Government of South Australia
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THE UNIVERSITY of ADELAIDE

Participant Information Sheet/Consent Form

Interventional Study - *Adult providing own consent*

Lyell McEwin Hospital

Title	Coronary and Peripheral Haemodynamic Studies in Angina with No Obstructive Coronary Artery Disease and International COVADIS Registry. (HREC/17/TQEH/156)
Protocol Number	Version 4, dated 30th October 2017
Principal Investigator	A/Prof Margaret Arstall
Associate Investigators	John Beltrame, Sharmalar Rajendran, Purendra Pati, Devan Mahadavan, Eng Lee Ooi, Doug McEvoy, Khin Hnin, James Geake, Matthew Chapman, Rosanna Tavella, Emily Aldridge, Melanie Wittwer

Part 1 What does my participation involve?

1. Introduction

You are invited to take part in the research project because you have been suffering from chest pain thought to be angina. Your treating doctors have requested you to have a coronary angiogram (standard of care) at the Lyell McEwin Hospital to examine your coronary arteries. If your coronary arteries are shown to be normal or have no significant blockage (no obstructive coronary artery disease), it is possible that either spasm of the coronary arteries (vasospastic angina) or alteration in how the small branches of your coronary arteries are working to supply blood to your heart muscle (coronary microvascular dysfunction) could be causing your angina. This project is using research tests to find out if you have coronary artery spasm or coronary microvascular dysfunction, blood tests which may predict future chest pain, and questionnaires to measure future chest pain. We also want to help advance understanding of coronary microvascular dysfunction throughout the world by adding your re- identifiable information to an international registry

This Participant Information Sheet and Consent Form tells you about the research project. It explains the tests and what the research involves. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or local doctor.
Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

Your decision to participate or not, will not affect your position on the coronary angiogram waiting list.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it, you are telling us that you:

- Understand what you have read
- Consent to take part in the research project
- Consent to the tests and research that are described
- Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2. What is the purpose of this research?

Angina (chest pain coming from the heart) results from insufficient blood supply to the heart muscle to meet the needs of the heart muscle. Angina is often present during exercise when the heart is working hard and needs a greater blood supply.

The research is to find out how many people have angina due to a blockage in their coronary arteries and how many have angina due to either vasospastic angina or coronary microvascular dysfunction. .

About 30% of people who have a coronary angiogram for angina do not have a fixed (there all of the time) coronary artery narrowing and are often told that no cause has been found for their chest pain.

This research project is testing for variable (comes and goes) narrowing of the coronary arteries which is not routinely done during angiograms. At the Lyell McEwin Hospital, we have a keen interest in this testing as some of these forms of angina are treatable. If not treated, then the risk of something serious happening, such as a heart attack or dying is very low, but frequent angina or chest pain can affect the person's quality of life. This research project is testing whether you have vasospastic angina and/or coronary microvascular dysfunction. This involves about 30 – 45 minutes extra testing time after the coronary angiogram has been completed.

People with vasospastic angina or coronary microvascular dysfunction may also have changes in how blood vessels in other parts of their body work (arm or leg blood vessels, eye blood vessels) and abnormal heart pumping reserves on a special heart test (stress echocardiography). Testing these blood vessels in other parts of the body may allow us to indirectly assess whether vasospastic angina or coronary microvascular dysfunction is present without needing to do an angiogram. If this research project works, we will be able to provide a safer and less invasive testing for future study of coronary microvascular dysfunction. These tests involve:

a) Testing of peripheral (arm or leg) blood vessels. At the Lyell McEwin Hospital, we use a TensioMed Arteriography device to analyse your pulse waveform.

b) Testing of eye blood vessels by taking a photo, in the same way that eye doctors examine your eyes.

c) Testing heart function using a low dose dobutamine stress echocardiogram test

The aim of these three non- invasive tests is to discover if they can be used to diagnose vasospastic angina or coronary microvascular dysfunction, rather than needing to do the invasive catheter/coronary angiogram test.

There are substances in our blood which can predict future risk of heart attacks but only in people whose angina is caused by atherosclerosis or blockage in their heart arteries. No one has studied whether these substances could help predict future risk in people with angina and no obstructive coronary artery disease. Two 10ml blood samples will be taken at the time of your coronary angiogram to test if you have higher levels of some of these substances and to see over time if any of these substances are associated with the amount of chest pain you may have in the next 12 months. With your consent any remaining blood will be stored for future testing of one or more of the substances that may affect how your blood vessels work.

