu and that participation in this type of study requires careful consideration. It may be appropriate to discuss participation with whānau / family members. We have included an optional section on the consent form for a whānau / family member to sign to indicate their support. The contact details for the administrator for He Kamaka Waiora (Māori Health Team) are provided below should their guidance be required.

WHO DO I CONTACT FOR MORE INFORMATION OR IF I HAVE CONCERNS?

If you have any questions, concerns or complaints about the study at any stage, you can contact:

Name, position: Dr James P. Fisher (Lead Investigator)  
Telephone number: 09 373 7599 | Ext 86320  
Email: jp.fisher@auckland.ac.nz

If you want to talk to someone who isn't involved with the study, you can contact an independent health and disability advocate on:
If you require Māori cultural support contact the administrator for He Kamaka Waiora (Māori Health Team) by telephoning 09 486 8324 ext 42324 and if you have any questions or complaints about the study you may contact the Auckland and Waitematā District Health Boards Māori Research Committee or Māori Research Advisor by phoning 09 4868920 ext 3204.

You can also contact the health and disability ethics committee (HDEC) that approved this study on:

Phone: 0800 4 ETHICS
Email: hdecs@moh.govt.nz
# Consent Form

Please tick to indicate you consent to the following

<table>
<thead>
<tr>
<th>Statement</th>
<th>Yes</th>
<th>No</th>
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<tbody>
<tr>
<td>I have read, or have had read to me in my first language, and I understand the Participant Information Sheet.</td>
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<tr>
<td>I have been given sufficient time to consider whether or not to participate in this study.</td>
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<tr>
<td>I have had the opportunity to use a legal representative, whanau/family support or a friend to help me ask questions and understand the study.</td>
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<tr>
<td>I am satisfied with the answers I have been given regarding the study and I have a copy of this consent form and information sheet.</td>
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<td>I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time without this affecting my medical care.</td>
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<tr>
<td>I consent to the research staff collecting and processing my information, including information about my health.</td>
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<td>If I decide to withdraw from the study, I agree that the information collected about me up to the point when I withdraw may continue to be processed.</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>I consent to my GP or current provider being informed about my participation in the study and of any significant abnormal results obtained during the study.</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>I agree to an approved auditor appointed by the New Zealand Health and Disability Ethic Committees, or any relevant regulatory authority or their approved representative reviewing my relevant medical records for the sole purpose of checking the accuracy of the information recorded for the study.</td>
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<tr>
<td>I understand that my participation in this study is confidential and that no material, which could identify me personally, will be used in any reports on this study.</td>
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<td>I understand the compensation provisions in case of injury during the study.</td>
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<td>I know who to contact if I have any questions about the study in general.</td>
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<tr>
<td>I understand my responsibilities as a study participant.</td>
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<tr>
<td>I wish to receive a summary of the results from the study.</td>
<td>Yes</td>
<td>No</td>
</tr>
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</table>
**Remaining Tissue instructions – please TICK ONE option**

I consent to any remaining samples(s) being disposed of using standard disposal methods at the end of this study

-or-

I wish to have any remaining samples disposed of using standard methods **AND** with an appropriate karakia at the end of research

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**Declaration by participant:**
I hereby consent to take part in this study.

Participant’s name:

Signature: Date:

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**Declaration by member of research team:**

I have given a verbal explanation of the research project to the participant, and have answered the participant’s questions about it.

I believe that the participant understands the study and has given informed consent to participate.

Researcher’s name:

Signature: Date:

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This study has been reviewed and approved by the Health and Disability Ethics Committee (20/NTA/29) on 6 August 2020 for 3 years.