Artificial Intelligence-assisted Diagnostics in Angina with No Obstructive Coronary Artery Disease

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1.1 Primary Objectives1. To document the prevalence of ischemic intracoronary electrocardiogram changes in ANOCA patients with equivocal acetylcholine provocation test results.2. To document the diagnostic efficacy of the 12-lead Holter ECG to...

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

Summary

ID

NL-OMON57079

Source
ToetsingOnline

Brief title
AI in ANOCA

Condition

- Coronary artery disorders

Synonym
Angina pectoris without obstructive coronary artery disease, unexplained chest pain

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Nederlandse Hartstichting

Intervention

Keyword: Angina with no obstructive coronary artery disease, ANOCA, Artificial Intelligence, Coronary vasosmotor disorder, Machine Learning

Outcome measures

Primary outcome

1. Percentage of patients with ischemic intracoronary electrocardiogram changes in ANOCA patients with equivocal acetylcholine provocation test results.

2. Sensitivity and specificity of 12-lead Holter ECG to identify ischemic ECG changes during acetylcholine-provoked myocardial ischemia as compared to simultaneous 12-lead surface ECG recordings.

3. Sensitivity and specificity of outpatient 12-lead Holter ECG to identify patients with a positive acetylcholine test result.

Secondary outcome

1. Development of an algorithm to optimize identification of ischemic ECG changes on the 12-lead Holter ECG.

2. Performance of the Holter ECG algorithm to discriminate between patients with and without positive acetylcholine provocation testing.

3. Development of an algorithm to detect beat-to-beat ischemic ECG changes on the intracoronary ECG.

4. Development of an algorithm to detect beat-to-beat ischemic ECG changes on the 12-lead surface ECG.

5. Development of an algorithm to quantify ischemic ECG changes on the 12-lead surface ECG and de intracoronary ECG.

Study description

Background summary

Ischemic heart disease (IHD) affects 126 million people and remains the number one cause of death and disability worldwide. Angina pectoris is an umbrella term describing symptoms of chest pain, chest tightness, or dyspnea related to IHD. Angina pectoris is diagnosed in 180.000 people in the Netherlands yearly. Diagnostics in angina pectoris remain focused on detecting obstructive epicardial coronary artery disease (CAD), which may lead to evidence-based treatment including medical therapy and coronary revascularization. However, among patients undergoing coronary angiography for angina pectoris, 40-70% have no CAD.(1) This is more common in women than in men and is associated with poor quality of life, increased risk of cardiovascular events, and high medical expenses due to ongoing symptoms, repeat (invasive) investigations and hospital admissions.(2-5) Although the reasons for angina pectoris without epicardial CAD are multifactorial, many of these patients have a disorder of coronary artery vasomotor function.(6) This term relates to the occurrence of vasospasm in the epicardial coronary artery or the microvasculature, to microvascular vasodilator dysfunction, or to a combination of these disorders. These conditions can be diagnosed during invasive coronary angiography by applying additional testing, referred to as coronary function testing (CFT). CFT involves the administration of acetylcholine to study endothelium-dependent vasodilatation and the susceptibility to coronary vasospasm, and the administration of adenosine to study endothelium-independent vasodilatation. The response to acetylcholine administration in terms of reproduction of anginal symptoms, electrocardiographic changes related to myocardial ischemia, and angiographic narrowing of the coronary arteries determines the likelihood of coronary vasospasm. Coronary blood flow responses to adenosine administration define the vasodilator capacity of the coronary circulation as the most important diagnostic marker of coronary microvascular dysfunction. Together, these results inform on the specific coronary vasomotor disorder in the individual patient. When performed routinely in patients with angina and no obstructive coronary artery disease (ANOCA), a vasomotor disorder is identified in up to 85% of patients.(6) Of these, the majority consists of forms of coronary vasospasm (80%), while only a few percent of patients have coronary microvascular dysfunction as the final diagnosis.(7) This is crucial, since coronary microvascular dysfunction can be diagnosed using non-invasive techniques, but invasive CFT is required to diagnose coronary vasospasm. Hence, invasive diagnostics are currently a must to adequately diagnose patients with ANOCA.

However, particularly in the diagnosis of coronary vasospasm, several caveats exist. The diagnosis of coronary vasospasm is based on international diagnostic criteria.(8) For epicardial coronary spasm, provocation should induce

epicardial coronary artery constriction of >90% in lumen diameter compared to the maximally vasodilated state, in combination with recognizable angina, and ischemic changes in the 12-lead electrocardiogram (ECG). For microvascular spasm, provocation should induce recognizable angina and ischemic changes in the 12-lead ECG. When patients do not fulfil these diagnostic criteria, the test is considered equivocal (1-2 positive criteria) or negative (0 positive criteria). An equivocal test result occurs in 25% of patients undergoing coronary function testing. The interpretation of the ECG is the most important caveat in the diagnosis of vasospasm because the sensitivity for myocardial ischemia of the standard 12-lead surface ECG is suboptimal in this patient population and the interpretation of subtle beat-to-beat ECG changes during acetylcholine administration is inherently difficult. These caveats of the ECG lead to a risk of misdiagnosis in this complex patient population. Besides the resulting uncertainty, physicians may not initiate medical therapy or are reluctant to intensify medical therapy in absence of a definitive diagnosis, leading to ongoing symptoms, repeat investigations and hospital admissions. Improving diagnostic certainty in coronary function testing is therefore an important goal to improve care for ANOCA patients.