International registry

The purpose of the registry is to help advance knowledge and understanding of coronary microvascular dysfunction throughout the world by adding your re-identifiable information to this registry. Re-identifiable information is defined as data that is put into the registry from which your identifiers (name, date of birth and contact details) have been removed and replaced by a code. However, the local researcher is able re-identify a specific participant if needed by referring to the separately stored data sheet at this study site, linking participant identity to the registry code. We do this to allow us to later add to the registry your health status obtained by annual phone calls for 5 years.

3. What does participation in this research involve?

You will be asked to sign the consent form prior to any study assessments being performed. To be eligible for this study, you must be a patient at the Lyell McEwin Hospital. There are no costs associated with participating in this research project, nor will you be paid.

Coronary Angiogram: *Standard Care – you have signed a consent form for this test already.*

If the coronary angiogram shows no significant blockage of your coronary arteries, you are able to take part in the research project which involves the following procedures:

- If you have not had a second tube inserted into your leg vein during the standard procedure, this will need to be inserted. A temporary pacing lead is passed through this second tube, into the right side of your heart, in order to allow pacing of the heart. Pacing of the heart means an electrical impulse is used to make the heart beat at a selected heart rate. For this test, the pacing lead is usually set to a heart rate of 60 beats per minute. This means that, as long as your heart rate is above 60, there will be no activation of the pacing lead. However, if your heart rate falls below 60 beats per minute, the pacing lead will activate and maintain a heart rate of 60 beats per minute until your pulse rate increases to 60 or more.

- A wire will be passed from your wrist artery into one of your heart arteries that will allow us to measure the pressure and blood flow down the artery. This method allows us to measure the function of the small arteries by measuring the difference before and after the spasm test. Passing the wire into the heart artery is a safe procedure and you will not feel it, with the risk of injuring the heart arteries very small (less than 1 in 1000).

Spasm test – *this involves giving two medications.*

- Adenosine is the agent used to widen the small arteries. This agent is given into an arm vein through a small tube. In addition to widening the small arteries, this substance may result in you feeling slightly breathless or having vague chest discomfort. As Adenosine has an extremely short duration of action, any sensations you may feel will only occur during the 2 minutes that the Adenosine is given. Adenosine is an approved medication for treating heart rhythm problems.

- Acetylcholine is the agent used to provoke spasm of the heart arteries and can also slow the heart rate: hence, the need for the temporary pacing lead described above. Acetylcholine has an extremely short duration of action (less than 1 minute). If you have coronary artery spasm, Acetylcholine put into the heart artery will probably result in chest pain from either a narrowing of the large arteries or slowing flow down the arteries. If the pain or spasm induced is significant, we will inject glyceryl trinitrate into your heart artery which will relax the heart artery. Glyceryl trinitrate is the same medication as used in angina tablets or spray that people put under their tongues. Acetylcholine is not a standard medication and although used frequently in the spasm test for 25 years, is an investigational medication and not formally approved by the Therapeutic Goods Administration.

- The additional small amount of radiation involved in this research project is limited to approximately two additional pictures of your heart arteries (a standard study usually involves 8-10 pictures being taken). As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 millisieverts (mSv) per year. The effective dose from this study is about 1.7mSv.

- During the coronary angiogram, we will be taking a 20ml blood sample for purposes of testing for markers of blood vessel function and further testing. (10ml pre-spasm testing and 10 ml post – spasm testing).

Additional Care related to the research project beyond the standard coronary angiogram:

- If no tube has been inserted into your leg vein for the standard coronary angiogram then a tube will be inserted into a leg vein. The tube in the leg vein is needed to pass the pacing lead described above. This tube will be removed outside the procedure room in a similar fashion to the artery tube as described in the standard care after the coronary angiogram.

- The remainder of what happens is the same as the procedure after a standard coronary angiogram - after removal of the artery and vein tubes you will have 1-2 hours bed rest. The nursing staff make regular checks on your leg and/or

arm to make sure there are no signs of bleeding from the sites where the tubes have been removed. The nursing staff will also make regular checks on the circulation in the arm or leg and regularly check on your pain levels and if necessary provide you with pain relief.

