Study Protocol, including Statistical Analysis plan: ExINOCA part 1

Official title - Ischemia with No Obstruction of Coronary Arteries: Underlying mechanisms and the impact of exercise training (EXINOCA)

Brief Title: Mechanisms Behind Microvascular Dysfunction in INOCA (ExINOCA-P1)

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Ethical application no. H-24005644 as approved by the Regional Ethical Committee of the Copenhagen Region (De Videnskabsetiske Komiteer Region Hovedstaden),
Phone: +4538666395
Email: vek@regionh.dk
Adress: Borgervænget 3, st. 2100 København Ø
The study is monitored by the Danish Data-protection Agency.

Study is planned to be conducted from October 2024-October 2027
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FDA Regulated Intervention: No Sponsor: Bispebjerg-Frederiksbjerg Hospital

Principal investigator: Eva Prescott, M.D., D.M.Sc., Prof.
Co-Principal investigator: Ylva Hellsten., Prof.
Co-investigators: Mads Fischer, PhD
Co-investigators: Signe Liner, MD, PhD candidate

Contacts/Locations

Eva Prescott, MD, DMSc

Telephone: 22572614

Email: Eva.Irene.Bossano.Prescott@regionh.dk

Central Contact Backup: Mads Fischer, Ph.D.

Telephone: 24485450

Email: mf@nexs.ku.dk

Study Officials: Ylva Hellsten, Professor

Department of Nutrition, Exercise and sports, University of Copenhagen

Locations: Frederiksberg Hospital, Dept. of Cardiology, Building 16, Y3, Nordre Fasanvej 57, Frederiksberg, Denmark, 2400

Short Description
This study aims to identify mechanisms underlying Coronary microvascular dysfunction (CMD) in angina and to assess whether exercise training can improve the condition.

In this study 30 patients with impaired coronary microvascular function and 30 asymptomatic controls will be studied to identify vascular and related molecular mechanisms underlying INOCA by investigating microvascular function in the heart and in cutaneous tissue, skeletal muscle, and adipose tissue.

Background
Recent evidence shows that INOCA can manifest from general microvascular disease affecting small arteries other than the coronary artery. For example, the vascular response in the finger of patients with coronary microvascular disease has been shown to be abnormal (8) and small arteries isolated from skin and adipose tissue of patients with coronary microvascular disease display increased response to the vasoconstrictor endothelin and reduced response to the endothelium dependent vasodilator acetylcholine when compared to controls (9,10). Other experiments have shown a shift in endothelial mediated vasodilation from nitric oxide to the vasodilator H_2O_2, and preliminary evidence indicates that this could be rectified through induction of the transcriptional coactivator PGC-1a (11). This is consistent with the evidence for inflammation associated with coronary microvascular disease (12).

The mechanistic findings are exceedingly interesting as they provide the first targets, which may potentially be exploited to treat patients with microvascular disease. Accordingly, there is strong preliminary data to suggest a way forward with respect to treatment of the large population – mostly women – with coronary microvascular disease. In the first part of this project two groups will be compared at baseline; a matched control group and a group with angina symptoms and reduced myocardial blood flow reserve as an indication of microvascular dysfunction; INOCA. The two groups are compared to allow for an assessment of functional and molecular mechanisms in angina patients with- versus without coronary microvascular dysfunction and to relate these aspects in both groups to a matched control group.

We have found that INOCA is associated with development of renal and cerebral microvascular disease (13) strongly suggesting that coronary microvascular disease is a manifestation of a generalized microvascular disease. As direct investigations of microcirculatory mechanisms in the human heart are difficult, the systemic aspect of microcirculatory dysfunction provides an excellent opportunity to study the microcirculation of more accessible organs in patients with INOCA. Accordingly, in the current project we will study the microcirculation in skeletal muscle, skin and adipose tissue of patients and matched control participants to obtain insight into the mechanisms underlying INOCA.