A readily available technique could improve detection of myocardial ischemia during coronary function testing. During CFT, a coronary guide wire is routinely advanced in the coronary artery which also allows obtaining an intracoronary ECG by attaching a sterile alligator clamp to a standard electrocardiogram lead.(9) This allows continuous recording of an intracoronary ECG throughout CFT on the same monitor as the 12-lead surface ECG. Pilot data indeed support that this technique can identify electrocardiographic changes related to myocardial ischemia during coronary function testing that are not apparent on the standard 12-lead surface ECG and can thereby increase sensitivity for myocardial ischemia during CFT.

Beyond improving invasive diagnosis of coronary vasospasm, the potential for non-invasive diagnostics deserves particular attention to reduce the risks associated with invasive coronary function testing and facilitate early diagnosis in this complex and rapidly expanding patient population. The diagnostic criteria for coronary vasospasm mainly drive on the association of reproducible anginal complaints and the simultaneous occurrence of ischaemic changes in the electrocardiogram, which together make a diagnosis of coronary vasospasm. Simultaneous invasive documentation of the presence or absence of epicardial vasospasm further allows to distinguish epicardial and microvascular vasospasm. The latter, however, currently bears little to no consequences both in terms of subsequent medical management, and in terms of prognosis. Hence, the non-invasive documentation of ischemic electrocardiographic changes in relation to spontaneous reproducible anginal complaints would allow to diagnose the presence of the vasospastic form of coronary vasomotor dysfunction. Since spontaneous episodes of anginal complaints are frequent in ANOCA patients, and tools for ambulatory electrocardiographic monitoring as well as its analysis have improved tremendously over time, we hypothesize that a large proportion of

patients could be adequately diagnosed using non-invasive ambulatory electrocardiographic monitoring.

Both for invasive and non-invasive diagnostics, the accuracy and feasibility of electrocardiographic data play a crucial role. Electrocardiographic data represent an area where machine learning techniques have progressively shown large potential for improving feasibility and accuracy of spot recordings, beat-to-beat data, and large longitudinal data registrations. If properly built, machine learning algorithms have a great potential in facilitating diagnosis both during CFT by allowing beat-to-beat quantification of ischemic ECG changes on both 12-lead ECG and intracoronary ECG registrations, as well as for ambulatory electrocardiographic registrations, where their use facilitates identification of potentially subtle ECG changes during prolonged recordings.

The goal of the (ai)NOCA study is to address these issues by aiming to optimize invasive diagnosis using intracoronary ECG registrations to enhance diagnostic efficacy for identification inducible myocardial ischemia during acetylcholine provocation testing, as well as by developing (machine learning) algorithms to enhance diagnostic efficacy of outpatient Holter ECG recordings to allow diagnosis of coronary vasospasm in the outpatient setting. Together, these goals lead to optimization of the diagnostic pathway for patients with ANOCA.

Study objective

1.1 Primary Objectives
1. To document the prevalence of ischemic intracoronary electrocardiogram changes in ANOCA patients with equivocal acetylcholine provocation test results.
2. To document the diagnostic efficacy of the 12-lead Holter ECG to identify ischemic ECG changes during acetylcholine-provoked chest pain.
3. To document the diagnostic efficacy of outpatient 12-lead Holter ECG monitoring to identify patients with a positive acetylcholine provocation test.

1.2 Secondary Objectives
1. To develop an algorithm to optimize identification of ischemic ECG changes on outpatient 12-lead Holter ECG monitoring.
2. To develop an algorithm that allows beat-to-beat detection of ischemic ECG changes on the intracoronary ECG during coronary function testing.
3. To develop an algorithm that allows beat-to-beat detection of ischemic ECG changes on the 12-lead surface electrocardiogram.
4. To develop an algorithm for quantification of acetylcholine-induced ischemic ECG changes on the intracoronary and surface electrocardiogram.

Study design

Observational study with non-invasive and invasive measurements.

Study burden and risks

There is no additional burden for the patients of obtaining an intracoronary electrocardiogram. Risks related to the electrophysiology part of this study are negligible. There is no direct benefit of participation in the study, but the study can only be performed in this patient population to advance care of future patients with the same clinical condition.

Contacts

Public
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584CX
NL
Scientific
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584CX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Clinical indication for comprehensive coronary function testing because of persisting chest discomfort at least 2 times per week despite current medical

therapy.
2. Absence of obstructive coronary artery disease with an indication for revascularization, documented by means of recent coronary computed tomography angiography (CCTA) or invasive coronary angiography (with invasive coronary pressure measurements if clinically indicated).
3. Patient is willing and able to provide written informed consent.

Exclusion criteria

1. Absence of chest discomfort after initiation of medical therapy.
2. Language barrier preventing sufficient understanding and communication in Dutch.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	11-12-2024
Enrollment:	250
Type:	Actual

Ethics review

Approved WMO

Date:	05-11-2024
Application type:	First submission
Review commission:	METC NedMec

Approved WMO

Date:	20-02-2025
Application type:	Amendment
Review commission:	METC NedMec

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
ClinicalTrials.gov	NCT06387693
CCMO	NL86726.041.24