- You will be allowed to go home a few hours after removing the tubes if the nursing staff are satisfied that you are stable. Discomfort from an angiogram may last for another 1 to 2 days and is easily relieved with paracetamol if required. You may notice some bruising at the site where the tubes were removed. If you notice an increase in pain or a lump developing at the site where the tubes were inserted or if any concern we advise you to call the nursing staff at the Coronary Care Unit 08-8182 9811 They are reachable 24 hours, 7 days a week and can arrange a review if needed.

NON-INVASIVE TESTING:

Low dose Dobutamine Stress Echocardiography:

- This is a special type of heart ultrasound which is performed in two parts.
- First, a cardiac scientist performs an echocardiogram using an ultrasound machine. An echocardiogram checks how your heart functions when resting. You lie on your left side. To ensure good contact between your skin and the detector, surgical jelly is placed at several different sites on your chest.
- In the second part of the test, your heart is exercised or 'stressed" with a drug called "Dobutamine" at low dose only. "Dobutamine" is a drug that copies the effect of exercise on the heart and makes the heart work faster and harder. A small needle is inserted into the back of your hand and the Dobutamine is given slowly through this needle over 3 to 5 minutes.This test is regarded as a standard test and Dobutamine is an approved medication..
- The test will be stopped if you have chest pain, become very tired or very short of breath (puffed).
- The test will take approximately 15 minutes in total.

Tensiomed Arteriograph:

- You will relax in a seated position for 5 minutes. Usual manual blood pressure measurements will be performed twice, with 1 minute interval between measurements.
- Following that, we will perform pulse waveform analysis by attaching the device cuff to your dominant forearm. Two measurements will be taken with 1 minute interval between measurements.
- The test will take approximately 15 minutes in total.

Retinal (Eye) Photography:

- You will rest in a dark room for 5 minutes. This will allow your pupils to dilate

naturally. Then, a photo will be taken of both eyes.

- You will experience a bright flash for less than 1 second with each photo, but no other side effects are expected.

- This test will take approximately 10 minutes in total.

The non-invasive tests of Low dose dobutamine stress echocardiography, Tensiomed Arteriography and Retinal Photography will be performed within 2 weeks of your coronary angiogram.

Health Related Outcomes Questionnaires:

- Seattle Angina Questionnaire (SAQ)
- EQ-5D
- Patient health Questionnaire (PHQ9)
  Note: These will be repeated at 1, 6 and 12 months follow-up and by telephone. Extreme responses on the questionnaires will be flagged to your general practitioner or acted upon as a standard of medical care.

International Registry :Coronary Vasomotion Disorders International Study Group (COVADIS) Registry

If you have coronary microvascular dysfunction you will be invited to participate in the international COVADIS Registry. This participation will last for 5 years from the day of enrolment.

Participants will undergo clinical assessments and receive standard medical care as determined by their treating physician. Participants will not receive experimental intervention or experimental treatment as a consequence of their participation in the registry study.

Data collection will be performed through the use of the electronic case report form established by the Japanese Coronary Spasm Association. Data collection will be in two phases:

1. Enrolment / Baseline data collection (already obtained from the onsite visit at which the diagnosis of coronary microvascular dysfunction was made)
   - Participants will be enrolled consecutively at a study site (e.g. non-selective enrolment of subjects meeting inclusion/exclusion criteria). The participant will confirm authorization through informed consent. Initial data collection, performed by the investigator, will include age, gender, marital status demographics, relevant medical history, cardiovascular risk factors, quality of life questionnaire, reasons of diagnosis of myocardial ischemia, information from the coronary artery angiogram, and medication use at baseline.

2. Follow up data collection (telephone)
   - The follow-up period for each participant is considered as the time from enrolment up to 5 years. During this period, participants will be contacted by telephone by the study staff every year.

During the follow-up interviews with you, the following data will be collected; occurrence of cardiovascular events, presence or absence of angina attack, smoking habit, blood tests, quality of life questionnaire and medications.

What treatment will I get if I do take part?
The research project results will enable specific treatment to be started if you have vasospastic angina. If you have coronary microvascular dysfunction, specific treatments may become available in the future.