Objective
The overarching aim of the project is to identify mechanisms underlying impaired coronary microvascular dysfunction in INOCA and to assess whether exercise training can improve the condition. The underlying premise is that microvascular dysfunction is a systemic disease and to fulfil our aim we will study multiple aspects of microvascular function in cardiac, skeletal muscle, fat and skin by different techniques. Although not part of this ethics application, these studies in humans will, in parallel

studies, be combined by studies in an animal model of INOCA.

The project consists of two parts with the following aims and hypotheses. The following statistical analysis plan apply for study part 1 (Mechanisms Behind Microvascular Dysfunction in INOCA (ExINOCA-P1))

Study Part I: To identify vascular and related molecular mechanisms underlying INOCA by investigating microvascular function in cardiac, cutaneous, skeletal muscle and adipose tissue.

Study Part II." Impact of Exercise Training on Ischemia With Non-Obstructive Coronary Arteries (INOCA): The ExINOCA Study" aim to determine the impact of a structured exercise training program on patients with INOCA on coronary microvascular function, symptom burden, physical capacity and systemic microvascular function and related mechanisms.

Study I and II are separate studies. However, we consider it correct to merge the two studies in one main study protocol as there will be overlap in angina patients included

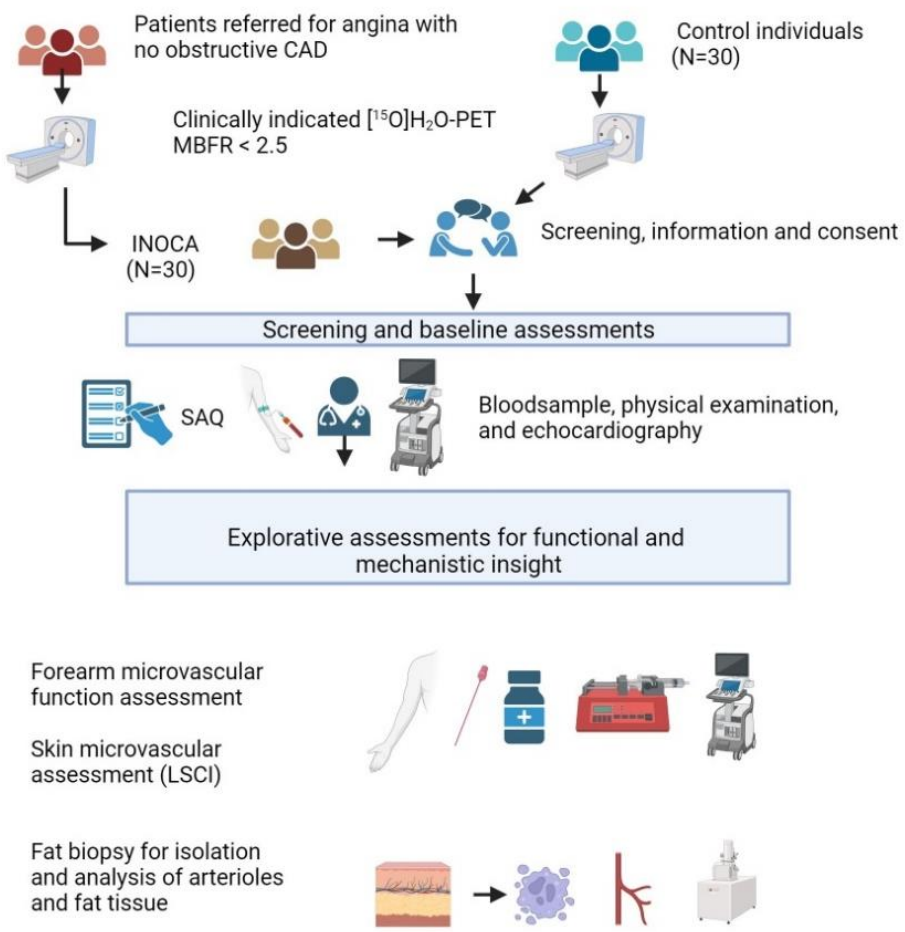
To provide the best overview, in the following we describe study Part I.

Hypotheses

The hypothesis of the overall project is that microvascular dysfunction is a systemic disease and that underlying mechanisms can be identified in several tissues in INOCA patients and moreover that the dysfunction can be reversed by a period of exercise training.

