# Assessment of microvascular alterations in patients with angina pectoris and no evidence of significant coronary artery disease

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Coronary artery disorders
Study type	Observational non invasive

# Summary

### ID

NL-OMON37954

**Source** ToetsingOnline

#### **Brief title**

Glycocalyx perturbation in patients with microvascular angina pectoris

### Condition

- Coronary artery disorders
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

**Synonym** Atherosclerosis;

**Research involving** Human

### **Sponsors and support**

**Primary sponsor:** Medisch Universitair Ziekenhuis Maastricht **Source(s) of monetary or material Support:** Ministerie van OC&W

#### Intervention

Keyword: Coronary artery disease, Glycocalyx, Magnetic resonance imaging, Perfusion

#### **Outcome measures**

#### **Primary outcome**

- MR perfusion imaging during resting conditions and adenosine infusion in a)

patients with proven coronary artery disease and b) patient with angina

pectoris but without significant coronary artery lesions.

- OPS imaging of the sublingual circulation to measure glycocalyx dimension and

barrier function before and after sublingual NTG administration in a) patients

with proven coronary artery disease, b) patient with angina pectoris but

without significant coronary artery lesions, and c) healthy controls.

#### Secondary outcome

n.a.

# **Study description**

#### **Background summary**

Atherosclerosis is currently the leading cause of death and disability in the developed world, often causing myocardial and cerebral infarction, kidney failure and peripheral arterial occlusive disease. Atherosclerosis is considered to be a chronic inflammatory response of the arterial wall, initiated by injury of the endothelium. The cause of this injury is unknown, but several factors, like hyperlipidemia, hypertension, smoking and toxins have been indicated to play a role in its pathogenesis. This injury of the endothelium causes an increased migration of leukocytes and lipids into the intima, hereby inducing chronic inflammation, endothelial dysfunction and

eventually formation of atherosclerosis.

Severe atherosclerotic obstruction of the coronary arteries causes ischemia of the myocardium and subsequent angina pectoris. However, a considerable number of patients with symptoms of chest pain during exercise have no relevant coronary artery stenosis. Between 10 and 20% of patients with typical angina chest pain have normal angiograms. In addition, percutaneous coronary intervention (PCI) of a non-significant coronary artery stenosis did not improve symptoms and outcome. In these patients the angina has been related to coronary microvascular dysfunction.

#### Magnetic Resonance perfusion imaging

MR perfusion imaging is a non-invasive method to quantify myocardial perfusion. Perfusion abnormalities can be detected in patients with coronary artery disease after pharmacologic stress with adenosine infusion. Normal tissue will respond to the vasodilator stimulus with further increase in myocardial perfusion, whereas a severe stenosis will have no perfusion reserve in rest and will therefore not be able to increase perfusion during stress. Several studies have demonstrated that MR perfusion imaging during intravenous administration of adenosine can detect subendocardial hypoperfusion in patients with typical angina but no significant coronary stenosis.This result implies that microvascular disease can cause myocardial ischemia and subsequent angina pectoris in patients without significant coronary artery disease at coronary angiography.

#### Non-invasive glycocalyx measurements

The endothelial glycocalyx, a  $\sim 0.5 \mu m$  thick, hydrated layer consisting of proteoglycans, glycosaminoglycans, and associated plasma proteins, forms the interface between the flowing blood and the endothelium. The glycocalyx plays a pivotal role in orchestrating microvascular homeostasis. Degradation of the glycocalyx in the microvasculature has been associated with an impaired shear-dependent NO production, an increased endothelial adhesion of leucocytes and platelets, and an increased water and protein permeability of the vessel wall. We propose that assessment of glycocalyx loss as a reflection of microvascular dysfunction, can be useful in patients with angina. A new, non-invasive method to measure local glycocalyx dimensions in individual microvascular blood vessels is orthogonal polarization spectral (OPS) or sidestream dark field (SDF) imaging of the sublingual circulation. This method has been validated. Previous data using intravital imaging in experimental animals showed that glycocalyx loss is associated with a reduced microvascular blood volume recruitment during vasodilator administration. It was observed that a healthy glycocalyx provides a protective coating to the vascular endothelial lining that is not accessible for flowing red blood cells, unless the glycocalyx is - transiently - exposed to a vasodilator such as nitro-glycerine (NTG). During exposure to NTG, the glycocalyx barrier function is transiently reduced in order to facilitate capillary perfusion and exchange. Thus, in addition to the measurement of glycocalyx dimension at rest