Will I have to come back to the clinic more often or remain in hospital for longer than would normally be the case?
Your participation in this study will not affect your inpatient stay or standard follow-up. You will attend Lyell McEwin Hospital Clinical Trial Unit for the non-invasive testing 2 weeks after the angiogram. The questionnaires will be performed, by phone calls at 1 month, 6 months and 12 months.

How long will my participation in the research project last?
You will be in the spasm and non-invasive testing project for 12 months and in the international registry for 5 years.

4. What do I have to do?

After signing the consent form and asking any questions you may have, you will proceed with the research project procedure as described above.

If you have obstructive coronary artery disease, you will be treated by your cardiologist with standard care.

If you have no significant obstructive coronary artery disease, and you agree to participate we will proceed with the extra spasm tests described above.

5. Other relevant information about the research project.

We expect that around 60 patients with angina will participate in this study at the Lyell McEwin Hospital.

This research has been initiated by the study doctor, A/Prof Margaret Arstall, and is supported by departmental funding

6. What are the possible benefits of taking part?

There is a potential benefit of this study. Acetylcholine testing allows a diagnosis of coronary microvascular dysfunction or coronary artery spasm to be made. If either is found, then appropriate treatment can be commenced for vasospastic angina and there is research occurring to identify treatments for coronary microvascular dysfunction. You can ask Dr Ooi for further information. You will receive the medical care that the treating medical officer considers appropriate at his/her discretion.

In regards to the low dose dobutamine stress echocardiography testing, TensioMed Arteriography testing, retinal photography, or blood testing, there may be no direct

benefit to you personally but there is a potential benefit of this study for future patients. If there is a link between the heart arteries and the heart function and arm and eye arteries we may be able to assess response to treatments for the different forms of Coronary Heart Disease in a non-invasive manner. The International registry may enable more rapid progress in understanding and treating microvascular angina.

7. What are the possible risks and disadvantages of taking part?

Spasm Test

The risks from the additional procedures during the coronary angiogram relating to this research protocol are outlined below:

- If the pacing lead activates to maintain your heart rate of 60 beats per minute it may cause an unusual sensation in the chest, like palpitations.

- A rare complication of inserting a temporary pacing lead is its penetration through the heart wall causing blood leakage into the surrounding heart (pericardial) sac. This complication can be life threatening. This complication has been estimated to occur in less than 1 in 1,000 procedures.This complication has occurred once during 233 spasm tests in Adelaide and the participant was rapidly treated with no long term adverse effects. Other complications that occur from temporary pacing leads are extremely rare: sustained abnormal heart rhythm; infection; and blood clots, which can travel to other parts of the body.

- Passing the wire into one of your heart arteries is a safe procedure used by many heart specialists and you will not feel it, with the risk of injuring the heart arteries being rare (less than 1 in 1000) and reduced by placement of the wire under x-ray guidance.

- Adenosine in higher doses than used in this project has been reported to result in a brief period of feeling breathless or having vague chest discomfort in I in 10 patients. This is a similar frequency to that found in other approved heart stress tests. With higher doses of Adenosine than used in this project, single events of aggravation of asthma and of nausea have been reported. Any disturbance to your breathing or lungs will be observed by way of a probe attached to your finger monitoring your breathing rate and blood oxygen levels and treated appropriately if needed.

- Acetylcholine may slow the heart rate and/or cause chest pain. If these effects occur they will be promptly treated. If the pain or spasm induced is significant, we will inject glyceryl trinitrate into your heart artery which will relax the heart artery. Glyceryl trinitrate is the same medication as used in angina tablets or spray that people put under their tongues. In a report of the experience of 299 patients having spasm testing with intracoronary Acetylcholine : 1 in 8 had chest pain ; 1 in 30 had a brief period of irregular heartbeat ; and 1 in 100 had a brief period of shortness of breath. .At TQEH/LMHS, we have performed over 100 spasm tests with no deaths, heart attacks or sustained episodes of irregular heartbeat.

- The blood samples (two 10 ml samples) will be taken during the testing from one of the tubes in your leg blood vessels – there is a slight risk of bleeding or infection at the site of the tube into the vein.

Dobutamine stress echocardiography:

- Dobutamine stress echocardiography has been a standard functional test performed in Cardiology testing laboratories over the last 20 years.