- **In Part I** (figure 1) the hypothesis is that coronary microvascular dysfunction is part of a systemic vascular dysfunction, and that we, by thorough assessment of microcirculatory function in several tissues (cardiac, skeletal muscle, skin and fat tissue), will be able to identify aspects of microvascular dysfunction and related molecular mechanisms underlying INOCA. Such mechanisms will be valuable as potential future therapeutic targets.

Fig. 1. Overview over baseline comparison between groups Study Part I



Methods

The current study is a clinical cross-sectional study in which a group of INOCA patients and a matched control group without angina are compared. The control group is included to allow for assessment of how the microvascular function compares between the patient and the control group.

Seventy (70) participants are recruited: 30 controls without angina, and 40 patients with angina and reduced myocardial blood flow reserve. The study is exploratory and conducted to obtain mechanistic insight into the pathophysiology of microvascular disease.

Based on the premise that microvascular dysfunction is a systemic disease, all participants will undergo assessment of cardiac microvascular function, stress echocardiography, forearm skeletal muscle- and skin microcirculation, and will have an adipose tissue biopsy taken for in vitro assessment of adipose microvascular function.

Measurements

Trial endpoints

As this study is exploratory there is no primary or secondary outcome. Exploratory outcomes include identification of microvascular mechanisms and related molecular pathways specific for INOCA (Please see table below for list of outcomes)

Table 1. List of outcomes in Study Part I

METHODS FOR ASSESSMENT	METHOD	SITE OF ASSESSMENT
Cardiac structure and function	Echocardiography during rest and stress	BFH/UCPH
Skin microvascular function	LSCI	BFH/UCPH
Skeletal muscle microvascular function	Brachial artery ultrasound Doppler in response to stimuli	BFH/UCPH
In vitro adipose tissue microvascular function	Myography, proteomics, transcriptomics	UCPH-BMI
Arterial compliance	Calculation made from intraarterial pressure and arterial diameter measured by ultrasound doppler	BFH/UCPH
Plasma HbA1c and lipids	Clinical chemical analysis	BFH
Plasma levels of markers related to vascular function	Mesoscale/ELISA	UCPH
Plasma levels of inflammatory markers	Mesoscale/ELISA/O-Link	BFH/UCPH
Arterial blood pressure	Automated blood pressure at rest and during exercise	BFH/UCPH

*Change in MBFR is defined as Myocardial Blood flow reserve $= \frac{\text{Global stress perfusion}}{\text{Global rest perfusion}}$, $ie\ unitless$. The primary analysis will be of comparison (intention to treat) of mean/median change in MBFR between the two groups.

**In the substudy the small arteries are derived from adipose tissue subsamples (first 20 participants in intervention group and first 20 participants from control group).

Department of Nutrition, Exercise, and Sports, University of Copenhagen (UCPH)
Department of Cardiology, Bispebjerg Frederiksberg Hospital (BFH)

Department of Biomedical Science, (UCPH-BMI)

Procedures

PET-scan with [15O]H2O

[^{15}O]H_2O-PET scan is an examination routinely used in clinical practice. At Bispebjerg Frederiksberg Hospital approximately 1000 [^{15}O]H_2O-PET scans are performed annually.

[^{15}O]H_2O-PET uses water labeled with the radioactive isotope oxygen-15 (^{15}O) as the radiotracer. This radiotracer is injected into the patient's bloodstream, allowing for the reconstruction of three-dimensional images of the distribution of the radiotracer in the body.

By dynamic measurements of the concentration of the radiotracer in the myocardium, it is possible to obtain information about blood flow and tissue perfusion, thereby aiding in the diagnosis and management of coronary artery disease (17,18).

For this procedure patients will have one peripheral venous catheter. They will be given continuous adenosine 0.14 mg/kg for 6 min to provoke vasodilation.

Participants are not allowed to drink or eat coffee, tea, dark chocolate, or any other substance containing caffeine for 24 hours before their [^{15}O]H_2O-PET scan [^{15}O]H_2O-PET involves a small amount of radiation and the use of a radioactive tracer.