(baseline), it is also essential to determine its response to NTG exposure.

#### Study objective

In the current study, we want to determine and correlate the results of both perfusion capacity (with MR imaging) and sublingual glycocalyx dimensions in a) patients with proven obstructive coronary artery disease and b) patients with angina but without significant coronary lesions (suspected to have microvascular disease). Furthermore, we want to compare the glycocalyx measurements in these two patients populations to sublingual glycocalyx dimensions in healthy controls. Since glycocalyx loss is found in the presence of cardiovascular risk factors and appears to be an early marker of microvascular dysfunction, we hypothesize that patients with angina but without significant coronary artery lesions are characterized by a compromised glycocalyx and are prone to coronary perfusion defects during adenosine administration. To address this hypothesis, we want to investigate MR-derived coronary perfusion together with sublingual glycocalyx dimensions in these patients and compare them with patients with proven coronary artery disease as well as healthy controls.

#### Clinical relevance and future applications

A substantial number of patients suffer from angina pectoris that cannot be explained by obstruction of epicardial coronary arteries (i.e. no obstructive coronary artery disease present on angiography). In these patients it is important to test whether the angina can be related to coronary microvascular dysfunction. Identification of angina caused by coronary microvascular dysfunction is important because of the associated adverse prognosis, including an increased risk of adverse cardiovascular events such as myocardial infarction, congestive heart failure, and sudden cardiac death. The current standard diagnostic tests to detect coronary artery disease, such as invasive or non-invasive coronary angiography, depict only epicardial coronary arteries and are not able to assess microvascular disease. As a result, a large patient population with angina-like symptoms, positive exercise ECG but without obstructive coronary artery disease on coronary angiogram currently remains undiagnosed and untreated. In these patients, diagnostic tests for microvascular dysfunction are lacking, let alone optimal treatment. MR perfusion imaging can be used to quantify myocardial perfusion and possibly identify myocardial ischemia due to microvascular disease. This non-invasive imaging technique therefore has the potential to diagnose microvascular dysfunction and evaluate new therapeutic strategies in patients without relevant coronary artery stenosis.

In addition, MRI-derived myocardial perfusion imaging will be related to sublingual glycocalyx dimensional estimates. Since glycocalyx loss appears to be an early marker for microvascular dysfunction, we propose that clinical sublingual glycocalyx imaging will suffice in the near future to diagnose individuals that are at risk for developing angina. Furthermore, previous research conducted in animals demonstrated that it is possible to pharmacologically 1) protect the glycocalyx against free radicals, 2) inhibit the proteolytic enzymes that break down the glycocalyx and 3) stimulate the production of the glycocalyx. A recent study reported that the glycocalyx perturbation and increased vascular permeability that is associated with diabetes can be partially restored by sulodexide administration. These developments can lead to new screening methods for patients with angina pectoris but without significant coronary artery disease and potentially also lead to the development of new therapeutic interventions for patients with (micro)vascular disease.

#### Objective 1

a) To image myocardial perfusion during resting conditions and adenosine infusion in a) patients with proven coronary artery disease, and b) patients with angina but without significant coronary artery lesions.

b) To determine whether patients with stable angina but without significant coronary lesions are associated with (subendocardial) perfusion deficits on MR perfusion imaging.