- The side effects of "dobutamine" includes headache, nausea, vomiting, restlessness, muscle cramps or weakness, chest pain, shortness of breath (feeling puffed), dizziness, palpitations and rash. The most common side effect is brief chest discomfort in about 1 in 10 participants. The risk from this test is minimal with the low dose of dobutamine used in this study.

TensioMed Arteriography:

- TensioMed Arteriography is similar to taking a blood pressure measurement with minimal discomfort and no foreseeable risk.

Retinal photography:

- Retinal photography participants will experience a bright flash for less than1second with each photo with no foreseeable risks.

International COVADIS Registry:

- No foreseeable risk.

8. Can I have other treatments during this research project?

You will need to stop any "Calcium Channel Blocker" and/or "Nitrates" medications for 48 hours prior to the coronary angiogram if your treating cardiologist has agreed. These can be restarted after the procedure. Whilst you are participating in this research project, we recommend that you continue to take all your current medications or treatments for your condition or for other reasons. It is important to tell your study doctor and the study staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments.

9. What if I withdraw from this research project?

If you decide to withdraw from this research project, please notify a member of the research team before you withdraw. If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the research team up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them when you withdraw from the research project. Withdrawal will not affect your relationship with the clinical staff or the hospital

Part 2 How is the research project being conducted?

10. What will happen to information about me?

By signing the consent form, you consent to the study doctor and relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential.

For the purposes of the study, you will be assigned a unique study ID number which cannot be traced back to your name or medical record number. However, this information is re-identifiable. Your re-identifiable information will be kept in a password-protected spreadsheet and only the people directly associated with the study will have access to this re-identifiable information.

The collected blood samples will be stored at the biobank facility in Robinson Research Institute laboratory at the Lyell McEwin Hospital. The information and samples will be kept for a minimum of 15 years as required by law.

Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law. Information about you may be obtained from your health records held at this and other health services for the purpose of this research.

By signing the consent form, you agree to the research team accessing health records if they are relevant to your participation in this research project. In accordance with South Australian privacy laws, you have a right to request access to the information about you that is collected and stored by the research team. You also have a right to request that any information with which you disagree be corrected.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified.

At the completion of the study and storage period, your data and samples will be destroyed according to SA Health policies.

11. Complaints and compensation?

In the unlikely event that you suffer any injuries or complications because of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment.

If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital. Your participation in this research study will not affect any rights you have to compensation under common law.

12. Who is organising the research?

This research project is being jointly conducted by the Lyell McEwin Hospital and the University of Adelaide. No member of the research team will receive a personal financial benefit from your involvement in this research project (other than his or her ordinary wages).

13. Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of the TQEH//LMH/MH.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

14. Further information and who to contact

The person you may need to contact will depend on the nature of your query as below:

Further Information concerning this project:

Name	Dr Eng Lee Ooi (1st Contact) /Dr Sharmalar Rajendran (2nd Contact)
Position	Study Investigator / Consultant Cardiologist
Telephone	8182 9000 – via switchboard (Monday to Friday – 9am to 4pm)

Any medical problems related to the procedure of study:

Name	On-duty Coronary Care Unit Nursing Staff.
Telephone	8182 9811 – (24 hours)

Local Site Complaints contact person:

Name	Alison Barr
Position	NALHN Research Governance Officer
Telephone	8182 9346
Email	healthnalhnrgo@sa.gov.au

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Review HREC Name	Human Research Ethics Committee (TQEH/LMH/MH)
HREC Executive Officer	Heather O'Dea
Telephone	8222 6841
Email	Health.CALHNResearchEthics@sa.gov.au

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Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the participant information sheets.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the project without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

I understand that, if I decide to discontinue the research project treatment, a member of the research team may request my permission to obtain access to my medical records for collection of follow-up information for the purposes of research and analysis.

I consent to:

Participating in the International Registry	Yes …	No … (tick as appropriate)
Having my blood stored for future non-genetic testing	Yes …	No … (tick as appropriate)

Name of Participant (please print) _____

Signature _____ Date _____

Name of Witness* to Participant's Signature (please print) _____

Signature _____ Date _____

* Only to be completed when the investigator is not present

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/ Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.