The healthcare professionals adhere to radiation safety protocols and regulations to ensure the patient receives the lowest possible radiation dose while still obtaining diagnostic images.

Maximum oxygen uptake

To determine maximal oxygen uptake, the participants complete a maximal incremental cycling test during which expired air is continuously analyzed. The test begins at a workload of 50 W with a continuous increase in power of 25 W per minute until exhaustion. If expected max capacity is <100W, the protocol will be adapted. During the test heart rate and blood pressure are continuously monitored. If expected maximal exercise capacity is <75 Watt an adapted protocol will be used. The same protocol will be used before and after intervention.

Echocardiography

Echocardiographic assessment will be conducted by ultrasound doppler at baseline, guided by a standardized protocol in accordance with internationally recognized consensus guidelines. This comprehensive protocol covers various aspects of cardiac structure and function, evaluation of the heart valve system, and assessment of cardiac vasculature.

Echocardiographic outcomes will encompass a range of parameters, including but not limited to left ventricular (LV) dimensions, LV mass, LV ejection fraction (LVEF), diastolic function, and left atrial volume (LAV).

Stress Echocardiography

Stress Echocardiography is performed with the study-participant in a supine bicycle. Echo-cardiography is performed under increasing resistance using a standardized protocol. This study will assess cardiac function during stress with particular emphasis on diastolic function.

Seattle Angina Questionnaire:

The Seattle Angina Questionnaire (SAQ) is a self-administered questionnaire used in cardiac patients to quantify angina based on five scales: physical limitation scale, anginal stability scale, anginal frequency scale, treatment satisfaction scale, and the disease perception scale. The questionnaire will

be in Danish. It will be answered electronically using REDCap, or by paper if the participant does not wish to do it electronically.

Skeletal muscle microcirculatory function

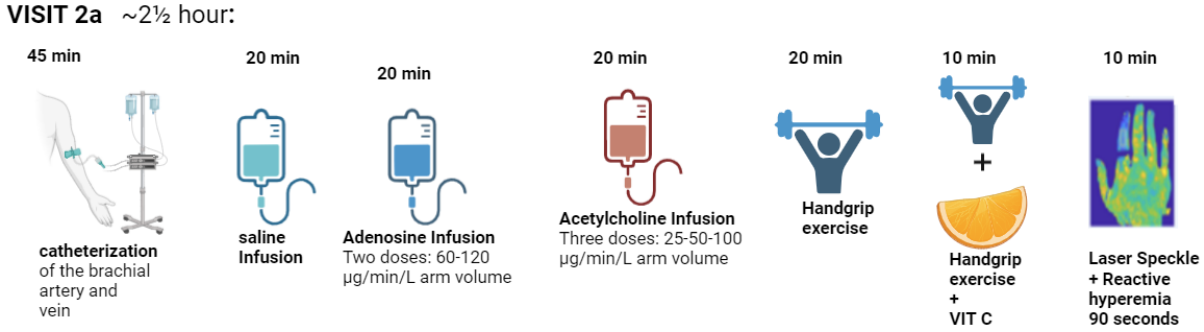
The procedure involves catheterization of the brachial artery and vein for blood sampling, intraarterial pressure measurement by a pressure transducer and for infusions of vasoactive compounds as described below. Catheters are placed under sterile conditions and after local anaesthesia of the skin with Lidocain. Throughout the experiments brachial artery blood flow is measured by ultrasound doppler. The procedure also involves short term (3-10 min) infusions of vasoactive compounds. Subjects will be randomly allocated to one out of two similar infusion protocols: A and B. The design for the two protocols is as follows:

Anthropometric measurements of the arm will be made to estimate arm volume for calculation of infusion dose. During the assessment of microvascular function heart rate and blood pressure are continuously monitored. After the experiment is completed, the catheters are removed and pressure is applied.

Protocol A.