#### Objective 2

a) To estimate the glycocalyx dimensions by sublingual OPS measurements, before and after sublingual NTG administration in a) patients with proven coronary artery disease, b) patients with angina but without significant coronary artery lesions and c) healthy controls.

b) To correlate the MRI-derived coronary perfusion capacity to sublingual OPS measurements in a) patients with proven coronary artery disease and b) patients with angina but without significant coronary artery lesions.

c) To compare the measurements of glycocalyx dimensions at rest (baseline) and after NTG exposure in a) patients with proven coronary artery disease, b) patients with angina but without significant coronary artery lesions, and c) healthy controls.

#### Study design

The study will be an observational case control study. The investigations can be performed in random order.

• OPS glycocalyx measurements (approximately 30 minutes) will be performed in all three study groups. OPS imaging of the sublingual microcirculation

Sublingual administration of NTG (1 spray dose)

Second OPS imaging of the sublingual microcirculation

 MRI perfusion scan (approximately 60 minutes) will only be performed in the two patient groups
 Preparations
 MR imaging (40 minutes)

#### Study burden and risks

MR stress perfusion imaging is currently a standard, safe, non-invasive diagnostic tool for patients with (suspected) coronary artery disease. Detailed imaging of myocardial perfusion in patients with and without significant coronary artery disease can lead to better insights into (micro)vascular disease and optimal treatment for patients.

The OPS imaging of the sublingual microcirculation is also a safe and painless test. However, subjects are restricted by a fasting period from midnight to their visit.

# Contacts

#### Public

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# **Trial sites**

#### **Listed location countries**

Netherlands

# **Eligibility criteria**

Age

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

### **Inclusion criteria**

General:

Subjects who want to participate in the study should be over 18 years of age and be able to give informed consent.;Patients with coronary artery disease:

These patients should have proven coronary artery disease, defined as >=50% diameter stenosis objectified by coronary angiography. ;Patients with suspected small vessel disease: These patients should have a positive exercise ECG but no evidence of significant coronary artery disease on their coronary angiogram. ;The time between the coronary angiogram and the MR perfusion scan and OPS imaging cannot exceed one year. It can be reasonably expected that the status of the coronaries will not have changed significantly over this time period if the symptoms of angina have not changed. ;Healthy controls:

These subjects must be free of angina pectoris or (a history of) coronary artery disease.

### **Exclusion criteria**

Patients:;General:

- Age < 18 years.
- Unable to give informed consent.;Other cardiac pathology:
- Atrial fibrillation.
- Unstable angina pectoris (persistent CCS class IV despite medical treatment).
- Cardiogenic shock.
- Congestive heart failure NYHA class >=III. ;Contraindication to adenosine side effects:
- AV-block (2nd or 3rd degree).
- Severe asthma.
- COPD Gold IV.;General contra-indications to MR imaging
- Non compatible metallic implant (vascular clip, neuro-stimulator, cochlear implant).
- Pacemaker or ICD.
- Claustrophobia.
- Body weight >130 kg.
- Contraindication to MRI contrast agent:
- Renal failure (GFR <= 30 mL/min) / chronic kidney disease stage 4 & 5. ;Healthy controls:;General:
- Age < 18 years.
- Unable to give informed consent.; Evidence of coronary artery disease:
- Angina pectoris.

- >= 50% diameter coronary stenosis objectified by coronary angiography or computed tomographic (CT) angiography.

- Previous myocardial infarction.
- Previous coronary revascularization.

# Study design

### Design

Study type: Observational non invasive		
Masking:	Open (masking not used)	
Control:	Uncontrolled	
Primary purpose:	Basic science	

### Recruitment

NL	
Recruitment status:	Recruitment stopped
Start date (anticipated):	16-02-2011
Enrollment:	60
Туре:	Actual

# **Ethics review**

Approved WMO	
Date:	29-12-2010
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO	
Date:	28-03-2012
Application type:	Amendment
Review commission:	MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC azM/UM (Maastricht)

# **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

ССМО

ID NL33245.068.10