Reduced Microvascular Blood Volume as a Driver of Coronary Microvascular Disease in Patients with Non Obstructive Coronary Artery Disease

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To investigate whether MBV is reduced in patients with NOCAD and signs and symptoms of ischemia, relative to healthy controls. The specific aims are 1) to investigate if MBV is reduced in NOCAD patients at baseline, 2) to investigate if MBV is...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Coronary artery disorders
Study type	Observational invasive

Summary

ID

NL-OMON49617

Source
ToetsingOnline

Brief title
MICORDIS study

Condition

- Coronary artery disorders

Synonym
coronary microvascular dysfunction, Non obstructive coronary artery disease

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum

Source(s) of monetary or material Support: Netherlands Heart Institute;Innovatiefonds Zorgverzekeringen;Jubileumfonds 50 jaar VUmc

Intervention

Keyword: Capillary recruitment, Coronary microvascular dysfunction, Myocardial blood volume, Non-obstructive coronary artery disease

Outcome measures

Primary outcome

The primary endpoint is the statistical difference in MBV between NOCAD patients and healthy controls. We compare MBV between groups at baseline, during hyperinsulinemia and during increased cardiac contraction.

MBV is measured using MCE. Hyperinsulinemia is induced by a two hour HE-clamp and cardiac stress with increased contraction is induced by the infusion of dobutamine.

Secondary outcome

The insulin-mediated capillary recruitment (*MBV) is the difference in MBV at baseline and after HE-clamp. Insulin-resistance is calculated using the M-value of the last half hour of HE-clamp.

1. MBV, MBF, *MBV, baseline characteristics, cardiovascular risk factors, questionnaire results, blood parameters and measurement indexes compared between males and females from the patient and control group.

2. Differences in MBV and MBF between baseline and after HE-clamp of the patient and control group and differences in MBV and MBF between baseline and after dobutamine stress of the patient and control group.

3. Baseline characteristics, cardiovascular risk factors, questionnaire results

and measurement indexes compared between the patient and control group.

4. MBV, MBF and *MBV compared between insulin resistant subjects and

non-insulin resistant subjects.

5. Correlation between MBV (+other related variables) measured with MCE and MBV

measured with CMR.

6. Protein expression and phosphorylation of microvascular endothelial cells

compared between the patient and control group.

Study description

Background summary

About 21-46% of patients (i.e. 65% women and 35% men) with signs and symptoms of ischemic heart disease have nonobstructive coronary artery disease (NOCAD). Patients with NOCAD are at increased risk of major adverse cardiac events and have worse prognosis compared to healthy people. The pathophysiology behind NOCAD still remains unresolved, but includes coronary microvascular dysfunction, spasm and impaired vascular effects of insulin. Myocardial blood flow (MBF) and myocardial blood volume (MBV) are important parameters of the coronary microcirculation. The coronary flow reserve (CFR) with infusion of adenosine is currently used to assess coronary microvascular dysfunction, although this technique might not be sensitive enough to detect coronary microvascular dysfunction because no evaluation of MBV is possible. Studies have shown that adenosine infusion increases MBF without an increase in MBV, but that increased myocardial oxygen consumption or hyperinsulinemia increases both MBF and MBV. Therefore, we hypothesize that dysregulation of the MBV contributes to coronary microvascular dysfunction in NOCAD patients with signs and symptoms of ischemic heart disease.

Study objective

To investigate whether MBV is reduced in patients with NOCAD and signs and symptoms of ischemia, relative to healthy controls. The specific aims are 1) to investigate if MBV is reduced in NOCAD patients at baseline, 2) to investigate if MBV is reduced in NOCAD patients during hyperinsulinemia and 3) to investigate if MBV is reduced in NOCAD patients during increased myocardial contraction.

Study design

The study is an observational cross-sectional cohort study. The patient group will undergo CFR measurement and coronary vasoreactivity testing during coronary angiogram. Both groups will undergo myocardial contrast echocardiography with an hyperinsulinemic euglycemic-clamp to induce hyperinsulinemia and dobutamine to increase contractility, cardiac magnetic resonance with T1-mapping and assessment of endothelial function in a non-invasive way with EndoPAT.

Study burden and risks

Study subjects do not directly benefit from participation, besides their contribution to increasing knowledge about NOCAD. Risks to participation are medium. Disadvantages to participation are minimal but include time consumption (i.e. 2 hospital visits) and uncomfortable feeling during adenosine or dobutamine infusion and EndoPAT.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patient group:
- Age > 40 years
- Signed informed consent
- Stable and chronic symptoms suggesting ischemic heart disease
- NOCAD on coronary angiography: coronary artery stenosis <= 50% and/or FFR > 0.80
- Prior transthoracic echocardiographic assessment
Control group:
- Age > 40 years
- Signed informed consent36 bgc

Exclusion criteria

- Age > 80 years
- Obstructive coronary artery disease, defined as more than 50% obstruction of any coronary artery
- FFR < 0.80
- Use of medication for the control group
- Persons working at the department of Cardiology from the VU university medical centre
- Persons involved in the study
- Family (partner, parents, child, brother or sister or statutory person) from persons working at the department of Cardiology from the VU university medical centre, or who are involved in the study
- Pregnancy
- History of coronary revascularization (e.g. percutaneous coronary intervention or coronary artery bypass grafting)
- History of coronary artery disease, or acute coronary syndrome (e.g. myocardial infarction and unstable angina pectoris)
- History of stroke
- History of cardiac arrhythmia*s
- History of heart valve disease
- Left ventricular dysfunction
- Congenital heart disease
- Insulin-dependent diabetes mellitus
- Extensive comorbidities (i.e. cancer, other chronic diseases)

- Impaired renal function, defined as creatinine > 100 and eGFR < 60.
- Symptomatic asthma or chronic obstructive pulmonary disease
- Known allergic reaction to contrast agent
- Insufficient echocardiographic imaging quality
- Contra-indications for CMR (e.g. severe claustrophobia, metal implants, severe renal failure, severe asthma and known hypersensitivity for gadolinium)
- Contra-indications for microbubble usage (e.g. right-to-left shunt, severe pulmonary hypertension, uncontrolled hypertension and adult respiratory distress syndrome)
- Contra-indications for adenosine usage (e.g. hypersensitivity to active substances, second or third degree atrio-ventricular block, sick sinus syndrome, long QT syndrome, severe hypertension, concomitant use of dipyridamole)
- Contra-indications for dobutamine usage (e.g. hypersensitivity to dobutamine, severe heart failure, acute pericarditis, myocarditis or endocarditis, aortic dissection or aneurysm, inadequately controlled arterial hypertension or hypotension, hypovolemia)

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	16-10-2018
Enrollment:	61
Type:	Actual

Ethics review

Approved WMO Date:	07-08-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-06-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-09-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-05-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL66532.029.18