- Infusion of adenosine, two doses (60-120 mikrog/min/l arm volume)
- Infusion of acetylcholine in three doses (Miochol-E, Bausch & Lomb Inc.) (25-50-100 mikrog/min/l arm volume)
- Handgrip exercise at 15% of maximal capacity for 14 min, first 4 min without infusion and then with 10 min of infusion of ascorbic acid (80 mg min/l arm volume).

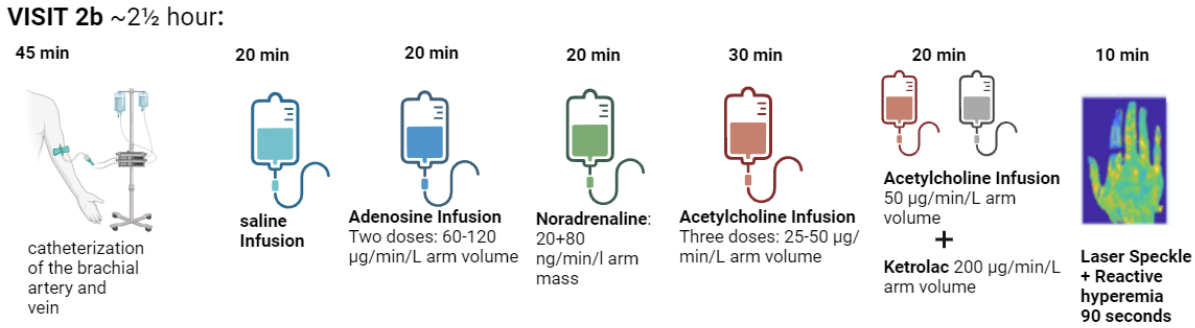
Illustration of Protocol A



Protocol B

- Infusion of adenosine, two doses (60-120 mikrog/min/l arm volume)
- Infusion of noradrenaline two doses (20-80 ng/min/l arm volume)
- Infusion of acetylcholine in two doses (Miochol-E, Bausch & Lomb Inc.) (25-50 mikrog/min/l arm volume)
- combined infusion of 50 mikrog/min/l arm volume acetylcholine and infusion of ketorolac (Toradol; Roche) (200 mikrog/min/l arm volume) for 5 min.

Illustration of Protocol B



Laser Speckle contrast Imaging (LSCI)

LSCI is an imaging technique that will help to visualize and quantify the blood perfusion of the skin (15).

The method will be used to quantify blood perfusion in the hand of the participant at resting baseline, after short term occlusion of the arm (reactive hyperaemia test) and during adenosine infusion (vasodilation) conducted concomitant with the measurements described above in *Skeletal muscle microcirculatory function*.

Description of the LSCI method: Laser light will be sent to the tissue and the reflected laser light is detected as a 'Speckle' pattern. This 'Speckle pattern' is used to make a map of the blood perfusion of the skin. The LSCI imaging will be performed using an LSCI system that was constructed in collaboration with Center for Functionally Integrative Neuroscience at Aarhus University Hospital. The system consists of a 785 nm laser that is equipped with a diffuser thereby enabling large-area illumination of the skin surface. A compact CMOS camera is used to detect the reflected laser light. The camera is equipped with a polarizing filter to eliminate the surface reflected laser light and optimize the visualization of the skin perfusion. Image data are acquired using dedicated data acquisition software and post-processed in MATLAB to generate blood flow index (BFI) and relative BFI images.

Reactive hyperemia test

Occlusion by application of a tourniquet will be conducted on the upper arm for 90 seconds.

Vasodilation test

Involves a stressor-test in which low-dose adenosine is given intraarterially. The procedure is conducted concomitant with the skeletal muscle microcirculation procedure when adenosine is infused.

Adipose tissue biopsy

Biopsies will be obtained either at The Department of Nutrition, Exercise and Sports or at Bispebjerg/Frederiksberg Hospital in collaboration with University of Copenhagen.

Under local anesthesia (lidocaine 10 mg/ml with adrenalin 5 µg/ml) an adipose tissue biopsy (3x0.5x0.5 cm) will be performed in sterile environment by a medical doctor or by a trained health care professional supervised by a medical doctor.

The biopsy will be obtained from the gluteal region, where a small boat-shaped incision is made following the natural creases of the skin. The adipose tissue, along with a small skin flap, is removed (1-2 cm^3). Subsequently, the subcutaneous tissue is closed with a self-absorbable suture, and the skin is sutured (approximately 3 stitches) that should be removed after 10 days. The wound is covered with a bandage that can be removed after 24 hours, but we recommend applying a new bandage until stich removal.

The adipose biopsies are immediately transferred to ice-cold physiological buffer and transported to the laboratory at the Biomedical Institute, University of Copenhagen for analysis and storing.

From these biopsies, segments of small arteries (diameter about 200 µm) will be promptly dissected free. One segment will be mounted in a myograph for recording of isometric tension (i.e., vasoconstriction and vasodilation) and for histochemical analysis, while the other segment will be snap-frozen for proteomic and histological analysis and the adipose tissue/perivascular adipose tissue will be

used for genomic and transcriptomic analysis (see below).

The following methods will be used on the free-dissected arteries:

Myography

In the excised artery, we will evaluate the relaxation to adenosine and to acetylcholine and the dependence of the response to prostaglandins. To evaluate the role of NO and H_2O_2 we will also evaluate the relaxation to acetylcholine after inhibition of the NO-synthase with L-NAME and after metabolism of H_2O_2 with catalase. We will further evaluate the vasoconstrictor response to the neurotransmitter noradrenaline and the vasodilator response to the beta-receptor agonist isoprenaline to obtain a comprehensive evaluation of the pharmacological characteristics of the small arteries. Finally, assessment of the endothelin-1 vasoconstriction will be performed.

Analysis of microvascular segments from adipose tissue and the adipose tissue:

We will map the proteome of the small arteries. This will be done by using an arterial segment (~2 mm) obtained from the adipose tissue sample.

In brief, digested peptides from arteries will be analyzed by liquid chromatography tandem mass spectrometry (LC-MS/MS), and data analysis will be used to identify proteins and their relative abundances, which enables statistical comparison.

Significantly regulated proteins will be subjected to gene-overrepresentation analysis that can identify biological pathway associations in the data. This unbiased technology is advantageous for gaining novel understanding of the underlying biological mechanisms responsible for the dysfunction of the small arteries and arterioles in patients with microvascular disease and effect of exercise training on these. This discovery-based approach is essential hypothesis-generating research that will enable us to define the mechanisms underlying INOCA, which we will be able to test in our functional experiments. To stimulate new research and therapeutic development, we plan to make all data acquired publicly available, thereby enabling other research groups to use the data via the ProteomeXchange database. A small fraction of the arteries and perivascular fat-tissue will be sectioned for histological analysis. The adipose tissue/perivascular adipose tissue will be analyzed for mRNA and proteins by use of RNA-sequencing and proteomic analysis. This analysis will be done as part of the aim to understand microvascular changes in INOCA and how training may influence the microvasculature. The analysis will enable an assessment of how changes in mRNA and proteins are altered in relation to structure and function of the tissue. The assessment includes isolation of cell nuclei from the fat biopsies.

Oxidative stress

A part of the biopsy (mainly fat cells, connective tissue, and small arteries) will be stained for lipid peroxidation as a measure of oxidative stress of the tissue. For this we will quantify malondialdehyde which is a general product of nonenzymatic peroxidation of polyunsaturated fatty and arachidonic acids as done by us before (14).

Medical History and Concomitant Medicine

Medical history will be registered at the baseline visit (V1) and evaluated in relation to the protocol's exclusion criteria. All medication that is necessary for the participants health and which is not in the protocol exclusion criteria may be continued during the study. At the following visits participant will be asked if they have taken any new medicine or changes in dosage since last visit. Medical History will be registered in the Medicine form in the CRF and changes will be registered in the Concomitant Medicine Form in the CRF.

Statistics

Sample size determination relates to the primary outcome myocardial blood flow reserve. Sample size calculations are based on a power of 0.80 and alpha level of 0.05. We regard 0.3 as a clinically relevant improvement in myocardial blood flow reserve. SD of repeated measurement has been 0.2-0.4 in previous studies. With a conservatively estimated SD of 0.50, alfa 0.05, power 0.8 and allowing for

15% drop-out, we will include 100 patients.

Inclusion Criteria

- Age>50
- Only for angina patients:
- Have CMD, defined as myocardial bloodflow reserve (MBFR) < 2.5 or hyperemic myocardial blood flow (hMBF) < 2.3ml/g/min
- No obstructive CAD as determined by the clinical assessment of [15O]H2O-PET
- Able and willing to provide informed consent

Exclusion Criteria

- Females of childbearing potential (defined as a premenopausal female capable of becoming pregnant). The female patient must either be postmenopausal, defined as amenorrhea for at least 1 year, or surgically sterile
- Heart failure, defined as left ventricular ejection fraction of less than 40%
- Uncontrolled hypertension defined as blood pressure above target 140/90 for all
- Co-morbidity resulting in <1 year expected survival
- Considered by the investigator, for any reason, to be an unsuitable candidate for the study.
- Unable or unwilling to exercise, e.g. due to arthritis or injury
- Already are regularly physically active and/or have a maximal oxygen uptake >45 ml/kg/min
- The subject has a known allergy to either: norepinephrine, adenosine, ketorolac, and or ascorbic acid (vitamin C).

Primary Outcome Measure:

1. Vascular function
   Vascular conductance measured by ultrasound doppler during infusion of acetylcholine

Secondary Outcome Measures:

2. Vascular function
   Vascular conductance measured by ultrasound doppler during infusion of Adenosine

3. Myocardial Blood flow reserve

Determined by the clinical assessment of [15O]H2O-PET

4. Skeletal Muscle Microvascular Function

Evaluated by brachial artery ultrasound Doppler in response to exercise stress to measure blood flow and vascular responsiveness in skeletal muscles.

5. Changes in isolated small artery reactivity assessed with myography

Analyzed using myograph to study the tone of smooth muscle cells

6. Arterial Compliance
   Determined by calculations made from intra-arterial pressure and arterial diameter measurements obtained via ultrasound Doppler to assess arterial compliance.

7. Plasma Lipids
   Conducted through clinical chemical analysis to measure levels of HDL, and triglycerides in the

blood, providing insights into lipid profiles.

8. Plasma HbA1c
   Conducted through clinical chemical analysis to measure levels of HbA1c in the blood, providing insights into glucose metabolism.

9. Plasma Levels of Markers Related to Vascular Function
   Assessed using Mesoscale/ELISA to quantify biomarkers associated with vascular function, providing insights into endothelial health and vascular integrity.

10. Plasma Levels of Inflammatory Markers

Measured using Mesoscale/ELISA/O-Link platforms to evaluate the presence and levels of inflammatory markers, indicating systemic inflammation.

11. Arterial Blood Pressure
    Monitored with automated blood pressure measurements at rest and during exercise to assess overall cardiovascular health and response to physical activity.

12. Cardiac Function
    Changes in stroke volume using echocardiography during rest and exercise stress

Other Pre-specified Outcomes:

1. Tone of smooth muscle cells
   Changes in isolated small artery reactivity assessed with myography

2. Proteomic and transcriptomic analyses
   Changes in gene and protein expressions patterns in small arteries

Time frame for all measures are: Baseline only

References

1. P. Brainin, D. Frestad, and E. Prescott, “The prognostic value of coronary endothelial and microvascular dysfunction in subjects with normal or non-obstructive coronary artery disease: A systematic review and meta-analysis.,” *Int J Cardiol*, vol. 254, pp. 1–9, 2018, doi: 10.1016/j.ijcard.2017.10.052.

2. J. Schroder *et al.*, “Coronary flow velocity reserve predicts adverse prognosis in women with angina and no obstructive coronary artery disease: results from the iPOWER study.,” *Eur Heart J*, vol. 42, no. 3, pp. 228–239, 2021, doi: 10.1093/eurheartj/ehaa944.

3. P. S. Douglas *et al.*, “Outcomes of anatomical versus functional testing for coronary artery disease.,” *N Engl J Med*, vol. 372, no. 14, pp. 1291–1300, 2015, doi: 10.1056/NEJMoa1415516.

4. J. Reeh *et al.*, “Prediction of obstructive coronary artery disease and prognosis in patients with suspected stable angina.,” *Eur Heart J*, vol. 40, no. 18, pp. 1426–1435, 2019, doi: 10.1093/eurheartj/ehy806.

5. R. O. Cannon, “Microvascular angina and the continuing dilemma of chest pain with normal coronary angiograms.,” *J Am Coll Cardiol*, vol. 54, no. 10, pp. 877–885, 2009, doi: 10.1016/j.jacc.2009.03.080.

6. C. J. Pepine *et al.*, “Coronary microvascular reactivity to adenosine predicts adverse outcome in women evaluated for suspected ischemia results from the National Heart, Lung and Blood Institute WISE (Women’s Ischemia Syndrome Evaluation) study.,” *J Am Coll Cardiol*, vol. 55, no. 25, pp. 2825–2832, 2010, doi: 10.1016/j.jacc.2010.01.054.

7. M. B. Britten, A. M. Zeiher, and V. Schächinger, “Microvascular dysfunction in angiographically normal or mildly diseased coronary arteries predicts adverse cardiovascular long-term outcome.,” *Coron Artery Dis*, vol. 15, no. 5, pp. 259–264, 2004, doi: 10.1097/01.mca.0000134590.99841.81.

8. P. K. Mehta *et al.*, “Mental stress peripheral vascular reactivity is elevated in women with coronary vascular dysfunction: Results from the NHLBI-sponsored Cardiac Autonomic Nervous System (CANS) study,” *Int J Cardiol*, vol. 251, pp. 8–13, Jan. 2018, doi: 10.1016/j.ijcard.2017.10.061.
9. T. J. Ford *et al.*, “Systemic microvascular dysfunction in microvascular and vasospastic angina.,” *Eur Heart J*, vol. 39, no. 46, pp. 4086–4097, 2018, doi: 10.1093/eurheartj/ehy529.
10. H. Allaqaband, D. D. Gutterman, and A. O. Kadlec, “Physiological Consequences of Coronary Arteriolar Dysfunction and Its Influence on Cardiovascular Disease.,” *Physiology.*, vol. 33, no. 5, pp. 338–347, 2018, doi: 10.1152/physiol.00019.2018.
11. A. O. Kadlec *et al.*, “PGC-1α (Peroxisome Proliferator-Activated Receptor γ Coactivator 1-α) Overexpression in Coronary Artery Disease Recruits NO and Hydrogen Peroxide during Flow-Mediated Dilation and Protects Against Increased Intraluminal Pressure,” *Hypertension*, vol. 70, no. 1, pp. 166–173, Jul. 2017, doi: 10.1161/HYPERTENSIONAHA.117.09289.
12. H. E. Suhrs *et al.*, “Inflammation, non-endothelial dependent coronary microvascular function and diastolic function-Are they linked?,” *PLoS One*, vol. 15, no. 7, p. e0236035, 2020, doi: 10.1371/journal.pone.0236035.
13. S. Højstrup *et al.*, “Coronary Microvascular Disease Assessed by 82-Rubidium Positron Emission Tomography Myocardial Perfusion Imaging Is Associated With Small Vessel Disease of the Kidney and Brain.,” *J Am Heart Assoc*, vol. 12, no. 12, p. e028767, 2023, doi: 10.1161/JAHA.122.028767.
14. C. Staehr *et al.*, “Migraine-Associated Mutation in the Na,K-ATPase Leads to Disturbances in Cardiac Metabolism and Reduced Cardiac Function.,” *J Am Heart Assoc*, vol. 11, no. 7, p. e021814, 2022, doi: 10.1161/JAHA.121.021814.
15. A. Lazaridis *et al.*, “Skin microvascular function, as assessed with laser speckle contrast imaging, is impaired in untreated essential and masked hypertension.,” *Hypertens Res*, vol. 45, no. 3, pp. 445–454, 2022, doi: 10.1038/s41440-021-00816-w.